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Editorial Board Member of *World Journal of Psychiatry*, Lenin Pavón, PhD, Professor, Laboratory of Psycho-immunology, National Institute of Psychiatry, "Ramón de la Fuente", Mexico City 14070, Mexico. lkuriaki@gmail.com

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OPINION REVIEW

Pharmacotherapy in autism spectrum disorders, including promising older drugs warranting trials

Jessica Hellings

Jessica Hellings, Department of Psychiatry, University of Missouri-Kansas City, Lee's Summit, MO 64063, United States

Corresponding author: Jessica Hellings, MB.BCh., MMed, Professor, Department of Psychiatry, University of Missouri-Kansas City, 300 SE Second St, Lee's Summit, MO 64063, United States. jessica.hellings@uhkc.org

Abstract

Available pharmacotherapies for autism spectrum disorders (ASD) are reviewed based on clinical and research experience, highlighting some older drugs with emerging evidence. Several medications show efficacy in ASD, though controlled studies in ASD are largely lacking. Only risperidone and aripiprazole have Federal Drug Administration approval in the United States. Methylphenidate (MPH) studies showed lower efficacy and tolerability for attention deficit hyperactivity disorder (ADHD) than in the typically developing (TD) population; atomoxetine demonstrated lower efficacy but comparable tolerability to TD outcomes. Guanfacine improved hyperactivity in ASD comparably to TD. Dextroamphetamine promises greater efficacy than MPH in ASD. ADHD medications reduce impulsive aggression in youth, and may also be key for this in adults. Controlled trials of the selective serotonin reuptake inhibitors citalopram and fluoxetine demonstrated poor tolerability and lack of efficacy for repetitive behaviors. Trials of antiseizure medications in ASD remain inconclusive, however clinical trials may be warranted in severely disabled individuals showing bizarre behaviors. No identified drugs treat ASD core symptoms; oxytocin lacked efficacy. Amitriptyline and loxapine however, show promise. Loxapine at 5-10 mg daily resembled an atypical antipsychotic in positron emission tomography studies, but may be weight-sparing. Amitriptyline at approximately 1 mg/kg/day used cautiously, shows efficacy for sleep, anxiety, impulsivity and ADHD, repetitive behaviors, and enuresis. Both drugs have promising neurotrophic properties.

Key Words: Autism; Pharmacotherapy; Dextroamphetamine; Loxapine; Amitriptyline; Minimally verbal; Neurotrophic

Core Tip: Most prescribing in autism spectrum disorders (ASD) is off-label; only risperidone and aripiprazole are Federal Drug Administration-approved in ASD, for irritability. Atypical antipsychotics are associated with metabolic side effects. Loxapine at 5-10 mg/day resembled an atypical antipsychotic in positron emission tomography studies; preliminary studies and clinical experience in ASD suggest efficacy and a promising metabolic profile. Controlled attention deficit hyperactivity disorder (ADHD) medication trials in ASD youth include methylphenidate, atomoxetine and guanfacine. The author recommends dextroamphetamine as an important treatment option for ADHD in ASD. Amitriptyline often improves impulsive aggression, self-injury, sleep, anxiety and enuresis. This article recommends additional older drug trials in ASD: Detroamphetamine, amitriptyline, loxapine, and lamotrigine for likely seizures.

INTRODUCTION

Autism spectrum disorder (ASD) is diagnosed using criteria of significant deficits in social communication and interaction, together with at least two types of restricted and repetitive interests and behaviors (RRBs)[1]. ASD develops prenatally and during early childhood. There is no longer an age cut-off for diagnosis, though it is often evident by age 1-3 years. The prevalence of ASD has risen globally since 2000. Two separate United States studies using the 2016 National Survey of Children's Health reported ASD prevalence of 1 in 40 children[2,3]. After decades there is still no definitive medication treatment for the core features of autism likely due to the heterogeneity of ASD, including various genetic causes. Recent studies with negative findings for core symptoms include oxytocin, bumetanide and selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram for RRBs[4]. A meta-analysis confirmed there are still no treatments with efficacy for RRBs[5].

In addition to core ASD disabilities, the majority of these individuals have other serious challenges affecting them. Approximately 30%-50% also have intellectual disability (ID)[6]. Those more severely affected for example by birth injuries may have hydrocephalus and cerebral palsy, along with varying degrees of motor paralysis. Although there is a tendency worldwide to diagnose ASD in high-functioning, milder cases, an estimated quarter of individuals with ASD have less than 20 words of expressive language and are thus minimally verbal[7]. Approximately 20%-40% of those with ASD also have epilepsy, with greater rates in the more severely affected[8], which includes minimally verbal individuals.

In addition, psychiatric illness occurs several times more commonly in those with ASD than in the general population[9,10]. Common presenting problems include hyperactivity, impulsive aggression, property destruction and self-injury, which are not Diagnostic and Statistical Manual-fifth edition-Text Revised (DSM-5-TR) diagnoses. A study of 1380 youth with ASD found that over two thirds (68%) manifested aggression towards a caregiver, and almost half (49%) showed aggression towards non-caregivers[11]. Psychiatrist training in the field of developmental disabilities is seriously lacking in most universities worldwide, and has marginally improved in the United States in the past 5 years[12,13]. Individuals with ASD and their caregivers have great difficulty identifying a provider in their geographical area who will treat them. The field still suffers from a serious lack of clinical trials to guide treatment of psychiatric comorbidity. Those providers who treat such patients must rely on the few ASD clinical trials published, experience gained by different medication trials, and extrapolation from studies in typically developing (TD) individuals.

An analysis of 33565 children with ASD, found that 35% received 2 or more psychotropic medications, while 15% received 3 or more[14]. Polypharmacy especially with antipsychotics is even greater in adults, when many non-psychiatric medications are also prescribed apart from psychotropic medications[15]. The lack of evidence base results inevitably in exposure of these individuals to repeated medication trials, an unnecessary burden of side effects, and attrition from care[16]. Individuals with ASD often have one or more comorbid DSM-5-TR diagnoses. Working DSM-5-TR diagnoses are important guides for selecting classes of medications. Diagnostic symptoms of DSM-5-TR diagnoses may be more difficult to recognize in those more severely affected, including the minimally verbal. The Diagnostic Manual of Intellectual Disabilities-2 (DM-ID2)[17] is a useful crosswalk for applying DSM-5 criteria to individuals with intellectual and developmental disorders and/or ASD. Clearly the verbal criteria for diagnoses are not used in the minimally verbal.

Only risperidone and aripiprazole are Federal Drug Administration (FDA)-approved in the United States for individuals with ASD and irritability. The few other drugs prospectively studied in

randomized controlled trials (RCTs) in ASD include methylphenidate (MPH), atomoxetine (ATX), guanfacine, the SSRIs fluoxetine and citalopram, and valproic acid[18]. Metformin, arbaclofen, lovastatin, trifinetide, 5-hydroxytryptamine7 (5-HT7) agonist ligands, flavonoids, and the dietary supplement sulforophane amongst others, are still being studied[4]. More RCTs are urgently needed for individuals with ASD/ID. While studies continue to test possible treatments for the core symptoms of ASD, even experts frequently run out of options for the many comorbidities, after many medication trials including clozapine have failed. It may also turn out that no one drug will target and treat the core symptoms in ASD, given the vast heterogeneity of genetic and other causes.

Behavior analysis and psychosocial treatments play a key role in any overall management plan, since problems due to environmental factors or maladaptive learning will not respond to medication treatments. This article highlights several available older medications, with decades of community use in the general population, that show promise in ASD. Emerging evidence about them includes preliminary observed efficacy, neurotrophic effects and apparent tolerability in low dose.

ATTENTION DEFICIT HYPERACTIVITY DISORDER: EXISTING STUDIES AND EMERGING EVIDENCE ON OTHER OLD MEDICATIONS

Symptoms of attention deficit hyperactivity disorder (ADHD) include inattention, distractibility, hyperactivity and impulsivity. ADHD in ASD is often associated with dangerous behaviors including impulsive aggression and self-injury[19]. Prior to DSM-5, ADHD was not recognized as a separate diagnosis for individuals with ASD. Since it does not manifest in all individuals with ASD but does so in a large proportion, notably 28%-68%[20] it is now included as a separate diagnosis. ADHD is increasingly identified and treated in adults with ASD; a recent study found high rates of ADHD in 63 tertiary-referred adults with ASD screened for psychiatric comorbidity, notably 68% for lifetime prevalence of ADHD[9]. Additionally, ADHD is less likely to improve after adolescence in youth with ASD than in the general population with ADHD. In the community, inattentive-type ADHD is the most common subtype found in ASD/ID, however it is often untreated.

The hyperactive-impulsive subtype of ADHD has poorer outcomes in individuals with ASD, related to the more disruptive nature of hyperactivity as well as a greater likelihood of impulsive aggression, self-injury and property destruction[19]. Affect dysregulation, the inability to properly regulate and modulate emotions, was not included in DSM-5 as a diagnostic feature of ADHD, but is emphasized in DM-ID2 as an important feature in individuals with developmental disabilities including ASD. The authors of the DSM-5 ADHD criteria later published an article emphasizing affect dysregulation as an important part of ADHD[21]. ADHD-associated mood fluctuations present an important source of impairment especially in those with developmental disabilities and ADHD. Especially in adults with ASD, the ADHD diagnosis may be overlooked, resulting in a bipolar or borderline personality disorder misdiagnosis.

ADHD medications are important for improving learning, speech and language, and executive functions including inhibitory self- control. These medications improve affect dysregulation in ASD, which often manifests as impulsive aggression when the person is frustrated. Response inhibition of affective fluctuations such as laughing or crying is impaired in ADHD, related to executive function deficits. A meta-analysis of executive function in ASD found that broad executive function deficits remain stable and do not improve across development in such individuals[22]. Obsessive compulsive disorder (OCD) is very commonly associated as well in ASD, and could complicate treatment of ADHD with stimulants since the latter may increase anxiety in a dose-related manner[23]. On the other hand, non-stimulant ADHD medications may help reduce OCD and repetitive behaviors in ASD, although studies are still needed. Medications for ADHD can be divided into stimulant and non-stimulant drug categories.

When to try stimulants in ASD?

Stimulants are more likely to show efficacy and tolerability in higher-functioning individuals with ASD who have predominantly ADHD symptoms in contrast to cases with OCD symptoms, prominent repetitive behaviors or self-injury. In the latter group, non-stimulant medications may be a more tolerable choice. Young children with ASD often begin their first ADHD medication trials when their disruptive behavior interferes with education of themselves and others in the classroom. As with TD young children with ADHD, the first drug tried is usually the stimulant MPH, in divided doses three times a day, up to 1 mg/kg/day or less; individual responses vary.

Dextroamphetamine (DEX) immediate release (ir) merits study in ASD, according to the author's decades-long experience. DEX has double the potency and duration of action as MPH, notably 4 to 6 h. A meta-analysis comparing efficacy of stimulants in 23 controlled studies for ADHD found a modest advantage of amphetamines over MPH for treating ADHD in pediatric patients[24]. Divided doses given morning, lunch time, and a half-dose at 4 pm if needed, totaling approximately 0.5 mg/kg/day or less give good coverage, better than MPH. Overall, DEX ir produces less lunch-time appetite suppression, less anxiety and irritability than long-acting stimulants according to author experience.

Despite the current low level of evidence for DEX in ASD, clinical trials are warranted, and patient trials in the office may be beneficial.

However, MPH is the only stimulant studied so far in ASD, with findings of lower tolerability and lower efficacy than in TD youth. Large studies include a multisite study by the group Research Units on Pediatric Psychopharmacology (RUPP)[25], and a Cochrane database systematic review[26]. The RUPP study of 72 children with ASD, aged 5 to 13 years, found all low doses studied were superior to placebo for hyperactivity and impulsivity. Subjects were pre-selected for ability to tolerate a test dose of MPH for a week. Total doses, each given for a week, were 0.125 mg/kg, 0.25 mg/kg, and 0.5 mg/kg and were deliberately low in order to minimize side effects. However only 49% were responders, a rate much lower than the 75% response rate in TD children. Even the greatest effect size of 0.54 was significantly lower than that for ADHD response in TD children. Side effect rates were approximately double those found in TD children, and 18% exited the study early due to intolerable side effects. These included irritability, decreased appetite, and insomnia. Parent-rated lethargy, social withdrawal, and inappropriate speech increased significantly. There are also two small RCT studies and one multisite study of MPH for ADHD in ASD. Two small RCT studies of MPH for aggression in ASD found benefit over placebo on the Aberrant Behavior Checklist-Irritability (ABC-I) subscale[27-29]. Intolerable side effects were common in the latter study also, including mood changes, agitation and abnormal movements.

The Cochrane systematic review[26] of MPH in children and adolescents with ASD included 4 crossover studies, totaling 113 children ages 5 to 13 years; most (83%) were boys. There was a significant benefit on teacher-rated inattention but insufficient data to perform an impulsivity-outcome meta-analysis. Treatment duration for each dose of MPH was 1 wk. High-dose MPH significantly improved hyperactivity as rated by teachers in 4 studies, 73 subjects, ($P < 0.001$) low quality evidence, and parents in 2 studies, 71 subjects ($P = 0.02$), low quality evidence. Ratings were on the hyperactivity subscale of the ABC. MPH clinical usefulness is also limited by its short half-life of 2-4 h.

Of the long-acting stimulants in ASD, only one small study has been published. This small study of 24 children, mean age 8.8 years, found significant benefit of MPH-extended release in ASD[30]. However this was not a representative ASD sample, since the participants' mean IQ was 85.0 (SD = 16.8). MPH-ER may be useful and more tolerable for example in high-functioning individuals with ASD. Comparative studies of long-acting stimulants are lacking in ASD, including for irritability[31]. Long-acting stimulants were designed to take effect and wear off gradually, and to reduce side effects and rebound effects in the general population with ADHD. However, clinical observations suggest that in ASD, long-acting stimulants may have even greater side effects than immediate-release preparations, including worsened anxiety, appetite suppression, self-injury, lip-licking, nail-picking, trichotillomania, and compulsive behaviors, in a dose-dependent manner. The more severe the ASD, the more of a problem such side effects present, although studies are needed. Therefore, non-stimulant ADHD medications may be preferable in these individuals.

When to try non-stimulant ADHD medications in ASD?

As stated, non-stimulant ADHD medications are preferable to stimulants for individuals who have more severe ASD, and those who also have prominent OCD, RRBs and self-injury. These include ATX, alpha agonists and tricyclic antidepressants (TCAs). Clinical experience in ASD suggests that these medications can be added to low-dose stimulants that are partially helpful if the person is unable to tolerate stimulant dose increases due to side effects. Several clinical trials in TD individuals have found efficacy and tolerability of ATX in combination with stimulants, although such combinations are not FDA-approved[32]. A recent review compared responses between MPH, ATX and guanfacine in 9 controlled studies of 430 children with ASD[33]. MPH and ATX were superior to placebo for ADHD. Poorer response was found in more cognitively disabled individuals.

Atomoxetine (ATX)

ATX is a noradrenergic reuptake inhibitor shown to produce improvements in inhibitory control as part of executive functions. Importantly, acute ATX administration increased behavioral inhibition as measured by a stop-signal task in adult ADHD not accompanied by ASD[34] as well as in normal adults without either ADHD or ASD[35]. Author experience confirms that ATX may be a good choice for impulsive aggression in ASD including in adults and minimally verbal individuals, and for poor focus and disorganization in higher-functioning individuals. A randomized, multisite 10-wk double-blind placebo-controlled trial of ATX, with or without parent training, was performed for ADHD in 128 children aged 5 to 14 years with ASD. ATX showed greatest efficacy together with parent- training, but also the drug alone was superior to placebo[36]. Overall, tolerability was good, to a maximum dose of 1.8 mg/kg/day; mean dose was 1.4 mg/kg/day. Dosing was divided into twice-daily doses, to reduce side effects. The most common side effects were nausea, decreased appetite, early morning wakening and fatigue. Suicidal ideation and QTc changes were not found, in contrast to findings in children without ASD[37]. In addition, another acute RCT study of 97 youths with ASD treated with ATX, including open long-term follow-up, showed moderately improved ADHD symptoms and side effects similar to those found in studies of ATX in youth with ADHD but no ASD[38,39].

ATX trials are warranted in ADHD in adults with ASD, especially for impulsive aggression, based on author experience. The strategy is to "start low and go slow" while response is observed for, using divided doses of twice a day to improve tolerability and coverage. A recent retrospective study disputes the need for extra caution however and found similar responses to ADHD treatments in adults with ADHD and ASD to those found in a comparison group with ADHD but no ASD[40]. The therapeutic window may be narrower in minimally verbal and lower-functioning individuals with more severe degrees of ASD, according to clinical experience. Should behavioral worsening occur after an ATX dose increase, the beneficial response is usually recaptured by dose reduction.

Amitriptyline

Amitriptyline in low doses may be especially useful if used with caution, in comparison with other available non-stimulant medications, despite a lack of comparative studies. TCAs including amitriptyline are second only to stimulants in ADHD efficacy, although most evidence for their use in ADHD is from studies of the second generation TCA desipramine in youth without ASD. An advantage over stimulants according to this author's experience is that amitriptyline may benefit ADHD, anxiety, OCD, gastrointestinal pain, headaches, enuresis and insomnia[15]. Though currently there is a low level of published evidence, prospective studies are warranted, in the author's opinion. A retrospective chart review on amitriptyline[41] published by the author's group examined 50 tertiary-referred children and adolescents with ASD, ADHD and high rates of aggression and self-injury, who received low dose AMI (mean dose 1.3 ± 0.6 mg/kg/day) with mean trough blood level of 114.1 ± 50.5 ng/mL. Response occurred clinically in 60% of patients at the final visit, and in 82% of patients for at least 50% of follow-up visits. Importantly, 30% had failed ATX, and 40% had failed 3 or more other ADHD medication trials. Amtriptyline was used in combination with stimulants, most often low dose DEX ir, and also low dose risperidone or aripiprazole. In the low doses used amitriptyline did not cause complaints of constipation or urinary retention. Side effects included QTc increase on routine electrocardiogram, which did not halt treatment except in 3 cases with QTc > 440, behavioral activation and worsening of aggression. Prospective, randomized controlled studies of amitriptyline in ASD are warranted.

While a 2014 Cochrane review[42] of TCAs in TD youth showed no serious adverse events associated with taking TCAs, mild increases in pulse rates and diastolic blood pressure occurred. Of note is that the overdose risk with TCAs is lower in individuals with ASD since most individuals including adults with ASD do not self-administer their medications. TCAs should not be prescribed for use in chaotic households or those with a risk of overdose by a family member.

Alpha agonists

The class of alpha-agonist drugs is FDA-approved for ADHD in TD children but not in ASD. Since these drugs may benefit tics and Tourette disorder, they are usually a first-line treatment choice in such individuals. This drug class includes guanfacine, clonidine, long-acting guanfacine (Intuniv TM) and long-acting clonidine XR (Kapvay TM). An 8-wk multisite study of extended-release guanfacine in 62 children with ASD and ADHD, mean age 8.5 years, found a significant improvement in comparison with placebo. Modal guanfacine ER dose was 3 mg/day (range 1-4 mg/day)[43]. The most common side effects were fatigue, drowsiness and decreased appetite. For subjects on guanfacine, blood pressure dropped in the initial 4 wk, but returned almost to baseline by week 8. Pulse rate also dropped but remained lower than baseline at week 8. A small study of clonidine[44] examined response of 8 male children with autistic disorder in a double-blind, placebo-controlled crossover design for ADHD symptoms. While parent-rated Conner's questionnaire ADHD ratings improved significantly during clonidine treatment, teacher ratings were not significantly improved except for oppositional behavior. Side effects included drowsiness and decreased activity. Due to their short half-lives, the immediate-release preparations of clonidine and guanfacine should be dosed 3 times a day. Dosing is built up gradually while monitoring for dizziness, hypotension and bradycardia. Other side effects include weight gain, sedation and irritability.

Although alpha agonists improve attention, studies in otherwise TD youth with ADHD have shown their combination use with a stimulant medication produces greater attentional improvement than does either alone. Combination treatments of alpha agonists and stimulants are FDA-approved for ADHD in the non-ASD population, but not in ASD. Clinical experience suggests however that alpha agonists may be less helpful for ADHD symptoms in adults with ASD.

Thus in the author's opinion, DEX, ATX and amitriptyline may be useful additions to treatment options for ADHD comorbid with ASD, including in adults.

EXISTING ANTIPSYCHOTIC STUDIES, AND EMERGING EVIDENCE FOR OTHER ANTIPSYCHOTICS

Antipsychotics are used to treat psychosis as well as irritability in ASD, and are classified into two classes: Atypical/novel antipsychotics and typical/classical antipsychotics. ASD core symptoms

including odd, stereotyped talk on unusual restricted topics of interest are still often misdiagnosed as schizophrenia symptoms in everyday practice. Psychosis can also be confused with bizarre behavior related to subclinical seizures, in which case antiseizure medications may help. Psychotic disorders can be comorbid with ASD, including schizophrenia, delusional disorder, unspecified psychosis, or as a component of a major mood disorder such as bipolar disorder, major depressive disorder or schizoaffective disorder[45].

Typical antipsychotics

Typical antipsychotics block dopamine D2 receptors to alleviate psychosis or mania, but produce motor side effects including acute dystonias, extrapyramidal side effects (EPS), tardive dyskinesia and more rarely, neuroleptic malignant syndrome which can be fatal. Haloperidol was studied in early trials by Campbell and colleagues, in young children, but found to produce tardive withdrawal movements[46, 47] and further studies were halted. According to clinical experience, typical antipsychotics often have a lag time to onset of response in individuals with ASD, and increasing the dose early in treatment especially of high potency antipsychotics like haloperidol may result in extremely severe EPS and dysphagia after a while, especially more severely disabled individuals, with resulting joint contractures [16]. Low potency typical antipsychotics including chlorpromazine produce hypotension, slowing, cognitive dulling and weight gain in those with developmental disabilities as well as in the general population. Thioridazine produced QTc prolongation and is no longer marketed.

The medium-potency, typical antipsychotic loxapine blocks serotonin as well as dopamine, and in low doses resembles an atypical antipsychotic in positron emission tomography (PET) studies, but with less or no weight gain[48-50] which will be discussed in more detail below. Atypical antipsychotics were designed to overcome these motor side effects of typical antipsychotics by a different mechanism of action, notably by blocking serotonin as well as dopamine receptors, amongst others. However an unanticipated side effect of the atypical antipsychotics turned out to be weight gain, Type II diabetes and multiple other medical side effects[51], which are more severe in those with developmental disabilities. Atypical antipsychotics also produce possible motor side effects including neuroleptic malignant syndrome and tardive dyskinesia in the general population but also in ASD.

Atypical antipsychotics

Only two antipsychotics are FDA-approved in ASD, for children ages 6 years and older with irritability, notably risperidone and aripiprazole. The RUPP multisite 8-wk risperidone RCT study of 101 children and adolescents, mean age 8.8 years, found significant efficacy of risperidone *vs* placebo for irritability on the Clinical Global Impressions-Improvement subscale[52], and the ABC-I subscale[29] at a mean dose of 1.8 mg/day. Effect size was 1.2. Side effects included significant weight gain, appetite increase in 73%, fatigue in 59%, and drowsiness in 49%, as well as prolactin elevation. The greatest benefits reported by parents were for self-injury and aggression. Another larger multisite RCT study of risperidone and parent training in 124 children and adolescents ages 4 through 13 found that parent training could lessen the dose of risperidone needed[53]. Risperidone doses were a mean of 2.26 mg/day or 0.071 mg/kg in the risperidone-only group, *vs* 1.98 mg/day or 0.066 mg/kg (*P* = 0.04, two-sided test) in the combination group of risperidone plus parent training.

Weight gain associated with risperidone treatment was marked, especially in some individuals in a double-blind crossover study performed by the author's group, of risperidone *vs* placebo for challenging behaviors in participants aged 6 to 65 with ID and ASD[54]. In a subset of 19 subjects over approximately a year, weight gain was as follows: Children (*n* = 5) ages 8 to 12 years gained 8.2 kg on average, adolescents (*n* = 6) aged 13 to 16 years gained 8.4 kg on average, and adults gained 5.4 kg on average[55]. Prolactin elevation is greater with risperidone than with other atypical antipsychotics. Breast development, galactorrhea and amenorrhea should be monitored[56]. It is important to monitor for weight gain and metabolic syndrome abnormalities, notably hypertension, glucose elevation, midline obesity, and triglyceride elevations. These are important predisposing factors for diabetes, stroke, myocardial infarction, and cognitive dysfunction and brain abnormalities[55]. In the author's experience, keeping risperidone doses low at or below 2 mg/day total, and splitting dosing to three times a day can help minimize weight gain. Importantly, clinical experience suggests that risperidone may be the most effective antipsychotic for self-injurious behavior.

A multisite RCT of aripiprazole in 218 children and adolescents with ASD, aged 6-17 years, mean age 9.3 years, found significant improvement in irritability in the aripiprazole *vs* the placebo group. Doses were 5, 10 or 15 mg/day in this 8-wk, parallel groups study. However, there was no protection against long-term relapse, the author agrees with this finding based on clinical practice, meaning that the efficacy may decrease over time, and increasing the dose may not recapture the initial good response. Side effects included sedation, the most common side effect leading to discontinuation, and significant weight gain[57]. Mean weight increases at week 8 were 0.3 kg for placebo, 1.3 kg for 5 mg/day, 1.3 kg for 10 mg/day and 1.5 kg for 15 mg/day groups, all *P* < 0.05 *vs* placebo. Importantly, aripiprazole in a low dose of 1 mg/day normalizes prolactin for example in an individual responding to risperidone who has elevated prolactin producing gynecomastia[58]. One small open pilot study compared olanzapine with haloperidol in children with autistic disorder[59] and one studied ziprasidone *vs* placebo[60] in ASD. Metformin for weight gain treatment with atypical antipsychotics was studied in a 16-wk, 4-center

multisite RCT of 60 children. Metformin was associated with reductions in future weight gain, notably body mass index (BMI) z-scores decreased significantly more from baseline to week 16 than in the placebo group (P = 0.003). However metformin did not alter lipid abnormalities, and gastrointestinal side effects identified included abdominal discomfort, abdominal pains and diarrhea[61] (in contrast to loxapine substitution discussed below).

Loxapine resembles an atypical antipsychotic at 5-10 mg/day

Loxapine shows promise clinically in adolescents and adults with ASD according to preliminary studies, and RCTs are warranted. This antipsychotic is a dibenzoxazepine tricyclic structure classified in the medium potency group of the typical antipsychotic class. Loxapine was designed in the 1980s to resemble clozapine but without the clozapine molecular component causing agranulocytosis. Loxapine has a history of extensive use in schizophrenia, usually at 40 to 80 mg/day (maximum dose of 200 mg/day) and may lack the marked weight gain and metabolic side effects of clozapine and other atypical antipsychotics[62]. A case report of a 10 year old female with autistic disorder who responded to loxapine 15 mg/day described its efficacy for treatment-resistant aggression and self-injurious behavior [63]. In low doses of 5 to 10 mg/day, loxapine resembles an atypical antipsychotic on PET brain studies, but lacks the weight gain and metabolic side effects[64,65]. A prospective 12-wk open trial of loxapine for irritability and aggression in 16 adolescents and adults with ASD[48], demonstrated that loxapine in low doses of 5 to 10 mg per day significantly improved irritability ratings on the ABC-I, with large pre- to post- treatment effect sizes on 4 subscales, d = 1.0-1.1. Fourteen of 16 subjects completed the study, all of whom had Clinical Global Impressions-Improvement scale ratings of Very Much Improved or Much Improved at week 12. Larger clinical trials are warranted.

A retrospective loxapine chart review, also by the author's group, of 15 outpatient adolescents and adults with ASD and irritability, illustrates the strategy of adding loxapine 5-10 mg/day, followed by extremely gradual taper of offending antipsychotics, which reversed weight gain, metabolic syndrome and insulin resistance including diabetes[49]. All those in the series had gained weight and manifested at least one other metabolic abnormality since starting on the baseline antipsychotic. Fourteen of the subjects were being treated with atypical antipsychotics and one received chlorpromazine, prior to addition of loxapine 5 to 10 mg daily, followed by behavioral improvement and then taper of the offending antipsychotic. Final loxapine dose in 12 subjects was 5 mg/day, and 10 mg/day in 2 subjects. At the time of chart review, all but one subject (93%) were Very Much Improved or Much Improved on CGI-I. Mean weight loss after an average of 17 mo (range 7 to 26 mo) on loxapine was -5.7 kg, with BMI reduction averaging -1.9. Mean reduction in triglycerides was -33.7 mg/dL (P = 0.03). Two subjects were tapered off metformin by their endocrinologists, and one person's insulin for Type II diabetes was discontinued. Weight loss did not differ in those already receiving metformin at the time of loxapine add-on (n = 4) though the numbers are small and the reader is therefore cautioned.

In a long-term outcomes chart review study, of 34 children, adolescents and adults with ASD, mean age 23.4 years (range 8 to 32 years), long-term low-dose loxapine at a mean dose of 8.9 mg/day (range 5 to 30 mg) was associated with lower rates of tardive dyskinesia and EPS than expected for a typical antipsychotic, mean treatment duration was 4.2 years[50]. Stahl[62] describes the addition of low doses of a classical antipsychotic to an atypical antipsychotic to "lead in" or "top up" the effect. Using loxapine add-on at 5-10 mg/day, the author has been able to minimize risperidone dose increases above 1.5-2 mg a day total of risperidone and this strategy appears weight-sparing.

Dysphagia and bowel obstruction associated with antipsychotics

A clinical word of caution is important regarding minimally verbal and neurologically impaired individuals treated with antipsychotics. Dysphagia is a common but often overlooked side effect of antipsychotics, predisposing to aspiration pneumonia and initiation of parenteral feeding after surgical insertion of gastrostomy tubes, which may then be life-long if the antipsychotic medications are not changed. Aspiration pneumonia is more common in those with severe developmental disabilities and minimally verbal individuals and those with cerebral palsy or quadriplegia treated with even moderate doses of antipsychotics, especially if the individual also receives concomitant cytochrome P450 2D6 (CYP2D6)-inhibiting SSRIs[66].

Substitution of the antipsychotic with other medications if needed, and gradual dose taper may allow swallowing improvement and normal eating reinstatement provided a repeat video swallow study is normal. A large study in non-psychiatric inpatients without ASD receiving antipsychotics mostly for delirium control found a significant association with aspiration pneumonia in comparison with a non-antipsychotic-exposed group[67]. The association magnitude was similar for typical and atypical antipsychotics. Also repeated ED and medical visits are commonly needed for ostomy revisions and infections. In clinical practice the problem is often magnified in individuals with spasticity by high dose anticholinergics such as baclofen or tizanidine. SSRIs that inhibit CYP2D6 may increase the effective dose of antipsychotics and other medications such that small-appearing doses actually are effectively much larger. In addition, such prescribing practices often lead to severe constipation, paralytic ileus, bowel obstruction and resection in individuals with severe disabilities. The author avoids using loxapine in individuals with severe disabilities and uses low dose risperidone in divided doses instead, due to the elevated dysphagia and EPS risks.

SSRI STUDIES IN ASD; AND WHAT DRUGS MAY HELP RRBs?

SSRI studies have not demonstrated efficacy for RRBs

While SSRIs may initially appear to help anxiety, depression and compulsive behaviors they may later worsen problems significantly and produce behavioral activation, especially in higher doses, in a dose-related manner. A 12-wk RCT study of 149 youth aged 5 to 17 years with ASD treated with citalopram, dosed up to 20 mg daily (mean dose 16 mg/day) for RRBs in ASD, was negative[68]. Overall there was no change in repetitive behavior but also significant side effects occurred. These included impuls-iveness, increased energy level, hyperactivity, decreased concentration, increased RRBs, insomnia, diarrhea and skin dryness and itching.

A 14-wk RCT study of 158 youth aged 5 to 17 years with ASD, treated with fluoxetine found no differences from placebo for RRBs as rated on the Child Yale-Brown Obsessive Compulsive Scale-Pervasive Developmental Disorders version[69]. Another fluoxetine RCT was also negative; Australian investigators randomized 146 youth aged 7.5 to 18 years with ASD to fluoxetine (20 mg/day if < 40 kg or 30 mg/day if ≥ 40 kg) or placebo. Any differences favoring fluoxetine were statistically nonsignificant after variables of gender, verbal abilities and baseline differences were controlled for. There was also no significant trend toward improvement on secondary outcome measures of RRBs, irritability, anxiety or global change[70]. An older, smaller RCT study of 39 youths aged 5-16 years found that a mean dose of 9.9 mg/day of fluoxetine was superior to placebo[71], however this has not been replicated. Some individual case studies and a case series suggested fluoxetine response however[72].

SSRIs are the most commonly prescribed drugs in ASD[4], although their use is not backed by study evidence. In the author's experience they may be helpful in high-functioning individuals with ASD for anxiety or depression. The Cochrane collaboration literature review of SSRIs in autism found no overall benefit in ASD, weighing positive and negative studies against each other[73]. In the author's experience, non-stimulant ADHD medications rather than SSRIs can help OCD and repetitive behaviors, including ATX and amitriptyline, this is anecdotal evidence but could be worth a try in the clinic. Many times the patient is presenting on an antipsychotic already. RRBs may relate also to ADHD symptoms, notably impulsivity, as part of a common cognitive impairment of executive function ("putting the breaks on") *i.e.* non-specific response inhibition[74]. These investigators found significant associations between repetitive speech and impulsive speech, between stereotyped behavior and overactivity, and between restricted preferences and impulsivity. This study further justifies the argument for studying non-stimulant ADHD medications for RRBs.

The TCA clomipramine reduced RRBs in one small study

Two TCAs typically targeting OCD, repetitive behaviors and hyperactivity, notably clomipramine and desipramine were compared with placebo in one double-blind study[75]. The investigators compared clomipramine to placebo in 12 subjects with autism using a crossover design, together with 12 different subjects completing a parallel trial of clomipramine *vs* desipramine. Clomipramine was superior to placebo and desipramine in reducing ratings on stereotypies, compulsive ritualized behaviors ($P < 0.05$) and anger, while desipramine was no different from placebo except in reducing hyperactivity. However in the author's experience substitution of amitriptyline for clomipramine in patients who present on clomipramine has produced greater global clinical improvements. This was an empirical observation made by the author's team in the 1990s that appears valid still today[41].

In a small cross-over study, 5 of 18 children (28%) treated with low dose fluvoxamine responded[76]. Fluvoxamine was found to benefit RRBs, maladaptive behavior, aggression and language in a small 12-wk RCT of 30 adults with autistic disorder[77]. Treatment studies of SSRIs or other classes of agents for depression and for suicidal behavior in ASD are lacking. For anxiety disorders in general in ASD, some smaller studies suggest the efficacy of citalopram, and some were positive for buspirone. One buspirone study in ASD found worsening of aggression and self-injury[78].

Maintenance benzodiazepines are avoided as a general principle in individuals with developmental disabilities, except for insomnia and as pre-sedation for blood tests and other procedures including dental work. Downsides include disinhibition effects, cognitive slowing and impairment, clumsiness, falls and injuries associated with benzodiazepine treatment.

HOW TO APPROACH ANTI-SEIZURE MEDICATIONS?

The therapeutic behavioral effects of anti-seizure medications in ASD for use other than seizures are inconclusive, according to available evidence. An RCT by the author's team of valproic acid for aggressive behavior in youth with ASD was negative, although some subjects appeared to benefit from it, likely related to the heterogeneity within ASD[79]. Another study found valproic acid to be beneficial for RRBs in ASD, however this finding has not been replicated. Worsening of behavior occurred in 4 of 13 cases[80]. Divalproex was effective for controlling irritability associated with fluoxetine treatment in ASD[81].

Clinical experience suggests a trial of anti-seizure medication such as valproic acid or lamotrigine (LTG) may be beneficial especially if seizures are known or suspected, and the presentation of behavior problems is bizarre or atypical. This pertains especially to minimally verbal individuals with severe ASD, who have very high rates of seizures, and those with a known history of traumatic brain injury.

For mood disorders

Apart from ADHD, bipolar disorder is another, much less common cause of impulsive aggression in ASD. A 25% lifetime prevalence for bipolar disorder *vs* 68% for ADHD was found in a tertiary-referred population of high-functioning adults with ASD[9]. Minimally verbal individuals may also present with bipolar-like illness however studies of this portion of the ASD spectrum are still needed. Although lithium may be helpful, anti-seizure medications are a first line of treatment for bipolar disorder in individuals with developmental disabilities.

Divalproex and carbamazepine

Mood-stabilizing anti-seizure medications including divalproex and carbamazepine are the first-line treatments for mania, mixed or rapid cycling bipolar disorder in the general population[82] as well as in individuals with developmental disabilities. Valproate/divalproex is FDA-approved for bipolar mania but not for acute bipolar depression in the general population. Divalproex can also be effective for acute mixed bipolar disorder[83]. Side effects include weight gain, polycystic ovarian syndrome, low blood platelets, alopecia, elevated liver enzymes and less often pancreatitis. In addition, divalproex can cause ASD if taken in early pregnancy[84]. Weight gain, hepatic enzymes and blood cell counts require monitoring.

Both divalproex and carbamazepine are available in extended-release formulations. Carbamazepine is weight-neutral but side effects may include nausea, vomiting, dizziness, drowsiness, dry mouth, constipation and unsteadiness. A rare but extremely serious potential side effect of carbamazepine is Stevens-Johnson syndrome, which may start as an influenza-like illness but progress to a blistering skin rash, skin peeling and death.

Lamotrigine (LTG)

LTG is the mood-stabilizing anti-seizure medication of choice for bipolar depression treatment as well as prophylaxis[85]. Apart from the vigilance needed for a serious skin rash again associated with Stevens-Johnson syndrome, and the need to start LTG slowly to try and prevent this, the longer-term profile of LTG is favorable in comparison with other anti-seizure medications. Another important use for consideration in psychiatry, according to author experience, is for suspected seizures including spells of eye-blinking, mouth movements or disorientation episodes accompanied by bizarre behavior presentations in ASD, as mentioned above.

Evidence for LTG is weaker for acute bipolar depression and rapid cycling bipolar disorder in the general population. LTG must be started extremely slowly by adding a low dose every 1 to 2 wk, and even more gradually if the individual is receiving divalproex (adding 25 mg every 2 wk), to avoid a potentially life-threatening skin rash that begins on the upper chest region. Skin rash signs include skin peeling, blistering, hives, itching and painful sores in the mouth or around the eyes. Other LTG side effects include blurred or double vision, poor motor coordination, headache, drowsiness, and difficulty thinking or speaking.

Gabapentin

Gabapentin is an add-on anti-seizure medication often prescribed off-label in psychiatry for various indications despite negative RCTs including for bipolar disorder. Rather than acting on gamma-amino butyric acid, gabapentin likely acts on calcium channels in the brain and spinal cord, and has few drug interactions since it is renally excreted. Gabapentin add-on to valproic acid and low dose antipsychotic was helpful in an open study by the author, in adults with developmental disabilities[86]. Gabapentin in divided doses 3 times a day, totaling 900 to 1800 mg a day were effective as add-on to valproic acid and low dose antipsychotic, and also in a subset replaced lithium and thus eliminated lithium side effects. Gabapentin side effects included dizziness and clumsiness; to prevent these it was started at 100 mg daily and increased slowly by only 100-200 mg per week, although prospective RCT studies are needed.

While lithium is still used in ASD, the side effects are often worse in those with developmental disabilities, and include polydipsia and polyuria (excessive thirst, drinking and enuresis) and tremor. Acute toxicity is a medical emergency requiring dialysis and intensive care units treatment, and is a greater risk in individuals with disabilities. Vomiting, diarrhea, failure to drink fluids for any reason, and certain medications including the angiotensin-converting enzyme inhibitor losartan predispose to toxicity[86].

Insomnia is very common in ASD and should not be interpreted as mania-related illness unless accompanied by other observable mania features. Another pitfall is that loud, rapid speech and outgoing personality may not be due to bipolar disorder but an enduring personality trait with a life-long history.

Anti-seizure medication-related behavioral side effects

Importantly, several anti-seizure medications while benefitting seizures may produce adverse behavioral effects. The latter may not have been considered by the neurologist if the seizures are adequately controlled. Therefore identification of such side effects by the psychiatrist is essential. Barbiturate-based anti-seizure medications including phenobarbital and phenytoin, and benzodiazepine-based medications, as well as vigabitrin often worsen behavior. Such medications may lead to an ADHD-like picture of affect dysregulation, hyperactivity, restlessness, impulsive aggression and self-injury[87]. Carbamazepine, oxcarbazepine, levetiracetam and topiramate may also worsen hyperactivity, mood or psychotic symptoms or other behavior problems. LTG and divalproex may be less likely to have behavioral side effects in adults with ASD according to clinical experience.

IN SUMMARY

Studies included followed a broad and thorough literature review of pharmacotherapy in ASD, in order to provide a clear overview of the topic as well as the author's expert opinion. For a summary of key points for pharmacotherapy in ASD (Table 1). Limitations of this opinion review include that aside from evidence-based guidelines, prescribing practices may be extremely variable, not only by country and region, but also by individual practitioners who may find other medications useful in ASD. The author has however attempted to provide a personal but balanced view overall. Regarding future drug treatments for core ASD symptoms it may not be possible for one drug to target and treat all of the many subtypes of ASD, given the many genetic and other causes. Of note is that while certain drugs such as ATX may not be available in all countries, amitriptyline is approved in many countries and is available in generic forms.

CLINICAL PEARLS GLEANED OVER MANY DECADES OF RESEARCH AND PRACTICE TREATING ALL AGES WITH DEVELOPMENTAL DISABILITIES

Environmental and emotional causes are more likely to respond to behavioral consultation: This can be key also in treatment resistance

It is important to emphasize that environmental and emotional causes of behavior problems will be more likely to respond to behavioral consultation and psychosocial interventions. Of late, there has been greater recognition of environmental contributors to psychiatric illness in the field in general. Abuse of all types is also more likely in vulnerable individuals such as those with developmental disabilities. Taking a detailed longitudinal history is essential, regarding likely environmental stressors such as family deaths or job losses, moves and staff changes leading to frustration and severe "protest" behavior problems including aggression, before making psychiatric diagnoses and trying medication treatments. Protest behaviors and use of aggression as communication are more likely especially if the individual has demonstrated consistently good functioning over one or more periods of time in their past. A developmental and childhood psychiatric history is also essential to understanding of presenting problems. Irritability can result from many non-psychiatric causes, including medical illness, lack of sleep, general frustration or unhappiness with a living situation. Treating just dimensional behavior problems, such as irritability or hyperactivity with single medications may be feasible for milder cases. As in other branches of medicine, if the diagnosis is wrong then the treatment will unlikely help.

Closer examination for ADHD and trying ADHD treatments pays off, including in females and adults with severe disabilities

This applies to ADHD wrongly diagnosed as bipolar disorder, since antipsychotics and mood stabilizers do not adequately treat ADHD-related impulsivity. This was a personal lesson the author learned early on in practice after specializing in treating this population. Females diagnosed with depression and recurrent suicidality may also respond to ADHD treatments, allowing for cautious taper of antidepressants. Parents and caregivers often describe a person with ADHD person as "anxious" since they rarely sit still, and "moody" due to lack of affect regulation associated with easy crying or laughing spells.

DEX, ATX and amitriptyline are useful for ADHD comorbid with ASD

Impulsive aggression such as cussing, hitting, kicking, biting, pinching and running off may respond to one or more ADHD treatments if the ADHD history and diagnosis are elicited. Many adults already received treatment for ADHD as children but once transitioning services happens the ADHD diagnosis is overlooked. Although only studies in TD individuals are available as discussed above, a combination of low dose stimulant together with a non-stimulant ADHD medication such as ATX, amitriptyline or guanfacine may be needed. Low dose risperidone may also be used in combination with the ADHD

Table 1 Key points for pharmacotherapy in autism spectrum disorders		
ADHD medications	**Antipsychotic medications**	**Anti-seizure medications**
Stimulants for high-functioning ASD: (1) Methyl-phenidate in young children; and (2) Dextroamphetamine immediate release in children, adolescents and adults is often useful	Risperidone: Especially useful for self-injurious behavior: Also useful in children for irritability and aggression in low, divided doses	Phenytoin and phenobarbital frequently worsen behavior. Replace with newer medications in consultation with neurologist
Non-stimulants for lower-functioning ASD: (1) Atomoxetine; (2) Amitriptyline; and (3) Guanfacine in low, divided doses if tics/Tourette disorder	Loxapine at 5-10 mg/day: Useful in adolescents and adults for irritability, aggression, or with risperidone as a weight-sparing strategy	Levotiracetam, carbamazepine, benzodiazepines, and others may also adversely affect behavior
For greater effect: Low-dose combination of stimulant and non-stimulant medications may be tried	Watch out for the following, especially with high-dose antipsychotics: Difficulty in swallowing or bowel obstructions in more severely disabled individuals	Gabapentin may be useful as an add-on to divalproex for bipolar disorder, instead of lithium

Selective serotonin reuptake inhibitors may reduce anxiety or depression in high-functioning individuals but are unlikely to alleviate repetitive/compulsive behaviors in autism spectrum disorders, and often cause activation and behavioral worsening. ASD: Autism spectrum disorders; ADHD: Attention deficit hyperactivity disorder.

treatments, although again only one study in the TD participants is available regarding this[88].

Two ADHD medications may be needed (stimulant and non-stimulant) possibly also together with low dose antipsychotic such as risperidone in moderate-to -severe cases with aggression. In the author's experience, ATX is frequently clinically useful for ADHD with impulsive aggression, including in more severely disabled individuals. The tolerable doses may be lower than in higher functioning individuals, although improvements may be regained if the dose is decreased again after behavioral worsening following a dose increase occurs. More studies are warranted. Amitriptyline in low doses can be extremely helpful for cases with insomnia, headaches, gastrointestinal issues, ADHD, impulsive aggression and OCD, used with caution and watching for drug interactions. Studies are warranted of amitriptyline for RRBs in ASD according to author experience.

Are RRBs part of the ADHD spectrum, and could they respond to ADHD treatments?

The study by Burbridge and coworkers[74] leading to the concept of RRBs as related to ADHD, in other words a type of motor impulsivity, may be key to guiding future studies for RRB etiology and treatments. One study found ATX was somewhat effective for RRBs in youth with ASD, which is promising[39]. No known treatment currently exists for core ASD features, likely due to the heterogeneity and many different genetic causes. Metformin, arbaclofen, lovastatin, trifinetide, 5-HT7 agonist ligands, flavonoids, cannabidiol, cannabis and the dietary supplement sulfurophane amongst others, are still being studied[4].

Risperidone remains useful in youth with severe irritability and may be helpful for self-injury; dose at ≤ 2 mg/day in divided doses

Dosing risperidone at or below 2 mg/day given in divided doses may mitigate weight gain and metabolic side effects, though individuals vary in this regard. Another author observation is that risperidone may be the most effective medication for self-injurious behaviors including self-biting, head- banging, self-hitting and others. Weight gain and metabolic side effects require monitoring.

Loxapine at 5-10 mg/day resembles an atypical antipsychotic but likely with emerging safety evidence of a more favorable metabolic profile

Loxapine is one of the main antipsychotics now used in practice by the author and several colleagues in other regions, for adolescents and adults with ASD, related to an empirical finding made over 2 decades ago and then the preliminary published studies discussed above. Addition of 5-10 mg/day of loxapine often produces significant clinical improvement in irritability and aggression, which if needed then allows very gradual taper of other antipsychotics which have caused excessive weight gain or produced too little response. While a common practice may be to follow schizophrenia guidelines and convert a treatment-resistant person to a depo antipsychotic, hoping for improved aggression control, adding loxapine, in the author's experience produces superior results overall. However loxapine is likely not suitable for more severely disabled individuals due to its potent dopamine blocking action that may cause dysphagia in them; low dose risperidone may be preferable in this setting. Olanzapine is another cause of dysphagia in those with more severe disabilities, according to clinical experience.

Gabapentin may be a useful add-on to divalproex and low dose antipsychotic if lithium is not a good choice for the individual patient

Published preliminary evidence on gabapentin add-on to valproate and low dose antipsychotic in ASD

may be useful when lithium is not tolerated due to side effects, or if lithium toxicity has already occurred once or more. Studies are needed.

SSRIs may be helpful in higher-functioning ASD for anxiety or depression, but not for RRBs

SSRIs remain the most widely prescribed drug class in ASD in the United States overall. Recent negative studies of citalopram and fluoxetine for RRBs in youth with ASD are helpful in this clarification. In many cases, high dose SSRIs worsen OCD and agitation, while gradual SSRI taper may lead to clinical improvements. Also, in cases involving SSRIs increasing the effective antipsychotic dose due to CYP2D6 inhibition, swallowing impairment and bowel motility problems may be reversed by gradual SSRI taper and medication revisions.

CONCLUSION

Existing studies in ASD are useful guides for clinical practice, but many more are still needed. Most prescribing in individuals with developmental disabilities is of clinical necessity off-label. Some older psychotropic medications with emerging evidence may extend and improve possible successful treatment options for clinicians serving individuals of all ages with ASD and severe behavior problems. Until controlled studies of these drugs become available, cautious clinical use starting with low doses and minding drug interactions may be justified. Another important focus should be alerts regarding possible ADHD with impulsive aggression, especially in females and in adults with ASD. The older medications worth trying include, but are clearly not limited to, DEX, ATX and amitriptyline for individuals with ADHD associated with impulsive aggression.

For irritability and psychotic comorbidity in adolescents and adults with ASD, preliminary published evidence and clinical experience point to loxapine in doses of 5-10 mg/day having atypical antipsychotic properties but likely with lower metabolic risk associated. For likely seizure activity associated with bizarre behaviors that is unable to be worked up *via* electroencephalogram due to lack of cooperation, LTG may be considered, especially in those with severe disabilities since they have higher rates of seizures. No medications have been identified and replicated so far to treat the core symptoms of autism, including RRBs. Drugs without demonstrated benefit for core symptoms include risperidone, oxytocin, bumetanide, buspirone, citalopram, fluoxetine, fluvoxamine and N-acetyl cysteine. While SSRIs are the most commonly prescribed drugs in ASD and may help individual patients, recent RCT studies did not show significant efficacy for RRBs in ASD, but rather a significant side effect burden including behavioral activation. Clinical trials of the older drugs discussed are warranted. All medications should be used in conjunction with other multimodal therapies including behavioral consultation, and selected for the individual patient.

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FOOTNOTES

REFERENCES

1 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Arlington (VA): American Psychiatric Association, 2022

2 **Kogan MD**, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, Perrin JM, Shattuck P, Kuhlthau KA, Harwood RL, Lu MC. The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children. *Pediatrics* 2018; **142** [PMID: 30478241 DOI: 10.1542/peds.2017-4161]

3 **Xu G**, Strathearn L, Liu B, Bao W. Prevalence of Autism Spectrum Disorder Among US Children and Adolescents, 2014-2016. *JAMA* 2018; **319**: 81-82 [PMID: 29297068 DOI: 10.1001/jama.2017.17812]

4 **Aishworiya R**, Valica T, Hagerman R, Restrepo B. An Update on Psychopharmacological Treatment of Autism Spectrum Disorder. *Neurotherapeutics* 2022; **19**: 248-262 [PMID: 35029811 DOI: 10.1007/s13311-022-01183-1]

5 **Yu Y**, Chaulagain A, Pedersen SA, Lydersen S, Leventhal BL, Szatmari P, Aleksic B, Ozaki N, Skokauskas N. Pharmacotherapy of restricted/repetitive behavior in autism spectrum disorder:a systematic review and meta-analysis. *BMC Psychiatry* 2020; **20**: 121 [PMID: 32164636 DOI: 10.1186/s12888-020-2477-9]

6 **Thurm A**, Farmer C, Salzman E, Lord C, Bishop S. State of the Field: Differentiating Intellectual Disability From Autism Spectrum Disorder. *Front Psychiatry* 2019; **10**: 526 [PMID: 31417436 DOI: 10.3389/fpsyt.2019.00526]

7 **Tager-Flusberg H**, Kasari C. Minimally verbal school-aged children with autism spectrum disorder: the neglected end of the spectrum. *Autism Res* 2013; **6**: 468-478 [PMID: 24124067 DOI: 10.1002/aur.1329]

8 **Besag FM**. Epilepsy in patients with autism: links, risks and treatment challenges. *Neuropsychiatr Dis Treat* 2018; **14**: 1-10 [PMID: 29296085 DOI: 10.2147/NDT.S120509]

9 **Joshi G**, Wozniak J, Petty C, Martelon MK, Fried R, Bolfek A, Kotte A, Stevens J, Furtak SL, Bourgeois M, Caruso J, Caron A, Biederman J. Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. *J Autism Dev Disord* 2013; **43**: 1314-1325 [PMID: 23076506 DOI: 10.1007/s10803-012-1679-5]

10 **Lai MC**, Kassee C, Besney R, Bonato S, Hull L, Mandy W, Szatmari P, Ameis SH. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *Lancet Psychiatry* 2019; **6**: 819-829 [PMID: 31447415 DOI: 10.1016/S2215-0366(19)30289-5]

11 **Kanne SM**, Mazurek MO. Aggression in children and adolescents with ASD: prevalence and risk factors. *J Autism Dev Disord* 2011; **41**: 926-937 [PMID: 20960041 DOI: 10.1007/s10803-010-1118-4]

12 **Marrus N**, Veenstra-Vanderweele J, Hellings JA, Stigler KA, Szymanski L, King BH, Carlisle LL, Cook EH Jr; American Academy of Child Adolescent Psychiatry (AACAP) Autism and Intellectual Disability Committee, Pruett JR Jr. Training of child and adolescent psychiatry fellows in autism and intellectual disability. *Autism* 2014; **18**: 471-475 [PMID: 24113341 DOI: 10.1177/1362361313477247]

13 **Marrus N**, Koth KA, Hellings JA, McDonald R, Gwynette MF, Muhle R, Lohr WD, Vasa RA. Psychiatry training in autism spectrum disorder and intellectual disability: Ongoing gaps and emerging opportunities. *Autism* 2023; **27**: 679-689 [PMID: 35920285 DOI: 10.1177/13623613221112197]

14 **Spencer D**, Marshall J, Post B, Kulakodlu M, Newschaffer C, Dennen T, Azocar F, Jain A. Psychotropic medication use and polypharmacy in children with autism spectrum disorders. *Pediatrics* 2013; **132**: 833-840 [PMID: 24144704 DOI: 10.1542/peds.2012-3774]

15 **Deb S**, Unwin G, Deb T. Characteristics and the trajectory of psychotropic medication use in general and antipsychotics in particular among adults with an intellectual disability who exhibit aggressive behaviour. *J Intellect Disabil Res* 2015; **59**: 11-25 [PMID: 24450426 DOI: 10.1111/jir.12119]

16 **Hellings JA**, Arnold LE, Han JC. Dopamine antagonists for treatment resistance in autism spectrum disorders: review and focus on BDNF stimulators loxapine and amitriptyline. *Expert Opin Pharmacother* 2017; **18**: 581-588 [PMID: 28335658 DOI: 10.1080/14656566.2017.1308483]

17 **Fletcher R**, Barnhill J, Cooper SA. Diagnostic Manual-Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability. New York: NADD Press, 2016

18 **Howes OD**, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, Loth E, McAlonan GM, McCracken JT, Parr JR, Povey C, Santosh P, Wallace S, Simonoff E, Murphy DG. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J Psychopharmacol* 2018; **32**: 3-29 [PMID: 29237331 DOI: 10.1177/0269881117741766]

19 **Hellings JA**, Reiersen AM, Arnold LE, Mao AR, Pearson DA, Aman MG, Handen BL, McLaren J. Attention-Deficit/Hyperactivity Disorder, In Diagnostic Manual-Intellectual Disability, Second edition, Eds. Fletcher RJ, Barnhill J, Cooper SA. New York: NADD Press, 2016

20 **Murray MJ**. Attention-deficit/Hyperactivity Disorder in the context of Autism spectrum disorders. *Curr Psychiatry Rep* 2010; **12**: 382-388 [PMID: 20694583 DOI: 10.1007/s11920-010-0145-3]

21 **Shaw P**, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry* 2014; **171**: 276-293 [PMID: 24480998 DOI: 10.1176/appi.ajp.2013.13070966]

22 **Demetriou EA**, Lampit A, Quintana DS, Naismith SL, Song YJC, Pye JE, Hickie I, Guastella AJ. Autism spectrum disorders: a meta-analysis of executive function. *Mol Psychiatry* 2018; **23**: 1198-1204 [PMID: 28439105 DOI: 10.1038/mp.2017.75]

23 **Arnsten AF**. Stimulants: Therapeutic actions in ADHD. *Neuropsychopharmacology* 2006; **31**: 2376-2383 [PMID: 16855530 DOI: 10.1038/sj.npp.1301164]

24 **Faraone SV**, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis.

Eur Child Adolesc Psychiatry 2010; **19**: 353-364 [PMID: 19763664 DOI: 10.1007/s00787-009-0054-3]

25   **Research Units on Pediatric Psychopharmacology Autism Network**. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry* 2005; **62**: 1266-1274 [PMID: 16275814 DOI: 10.1001/archpsyc.62.11.1266]

26   **Sturman N**, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. *Cochrane Database Syst Rev* 2017; **11**: CD011144 [PMID: 29159857 DOI: 10.1002/14651858.CD011144.pub2]

27   **Handen BL**, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Autism Dev Disord* 2000; **30**: 245-255 [PMID: 11055460 DOI: 10.1023/a:1005548619694]

28   **Quintana H**, Birmaher B, Stedge D, Lennon S, Freed J, Bridge J, Greenhill L. Use of methylphenidate in the treatment of children with autistic disorder. *J Autism Dev Disord* 1995; **25**: 283-294 [PMID: 7559293 DOI: 10.1007/BF02179289]

29   **Aman MG**, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic* 1985; **89**: 485-491 [PMID: 3993694]

30   **Pearson DA**, Santos CW, Aman MG, Arnold LE, Casat CD, Mansour R, Lane DM, Loveland KA, Bukstein OG, Jerger SW, Factor P, Vanwoerden S, Perez E, Cleveland LA. Effects of extended release methylphenidate treatment on ratings of attention-deficit/hyperactivity disorder (ADHD) and associated behavior in children with autism spectrum disorders and ADHD symptoms. *J Child Adolesc Psychopharmacol* 2013; **23**: 337-351 [PMID: 23782128 DOI: 10.1089/cap.2012.0096]

31   **Ghanizadeh A**, Molla M, Olango GJ. The effect of stimulants on irritability in autism comorbid with ADHD: a systematic review. *Neuropsychiatr Dis Treat* 2019; **15**: 1547-1555 [PMID: 31239689 DOI: 10.2147/NDT.S194022]

32   **Treuer T**, Gau SS, Méndez L, Montgomery W, Monk JA, Altin M, Wu S, Lin CC, Dueñas HJ. A systematic review of combination therapy with stimulants and atomoxetine for attention-deficit/hyperactivity disorder, including patient characteristics, treatment strategies, effectiveness, and tolerability. *J Child Adolesc Psychopharmacol* 2013; **23**: 179-193 [PMID: 23560600 DOI: 10.1089/cap.2012.0093]

33   **Rodrigues R**, Lai MC, Beswick A, Gorman DA, Anagnostou E, Szatmari P, Anderson KK, Ameis SH. Practitioner Review: Pharmacological treatment of attention-deficit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a systematic review and meta-analysis. *J Child Psychol Psychiatry* 2021; **62**: 680-700 [PMID: 32845025 DOI: 10.1111/jcpp.13305]

34   **Chamberlain SR**, Hampshire A, Müller U, Rubia K, Del Campo N, Craig K, Regenthal R, Suckling J, Roiser JP, Grant JE, Bullmore ET, Robbins TW, Sahakian BJ. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. *Biol Psychiatry* 2009; **65**: 550-555 [PMID: 19026407 DOI: 10.1016/j.biopsych.2008.10.014]

35   **Chamberlain SR**, Del Campo N, Dowson J, Müller U, Clark L, Robbins TW, Sahakian BJ. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. *Biol Psychiatry* 2007; **62**: 977-984 [PMID: 17644072 DOI: 10.1016/j.biopsych.2007.03.003]

36   **Handen BL**, Aman MG, Arnold LE, Hyman SL, Tumuluru RV, Lecavalier L, Corbett-Dick P, Pan X, Hollway JA, Buchan-Page KA, Silverman LB, Brown NV, Rice RR Jr, Hellings J, Mruzek DW, McAuliffe-Bellin S, Hurt EA, Ryan MM, Levato L, Smith T. Atomoxetine, Parent Training, and Their Combination in Children With Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 905-915 [PMID: 26506581 DOI: 10.1016/j.jaac.2015.08.013]

37   **Tumuluru RV**, Corbett-Dick P, Aman MG, Smith T, Arnold LE, Pan X, Buchan-Page KA, Brown NV, Ryan MM, Hyman SL, Hellings J, Williams C, Hollway JA, Lecavalier L, Rice RR Jr, McAuliffe-Bellin S, Handen BL. Adverse Events of Atomoxetine in a Double-Blind Placebo-Controlled Study in Children with Autism. *J Child Adolesc Psychopharmacol* 2017; **27**: 708-714 [PMID: 28509573 DOI: 10.1089/cap.2016.0187]

38   **Harfterkamp M**, van de Loo-Neus G, Minderaa RB, van der Gaag RJ, Escobar R, Schacht A, Pamulapati S, Buitelaar JK, Hoekstra PJ. A randomized double-blind study of atomoxetine *vs* placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 2012; **51**: 733-741 [PMID: 22721596 DOI: 10.1016/j.jaac.2012.04.011]

39   **Harfterkamp M**, Buitelaar JK, Minderaa RB, van de Loo-Neus G, van der Gaag RJ, Hoekstra PJ. Atomoxetine in autism spectrum disorder: no effects on social functioning; some beneficial effects on stereotyped behaviors, inappropriate speech, and fear of change. *J Child Adolesc Psychopharmacol* 2014; **24**: 481-485 [PMID: 25369243 DOI: 10.1089/cap.2014.0026]

40   **Muit JJ**, Bothof N, Kan CC. Pharmacotherapy of ADHD in Adults With Autism Spectrum Disorder: Effectiveness and Side Effects. *J Atten Disord* 2020; **24**: 215-225 [PMID: 31625426 DOI: 10.1177/1087054719866255]

41   **Bhatti I**, Thome A, Smith PO, Cook-Wiens G, Yeh HW, Gaffney GR, Hellings JA. A retrospective study of amitriptyline in youth with autism spectrum disorders. *J Autism Dev Disord* 2013; **43**: 1017-1027 [PMID: 23135317 DOI: 10.1007/s10803-012-1647-0]

42   **Otasowie J**, Castells X, Ehimare UP, Smith CH. Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev* 2014; CD006997 [PMID: 25238582 DOI: 10.1002/14651858.CD006997.pub2]

43   **Scahill L**, McCracken JT, King BH, Rockhill C, Shah B, Politte L, Sanders R, Minjarez M, Cowen J, Mullett J, Page C, Ward D, Deng Y, Loo S, Dziura J, McDougle CJ; Research Units on Pediatric Psychopharmacology Autism Network. Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder. *Am J Psychiatry* 2015; **172**: 1197-1206 [PMID: 26315981 DOI: 10.1176/appi.ajp.2015.15010055]

44   **Jaselskis CA**, Cook EH Jr, Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol* 1992; **12**: 322-327 [PMID: 1479049]

45   **Hassiotis A**, Fodor-Wynne L, Fleisher M.   Schizophrenia and other psychotic disorders. In: Fletcher RJ, Barnhill J, Cooper S (Eds.). Diagnostic-Manual-Intellectual Disability: Textbook of Mental disorders in Persons with Intellectual Disability. New York: NADD Press, 2016

46   **Campbell M**, Geller B, Cohen IL. Current status of drug research and treatment with autistic children. *J Pediatr Psychol* 1977; **2**: 153-161 [DOI: 10.1093/jpepsy/2.4.153]

47   **Perry R**, Campbell M, Adams P, Lynch N, Spencer EK, Curren EL, Overall JE. Long-term efficacy of haloperidol in autistic children: continuous *vs* discontinuous drug administration. *J Am Acad Child Adolesc Psychiatry* 1989; **28**: 87-92 [PMID: 2914841 DOI: 10.1097/00004583-198901000-00016]

48   **Hellings JA**, Reed G, Cain SE, Zhou X, Barth FX, Aman MG, Palaguachi GI, Mikhnev D, Teng R, Andridge R, Logan M, Butler MG, Han JC. Loxapine add-on for adolescents and adults with autism spectrum disorders and irritability. *J Child Adolesc Psychopharmacol* 2015; **25**: 150-159 [PMID: 25782098 DOI: 10.1089/cap.2014.0003]

49   **Jain S**, Andridge R, Hellings JA. Loxapine for Reversal of Antipsychotic-Induced Metabolic Disturbances: A Chart Review. *J Autism Dev Disord* 2016; **46**: 1344-1353 [PMID: 26687568 DOI: 10.1007/s10803-015-2675-3]

50   **Hellings JA**, Jadhav M, Jain S, Jadhav S, Genovese A. Low Dose Loxapine: Neuromotor Side Effects and Tolerability in Autism Spectrum Disorders. *J Child Adolesc Psychopharmacol* 2015; **25**: 618-624 [PMID: 26485086 DOI: 10.1089/cap.2014.0145]

51   **Hellings JA**, Jain S.   The interface between medical and psychiatric disorders. In: Hemmings C & Bouras N. Psychiatric and Behavioral Disorders in Intellectual and Developmental Disabilities. Cambridge, UK: Cambridge University Press, 2016

52   **McCracken JT**, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D; Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347**: 314-321 [PMID: 12151468 DOI: 10.1056/NEJMoa013171]

53   **Scahill L**, McDougle CJ, Aman MG, Johnson C, Handen B, Bearss K, Dziura J, Butter E, Swiezy NG, Arnold LE, Stigler KA, Sukhodolsky DD, Lecavalier L, Pozdol SL, Nikolov R, Hollway JA, Korzekwa P, Gavaletz A, Kohn AE, Koenig K, Grinnon S, Mulick JA, Yu S, Vitiello B; Research Units on Pediatric Psychopharmacology Autism Network. Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. *J Am Acad Child Adolesc Psychiatry* 2012; **51**: 136-146 [PMID: 22265360 DOI: 10.1016/j.jaac.2011.11.010]

54   **Hellings JA**, Zarcone JR, Reese RM, Valdovinos MG, Marquis JG, Fleming KK, Schroeder SR. A crossover study of risperidone in children, adolescents and adults with mental retardation. *J Autism Dev Disord* 2006; **36**: 401-411 [PMID: 16596465 DOI: 10.1007/s10803-006-0078-1]

55   **Hellings JA**, Zarcone JR, Crandall K, Wallace D, Schroeder SR. Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. *J Child Adolesc Psychopharmacol* 2001; **11**: 229-238 [PMID: 11642473 DOI: 10.1089/10445460152595559]

56   **Hellings JA**, Zarcone JR, Valdovinos MG, Reese RM, Gaughan E, Schroeder SR. Risperidone-induced prolactin elevation in a prospective study of children, adolescents, and adults with mental retardation and pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 2005; **15**: 885-892 [PMID: 16379508 DOI: 10.1089/cap.2005.15.885]

57   **Marcus RN**, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, Aman MG. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry* 2009; **48**: 1110-1119 [PMID: 19797985 DOI: 10.1097/CHI.0b013e3181b76658]

58   **Shores LE**. Normalization of risperidone-induced hyperprolactinemia with the addition of aripiprazole. *Psychiatry (Edgmont)* 2005; **2**: 42-45 [PMID: 21179629]

59   **Malone RP**, Cater J, Sheikh RM, Choudhury MS, Delaney MA. Olanzapine *vs* haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 887-894 [PMID: 11501687 DOI: 10.1097/00004583-200108000-00009]

60   **Malone RP**, Delaney MA, Hyman SB, Cater JR. Ziprasidone in adolescents with autism: an open-label pilot study. *J Child Adolesc Psychopharmacol* 2007; **17**: 779-790 [PMID: 18315450 DOI: 10.1089/cap.2006.0126]

61   **Anagnostou E**, Aman MG, Handen BL, Sanders KB, Shui A, Hollway JA, Brian J, Arnold LE, Capano L, Hellings JA, Butter E, Mankad D, Tumuluru R, Kettel J, Newsom CR, Hadjiyannakis S, Peleg N, Odrobina D, McAuliffe-Bellin S, Zakroysky P, Marler S, Wagner A, Wong T, Macklin EA, Veenstra-VanderWeele J. Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 2016; **73**: 928-937 [PMID: 27556593 DOI: 10.1001/jamapsychiatry.2016.1232]

62   **Stahl SM**.   Essential psychopharmacology of antipsychotics and mood stabilizers. Cambridge, UK: Cambridge University Press, 2002

63   **Reinblatt SP**, Abanilla PK, Jummani R, Coffey B. Loxapine treatment in an autistic child with aggressive behavior: therapeutic challenges. *J Child Adolesc Psychopharmacol* 2006; **16**: 639-643 [PMID: 17069553 DOI: 10.1089/cap.2006.16.639]

64   **Li Z**, Ichikawa J, Meltzer HY. A comparison of the effects of loxapine with ziprasidone and thioridazine on the release of dopamine and acetylcholine in the prefrontal cortex and nucleus accumbens. *Psychopharmacology (Berl)* 2003; **167**: 315-323 [PMID: 12664192 DOI: 10.1007/s00213-003-1418-x]

65   **Kapur S**, Zipursky R, Remington G, Jones C, McKay G, Houle S. PET evidence that loxapine is an equipotent blocker of 5-HT2 and D2 receptors: implications for the therapeutics of schizophrenia. *Am J Psychiatry* 1997; **154**: 1525-1529 [PMID: 9356559 DOI: 10.1176/ajp.154.11.1525]

66   **Singh SC**, Singh S, Hellings JA.   Antipsychotics, Dysphagia, Aspiration Pneumonia, Bowel Obstruction and Related Surgeries in Adults with Severe Developmental Disabilities. Proceedings of the American Psychiatric Association Virtual Annual Meeting, 2021: 5-47. Available from: https://www.psychiatry.org/psychiatrists/meetings

67   **Herzig SJ**, LaSalvia MT, Naidus E, Rothberg MB, Zhou W, Gurwitz JH, Marcantonio ER. Antipsychotics and the Risk of Aspiration Pneumonia in Individuals Hospitalized for Nonpsychiatric Conditions: A Cohort Study. *J Am Geriatr Soc* 2017; **65**: 2580-2586 [PMID: 29095482 DOI: 10.1111/jgs.15066]

68   **King BH**, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, Donnelly CL, Anagnostou E, Dukes K, Sullivan L, Hirtz D, Wagner A, Ritz L; STAART Psychopharmacology Network. Lack of efficacy of citalopram in children with

autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry* 2009; **66**: 583-590 [PMID: 19487623 DOI: 10.1001/archgenpsychiatry.2009.30]

69   **Herscu P**, Handen BL, Arnold LE, Snape MF, Bregman JD, Ginsberg L, Hendren R, Kolevzon A, Melmed R, Mintz M, Minshew N, Sikich L, Attalla A, King B, Owley T, Childress A, Chugani H, Frazier J, Cartwright C, Murphy T; Autism Speaks Autism Clinical Trials Network. The SOFIA Study: Negative Multi-center Study of Low Dose Fluoxetine on Repetitive Behaviors in Children and Adolescents with Autistic Disorder. *J Autism Dev Disord* 2020; **50**: 3233-3244 [PMID: 31267292 DOI: 10.1007/s10803-019-04120-y]

70   **Reddihough DS**, Marraffa C, Mouti A, O'Sullivan M, Lee KJ, Orsini F, Hazell P, Granich J, Whitehouse AJO, Wray J, Dossetor D, Santosh P, Silove N, Kohn M. Effect of Fluoxetine on Obsessive-Compulsive Behaviors in Children and Adolescents With Autism Spectrum Disorders: A Randomized Clinical Trial. *JAMA* 2019; **322**: 1561-1569 [PMID: 31638682 DOI: 10.1001/jama.2019.14685]

71   **Hollander E**, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, Iyengar R. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology* 2005; **30**: 582-589 [PMID: 15602505 DOI: 10.1038/sj.npp.1300627]

72   **Cook EH Jr**, Rowlett R, Jaselskis C, Leventhal BL. Fluoxetine treatment of children and adults with autistic disorder and mental retardation. *J Am Acad Child Adolesc Psychiatry* 1992; **31**: 739-745 [PMID: 1644739 DOI: 10.1097/00004583-199207000-00024]

73   **Williams K**, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev* 2013; CD004677 [PMID: 23959778 DOI: 10.1002/14651858.CD004677.pub3]

74   **Burbidge C**, Oliver C, Moss J, Arron K, Berg K, Furniss F, Hill L, Trusler K, Woodcock K. The association between repetitive behaviours, impulsivity and hyperactivity in people with intellectual disability. *J Intellect Disabil Res* 2010; **54**: 1078-1092 [PMID: 20977516 DOI: 10.1111/j.1365-2788.2010.01338.x]

75   **Gordon CT**, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry* 1993; **50**: 441-447 [PMID: 8498878 DOI: 10.1001/archpsyc.1993.01820180039004]

76   **Sugie Y**, Sugie H, Fukuda T, Ito M, Sasada Y, Nakabayashi M, Fukashiro K, Ohzeki T. Clinical efficacy of fluvoxamine and functional polymorphism in a serotonin transporter gene on childhood autism. *J Autism Dev Disord* 2005; **35**: 377-385 [PMID: 16119478 DOI: 10.1007/s10803-005-3305-2]

77   **McDougle CJ**, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry* 1996; **53**: 1001-1008 [PMID: 8911223 DOI: 10.1001/archpsyc.1996.01830110037005]

78   **King BH**, Davanzo P. Buspirone treatment of aggression and self-injury in autistic and non-autistic persons with severe mental retardation. *Dev Brain Dysfunc* 1996; **90**: 22-31

79   **Hellings JA**, Weckbaugh M, Nickel EJ, Cain SE, Zarcone JR, Reese RM, Hall S, Ermer DJ, Tsai LY, Schroeder SR, Cook EH. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 2005; **15**: 682-692 [PMID: 16190799 DOI: 10.1089/cap.2005.15.682]

80   **Hollander E**, Soorya L, Wasserman S, Esposito K, Chaplin W, Anagnostou E. Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. *Int J Neuropsychopharmacol* 2006; **9**: 209-213 [PMID: 16316486 DOI: 10.1017/S1461145705005791]

81   **Anagnostou E**, Esposito K, Soorya L, Chaplin W, Wasserman S, Hollander E. Divalproex *vs* placebo for the prevention of irritability associated with fluoxetine treatment in autism spectrum disorder. *J Clin Psychopharmacol* 2006; **26**: 444-446 [PMID: 16855475 DOI: 10.1097/01.jcp.0000227703.72117.bc]

82   **Hellings JA**. Psychopharmacology of mood disorders in persons with mental retardation and autism. *MRDD Res Rev* 1999; **5**: 270-278 [DOI: 10.1002/(SICI)1098-2779(1999)5:4<270::AID-MRDD4>3.0.CO;2-I]

83   **Bobo WV**. The Diagnosis and Management of Bipolar I and II Disorders: Clinical Practice Update. *Mayo Clin Proc* 2017; **92**: 1532-1551 [PMID: 28888714 DOI: 10.1016/j.mayocp.2017.06.022]

84   **Macfarlane A**, Greenhalgh T. Sodium valproate in pregnancy: what are the risks and should we use a shared decision-making approach? *BMC Pregnancy Childbirth* 2018; **18**: 200 [PMID: 29859057 DOI: 10.1186/s12884-018-1842-x]

85   **Ng F**, Hallam K, Lucas N, Berk M. The role of lamotrigine in the management of bipolar disorder. *Neuropsychiatr Dis Treat* 2007; **3**: 463-474 [PMID: 19300575]

86   **Hellings JA**. Much improved outcome with gabapentin-divalproex combination in adults with bipolar disorders and developmental disabilities. *J Clin Psychopharmacol* 2006; **26**: 344-346 [PMID: 16702908 DOI: 10.1097/01.jcp.0000219924.04058.99]

87   **Chen B**, Choi H, Hirsch LJ, Katz A, Legge A, Buchsbaum R, Detyniecki K. Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* 2017; **76**: 24-31 [PMID: 28931473 DOI: 10.1016/j.yebeh.2017.08.039]

88   **Aman MG**, Bukstein OG, Gadow KD, Arnold LE, Molina BS, McNamara NK, Rundberg-Rivera EV, Li X, Kipp H, Schneider J, Butter EM, Baker J, Sprafkin J, Rice RR Jr, Bangalore SS, Farmer CA, Austin AB, Buchan-Page KA, Brown NV, Hurt EA, Grondhuis SN, Findling RL. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 47-60.e1 [PMID: 24342385 DOI: 10.1016/j.jaac.2013.09.022]

Operational definitions and measurement of externalizing behavior problems: An integrative review including research models and clinical diagnostic systems

Lidia Torres-Rosado, Oscar M Lozano, Manuel Sanchez-Garcia, Fermín Fernández-Calderón, Carmen Diaz-Batanero

Lidia Torres-Rosado, Oscar M Lozano, Manuel Sanchez-Garcia, Fermín Fernández-Calderón, Carmen Diaz-Batanero, Department of Clinical and Experimental Psychology, University of Huelva, Huelva 21071, Spain

Oscar M Lozano, Manuel Sanchez-Garcia, Fermín Fernández-Calderón, Carmen Diaz-Batanero, Research Center for Natural Resources, Health and Environment, University of Huelva, Huelva 21071, Spain

Corresponding author: Carmen Diaz-Batanero, PhD, Associate Professor, Department of Clinical and Experimental Psychology, University of Huelva, Campus El Carmen, Avda Fuerzas Armadas s/n, Huelva 21071, Spain. carmen.diaz@dpsi.uhu.es

Abstract

Measurement of externalizing disorders such as antisocial disorders, attention-deficit/hyperactivity disorder or borderline disorder have relevant implications for the daily lives of people with these disorders. While the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) have provided the diagnostic framework for decades, recent dimensional frameworks question the categorical approach of psychopathology, inherent in traditional nosotaxies. Tests and instruments develop under the DSM or ICD framework preferentially adopt this categorical approach, providing diagnostic labels. In contrast, dimensional measurement instruments provide an individualized profile for the domains that comprise the externalizing spectrum, but are less widely used in practice. Current paper aims to review the operational definitions of externalizing disorders defined under these different frameworks, revise the different measurement alternatives existing, and provide an integrative operational definition. First, an analysis of the operational definition of externalizing disorders among the DSM/ICD diagnostic systems and the recent Hierarchical Taxonomy of Psychopathology (HiTOP) model is carried out. Then, in order to analyze the coverage of operational definitions found, a description of measurement instruments among each conceptualization is provided. Three phases in the development of the ICD and DSM diagnosis systems can be observed with direct implications for measurement. ICD and DSM versions have progressively introduced systematicity, providing more detailed descriptions of diagnostic criteria and categories that ease the measurement instrument

development. However, it is questioned whether the DSM/ICD systems adequately modelize externalizing disorders, and therefore their measurement. More recent theoretical approaches, such as the HiTOP model seek to overcome some of the criticism raised towards the classification systems. Nevertheless, several issues concerning this model raise mesasurement challenges. A revision of the instruments underneath each approach shows incomplete coverage of externalizing disorders among the existing instruments. Efforts to bring nosotaxies together with other theoretical models of psychopathology and personality are still needed. The integrative operational definition of externalizing disorders provided may help to gather clinical practice and research.

Core Tip: Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases have evolved as a clinical tool but with several limitations associated to the operational definition for measuring externalizing disorders. Approaches such a Hierarchical Taxonomy of Psychopathology improve the conceptualization giving a general framework for psychopathology, although providing a more complex solution for clinicians. Present review shows a lack of measurement instruments integrating new theoretical advances and clinical utility.

INTRODUCTION

The measurement of mental disorders, like any other construct, is a complex process. In addition, unlike other psychological constructs, the measurement of mental disorders can have important implications for the daily lives of people with these disorders and their relatives. Mental disorders in the externalizing spectrum [*e.g.,* antisocial disorders, attention-deficit/hyperactivity disorder (ADHD), borderline disorder] are characterized by problematic behaviors that involve the self and especially interpersonal functioning[1,2]. Thus, these disorders can impact the educational development of young people[3,4] work activity[5], and even cause problems with serious legal consequences[6,7]. Thus, the correct diagnosis of these disorders will not only allow for adequate therapeutic planning but may also affect the living conditions of those affected. In this regard, and as established by the Standards for Educational and Psychological Measurement[8], the development of appropriate measurement instruments for these disorders requires a careful process of design, application, and interpretation of their scores.

Various tests have been developed for measuring externalizing disorders and associated problem behaviors based on various operational definitions. In this respect, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) have been the main theoretical bases for the development of a wide variety of these measurement instruments[9,10]. However, these nosotaxies have been updated in successive editions of these manuals, leading to changes in the diagnostic criteria used to operationalize externalizing disorders. In addition, another set of tests widely used as diagnostic tools was developed outside these classifications[11,12]. One example is the Wender-Utah Scale (WURS), which uses the operational definition of ADHD based on the Wender-Utah criteria[13,14].

In parallel to the above, new theoretical approaches have emerged in recent years that address the conceptualization and classification of these disorders from a dimensional approach. Some of these models focus on personality disorders (PDs), including externalizing disorders, such as the Alternative Model of PDs (AMPD)[15] and the ICD-11 personality model[16]. Other models include PDs and other psychopathological disorders within the externalizing spectrum. These include the Hierarchical Taxonomy of Psychopathology (HiTOP) model[17] or the conceptualization of externalizing behaviors proposed in the Minnesota Multiphasic Personality Inventory (MMPI)[18]. The variety of theoretical approaches to externalizing disorders implies a multitude of operational definitions for these disorders.

Therefore, the tests used to measure them use different content. That is, each operational definition generates a test that is conceptually different from the rest, and it is necessary to reflect on the extent to which tests with different operational definitions are measuring the same mental disorders, thus allowing for a comparison of their results and applicability.

In the field of measurement, it is necessary to differentiate tests that measure externalizing disorders to obtain a diagnostic label from those aimed at obtaining a dimensional psychopathological profile. The former is most commonly theoretically based on the DSM or ICD and preferentially adopts a categorical approach. That is, they use scoring systems that allow differentiation between the presence or absence of a disorder [*e.g.*, Structured Clinical Interview for DSM (SCID)[19-21], Composite International Diagnostic Interview (CIDI)[22]] or in three or four categories according to the severity of the disorder [23,24]. Due to the parsimony and utility of categorical measures, these have been the most widely used in both research and clinical settings, being considered particularly suitable for decision-making in a multitude of contexts (*e.g.*, social, judicial, and clinical). In addition, for such instruments, it is desirable to estimate their reliability through test-retest procedures and to provide evidence of validity based on expert judgment, as well as on the sensitivity and specificity of the scores.

In contrast, dimensional measurement instruments provide an individualized profile for the domains that comprise the externalizing spectrum. Examples of these tests are the Adult Self Report (ASR)[25]; the MMPI-2[18] and the Personality Assessment Inventory (PAI)[26,27]. These profiles are determined by applying a set of items that assess facets, traits, or behaviors on dimensional scales and whose combination of scores provides the possible presence of one or other disorders. This scoring system has become more relevant in recent years due to the possibility of carrying out transdiagnostic interventions [28]. However, these dimensional instruments are less widely used in practice. This is due, on the one hand, to the difficulties in generating a diagnostic label from these instruments, while on the other hand, fewer instruments are available within these approaches, with the majority only used for assessing personality traits.

Given the issues associated with the operational definition and scoring systems of the tests, a review of the specialized literature advocates the benefit of using dimensional models, as they more adequately capture the nature of the disorders[29-31]. However, it should not be forgotten that, to date, clinical practice is strongly associated with using categorical diagnoses. In this sense, some authors propose the need to adopt a hybrid conception, according to which it is possible to use tests with dimensional scores but indicating cutoffs that allow for identifying the presence or absence of a disorder[32-34]. While this approach can be practical and useful, when applying such instruments we should not overlook the impact on measuring the disorder in terms of content validity. With this in mind, this paper aims to review the theoretical frameworks underpinning the operational definitions used in the design of tests that assess externalizing disorders along with the most frequently used tests and their various implications. Finally, a proposed operational definition for a test is presented that integrates different theoretical perspectives, with the aim of achieving conceptual equivalence.

OPERATIONAL DEFINITIONS FOR MEASURING EXTERNALIZING BEHAVIORS

The specialized literature review reveals the existence of multiple and diverse theoretical frameworks that have helped to develop tests to measure externalizing disorders or problem behaviors. The analysis of operational definitions allows us to differentiate between those that use the criteria specified in the DSM and ICD diagnostic classification systems and another set of tests that use operational definitions based on other psychopathological models. In addition, the analysis of these definitions allows a better contextualization of the utility and relevance of each measurement instrument. The main theoretical frameworks used, and their operational definitions are discussed below.

Operational definitions based on the DSM/ICD classification systems

The DSM/ICD classification systems have generated versions with varying degrees of modification in their diagnostic criteria. From the first versions of these nosotaxies in the 1950s to the current DSM-5 and ICD-11, it is possible to identify three main stages concerning the definition of mental disorders, which have affected the operational definitions of the tests developed: (1) A first stage in which disorders were conceptualized through brief clinical or phenomenological descriptions (DSM-I and DSM-II, and ICD-6 to ICD-9); (2) A second stage that involved a paradigm shift, such that disorders are operationalized through the presence of a given number of diagnostic criteria (DSM-III to DSM-IV-TR, and ICD-10); and (3) Finally, a third stage characterized by the incorporation of diagnostic criteria and traits to be assessed in dimensional terms, particularly in PDs.

In the first stage, an analysis of the first versions of the ICD-6[10] and DSM-I[9] nosotaxies has revealed that the categories included in these diagnostic systems did not include operational definitions *per se.* ICD-6 aimed to serve as a statistical classification system rather than a diagnostic system, incorporating only the different categories and associated numerical codes, while the DSM-I provided brief clinical descriptions characterizing each disorder. The assessment and measurement of the disorders were based on the judgment of the clinician or researcher who relied on the descriptions

provided by DSM-I. Concerning the disorders, ICD-6 included 26 diagnostic categories, grouped into three major groups: Psychosis, psychoneurotic disorders, and disorders of character, behavior, and intelligence. These categories were maintained in the ICD-7 version[35], except for corrected errors. The descriptions provided in the DSM-I were based on psychodynamic etiologies resulting from the prevailing American trend at that time. In this sense, the DSM-I defined disorders as "reactions", emphasizing that the subject's maladaptation to environmental stressors could be the cause of the mental disorder.

The ICD-8[36] and DSM-II[37] versions introduced changes to increase their systematicity. Specifically, ICD-8 provided a glossary of descriptions of the diagnostic categories, and, as in DSM-II and ICD-9[38], the descriptions are incorporated directly into the diagnostic categories. Including these descriptions favored the development of instruments for measuring disorders, providing the first operational definitions. In addition, it should be noted that among the two nosotaxies, some categories were unified, which led to a convergence in the measurement of disorders using both classification systems.

In summary, this first stage comprises the versions ICD-6 (1948), DSM-I (1952), ICD-7 (1955), ICD-8 (1967), DSM-II (1968), ICD-9 (1975), characterized by the absence of a definition based on operational criteria. However, each new version shows a tendency toward greater categorization and specificity. This was evidenced by an increased specificity of the recognized mental disorders collected in multiple subdivisions of the disorder categories (*e.g.*, eight new alcoholic brain syndromes were defined). Moreover, the definition of mental illness was broadened to include not only the more severe extremes of psychopathology but also milder symptoms that might be observed in the general population and not exclusively in the clinical population.

The fact that measurement was left completely open to interpretation by the clinician limited the use of early versions of the nosotaxies for systematically measuring mental disorders. Criticism soon emerged against the absence of criteria, the use of diagnostic labels without an identity of concepts, and poor reliability of clinical judgment due to interpretative ambiguity arising from the narrow definitions [39-41]. It is not surprising, therefore, that measurement instruments for mental disorders in this early stage were scarce in the literature. A bibliographic search in the Pubmed and PsycInfo databases with the keyword "assessment", confined to the years corresponding to these editions of the classification systems (between 1948, year of publication of ICD-6, and 1980, year of publication of DSM-III), reveals, firstly, the non-existence of diagnostic instruments based on the first versions of the DSM and the ICD. The existing instruments at this stage (*e.g.*, Assessment of Personality[42]) offer measures framed within psychopathological models far removed from these nosotaxies. In the words of Mayes and Horwitz[43], large-scale clinical research based on these versions of diagnostic systems was impossible since the lack of reliable diagnostic categories in the manuals prevented replication by researchers.

The beginning of the second stage of establishing definitions of disorders from nosotaxies was marked by the publication of DSM-III[19]. This version constituted a shift in the psychiatric paradigm of classification systems[44] and thus in the definition of disorders. Advances in psychometrics were applied to psychiatric assessment, leading to a tendency towards quantifying disorders through tests, rating scales, and checklists, which became a standard in mental health research and practice. In turn, the declining use of psychodynamic paradigms led to the abandonment of psychodynamic terms and etiologies, which were difficult to measure psychometrically[45-47].

To a large extent, the operational definitions proposed in this second stage aimed to achieve reliable and valid diagnoses from a metric perspective. To this end, expert consensus was used to define the diagnostic criteria[48], which were used to operationally define the tests. However, it should be noted that the delimitation of diagnostic criteria followed a descriptive approach as opposed to biological or psychological models. Therefore, this conceptualization has been described as atheoretical, its aim being to describe signs or symptoms without proposing explanations or etiological models[45,49]. Furthermore, it is worth noting the polythetic nature of the criteria included in the diagnostic systems of this second stage. That is, the operational definition encompassed criteria in which no particular one was necessary but instead required a combination of various criteria from a defined set. Consequently, the measurement of disorders derived from this scoring system made it possible for two people to obtain the same diagnosis despite being phenotypically different based on their diagnostic criteria.

Another noteworthy aspect from a psychometric perspective is that, at this stage, the diagnostic criteria refer to a level of impairment or dysfunction of individuals. That is, thresholds are implicitly set for deciding whether the presence of a symptom generates significant distress and impairment for individuals and their context[50]. However, an individual assessment of each clinician and researcher was used to determine the level of impairment, and therefore it was open to interpretation and subject to ambiguity depending on who made the diagnosis. In any case, the inclusion of this assessment showed the need to differentiate between normal and pathological[51]. Consequently, on the one hand, measures of functioning began to emerge that sought to operationalize and measure the term dysfunctionality to support a clinical judgment of the level of impairment (*i.e.*, Health-Sickness Rating Scale, Global Assessment Scale). On the other hand, these scales - which initially appeared independently of the classification systems - were subsequently adopted by them. Thus, from DSM-III-R[52] onwards, the Global Assessment of Functioning Scale[53,54] and the Global Activity Evaluation Scale were incorporated as a measure of functioning in axis V of DSM-IV[55]. In the case of the ICD, dysfunc-

tionality was measured through the incorporation of the World Health Organization Short Disability Assessment Schedule[56], included in axis II of the Multiaxial Adult Version of the ICD-10 version[57]. On the other hand, symptoms were identified that caused clinically significant distress to individuals. However, they did not have a syndromic entity *per se,* leading to the emergence of the category "not otherwise specified".

Finally, from a psychometric standpoint, it was also important to organize externalizing disorders into different sections. Thus, impulse control and substance use disorders were included in one group (Axis I), while PDs (narcissistic, histrionic, paranoid, borderline, and antisocial) were included in Axis II [52,58]. This separation of disorders has repercussions for the operational definition of the disorders, considering PDs as a different entity from other psychopathological disorders, thus using different terms to definition one or the other section. Axis I disorders were mainly defined based on symptoms or signs. In contrast, Axis II disorders were defined on the basis of traits, the latter being considered more stable psychopathological attributes. As a result of this approach, tests based on nosotaxies are also distinguished according to whether the items assess symptoms (psychopathology) or traits (personality).

While this conceptualization of externalizing disorders and behaviors has had many positive consequences for their measurement, it also has limitations in psychometric terms. The World Health Organization pointed out that the definitions proposed in the ICD-10 version did not provide sufficient information for a reliable implementation of the diagnoses in the clinical context[59]. Therefore, to improve diagnostic reliability, several guidelines were published providing definitions and instructions for establishing diagnoses (Clinical Descriptions and diagnostic guidelines[59] and Diagnostic Criteria for Research[60]). In addition, diagnostic interviews incorporated as items transcriptions of the diagnostic criteria for nosotaxies, including indications on the inclusion or exclusion of diagnoses.

Finally, it should be noted that despite attempts during this stage to unify criteria between the different nosotaxias emerging from the World Health Organization and American Psychological Association, some authors argue that only a very small proportion of these categories are similar[61]. Consequently, diagnostic tools derived from these classification systems may provide a clinical diagnosis with a similar label, albeit based on different operational definitions.

The third stage in the operational definitions of nosotaxias is found in the recent DSM-5[15] and ICD-11[16] versions. Here, the changes in the conceptualization of the disorders mark the beginning of a paradigm shift in the operational definitions of the disorders. On the one hand, both versions aim to improve the clinical utility of the diagnostic criteria and to ground existing etiological and neurobiological research in the definitions of disorders, thus providing a theoretical framework for their classification. Similarly, one of the main changes was to introduce emerging evidence in favor of dimensional models into the conceptualization of psychopathology. In this sense, changes have been made concerning substance use disorder that affect its operational definition, unifying the concepts of abuse and dependence. In addition, some diagnostic criteria have been eliminated, while new criteria have been incorporated. There has been a shift from a categorical to a dimensional diagnosis, where the addition of diagnostic criteria has repercussions for diagnosing the severity of dependence. Likewise, changes affecting the operational definition of ADHD have also been noted, primarily the need to present fewer symptoms to diagnose ADHD in adults.

However, the main changes observed in both nosotaxias are associated with PDs. Although the DSM-5 proposes a diagnostic approach that maintains the DSM-IV criteria to preserve continuity with clinical practice, it also includes in a final section (section III) an AMPD that defines two criteria for the identification of PD. Criterion A establishes the need to assess personality dysfunction, while criterion B assesses 25 facets and traits organized into five more general personality domains, providing the typology of that dysfunction. The assessment of the 25 facets allows delineating a dimensional psychopathological profile, and the identification of elevation in certain facets indicates the presence of a PD. In this section III, we shift from defining ten PDs to six, of which three could be framed within the externalizing dimension (namely, narcissistic, antisocial, and borderline, as well as a trait-specified PD in the manner of PD not otherwise specified). While section III of the DSM-5 specifies which facets would indicate the presence of a PD, it does not unequivocally state the pathology threshold for each of the facets assessed. The combined assessment of criterion A and criterion B establishes the presence of PD and profile typology, respectively.

ICD-11 also eliminates the categorical diagnoses of PD, incorporating a continuous measure based on the assessment of personality domains. Like the DSM-5's AMPD, ICD-11 PD is operationalized according to two measures: A measure of personality functioning (severity of personality dysfunction) and another measure characterized by five general traits or domains. The combination of these two measures establishes the presence of the disorder. From a metric perspective, the measure of personality functioning (criterion A: Level of personality functioning for DSM-5 and severity of personality dysfunction for ICD-11) aims at establishing a threshold to differentiate normality from psychopathology. According to DSM-5, criterion A is operationalized according to two broad dimensions: self (identity and self-direction) and interpersonal functioning (empathy and intimacy). ICD-11, on the other hand, incorporates a functioning criterion focusing on harm to others and occupational roles to establish the diagnosis of PD on a continuum of severity[16]. Including the functioning measure in both models is conceptually significant, implying that the presence of an extreme trait would not necessarily be

pathological if dysfunction is not identified.

Similarities are also found in the operational definition of traits/domains offered by the ICD and DSM dimensional personality models. Both models identify five major domains, of which they share four in common. While the AMPD defines the domains of negative affect, detachment, antagonism, disinhibition, and psychoticism, the ICD-11 defines the domains of negative affectivity, detachment, dissociality, dishinibition, and anankastia. However, there are also differences between the two systems. The AMPD operationalizes its dimensions into 25 facets and traits, the combination of which generates personality profiles defining the disorders. However, the ICD-11 considered that this information added unnecessary complexity to the classification[62], so the definition is operationalized at the level of dimensions but not facets. These differences have implications from a metric point of view. Thus, tests from the AMPD model offer a measure of the domains based on the 25 facets to define the disorders. In contrast, those tests that assess according to the ICD model offer only an interpretable measure of the domains. Consequently, the degree of operationalization for test design is greater when applying the DSM-5 AMPD model than the dimensional diagnostic model arising from the ICD-11.

Concerning these models, it should be noted that despite the distinction between the measurement of the level of functioning and the measurement of the traits/domains, the specialized literature has revealed the controversy generated by this distinction. On the one hand, some authors point to an overlap between these two criteria, assuming that assessing pathological traits and facets is an implicit measure of pathological functioning[63,64]. Indeed, psychometric studies based on factor analyses indicate that measures of criterion A and criterion B cluster into common factors when both measures are included in factor analysis[64,65]. On the other hand, this overlap is explained based on the high correlations between dysfunction and pathological traits. Along these lines, some authors argue that the four lower dimensions of criterion A (identity, self-direction, intimacy, and empathy) were conceptualized as indicators of the general dimension of dysfunction[66] and therefore, only one general measure could be used.

On the other hand, the empirical results show a distinction concerning how each criterion A subdimensions are grouped with certain criterion B domains. Specifically, measures of self-functioning are grouped with the negative affect and detachment domains, while measures of interpersonal functioning load on the same factors as measures from the disinhibition and antagonism[63,67,68] domains. Thus, the overlap could be a manifestation of how PTs are expressed and associated with a continuum of severity and how this severity could have a greater impact on an interpersonal or self domain[66,69].

Operational definition of externalizing behavior proposed by HiTOP

The delineation of diagnoses based on diagnostic systems has raised several criticisms[30,70]. Such criticisms include the possibility that the high comorbidity observed between some disorders could reflect, from a metric point of view, a lack of specificity in the diagnostic criteria. This lack of specificity could impact tests based on these classification systems. In addition, the low diagnostic reliability of various diagnostic categories has been highlighted along with the arbitrary nature of the thresholds established to determine a behavior or pathological trait[71,72]. These criticisms are coupled with neurobiological evidence showing that psychopathology is not distinct from normality[30,73,74].

Consequently, other models and taxonomies are emerging that address psychopathology in a cohesive manner, encompassing externalizing personality and behavioral disorders. Possibly one of the most widely supported theoretical models is the HiTOP[17]. This model has introduced several changes: (1) It proposes a hierarchical structure of psychopathology; (2) It adopts a dimensional definition of symptoms, facets, and disorders; and (3) It integrates personality and psychopathology into a single model. The implications of these changes concerning test design are discussed below.

First, the HiTOP[17] defines a general psychopathology framework through a hierarchical structure. Thus, the model specifies (at the lowest level) a set of symptoms and components (*e.g.,* hostility, inattention). These are grouped into syndromes and disorders at the middle level of the hierarchy (*e.g.,* substance use disorder, antisocial PD) and, in turn, are organized into higher structures or spectra (*e.g.,* externalizing spectrum, internalizing spectrum) - that encompass disorders with a common etiology. Finally, at the top level of the hierarchy, a general psychopathology factor (p-factor) is defined that groups the remaining spectra (internalizing, externalizing, and thought disorder)[17]. This hierarchical structure aims to reflect the possibility that different disorders may have common etiological factors[73, 75-77]. Therefore, the definition of higher levels is intended to provide an explanatory framework for the co-occurrence of disorders by grouping those disorders with higher co-occurrence into a single factor.

This conceptual advantage poses, however, some challenges in relation to the development of instruments within this approach. On the one hand, the grouping of lower-level facets and symptoms into general factors through a bottom-up approach has been developed on the basis of existing structural evidence in the literature, such as that obtained regarding the AMPD. This evidence, however, is inconsistent[78,79] with certain facets being interstitial (located in more than one domain) and others located in the wrong domain (facets with factor loadings in domains not defined in the models). Moreover, these inconsistent findings have also been noted in other parts of the model[80,81] making it difficult to translate them into a unified operational definition. Moreover, it is also important

to note that the hierarchical structure of the HiTOP implicitly assumes that higher-level latent factors (*e.g.*, internalizing) are the cause of covariation between lower-level symptoms (*e.g.*, fatigue, anhedonia), but the model is unable to represent direct relationships between lower-order elements (*e.g.*, fatigue may lead directly to anhedonia)[82]. These relationships, for example, are better captured through newly emerging network models[83,84]. Finally, it is important to determine at which level of the hierarchy operationalization occurs so that assessment of different components of the same level shows equivalent specificity or generality[85].

The second element of HiTOP with implications for the measurement of disorders is related to the conceptualization of disorders as a continuum from normality to pathology and defines a set of dimensions at all levels of the hierarchy. This dimensionality at the lower levels allows us to account for the variability of patients within the same disorder[30,86] and simultaneously aims to solve the problem of arbitrariness in the pathological thresholds. From a measurement perspective, adopting a dimensional approach increases the reliability of the measure and is shown to be a better model for explaining and predicting the chronicity of disorders[82]. However, this element also poses some measurement challenges. On the one hand, such a model is intended to be applied in the clinical setting and thus should facilitate clinicians' decision-making regarding administration of treatments or determining the time of discharge. On the other hand, for these decision-making processes, there is still a need to establish cutoff points to assist clinicians. According to the authors of the model, while diagnosis is oriented toward profiling the severity of a patient's symptoms, these thresholds can be established according to empirical evidence[28]. Although these cutoff points have begun to be defined for some parts of the model[87] many other parts still lack such guidance. Another alternative for interpreting HiTOP-compliant measure scores is to use normative data that transforms a patient's score into standardized scores[28]. However, it should be noted that many studies have been conducted with community samples, thus excluding those scores that fall within the pathological range. When interpreting a patient's score, this could be problematic.

The third relevant aspect of HiTOP for the operational definition of disorders concerns the integration of available structural evidence on psychopathology and personality[28,86,88-90]. Thus, personality and conduct disorders would fall under the same explanatory framework, eliminating the differentiation between personality and psychopathology. However, this aspect could be problematic, considering the time frame used for assessing symptoms and signs[90]. While personality facets (*e.g.,* Callousness) are conceptualized as stable characteristics and traditionally include broad assessment timeframes, behaviors or symptoms are understood as evidence of a person's one-off state (*e.g.,* Substance use, assessed with a shorter timeframe). Grouping personality facets and behaviors in the same model is challenging when assessing different time frames. This is especially relevant as different spectrums of the HiTOP taxonomy would be operationally defined to a greater extent by symptoms, while for others this is traits or a combination of both[85].

Concerning the structure of the externalizing spectrum, the HiTOP model, in its original version[17] proposes a definition according to two separate dimensions: Antagonistic externalizing and disinhibited externalizing. While the former includes aggressive traits and behaviors (especially in interpersonal contexts), disinhibited externalizing groups together traits and behaviors that manifest difficulty in controlling impulses. The operationalization of the externalizing spectrum in these two dimensions is supported by the replication of this structure in several previous models, albeit with different descriptive labels[91-93]. In addition, after the publication of HiTOP, this structure has received support from factor analyses and meta-analyses[89,94]. Furthermore, according to the model, taken together, these two dimensions - externalizing antagonism and disinhibition - contribute toward explaining antisocial and aggressive behavior[90].

The authors proposing HiTOP have worked along two lines concerning measurement. On the one hand, they have provided a list of previously available instruments that offer a HiTOP-compatible measure[17,85]. Within the externalizing spectrum, the Externalizing Spectrum Inventory (ESI)[74] stands out among the recommended instruments, as this instrument provides the most comprehensive - although not complete - measure of the two dimensions of the externalizing spectrum. On the other hand, the Measures Development Workgroup of the HiTOP is currently developing instruments specifically designed according to the model. Unfortunately, no measure is yet available, although Mullins-Sweatt *et al*[90] reviewed the externalizing facets that serve as an operational definition for a proposed externalizing spectrum measurement instrument.

INSTRUMENTS FOR MEASURING DISINHIBITED AND ANTAGONISTIC EXTERNALIZING DISORDERS

It has previously been shown that there are various ways of operationalizing the externalizing constructs associated with the problem behaviors that are central to this study, focusing on nosotaxias and HiTOP as the most valid classification systems. However, a specialized literature review shows that there are still more existing measurement instruments for externalizing problem behaviors. After reviewing these instruments, we would like to point out several aspects. First, many published tests and

scales do not clarify the underlying operational definitions. This inadequacy may be due to the authors' negligence or aspects associated with editorial policies. In either case, failure to specify operational definitions results in a lack of specificity regarding the measured constructs. Another aspect that the authors noted in their review was the inconsistent use between the application of the psychometric techniques and the evidence they intended to provide. For example, there is an indiscriminate use of the factor analysis technique (in its exploratory, confirmatory, or exploratory structural equation modeling variants) to determine the structure of an instrument without conceptually delimiting the underlying theoretical structure. Consequently, we have observed how authors eliminate items with factor loadings below a specific arbitrary threshold[95,96], correlate item errors to improve fit indexes[97-99], or establish cross-loading without reflecting on the impact on the test content validity[99]. Finally, we would like to warn that the availability of a large number of tests, as is currently observed, most likely results in atomization in the measurement of these constructs, which is counterproductive for making progress in acquiring knowledge of these mental disorders. Given this, efforts should focus on targeting fewer instruments that are rigorously developed and versatile in their applications.

The following is a brief description of various interviews and tests available in the specialized literature that allow the measurement of externalizing problem behaviors. The selected instruments listed respond to their impact concerning their use in scientific publications and their clinical interest. Moreover, considering the large amount of psychometric evidence available, the authors have chosen to describe only and exclusively those metric aspects most directly associated with their underlying operational definition.

Instruments with diagnostic targets developed from the DSM and ICD

Diagnostic interviews to assess different disorders: Instruments that make clinical diagnoses are usually based on the DSM and ICD nosotaxias. Therefore, these diagnostic classifications form the basis for the operational definitions of these tests. These instruments provide a categorical scoring system that determines the absence or presence of a disorder. They are usually structured or semi-structured interviews whose items largely reproduce the wording of the diagnostic criteria that appear in the above nosotaxias. These items are often accompanied by clarifications to assist clinicians in the scoring process.

For the most part, changes in the diagnostic criteria of the different versions of the ICD and DSM have been reflected in updated versions of these structured and semi-structured interviews through modifications to their items. Considering the diffusion in their administration, the main structured clinical interviews that measure mental disorders - and therefore include externalizing disorders associated with problem behaviors - are the SCID-5[20,21] the CIDI[22], the Mini International Neuropsychiatric Interview (MINI)[100], Psychiatric Research Interview for substance and mental disorders (PRISM)[101] and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[102]. However, there are differences between these interviews. The SCID, PRISM, and MINI interviews use the DSM diagnostic criteria to diagnose disorders, while CIDI and SCAN allow diagnosis from both nosotaxias. Moreover, there are also differences in the level of structuring of the interviews. This is why the skill level of those administering the interviews is relevant for obtaining reliable and valid diagnoses - the less structured the interview, the greater the need for interviewers to be adequately trained.

The SCID is an interview that highlights the distinction between the assessment of psychopathological disorders and PDs, publishing separate versions for both disorders[19-21]: SCID-I for DSM-IV Axis I disorders and SCID-II for DSM-IV Axis II. The changes introduced in the DSM-5 have been transferred to this diagnostic interview, developing the SCID-5-CV for psychopathological disorders and the SCID-PD for PDs. Concerning the disorders of concern in the present work, the SCID-5-CV is administered to assess substance use disorder and ADHD. The SCID-5-PD is administered to measure histrionic, narcissistic, borderline, and antisocial PD.

The CIDI[22] is an interview developed by the World Health Organization which has subsequently been updated[103,104], giving rise to the different versions of this structured interview. From a metric perspective, the latest version of this interview provides an evaluation according to DSM-IV and ICD-10 criteria. However, its items are not a translation of the diagnostic criteria of the nosotaxias. Among its distinctive features, it should be noted that this interview includes questions on general health followed by those associated with the diagnosis. These questions are designed to provide a screening tool that reduces the administration time of the instrument and limit interviewee fatigue, thus improving the validity of the information obtained. It also includes scales on clinical severity and impairment to determine whether the symptoms experienced by respondents produce clinically relevant distress.

The MINI is a structured interview aimed at screening for the presence of disorders[100]. It primarily focuses on measuring internalizing disorders. Among the externalizing antagonistic and disinhibiting disorders, the MINI plus version includes the assessment of substance use disorder, ADHD, and antisocial PD. The latest version of the MINI adapted to DSM-5 (MINI-7.0.2) does not include the assessment of ADHD. For measuring the disorders, the items of this interview are worded very similarly to the DSM-5 diagnostic criteria and its scoring system also reproduces that indicated in the DSM-5 for each disorder. Due to the lack of in-depth exploration of the possible presence of mental disorders, the MINI is considered primarily a screening interview.

The PRISM is a semi-structured interview designed to improve the reliability and diagnostic validity of psychiatric disorders in patients with substance use disorder[101]. This is because these patients mimic numerous symptoms present in other mental disorders[105]. Therefore, providing an instrument to identify when mental disorders are primary and induced by substance use was considered relevant. From a psychometric perspective, therefore, this interview aims to provide high specificity in diagnosing the disorders assessed. However, due to the detailed exploration involved in this interview, its duration is long. For this reason, computerized versions have been developed to reduce administration time. There is currently a version of the PRISM adapted to the DSM-5[106].

Substance use disorder specific assessment instruments: The assessment of substance use disorders based on the diagnostic systems is mainly achieved through the diagnostic interviews mentioned above. In addition to these, other diagnostic interviews and scales specific to substance use disorder have been shown to be useful for diagnosis.

The Substance Dependence Severity Scale (SDSS)[107,108] is a semi-structured diagnostic interview specifically used for substance use, whose items allow a diagnostic assessment according to DSM-IV and ICD-10 criteria. A Spanish version evaluates substance use disorder according to DSM-5[109,110]. This instrument consists of 16 items that operationalize the 11 diagnostic criteria proposed in the DSM-5. The items of the SDSS can be sectioned into two parts: A screening section and another section that assesses the severity of the substance use disorder. One of the characteristics of this interview is that, although it is guided by diagnostic criteria, it conducts the assessment using a time frame of the previous month, as opposed to the last 12 months used by the classification systems. This time frame is motivated by the search for the sensitivity of the scores to detect changes in patients[107,108]. To be congruent with making the diagnosis according to DSM criteria and to make the scores sensitive to changes in patients, a scoring system has been designed which is compatible with the DSM diagnostic procedure, which, in addition, provides a continuous score.

Problems associated with substance use have also been assessed employing other instruments which, although based on the diagnostic criteria of nosotaxias, do not pursue a diagnostic purpose as such. One such instrument is the Severity Dependence Scale[11]. This brief 5-item self-administered scale provides a severity score for drug dependence and is designed to measure the psychological aspects of dependence experienced by drug users. To this end, its items focus on measuring compulsive drug use, the individual's worry and anxiety about their own drug use, and feelings of impaired control over their drug use. Thus, although its items are based on the diagnostic criteria for nosotaxias, not all diagnostic criteria are operationalized in this instrument. This scale has been studied by adapting it to different drugs, and studies have confirmed its psychometric properties in users of heroin, cocaine, and amphetamine[11] alcohol[111], marijuana[112,113] ketamine[114] and codeine[115]. The Short Alcohol Dependence Data Questionnaire[116] assesses the severity of alcohol use disorder through 15 self-administered items. These items focus on measuring drinking habits and the physical and mental effects of drinking. Another scale that allows an assessment of alcohol consumption is the Severity of Dependence Questionnaire (SADQ)[117]. The current form of the SADQ is a 20-item questionnaire that assesses physical signs of withdrawal, affective signs of withdrawal, craving, quantity, frequency of drinking, and the speed of recovery from withdrawal symptoms. The Alcohol Use Disorders Identification Test[118] is a specific screening test for detecting problematic alcohol use. Its items operationalize some of the diagnostic criteria for nosotaxies, and due to its simplicity, this instrument is widely used in clinical and research settings.

Specific ADHD assessment instruments: Most instruments that assess ADHD are based on the diagnostic criteria for nosotaxies. However, some differences between them are worth noting. The following describes the most commonly used instruments and their main characteristics under a psychometric approach.

The Adult ADHD Self Report Scale (ASRS)[119,120] is a screening scale that operationalizes the diagnostic criteria proposed in the DSM-IV through 18 items. It also offers three types of scores (inattention score, hyperactivity score, and total score) according to the clinical signs of ADHD. It is, therefore, a scale that largely reflects the diagnostic procedure based on nosotaxies. However, its items do not explore the presence of the disorder in depth, and it is thus considered more of a screening than a diagnostic instrument.

The Current Symptoms Scales[121] is an 18-item instrument that can be completed by an observer (CSS-OR) and/or self-administered (CSS-SR). The 18 items describe the DSM-IV diagnostic criteria included in the inattention and hyperactivity/impulsivity domains. In addition, this instrument differs from others in that it includes a scale to assess the intensity with which the symptoms interfere with the individual's functioning in various areas of their life (work, family life, or money management).

The Connors Adult ADHD Rating Scale (CAARS)[122] is available in different versions (large version: 66 items, short version: 26 items, and screening version: 30 items), with two main formats: One self-report and one observational (CAARS-SR and CAARS-OR, respectively). This scale uses items based on - but not exclusively guided by - diagnostic classifications. Thus, it offers more items to explore inattention, hyperactivity, impulsivity, or self-concept. In addition, an index of the probable presence of ADHD can be derived from its scores along with indicators of the inconsistency of responses.

The WURS[13,14] is a scale that retrospectively assesses ADHD symptoms in childhood. This scale has two versions (the original version with 61 items and the short version with 25 items). This scale generates scores for hyperactivity, attention deficit, and impulsivity, along with emotional lability and behavior problems. The contents of this scale are based on the Utah criteria. Thus, while the WURS does not assess the criteria for nosotaxies *per se*, its cutoff scores (36 and 46) have shown to be useful for diagnostic categorization.

Specific instruments for the assessment of personality domains: The shift towards the definition of disorders based on personality traits has led to the emergence of various instruments aligned with this theoretical premise. The present study will characterize psychometrically those instruments that assess the dimensions of the externalizing spectrum underpinning the disorders associated with behavior problems corresponding to the antagonism and disinhibition domains of the DSM-5 and aligned with the dissociality and disinhibition domains, respectively, of the ICD-11[123]. Furthermore, among the existing instruments, the present study will analyze those that are most widely used, such as the Personality Inventory for DSM-5-PID-5-[33] and the Personality Inventory for ICD-11 (PiCD)[124].

The PID-5[33,34] assesses 25 facets/traits proposed in the AMPD, including those for disinhibition and antagonism. The original version of this instrument includes 220 items. Subsequently, other reduced versions of 100 items (PID-5-SBF)[125] and 25 items[126] have been published. This latest version (PID-BF) only provides a score for the domains. This instrument has been adapted to numerous languages[127-133], with considerable psychometric evidence. Thus, the review conducted by Al-Dajani *et al*[134] showed, in terms of reliability, alpha values ranging between 0.72 and 0.96. Regarding test-retest reliability, values above 0.90 have been reported for all dimensions. In terms of validity evidence based on the relationship with other variables, it has been found that the structure of the PID-5 converges with the FFM model[135]. Correlations above 0.60 have been reported in the convergence between disinhibition and antagonism with their respective counterparts in the NEO-PI-R and NEO-PI-3[67,136-138]. Regarding the factor structure, most factor analyses show that the factor for externalizing divided into two sub-factors is congruent with the domains of externalizing and disinhibition. It should be noted that this instrument allows the identification of personality traits and facets, and some authors have subsequently analyzed the congruence of these profiles with the categorical diagnoses of nosotaxies[69,67,129,139].

The PiCD[124] has been developed to measure the dimensional personality model proposed by the ICD. The PiCD assesses the five domains proposed by ICD-11, including the three specific externalizing domains of dissociality, disinhibition, and anankastia traits. This instrument includes 60 items, so the five domains are assessed based on 12 items each. Psychometric studies of the PiCD have shown adequate internal consistency coefficients[124,139-143]. Concerning evidence of convergent validity, PiCD scores have shown significant relationships with their counterparts in other personality models [140-142,144]. In the case of the disinhibition and dissocial dimensions, high correlations have been found with their convergent scales but not with scores measuring anankastia[140]. Regarding the factor structure, some studies replicate the five proposed theoretical factors[62,124,145], while other authors point to an overlap between the disinhibition and anankastia factors[140,144]. Although PiCD proposes a primarily domain-based measure congruent with DSM-5, Bach *et al*[146] developed scoring algorithms for the ICD-11 facets based on the PID-5 dimensions, finding a good fit for the disinhibition, antagonism/dissocial, and anankastia dimensions. These results have subsequently been replicated in other studies[147,148].

Instruments for assessing the antagonism and disinhibition externalizing domains compatible with other psychopathological models

In addition to the instruments mentioned above, other tests and scales allow the assessment of the traits included in the externalizing antagonistic and disinhibition domains that do not adopt the DSM and ICD classifications as a basis for operational definition. The items of these instruments do not tend to reproduce the diagnostic criteria of nosotaxies. Rather, their items are organized for the measurement of traits and facets, usually on a severity scale, which is indicative of the presence of problem behaviors or disorders.

On the other hand, it should be noted that numerous instruments measure each of the antagonistic and disinhibited problem behaviors. However, in the present work, we will incorporate instruments that measure more than one of these problem behaviors or disorders. In this regard, it should be noted that, as Mullins-Sweatt *et al*[90] reported, an instrument is currently being developed to measure problem behaviors and disorders within the externalizing spectrum.

One of the instruments worthy of note is the Achenbach System of Empirically Based Assessment (ASEBA)[149]. This assessment system integrates instruments for measuring various behaviors, competencies, and interpersonal problems. Its objective is concerned with detecting problematic behaviors that can be the object of clinical intervention, although it distances itself from the use of diagnostic categories proposed in the nosotaxies. This assessment system can identify profiles concerning various behaviors, including those framed within the externalizing spectrum. Its scales include the ASR and the Adult Checklist[150,151], which report on adaptive and problematic behaviors, including drug use.

The MMPI was originally developed by Hathaway & McKinley[152,153], and the third version (MMPI-3)[154] has been recently published. In its three updates, this instrument retains the aim of providing assessors with a clinical profile that contributes to the characterization of individuals in a comprehensive manner. Therefore, its different versions include many scales that are organized to provide trait and behavioral scores while providing scores from high-order scales, including specific scores associated with the antagonism and disinhibition domains.

The PAI[26,27] is another instrument that assesses various personality traits and facets, including the disinhibition and antagonism domains. It is an instrument whose aim is not only to provide clinically relevant information for diagnosis but also useful information for planning the treatment of patients. In this sense, the authors selected those syndromes that, at the time of their development, had the greatest relevance in the nosology of psychopathology and usefulness in clinical practice. In turn, the operational definition of these syndromes was based on a review of the specialized literature to identify the most central components. Subsequent versions of the PAI have included new scales that currently measure a wide range of behaviors and traits that allow for establishing detailed profiles of the persons assessed.

Krueger *et al*[74] developed the ESI to test a comprehensive model of externalizing disorders. To this end, the authors reviewed the literature and focused on how certain disorders (*i.e.*, substance use disorders or antisocial behavior disorders) could have common etiological bases and, therefore, should be integrated into the same continuum. Under this premise, the authors developed the ESI to provide scores for personality and behavioral domains based not on phenotypic manifestations but on the underlying common structure of these domains. From here, to develop the items the authors adopted/ modified items from existing measurement scales, and also designed items based on the DSM-IV-TR diagnostic criteria.

INTEGRATION PROPOSAL

For years, several authors have postulated the need for integrative models based on the classic DSM and ICD approaches combined with other empirical models that address the underlying bases of the different disorders[155,44]. This approach is, for example, followed by the AMPD or the ICD for PDs. While recognizing the value and interest of these efforts, it should not be overlooked that moving from a model with categories that determine the presence or absence of a disorder to one in which profiles are developed to identify traits and facets with normal/pathological functioning, implies a considerable leap. Consequently, many clinicians may be unable to determine which clinical and pharmacological interventions are most appropriate for their patients. Likewise, considering the nature of the disorders addressed in this paper, professionals in the judicial and educational fields (among others) must become familiar with these new approaches to make the right decisions. However, the existing empirical evidence[30,31,70] and the promising results obtained in clinical settings with transdiagnostic interventions[156,157] suggest the need to adopt these new models.

As our review has shown, while efforts have been made to bring nosotaxies together with other theoretical models of psychopathology and personality, these have not played a prominent role in practice. However, nowadays, with the major development of models such as HiTOP, we may be moving closer to achieving convergence between these approaches, and to this end, tests and scales may play a central role.

Our research group is currently developing an instrument to measure the variable 'Externalizing disorder in adulthood' with the aim of constructing a test to identify profiles along the Agreeableness-Antagonism and Conscientiousness-Disinhibition continuums. In addition, our objective is to develop items that constitute indicators that can be used to determine the presence (or absence) of externalizing disorders according to DSM-5. Thus, the framework underpinning the operational definition of the test will be the HiTOP model[17,90] and the DSM-5 diagnostic criteria[15] and in the latter case, integrating the proposals of the alternative personality model and the diagnostic criteria of section II.

Our proposal begins with the definition of 'Externalizing disorder in adulthood' as "a set of maladaptive and/or problematic behaviors and personality traits that manifest themselves through outwardly directed behaviors, which cause deterioration in social relationships and interfere with the normal functioning of the person who presents them and their environment". This construct, congruent with that stipulated in the HiTOP, presents a hierarchical structure that integrates two major dimensions: Antagonism and disinhibition, divided into facets and traits. The disorders to be integrated are antisocial, narcissistic, paranoid, borderline, histrionic, ADHD, and oppositional defiant disorder. Substance use disorder, intermittent explosive disorder, and conduct disorder are not included for several reasons: (1) Concerning substance use disorder, there is abundant specialized literature showing that although it falls within the antagonism and disinhibition domains, these always clearly form an independent factor[158,159]. This means that some of the existing scales[107-109] can currently be used for their without disrupting the assessment of these two domains; (2) Explosive-intermittent disorder is not included due to the difficulty in identifying clear diagnostic criteria. Specifically, the DSM-5 only offers a list of behaviors or problems that must be present, although it does not define any criteria to determine their presence/absence; and (3) Conduct disorder is not included due to the lack of

adaptation of the set of diagnostic criteria to the adult population.

The DSM-5 definitions of facets and traits and those proposed by Mullins-Sweatt *et al*[90] have been adopted to delineate the operational definition. However, as indicated, our proposal integrates facets and traits with the criteria specified in section II of the DSM-5. In this sense, the research team members have reviewed the specialized literature to reach the proposal shown in Table 1. This table shows, for example, that the diagnostic criteria for antisocial PD fall within the two dimensions of our model: Five of the seven criteria refer to facets of disinhibition, and two of them to antagonism. For example, criterion 6, "Consistent irresponsibility, manifested by repeated inability to maintain consistent work behavior or meet financial obligations" corresponds to "Irresponsibility". It is therefore proposed that in the final version of the test, within the items measuring this facet, there should be items whose content deals with this diagnostic criterion.

Establishing equivalence between facets/traits and diagnostic criteria provides a conceptually equivalent operational definition. Thus, the test resulting from this definition may be of interest to professionals in various fields. First, quantitative data can be obtained to locate people along different continuums of facets, dimensions, and the externalizing spectrum. From a research standpoint, it will be possible to verify the hierarchical structure of externalizing behavior problems in the adult population and to analyze, through statistical models, their relationships with other variables of interest. Second, regarding clinical application, professionals will be offered equivalence scores that will allow them to determine the presence/absence of a given diagnostic criterion and, taking into account the relevant diagnostic criteria, the existence (or not) of the corresponding PD. The operational definition provided in present manuscript is a preliminary approach that attempts to combine the theoretical advances, result of the most recent empirical research, with the clinical practice, based on the nosotaxies internationally used.

CONCLUSION

Present work highlights the importance of that measurement of externalizing spectrum disorders has for people's living conditions[3-7]. The development of measurement instruments for these disorders requires a careful process of design, application, and interpretation[8]. The bibliographic review undergone show that among the available instruments, there are those framed within categorical diagnostic systems (DSM and ICD); those arising from recent dimensional theoretical approaches (AMPD or HiTOP) and other instruments with operational definitions in specific theoretical frameworks. While categorical approaches provide useful tools to facilitate clinical decision-making, dimensional approaches have extensive empirical support as better capturing the nature of the disorders and allow greater understanding of psychopathological phenomena[28].

On one hand, our review note that the different operational definitions used in these tests under the different frameworks, hinder the comparison of the findings and applicability. Regarding the definitions based on diagnostic classification systems, these have undergone an evolution throughout the different editions with three phases. While the first editions constituted mere statistical classification systems, later versions incorporated descriptions of diagnostic categories[9,10], providing the first operational definitions of psychological disorders in general and externalizing disorders in particular.

The development of measuring instruments for these disorders did not, therefore, truly flourish until diagnostic criteria were included on these taxonomies[43] on a second phase. The inclusion of these criteria lead to a tendency towards quantifying disorders through tests, rating scales, and checklists. In addition, the criterion of dysfunction to consider the presence of a disorder were incorporated into these taxonomies[50], which led to the development of new measures for the assessment of impairment[53-57]. However, while systematization in assessment increased, many of the instruments developed from this perspective have been criticized for lacking an etiological theoretical framework[45,49]. Also, the differentiation between Axis I (substance use and impulse control disorders) and Axis II (PDs) on these classification systems[52,58], caused that tests based on nosotaxies either assess symptoms (psychopathology) or traits (personality).

The assessment of disorders based on these categorical classifications in this second phase, has been criticized in a number of ways[30,70]. Criticisms included the observation of high rates of comorbidity - due to the lack of specificity of diagnostic criteria - and the arbitrary nature of the thresholds between normal and pathological behavior[71,72]. On the third phase of evolution of diagnostic classifications, latest versions of DSM and ICD had begun a shift towards a dimensional operationalization of mental disorders. The AMPD model included in DSM-5 Section III[15] and the ICD-11[16] constitute two first proposals for a dimensional classification of PDs. Again, it can be noted that the measurement of functioning play a relevant role on these proposals for defining the threshold that differentiate normality from pathology. However, empirical evidence show mixed results regarding the overlap when measuring functioning and pathological traits[64-69].

In addition to the operational definition of externalizing disorders provided in the different taxonomies, our review analyzed another recent dimensional model: The HiTOP model[17]. This recent dimensional model had provided an extended classification system that address all types of psycho-

Table 1 Relationship between diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders-5) and externalizing facets-dimensions

Externalizing disorders in adulthood			Internalizing
DSM-5 disorders (diagnostic criteria)	Disinhibition	Antagonism	
Antisocial [Personality disorder, diagnostic criteria section II (3/7)]	Non-compliance with standards (criterion 1)	Deception/fraud (criterion 2)	
	Impulsivity (criterion 3)	(Lack of) empathy (criterion 7)	
	Aggression (physical) (criterion 4)		
	Risk-taking (criterion 5)		
	Irresponsibility (criterion 6)		
Narcissistic personality disorder [Diagnostic criteria (5/9)]		Grandiosity (criteria 1, 2, 3, 5, 8, and 9)	
		Attention seeking (criterion 4)	
		Exploitation (criterion 6)	
		(Lack of) empathy (criterion 7)	
Paranoid personality disorder [Diagnostic criteria (4/7)]		Mistrust (criteria 1-4, and 7)	
		Hostility (criteria 5 and 6)	
Borderline personality disorder [Diagnostic criteria (5/9)]			Separation anxiety (criterion 1)
			Affective lability (criteria 2 and 6)
			Altered self-perception (criterion 3)
	Risk-taking (criterion 4)		
			Suicide (criterion 5)
			Depression (criterion 7)
		Hostility (criterion 8)	
			Dissociation (criterion 9)
Histrionic personality disorder [Diagnostic criteria (5/8)]		Attention seeking (criteria 1, 2, 4, and 6)	
			Affective lability (criterion 3)
			Superficiality (criterion 5)
			Suggestibility (criterion 7)
			Altered social perception (criterion 8)
ADHD [Inattention (5/9)]	Inattention (criteria a-i)		
Hyperactivity and impulsivity (5/9)	Hyperactivity (criteria a-f)		
	Impulsivity (criteria g-i)		
Oppositional defiant disorder [Diagnostic criteria (4/8)]		Hostility (criteria 1-3 and 8)	
		Rebellion (criteria 4-7)	

DSM: Diagnostic and Statistical Manual of Mental Disorders.

pathology. Regarding externalizing disorders, it provides a coherent theoretical background for explaining comorbidity through the definition of general factors - Antagonistic externalizing and Disinhibited externalizing, grouped in the Externalizing spectrum - that group co-occurring symptoms. This hierarchical structure however, is not clearly supported by empirical evidence[78-81], appear to ignore the direct relations between the lower level elements[82-84], and provide challenges on the operational definition under the different levels of the model. The dimensional conceptualization increases the reliability of the measure, although requires to establish empirical based cutoff points to

assist clinicians[82]. Finally, considering HiTOP model gather personality and conduct disorders, measuring sign and traits under the same instrument can pose differences on the time frame of assessment.

On the other hand, the review of existing instruments for measuring externalizing disorders have shown a large amount of test, resulting in an atomization in the measurement. This implies that researchers and practicioners should carefully revise the operational definition and target of each instrument to ensure a good choice of measurement instrument for a specific purpose, although our review show that this information may be of difficult access or not clear. Among the structured interviews developed under the classification systems, it is worth mentioning the SCID-5[20,21], the MINI[95], and the PRISM[96] under the DSM framework and the CIDI[22], and the SCAN[97] allowing diagnosis under both DSM and CIE taxonomies. Less structured interviews such as the PRISM or the CIDI, require interviewers to be adequately trained. Regarding instrument for assessing specific disorders, our review suggests the ASRS[119,120], the Current Symptoms Scales[121], the CAARS[122] within the DSM criteria and the WURS[13,14] based on the Utah criteria are the most frequent measurement instruments. On personality, due to the emergence of dimensional personality models, it can be found measurement instruments within dimensional frameworks such as the PID-5[33,34], the NEO-PI-R, NEO-P-3[67,136-138] and PiCD[124]. Other dimensional instruments targeted to measure antagonism and disinhibition include the ASEBA[149], MMPI[152-154], the PAI[26,27] and the ESI[74].

Present review show that the different instruments identified are either designed under a diagnostic taxonomy framework which allow a categorization of the respondents or under theoretical framework derived from research that delineate dimensional profiles. As our review suggests, efforts to bring nosotaxies together with other theoretical models have not played a prominent role in practice. We provide a preliminary operational definition that attempts to combine both approaches.

FOOTNOTES

ORCID number: Lidia Torres-Rosado 0000-0002-5969-994X; Oscar M Lozano 0000-0003-2722-6563; Manuel Sanchez-Garcia 0000-0003-3375-8347; Fermín Fernández-Calderón 0000-0002-2981-1670; Carmen Diaz-Batanero 0000-0003-3392-4683.

REFERENCES

1 **Lynam DR**, Leukefeld C, Clayton RR. The contribution of personality to the overlap between antisocial behavior and substance use/misuse. *Aggress Behav* 2003; **29**: 316-331 [DOI: 10.1002/ab.10073]

2 **Krueger RF**, Markon KE, Patrick CJ, Iacono WG. Externalizing psychopathology in adulthood: a dimensional-spectrum conceptualization and its implications for DSM-V. *J Abnorm Psychol* 2005; **114**: 537-550 [PMID: 16351376 DOI: 10.1037/0021-843X.114.4.537]

3 **Daley D**, Birchwood J. ADHD and academic performance: why does ADHD impact on academic performance and what can be done to support ADHD children in the classroom? *Child Care Health Dev* 2010; **36**: 455-464 [PMID: 20074251 DOI: 10.1111/j.1365-2214.2009.01046.x]

4 **Hinshaw SP**. Externalizing behavior problems and academic underachievement in childhood and adolescence: causal

relationships and underlying mechanisms. *Psychol Bull* 1992; **111**: 127-155 [PMID: 1539086 DOI: 10.1037/0033-2909.111.1.127]

5   **Fawns T**. Attention Deficit and Hyperactivity Disorder. *Prim Care* 2021; **48**: 475-491 [PMID: 34311852 DOI: 10.1016/j.pop.2021.05.004]

6   **Ybrandt H**. Risky alcohol use, peer and family relationships and legal involvement in adolescents with antisocial problems. *J Drug Educ* 2010; **40**: 245-264 [PMID: 21313985 DOI: 10.2190/DE.40.3.c]

7   **Border R**, Corley RP, Brown SA, Hewitt JK, Hopfer CJ, Stallings MC, Wall TL, Young SE, Rhee SH. Predictors of adult outcomes in clinically- and legally-ascertained youth with externalizing problems. *PLoS One* 2018; **13**: e0206442 [PMID: 30383806 DOI: 10.1371/journal.pone.0206442]

8   **American Educational Research Association**. The Standards for Educational and Psychological Testing. [cited 19 November 2022]. Available from: https://www.apa.org/science/programs/testing/standards

9   **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders (DSM-I). Washington: American Psychiatric Association, 1952

10 **World Health Organization**. Manual of the international statistical classification of diseases, injuries, and causes of death: sixth revision of the International lists of diseases and causes of death, adopted 1948. [cited 19 November 2022]. Available from: https://apps.who.int/iris/handle/10665/42893

11 **Gossop M**, Darke S, Griffiths P, Hando J, Powis B, Hall W, Strang J. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction* 1995; **90**: 607-614 [PMID: 7795497 DOI: 10.1046/j.1360-0443.1995.9056072.x]

12 **Raistrick D**, Dunbar G, Davidson R. Development of a questionnaire to measure alcohol dependence. *Br J Addict* 1983; **78**: 89-95 [PMID: 6573181 DOI: 10.1111/j.1360-0443.1983.tb02484.x]

13 **Ward MF**, Wender PH, Reimherr FW. The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. *Am J Psychiatry* 1993; **150**: 885-890 [PMID: 8494063 DOI: 10.1176/ajp.150.6.885]

14 **Wender PH**. Attention-deficit hyperactivity disorder in adults. New York: Oxford University Press, 1995

15 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Washington: American Psychiatric Association, 2013

16 ICD-11 for Mortality and Morbidity Statistics. [cited 19 November 2022]. Available from: https://icd.who.int/browse11/l-m/en

17 **Kotov R**, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, Brown TA, Carpenter WT, Caspi A, Clark LA, Eaton NR, Forbes MK, Forbush KT, Goldberg D, Hasin D, Hyman SE, Ivanova MY, Lynam DR, Markon K, Miller JD, Moffitt TE, Morey LC, Mullins-Sweatt SN, Ormel J, Patrick CJ, Regier DA, Rescorla L, Ruggero CJ, Samuel DB, Sellbom M, Simms LJ, Skodol AE, Slade T, South SC, Tackett JL, Waldman ID, Waszczuk MA, Widiger TA, Wright AGC, Zimmerman M. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol* 2017; **126**: 454-477 [PMID: 28333488 DOI: 10.1037/abn0000258]

18 **Butcher JN**, Dahlstrom WG, Graham JR, Tellegen A, Kaemmer B. Manual for the restandardized Minnesota Multiphasic Personality Inventory: MMPI-2. Minneapolis: University of Minnesota Press, 1989

19 **Kendell RE**. Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. *Am J Psychiatry* 2006 [DOI: 10.1176/ajp.145.10.1301]

20 **Spitzer RL**, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry* 1992; **49**: 624-629 [PMID: 1637252 DOI: 10.1001/archpsyc.1992.01820080032005]

21 **First M**, Williams J, Karg R, Spitzer R. Structured Clinical Interview for DSM-5 (SCID-5 for DSM-5). Arlington, VA, American Psychiatric Association, 2017

22 **World Health Organization**. The Composite International Diagnostic Interview (CIDI) web site. [cited 19 November 2022]. Available from: https://apps.who.int/iris/handle/10665/267892

23 **Hasin DS**, Fenton MC, Beseler C, Park JY, Wall MM. Analyses related to the development of DSM-5 criteria for substance use related disorders: 2. Proposed DSM-5 criteria for alcohol, cannabis, cocaine and heroin disorders in 663 substance abuse patients. *Drug Alcohol Depend* 2012; **122**: 28-37 [PMID: 21963333 DOI: 10.1016/j.drugalcdep.2011.09.005]

24 **Hasin DS**, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, Compton WM, Crowley T, Ling W, Petry NM, Schuckit M, Grant BF. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 2013; **170**: 834-851 [PMID: 23903334 DOI: 10.1176/appi.ajp.2013.12060782]

25 **Achenbach TM**, Rescorla LA. Manual for the ASEBA Adult Forms and Profiles. University of Vermont, Research Center for Children, Youth and Families. [cited 19 November 2022]. Available from: https://aseba.org/wp-content/uploads/2019/01/ASEBA-Reliability-and-Validity-Adult.pdf

26 **Morey LC**. Personality Assessment Inventory. Washington: American Psychological Association, 1991 [DOI: 10.1037/t03903-000]

27 **Morey LC**. Personality Assessment Inventory (PAI): professional manual (2nd ed). Odessa, FL: Psychological Assessment Resources, 2007

28 **Ruggero CJ**, Kotov R, Hopwood CJ, First M, Clark LA, Skodol AE, Mullins-Sweatt SN, Patrick CJ, Bach B, Cicero DC, Docherty A, Simms LJ, Bagby RM, Krueger RF, Callahan JL, Chmielewski M, Conway CC, De Clercq B, Dornbach-Bender A, Eaton NR, Forbes MK, Forbush KT, Haltigan JD, Miller JD, Morey LC, Patalay P, Regier DA, Reininghaus U, Shackman AJ, Waszczuk MA, Watson D, Wright AGC, Zimmermann J. Integrating the Hierarchical Taxonomy of Psychopathology (HiTOP) into clinical practice. *J Consult Clin Psychol* 2019; **87**: 1069-1084 [PMID: 31724426 DOI: 10.1037/ccp0000452]

29 **Krueger RF**. The structure of common mental disorders. *Arch Gen Psychiatry* 1999; **56**: 921-926 [PMID: 10530634 DOI: 10.1001/archpsyc.56.10.921]

30 **Forbush KT**, Watson D. The structure of common and uncommon mental disorders. *Psychol Med* 2013; **43**: 97-108

[PMID: 22613885 DOI: 10.1017/S0033291712001092]

31   **Hengartner MP**, Lehmann SN. Why Psychiatric Research Must Abandon Traditional Diagnostic Classification and Adopt a Fully Dimensional Scope: Two Solutions to a Persistent Problem. *Front Psychiatry* 2017; **8**: 101 [PMID: 28638352 DOI: 10.3389/fpsyt.2017.00101]

32   **Zanarini MC**, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). *J Pers Disord* 2003; **17**: 568-573 [PMID: 14744082 DOI: 10.1521/pedi.17.6.568.25355]

33   **Krueger RF**, Derringer J, Markon KE, Watson D, Skodol AE. Initial construction of a maladaptive personality trait model and inventory for DSM-5. *Psychol Med* 2012; **42**: 1879-1890 [PMID: 22153017 DOI: 10.1017/S0033291711002674]

34   **Krueger RF**, Markon KE. The role of the DSM-5 personality trait model in moving toward a quantitative and empirically based approach to classifying personality and psychopathology. *Annu Rev Clin Psychol* 2014; **10**: 477-501 [PMID: 24329179 DOI: 10.1146/annurev-clinpsy-032813-153732]

35   **World Health Organization**.   Manual of the international statistical classification of diseases, injuries, and causes of death: based on the recommendations of the seventh revision Conference, 1955, and adopted by the ninth World Health Assembly under the WHO Nomenclature Regulations. [cited 19 November 2022]. Available from: https://apps.who.int/iris/handle/10665/42900.

36   **World Health Organization**.   Manual of the international statistical classification of disease, injuries, and causes of death. Based on the recommendations of the eighth revision conference, 1965, and adopted by the Nineteenth World Health Assembly. [cited 19 November 2022]. Available from: https://apps.who.int/iris/handle/10665/70934

37   **American Psychiatric Association**.   Diagnostic and statistical manual of mental disorders (2nd ed). Washington: American Psychiatric Association, 1968

38   **World Health Organization**, International Conference for the Ninth Revision of the International Classification of Diseases.   Manual of the international statistical classification of diseases, injuries, and causes of death: based on the recommendations of the ninth revision conference, 1975, and adopted by the Twenty-ninth World Health Assembly, 1975 revision. [cited 19 November 2022]. Available from: https://apps.who.int/iris/handle/10665/40492

39   **Eysenck HJ**. The scientific study of personality. *British J Statis Psychol* 1953 [DOI: 10.1111/j.2044-8317.1953.tb00132.x]

40   **Cattell RB**.   Personality and Motivation Structure and Measurement. [cited 19 November 2022]. Available from: https://psycnet.apa.org/record/1958-03918-000

41   **Cronbach LJ**, Meehl PE. Construct validity in psychological tests. *Psychol Bull* 1955; **52**: 281-302 [PMID: 13245896 DOI: 10.1037/h0040957]

42   **Eysenck HJ**, Eysenck SBG.   Manual of the Eysenck Personality Questionnaire (Junior and Adult). Londres: Hodder and Stoughton, 1975

43   **Mayes R**, Horwitz AV. DSM-III and the revolution in the classification of mental illness. *J Hist Behav Sci* 2005; **41**: 249-267 [PMID: 15981242 DOI: 10.1002/jhbs.20103]

44   **Clark LA**, Cuthbert B, Lewis-Fernández R, Narrow WE, Reed GM. Three Approaches to Understanding and Classifying Mental Disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychol Sci Public Interest* 2017; **18**: 72-145 [PMID: 29211974 DOI: 10.1177/1529100617727266]

45   Transplantation. *Curr Opin Immunol* 1989; **1**: 1257-1295 [PMID: 2679764 DOI: 10.1016/0952-7915(89)90024-1]

46   **Maser JD**, Patterson T. Spectrum and nosology: implications for DSM-V. *Psychiatr Clin North Am* 2002; **25**: 855-885, viii [PMID: 12462864 DOI: 10.1016/s0193-953x(02)00022-9]

47   **Zachar P**, Kendler KS. The Philosophy of Nosology. *Annu Rev Clin Psychol* 2017; **13**: 49-71 [PMID: 28482691 DOI: 10.1146/annurev-clinpsy-032816-045020]

48   **Spitzer RL**, Endicott J, Robins E. Clinical criteria for psychiatric diagnosis and DSM-III. *Am J Psychiatry* 1975; **132**: 1187-1192 [PMID: 1172654 DOI: 10.1176/ajp.132.11.1187]

49   **Möller HJ**. Systematic of psychiatric disorders between categorical and dimensional approaches: Kraepelin's dichotomy and beyond. *Eur Arch Psychiatry Clin Neurosci* 2008; **258** Suppl 2: 48-73 [PMID: 18516518 DOI: 10.1007/s00406-008-2004-3]

50   **Narrow WE**, Rae DS, Robins LN, Regier DA. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. *Arch Gen Psychiatry* 2002; **59**: 115-123 [PMID: 11825131 DOI: 10.1001/archpsyc.59.2.115]

51   **Aftab A**, Ryznar E. Conceptual and historical evolution of psychiatric nosology. *Int Rev Psychiatry* 2021; **33**: 486-499 [PMID: 33047992 DOI: 10.1080/09540261.2020.1828306]

52   **American Psychiatric Association**.   Diagnostic and statistical manual of mental disorders (3rd ed, Rev). Washington: American Psychiatric Association, 1987

53   **Bech P**, Malt UF, Dencker SJ, Ahlfors UG. Scales for assessment of diagnosis and severity of mental disorders. *Acta Psychiatr Scand Suppl* 1993; **372**: 1-87 [PMID: 8317228 DOI: 10.1111/j.1600-0447.1993.tb05583.x]

54   **Endicott J**, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976; **33**: 766-771 [PMID: 938196 DOI: 10.1001/archpsyc.1976.01770060086012]

55   **American Psychiatric Association**.   Diagnostic and statistical manual of mental disorders, 4th ed. Washington: American Psychiatric Association, 1994

56   **Janca A**, Kastrup M, Katschnig H, López-Ibor JJ Jr, Mezzich JE, Sartorius N. The World Health Organization Short Disability Assessment Schedule (WHO DAS-S): a tool for the assessment of difficulties in selected areas of functioning of patients with mental disorders. *Soc Psychiatry Psychiatr Epidemiol* 1996; **31**: 349-354 [PMID: 8952375 DOI: 10.1007/BF00783424]

57   **World Health Organization**.   International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. [cited 19 November 2023]. Available from: https://apps.who.int/iris/handle/10665/246208

58   **American Psychiatric Association**.   Diagnostic and statistical manual of mental disorders (4th ed, rev). Washington:

American Psychiatric Association, 2000

59 **World Health Organization**. The ICD-10 classification of mental and behavioral disorders: Clinical descriptions and diagnostic guidelines. [cited 19 November 2022]. Available from: https://www.who.int/publications/i/item/9241544228

60 **World Health Organization**. The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research. [cited 19 November 2022]. Available from: https://www.who.int/publications/i/item/9241544554

61 **First MB**. Harmonisation of ICD-11 and DSM-V: opportunities and challenges. *Br J Psychiatry* 2009; **195**: 382-390 [PMID: 19880924 DOI: 10.1192/bjp.bp.108.060822]

62 **Tyrer P**, Crawford M, Mulder R, Blashfield R, Farnam A, Fossati A, Kim YR, Koldobsky N, Lecic-Tosevski D, Ndetei D, Swales M, Clark LA, Reed GM. The rationale for the reclassification of personality disorder in the 11th revision of the international classification of diseases (ICD-11). *Personal Ment Health* 2011 [DOI: 10.1002/pmh.190]

63 **Sleep CE**, Lynam DR, Widiger TA, Crowe ML, Miller JD. Difficulties with the conceptualization and assessment of Criterion A in the DSM-5 alternative model of personality disorder: A reply to Morey (2019). *Psychol Assess* 2019; **31**: 1200-1205 [PMID: 31580133 DOI: 10.1037/pas0000758]

64 **Widiger TA**, McCabe GA. The Alternative Model of Personality Disorders (AMPD) from the Perspective of the Five-Factor Model. *Psychopathology* 2020; **53**: 149-156 [PMID: 32526758 DOI: 10.1159/000507378]

65 **Zimmermann J**, Böhnke JR, Eschstruth R, Mathews A, Wenzel K, Leising D. The latent structure of personality functioning: Investigating criterion a from the alternative model for personality disorders in DSM-5. *J Abnorm Psychol* 2015; **124**: 532-548 [PMID: 26052618 DOI: 10.1037/abn0000059]

66 **Morey LC**. Thoughts on the assessment of the DSM-5 alternative model for personality disorders: Comment on Sleep *et al* (2019). *Psychol Assess* 2019; **31**: 1192-1199 [PMID: 31580132 DOI: 10.1037/pas0000710]

67 **Few LR**, Miller JD, Rothbaum AO, Meller S, Maples J, Terry DP, Collins B, MacKillop J. Examination of the Section III DSM-5 diagnostic system for personality disorders in an outpatient clinical sample. *J Abnorm Psychol* 2013; **122**: 1057-1069 [PMID: 24364607 DOI: 10.1037/a0034878]

68 **Sleep CE**, Weiss B, Lynam DR, Miller JD. The DSM-5 section III personality disorder criterion a in relation to both pathological and general personality traits. *Personal Disord* 2020; **11**: 202-212 [PMID: 31804130 DOI: 10.1037/per0000383]

69 **Hopwood CJ**, Thomas KM, Markon KE, Wright AG, Krueger RF. DSM-5 personality traits and DSM-IV personality disorders. *J Abnorm Psychol* 2012; **121**: 424-432 [PMID: 22250660 DOI: 10.1037/a0026656]

70 **Markon KE**, Chmielewski M, Miller CJ. The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. *Psychol Bull* 2011; **137**: 856-879 [PMID: 21574681 DOI: 10.1037/a0023678]

71 **Chmielewski M**, Clark LA, Bagby RM, Watson D. Method matters: Understanding diagnostic reliability in DSM-IV and DSM-5. *J Abnorm Psychol* 2015; **124**: 764-769 [PMID: 26098046 DOI: 10.1037/abn0000069]

72 **Regier DA**, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. *World Psychiatry* 2013; **12**: 92-98 [PMID: 23737408 DOI: 10.1002/wps.20050]

73 **Krueger RF**, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J Abnorm Psychol* 2002; **111**: 411-424 [PMID: 12150417 DOI: 10.1037/0021-843X.111.3.411]

74 **Krueger RF**, Markon KE, Patrick CJ, Benning SD, Kramer MD. Linking antisocial behavior, substance use, and personality: an integrative quantitative model of the adult externalizing spectrum. *J Abnorm Psychol* 2007; **116**: 645-666 [PMID: 18020714 DOI: 10.1037/0021-843X.116.4.645]

75 **Krueger RF**, South SC. Externalizing disorders: cluster 5 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009; **39**: 2061-2070 [PMID: 19796431 DOI: 10.1017/S0033291709990328]

76 **Elam KK**, DiLalla LF. An Introduction to the Special Issue: Developmental Behavior Genetics and Externalizing Psychopathology. *Behav Genet* 2021; **51**: 443-447 [PMID: 34304323 DOI: 10.1007/s10519-021-10078-4]

77 **Carroll SL**, Clark DA, Hyde LW, Klump KL, Burt SA. Continuity and Change in the Genetic and Environmental Etiology of Youth Antisocial Behavior. *Behav Genet* 2021; **51**: 580-591 [PMID: 34061264 DOI: 10.1007/s10519-021-10066-8]

78 **Clark LA**, Watson D. The trait model of the DSM-5 alternative model of personality disorder (AMPD): A structural review. *Personal Disord* 2022; **13**: 328-336 [PMID: 35787115 DOI: 10.1037/per0000568]

79 **Watters CA**, Bagby RM, Sellbom M. Meta-analysis to derive an empirically based set of personality facet criteria for the alternative DSM-5 model for personality disorders. *Personal Disord* 2019; **10**: 97-104 [PMID: 30520649 DOI: 10.1037/per0000307]

80 **Watson D**, Clark LA, Simms LJ, Kotov R. Classification and assessment of fear and anxiety in personality and psychopathology. *Neurosci Biobehav Rev* 2022; **142**: 104878 [PMID: 36116575 DOI: 10.1016/j.neubiorev.2022.104878]

81 **Watson D**, Levin-Aspenson HF, Waszczuk MA, Conway CC, Dalgleish T, Dretsch MN, Eaton NR, Forbes MK, Forbush KT, Hobbs KA, Michelini G, Nelson BD, Sellbom M, Slade T, South SC, Sunderland M, Waldman I, Witthöft M, Wright AGC, Kotov R, Krueger RF; HiTOP Utility Workgroup. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum. *World Psychiatry* 2022; **21**: 26-54 [PMID: 35015357 DOI: 10.1002/wps.20943]

82 **Lin SY**, Eaton NR. From Research to Practice: Clinical Utility of Quantitative Nosology. 2020 Preprint. Available from: OSF Preprints [DOI: 10.31219/osf.io/fk9xq]

83 **Contreras A**, Nieto I, Valiente C, Espinosa R, Vazquez C. The Study of Psychopathology from the Network Analysis Perspective: A Systematic Review. *Psychother Psychosom* 2019; **88**: 71-83 [PMID: 30889609 DOI: 10.1159/000497425]

84 **Robinaugh DJ**, Hoekstra RHA, Toner ER, Borsboom D. The network approach to psychopathology: a review of the literature 2008-2018 and an agenda for future research. *Psychol Med* 2020; **50**: 353-366 [PMID: 31875792 DOI: 10.1017/S0033291719003404]

85 **Simms LJ**, Wright AGC, Cicero D, Kotov R, Mullins-Sweatt SN, Sellbom M, Watson D, Widiger TA, Zimmermann J. Development of Measures for the Hierarchical Taxonomy of Psychopathology (HiTOP): A Collaborative Scale

Development Project. *Assessment* 2022; **29**: 3-16 [PMID: 34013772 DOI: 10.1177/10731911211015309]

86   **Krueger RF**, Hobbs KA, Conway CC, Dick DM, Dretsch MN, Eaton NR, Forbes MK, Forbush KT, Keyes KM, Latzman RD, Michelini G, Patrick CJ, Sellbom M, Slade T, South SC, Sunderland M, Tackett J, Waldman I, Waszczuk MA, Wright AGC, Zald DH, Watson D, Kotov R; HiTOP Utility Workgroup. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum. *World Psychiatry* 2021; **20**: 171-193 [PMID: 34002506 DOI: 10.1002/wps.20844]

87   **Stasik-O'Brien SM**, Brock RL, Chmielewski M, Naragon-Gainey K, Koffel E, McDade-Montez E, O'Hara MW, Watson D. Clinical Utility of the Inventory of Depression and Anxiety Symptoms (IDAS). *Assessment* 2019; **26**: 944-960 [PMID: 30043620 DOI: 10.1177/1073191118790036]

88   **DeYoung CG**, Chmielewski M, Clark LA, Condon DM, Kotov R, Krueger RF, Lynam DR, Markon KE, Miller JD, Mullins-Sweatt SN, Samuel DB, Sellbom M, South SC, Thomas KM, Watson D, Watts AL, Widiger TA, Wright AGC; HiTOP Normal Personality Workgroup. The distinction between symptoms and traits in the Hierarchical Taxonomy of Psychopathology (HiTOP). *J Pers* 2022; **90**: 20-33 [PMID: 32978977 DOI: 10.1111/jopy.12593]

89   **Ringwald WR**, Forbes MK, Wright AGC. Meta-analysis of structural evidence for the Hierarchical Taxonomy of Psychopathology (HiTOP) model. *Psychol Med* 2021; 1-14 [PMID: 33988108 DOI: 10.1017/S0033291721001902]

90   **Mullins-Sweatt SN**, Bornovalova MA, Carragher N, Clark LA, Corona Espinosa A, Jonas K, Keyes KM, Lynam DR, Michelini G, Miller JD, Min J, Rodriguez-Seijas C, Samuel DB, Tackett JL, Watts AL. HiTOP Assessment of Externalizing Antagonism and Disinhibition. *Assessment* 2022; **29**: 34-45 [PMID: 34823365 DOI: 10.1177/10731911211033900]

91   **Frick PJ**, White SF. Research review: the importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior. *J Child Psychol Psychiatry* 2008; **49**: 359-375 [PMID: 18221345 DOI: 10.1111/j.1469-7610.2007.01862.x]

92   **Lilienfeld SO**, Widows MR.   Psychopathic Personality InventoryTM-Revised. [cited 20 November 2022]. Available from: https://www.parinc.com/Products/Pkey/331

93   **Lynam DR**, Widiger TA. Using a general model of personality to identify the basic elements of psychopathy. *J Pers Disord* 2007; **21**: 160-178 [PMID: 17492919 DOI: 10.1521/pedi.2007.21.2.160]

94   **Pianowski G**, Carvalho LF, Miguel FK. Investigating the Spectra constellations of the Hierarchical Taxonomy of Psychopathology (HiTOP) model for personality disorders based on empirical data from a community sample. *Braz J Psychiatry* 2019; **41**: 148-152 [PMID: 30758432 DOI: 10.1590/1516-4446-2018-0015]

95   **Pechorro P**, Hidalgo V, Nunes C, Jiménez L. Confirmatory Factor Analysis of the Antisocial Process Screening Device. *Int J Offender Ther Comp Criminol* 2016; **60**: 1856-1872 [PMID: 26138352 DOI: 10.1177/0306624X15588903]

96   **Gao Y**, Zhang W. Confirmatory Factor Analyses of Self- and Parent- Report Inventory of Callous-Unemotional Traits in 8- to 10-Year-Olds. *J Psychopathol Behav Assess* 2016; **38**: 331-340 [PMID: 28255197 DOI: 10.1007/s10862-015-9527-5]

97   **Ali AM**, Hendawy AO, Almarwani AM, Alzahrani N, Ibrahim N, Alkhamees AA, Kunugi H. The Six-Item Version of the Internet Addiction Test: Its Development, Psychometric Properties, and Measurement Invariance among Women with Eating Disorders and Healthy School and University Students. *Int J Environ Res Public Health* 2021; **18** [PMID: 34886068 DOI: 10.3390/ijerph182312341]

98   **Lyons Usher AM**, Leon SC, Stanford LD, Holmbeck GN, Bryant FB. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Functioning (BRIEF) in children and adolescents with ADHD. *Child Neuropsychol* 2016; **22**: 907-918 [PMID: 26156531 DOI: 10.1080/09297049.2015.1060956]

99   **Weekers LC**, Hutsebaut J, Kamphuis JH. The Level of Personality Functioning Scale-Brief Form 2.0: Update of a brief instrument for assessing level of personality functioning. *Personal Ment Health* 2019; **13**: 3-14 [PMID: 30230242 DOI: 10.1002/pmh.1434]

100   **Sheehan DV**, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** Suppl 20: 22-33;quiz 34 [PMID: 9881538]

101   **Hasin DS**, Trautman KD, Miele GM, Samet S, Smith M, Endicott J. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry* 1996; **153**: 1195-1201 [PMID: 8780425 DOI: 10.1176/ajp.153.9.1195]

102   **Wing JK**, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry* 1990; **47**: 589-593 [PMID: 2190539 DOI: 10.1001/archpsyc.1990.01810180089012]

103   **Peters L**, Andrews G. Procedural validity of the computerized version of the Composite International Diagnostic Interview (CIDI-Auto) in the anxiety disorders. *Psychol Med* 1995; **25**: 1269-1280 [PMID: 8637956 DOI: 10.1017/s0033291700033237]

104   **Kessler RC**, Ustün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 2004; **13**: 93-121 [PMID: 15297906 DOI: 10.1002/mpr.168]

105   **Torrico Linares E**, Vélez Moreno A, Ruiz Villalba E, Fernández Calderón F, Hernández Cordero A, Rámirez López J. TDAH en pacientes con adicción a sustancias: análisis de la prevalencia y de los problemas relacionados con el consumo en una muestra atendida en un servicio de tratamiento ambulatorio. *Trastor Adict* 2012; **14**: 89-95 [DOI: 10.1016/S1575-0973(12)70050-8]

106   **Hasin D**, Shmulewitz D, Stohl M, Greenstein E, Roncone S, Aharonovich E, Wall M. Test-retest reliability of DSM-5 substance disorder measures as assessed with the PRISM-5, a clinician-administered diagnostic interview. *Drug Alcohol Depend* 2020; **216**: 108294 [PMID: 33007702 DOI: 10.1016/j.drugalcdep.2020.108294]

107   **Miele GM**, Carpenter KM, Smith Cockerham M, Trautman KD, Blaine J, Hasin DS. Substance Dependence Severity Scale (SDSS): reliability and validity of a clinician-administered interview for DSM-IV substance use disorders. *Drug Alcohol Depend* 2000; **59**: 63-75 [PMID: 10706976 DOI: 10.1016/s0376-8716(99)00111-8]

108   **Miele GM**, Carpenter KM, Smith Cockerham M, Dietz Trautman K, Blaine J, Hasin DS. Concurrent and predictive validity of the Substance Dependence Severity Scale (SDSS). *Drug Alcohol Depend* 2000; **59**: 77-88 [PMID: 10706977 DOI: 10.1016/s0376-8716(99)00110-6]

109   **Dacosta-Sánchez D**, Fernández-Calderón F, González-Ponce B, Díaz-Batanero C, Lozano ÓM. Severity of Substance Use Disorder: Utility as an Outcome in Clinical Settings. *Alcohol Clin Exp Res* 2019; **43**: 869-876 [PMID: 30861142 DOI: 10.1111/acer.14020]

110   **Vélez-Moreno A**, González-Saiz F, Ramírez López J, Torrico Linares E, Fernández-Calderón F, Rojas AJ, Lozano ÓM. [Spanish adaptation of the Substance Dependence Severity Scale: preliminar results]. *Adicciones* 2013; **25**: 339-347 [PMID: 24217503 DOI: 10.20882/adicciones.36]

111   **Lawrinson P**, Copeland J, Gerber S, Gilmour S. Determining a cut-off on the Severity of Dependence Scale (SDS) for alcohol dependence. *Addict Behav* 2007; **32**: 1474-1479 [PMID: 17081703 DOI: 10.1016/j.addbeh.2006.09.005]

112   **Cuenca-Royo AM**, Sánchez-Niubó A, Forero CG, Torrens M, Suelves JM, Domingo-Salvany A. Psychometric properties of the CAST and SDS scales in young adult cannabis users. *Addict Behav* 2012; **37**: 709-715 [PMID: 22386300 DOI: 10.1016/j.addbeh.2012.02.012]

113   **van der Pol P**, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Reliability and validity of the Severity of Dependence Scale for detecting cannabis dependence in frequent cannabis users. *Int J Methods Psychiatr Res* 2013; **22**: 138-143 [PMID: 23670783 DOI: 10.1002/mpr.1385]

114   **Fernández-Calderón F**, Vidal-Giné C, López-Guerrero J, Lozano-Rojas ÓM. Reliability, convergent and structural validity and cut-off score of the Severity of Dependence Scale for recreational ketamine users. *Addict Behav* 2016; **60**: 1-7 [PMID: 27082261 DOI: 10.1016/j.addbeh.2016.03.016]

115   **Deluca P**, Foley M, Dunne J, Kimergård A. The Severity of Dependence Scale (SDS) for Codeine: Preliminary Investigation of the Psychometric Properties of the SDS in an Online Sample of Codeine Users From the UK. *Front Psychiatry* 2021; **12**: 595706 [PMID: 33868038 DOI: 10.3389/fpsyt.2021.595706]

116   **Davidson R**, Raistrick D. The validity of the Short Alcohol Dependence Data (SADD) Questionnaire: a short self-report questionnaire for the assessment of alcohol dependence. *Br J Addict* 1986; **81**: 217-222 [PMID: 3458489 DOI: 10.1111/j.1360-0443.1986.tb00319.x]

117   **Stockwell T**, Hodgson R, Edwards G, Taylor C, Rankin H. The development of a questionnaire to measure severity of alcohol dependence. *Br J Addict Alcohol Other Drugs* 1979; **74**: 79-87 [PMID: 283831 DOI: 10.1111/j.1360-0443.1979.tb02415.x]

118   **World Health Organization**.   AUDIT: the Alcohol Use Disorders Identification Test: guidelines for use in primary health care. [cited 19 November 2022]. Available from: https://www.who.int/publications/i/item/WHO-MSD-MSB-01.6a

119   **Adler LA**, Spencer T, Faraone SV, Kessler RC, Howes MJ, Biederman J, Secnik K. Validity of pilot Adult ADHD Self-Report Scale (ASRS) to Rate Adult ADHD symptoms. *Ann Clin Psychiatry* 2006; **18**: 145-148 [PMID: 16923651 DOI: 10.1080/10401230600801077]

120   **Kessler RC**, Adler L, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol Med* 2005; **35**: 245-256 [PMID: 15841682 DOI: 10.1017/s0033291704002892]

121   **Barkley RA**. Attention-deficit hyperactivity disorder. *Sci Am* 1998; **279**: 66-71 [PMID: 9725940 DOI: 10.1038/scientificamerican0998-66]

122   **Conners CK**, Erhardt D, Sparrow E.   Conners' Adult ADHD Rating Scales (CAARS). Technical Manual. [cited 19 November 2022]. Available from: http://www.pearsonclinical.co.uk/Psychology/AdultMentalHealth/AdultMentalHealth/ConnersAdultADHDRatingScales(CAARS)/ConnersAdultADHDRatingScales(CAARS).aspx

123   **Mulder RT**. ICD-11 Personality Disorders: Utility and Implications of the New Model. *Front Psychiatry* 2021; **12**: 655548 [PMID: 34040555 DOI: 10.3389/fpsyt.2021.655548]

124   **Oltmanns JR**, Widiger TA. A self-report measure for the ICD-11 dimensional trait model proposal: The personality inventory for ICD-11. *Psychol Assess* 2018; **30**: 154-169 [PMID: 28230410 DOI: 10.1037/pas0000459]

125   **Maples JL**, Carter NT, Few LR, Crego C, Gore WL, Samuel DB, Williamson RL, Lynam DR, Widiger TA, Markon KE, Krueger RF, Miller JD. Testing whether the DSM-5 personality disorder trait model can be measured with a reduced set of items: An item response theory investigation of the Personality Inventory for DSM-5. *Psychol Assess* 2015; **27**: 1195-1210 [PMID: 25844534 DOI: 10.1037/pas0000120]

126   **American Psychiatric Association**.   The Personality Inventory for DSM-5-Brief Form (PID-5-BF)-Adult. [cited 19 November 2022]. Available from: https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM5_The-Personality-Inventory-For-DSM-5-Brief-Form-Adult.pdf

127   **Bach B**, Maples-Keller JL, Bo S, Simonsen E. The alternative DSM-5 personality disorder traits criterion: A comparative examination of three self-report forms in a Danish population. *Personal Disord* 2016; **7**: 124-135 [PMID: 26642229 DOI: 10.1037/per0000162]

128   **Debast I**, Rossi G, van Alphen SPJ. Construct Validity of the DSM-5 Section III Maladaptive Trait Domains in Older Adults. *J Pers Disord* 2017; **31**: 671-688 [PMID: 28072042 DOI: 10.1521/pedi_2017_31_274]

129   **Fossati A**, Somma A, Borroni S, Markon KE, Krueger RF. The Personality Inventory for DSM-5 Brief Form: Evidence for Reliability and Construct Validity in a Sample of Community-Dwelling Italian Adolescents. *Assessment* 2017; **24**: 615-631 [PMID: 26676917 DOI: 10.1177/1073191115621793]

130   **Combaluzier S**, Gouvernet B, Menant F, Rezrazi A. [Validation of a French translation of Krueger's personality inventory for DSM-5 in its brief form (PID-5 BF)]. *Encephale* 2018; **44**: 9-13 [PMID: 27692349 DOI: 10.1016/j.encep.2016.07.006]

131   **Pires R**, Sousa Ferreira A, Gonçalves B, Henriques-Calado J, Paulino M. The Portuguese version of the Personality Inventory for the DSM-5 in a community and a clinical sample. *Personal Ment Health* 2019; **13**: 40-52 [PMID: 30456905 DOI: 10.1002/pmh.1437]

132   **Gutiérrez F**, Aluja A, Peri JM, Calvo N, Ferrer M, Baillés E, Gutiérrez-Zotes JA, Gárriz M, Caseras X, Markon KE, Krueger RF. Psychometric Properties of the Spanish PID-5 in a Clinical and a Community Sample. *Assessment* 2017; **24**: 326-336 [PMID: 26391204 DOI: 10.1177/1073191115606518]

133   **Díaz-Batanero C**, Ramírez-López J, Domínguez-Salas S, Fernández-Calderón F, Lozano ÓM. Personality Inventory for DSM-5-Short Form (PID-5-SF): Reliability, Factorial Structure, and Relationship With Functional Impairment in Dual Diagnosis Patients. *Assessment* 2019; **26**: 853-866 [PMID: 29117705 DOI: 10.1177/1073191117739980]

134   **Al-Dajani N**, Gralnick TM, Bagby RM. A Psychometric Review of the Personality Inventory for DSM-5 (PID-5): Current Status and Future Directions. *J Pers Assess* 2016; **98**: 62-81 [PMID: 26619968 DOI: 10.1080/00223891.2015.1107572]

135   **Costa PT**, McCrae RR. The five-factor model of personality and its relevance to personality disorders. *J Pers Disord* 1992; **6**: 343-359 [DOI: 10.1521/pedi.1992.6.4.343]

136   **Gore WL**, Widiger TA. The DSM-5 dimensional trait model and five-factor models of general personality. *J Abnorm Psychol* 2013; **122**: 816-821 [PMID: 23815395 DOI: 10.1037/a0032822]

137   **Watson D**, Stasik SM, Ro E, Clark LA. Integrating normal and pathological personality: relating the DSM-5 trait-dimensional model to general traits of personality. *Assessment* 2013; **20**: 312-326 [PMID: 23596272 DOI: 10.1177/1073191113485810]

138   **Zimmermann J**, Altenstein D, Krieger T, Holtforth MG, Pretsch J, Alexopoulos J, Spitzer C, Benecke C, Krueger RF, Markon KE, Leising D. The structure and correlates of self-reported DSM-5 maladaptive personality traits: findings from two German-speaking samples. *J Pers Disord* 2014; **28**: 518-540 [PMID: 24511899 DOI: 10.1521/pedi_2014_28_130]

139   **Jopp AM**, South SC. Investigating the Personality Inventory for DSM-5 using self and spouse reports. *J Pers Disord* 2015; **29**: 193-214 [PMID: 25102086 DOI: 10.1521/pedi_2014_28_153]

140   **Crego C**, Widiger TA. The convergent, discriminant, and structural relationship of the DAPP-BQ and SNAP with the ICD-11, DSM-5, and FFM trait models. *Psychol Assess* 2020; **32**: 18-28 [PMID: 31328932 DOI: 10.1037/pas0000757]

141   **Oltmanns JR**, Widiger TA. Evaluating the assessment of the ICD-11 personality disorder diagnostic system. *Psychol Assess* 2019; **31**: 674-684 [PMID: 30628821 DOI: 10.1037/pas0000693]

142   **Oltmanns JR**, Widiger TA. The Five-Factor Personality Inventory for ICD-11: A facet-level assessment of the ICD-11 trait model. *Psychol Assess* 2020; **32**: 60-71 [PMID: 31414852 DOI: 10.1037/pas0000763]

143   **Carnovale M**, Sellbom M, Bagby RM. The Personality Inventory for ICD-11: Investigating reliability, structural and concurrent validity, and method variance. *Psychol Assess* 2020; **32**: 8-17 [PMID: 31556679 DOI: 10.1037/pas0000776]

144   **Somma A**, Gialdi G, Fossati A. Reliability and construct validity of the Personality Inventory for ICD-11 (PiCD) in Italian adult participants. *Psychol Assess* 2020; **32**: 29-39 [PMID: 31414851 DOI: 10.1037/pas0000766]

145   **Mulder RT**, Horwood J, Tyrer P, Carter J, Joyce PR. Validating the proposed ICD-11 domains. *Personal Ment Health* 2016; **10**: 84-95 [PMID: 27120419 DOI: 10.1002/pmh.1336]

146   **Bach B**, Sellbom M, Kongerslev M, Simonsen E, Krueger RF, Mulder R. Deriving ICD-11 personality disorder domains from dsm-5 traits: initial attempt to harmonize two diagnostic systems. *Acta Psychiatr Scand* 2017; **136**: 108-117 [PMID: 28504853 DOI: 10.1111/acps.12748]

147   **Bach B**, Sellbom M, Skjernov M, Simonsen E. ICD-11 and DSM-5 personality trait domains capture categorical personality disorders: Finding a common ground. *Aust N Z J Psychiatry* 2018; **52**: 425-434 [PMID: 28835108 DOI: 10.1177/0004867417727867]

148   **Sellbom M**, Solomon-Krakus S, Bach B, Bagby RM. Validation of Personality Inventory for DSM-5 (PID-5) algorithms to assess ICD-11 personality trait domains in a psychiatric sample. *Psychol Assess* 2020; **32**: 40-49 [PMID: 31204821 DOI: 10.1037/pas0000746]

149   **Achenbach TM**. The classification of children's psychiatric symptoms: a factor-analytic study. *Psychol Monogr* 1966; **80**: 1-37 [PMID: 5968338 DOI: 10.1037/h0093906]

150   **Achenbach TM**, Rescorla LA.   Manual for the ASEBA adult forms & profiles. Burlington: University of Vermont, 2003

151   **Achenbach TM**, Ivanova MY, Rescorla LA. Empirically based assessment and taxonomy of psychopathology for ages 1½-90+ years: Developmental, multi-informant, and multicultural findings. *Compr Psychiatry* 2017; **79**: 4-18 [PMID: 28356192 DOI: 10.1016/j.comppsych.2017.03.006]

152   **Hathaway SR**, McKinley JC. A multiphasic personality schedule (Minnesota): I. Construction of the schedule. *J Psychol* 1940; **10**: 249-254 [DOI: 10.1080/00223980.1940.9917000]

153   **Hathaway SR**, McKinley JC.   Minnesota Multiphasic Personality Inventory; manual (revised). Minneapolis: Psychological corporation, 1951

154   **Ben-Porath YS**, Tellegen A.   Minnesota Multiphasic Personality Inventory-3 (MMPI-3): Technical manual. Minneapolis: University of Minnesota Press, 2020

155   **Krueger RF**, Kotov R, Watson D, Forbes MK, Eaton NR, Ruggero CJ, Simms LJ, Widiger TA, Achenbach TM, Bach B, Bagby RM, Bornovalova MA, Carpenter WT, Chmielewski M, Cicero DC, Clark LA, Conway C, DeClercq B, DeYoung CG, Docherty AR, Drislane LE, First MB, Forbush KT, Hallquist M, Haltigan JD, Hopwood CJ, Ivanova MY, Jonas KG, Latzman RD, Markon KE, Miller JD, Morey LC, Mullins-Sweatt SN, Ormel J, Patalay P, Patrick CJ, Pincus AL, Regier DA, Reininghaus U, Rescorla LA, Samuel DB, Sellbom M, Shackman AJ, Skodol A, Slade T, South SC, Sunderland M, Tackett JL, Venables NC, Waldman ID, Waszczuk MA, Waugh MH, Wright AGC, Zald DH, Zimmermann J. Progress in achieving quantitative classification of psychopathology. *World Psychiatry* 2018; **17**: 282-293 [PMID: 30229571 DOI: 10.1002/wps.20566]

156   **Sloan E**, Hall K, Moulding R, Bryce S, Mildred H, Staiger PK. Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: A systematic review. *Clin Psychol Rev* 2017; **57**: 141-163 [PMID: 28941927 DOI: 10.1016/j.cpr.2017.09.002]

157   **Dalgleish T**, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: Current status and future directions. *J Consult Clin Psychol* 2020; **88**: 179-195 [PMID: 32068421 DOI: 10.1037/ccp0000482]

158   **Markon KE**. Modeling psychopathology structure: a symptom-level analysis of Axis I and II disorders. *Psychol Med* 2010; **40**: 273-288 [PMID: 19515267 DOI: 10.1017/S0033291709990183]

159   **Wright AG**, Simms LJ. A metastructural model of mental disorders and pathological personality traits. *Psychol Med* 2015; **45**: 2309-2319 [PMID: 25903065 DOI: 10.1017/S0033291715000252]

REVIEW

Psychiatrists' occupational stigma conceptualization, measurement, and intervention: A literature review

Xiao-Li Shi, Lu-Yao Li, Zhi-Guang Fan

Xiao-Li Shi, Lu-Yao Li, Zhi-Guang Fan, School of Education, Jilin International Studies University, Changchun 130000, Jilin Province, China

Corresponding author: Zhi-Guang Fan, PhD, Associate Professor, School of Education, Jilin International Studies University, 3658 Jingyue Street, Changchun 130000, Jilin Province 130117, China. fanyqm@126.com

Abstract

Psychiatrists require frequent contact with and treatment of patients with mental illnesses. Due to the influence of associative stigma, psychiatrists may also be targets of stigma. Occupational stigma warrants special consideration because it significantly affects psychiatrists' career advancement, well-being, and their patients' health. Given that there is no complete summary of this issue, this study reviewed the existing literature on psychiatrists' occupational stigma to clearly synthesize its concepts, measurement tools, and intervention strategies. Herein, we emphasize that psychiatrists' occupational stigma is a multifaceted concept that simultaneously encompasses physically, socially, and morally tainted aspects. Currently, standardized methods to specifically measure psychiatrists' occupational stigma are lacking. Interventions for psychiatrists' occupational stigma may consider the use of protest, contact, education, comprehensive and systematic methods, as well as the use of psychotherapeutic approaches. This review provides a theoretical basis for the development of relevant measurement tools and intervention practices. Overall, this review seeks to raise public awareness of psychiatrists' occupational stigma, thereby promoting psychiatric professionalism and reducing its stigma.

Key Words: Psychiatrists; Occupational stigma; Conceptualization; Measurement; Intervention; Associative stigma

Core Tip: Psychiatrists' occupational stigma, an area that is little noticed, deserves more attention from the public and professionals considering its negative effects. This study aimed to elucidate its concept, explore the potential measurement tools, and focus on effective interventions by comprehensively reviewing related literature. It is expected to encourage more studies in this field.

INTRODUCTION

Stigma is a form of social classification. Occupational stigma results when people make derogatory, insulting, or negative comments about others practicing their occupation[1]. Occupational stigma is the negative labeling of a profession that the general public views as having dishonorable, humiliating, and shameful features, leading to negative consequences of social exclusion, status loss, demeaning, discrimination, and pessimistic rejection[2-4]. Although stigma arises from dirty work in common sense, any occupation can face various levels and types of stigma[3]. Physicians, a typically prestigious profession [5], also suffer from stigma that seriously jeopardizes health care career development[6,7]. Furthermore, psychiatrists may experience intense stigma due to the nature of their profession and the population they serve[8]. A study of trainee psychiatrists found that 75% of individuals heard denigrating or humiliating remarks about the psychiatric profession[9].

Occupational stigma exerts negative impact on psychiatrists' career advancement, well-being, and patients' health. More specifically, the stigma may cause burnout, job dissatisfaction, and low professional value[10-17], and can act as a strong predictor of health and well-being[18,19]. Numerous studies have demonstrated that occupational stigma contributes to practitioners' withdrawal behaviors and the propensity for resignation[14,20-22]. At present, the shortage of psychiatrists cannot meet the demands of mental health workforce development[23]. Alarmingly, a study suggested that just about half of psychiatry college graduates moved on to work in related disciplines[24]. It has shown that occupational stigma plays a major role in that kind of phenomenon[25-28]. In addition, as a consequence of stigma, medical students rarely consider psychiatry a future career option, with the perception of taking psychiatrists as having low professional prestige and respect[29-31]. The professional shortage in psychiatry has been existing considering the insufficient medical graduates attracted by psychiatry[32, 33].

Moreover, it is noteworthy that stigma can straightly influence the establishment of the well physician-patient relationship and the treatment process. Stigma is classified as either public stigma or self-stigma, in which patients' stigma toward psychiatrists falls under the former[34]. That public stigma can reduce patient compliance and help-seeking behavior, thereby impeding treatment[32,35]. For another, psychiatrists' self-stigma may result in an increase in defensive medical behavior[36], such as little communication with patients, unnecessary testing, excessive medication, refusal, or referral[37-39], leading to not only health-care costs rise and poor medical relationship but also the potential negative impact on patient health and treatment effect[40].

In conclusion, psychiatrists influenced by associative stigma are perceived as a heavily stigmatized profession. Despite numerous studies showing that occupational stigma exerts a significant negative impact on the development of psychiatry, there is little literature reviewing psychiatrists' occupational stigma. To that end, the purpose of this literature review is to provide a comprehensive overview of the concept, measurement, and intervention of psychiatrists' occupational stigma by reviewing the extant literature, with the prospect of providing a theoretical reference for future research.

LITERATURE SEARCH

The authors sequentially searched the PubMed, Web of Science, and Reference Citation Analysis (https://www.referencecitationanalysis.com/) databases for articles containing a cross combination of the following topical keywords: "Psychiatrist," "stigma," "occupational stigma," "stress," "negative affect," "career satisfaction," "dirty work," "healthcare workers," "associative stigma," "psychiatry," "mental health professionals," "self-stigma," "mental illness," "intervention," "measurement," and "anti-stigma." March 2023 was the deadline for the keyword search, which yielded an initial total of 21098 papers. Literature selection criteria, as decided between the professor and students, were as follows: First, include a study relevant to and representative of the topic; second, any such study should be published in English or French; third, exclude duplicates. After review 195 papers met the selection

criteria and 20903 papers were excluded.

CONCEPTUALIZATION OF PSYCHIATRISTS' OCCUPATIONAL STIGMA

Research on occupational stigma can be traced back to Hughes[2] and his exploration of dirty work[2]. Impressive findings have been attained in the following studies that explore occupational stigma across practically all professions[3,41,42]. In his research on dirty work, Hughes[2] classified occupational stigma into three categories: physically, socially, and morally tainted in the aspect of work content[2]. Based on this, Ashforth and Kreiner[43] provided a precise definition of the three different forms of stigma[43]. Particularly, the term "physically tainted" refers to jobs that involve direct contact with trash, death, or filth[44,45] such as cleaner and mortician, or directly working in dangerous and harmful environment[46,47] such as firefighter and miner. The term "socially tainted" describes jobs like prison guards and infectious disease doctors that require regular contact with stigmatized groups as part of their duties[48,49], as well as those like nannies and tour guides that include a servant-subordinate relationship[50,51]. The term "morally tainted" refers to occupations that are viewed as being sinful and unethical[52,53] such as doctor who perform abortions or sex worker, as well as occupations with leading and deceptive traits[54,55] such as anchors who lead viewers to spend money and poker players who deceive their opponents. It is critical to note that one type of stigma may predominate in a given occupation, or two or even three types of stigma may exist concurrently[3,43]. Stenger *et al*[56] extended the three-dimensional classification, arguing that occupational stigma is a negative stereotype formed by the public of certain occupations' work images, social relations, or ethics[56].

In a follow-up study, Kreiner *et al*[3] further proposed the concepts of "breadth" and "depth" of taint applied to work tasks undertaken[3]. Breadth refers to the centrality of stigma in occupational identity, and the frequency of stigma-related behaviors occurring. Depth refers to the degree to which a practitioner is directly exposed to dirt. Accordingly, occupational stigma was further divided into pervasive stigma, compartmentalized stigma, diluted stigma and idiosyncratic stigma. At the same time, Ashforth and Kreiner[42] took occupational reputation as an important dimension of occupational stigma division, and then divided occupational stigma into high/low reputation physically tainted, high/low reputation socially tainted, and high/low reputation morally tainted[42]. In a recent study, Zhang *et al* [57] analyzed the four-level stigma literature of individual, occupational, organizational, and industry, and divided the sources of stigma into six types (physical, tribal, moral, servile, emotional, associational), which extended the three-dimensional classification of occupational stigma. The sources of occupational stigma are considered to include these six types. At the same time, five characteristics of stigma (concealability, controllability, centrality, disruptiveness, malleability) are further proposed. Scholars believe that the types of stigma source and the characteristics of stigma under different social conditions will jointly influence the formation of stigma[57].

At present, different scholars do not consistently agree on the concept of occupational stigma. The above-mentioned concepts of stigma proposed by Hughes[2], Ashforth and Kreine[41] are most commonly used in related studies. To this end, this study also defines the concept of occupational stigma toward psychiatrists in the aspect of physical, social and moral, and explores the specific causes of occupational stigma.

People with mental illnesses are frequently labeled as "violent," "offensive," "dangerous," and "aggressive"[58]. Compared to doctors in other clinical departments, the public attempts to consider that psychiatrists are more likely to encounter with violence and operate in a riskier setting[59,60], which were confirmed in a survey of psychiatric healthcare professionals[61]. In a study based on a sample in China, it was found that 78% of psychiatrists reported having experienced verbal abuse, compared to more than 30% who had experienced physical abuse[62]. Similar findings about psychiatrists' susceptibility to being hurt in medical injury incidents were discovered in surveys conducted in Germany[63], Ghana[64], Turkey[65], and Kuwait[66]. Psychiatrists are considered physically tainted because of the hazardous work environment.

For psychiatrists, associative stigma serves as a major source of occupational stigma[67,68]. Due to their frequent interactions with and treatment of patients with mental illness, psychiatrists may experience associative stigma that their clients may attach to them[9,69]. Patients with mental illness are a highly stigmatized group[70,71]. Their image is portrayed as negative, dangerous, and dishonest, and their social value is severely diminished[72]. To a large extent, the formation and development of stigma toward mental illness result from both religion and culture[73]. People with mental illness were thought to be possessed by evil spirits in Christianity[74] and Islam[75]. Expulsions and floggings, the confinement of mentally ill persons in jails and insane asylums, or even burning as a form of torture were all common practices in medieval Europe including Switzerland, Germany, and France[72]. Moreover, the thought of saving face is strongly ingrained in Chinese Confucian culture[76]. Concealing or avoiding the information that a family member suffers from a mental illness is typically done to preserve the family's reputation[68]. Even today, many people who suffer from mental illness and their family members still refrain from disclosing their situations to others for fear of prejudice and rejection. This ubiquitous phenomenon exists in nations where collectivist principles are valued[77,78]. The low

use of mental health services is partly caused by the stigma around mental illness[79]. Being socially tainted is, therefore, the most typical trait of psychiatrists' occupational stigma.

The possibility of being morally tainted among psychiatrists should not be overlooked. In treating people with mental illness, coercive measures such as seclusion, restraint, and forced medication are widely used[80]. Although patients perceive coercion as harmful to the treatment, healthcare professionals take it as an effective method of caring for, protecting, and treating patients[81]. Coercive measures have been the subject of heated debate in medical ethics, as well as legal scrutiny. Then, alternative options are sought and implemented by psychiatrists actively[82]. On the one hand, psychiatrists frequently consider physical and chemical restraints necessary, but on the other hand, they also recognize their potential to undermine patient rights and negatively impact the therapeutic relationship [83]. Therefore, it is understandable that psychiatrists may experience criticism, moral condemnation, and perceived intense moral pressure due to the dangers that coercive tactics may cause[84]. Now, an increasing number of researchers are advocating for improvements in the clinical practice of mental health medicine in order to reduce the use of coercive tactics[85]. In addition, electroconvulsive therapy (ECT) is frequently utilized to treat a variety of psychiatric diseases, including depression[86] and schizophrenia[87], with positive effects. However, ECT has been stigmatized and used as "proof" of psychiatrists' violence and harm to patients due to the media and the antipsychiatry movement[88]. As a result, psychiatrists also experience being morally tainted.

As illustrated above, the psychiatrists' occupational stigma is a complex idea that calls for multidimensional interpretations. Psychiatrists are seen as simultaneously being physically tainted, socially tainted, and morally tainted considering the potentially dangerous work environment, their exposure to and treatment of highly stigmatized populations, and the use of controversial and aggressive treatment methods. Occupational stigma could result in detrimental consequences for psychiatrists including isolation, discrimination, and loss of status and then made itself an indispensable factor to impede the advancement of medical and health services in mental health.

THE MEASUREMENT OF PSYCHIATRISTS' OCCUPATIONAL STIGMA

To date, no occupational stigma scales have been developed for psychiatrists. In such a pertinent quantitative investigation, this can be accomplished by adapting other occupational stigma instruments (see Table 1). There are four different categories of scales that can be used to gauge public stigma toward psychiatrists. One type is that one dimension or more of the scale's items indicates occupational stigma. Richmond *et al*[89] created the psychometrically reliable Trust in Doctors in General (T-DiG) and Trust in the Health Care Team scales (THCT) to assess public trust in medical professionals and healthcare teams. Both the T-DiG and THCT include 29 items, which are from seven dimensions that refer to stigma-based discrimination, communication skills, system trust, loyalty, confidentiality, fairness, and general trust[89]. The stigma-based discrimination dimension contains three items that doctors or people who work in health care would unfairly treat patients with a history of mental illness, HIV, or drug abuse. Although T-DiG and THCT can reflect the public occupational stigma against physicians to some extent, the richness of occupational stigma is not accessible by measuring a single dimension of the scale. Meanwhile, occupational stigma, the complex concept, must be examined from multiple perspectives. The T-DiG and THCT contain only one item, physicians' unfair treatment of patients with a history of mental illness, and can only assess specific aspects of occupational stigma.

The second is to measure patients' occupational stigma against physicians. Fan *et al*[90] developed the Patient Toward Physician Occupational Stigma Scale (PPOSS), which consists of 19 items divided into three dimensions, namely stereotype, prejudice, and discrimination. The cognitive, affective, and behavioral components of occupational stigma are measured respectively[90]. Although the PPOSS was created specifically to assess physicians' occupational stigma, there are significant differences between physicians in different departments regarding the source, type, and extent of occupational stigma[49,52, 91,92]. Psychiatric patients were not chosen as the study subjects during the development of the PPOSS, and items reflecting the psychiatrists' professional characteristics were lacking. As a result, more evidence is needed to determine whether the PPOSS is suitable for assessing patients' occupational stigma toward psychiatrists.

The third is to measure the public's social distance from physicians to examine their stigmatizing attitudes. A key element of psychological distance is social distance, which measures the degree of intimacy between various groups and between people within the same cohort[93]. The Social Distance Scale (SDS) has been utilized as a measurement tool in a study to examine public stigma and public behavioral inclinations toward physicians[94]. However, the SDS was originally designated not to measure occupational stigma but to measure the public distance perception between various nations, ethnic groupings, races, or groups[95]. The concepts of social isolation and occupational stigma are not interchangeable because they have obvious distinctions. Currently, the SDS is employed in research on occupational stigma less frequently, particularly when assessing public stigma toward physicians. Only a small number of studies used the scale[96].

Table 1 Measurement tool of psychiatrists' occupational stigma

Scale title	Target	Content	Item	Dimension
[89]THCT	Public	Measure public trust in medical professionals and health care team	29	7 dimensions: Stigma-based discrimination; communication skills; system trust; loyalty; confidentiality; fairness; general trust
[90]PPOSS	Patients	Measure the cognitive, affective, and behavioral components of occupational stigma	19	3 dimensions: Stereotype (6 items); prejudice (7 items); discrimination (6 items)
[94]SDS	Public	Measure stigmatizing public perceptions of and behavioral inclinations toward the physicians	8	Single dimension
[97]Public attitudes towards psychiatrists' questionnaire	Public	Measure the public's unfavorable views and impressions of psychiatrists' professionalism, mental health, occupational authority and ethical standards	8	Single dimension
[98]OSCS	Practitioners	Measure the stigma awareness of practitioners in the service industry	6	Single dimension
[100]E16-COVID19-S	Practitioners	Measure specific aspects of physician occupational stigma	16	3 dimensions: Personalized stigma (8 items); concerns of disclosure and public attitudes (5 items); negative experiences (3 items)
[101]PSCP	Physicians	Measure perception of COVID-19-induced stigma in healthcare workers	10	2 dimensions: Environmental stigmatization; the perception of personal stigmatization
[103]Self-designed stigma questionnaire	Physicians	Measure mental health stigma	12	Single dimension
[104]DAQ	Medical students	Measure stigmatization of physicians suffering from mental disorders	3	Single dimension
[105]SOSS-D	Doctors	Measure the stigma of occupational stress and burnout among physicians	11	3 dimensions: Perceived structural stigma (5 items); perceived individual stigma (3 items); perceived other related stigma (3 items)
[106]MHPSS	Mental Health Professionals	Measure occupational stress and burnout stigma in mental health professionals	13	4 dimensions: Perceived other stigma (3 items); perceived structural stigma (4 items); personal stigma (3 items);self-stigma (3 items)
[107]PIOSS	Physicians	Measure physicians' identification with negative labels, perceptions of devaluation and discrimination, as well as the denial and disapproval of their own profession	19	3 dimensions: Label identification (5 items); status loss (8 items); career denial (6 items)
[108]FSS	Forensic	Measure internalized occupational stigma	12	2 dimensions: Dangerousness/unpredictability (7 items); responsibility/blame (5 items)
[13]Mental health professionals' questionnaire	Mental health professionals	Measure the perceived associative stigma	4	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale a)	Psychiatrists	Measure perceived stigma in terms of the perception of societal stereotypes	16	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale b)	Psychiatrists	Measure self-stigma in terms of stereotype agreement	16	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale c)	Psychiatrists	Measure perceived stigma in terms of structural discrimination	5	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale d)	Psychiatrists	Measure discrimination experiences	13	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale e)	Psychiatrists	Measure stigma outcomes	5	Single dimension

COVID-19: Coronavirus disease 2019; DAQ: Discriminative attitude questionnaire; FSS: Forensic Stigma Scale; OSCS: Occupational Stigma Consciousness Scale; PIOSS: Physician Internalized Occupational Stigma Scale; PPOSS: Patient Toward Physician Occupational Stigma Scale; PSCP: Perception of Stigma due to COVID-19 in Physicians; SDS: Social Distance Scale; SOSS-D: Stigma of Occupational Stress Scale for Doctors; THCT: Trust in doctors in general and Trust in the health care team scales.

Fourth, a non-standard assessment method was used to examine the public's negative perceptions of psychiatrists. Ta *et al*[97] used a self-designed Public attitudes towards psychiatrists questionnaire with eight items to assess public perceptions of psychiatrists. The questionnaire mainly measured the public's negative attitude and views of psychiatrists' professionalism, mental health, occupational authority and ethical standards[97]. Nevertheless, it is hard to state the reliability and validity of the research results because the questionnaire's reliability and validity were not assessed.

The scales that can be used to measure the self-stigma of psychiatrists could be divided into four categories. The first is the scale used to gauge psychiatrists' sensitivity to stigma. The Occupational Stigma Consciousness Scale (OSCS) is the most frequently used tool in studies on physicians' occupational stigma. The OSCS comprises six one-dimensional items that assess practitioners' perceptions of public stigmatization of their work. However, the OSCS was originally developed based on call center service workers and was primarily used to assess the stigma awareness of practitioners in the service industry[98]. According to the needs of researchers' studies, they appropriately adapted the scale for use in quantitative studies of various occupational stigma in subsequent studies[99]. It should not be ignored that psychiatrists are part of a high-prestige profession that differs significantly from dirty work regarding stigma manifestations and negative consequences.

The second is the scale for measuring specific aspects of physician occupational stigma. Based on the severe acute respiratory syndrome stigma scale, Mostafa *et al*[100] developed the new coronavirus disease 2019 (COVID-19) Stigma Scale (E16-COVID19-S)[100]. Similar to this, Oktar *et al*[101] developed the Perception of Stigma due to COVID-19 in Physicians (PSCP) with 10 items, including two dimensions that are environmental stigma and individual stigma perception[101]. These two scales measure specific components of physicians' occupational stigma, but fail to reflect its full spectrum of connotations.

The stigmatization of occupational stress and burnout among physicians has been the research focus in this field. For instance, Riley *et al*[102] discovered that physicians experience high stigma in mental health, work stress and burnout, manifested as inability to admit vulnerability and insistence on working, even if unwell[102]. A study by Wijeratne *et al*[103] on physicians' mental health stigma found that they tend to conceal their mental health conditions from colleagues and are less likely to seek help because there is a belief that physicians suffering from depression or anxiety disorders are perceived as untrustworthy[103]. This study applied a self-designed 12-item stigma questionnaire as a survey tool, which was not strictly tested for reliability nor validity, but only reported internal consistency coefficient values. Zarzycki *et al*[104] adopted a self-designed Discriminative Attitude Questionnaire (DAQ) to examine medical students' stigmatization of physicians with mental disorders[104]. The DAQ includes only three non-standardized items and is only applicable for assessing stigma regarding mental disorders. Furthermore, Clough *et al*[105] developed the 11-item Stigma of Occupational Stress Scale for Doctors (SOSS-D). There are three dimensions extracted in the SOSS-D including perceived structural stigma, perceived individual stigma, and perceived other related stigma[105]. To measure occupational stress and burnout stigma in mental health professionals, Clough *et al*[106] created the Mental Health Professional Stigma Scale (MHPSS)[106]. There are 17 items total in the MHPSS, which are broken down into four dimensions: Perceived other stigma, perceived structural stigma, personal stigma, and self-stigma. Stigmatizing attitudes, stress and burnout among psychiatrists can pose serious threats to their professional development. However, scales for measuring the stigma of occupational stress and burnout specifically among psychiatrists are lacking and should be developed in future research.

The third part include scales for assessing physicians' internalized occupational stigma. Fan *et al*[107] created a 19-item Physician Internalized Occupational Stigma Scale (PIOSS) divided into three dimensions including label identification, status loss, and career denial. The PIOSS scale is primarily used to evaluate physicians' identification with negative labels, perceptions of devaluation and discrimination, and denial and disapproval of their profession[107]. Besides, Healey *et al*[108] developed the Forensic Stigma Scale (FSS) with 12 items falling into two dimensions that refer to danger/unpredictability and blame/responsibility[108]. Although PIOSS and FSS have strong validity and reliability, the study subject did not include psychiatrists.

Fourth, there is a non-standard tool for assessing the perception of stigma among psychiatrists. A self-designed mental health professional's questionnaire was used in the study by Verhaeghe *et al*[109] Four items comprise the questionnaire, which mainly measures the perceived associative stigma among psychiatrists and other mental health professionals. However, Cronbach's alpha coefficient for the questionnaire was just 0.51 since it had not undergone a rigorous reliability test[109].

Fifth, there is a scale specifically designed to measure the occupational stigma of psychiatrists. The World Psychiatric Association (WPA) has developed specific action plans to reduce the stigma toward psychiatry and psychiatrists. One of the essential tasks is to develop standardized questionnaires[110]. The basic version comprises five scales: (1) Perceived stigma in terms of the perception of societal stereotypes; (2) self-stigma in terms of stereotype agreement; (3) perceived stigma in terms of structural discrimination; (4) discrimination experiences; and (5) stigma outcomes. The scales (1) and (2) consist of 16 items measuring the professionals' competence, professional conduct, and personality, as well as the stigma of psychiatry as a medical specialty and its treatment methods. Scale (3) and scale (5), consisting of five items, assesses the social aspects of stigma and the negative consequences of stigma. Scale (4)

consists of 13 items, assessing experiences made in contact with doctors from other disciplines and experiences made in personal life. The scale developed by the WPA is a valid tool for assessing the internalization of occupational stigma among psychiatrists.

THE INTERVENTION OF PSYCHIATRISTS' OCCUPATIONAL STIGMA

The study of stigma intervention strategies has been the main research subject in the stigma field. To effectively intervene with various demographics and stigma, the approaches used can be cross-referenced[111,112]. In a systematic evaluation of stigma intervention strategies, which included research findings from various countries (low-, middle-, and high-income), stigmatized populations (such as those with AIDS, mental health disorders, and leprosy), intervention targets (such as medical personnel, family members, and community members), and intervention strategies (such as contact, education, and training), the analysis discovered some similarities in the strategies, measures, and intervention outcomes achieved when intervening with different types of stigma[113]. A review of stigma intervention strategies can serve as a theoretical foundation for psychiatrists' occupational stigma intervention practice. Stigma intervention strategies can be roughly classified into six categories.

First, the protest approach is a strategy for the stigmatized community to voice their opinions and express their disapproval through public declarations, media exposure, and stigma-related commercials to minimize stigma[114]. However, protest tactics risk escalating stigma, leading to public conflict and rebellion[115]. Therefore, they are used relatively infrequently. Furthermore, compared to more conventional rallies and demonstrations, the usage of social media platforms on the internet is growing. For instance, rebuttals to stigmatizing attitudes about mental illness are shared on Twitter during Mental Health Awareness Week, an annual effort in May[116]. Similarly, Depression Awareness Week is coordinated on Twitter with the primary objective of lowering the stigma attached to mental illness [117].

Second, educational strategies are applied to alter erroneous beliefs and reduce stigma by delivering accurate information to the intervention target[118]. A few commonly employed techniques are class lectures, anti-stigma training, special lectures, workshops, role plays, case studies, watching instructional videos, reading professional publications, and creating self-reflection reports (see Table 2). In the pertinent literature, more attention is paid to the stigmatization of medical professionals and the general public toward people with mental illnesses. In contrast, relatively few research studies have been conducted on psychiatrists' occupational stigma. Educational strategies effectively change healthcare professionals' attitudes toward patients with mental illnesses and increase contact willingness and frequency[119-122]. Besides that, it is conducive to reducing self-stigma in patients with mental illnesses through education[123]. Moreover, interventions can be implemented in stand-alone educational formats, such as workshops[124] and educational videos[125], or in a combination of formats to achieve more significant results. For example, in Education Not Discrimination[126] and Mental Health First Aid[127], a combination of presentations, videos, action plan ideas, case discussions, and role plays is used.

Third, the contact strategy aims to strengthen relationships with stigmatized people to alleviate adverse stereotypes. In stigma interventions, the contact strategy has been applied most frequently and has produced promising benefits[128]. It is possible to boost intergroup connections and minimize prejudice by increasing the frequency of public contact with stigmatized individuals, especially high-quality contact[129]. According to Corrigan *et al*[130], contact approaches are approximately three times more effective than educational strategies with more prominent and persistent impact[130]. Even short-term exposure has the potential to improve attitudes and understanding about stigma[131] and lower stigma levels[132]. The question of how to accomplish the desired intervention outcomes and guarantee the effectiveness of the contact method has always been the focus of scholars[131]. Corrigan *et al*[133] proposed that the most critical factors influencing the effectiveness of interventions are design, target, staff, message, evaluation and follow-up in five areas[133]. Specifically, the intervention can be delivered face-to-face, with a person with extensive life experience serving as a speaker, designing a program that matches the target audience's characteristics and delivering the intervention through storytelling. After the intervention's completion, evaluation and follow-up of the intervention effects are also required[134].

In terms of forms of intervention, direct and indirect contact are included[135].Direct contact as a promising anti-stigma strategy can improve communication and cooperation between patients with mental illnesses and other patients, as well as between patients and family members and the general public[136]. By increasing contact between health science students and people with mental illnesses in the Co-Production with Dialogue Program for Reducing Stigma, it is possible to significantly reduce public stigma and improve mutual understanding between patients and students[137]. Psychoeducational materials, face-to-face workshops, and interventions based on cognitive behavioral therapy were generally well received in the workplace-based multi-country intervention tackling depression, anxiety, and mental illness-related stigma study[138]. In the "Honest, Open, Proud" project, self-exposure and community-based participatory research were used to reduce self-stigma among individuals with

Table 2 Intervention of education

Strategy	Target	Content	Objective
[119]Education training	Family caregivers of patients with schizophrenia	Teaching related knowledge and skills (90 min/8 sessions)	Reduce stigma toward patients with schizophrenia
[120]Anti-stigma training	Care assistant workers	Financial assistance policy of care assistant workers + mental health knowledge (2 h) + stigma related to mental illness (1 h)	Reduce stigma toward patients with mental illness
[121]Anti-stigma training	Community mental health staff	Two parts: Knowledge introduction + stigma related to mental illness (1 d)	Increase mental health knowledge; Reduce stigma toward patients with mental illness and social distance
[122]Anti-stigma training	Probation officers	Six modules in PPT about overview of severe and persistent mental illnesses; information about key diagnoses and the medications; services associated with those diagnoses	Increase mental health knowledge; Reduce stigma toward mental illness and behavior tendency
[123]NECT	Persons with severe mental illness	20 sessions (1 h): (1) Introduction (1 wk); (2) Psychoeducation (3 wk); (3) Cognitive restructuring (8 wk); and (4) Narrative enhancement (8 wk)	Reduce stigma toward mental illness
[124]Educational workshop	High School Students	Classroom-based workshop: (1) Introduction: Mental illness and public stigma; (2) Education; and (3) Treatment of mental illness and available community resources (1 h)	Reduce stigma toward mental illness
[125]Educational videos	High school students and college students	Educational film (10 min): (1) BMM about mental illness; or (2) RCM advocated by experts	Reduce more stigma in BMM than RCM
[126]END	Medical students	Short lecture; testimonies about the experiences and stigma; role-plays	Increase mental health knowledge; Reduce stigma toward mental illness and behavior tendency
[127]Mental health first aid training	Pharmacy and non-pharmacy students	Identify, understand, and respond to signs of mental illnesses and substance use disorders (8 h); Methods: Videos, role play sessions, action plan creation, discussion, and other interactive activities	Reduce stigma toward mental illness

BMM: Biomedical messages; END: Education not discrimination project; NECT: Narrative enhancement cognitive therapy; PPT: Power point; RCM: Recommended messages.

mental illness[139].

The typical indirect contact method is video contact. Researchers prefer video contact because of its low cost, broad audience reach, reusability, low resource possession, and ease of dissemination[130]. Short video interventions are an essential and effective intervention in studies of depression stigma and help-seeking attitude stigma[140], mental health-related stigma[141], and mental illness stigma[142].

Fourth, comprehensive strategies combine two or all three of the protest, education, and contact strategies. Education and contact strategies are most frequently employed (see Table 3). For instance, Tan *et al*[143] discovered that increasing interaction (direct contact) and attending lectures (education) improved people's attitudes and levels of acceptance toward those who suffer from depression[143]. Furthermore, a three-stage intervention paradigm was subsequently developed by Ahuja *et al*[144]. Specifically, participants in the intervention were required to watch a dance drama to learn about common misconceptions and correct perceptions of mental illness. Then, individuals were asked to listen to an informational lecture and directly communicate with people suffering from mental illness. Hawke *et al*[145] used an indirect intervention strategy, showing the recorded stage play to healthcare providers, college students, people with bipolar disorder and their friends and family members, and the general public. The findings revealed that education and exposure *via* video approach similarly reduced the stigma of bipolar disorder among intervention subjects and had sound delayed effects[145].

Some studies have attempted to integrate anti-stigma education into school curricula. Ma *et al*[146], for example, designed a teaching component covering knowledge, experience, and action, as well as education strategies, direct contact, and indirect contact, to reduce the stigma of mental illness among medical students[146]. Case discussions and systematic curriculum instruction[147,148] can be used to achieve intervention goals[149]. Both educational and direct contact strategies, as well as educational and indirect contact strategies, have demonstrated practical intervention effects[150-168]. However, in a study of an adolescent population, educational strategies alone were superior to combined education and contact strategies in reducing mental illness stigma[165]. The researchers suggest that the young age of the intervention subjects may have contributed to this result and that contact strategies should be used with caution when intervening with adolescents. As a result, more evidence is needed to determine whether the combined strategy is superior to the single intervention strategy in various age groups.

Fifth, systematic intervention strategies emphasize the importance of considering the interplay of factors at different levels when intervening with stigma and integrating different types of intervention

Table 3 Intervention of comprehensive strategies

Strategy	Type	Content	Target	Objective
[143]Lecture	Education + direct contact	Video + personal experience + questions and answers (50 min)	Undergraduate	Increase knowledge of depression and help-seeking willingness
[144]Three-stage intervention paradigm	Education + direct contact + indirect contact	Dance-drama + lectures + direct contact (2 h)	Undergraduate	Increase understanding and tolerance toward patients with mental illness; Decrease negative review, negative labels and social distance toward patients with mental illness
[145]Filmed theatrical intervention based on a personal narrative	Education + indirect contact	Filmed version of a one-woman stage play performed by a recognized educator and speaker on the lived experience of mental illness and recovery (50-min)	Health-care service providers, university students in a health-care-related course, people with BD and their friends and family members and the general public	Decrease stigma toward people with BD among health-care service provider (significant/sustainable); others (more limited)
[146]Course	Education + direct contact + indirect contact	Lecture + watch videos/movie + in-class discussion + direct contact + roleplay + action project (18 wk)	Occupational therapy students	Decrease stigma toward mental illness and social distance
[147]Course	Education + direct contact + indirect contact	Teaching (42 h) + movie (3/4 h) + contact + presentations (2 h) + clinical correlations (6 h)	Medical students	Increase student confidence; Decrease stigma toward mental illness
[148]Course	Education + direct contact + indirect contact	Face-to-face (45 min) + video-based contact (40 min) + educational lecture (90-min)	Medical students	Decrease stigma toward mental illness
[149]Case discussion	Education + direct contact + indirect contact	Document patient strengths and treatment recommendations; Group presentation discussion (10 wk)	Primary care providers	Increase willingness to help and hope for recovery; Decrease negative stereotypes
[150]Course	Education + direct contact	Personal experience + questions and answers (69-90 min)	Pharmacy students	Decrease stigma toward mental illness
[151]Workshop	Education + direct contact	Workshop (4 d): Knowledge teaching + personal experience + questions and answers	Public Health Services administrators	Decrease stigma toward patients with mental illness
[152]Workshop	Education + direct contact	Workshop (1 h): Knowledge teaching + personal experience	Social work students	Decrease stigma toward mental illness
[153]Course	Education + direct contact	Panel discussion (2 h) + visit rehabilitation center + Small group discussion (20 min)	Medical students	Decrease stigma toward patients with mental illness and psychiatry
[154]Curriculum	Education + direct contact	Courses + clinical practice + stigma views and policy (14 d)	Community mental health staff	Increase related knowledge; Decrease stigma
[155]Education program	Education + direct contact	Enhancing contact model: Psychoeducational training (4 wk) + single and group family contact (8 wk)	Family caregivers of persons with schizophrenia	Decrease stigma toward mental illness
[156]Education program	Education + direct contact	Lectures (2 h) + contact with people with lived experience of mental illness (1 h)	Community health and care staff	Decrease stigma toward mental illness
[157]Course	Education + indirect contact	Teaching + videos (3 h)	Psychology students	Improve attitude toward schizophrenia
[158]Virtual program	Education + indirect contact	Three consecutive interventions (14 h/2 d): 2 sessions (2.5 h) + e-contact (3.5 h) + project-based learning (5.5 h)	University students	Decrease stigma toward mental disorders
[159]Educational video	Education + indirect contact	Social contact film with general mental health education (30 min/2 mo intervals in 1 year)	University students	Decrease mental illness-related stigma
[160]Course	Education + indirect contact	Interactive workshop-style sessions (3.5 h/15 wk)	Primary care physicians	Increase skill and confidence; Decrease stigma toward mental illness
[161]Educational	Education +	Video-based contact intervention	Primary care nurses	Improve attitude toward patients with

Video	indirect contact	(VBCI): Elements of psychoeducation and interviews (5 min)		mental illness in short term
[163]Educational video	Education + indirect contact	YouTube videos (5-10 min)	Muslin adults aged 18 and over	Decrease stigma toward mental illness
[164]Lecture	Education + direct contact	Personal experience + Interaction	High school students	Decrease stigma toward mental illness
[165]Education program	Education + direct contact	Educational program (1 d)	Adolescents	Education decreases stigma toward mental illness; Direct contact fails
[166]Course	Education + direct contact	Education with PBL: Problem-based learning model + direct contact	Nursing students	Improve positive attitude toward mental illness
[167]Online focus group	Education + direct contact + indirect contact	Education + relationship strategies + media contact	Senior undergraduate nursing students	Minimize the negative impact on the people they take care of
[168]Sessions	Education + direct contact	Five sessions (3 d)	Caregivers of mental health service users	Improve family relations and understanding of mental illness

BD: Bipolar disorder.

strategies into a unified framework[162]. According to Heijnders and Van Der Meij[169], the effects obtained by employing a single level of intervention strategy or intervening with a single target group are frequently insufficient and necessitate the integration of multiple factors[169]. As a result, Cook *et al* [170] developed a three-level ecosystem model that divides stigma intervention strategies into individual, interpersonal, and structural levels, arguing that interventions at any level can affect the effectiveness of interventions at other levels[170]. Individual-level interventions concentrate on enhancing coping mechanisms used by stigmatized individuals or altering the attitudes and conduct of stigma abusers. By enhancing engagement and contact between the group of stigma abusers and the group being stigmatized, interpersonal interventions aim to reduce intergroup barriers and foster greater mutual understanding. Through the creation of pertinent laws and regulations to lessen prejudice and discrimination, intervention at the structural level is primarily seen from the perspective of the socio-political environment.

Additionally, Heijnders and Van Der Meij[169] suggested a five-level stigma intervention program (individual level, interpersonal level, social level, organizational and institutional level, and governmental level)[169]. In particular, professional counselling and therapy can be used at the individual level to help the stigmatized population cope with stigma; interventions at the interpersonal level concentrate on improving how the stigmatized population interacts with the elements of their environment in order to gain care and support; and interventions at the social level focus on changing public attitudes through education, advocacy, or contact strategies. At the organizational and institutional levels, specialized training or the development of internal systems can be adopted to reduce stigma in a group, organization, or institution; at the government level, interventions focus on the establishment of relevant laws and policies, as well as the use of coercive measures, to reduce stigmatized speech and behavior.

Sixth, increasing researchers have attempted to incorporate psychotherapeutic approaches and techniques into stigma interventions and have achieved promising results (see Table 4). Hong *et al*[171] used mindfulness training to intervene with self-stigma in depressed patients and got excellent and long-lasting results[171]. It was found by Clinton *et al*[172] that Positive Empathy Intervention (imagining positive contact with the stigmatized person and establishing a positive emotional connection) was superior to traditional contact methods in terms of stigma reduction[172]. Cognitive-behavioral Intervention and Wise Intervention have been shown to increase perceived social support and reduce self-stigma in individuals[173,174]. Furthermore, Visual Information Image Interventions [175] and Work Integration[176] assist individuals in gaining correct knowledge, changing perceptions, and enhancing social inclusion, thereby reducing stigma.

Art Therapy is currently widely applied in the work practice of mental health education in schools. When intervening with the stigma of mental illness in adolescents, art therapy methods such as film, drama, and role-playing can be adopted[177,178]. Picture storytelling or fiction writing can enable the individual's indirect contact with an AIDS patient[179]. The Petkari's study[180] discovered that watching a series of movies about mental illness (over 10 wk) accelerated college students' agency, compassion, and proximity toward patients[180]. Acceptance and Commitment Therapy (ACT), based on relational framework theory, has been dubbed the "Third Wave" of behavioral therapy[181]. In interventions for weight stigma[182], substance use disorder stigma[183], and homosexuality stigma [181], ACT has shown significant positive effects. Furthermore, Narrative Therapy[184], Written

Table 4 Other intervention strategies

Strategy	Objective
[171]Positive thinking training	Intervene with self-stigma in depressed patients
[172]Positive empathy intervention	Establish a positive emotional connection with stigmatized person to reduce stigma
[173]Cognitive-behavioral intervention	Reduce self-stigma associated with mental illness
[174]Wise intervention	Increase perceived social support; Reduce personal discrimination
[175]Visual information image intervention	Increase sense of support and engagement; Reduce stigma
[176]Work integration	Reduce perceived stigma of workers with serious mental illness
[177-180]Art therapy	Reduce mental illness stigma of adolescents
ACT	Reduce weight stigma[182], substance use disorder stigma[183], and homosexuality stigma[181]
[184]Narrative Therapy	Reduce the level of stigma for patients with permanent enterostomies
[185]Written expression-based emotional intervention	Reduce negative emotion
[186]Sand tray therapy	Improve the development of self-esteem in sexually abused adolescents
[187]CBGT	Reduce the level of stigma in the population of people living with HIV
[188]Intergenerational choir	Reduce the stigma of Alzheimer's patients and increasing positive attitudes
[189]FSM	Reduce stigma and promote mental health help-seeking behavior

ACT: Acceptance and commitment therapy; CBGT: Compassion-based group therapy; FSM: Fresh start mindset framing.

Expression-based Emotional Intervention[185], Sand Tray Therapy[186], Compassion-Based Group Therapy[187], Intergenerational Choir[188], and Fresh Start Mindset Framing[189] can be used as stigma interventions.

To summarize, in the intervention of psychiatrists' occupational stigma, protest, education, contact, integrated and systematic intervention strategies, and multiple approaches such as positive thinking training, cognitive behavioral therapy, ACT, and art therapy are available to be adopted. In order to achieve optimal results, the appropriate intervention method must be chosen based on the characteristics of the intervention target. It should be noted that while the above intervention strategies have been applied to various types of stigma interventions with positive results, more evidence is needed to support whether the strategies mentioned above are applicable to psychiatrists' occupational stigma interventions and how they can be implemented to achieve significant intervention effects.

DISCUSSION

In summary, previous studies have yielded results regarding the concept, measurement, and intervention of psychiatrists' occupational stigma. Nevertheless, there is room for improvement in this field. This review aimed to elaborate on the thinking and practices of related issues. Therefore, future research should consider improving on the four aspects outlined below.

First, clarify and refine the concept of psychiatrists' occupational stigma. Although various scholars have defined the concept of occupational stigma, related research has focused more on dirty work. Indeed, there is a paucity of research specifically on psychiatrists' occupational stigma. Based on Ashforth and Kreiner's research[43], this paper elaborates on the sources and dimensions of psychiatrists' occupational stigma, namely physically, socially, and morally. This theoretical framework allows for the development of relevant quantitative research and intervention studies. Although Ashforth and Kreiner's concept[43] of occupational stigma has gained widespread acceptance, it is not formally classified other than according to the work content of an occupation. As such, it does not reflect the cognitive, emotional or behavioral components of occupational stigma. In addition, the understanding of occupational stigma is not consistent across disciplines. Future research should combine theories from other disciplines (including individual cognitive models, social identity theory, self-verification perspectives, and other conceptual models) to further explore and extend the conceptual connotations of psychiatrists' occupational stigma. Furthermore, the theoretical framework of occupational stigma should be combined with statistical analysis to determine the multiple dimensions of psychiatrists' occupational stigma. This study provides such a theoretical basis for future measurement and intervention studies.

Second, develop specific tools to measure psychiatrists' occupational stigma. Lately, as public awareness of the harm of occupational stigma has increased, relevant measurement tools have been refined. However, some existing instruments are not sufficiently reliable nor valid, and tools specifically designed to assess psychiatrists' occupational stigma are lacking. As no consensus exists on the conceptual and operationalization scope of occupational stigma, there is inconsistency in developing relevant dimensional and measurement scales. Furthermore, most tools lack rigorous cross-cultural consistency. Future research should consider the following: (1) Define the dimensional scale and classification of psychiatrists' occupational stigma based on a multidisciplinary synthesis; (2) Develop special assessment tools for different stigma types (public stigma and self-stigma) and cohorts (psychiatrists, psychiatric students, mental illness patients, patients' families, and the public); (3) Expand the sample scope across different races, countries and age ranges to determine the impact of cross-cultural backgrounds and generational effects on the results; and (4) Based on traditional self-reporting questionnaires, adopt more indirect survey methods such as virtual reality technology, videos, or games allowing for measurement methods with higher ecological validity and aligned to life situations that yield a realistic and contextualized understanding.

Third, improve intervention strategies for psychiatrists' occupational stigma. Intervention strategies specifically applicable to psychiatrists' occupational stigma are currently lacking. Initially, when intervening for psychiatrists' occupational stigma, other types of stigma intervention strategies may be considered. However, undoubtedly these could lead to biases in the effectiveness of the intervention. Therefore, future studies should test whether existing intervention strategies are suitable for psychiatrists. Follow-up horizontal comparison and longitudinal studies can be conducted on the effects of the three common intervention strategies (protest, education, and contact), as well as integrated, systematic, or other strategies, seeking to find the most appropriate traditional intervention strategies and setting for psychiatrists. It is necessary to acknowledge that stigma may exacerbate or impede such processes as psychological[190,191] and behavioral responses[192,193] or social relationships, intensifying stress and burnout that could result in mental health disorders. Some studies have demonstrated that educational interventions which provide in-depth information about the negative effects of stigma on mental health professionals can be effective in decreasing stigma, especially for general healthcare professionals with little or no formal mental health training. Alternatively, future research should develop unique, simple, and effective intervention strategies tailored to the characteristics of psychiatrists. Combining intervention studies with experimental studies could identify simple and accessible ways to reduce occupational public stigma directed toward, and self-stigma experienced by, psychiatrists. Importantly also consider that the effects of a particular intervention may not be uniform among psychiatrists from different countries, cultural backgrounds, or years of practice. Thus, when formulating intervention strategies, full consideration should be given to differences in intervention targets.

Fourth, identify cross-cultural consistency or differences in psychiatrists' occupational stigma. Self-evidently, psychiatrists' occupational stigma can vary culturally. Future research should explore the consistency or differences in occupational stigma concepts, measurements, and interventions among psychiatrists in cross-cultural settings. For example, in Chinese culture, traditional ideas conveyed across millennia, such as Confucianism, Taoism, Buddhism, and folklore, have influenced Chinese thinking and behavior towards self-regulation; this combined with strong family values and a face-saving culture, deems mental illness as both a personal sin and a family shame[194]. Other regions may have different stigma levels toward mental illness[195], so cultural traditions may influence the inception of psychiatrists' occupational stigma. Is it possible that perceptions of psychiatrists' occupational stigma differ across cultures? Dose this influence the measurement and treatment of psychiatrists' occupational stigma? Such interrogations have yet to be confirmed through in-depth research.

LIMITATIONS

It should be acknowledged that there were certain deficiencies in the process of screening and synthesizing many studies in this literature review. First, the selection criterion, which only considered English and French literature, was limiting. Therefore, it is possible that relevant studies that satisfied other inclusion criteria were excluded. Thus, overall integrity is somewhat lacking. Second, the literature search was carried out by both professors and students. Irrelevant studies, duplicates, or those arising from incorrect search results were excluded. However, given the excessive literature search results, no secondary duplication test was undertaken. Therefore, it is impossible to determine whether excluded studies should have been included, indicating a lack of rigor. Finally, this review was based on the authors' analyses and synthesis of the literature; although the study seeks to remain objective, it contains some subjectivity.

CONCLUSION

By surveying the existing literature, this literature review has proposed a theoretical reference of the concept, measurement, and intervention methods for psychiatrists' occupational stigma. Psychiatrists' occupational stigma is a complex concept that should be interpreted in multiple dimensions. Psychiatrists are associated with three types of stigma (physical, social, and moral taint) because of the dangers of their work environment, their exposure to and treatment of high-stigma groups, or their use of controversial or aggressive treatments. Currently, there is no occupational stigma scale applicable specifically to psychiatrists. Relevant quantitative research could achieve this by adapting other occupational stigma scales. Table 1 summarizes eight possible categories of occupational stigma measurement tools for psychiatrists, including four types for public stigma and another four for self-stigma. Currently, there are few studies on occupational stigma interventions for psychiatrists. Therefore, a theoretical reference for identifying relevant intervention practices for psychiatrists' occupational stigma is required. This study has classified such stigma intervention strategies into six categories: Protest, education (Table 2), contact, comprehensive strategies (Table 3), systemic strategies, and means of incorporating psychotherapeutic approaches (Table 4).

Given that research on psychiatrists' occupational stigma has received insufficient attention and discussion in the academic community, this study provided a theoretical basis and support for future practical research. The theoretical significance of this review lies in that it refines the concept and structure of psychiatrists' occupational stigma, expands the general research field of occupational stigma, and encourages the mutual discussion of multi-disciplinary occupational stigma theories. This study further outlines relevant empirical research for the development of specialized measurement tools and creative implementations of effective interventions to reduce psychiatrists' occupational stigma, thereby promoting the healthy development of psychiatry and physician-patient relationships.

FOOTNOTES

ORCID number: Xiao-Li Shi 0000-0001-5248-9299; Lu-Yao Li 0000-0002-4364-1751; Zhi-Guang Fan 0000-0001-9959-4432.

REFERENCES

1   **Kreiner G**, Mihelcic CA, Mikolon S. Stigmatized Work and Stigmatized Workers. *Annu Rev Organ Psychol Organ Behav* 2022; **9**: 95-120 [DOI: 10.1146/annurev-orgpsych-012420-091423]

2   **Hughes EC**. Men and their work. Quid Pro, LLC., 1958

3   **Kreiner GE**, Ashforth BE, Sluss DM. Identity Dynamics in Occupational Dirty Work: Integrating Social Identity and System Justification Perspectives. *Organ Sci* 2006; **17**: 619-636 [DOI: 10.1287/orsc.1060.0208]

4   **Link BG**, Phelan JC. Conceptualizing Stigma. *Annu Rev Sociol* 2001; **27**: 363-385 [DOI: 10.1146/annurev.soc.27.1.363]

5   **Fujishiro K**, Xu J, Gong F. What does "occupation" represent as an indicator of socioeconomic status?: exploring occupational prestige and health. *Soc Sci Med* 2010; **71**: 2100-2107 [PMID: 21041009 DOI: 10.1016/j.socscimed.2010.09.026]

6   **Feingold JH**, Drossman DA. Deconstructing stigma as a barrier to treating DGBI: Lessons for clinicians. *Neurogastroenterol Motil* 2021; **33**: e14080 [PMID: 33484225 DOI: 10.1111/nmo.14080]

7   **Sharma S**, Lal Gautam P, Sharma S, Kaur A, Bhatia N, Singh G, Kaur P, Kumar A. Questionnaire-based Evaluation of Factors Leading to Patient-physician Distrust and Violence against Healthcare Workers. *Indian J Crit Care Med* 2019; **23**: 302-309 [PMID: 31406431 DOI: 10.5005/jp-journals-10071-23203]

8   **Gaebel W**, Zäske H, Zielasek J, Cleveland HR, Samjeske K, Stuart H, Arboleda-Florez J, Akiyama T, Baumann AE, Gureje O, Jorge MR, Kastrup M, Suzuki Y, Tasman A, Fidalgo TM, Jarema M, Johnson SB, Kola L, Krupchanka D, Larach V, Matthews L, Mellsop G, Ndetei DM, Okasha TA, Padalko E, Spurgeoun JA, Tyszkowska M, Sartorius N. Stigmatization of psychiatrists and general practitioners: results of an international survey. *Eur Arch Psychiatry Clin Neurosci* 2015; **265**: 189-197 [PMID: 25190351 DOI: 10.1007/s00406-014-0530-8]

9   **Catthoor K**, Hutsebaut J, Schrijvers D, De Hert M, Peuskens J, Sabbe B. Preliminary study of associative stigma among trainee psychiatrists in Flanders, Belgium. *World J Psychiatry* 2014; **4**: 62-68 [PMID: 25250223 DOI: 10.5498/wjp.v4.i3.62]

10   **Lai JYM**, Chan KW, Lam LW. Defining who you are not: The roles of moral dirtiness and occupational and organizational disidentification in affecting casino employee turnover intention. *J Bus Res* 2013; **66**: 1659-1666 [DOI: 10.1016/j.jbusres.2012.12.012]

11   **Baran BE**, Rogelberg SG, Carello Lopina E, Allen JA, Spitzmüller C, Bergman M. Shouldering a silent burden: The toll of dirty tasks. *Hum Relat* 2012; **65**: 597-626 [DOI: 10.1177/0018726712438063]

12   **Huang B**, Ma L, Huang L. My Work Is Meaningless: The Consequences of Perceived Occupational Stigma for Employees in High-Prestige Occupations. *Front Psychol* 2022; **13**: 715188 [PMID: 35572310 DOI: 10.3389/fpsyg.2022.715188]

13   **Daniela RE**, Andrea S, Peter F. Psychiatrists' self-stigma, the DGPPN guideline for psychosocial interventions, and contemporary treatment strategies. *Eur Arch Psychiatry Clin Neurosci* 2015; **265**: 171-2 [PMID: 25708457 DOI: 10.1007/s00406-015-0586-0]

14   **Yao H**, Wang P, Tang YL, Liu Y, Liu T, Liu H, Chen Y, Jiang F, Zhu J. Burnout and job satisfaction of psychiatrists in China: a nationwide survey. *BMC Psychiatry* 2021; **21**: 593 [PMID: 34819029 DOI: 10.1186/s12888-021-03568-6]

15   **Shanafelt TD**, West CP, Sinsky C, Trockel M, Tutty M, Satele DV, Carlasare LE, Dyrbye LN. Changes in Burnout and Satisfaction With Work-Life Integration in Physicians and the General US Working Population Between 2011 and 2017. *Mayo Clin Proc* 2019; **94**: 1681-1694 [PMID: 30803733 DOI: 10.1016/j.mayocp.2018.10.023]

16   **Zhang Y**, Feng X. The relationship between job satisfaction, burnout, and turnover intention among physicians from urban state-owned medical institutions in Hubei, China: a cross-sectional study. *BMC Health Serv Res* 2011; **11**: 235 [PMID: 21943042 DOI: 10.1186/1472-6963-11-235]

17   **Tateno M**, Jovanović N, Beezhold J, Uehara-Aoyama K, Umene-Nakano W, Nakamae T, Uchida N, Hashimoto N, Kikuchi S, Wake Y, Fujisawa D, Ikari K, Otsuka K, Takahashi K, Okugawa G, Watanabe N, Shirasaka T, Kato TA. Suicidal ideation and burnout among psychiatric trainees in Japan. *Early Interv Psychiatry* 2018; **12**: 935-937 [PMID: 28786526 DOI: 10.1111/eip.12466]

18   **West CP**, Dyrbye LN, Shanafelt TD. Physician burnout: contributors, consequences and solutions. *J Intern Med* 2018; **283**: 516-529 [PMID: 29505159 DOI: 10.1111/joim.12752]

19   **Patel RS**, Bachu R, Adikey A, Malik M, Shah M. Factors Related to Physician Burnout and Its Consequences: A Review. *Behav Sci (Basel)* 2018; **8** [PMID: 30366419 DOI: 10.3390/bs8110098]

20   **Pinel EC**, Paulin N. Stigma Consciousness at Work. *Basic Appl Soc Psychol* 2005; **27**: 345-352 [DOI: 10.1207/s15324834basp2704_7]

21   Wildes VJ. Stigma in Food Service Work: How it Affects Restaurant Servers' Intention to Stay in the Business or Recommend a Job to Another. Tour Hosp Res 2005; 5: 213-233 DOI:10.1057/palgrave.thr.6040022

22   **Jiang F**, Hu L, Rakofsky J, Liu T, Wu S, Zhao P, Hu G, Wan X, Liu H, Liu Y, Tang YL. Sociodemographic Characteristics and Job Satisfaction of Psychiatrists in China: Results From the First Nationwide Survey. *Psychiatr Serv* 2018; **69**: 1245-1251 [PMID: 30301449 DOI: 10.1176/appi.ps.201800197]

23   **Liang D**, Mays VM, Hwang WC. Integrated mental health services in China: challenges and planning for the future. *Health Policy Plan* 2018; **33**: 107-122 [PMID: 29040516 DOI: 10.1093/heapol/czx137]

24   **Lambert TW**, Turner G, Fazel S, Goldacre MJ. Reasons why some UK medical graduates who initially choose psychiatry do not pursue it as a long-term career. *Psychol Med* 2006; **36**: 679-684 [PMID: 16426488 DOI: 10.1017/S0033291705007038]

25   **Maidment R**, Livingston G, Katona C, McParland M, Noble L. Change in attitudes to psychiatry and intention to pursue psychiatry as a career in newly qualified doctors: a follow-up of two cohorts of medical students. *Med Teach* 2004; **26**: 565-569 [PMID: 15763837 DOI: 10.1080/01421590410001711562]

26   **Ndetei DM**, Khasakhala L, Ongecha-Owuor F, Kuria M, Mutiso V, Syanda J, Kokonya D. Attitudes toward psychiatry: a survey of medical students at the University of Nairobi, Kenya. *Acad Psychiatry* 2008; **32**: 154-159 [PMID: 18349338 DOI: 10.1176/appi.ap.32.2.154]

27   **Niaz U**, Hassan S, Hussain H, Saeed S. Attitudes towards Psychiatry in Pre-Clinical and Post-Clinical Clerkships in Different Medical Colleges of Karachi. *Pak J Med Sci* 2003; **19**: 253-263

28   **Niedermier JA**, Bornstein R, Brandemihl A. The junior medical student psychiatry clerkship: curriculum, attitudes, and test performance. *Acad Psychiatry* 2006; **30**: 136-143 [PMID: 16609120 DOI: 10.1176/appi.ap.30.2.136]

29   **Holmes D**, Tumiel-Berhalter LM, Zayas LE, Watkins R. "Bashing" of medical specialties: students' experiences and recommendations. *Fam Med* 2008; **40**: 400-406 [PMID: 18773777]

30   **Motlová LB**, Janoušková M, Formánek T, Goetz M, Holub D, Hubeňák J, Kašpárek T, Látalová K, Papežová H, Světlák M, Šilhán P, Trančík P, Vevera J, Balon R. Medical Students' Career Choice and Attitudes Toward Psychiatry: Case of the Czech Republic. *Acad Psychiatry* 2020; **44**: 751-755 [PMID: 33000447 DOI: 10.1007/s40596-020-01311-z]

31   **Cutler JL**, Harding KJ, Mozian SA, Wright LL, Pica AG, Masters SR, Graham MJ. Discrediting the notion "working with 'crazies' will make you 'crazy'": addressing stigma and enhancing empathy in medical student education. *Adv Health Sci Educ Theory Pract* 2009; **14**: 487-502 [PMID: 18766453 DOI: 10.1007/s10459-008-9132-4]

32   **Lindsey W**, John S, Erick M. Factors Influencing Medical School Graduates Toward a Career in Psychiatry: Analysis from the 2011–2013 Association of American Medical Colleges Graduation Questionnaire. *Acad Psychiatry* 2015; **40**: 255-260 [PMID: 25697263 DOI: 10.1007/s40596-015-0287-z]

33   **Balon R**, Franchini GR, Freeman PS, Hassenfeld IN, Keshavan MS, Yoder E. Medical Students' Attitudes and Views of Psychiatry: 15 Years Later. *Acad Psychiatry* 1999; **23**: 30-36 [DOI: 10.1007/BF03340033]

34   **Möller-Leimkühler AM**, Möller HJ, Maier W, Gaebel W, Falkai P. EPA guidance on improving the image of psychiatry. *Eur Arch Psychiatry Clin Neurosci* 2016; **266**: 139-154 [PMID: 26874959 DOI: 10.1007/s00406-016-0678-5]

35   **Sun KS**, Lam TP, Lam KF, Lo TL. Barriers and facilitators for psychiatrists in managing mental health patients in Hong Kong-Impact of Chinese culture and health system. *Asia Pac Psychiatry* 2018; **10** [PMID: 28371455 DOI: 10.1111/appy.12279]

36   **Passmore K**, Leung WC. Defensive practice among psychiatrists: a questionnaire survey. *Postgrad Med J* 2002; **78**: 671-673 [PMID: 12496324 DOI: 10.1136/pmj.78.925.671]

37   **Reuveni I**, Pelov I, Reuveni H, Bonne O, Canetti L. Cross-sectional survey on defensive practices and defensive behaviours among Israeli psychiatrists. *BMJ Open* 2017; **7**: e014153 [PMID: 28320795 DOI: 10.1136/bmjopen-2016-014153]

38   **Studdert DM**, Mello MM, Sage WM, DesRoches CM, Peugh J, Zapert K, Brennan TA. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. *JAMA* 2005; **293**: 2609-2617 [PMID: 15928282 DOI: 10.1001/jama.293.21.2609]

39   **Beale C**. Magical thinking and moral injury: exclusion culture in psychiatry. *BJPsych Bull* 2022; **46**: 16-19 [PMID: 34517935 DOI: 10.1192/bjb.2021.86]

40   **Helingoe KE**, Cullum S, Ng L. Stigma in Consultation Liaison Psychiatry: A Qualitative Study of Trainee Psychiatrists. *Australas Psychiatry* 2022; **30**: 658-662 [PMID: 35139666 DOI: 10.1177/10398562211064221]

41   **Ashforth BE**, Kreiner GE. Dirty Work and Dirtier Work: Differences in Countering Physical, Social, and Moral Stigma. *Manag Organ Rev* 2014; **10**: 81-108 [DOI: 10.1111/more.12044]

42   **Ashforth BE**, Kreiner GE, Clark MA, Fugate M. Normalizing Dirty Work: Managerial Tactics for Countering Occupational Taint. *Acad Manage J* 2007; **50**: 149-174 [DOI: 10.5465/amj.2007.24162092]

43   **Ashforth BE**, Kreiner GE. 'How Can You Do It?': Dirty Work and the Challenge of Constructing a Positive Identity. Acad Manage Rev 1999; 24: 413 [DOI: 10.2307/259134]

44   **Benjamin O**, Bernstein D, Motzafi-Haller P. Emotional Politics in Cleaning Work: The Case of Israel. *Hum Relat* 2011; **64**: 337-357 [DOI: 10.1177/0018726710378383]

45   **Carden P**. Rising from the Dead: Delimiting Stigma in the Australian Funeral Industry. *Health Sociol Rev* 2001; **10**: 79-87 [DOI: 10.5172/hesr.2001.10.2.79]

46   **Johnson CC**, Vega L, Kohalmi AL, Roth JC, Howell BR, Van Hasselt VB. Enhancing Mental Health Treatment for the Firefighter Population: Understanding Fire Culture, Treatment Barriers, Practice Implications, and Research Directions. *Prof Psychol Res Pract* 2020; **51**: 304-311 [DOI: 10.1037/pro0000266]

47   **Maibvise C**, Shongwe M, Jele V, Dlamini P, Chiviya W. Perceptions about tuberculosis and perceived tuberculosis-related stigma and associated factors among the mining community in Eswatini. *Afr Health Sci* 2022; **22**: 551-559 [PMID: 36032435 DOI: 10.4314/ahs.v22i1.64]

48   **Tracy SJ**. The Construction of Correctional Officers: Layers of Emotionality behind Bars. *Qual Inq* 2004; **10**: 509-533 [DOI: 10.1177/1077800403259716]

49   **Lohiniva AL**, Kamal W, Benkirane M, Numair T, Abdelrahman M, Saleh H, Zahran A, Talaat M, Kandeel A. HIV Stigma Toward People Living With HIV and Health Providers Associated With Their Care: Qualitative Interviews With Community Members in Egypt. *J Assoc Nurses AIDS Care* 2016; **27**: 188-198 [PMID: 26718817 DOI: 10.1016/j.jana.2015.11.007]

50   **Lim N**, Paul AM. Stigma on a Spectrum: Differentiated Stigmatization of Migrant Domestic Workers' Romantic Relationships in Singapore. *Gend Place Cult* 2021; **28**: 22-44 [DOI: 10.1080/0966369X.2019.1710474]

51   **Li Y**, Song Y, Wang M, Huan T-C (T. C.). The Influence of Tour Guides' Service Quality on Tourists' Tour Guide Stigma Judgment: An Asian Perspective. *J Hosp Tour Manag* 2021; **48**: 551-560 [DOI: 10.1016/j.jhtm.2021.08.011]

52   **Aniteye P**, O'Brien B, Mayhew SH. Stigmatized by association: challenges for abortion service providers in Ghana. *BMC Health Serv Res* 2016; **16**: 486 [PMID: 27612453 DOI: 10.1186/s12913-016-1733-7]

53   **Stardust Z**, Treloar C, Cama E, Kim J. 'I Wouldn't Call the Cops if I was being Bashed to Death': Sex Work, Whore Stigma and the Criminal Legal System. *Int J Crime Justice Soc Democr* 2021; **10** [DOI: 10.5204/ijcjsd.1894]

54   **Wang S**. Intimate Situations, and the Circulation Of Same-Sex Affect: Monetizing Affective Encounters on Blued. *Sexualities* 2020; **23**: 934-950 [DOI: 10.1177/1363460719872724]

55   **Vines M**, Linders A. The Dirty Work of Poker: Impression Management and Identity. *Deviant Behav* 2016; **37**: 1064-1076 [DOI: 10.1080/01639625.2016.1169740]

56   **Stenger S**, Roulet TJ. Pride Against Prejudice? The Stakes of Concealment and Disclosure of a Stigmatized Identity for Gay and Lesbian Auditors. *Work Employ Soc* 2018; **32**: 257-273 [DOI: 10.1177/0950017016682459]

57   **Zhang R**, Wang MS, Toubiana M, Greenwood R. Stigma Beyond Levels: Advancing Research on Stigmatization. *Acad Manag Ann* 2021; **15**: 188-222 [DOI: 10.5465/annals.2019.0031]

58   **Katschnig H**. Psychiatry's contribution to the public stereotype of schizophrenia: Historical considerations. *J Eval Clin Pract* 2018; **24**: 1093-1100 [PMID: 30112785 DOI: 10.1111/jep.13011]

59   **Pescosolido BA**, Manago B, Monahan J. Evolving Public Views On The Likelihood Of Violence From People With Mental Illness: Stigma And Its Consequences. *Health Aff (Millwood)* 2019; **38**: 1735-1743 [PMID: 31589533 DOI: 10.1377/hlthaff.2019.00702]

60   **Terkelsen TB**, Larsen IB. Fear, danger and aggression in a Norwegian locked psychiatric ward: Dialogue and ethics of care as contributions to combating difficult situations. *Nurs Ethics* 2016; **23**: 308-317 [PMID: 25552587 DOI: 10.1177/0969733014564104]

61   **Kelly EL**, Fenwick K, Brekke JS, Novaco RW. Well-Being and Safety Among Inpatient Psychiatric Staff: The Impact of Conflict, Assault, and Stress Reactivity. *Adm Policy Ment Health* 2016; **43**: 703-716 [PMID: 26377816 DOI: 10.1007/s10488-015-0683-4]

62   **Chen Y**, Wang P, Zhao L, He Y, Chen N, Liu H, Liu Y, Liu T, Tang YL, Jiang F, Zhu J. Workplace Violence and Turnover Intention Among Psychiatrists in a National Sample in China: The Mediating Effects of Mental Health. *Front Psychiatry* 2022; **13**: 855584 [PMID: 35782425 DOI: 10.3389/fpsyt.2022.855584]

63   **Alhassan RK**, Poku KA.   Experiences of Frontline Nursing Staff on Workplace Safety and Occupational Health Hazards in Two Psychiatric Hospitals in Ghana BMC Public Health 2018; 18: 701 [PMID: 29875015 DOI: 10.1186/s12889-018-5620-5]

64   **Eisele F**, Flammer E, Steinert T. Incidents of aggression in German psychiatric hospitals: Is there an increase? *PLoS One* 2021; **16**: e0245090 [PMID: 33400702 DOI: 10.1371/journal.pone.0245090]

65   **Kılınçel O**, Erzin G, Kılınçel Ş, Hun Şenol S, Ceylan D, Acar M, Gürcan A, Çapraz N. Profile of Young Psychiatrists: A cross-sectional survey study from Turkey (eng). *J Clin Psychiatry* 2021; **24**: 278-287 [DOI: 10.5505/kpd.2021.15428]

66   **Farid Ali A**, Khalid AS, Muhammad Ajmal Z. Violence Against Medical Staff: Prevalence and Effects of Violence Against Psychiatrists in Kuwait. *KMJ-Kuwait Med J* 2009; 41: 322-326

67   **Lin X**, Rosenheck R, Sun B, Xie G, Zhong G, Tan C, Li Z, Yu M, He H. Associative stigma experienced by mental health professionals in China and the United States. *Soc Psychiatry Psychiatr Epidemiol* 2019; **54**: 745-753 [PMID: 30542960 DOI: 10.1007/s00127-018-1643-6]

68   **Shibre T**, Negash A, Kullgren G, Kebede D, Alem A, Fekadu A, Fekadu D, Madhin G, Jacobsson L. Perception of stigma among family members of individuals with schizophrenia and major affective disorders in rural Ethiopia. *Soc Psychiatry Psychiatr Epidemiol* 2001; **36**: 299-303 [PMID: 11583460 DOI: 10.1007/s001270170048]

69   **Ebsworth SJ**, Foster JLH. Public perceptions of mental health professionals: stigma by association? *J Ment Health* 2017; **26**: 431-441 [PMID: 27596719 DOI: 10.1080/09638237.2016.1207228]

70   **Rüsch N**, Angermeyer MC, Corrigan PW. Mental illness stigma: concepts, consequences, and initiatives to reduce stigma. *Eur Psychiatry* 2005; **20**: 529-539 [PMID: 16171984 DOI: 10.1016/j.eurpsy.2005.04.004]

71   **Corrigan PW**, Miller FE.   Shame, Blame, and Contamination: A Review of the Impact of Mental Illness Stigma on Family Members. J Ment Health 2004; 13: 537-548 [DOI: 10.1080/09638230400017004]

72   **Rössler W**. The stigma of mental disorders: A millennia-long history of social exclusion and prejudices. *EMBO Rep* 2016; **17**: 1250-1253 [PMID: 27470237 DOI: 10.15252/embr.201643041]

73   **Zolezzi M**, Alamri M, Shaar S, Rainkie D. Stigma associated with mental illness and its treatment in the Arab culture: A systematic review. *Int J Soc Psychiatry* 2018; **64**: 597-609 [PMID: 30019976 DOI: 10.1177/0020764018789200]

74   **Lloyd CEM**. Contending with Spiritual Reductionism: Demons, Shame, and Dividualising Experiences Among Evangelical Christians with Mental Distress. *J Relig Health* 2021; **60**: 2702-2727 [PMID: 33991287 DOI: 10.1007/s10943-021-01268-9]

75   **Ciftci A**, Jones N, Corrigan PW.   Mental Health Stigma in the Muslim Community. J Muslim Ment Health 2013; 7 [DOI: 10.3998/jmmh.10381607.0007.102]

76   **Hwang K-K**, Han K-H.   Face and Morality in Confucian society. In: Bond MH, editor. Oxford Handbook of Chinese Psychology. 1st ed. Oxford University Press, 2012: 479-498 [DOI: 10.1093/oxfordhb/9780199541850.013.0029]

77   **Yang LH**, Kleinman A. 'Face' and the embodiment of stigma in China: the cases of schizophrenia and AIDS. *Soc Sci Med* 2008; **67**: 398-408 [PMID: 18420325 DOI: 10.1016/j.socscimed.2008.03.011]

78   **Thornicroft G**, Brohan E, Rose D, Sartorius N, Leese M; INDIGO Study Group. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. *Lancet* 2009; **373**: 408-415 [PMID: 19162314 DOI: 10.1016/S0140-6736(08)61817-6]

79   **Kudva KG**, El Hayek S, Gupta AK, Kurokawa S, Bangshan L, Armas-Villavicencio MVC, Oishi K, Mishra S, Tiensuntisook S, Sartorius N. Stigma in mental illness: Perspective from eight Asian nations. *Asia Pac Psychiatry* 2020; **12**: e12380 [PMID: 31922363 DOI: 10.1111/appy.12380]

80   **Völlm B**, Nedopil N, editor.   The Use of Coercive Measures in Forensic Psychiatric Care: Legal, Ethical and Practical Challenges. Switzerland: Springer Cham, 2016 [DOI: 10.1007/978-3-319-26748-7]

81   **McLaughlin P**, Giacco D, Priebe S. Use of Coercive Measures during Involuntary Psychiatric Admission and Treatment Outcomes: Data from a Prospective Study across 10 European Countries. *PLoS One* 2016; **11**: e0168720 [PMID: 28033391 DOI: 10.1371/journal.pone.0168720]

82   **Teichert M**, Schäfer I, Lincoln TM. [Where there's a Will, there's a Way? A nationwide Online-Survey of Psychiatrists about the Use of Alternatives to Coercive Measures]. *Psychiatr Prax* 2016; **43**: 101-106 [PMID: 25526502 DOI: 10.1055/s-0034-1387431]

83   **Gowda GS**, Lepping P, Ray S, Noorthoorn E, Nanjegowda RB, Kumar CN, Math SB. Clinician attitude and perspective on the use of coercive measures in clinical practice from tertiary care mental health establishment - A cross-sectional study. *Indian J Psychiatry* 2019; **61**: 151-155 [PMID: 30992609 DOI: 10.4103/psychiatry.IndianJPsychiatry_336_18]

84   **Voskes Y**, Evenblij K, Noorthoorn E, Porz R, Widdershoven G. [Moral case deliberation about coercion in psychiatry. Dilemmas, value and implementation]. *Psychiatr Prax* 2014; **41**: 364-370 [PMID: 25295977 DOI: 10.1055/s-0034-1370292]

85   **Hui A**, Middleton H, Völlm B. Coercive Measures in Forensic Settings: Findings from the Literature. *Int J Forensic Ment Health* 2013; **12**: 53-67 [DOI: 10.1080/14999013.2012.740649]

86   **Ma ML**, He LP. Electroconvulsive therapy plays an irreplaceable role in treatment of major depressive disorder. *World J Clin Cases* 2022; **10**: 5515-5517 [PMID: 35812666 DOI: 10.12998/wjcc.v10.i16.5515]

87   **Gong J**, Cui LB, Zhao YS, Liu ZW, Yang XJ, Xi YB, Liu L, Liu P, Sun JB, Zhao SW, Liu XF, Jia J, Li P, Yin H, Qin W. The correlation between dynamic functional architecture and response to electroconvulsive therapy combined with antipsychotics in schizophrenia. *Eur J Neurosci* 2022; **55**: 2024-2036 [PMID: 35388553 DOI: 10.1111/ejn.15664]

88   **Bahji A**. The Rise, Fall, and Resurgence of Electroconvulsive Therapy. *J Psychiatr Pract* 2022; **28**: 440-444 [PMID: 36355582 DOI: 10.1097/PRA.0000000000000666]

89   **Richmond J**, Boynton MH, Ozawa S, Muessig KE, Cykert S, Ribisl KM. Development and Validation of the Trust in My Doctor, Trust in Doctors in General, and Trust in the Health Care Team Scales. *Soc Sci Med* 2022; **298**: 114827 [PMID: 35255277 DOI: 10.1016/j.socscimed.2022.114827]

90   **Fan Z**, Chen H, Wu H, Zhang X. Patient Toward Physician Occupational Stigma Scale: Development of the Chinese Version. *Psychol Res Behav Manag* 2022; **15**: 2117-2127 [PMID: 35983020 DOI: 10.2147/PRBM.S375032]

91   **Dempsey B**, Favier M, Mullally A, Higgins MF. Exploring providers' experience of stigma following the introduction of

more liberal abortion care in the Republic of Ireland. *Contraception* 2021; **104**: 414-419 [PMID: 33864811 DOI: 10.1016/j.contraception.2021.04.007]

92   **Uvais NA**, Shihabudheen P, Hafi NAB. Perceived Stress and Stigma Among Doctors Working in COVID-19-Designated Hospitals in India. *Prim Care Companion CNS Disord* 2020; **22** [PMID: 32731315 DOI: 10.4088/PCC.20br02724]

93   **Low LF**, Purwaningrum F. Negative stereotypes, fear and social distance: a systematic review of depictions of dementia in popular culture in the context of stigma. *BMC Geriatr* 2020; **20**: 477 [PMID: 33203379 DOI: 10.1186/s12877-020-01754-x]

94   **Shiu C**, Chen WT, Hung CC, Huang EP, Lee TS. COVID-19 stigma associates with burnout among healthcare providers: Evidence from Taiwanese physicians and nurses. *J Formos Med Assoc* 2022; **121**: 1384-1391 [PMID: 34654583 DOI: 10.1016/j.jfma.2021.09.022]

95   **Lucas J**, Phelan J. Influence and Social Distance Consequences Across Categories of Race and Mental Illness. *Soc Ment Health* 2018; **9**: 215686931876112 [DOI: 10.1177/2156869318761125]

96   **Crowley F**, Doran J. COVID-19, Occupational Social Distancing and Remote Working Potential: An Occupation, Sector and Regional Perspective. *Reg Sci Policy Pract* 2020; **12** [DOI: 10.1111/rsp3.12347]

97   **Ta TMT**, Böge K, Cao TD, Schomerus G, Nguyen TD, Dettling M, Mungee A, Martensen LK, Diefenbacher A, Angermeyer MC, Hahn E. Public attitudes towards psychiatrists in the metropolitan area of Hanoi, Vietnam. *Asian J Psychiatr* 2018; **32**: 44-49 [PMID: 29207317 DOI: 10.1016/j.ajp.2017.11.031]

98   **Shantz A**, Booth JE. Service Employees and Self-Verification: The Roles of Occupational Stigma Consciousness and Core Self-Evaluations. *Hum Relat* 2014; **67**: 1439-1465 [DOI: 10.1177/0018726713519280]

99   **Zhao Y**, Zhan J. Platform Riders' Occupational Stigma Consciousness and Workplace Deviant Behavior: the Mediating Role of Self-depletion. *Balt J Manag* 2022; **17**: 233-249 [DOI: 10.1108/BJM-06-2021-0215]

100 **Mostafa A**, Mostafa NS, Ismail N. Validity and Reliability of a COVID-19 Stigma Scale Using Exploratory and Confirmatory Factor Analysis in a Sample of Egyptian Physicians: E16-COVID19-S. *Int J Environ Res Public Health* 2021; **18** [PMID: 34069754 DOI: 10.3390/ijerph18105451]

101 **Oktar D**, Aydoğan S, Sungur S, Önsüz M, Metintas S, Kosger F, Altinoz E. Reliability and Validity of the Perception of Stigma due to COVID-19 in Physicians. *Eur J Public Health* 2021; 31: 275 [DOI: 10.1093/eurpub/ckab164.718]

102 **Riley R**, Buszewicz M, Kokab F, Teoh K, Gopfert A, Taylor AK, Van Hove M, Martin J, Appleby L, Chew-Graham C. Sources of work-related psychological distress experienced by UK-wide foundation and junior doctors: a qualitative study. *BMJ Open* 2021; **11**: e043521 [PMID: 34162634 DOI: 10.1136/bmjopen-2020-043521]

103 **Wijeratne C**, Johnco C, Draper B, Earl J. Doctors' reporting of mental health stigma and barriers to help-seeking. *Occup Med (Lond)* 2021; **71**: 366-374 [PMID: 34534344 DOI: 10.1093/occmed/kqab119]

104 **Zarzycki MZ**, Goetz Z, Flaga-Łuczkiewicz M. What do medical students think about medical doctors with mental health issues? *Psychol Health Med* 2020; **25**: 623-629 [PMID: 32019331 DOI: 10.1080/13548506.2020.1724309]

105 **Clough BA**, Ireland MJ, March S. Development of the SOSS-D: a scale to measure stigma of occupational stress and burnout in medical doctors. *J Ment Health* 2019; **28**: 26-33 [PMID: 28868957 DOI: 10.1080/09638237.2017.1370642]

106 **Clough BA**, Hill M, Delaney M, Casey LM. Development of a measure of stigma towards occupational stress for mental health professionals. *Soc Psychiatry Psychiatr Epidemiol* 2020; **55**: 941-951 [PMID: 31897577 DOI: 10.1007/s00127-019-01820-9]

107 **Fan Z**, Cong X, Tao M, Wu S, Gao P. Development of the Chinese Version of the Physician Internalized Occupational Stigma Scale (PIOSS). *Psychol Res Behav Manag* 2022; **15**: 3445-3459 [PMID: 36471790 DOI: 10.2147/PRBM.S386724]

108 **Healey LV**. The psychometric properties of the Forensic Stigma Scale (FSS). *Int J Law Psychiatry* 2022; **83**: 101804 [PMID: 35772282 DOI: 10.1016/j.ijlp.2022.101804]

109 **Verhaeghe M**, Bracke P. Associative stigma among mental health professionals: implications for professional and service user well-being. *J Health Soc Behav* 2012; **53**: 17-32 [PMID: 22382718 DOI: 10.1177/0022146512439453]

110 **Gaebel W**, Zäske H, Cleveland HR, Zielasek J, Stuart H, Arboleda-Florez J, Akiyama T, Gureje O, Jorge MR, Kastrup M, Suzuki Y, Tasman A, Sartorius N. Measuring the stigma of psychiatry and psychiatrists: development of a questionnaire. *Eur Arch Psychiatry Clin Neurosci* 2011; **261** Suppl 2: S119-S123 [PMID: 21947511 DOI: 10.1007/s00406-011-0252-0]

111 **Mittal D**, Sullivan G, Chekuri L, Allee E, Corrigan PW. Empirical Studies of Self-Stigma Reduction Strategies: A Critical Review of the Literature. *Psychiatr Serv* 2012; **63**: 974-981 [PMID: 22855130 DOI: 10.1176/appi.ps.201100459]

112 **Jeffrey JB**, Christine B, Trisha BJ, Melissa Z. Addressing mental health stigma among young adolescents: evaluation of a youth-led approach. *Health Soc Work* 2014; **39**: 73-80 [PMID: 24946423 DOI: 10.1093/hsw/hlu008]

113 **Hartog K**, Hubbard CD, Krouwer AF, Thornicroft G, Kohrt BA, Jordans MJD. Stigma reduction interventions for children and adolescents in low- and middle-income countries: Systematic review of intervention strategies. *Soc Sci Med* 2020; **246**: 112749 [PMID: 31978636 DOI: 10.1016/j.socscimed.2019.112749]

114 Poole AH. "Tearing the Shroud of Invisibility": Communities of Protest Information Practices and the Fight for LGBTQ Rights in US Librarianship. *Libr Q* 2020; **90**: 530-562 [DOI: 10.1086/710255]

115 **Corrigan PW**, Penn DL. Lessons from social psychology on discrediting psychiatric stigma. *Am Psychol* 1999; **54**: 765-776 [PMID: 10510666 DOI: 10.1037/0003-066X.54.9.765]

116 **Makita M**, Mas-Bleda A, Morris S, Thelwall M. Mental Health Discourses on Twitter during Mental Health Awareness Week. *Issues Ment Health Nurs* 2021; **42**: 437-450 [PMID: 32926796 DOI: 10.1080/01612840.2020.1814914]

117 **Koteyko N**, Atanasova D. Mental Health Advocacy on Twitter: Positioning in Depression Awareness Week tweets. *Discourse Context Media* 2018; **25**: 52-59 [DOI: 10.1016/j.dcm.2018.04.007]

118 **Laura JA**, Sarah EG, Racheal AR. Key Ingredients—Target Groups, Methods and Messages, and Evaluation—of Local-Level, Public Interventions to Counter Stigma and Discrimination: A Lived Experience Informed Selective Narrative Literature Review. *Community Ment Health J* 2017; **54**: 312-333 [PMID: 29185150 DOI: 10.1007/s10597-017-0189-5]

119 **Esmaeili AA**, Saeidi A, Mohammadi Y, Raeisoon M. The effect of group psychological training on the attitude of family caregivers of patients with schizophrenia. *Heliyon* 2022; **8**: e09817 [PMID: 35874056 DOI: 10.1016/j.heliyon.2022.e09817]

120   **Li J**, Fan Y, Zhong HQ, Duan XL, Chen W, Evans-Lacko S, Thornicroft G. Effectiveness of an anti-stigma training on improving attitudes and decreasing discrimination towards people with mental disorders among care assistant workers in Guangzhou, China. *Int J Ment Health Syst* 2019; **13**: 1 [PMID: 30622627 DOI: 10.1186/s13033-018-0259-2]

121   **Li J**, Li J, Huang Y, Thornicroft G. Mental health training program for community mental health staff in Guangzhou, China: effects on knowledge of mental illness and stigma. *Int J Ment Health Syst* 2014; **8**: 49 [PMID: 25520750 DOI: 10.1186/1752-4458-8-49]

122   **Tomar N**, Ghezzi MA, Brinkley-Rubinstein L, Wilson AB, Van Deinse TB, Burgin S, Cuddeback GS. Statewide mental health training for probation officers: improving knowledge and decreasing stigma. *Health Justice* 2017; **5**: 11 [PMID: 29143153 DOI: 10.1186/s40352-017-0057-y]

123   **Yanos PT**, Roe D, West ML, Smith SM, Lysaker PH. Group-based treatment for internalized stigma among persons with severe mental illness: findings from a randomized controlled trial. *Psychol Serv* 2012; **9**: 248-258 [PMID: 22545821 DOI: 10.1037/a0028048]

124   **Ke S**, Lai J, Sun T, Yang MM, Wang JC, Austin J. Healthy young minds: the effects of a 1-hour classroom workshop on mental illness stigma in high school students. *Community Ment Health J* 2015; **51**: 329-337 [PMID: 25017811 DOI: 10.1007/s10597-014-9763-2]

125   **Ojio Y**, Yamaguchi S, Ohta K, Ando S, Koike S. Effects of biomedical messages and expert-recommended messages on reducing mental health-related stigma: a randomised controlled trial. *Epidemiol Psychiatr Sci* 2019; **29**: e74 [PMID: 31753045 DOI: 10.1017/S2045796019000714]

126   **Friedrich B**, Evans-Lacko S, London J, Rhydderch D, Henderson C, Thornicroft G. Anti-stigma training for medical students: the Education Not Discrimination project. *Br J Psychiatry Suppl* 2013; **55**: s89-s94 [PMID: 23553700 DOI: 10.1192/bjp.bp.112.114017]

127   **McCormack Z**, Gilbert JL, Ott C, Plake KS. Mental health first aid training among pharmacy and other university students and its impact on stigma toward mental illness. *Curr Pharm Teach Learn* 2018; **10**: 1342-1347 [PMID: 30527363 DOI: 10.1016/j.cptl.2018.07.001]

128   **Sreeram A**, Cross WM, Townsin L. Anti-stigma initiatives for mental health professionals-A systematic literature review. *J Psychiatr Ment Health Nurs* 2022; **29**: 512-528 [PMID: 35500153 DOI: 10.1111/jpm.12840]

129   **Martínez-Martínez C**, Sánchez-Martínez V, Sales-Orts R, Dinca A, Richart-Martínez M, Ramos-Pichardo JD. Effectiveness of direct contact intervention with people with mental illness to reduce stigma in nursing students. *Int J Ment Health Nurs* 2019; **28**: 735-743 [PMID: 30693628 DOI: 10.1111/inm.12578]

130   **Corrigan PW**, Morris SB, Michaels PJ, Rafacz JD, Rüsch N. Challenging the public stigma of mental illness: a meta-analysis of outcome studies. *Psychiatr Serv* 2012; **63**: 963-973 [PMID: 23032675 DOI: 10.1176/appi.ps.201100529]

131   **Thornicroft G**, Mehta N, Clement S, Evans-Lacko S, Doherty M, Rose D, Koschorke M, Shidhaye R, O'Reilly C, Henderson C. Evidence for effective interventions to reduce mental-health-related stigma and discrimination. *Lancet* 2016; **387**: 1123-1132 [PMID: 26410341 DOI: 10.1016/S0140-6736(15)00298-6]

132   **Yamaguchi S**, Wu SI, Biswas M, Yate M, Aoki Y, Barley EA, Thornicroft G. Effects of short-term interventions to reduce mental health-related stigma in university or college students: a systematic review. *J Nerv Ment Dis* 2013; **201**: 490-503 [PMID: 23719324 DOI: 10.1097/NMD.0b013e31829480df]

133   **Corrigan PW**, Vega E, Larson J, Michaels PJ, McClintock G, Krzyzanowski R, Gause M, Buchholz B. The California schedule of key ingredients for contact-based antistigma programs. *Psychiatr Rehabil J* 2013; **36**: 173-179 [PMID: 23834612 DOI: 10.1037/prj0000006]

134   **Corrigan PW**, Michaels PJ, Vega E, Gause M, Larson J, Krzyzanowski R, Botcheva L. Key ingredients to contact-based stigma change: a cross-validation. *Psychiatr Rehabil J* 2014; **37**: 62-64 [PMID: 24417232 DOI: 10.1037/prj0000038]

135   **Janoušková M**, Tušková E, Weissová A, Trančík P, Pasz J, Evans-Lacko S, Winkler P. Can video interventions be used to effectively destigmatize mental illness among young people? A systematic review. *Eur Psychiatry* 2017; **41**: 1-9 [PMID: 28049074 DOI: 10.1016/j.eurpsy.2016.09.008]

136   **Adu J**, Oudshoorn A, Anderson K, Marshall CA, Stuart H. Social Contact: Next Steps in an Effective Strategy to Mitigate the Stigma of Mental Illness. *Issues Ment Health Nurs* 2022; **43**: 485-488 [PMID: 34652979 DOI: 10.1080/01612840.2021.1986757]

137   **Nakanishi E**, Tamachi M, Hashimoto T. Effectiveness of a Co-Production with Dialogue Program for Reducing Stigma against Mental Illness: A Quasi-Experimental Study with a Pre- and Post-Test Design. *Int J Environ Res Public Health* 2022; **19** [PMID: 36361212 DOI: 10.3390/ijerph192114333]

138   **Hogg B**, Moreno-Alcázar A, Tóth MD, Serbanescu I, Aust B, Leduc C, Paterson C, Tsantila F, Abdulla K, Cerga-Pashoja A, Cresswell-Smith J, Fanaj N, Meksi A, Ni Dhalaigh D, Reich H, Ross V, Sanches S, Thomson K, Van Audenhove C, Pérez V, Arensman E, Purebl G, Amann BL; MENTUPP consortium members. Supporting employees with mental illness and reducing mental illness-related stigma in the workplace: an expert survey. *Eur Arch Psychiatry Clin Neurosci* 2023; **273**: 739-753 [PMID: 35867155 DOI: 10.1007/s00406-022-01443-3]

139   **Qin S**, Sheehan L, Yau E, Chen Y, Wang Y, Deng H, Lam C, Chen Z, Zhao L, Gan S, Mao H, Mo X, Yang L, Zhang F, Corrigan P, CBPR Team. Adapting and Evaluating a Strategic Disclosure Program to Address Mental Health Stigma Among Chinese. *Int J Ment Health Addict* 2022 [DOI: 10.1007/s11469-022-00911-0]

140   **Conceição V**, Rothes I, Gusmão R. The effects of a video-based randomized controlled trial intervention on depression stigma and help-seeking attitudes in university students. *Psychiatry Res* 2022; **308**: 114356 [PMID: 34972028 DOI: 10.1016/j.psychres.2021.114356]

141   **Winkler P**, Janoušková M, Kožený J, Pasz J, Mladá K, Weissová A, Tušková E, Evans-Lacko S. Short video interventions to reduce mental health stigma: a multi-centre randomised controlled trial in nursing high schools. *Soc Psychiatry Psychiatr Epidemiol* 2017; **52**: 1549-1557 [PMID: 29101447 DOI: 10.1007/s00127-017-1449-y]

142   **Clement S**, van Nieuwenhuizen A, Kassam A, Flach C, Lazarus A, de Castro M, McCrone P, Norman I, Thornicroft G. Filmed v. live social contact interventions to reduce stigma: randomised controlled trial. *Br J Psychiatry* 2012; **201**: 57-64 [PMID: 22157800 DOI: 10.1192/bjp.bp.111.093120]

143   **Tan GTH**, Shahwan S, Abdin E, Lau JH, Goh CMJ, Ong WJ, Samari E, Kwok KW, Chong SA, Subramaniam M.

Recognition of Depression and Help-Seeking Preference Among University Students in Singapore: An Evaluation of the Impact of Advancing Research to Eliminate Mental Illness Stigma an Education and Contact Intervention. *Front Psychiatry* 2021; **12**: 582730 [PMID: 34054591 DOI: 10.3389/fpsyt.2021.582730]

144   **Ahuja K**, Dhillon M, Juneja A, Sharma B. Breaking Barriers: An Education and Contact Intervention to Reduce Mental Illness Stigma among Indian College Students. *Psychosoc Interv* 2017; **26** [DOI: 10.1016/j.psi.2016.11.003]

145   **Hawke LD**, Michalak EE, Maxwell V, Parikh SV. Reducing stigma toward people with bipolar disorder: impact of a filmed theatrical intervention based on a personal narrative. *Int J Soc Psychiatry* 2014; **60**: 741-750 [PMID: 24351967 DOI: 10.1177/0020764013513443]

146   **Ma HI**, Hsieh CE. An Anti-Stigma Course for Occupational Therapy Students in Taiwan: Development and Pilot Testing. *Int J Environ Res Public Health* 2020; **17** [PMID: 32756448 DOI: 10.3390/ijerph17155599]

147   **Papish A**, Kassam A, Modgill G, Vaz G, Zanussi L, Patten S. Reducing the stigma of mental illness in undergraduate medical education: a randomized controlled trial. *BMC Med Educ* 2013; **13**: 141 [PMID: 24156397 DOI: 10.1186/1472-6920-13-141]

148   **Fernandez A**, Tan KA, Knaak S, Chew BH, Ghazali SS. Effects of Brief Psychoeducational Program on Stigma in Malaysian Pre-clinical Medical Students: A Randomized Controlled Trial. *Acad Psychiatry* 2016; **40**: 905-911 [PMID: 27527730 DOI: 10.1007/s40596-016-0592-1]

149   **Flanagan EH**, Buck T, Gamble A, Hunter C, Sewell I, Davidson L. "Recovery Speaks": A Photovoice Intervention to Reduce Stigma Among Primary Care Providers. *Psychiatr Serv* 2016; **67**: 566-569 [PMID: 26766754 DOI: 10.1176/appi.ps.201500049]

150   **Patten SB**, Remillard A, Phillips L, Modgill G, Szeto ACh, Kassam A, Gardner DM. Effectiveness of contact-based education for reducing mental illness-related stigma in pharmacy students. *BMC Med Educ* 2012; **12**: 120 [PMID: 23216787 DOI: 10.1186/1472-6920-12-120]

151   **Villani M**, Kovess-Masfety V. Could a short training intervention modify opinions about mental illness? A case study on French health professionals. *BMC Psychiatry* 2017; **17**: 133 [PMID: 28390399 DOI: 10.1186/s12888-017-1296-0]

152   **Rubio-Valera M**, Aznar-Lou I, Vives-Collet M, Fernández A, Gil-Girbau M, Serrano-Blanco A. Reducing the Mental Health-Related Stigma of Social Work Students: A Cluster RCT. *Res Soc Work Pract* 2018; **28**: 164-172 [DOI: 10.1177/1049731516641492]

153   **Amsalem D**, Gothelf D, Dorman A, Goren Y, Tene O, Shelef A, Horowitz I, Dunsky LL, Rogev E, Klein EH, Mekori-Domachevsky E, Fischel T, Levkovitz Y, Martin A, Gross R. Reducing Stigma Toward Psychiatry Among Medical Students: A Multicenter Controlled Trial. *Prim Care Companion CNS Disord* 2020; **22** [PMID: 32135042 DOI: 10.4088/PCC.19m02527]

154   **Li J**, Li J, Thornicroft G, Yang H, Chen W, Huang Y. Training community mental health staff in Guangzhou, China: evaluation of the effect of a new training model. *BMC Psychiatry* 2015; **15**: 263 [PMID: 26503370 DOI: 10.1186/s12888-015-0660-1]

155   **Ran MS**, Wang YZ, Lu PY, Weng X, Zhang TM, Deng SY, Li M, Luo W, Wong IY, Yang LH, Thornicroft G, Lu L. Effectiveness of enhancing contact model on reducing stigma of mental illness among family caregivers of persons with schizophrenia in rural China: A cluster randomized controlled trial. *Lancet Reg Health West Pac* 2022; **22**: 100419 [PMID: 35257121 DOI: 10.1016/j.lanwpc.2022.100419]

156   **Zhang W**, Henderson C, Magnusdottir E, Chen W, Ma N, Ma H, Thornicroft G. Effect of a contact-based education intervention on reducing stigma among community health and care staff in Beijing, China: Pilot randomized controlled study. *Asian J Psychiatr* 2022; **73**: 103096 [PMID: 35430494 DOI: 10.1016/j.ajp.2022.103096]

157   **Magliano L**, Rinaldi A, Costanzo R, De Leo R, Schioppa G, Petrillo M, Read J. Improving psychology students' attitudes toward people with schizophrenia: A quasi-randomized controlled study. *Am J Orthopsychiatry* 2016; **86**: 253-264 [PMID: 26963178 DOI: 10.1037/ort0000161]

158   **Rodríguez-Rivas ME**, Cangas AJ, Fuentes-Olavarría D. Controlled Study of the Impact of a Virtual Program to Reduce Stigma Among University Students Toward People With Mental Disorders. *Front Psychiatry* 2021; **12**: 632252 [PMID: 33633613 DOI: 10.3389/fpsyt.2021.632252]

159   **Koike S**, Yamaguchi S, Ojio Y, Ohta K, Shimada T, Watanabe K, Thornicroft G, Ando S. A randomised controlled trial of repeated filmed social contact on reducing mental illness-related stigma in young adults. *Epidemiol Psychiatr Sci* 2018; **27**: 199-208 [PMID: 27989255 DOI: 10.1017/S2045796016001050]

160   **Beaulieu T**, Patten S, Knaak S, Weinerman R, Campbell H, Lauria-Horner B. Impact of Skill-Based Approaches in Reducing Stigma in Primary Care Physicians: Results from a Double-Blind, Parallel-Cluster, Randomized Controlled Trial. *Can J Psychiatry* 2017; **62**: 327-335 [PMID: 28095259 DOI: 10.1177/0706743716686919]

161   **Ng YP**, Rashid A, O'Brien F. Determining the effectiveness of a video-based contact intervention in improving attitudes of Penang primary care nurses towards people with mental illness. *PLoS One* 2017; **12**: e0187861 [PMID: 29131841 DOI: 10.1371/journal.pone.0187861]

162   **Hatzenbuehler ML**, Phelan JC, Link BG. Stigma as a fundamental cause of population health inequalities. *Am J Public Health* 2013; **103**: 813-821 [PMID: 23488505 DOI: 10.2105/AJPH.2012.301069]

163   **Hankir A**, Abi Rached M, Zaman R. Pioneering an Innovative Intervention to Reduce Mental Health Related Stigma in Muslim Communities: A Protocol. *Psychiatr Danub* 2021; **33**: 69-73 [PMID: 34862896]

164   **Chen SP**, Koller M, Krupa T, Stuart H. Contact in the Classroom: Developing a Program Model for Youth Mental Health Contact-Based Anti-stigma Education. *Community Ment Health J* 2016; **52**: 281-293 [PMID: 26429792 DOI: 10.1007/s10597-015-9944-7]

165   **Chisholm K**, Patterson P, Torgerson C, Turner E, Jenkinson D, Birchwood M. Impact of contact on adolescents' mental health literacy and stigma: the SchoolSpace cluster randomised controlled trial. *BMJ Open* 2016; **6**: e009435 [PMID: 26895983 DOI: 10.1136/bmjopen-2015-009435]

166   **Duman ZÇ**, Günüşen NP, İnan FŞ, Ince SÇ, Sari A. Effects of two different psychiatric nursing courses on nursing students' attitudes towards mental illness, perceptions of psychiatric nursing, and career choices. *J Prof Nurs* 2017; **33**: 452-459 [PMID: 29157575 DOI: 10.1016/j.profnurs.2017.06.005]

167   **Valentim O**, Moutinho L, Laranjeira C, Querido A, Tomás C, Longo J, Carvalho D, Gomes J, Morgado T, Correia T. "Looking beyond Mental Health Stigma": An Online Focus Group Study among Senior Undergraduate Nursing Students. *Int J Environ Res Public Health* 2023; **20** [PMID: 36901609 DOI: 10.3390/ijerph20054601]

168   **Monnapula-Mazabane P**, Petersen I. Feasibility and acceptability of a mental health stigma intervention for low-income South African caregivers: A qualitative investigation. *S Afr J Psychiatr* 2022; **28**: 1824 [PMID: 35402016 DOI: 10.4102/sajpsychiatry.v28i0.1824]

169   **Heijnders M**, Van Der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. *Psychol Health Med* 2006; **11**: 353-363 [PMID: 17130071 DOI: 10.1080/13548500600595327]

170   **Cook JE**, Purdie-Vaughns V, Meyer IH, Busch JTA. Intervening within and across levels: a multilevel approach to stigma and public health. *Soc Sci Med* 2014; **103**: 101-109 [PMID: 24513229 DOI: 10.1016/j.socscimed.2013.09.023]

171   **Hong S**, Satyshur MD, Burnett-Zeigler I. The association of mindfulness and depression stigma among African American women participants in a mindfulness-based intervention: A pilot study. *Transcult Psychiatry* 2022; 13634615221076709 [PMID: 35505619 DOI: 10.1177/13634615221076709]

172   **Clinton AJ**, Pollini RA. Using Positive Empathy Interventions to Reduce Stigma Toward People Who Inject Drugs. *Front Psychol* 2021; **12**: 616729 [PMID: 34305698 DOI: 10.3389/fpsyg.2021.616729]

173   Young DK-W. Cognitive Behavioral Therapy Group for Reducing Self-Stigma for People With Mental Illness. *Res Soc Work Pract* 2018; **28**: 827-837 [DOI: 10.1177/1049731516681849]

174   **Lu T**, Guo Z, Li H, Zhang X, Ren Z, Yang W, Wei L, Huang L. Effects of Wise Intervention on Perceived Discrimination Among College Students Returning Home From Wuhan During the COVID-19 Outbreak. *Front Psychol* 2021; **12**: 689251 [PMID: 34163414 DOI: 10.3389/fpsyg.2021.689251]

175   **Siegel J**, Yassi A, Rau A, Buxton JA, Wouters E, Engelbrecht MC, Uebel KE, Nophale LE. Workplace interventions to reduce HIV and TB stigma among health care workers - Where do we go from here? *Glob Public Health* 2015; **10**: 995-1007 [PMID: 25769042 DOI: 10.1080/17441692.2015.1021365]

176   **Villotti P**, Zaniboni S, Corbière M, Guay S, Fraccaroli F. Reducing perceived stigma: Work integration of people with severe mental disorders in Italian social enterprise. *Psychiatr Rehabil J* 2018; **41**: 125-134 [PMID: 29698004 DOI: 10.1037/prj0000299]

177   **Gaiha SM**, Salisbury TT, Usmani S, Koschorke M, Raman U, Petticrew M. Effectiveness of arts interventions to reduce mental-health-related stigma among youth: a systematic review and meta-analysis. *BMC Psychiatry* 2021; **21**: 364 [PMID: 34294067 DOI: 10.1186/s12888-021-03350-8]

178   **Zeppegno P**, Gramaglia C, Feggi A, Lombardi A, Torre E. The effectiveness of a new approach using movies in the training of medical students. *Perspect Med Educ* 2015; **4**: 261-263 [PMID: 26346496 DOI: 10.1007/s40037-015-0208-6]

179   **Teti M**, Schulhoff AM, Koegler E, Saffran L, Bauerband LA, Shaffer V. Exploring the Use of Photo-Stories and Fiction Writing to Address HIV Stigma Among Health Professions Students. *Qual Health Res* 2019; **29**: 260-269 [PMID: 30095044 DOI: 10.1177/1049732318790939]

180   **Petkari E**. Building Beautiful Minds: Teaching Through Movies to Tackle Stigma in Psychology Students in the UAE. *Acad Psychiatry* 2017; **41**: 724-732 [PMID: 28577114 DOI: 10.1007/s40596-017-0723-3]

181   **Yadavaia JE**, Hayes SC. Acceptance and Commitment Therapy for Self-Stigma Around Sexual Orientation: A Multiple Baseline Evaluation. *Cogn Behav Pract* 2012; **19**: 545-559 [DOI: 10.1016/j.cbpra.2011.09.002]

182   **Levin ME**, Potts S, Haeger J, Lillis J. Delivering Acceptance and Commitment Therapy for Weight Self-Stigma Through Guided Self-Help: Results From an Open Pilot Trial. *Cogn Behav Pract* 2018; **25**: 87-104 [DOI: 10.1016/j.cbpra.2017.02.002]

183   **Gul M**, Aqeel M. Acceptance and Commitment Therapy for Treatment of Stigma and Shame in Substance Use Disorders: A Double-Blind, Parallel-Group, Randomized Controlled Trial. *J Subst Use* 2020; **26**: 4, 413-419 [DOI: 10.1080/14659891.2020.1846803]

184   **Sun L**, Liu X, Weng X, Deng H, Li Q, Liu J, Luan X. Narrative therapy to relieve stigma in oral cancer patients: A randomized controlled trial. *Int J Nurs Pract* 2022; **28**: e12926 [PMID: 33817894 DOI: 10.1111/ijn.12926]

185   **Ironson G**, Bira L, Hylton E. Positive and negative emotional expression measured from a single written essay about trauma predicts survival 17 years later in people living with HIV. *J Psychosom Res* 2020; **136**: 110166 [PMID: 32559504 DOI: 10.1016/j.jpsychores.2020.110166]

186   **Tornero MDLA**, Capella C. Change during Psychotherapy through Sand Play Tray in Children That Have Been Sexually Abused. *Front Psychol* 2017; **8**: 617 [PMID: 28522978 DOI: 10.3389/fpsyg.2017.00617]

187   **Skinta MD**, Lezama M, Wells G, Dilley JW. Acceptance and Compassion-Based Group Therapy to Reduce HIV Stigma. *Cogn Behav Pract* 2015; **22**: 481-490 [DOI: 10.1016/j.cbpra.2014.05.006]

188   **Harris PB**, Caporella CA. An intergenerational choir formed to lessen Alzheimer's disease stigma in college students and decrease the social isolation of people with Alzheimer's disease and their family members: a pilot study. *Am J Alzheimers Dis Other Demen* 2014; **29**: 270-281 [PMID: 24413542 DOI: 10.1177/1533317513517044]

189   **Lee Y**, Yoon HJ, Joo J. Role of Fresh Start Mindset Framing in Reducing Stigma and Promoting Mental Health Help-Seeking Behavior. *J Consum Behav* 2023; cb.2155 [DOI: 10.1002/cb.2155]

190   **Tajti J**, Szok D, Csáti A, Szabó Á, Tanaka M, Vécsei L. Exploring Novel Therapeutic Targets in the Common Pathogenic Factors in Migraine and Neuropathic Pain. *Int J Mol Sci* 2023; **24** [PMID: 36835524 DOI: 10.3390/ijms24044114]

191   **Tanaka M**, Szabó Á, Vécsei L. Integrating Armchair, Bench, and Bedside Research for Behavioral Neurology and Neuropsychiatry: Editorial. *Biomedicines* 2022; **10** [PMID: 36551755 DOI: 10.3390/biomedicines10122999]

192   **Battaglia S**, Cardellicchio P, Di Fazio C, Nazzi C, Fracasso A, Borgomaneri S. Stopping in (e)motion: Reactive action inhibition when facing valence-independent emotional stimuli. *Front Behav Neurosci* 2022; **16**: 998714 [PMID: 36248028 DOI: 10.3389/fnbeh.2022.998714]

193   **Tanaka M**, Szabó Á, Spekker E, Polyák H, Tóth F, Vécsei L. Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan-Kynurenine Metabolic System. *Cells* 2022; **11** [PMID: 36010683 DOI: 10.3390/cells11162607]

194   **Lam C**, Tsang H, Corrigan P, Lee Y-T, Angell B, Shi K, H. J, Larson J. Chinese Lay Theory and Mental Illness Stigma: Implications for Research and Practices. *J Rehabil* 2010; **76**: 35-40

195   **Ran MS**, Hall BJ, Su TT, Prawira B, Breth-Petersen M, Li XH, Zhang TM. Stigma of mental illness and cultural factors in Pacific Rim region: a systematic review. *BMC Psychiatry* 2021; **21**: 8 [PMID: 33413195 DOI: 10.1186/s12888-020-02991-5]

Epigenetics in psychiatry: Beyond DNA methylation

Katarina Kouter, Iris Šalamon Arčan, Alja Videtič Paska

Katarina Kouter, Faculty of Medicine, Institute of Microbiology and Immunology, University of Ljubljana, Ljubljana 1000, Slovenia

Iris Šalamon Arčan, Alja Videtič Paska, Faculty of Medicine, Institute of Biochemistry and Molecular Genetics, University of Ljubljana, Ljubljana 1000, Slovenia

Corresponding author: Alja Videtič Paska, PhD, Associate Professor, Faculty of Medicine, Institute of Biochemistry and Molecular Genetics, University of Ljubljana, Vrazov trg 2, Ljubljana 1000, Slovenia. alja.videtic@mf.uni-lj.si

Abstract

The global burden of psychopathologies appears to be underestimated, since the global psychiatric disorder burden is exceeding other medical burdens. To be able to address this problem more effectively, we need to better understand the etiology of psychiatric disorders. One of the hallmarks of psychiatric disorders appears to be epigenetic dysregulation. While some epigenetic modifications (such as DNA methylation) are well known and studied, the roles of others have been investigated much less. DNA hydroxymethylation is a rarely studied epigenetic modification, which as well as being an intermediate stage in the DNA demethylation cycle is also an independent steady cell state involved in neuro-development and plasticity. In contrast to DNA methylation, DNA hydroxy-methylation appears to be related to an increase in gene expression and subsequent protein expression. Although no particular gene or genetic locus can be at this point linked to changes in DNA hydroxymethylation in psychiatric disorders, the epigenetic marks present good potential for biomarker identi-fication because the epigenetic landscape is a result of the interplay between genes and environment, which both influence the development of psychiatric disorders, and because hydoxymethylation changes are particularly enriched in the brain and in synapse-related genes.

Core Tip: DNA hydroxymethylation is one of the least investigated epigenetic mechanisms but based on currently available results it is abundant in the brain, thus potentially influencing the development of psychiatric disorders through modulation of gene expression. Currently no particular genetic locus or gene can be linked to hydroxymethylation in psychiatric disorders. However, the dynamics in gene expression of the ten-eleven translocation enzymes that catalyze hydroxymethylation have been demonstrated, and changes in hydroxymethylation levels when comparing healthy subjects with psychiatric disorders can be determined using genome-wide and candidate gene approaches.

INTRODUCTION

The global burden of psychiatric disorders

Psychiatric disorders comprise different types of mental disorder, including anxiety disorder, major depressive disorder (MDD), bipolar disorder (BP), post-traumatic stress disorder, schizophrenia (SZ), eating disorders, neurodevelopmental disorders, disruptive behavior, and dissocial disorders. All disorders have in common a clinically significant disturbance in an individual's cognition, emotional regulation, or behavior and are normally associated with distress or impairment in important areas of functioning. In 2019, there were 970 million people around the world living with a psychiatric disorder. More than half of those people struggle with anxiety disorder (301 million) or depression (280 million), both of which are also common in children and adolescents. BP was experienced by 40 million people, and SZ by approximately 24 million people[1]. Obsessive-compulsive disorder (OCD) affects 1%-3% of the worldwide population[2]. Suicide is strongly connected with psychiatric disorders (in particular, depression and BP). However, many suicides happen impulsively in moments of crisis, such as breakdown in the ability to deal with life stressors, such as financial or relationship problems, chronic pain, or illness. More than 700000 people die due to suicide and there are many more people attempting it[3]. 13% of the global population is living with a psychiatric disorder which has a substantial effect on all areas of life, such as school or work performance, relationships with family and friends, and the ability to participate in the community[4]. Besides social impact, there is also an economic burden that costs the global economy US$ 1 trillion each year[5].

Biomarkers and psychiatric disorders

A biomarker is a measurable indicator of some biological state or condition. Diagnostic biomarkers serve for narrowing down diagnoses specific to an individual patient[6]. In the field of psychiatry, diagnoses are made based on psychiatric examination using the Diagnostic and Statistical Manual or Mental Disorders or International Classification of Diseases[7,8]. As clinical presentations of the same psychiatric disorders are heterogeneous, identifying biomarkers is essential step to facilitate diagnosis through markers that allow stratification of groups within the syndrome, early detection of the disease, prescribing the right medications, and improving treatment outcome[6]. Several factors, including genetic, neurobiological, cultural, and life experiences and their interplay contribute to psychiatric disorders. Heritability plays one part in understanding pathogenesis. For example, for the development of SZ and BP there is an approximately 80% contribution of heritability, while this drops to only around 40% for depression and suicidality[9]. Scientists have tried to understand the association of genetic polymorphisms on bigger cohorts by way of genome-wide association studies (GWAS), but there still remain many unanswered questions. This indicates that environmental factors also need to be taken into account[10]. Epigenetic mechanisms such as DNA methylation and hydroxymethylation, histone tail modifications and non-coding RNAs, respond to environmental factors and cause changes in gene expression or translation without changing DNA sequence[9]. The final biological outcome results from the interplay between different epigenetic mechanisms. In recent years hydroxymethylation has received increasing attention in the "neuroepigenome"[10]. There is particular interest in hydroxy-methylation because it is highly enriched in brain and synapse-related genes, and exhibits dynamic regulation during development[11].

EPIGENETICS OF PSYCHIATRIC DISORDERS

DNA methylation

Mental disorders are influenced by many biological and external factors that can be linked together by epigenetics[9,12]. The term epigenetics describes innate (hereditary) or lifetime-acquired changes in gene expression that do not originate from differences in DNA sequence[13]. Epigenetics can thus help us understand the delicate interplay of environmental and genetic influences within the cell. One of the commonly studied mechanisms of epigenetic regulation is DNA methylation and the changes in its pattern. During the DNA methylation process a single methyl group is attached to the 5' C site of the cytosine, making the cytosine either methylated or, when removed, unmethylated. DNA methylation can have a significant effect on the regulation of gene expression[14]. While DNA methylation is still the best researched and understood epigenetic modification, other types (such as noncoding RNAs) are getting more recognition[15,16].

DNA hydroxymethylation

DNA methylation was long thought of as a binary state; whether the switch was turned on (resulting in a methylated cytosine) or off (resulting in an unmethylated cytosine). However more recently it has been discovered that methylation can have stable intermediate stages, which can happen during the process of demethylation. Active demethylation is catalyzed by enzymes of the ten-eleven translocation (TET) family and the enzyme thymine-DNA glycosylase mediated base excision. TET family proteins (the enzymes TET1, TET2 and TET3) are 2-oxoglutarate and Fe(II)-dependent dioxygenases, which catalyze 5-methylcytosine (5mC) conversion to 5-hydroxymethycytosine (5hmC) (illustrated in Figure 1). DNA hydroxymethylation was first described in 1972 but it was only in 2009 that 5hmC was identified as an oxidation metabolite of DNA methylation[17,18]. 5hmCs are often localized in gene bodies and untranslated regions. Compared to methylation, levels of 5hmC are lower (roughly 10% of methylation levels), but a high abundance of 5hmC is observed in the central nervous system. Animal studies demonstrate that DNA hydroxymethylation appears to be important during neurodevelopment as levels of 5hmC in mice embryos increase in the absence of demethylation, making it a stable cell state. This is confirmed by many animal studies[19]. 5hmC can be recognized by specific binding proteins, and can be maintained through cell division[20]. While its exact role in adult brain is not known, it appears that DNA hydroxymethylation can affect neuroplasticity and neurotransmission. 5hmC as such serves a dual role, not only as an intermediate of active demethylation but also as an important mark of epigenetic regulation. As with DNA methylation, numerous environmental factors such as medication, stress and pollutants can affect levels of 5hmC[19].

Like DNA methylation, DNA hydroxymethylation also affects gene expression, but the manner and direction (upregulation or downregulation of gene expression) are not as well characterized as for DNA methylation. Nevertheless, research indicates that DNA hydroxymethylation of the gene body leads to increased gene expression. Enrichment of DNA hydroxymethylation is also often observed at 5' splicing sites, enhancers and CpG island borders[21].

METHODS FOR DNA HYDROXYMETHYLATION DETECTION

Several methods are available for the analysis of DNA hydroxymethylation, following in the footsteps of DNA methylation methods. For DNA methylation, bisulfite conversion of DNA is the gold standard. During the conversion, unmethylated cytosines are deaminated, allowing methylated cytosines to be identified. However, the classical bisulfite conversion approach does not work for DNA hydroxy-methylation because it is not possible to distinguish between methylated and hydroxymethylated cytosines[22]. Since the ratio of methylation to hydroxymethylation is approximately 9 to 1 in favor of methylation other approaches are needed to measure hydroxymethylation[23]. When the number of target genes is small, the candidate gene approach is most appropriate. When the number of target genes increases, a genome-wide approach is usually better in terms of finances, time, and information. Therefore, the selection of the appropriate method for DNA hydroxymethylation analysis should be based on the broader experimental design. Since genome-wide methods are more commonly used for 5hmC assessment, this section focuses only on such methods.

Genome-wide methods for detecting DNA hydroxymethylation

Genome-wide approaches are often better than candidate gene approaches when studying lesser-known epigenetic states such as hydroxymethylation. In addition, psychiatric disorders are complex behaviors that likely involve multiple genes. Currently, there are several methods. Some methods use restriction enzymes and glucosylation (the process by which β-glucosyltransferase specifically transfers a glucose unit to 5hmC, resulting in glucosylated 5hmC). One example is Aba-seq, which uses a restriction endonuclease AbaSI that selectively recognizes glucosylated 5hmC and cleaves DNA in its vicinity (within approximately 10 base pairs)[24]. Another example is Reduced Representation Hydroxy-methylation Profiling, in which DNA is first digested with the enzyme MspI, which recognizes and

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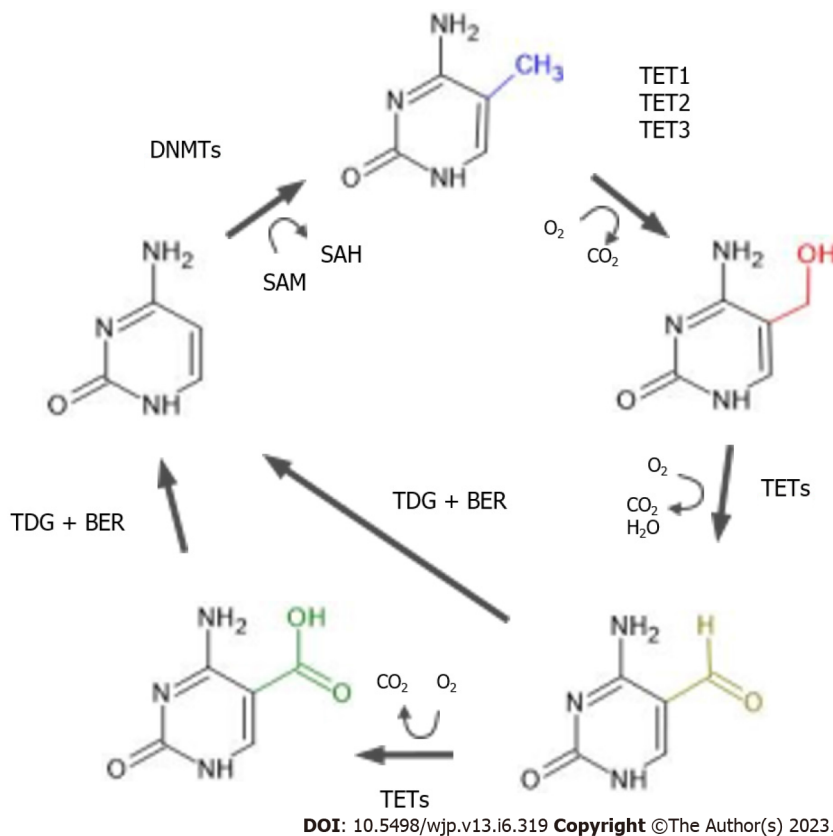
Figure 1 (De)methylation cycle of cytosine. Cytosines can be modified as a result of specific enzyme activity. DNA methyltransferases produce 5-methyl cytosine, which can be further oxidized to 5-hydroxymethyl cytosine by ten-eleven translocation enzymes. Further, two oxidative derivates, 5-formylcytosine and 5-carboxylcytosine, can also be generated and converted back to a cytosine form. BER: Base excision repair; DNMTs: DNA methyltransferases; SAH: S-adenosylhomocysteine; SAM: S-adenosyl methionine TET1: Ten-eleven translocation 1; TET2: Ten-eleven translocation 2; TET3: Ten-eleven translocation 3; TDG: Thymine-DNA-glycosylase.

cleaves the 5'-CCGG sequence. 5hmCs are later glucosylated, which prevents MspI from further cleavage, so that only fragments containing 5hmC are prevented from enzymatic digestion[25].

Tet-assisted bisulfite sequencing (TAB-seq) also takes advantage of glucosylation of 5hmC. After the glucosylation step, the DNA is oxidized using Tet proteins. The glucosylated 5hmC is retained, while 5mC converts to 5-carboxylcytosine (5caC). This oxidized DNA is then treated with bisulfite conversion and polymerase chain reaction (PCR) amplification, where unmethylated cytosines and 5mC (now 5caC) are converted to thymine, while glucosylated 5hmCs become cytosines. TAB-seq is more appropriate when only the 5hmC content is of interest[26].

A more complex method is a variant of bisulfite sequencing called oxidative bisulfite sequencing (oxBs-seq). In oxBs-seq, the sample of interest is divided into two parts; one part is subjected to bisulfite treatment, and after PCR amplification both 5hmC and 5mC are observed as cytosines. The second part of the sample is oxidized before bisulfite treatment, converting 5hmC to 5fC and after PCR amplification to thymine, with 5mC seen as cytosines. This parallel sequencing of the same sample allows accurate detection of 5hmC but increases the price because very high coverage is required[27].

Immuno-dot blot methods use antibodies that can recognize 5-hydroxymethylcytosine. A major advantage of these methods is their relative simplicity in terms of wet-lab work. They provide information on global DNA hydroxymethylation throughout the genome and provide a single numerical measure. The results do not provide detailed information on the state of hydroxymethylation in specific genomic regions, but can be used to provide a comprehensive overview of the state of hydroxymethylation in the genome[28]. A more complex immune approach uses the combination of hydroxymethylation-specific antibodies with next generation sequencing. In antibody-based methods such as hydroxymethylated DNA immunoprecipitation sequencing, DNA is cut into short fragments. Using antibodies against hydroxymethylation, only the hydroxymethylated DNA is isolated from the mixture of DNA fragments. A library is created from the purified DNA fragments and sequenced using next-generation sequencing[29]. Compared with oxBs-seq, this is a less costly option. It does not provide base pair resolution, but a resolution of a few hundred base pairs is usually sufficient for regional overview and gene identification[23,30].

Nanopore technologies is a third-generation (long-read) sequencing approach. Compared with the commonly used Illumina approach of "sequencing by synthesis", sequencing with Nanopore techno-

logies is based on small changes in current. During sequencing, DNA strands pass through protein nanopores about 1.8 nanometers in diameter embedded in a polymer membrane. As DNA strands enter the pore, the current changes according to the DNA bases that are inside the pore (about 6 DNA bases at a time). This also allows detection of epigenetic changes[31]. The advantage of this method is that it provides genome-wide information, while long reads (up to several Mb = 10^6 base pairs) allow detection of rare variants/deletions/insertions/repetitive regions as well as epigenetic DNA changes (both DNA methylation and hydroxymethylation), all in a single sample. This reduces the possibility of biological and technical errors. Although the price per sample is high (the total cost is nearly € 1000 per sample), it allows a much more detailed examination of a sample[32].

CURRENT OVERVIEW OF DNA HYDROXYMETHYLATION STUDIES AND PSYCHIATRIC DISORDERS

As mentioned above, psychiatric disorders are multifactorial disorders influenced by both genetic and epigenetic factors. As epigenetic mechanisms show a high degree of tissue specificity, the best biological source (tissue or organ) for studying psychiatric disorders is therefore the brain. Studies often focus on brain regions related to emotional and behavioral responses, and cognitive and executive control functions. These often-studied regions include the limbic system (hippocampus) and the prefrontal cortex (PFC) (Brodmann area 9 in the dorsolateral PFC)[33,34]. Since the brain is not accessible during life, other peripheral, more easily accessible tissues, such as blood, are often included in studies of psychiatric disorders as well. In the following paragraphs the available studies on DNA hydroxy-methylation are summarized, with more technical data presented in Table 1.

DNA hydroxymethylation and suicidal behavior

In the field of suicidal behavior only two studies have been published that examined the pattern of DNA hydroxymethylation in suicide completers. Gross *et al*[35] examined DNA hydroxymethylation levels in PFC of male suicide completers with MDD. Compared to the control group, no global changes in DNA hydroxymethylation distribution were observed. They did however observe 550 differentially hydroxymethylated CpG sites in the genome. Lutz *et al*[36] included DNA hydroxymethylation analysis of opioid related genes in three brain regions (anterior cingulate cortex, thalamus and anterior insula). Suicide completers who experienced child abuse showed decreased level of DNA hydroxymethylation, while suicide completers with no history of child abuse did not. The decrease in DNA hydroxy-methylation may therefore be a mark of child abuse.

DNA hydroxymethylation and SZ

SZ is a complex, multifactorial disease that causes psychosis. Psychotic symptoms include changes that affect personal and occupational life, *e.g.*, positive symptoms such as hallucinations, delusions, thought and movement disorder, and negative and cognitive symptoms[37]. SZ manifests in late adolescence or early adulthood. Due to psychotic symptoms, SZ is also accompanied by an elevated risk of suicide, which reduces life expectancy for people developing it[38].

Factors that contribute to the development of SZ are both genetic and environmental[39]. Large-scale GWAS has highlighted a large number of variants with small effects which are highly heterogeneous between individuals. The importance of environmental factors is studied through epigenetics. Genome-wide approach and specific candidate gene studies have shown differences in DNA methylation and histone modifications in schizophrenic patients. Associated genes are involved in axon and dendrite extension, oligodendrocyte differentiation, regulation of GABAergic transmission, metabolism of dopamine, and glutamate and serotonin receptors[40].

Candidate gene studies have shown hyper- and hypo-methylated genes in brain tissue in concordance with studies on peripheral tissue (whole blood, peripheral leukocytes, or saliva). However, the results of DNA methylation studies are not always similar between male and female patients. Moreover, many interesting results from DNA methylation studies have pushed interest toward DNA hydroxymethylation. Even though there are not as many studies investigating hydroxymethylation, and much more work needs to be done, some interesting results have been obtained[40].

The level of 5mC is increased in both male and female SZ patients, but 5hmC level in peripheral blood is increased in males and decreased in females compared to controls. Furthermore, 5mC globally increased with age in all participants (schizophrenic and controls), but there was no significant correlation with age for the 5hmC level[41]. An increased level of 5hmC was also reported in the promoter of the *GABRB2* gene in peripheral white blood cells of patients with SZ compared with controls. Furthermore, they found a correlation between promoter 5mC and 5hmC levels, with single nucleotide polymorphisms in patients with SZ. Heterozygous (C/A) genotypes of rs72815526 were correlated with increased 5hmC levels whereas heterozygous (C/T) genotypes of rs3811997 were correlated with decreased 5mC levels[42].

Table 1 Detailed data on DNA hydroxymethylation studies and psychiatric disorders

Ref.	Studied disorder	Subjects	Tissue	Method	Main results
Gross *et al* [35], 2017	Suicidal behavior/major depressive disorder	Subjects with major depressive disorder; *n* = 19 and psychiatrically healthy controls; *n* = 19	Prefrontal cortex	AbaSI sequencing	No differences in 5hmC density across the genome. Site-specific differential hydroxymethylation in the depressed brain
Lutz *et al* [36], 2018	Suicidal behavior	Suicide completers (severe child abuse history); *n* = 30, suicide completers (no child abuse history); *n* = 30 and control group; *n* = 34	Anterior insula	Targeted oxidative bisulfite sequencing	Childhood abuse in the past is associated with decreased hydroxy-methylation of Kappa Intron 2
Jiang *et al* [41], 2017	Schizophrenia	Schizophrenic subjects; *n* = 264 and controls; *n* = 221	Peripheral blood	Dot blot-based measurement	5hmC levels increased in male SZ patients but decreased levels in female SZ patients
Zong *et al* [42], 2017	Schizophrenia	Schizophrenic subjects; *n* = 279 and controls; *n* = 256	Peripheral white blood cells	HpaII/MspI restriction-based EpiMark 5hmC/5mC Analysis Kit followed by qPCR	5hmC increased in the promoter of the *GABRB2* gene; correlation between heterozygous genotype rs72815526 (C/A) and 5hmC levels increased
Gavin *et al* [44], 2012	Schizophrenia and bipolar disorder	Schizophrenic subjects; *n* = 15, subjects with bipolar disorder; *n* = 11, and controls; *n* = 15	Parietal cortex (Brodmann area 39-40)	hMeDIP	5hmC increased at the promoter IXabcd of the *BDNF* gene
Dong *et al* [45], 2012	Schizophrenia and bipolar disorder	Schizophrenic subjects; *n* = 10, subjects with bipolar disorder; *n* = 9, and controls; *n* = 11	Inferior parietal lobule	Immuno-dot-blot analysis	5hmC increased at the *GAD67* gene at -537 to -415, and -145 to +21; 5hmC increased at the *BDNF* IXabcd gene at -60 to +50 not within *BDNF* exon IXd at +1185 to +1305
D'Addario *et al*[57], 2019	Obsessive compulsive disorder	Obsessive compulsive disorder; *n* = 35, and controls; *n* = 32	Peripheral blood mononuclear cells	Bisulfite conversion or oxidative bisulfite conversion, followed by pyrosequencing	*BDNF* hydroxymethlation decreased at promoter exon I; no changes in promoter exon IV and IX
Clark *et al* [60], 2022	Substance use disorder	Alcohol use disorder; *n* = 25, and controls; *n* = 25	Prefrontal cortex (Brodmann area 10)	Selective chemical labelling and enrichment of hmC (hMe-Seal)	*BAIAP2* hydroxymethylation increased

5hmC: 5-hydroxymethycytosine; SZ: Schizophrenia; 5mc: 5-methylcytosine; qPCR: Quantitative real-time polymerase chain reaction; BDNF: Brain-derived neurotrophic factor.

DNA hydroxymethylation and BP

BP is a chronic psychiatric disorder characterized by unusual shifts in mood, energy, activity levels, and concentration. Impulsive reckless behavior leads to an increased risk of suicide[43]. Since SZ and BP are both psychoses, some studies have been made on a combined group of people with SZ and BP[44,45].

A number of studies address DNA methylation in patients with BP but just two have investigated hydroxymethylation where patients with BP were included in the study alongside patients with SZ, forming a combined group of psychotic illnesses. In a study made on parietal cortical samples from psychotic patients (Brodmann area[39,40]), an increase in 5mC and 5hmC was observed at the promoter IXabcd of the brain-derived neurotrophic factor (*BDNF*) gene. This result was also associated with reduced transcription of the *BDNF* gene[44]. In another study on the inferior parietal lobule of psychotic patients increased expression of the *TET1* gene was detected. Consistent with the increase of expression the *TET1* gene, there was an increased level of 5hmC. Specifically, higher 5hmC levels were observed at the glutamate decarboxylase 67 gene at positions -537 to -415 and -145 to +21 in psychosis patients *vs* control. There was also an increase in 5hmC at the BDNF IXabcd gene at position -60 to +50 in psychosis patients *vs* control, but not within *BDNF* exon IXd at +1185 to +1305[45].

DNA hydroxymethylation and MDD

MDD is the psychiatric disorder that contributes the most to the global health burden, and is the primary cause of disability globally. The environmental factors that increase the risk of MDD the most are stress and exposure to adverse life events, meta-analyses and genome-wide studies have shown that genetic factors also contribute to its development, contributing about 40%[46].

The DNA methylation studies were summarized in a recent systematic review[47]. Out of 67 studies 61 were performed on blood samples and thus lacked information on the status of DNA methylation in the central nervous system. Among the already well-established genes, hypermethylation of BDNF and the serotonin transporter gene showed association with depression on general or MDD. Results of other genes showed mixed results[47].

Only two studies on hydroxymethylation in MDD have been reported so far the studies by Gross *et al* [35] and Lutz *et al*[36] mentioned previously. In both studies the brain tissue of subjects with MDD who died due to suicide was used, making it difficult to link the observed differences to MDD alone.

Although studies in human are lacking, three studies on mice strain C57BL/6 have been reported, all investigating the TET enzymes. Feng *et al*[48] applied chronic stress, and determined decreased levels of expression of *TET1* in the nucleus accumbens in stress-susceptible mice. In a *TET1* knockout genes related to the immune system were demonstrated to be the most highly dysregulated. Zhang *et al*[49] examined the *TET2* knockout animals, and identified some hydroxymethylated regions that overlapped with known depression-associated loci. They also showed abnormal translocation of TET2 protein from the cytosol to the nucleus in chronic stress induced mice. Cheng *et al*[50] showed that chronic restraint stress induced depression-like behavior in mice and reduced hydroxymethylation of the PFC. Knocking out *TET1* resulted in resistance to chronic restraint stress, while a knockout of *TET2* increased the susceptibility to chronic restraint stress[50]. The above results indicate that hydroxymethylation exhibits dynamic changes in response to stress-induced stimuli, resulting in changes of epigenetically regulated gene expression.

DNA hydroxymethylation and OCD

OCD is a psychiatric disorder characterized by obsessions and compulsions of various natures and degrees, and is in the majority of cases accompanied by at least one comorbid psychiatric disorder, most commonly MDD[51]. OCD is a heritable disorder with a polygenic background. Candidate gene and genome-wide studies suggest that the serotonergic, dopaminergic, and glutamatergic systems, and the interaction between them, contribute to the risk of the OCD[52]. Important contributing environmental factors are perinatal complications, childhood trauma, reproductive cycle events, and stressful life events[51].

Epigenetic studies of OCD have mostly investigated DNA methylation. Using the genome-wide approach, covering over 485000 CpG sites, genes previously associated with OCD were detected[53]. With the candidate gene approach the oxytocin receptor and serotonin transporter genes were interrogated. The results were mixed, showing both higher and lower level of methylation in OCD patients compared to controls[54-56].

In the context of the candidate gene approach *BDNF* methylation and hydroxymethylation have also been analyzed. Expression of *BDNF* in peripheral blood mononuclear cells demonstrated broad association with OCD, showing an increase in gene expression, as well as significant correlation of both lower methylation and higher hydroxymethylation at promoter exon I[57]. The results were replicated on saliva samples, showing lower levels of methylation in OCD compared to controls[2].

DNA hydroxymethylation and substance use disorder

Substance use disorder (SUD) is a mental disorder with a range of symptoms from moderate to severe. The most severe SUD is addiction. SUD affects a person's brain and behavior, which leads to the uncontrollable use of substances, such as drugs, alcohol, and medications[58]. It is common that people with SUD are also diagnosed with mental disorders and vice versa. Common mental disorders that co-occur with SUD are depression, BP, attention-deficit hyperactivity disorder, psychotic illness, borderline personality disorder, and antisocial personality disorder[59]. There are three suggestions for their joint occurrence. Firstly, common risk factors might contribute to SUD and other mental disorders; secondly, mental disorders can contribute to substance use and SUD; thirdly, substance use and SUD contribute to the development of other mental disorders[58]. It is estimated that there is a 40%-60% genetic contribution to vulnerability for developing SUD. For example, genetic vulnerability can be seen through changes in the degradation of the consumed, inhaled, or injected substance[59]. Moreover, there are also environmental factors that work through the epigenome[60].

There are several studies investigating 5hmC changes in the brains of people with SUD[61]. Clark *et al* [60] showed a difference in 5hmC of the BAIAP2 gene in the PFC from people with alcohol use disorder (AUD)[60]. One study showed differential expression of TET1 in the cerebellum of people with AUD, but no differences in 5hmC in the promoter of GABAergic genes[62]. More studies of SUD were made on model organisms, where they found 5hmC alteration after cocaine and methamphetamine administration[48,63,64], and a higher global 5hmC level was observed in nucles accumbens after ethanol administration[65].

CONCLUSION

In treatment of psychiatric disorders there is currently only a limited selection of validated biomarkers in use (*e.g.,* electrophysiological biomarkers, neuropsychological biomarkers, brain imaging biomarkers, blood biomarkers), while molecular-genetic markers particularly have not yet entered the routine practice. The selection of treatment is based on clinical interview. In many cases patients do not respond to the medication prescribed or their treatment is changed too quickly due to side effects, since the response to the same medication can be highly variable among patients. Thus, the screening of a

patient's genetic background could improve the selection of a suitable medicine(s) based on an individual's genetic background, taking into account pharmacokinetic and pharmacodynamics parameters. These specific differences in gene makeup have been tested in genes responsible for drug metabolism, however other genes also show changes that can significantly affect the development of disease. Shortly after the beginning of the millennium the human genome was sequenced, initiating exponential growth of genome-wide studies that continues until today. It has become evident that psychiatric disorders are polygenic, and that changes in gene sequences (*e.g.,* single nucleotide polymorhpisms, copy number variations) contribute small effects which result in the development of the disorder, also through genetic pleiotropy and epistasis. However, the results of these studies have been mixed, identifying different genes, so no particular genetic locus can be linked to a given psychiatric disorder and used as a biomarker. Since psychiatric disorders show a significant proportion of environmental risk factors, the study of epigenetics has become an important approach to linking genetics with environmental effects, and might therefore provide applicable biomarkers for diagnosis and treatment.

The majority of epigenetic studies have interrogated DNA methylation as the prime epigenetic mark, but again these have produced mixed results at the level of genome-wide analysis, while the candidate gene approach has confirmed the importance of genes involved in neurotransmission and neurotrophic growth factors. Since the development of psychiatric disorders stems from disrupted signaling in the brain DNA hydroxymethylation, which can affect neuroplasticity and neurotransmission, has become an interesting research field. To date not many studies are available, as this area develops, and joint studies on transcriptional regulation are carried out, we expect to be able to improve effects evoked by pharmacotherapy with beneficial effects on patients' health.

As is the case with genetic biomarkers, epigenetic biomarkers are not currently useful in a clinical setting, and many gaps remain in the understanding of their function. To advance our understanding of potential biomarkers, more studies simultaneously interrogating the status of the brain and peripheral tissue such as blood or even saliva are needed. Biomarkers showing good overlap between different tissue types could become key elements of validation studies on bigger, clinically well-defined cohorts, helping to discern the molecular mechanisms of psychiatric disorder development, diagnosis and treatment.

ORCID number: Katarina Kouter 0000-0002-1051-959X; Iris Šalamon Arčan 0000-0002-7483-306X; Alja Videtič Paska 0000-0002-1182-5417.

REFERENCES

1   **World Health Organization**.   Mental disorders. [cited 18 November 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-disorders

2   **D'Addario C**, Macellaro M, Bellia F, Benatti B, Annunzi E, Palumbo R, Conti D, Fasciana F, Vismara M, Varinelli A, Ferrara L, Celebre L, Viganò C, Dell'Osso B. In Search for Biomarkers in Obsessive-Compulsive Disorder: New Evidence on Saliva as a Practical Source of DNA to Assess Epigenetic Regulation. *Curr Med Chem* 2022; **29**: 5782-5791 [PMID: 34879796 DOI: 10.2174/0929867328666211208115536]

3   **World Health Organization**.   Suicide. [cited 18 November 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide

4   **World Health Organization**.   World mental health report: transforming mental health for all. [cited 18 November 2022]. Available from: https://www.who.int/publications/i/item/9789240049338

5   **The Lancet Global Health**. Mental health matters. *Lancet Glob Health* 2020; **8**: e1352 [PMID: 33069297 DOI: 10.1016/S2214-109X(20)30432-0]

6   **García-Gutiérrez MS**, Navarrete F, Sala F, Gasparyan A, Austrich-Olivares A, Manzanares J. Biomarkers in Psychiatry: Concept, Definition, Types and Relevance to the Clinical Reality. *Front Psychiatry* 2020; **11**: 432 [PMID: 32499729 DOI: 10.3389/fpsyt.2020.00432]

7   **American Psychiatric Association**.   Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Washington: American Psychiatric Publishing, 2013

8   **World Health Organization**.   International Classification of Diseases 11th Revision. [cited 15 November 2022]. Available from: https://icd.who.int/en

9   **Nestler EJ**, Peña CJ, Kundakovic M, Mitchell A, Akbarian S. Epigenetic Basis of Mental Illness. *Neuroscientist* 2016; **22**: 447-463 [PMID: 26450593 DOI: 10.1177/1073858415608147]

10   **Cariaga-Martinez A**, Alelú-Paz R. Rethinking the Epigenetic Framework to Unravel the Molecular Pathology of Schizophrenia. *Int J Mol Sci* 2017; **18** [PMID: 28387726 DOI: 10.3390/ijms18040790]

11   **Kato T**, Iwamoto K. Comprehensive DNA methylation and hydroxymethylation analysis in the human brain and its implication in mental disorders. *Neuropharmacology* 2014; **80**: 133-139 [PMID: 24389572 DOI: 10.1016/j.neuropharm.2013.12.019]

12   **Turecki G**, Brent DA, Gunnell D, O'Connor RC, Oquendo MA, Pirkis J, Stanley BH. Suicide and suicide risk. *Nat Rev Dis Primers* 2019; **5**: 74 [PMID: 31649257 DOI: 10.1038/s41572-019-0121-0]

13   **Allis CD**, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet* 2016; **17**: 487-500 [PMID: 27346641 DOI: 10.1038/nrg.2016.59]

14   **Deaton AM**, Bird A. CpG islands and the regulation of transcription. *Genes Dev* 2011; **25**: 1010-1022 [PMID: 21576262 DOI: 10.1101/gad.2037511]

15   **Cheung S**, Woo J, Maes MS, Zai CC. Suicide epigenetics, a review of recent progress. *J Affect Disord* 2020; **265**: 423-438 [PMID: 32090769 DOI: 10.1016/j.jad.2020.01.040]

16   **Girdhar K**, Rahman S, Dong P, Fullard JF, Roussos P. The Neuroepigenome: Implications of Chemical and Physical Modifications of Genomic DNA in Schizophrenia. *Biol Psychiatry* 2022; **92**: 443-449 [PMID: 35750513 DOI: 10.1016/j.biopsych.2022.04.018]

17   **Kriaucionis S**, Heintz N. The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. *Science* 2009; **324**: 929-930 [PMID: 19372393 DOI: 10.1126/science.1169786]

18   **Tahiliani M**, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, Agarwal S, Iyer LM, Liu DR, Aravind L, Rao A. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science* 2009; **324**: 930-935 [PMID: 19372391 DOI: 10.1126/science.1170116]

19   **Nikolac Perkovic M**, Videtic Paska A, Konjevod M, Kouter K, Svob Strac D, Nedic Erjavec G, Pivac N. Epigenetics of Alzheimer's Disease. *Biomolecules* 2021; **11** [PMID: 33573255 DOI: 10.3390/biom11020195]

20   **Lunnon K**, Hannon E, Smith RG, Dempster E, Wong C, Burrage J, Troakes C, Al-Sarraj S, Kepa A, Schalkwyk L, Mill J. Variation in 5-hydroxymethylcytosine across human cortex and cerebellum. *Genome Biol* 2016; **17**: 27 [PMID: 26883014 DOI: 10.1186/s13059-016-0871-x]

21   **Wen L**, Tang F. Genomic distribution and possible functions of DNA hydroxymethylation in the brain. *Genomics* 2014; **104**: 341-346 [PMID: 25205307 DOI: 10.1016/j.ygeno.2014.08.020]

22   **Hong SR**, Shin KJ. Bisulfite-Converted DNA Quantity Evaluation: A Multiplex Quantitative Real-Time PCR System for Evaluation of Bisulfite Conversion. *Front Genet* 2021; **12**: 618955 [PMID: 33719336 DOI: 10.3389/fgene.2021.618955]

23   **Kochmanski J**, Bernstein AI. The Impact of Environmental Factors on 5-Hydroxymethylcytosine in the Brain. *Curr Environ Health Rep* 2020; **7**: 109-120 [PMID: 32020534 DOI: 10.1007/s40572-020-00268-3]

24   **Sun Z**, Terragni J, Borgaro JG, Liu Y, Yu L, Guan S, Wang H, Sun D, Cheng X, Zhu Z, Pradhan S, Zheng Y. High-resolution enzymatic mapping of genomic 5-hydroxymethylcytosine in mouse embryonic stem cells. *Cell Rep* 2013; **3**: 567-576 [PMID: 23352666 DOI: 10.1016/j.celrep.2013.01.001]

25   **Petterson A**, Chung TH, Tan D, Sun X, Jia XY. RRHP: a tag-based approach for 5-hydroxymethylcytosine mapping at single-site resolution. *Genome Biol* 2014; **15**: 456 [PMID: 25248841 DOI: 10.1186/s13059-014-0456-5]

26   **Yu M**, Hon GC, Szulwach KE, Song CX, Zhang L, Kim A, Li X, Dai Q, Shen Y, Park B, Min JH, Jin P, Ren B, He C. Base-resolution analysis of 5-hydroxymethylcytosine in the mammalian genome. *Cell* 2012; **149**: 1368-1380 [PMID: 22608086 DOI: 10.1016/j.cell.2012.04.027]

27   **Booth MJ**, Ost TW, Beraldi D, Bell NM, Branco MR, Reik W, Balasubramanian S. Oxidative bisulfite sequencing of 5-methylcytosine and 5-hydroxymethylcytosine. *Nat Protoc* 2013; **8**: 1841-1851 [PMID: 24008380 DOI: 10.1038/nprot.2013.115]

28   **de Dieuleveult M**.   Analysis of DNA methylation and hydroxymethylation: Easy and fast Dot Blot protocol. 2019 [DOI: 10.13140/RG.2.2.28807.85927/1]

29   **Tan L**, Xiong L, Xu W, Wu F, Huang N, Xu Y, Kong L, Zheng L, Schwartz L, Shi Y, Shi YG. Genome-wide comparison of DNA hydroxymethylation in mouse embryonic stem cells and neural progenitor cells by a new comparative hMeDIP-seq method. *Nucleic Acids Res* 2013; **41**: e84 [PMID: 23408859 DOI: 10.1093/nar/gkt091]

30   **Ficz G**, Branco MR, Seisenberger S, Santos F, Krueger F, Hore TA, Marques CJ, Andrews S, Reik W. Dynamic regulation of 5-hydroxymethylcytosine in mouse ES cells and during differentiation. *Nature* 2011; **473**: 398-402 [PMID: 21460836 DOI: 10.1038/nature10008]

31   **Steinbock LJ**, Radenovic A. The emergence of nanopores in next-generation sequencing. *Nanotechnology* 2015; **26**: 074003 [PMID: 25643284 DOI: 10.1088/0957-4484/26/7/074003]

32   **Liu Y**, Cheng J, Siejka-Zielińska P, Weldon C, Roberts H, Lopopolo M, Magri A, D'Arienzo V, Harris JM, McKeating JA, Song CX. Accurate targeted long-read DNA methylation and hydroxymethylation sequencing with TAPS. *Genome Biol* 2020; **21**: 54 [PMID: 32127008 DOI: 10.1186/s13059-020-01969-6]

33   **Mirza S**, Docherty AR, Bakian A, Coon H, Soares JC, Walss-Bass C, Fries GR. Genetics and epigenetics of self-injurious thoughts and behaviors: Systematic review of the suicide literature and methodological considerations. *Am J Med Genet B Neuropsychiatr Genet* 2022; **189**: 221-246 [PMID: 35975759 DOI: 10.1002/ajmg.b.32917]

34   **Šalamon Arčan I**, Kouter K, Videtič Paska A. Depressive disorder and antidepressants from an epigenetic point of view. *World J Psychiatry* 2022; **12**: 1150-1168 [PMID: 36186508 DOI: 10.5498/wjp.v12.i9.1150]

35   **Gross JA**, Pacis A, Chen GG, Drupals M, Lutz PE, Barreiro LB, Turecki G. Gene-body 5-hydroxymethylation is associated with gene expression changes in the prefrontal cortex of depressed individuals. *Transl Psychiatry* 2017; **7**: e1119 [PMID: 28485726 DOI: 10.1038/tp.2017.93]

36   **Lutz PE**, Gross JA, Dhir SK, Maussion G, Yang J, Bramoulle A, Meaney MJ, Turecki G. Epigenetic Regulation of the Kappa Opioid Receptor by Child Abuse. *Biol Psychiatry* 2018; **84**: 751-761 [PMID: 28886759 DOI: 10.1016/j.biopsych.2017.07.012]

37   **World Health Organization**.   Schizophrenia. [cited 16 November 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/schizophrenia

38   **Trubetskoy V**, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, Bryois J, Chen CY, Dennison CA, Hall LS, Lam M, Watanabe K, Frei O, Ge T, Harwood JC, Koopmans F, Magnusson S, Richards AL, Sidorenko J, Wu Y, Zeng J, Grove J, Kim M, Li Z, Voloudakis G, Zhang W, Adams M, Agartz I, Atkinson EG, Agerbo E, Al Eissa M, Albus M, Alexander M, Alizadeh BZ, Alptekin K, Als TD, Amin F, Arolt V, Arrojo M, Athanasiu L, Azevedo MH, Bacanu SA, Bass NJ, Begemann M, Belliveau RA, Bene J, Benyamin B, Bergen SE, Blasi G, Bobes J, Bonassi S, Braun A, Bressan RA, Bromet EJ, Bruggeman R, Buckley PF, Buckner RL, Bybjerg-Grauholm J, Cahn W, Cairns MJ, Calkins ME, Carr VJ, Castle D, Catts SV, Chambert KD, Chan RCK, Chaumette B, Cheng W, Cheung EFC, Chong SA, Cohen D, Consoli A, Cordeiro Q, Costas J, Curtis C, Davidson M, Davis KL, de Haan L, Degenhardt F, DeLisi LE, Demontis D, Dickerson F, Dikeos D, Dinan T, Djurovic S, Duan J, Ducci G, Dudbridge F, Eriksson JG, Fañanás L, Faraone SV, Fiorentino A, Forstner A, Frank J, Freimer NB, Fromer M, Frustaci A, Gadelha A, Genovese G, Gershon ES, Giannitelli M, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, González Peñas J, González-Pinto A, Gopal S, Gratten J, Green MF, Greenwood TA, Guillin O, Gülöksüz S, Gur RE, Gur RC, Gutiérrez B, Hahn E, Hakonarson H, Haroutunian V, Hartmann AM, Harvey C, Hayward C, Henskens FA, Herms S, Hoffmann P, Howrigan DP, Ikeda M, Iyegbe C, Joa I, Julià A, Kähler AK, Kam-Thong T, Kamatani Y, Karachanak-Yankova S, Kebir O, Keller MC, Kelly BJ, Khrunin A, Kim SW, Klovins J, Kondratiev N, Konte B, Kraft J, Kubo M, Kučinskas V, Kučinskiene ZA, Kusumawardhani A, Kuzelova-Ptackova H, Landi S, Lazzeroni LC, Lee PH, Legge SE, Lehrer DS, Lencer R, Lerer B, Li M, Lieberman J, Light GA, Limborska S, Liu CM, Lönnqvist J, Loughland CM, Lubinski J, Luykx JJ, Lynham A, Macek M Jr, Mackinnon A, Magnusson PKE, Maher BS, Maier W, Malaspina D, Mallet J, Marder SR, Marsal S, Martin AR, Martorell L, Mattheisen M, McCarley RW, McDonald C, McGrath JJ, Medeiros H, Meier S, Melegh B, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mitjans M, Molden E, Molina E, Molto MD, Mondelli V, Moreno C, Morley CP, Muntané G, Murphy KC, Myin-Germeys I, Nenadić I, Nestadt G, Nikitina-Zake L, Noto C, Nuechterlein KH, O'Brien NL, O'Neill FA, Oh SY, Olincy A, Ota VK, Pantelis C, Papadimitriou GN, Parellada M, Paunio T, Pellegrino R, Periyasamy S, Perkins DO, Pfuhlmann B, Pietiläinen O, Pimm J, Porteous D, Powell J, Quattrone D, Quested D, Radant AD, Rampino A, Rapaport MH, Rautanen A, Reichenberg A, Roe C, Roffman JL, Roth J, Rothermundt M, Rutten BPF, Saker-Delye S, Salomaa V, Sanjuan J, Santoro ML, Savitz A, Schall U, Scott RJ, Seidman LJ, Sharp SI, Shi J, Siever LJ, Sigurdsson E, Sim K, Skarabis N, Slominsky P, So HC, Sobell JL, Söderman E, Stain HJ, Steen NE, Steixner-Kumar AA, Stögmann E, Stone WS, Straub RE, Streit F, Strengman E, Stroup TS, Subramaniam M, Sugar CA, Suvisaari J, Svrakic DM, Swerdlow NR, Szatkiewicz JP, Ta TMT, Takahashi A, Terao C, Thibaut F, Toncheva D, Tooney PA, Torretta S, Tosato S, Tura GB, Turetsky BI, Üçok A, Vaaler A, van Amelsvoort T, van Winkel R, Veijola J, Waddington J, Walter H, Waterreus A, Webb BT, Weiser M, Williams NM, Witt SH, Wormley BK, Wu JQ, Xu Z, Yolken R, Zai CC, Zhou W, Zhu F, Zimprich F, Atbaşoğlu EC, Ayub M, Benner C, Bertolino A, Black DW, Bray NJ, Breen G, Buccola NG, Byerley WF, Chen WJ, Cloninger CR, Crespo-Facorro B, Donohoe G, Freedman R, Galletly C, Gandal MJ, Gennarelli M, Hougaard DM, Hwu HG, Jablensky AV, McCarroll SA, Moran JL, Mors O, Mortensen PB, Müller-Myhsok B, Neil AL, Nordentoft M, Pato MT, Petryshen TL, Pirinen M, Pulver AE, Schulze TG, Silverman JM, Smoller JW, Stahl EA, Tsuang DW, Vilella E, Wang SH, Xu S; Indonesia Schizophrenia Consortium; PsychENCODE; Psychosis Endophenotypes International Consortium; SynGO Consortium, Adolfsson R, Arango C, Baune BT, Belangero SI, Børglum AD, Braff D, Bramon E, Buxbaum JD, Campion D, Cervilla JA, Cichon S, Collier DA, Corvin A, Curtis D, Forti MD, Domenici E, Ehrenreich H, Escott-Price V, Esko T, Fanous AH, Gareeva A, Gawlik M, Gejman PV, Gill M, Glatt SJ, Golimbet V, Hong KS, Hultman CM, Hyman SE, Iwata N, Jönsson EG, Kahn RS, Kennedy JL, Khusnutdinova E, Kirov G, Knowles JA, Krebs MO, Laurent-Levinson C, Lee J, Lencz T, Levinson DF, Li QS, Liu J, Malhotra AK, Malhotra D, McIntosh A, McQuillin A, Menezes PR, Morgan VA, Morris DW, Mowry BJ, Murray RM, Nimgaonkar V, Nöthen MM, Ophoff RA, Paciga SA, Palotie A, Pato CN, Qin S, Rietschel M, Riley BP, Rivera M, Rujescu D, Saka MC, Sanders AR, Schwab SG, Serretti A, Sham PC, Shi Y, St Clair D, Stefánsson H, Stefansson K, Tsuang MT, van Os J, Vawter MP, Weinberger DR, Werge T, Wildenauer DB, Yu X, Yue W, Holmans PA, Pocklington AJ, Roussos P, Vassos E, Verhage M, Visscher PM, Yang J, Posthuma D, Andreassen OA, Kendler KS, Owen MJ, Wray NR, Daly MJ, Huang H, Neale BM, Sullivan PF, Ripke S,

Walters JTR, O'Donovan MC; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022; **604**: 502-508 [PMID: 35396580 DOI: 10.1038/s41586-022-04434-5]

39   **National Institute of Mental Health**. Schizophrenia. [cited 20 November 2022]. Available from: https://www.nimh.nih.gov/health/topics/schizophrenia

40   **Khavari B**, Cairns MJ. Epigenomic Dysregulation in Schizophrenia: In Search of Disease Etiology and Biomarkers. *Cells* 2020; **9** [PMID: 32764320 DOI: 10.3390/cells9081837]

41   **Jiang T**, Zong L, Zhou L, Hou Y, Zhang L, Zheng X, Han H, Li S, Zhang W, Zhang J, Deng C, Jia Y, Zhao C. Variation in global DNA hydroxymethylation with age associated with schizophrenia. *Psychiatry Res* 2017; **257**: 497-500 [PMID: 28841512 DOI: 10.1016/j.psychres.2017.08.022]

42   **Zong L**, Zhou L, Hou Y, Zhang L, Jiang W, Zhang W, Wang L, Luo X, Wang S, Deng C, Peng Z, Li S, Hu J, Zhao H, Zhao C. Genetic and epigenetic regulation on the transcription of GABRB2: Genotype-dependent hydroxymethylation and methylation alterations in schizophrenia. *J Psychiatr Res* 2017; **88**: 9-17 [PMID: 28063323 DOI: 10.1016/j.jpsychires.2016.12.019]

43   **National Institute of Mental Health**. Bipolar Disorder. [cited 20 November 2022]. Available from: https://www.nimh.nih.gov/health/topics/bipolar-disorder

44   **Gavin DP**, Sharma RP, Chase KA, Matrisciano F, Dong E, Guidotti A. Growth arrest and DNA-damage-inducible, beta (GADD45b)-mediated DNA demethylation in major psychosis. *Neuropsychopharmacology* 2012; **37**: 531-542 [PMID: 22048458 DOI: 10.1038/npp.2011.221]

45   **Dong E**, Gavin DP, Chen Y, Davis J. Upregulation of TET1 and downregulation of APOBEC3A and APOBEC3C in the parietal cortex of psychotic patients. *Transl Psychiatry* 2012; **2**: e159 [PMID: 22948384 DOI: 10.1038/tp.2012.86]

46   **Penner-Goeke S**, Binder EB. Epigenetics and depression. *Dialogues Clin Neurosci* 2019; **21**: 397-405 [PMID: 31949407 DOI: 10.31887/DCNS.2019.21.4/ebinder]

47   **Li M**, D'Arcy C, Li X, Zhang T, Joober R, Meng X. What do DNA methylation studies tell us about depression? *Transl Psychiatry* 2019; **9**: 68 [PMID: 30718449 DOI: 10.1038/s41398-019-0412-y]

48   **Feng J**, Pena CJ, Purushothaman I, Engmann O, Walker D, Brown AN, Issler O, Doyle M, Harrigan E, Mouzon E, Vialou V, Shen L, Dawlaty MM, Jaenisch R, Nestler EJ. Tet1 in Nucleus Accumbens Opposes Depression- and Anxiety-Like Behaviors. *Neuropsychopharmacology* 2017; **42**: 1657-1669 [PMID: 28074830 DOI: 10.1038/npp.2017.6]

49   **Zhang Q**, Hu Q, Wang J, Miao Z, Li Z, Zhao Y, Wan B, Allen EG, Sun M, Jin P, Xu X. Stress modulates Ahi1-dependent nuclear localization of ten-eleven translocation protein 2. *Hum Mol Genet* 2021; **30**: 2149-2160 [PMID: 34218273 DOI: 10.1093/hmg/ddab179]

50   **Cheng Y**, Sun M, Chen L, Li Y, Lin L, Yao B, Li Z, Wang Z, Chen J, Miao Z, Xin N, Huang L, Allen EG, Wu H, Xu X, Jin P. Ten-Eleven Translocation Proteins Modulate the Response to Environmental Stress in Mice. *Cell Rep* 2018; **25**: 3194-3203.e4 [PMID: 30540950 DOI: 10.1016/j.celrep.2018.11.061]

51   **Mahjani B**, Bey K, Boberg J, Burton C. Genetics of obsessive-compulsive disorder. *Psychol Med* 2021; **51**: 2247-2259 [PMID: 34030745 DOI: 10.1017/S0033291721001744]

52   **Pauls DL**, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nat Rev Neurosci* 2014; **15**: 410-424 [PMID: 24840803 DOI: 10.1038/nrn3746]

53   **Yue W**, Cheng W, Liu Z, Tang Y, Lu T, Zhang D, Tang M, Huang Y. Genome-wide DNA methylation analysis in obsessive-compulsive disorder patients. *Sci Rep* 2016; **6**: 31333 [PMID: 27527274 DOI: 10.1038/srep31333]

54   **Cappi C**, Diniz JB, Requena GL, Lourenço T, Lisboa BC, Batistuzzo MC, Marques AH, Hoexter MQ, Pereira CA, Miguel EC, Brentani H. Epigenetic evidence for involvement of the oxytocin receptor gene in obsessive-compulsive disorder. *BMC Neurosci* 2016; **17**: 79 [PMID: 27903255 DOI: 10.1186/s12868-016-0313-4]

55   **Grünblatt E**, Marinova Z, Roth A, Gardini E, Ball J, Geissler J, Wojdacz TK, Romanos M, Walitza S. Combining genetic and epigenetic parameters of the serotonin transporter gene in obsessive-compulsive disorder. *J Psychiatr Res* 2018; **96**: 209-217 [PMID: 29102815 DOI: 10.1016/j.jpsychires.2017.10.010]

56   **Park CI**, Kim HW, Jeon S, Kang JI, Kim SJ. Reduced DNA methylation of the oxytocin receptor gene is associated with obsessive-compulsive disorder. *Clin Epigenetics* 2020; **12**: 101 [PMID: 32631409 DOI: 10.1186/s13148-020-00890-w]

57   **D'Addario C**, Bellia F, Benatti B, Grancini B, Vismara M, Pucci M, De Carlo V, Viganò C, Galimberti D, Fenoglio C, Scarpini E, Maccarrone M, Dell'Osso B. Exploring the role of BDNF DNA methylation and hydroxymethylation in patients with obsessive compulsive disorder. *J Psychiatr Res* 2019; **114**: 17-23 [PMID: 31004918 DOI: 10.1016/j.jpsychires.2019.04.006]

58   **National Institute of Mental Health**. Substance Use and Co-Occurring Mental Disorders. [cited 20 November 2022]. Available from: https://www.nimh.nih.gov/health/topics/substance-use-and-mental-health

59   **National Institute on Drug Abuse**. Common Comorbidities with Substance Use Disorders Research Report. [cited 20 November 2022]. Available from: https://nida.nih.gov/publications/research-reports/common-comorbidities-substance-use-disorders/introduction

60   **Clark SL**, Chan RF, Zhao M, Xie LY, Copeland WE, Penninx BWJH, Aberg KA, van den Oord EJCG. Dual methylation and hydroxymethylation study of alcohol use disorder. *Addict Biol* 2022; **27**: e13114 [PMID: 34791764 DOI: 10.1111/adb.13114]

61   **Cadet JL**, Jayanthi S. Epigenetics of addiction. *Neurochem Int* 2021; **147**: 105069 [PMID: 33992741 DOI: 10.1016/j.neuint.2021.105069]

62   **Gatta E**, Auta J, Gavin DP, Bhaumik DK, Grayson DR, Pandey SC, Guidotti A. Emerging Role of One-Carbon Metabolism and DNA Methylation Enrichment on δ-Containing GABAA Receptor Expression in the Cerebellum of Subjects with Alcohol Use Disorders (AUD). *Int J Neuropsychopharmacol* 2017; **20**: 1013-1026 [PMID: 29020412 DOI: 10.1093/ijnp/pyx075]

63   **Jayanthi S**, Gonzalez B, McCoy MT, Ladenheim B, Bisagno V, Cadet JL. Methamphetamine Induces TET1- and TET3-Dependent DNA Hydroxymethylation of Crh and Avp Genes in the Rat Nucleus Accumbens. *Mol Neurobiol* 2018; **55**: 5154-5166 [PMID: 28842817 DOI: 10.1007/s12035-017-0750-9]

64   **Anier K**, Urb M, Kipper K, Herodes K, Timmusk T, Zharkovsky A, Kalda A. Cocaine-induced epigenetic DNA modification in mouse addiction-specific and non-specific tissues. *Neuropharmacology* 2018; **139**: 13-25 [PMID: 29964092 DOI: 10.1016/j.neuropharm.2018.06.036]

65   **Niinep K**, Anier K, Eteläinen T, Piepponen P, Kalda A. Repeated Ethanol Exposure Alters DNA Methylation Status and Dynorphin/Kappa-Opioid Receptor Expression in Nucleus Accumbens of Alcohol-Preferring AA Rats. *Front Genet* 2021; **12**: 750142 [PMID: 34899839 DOI: 10.3389/fgene.2021.750142]

Psychological trauma, posttraumatic stress disorder and trauma-related depression: A mini-review

Shi-Kai Wang, Min Feng, Yu Fang, Liang Lv, Gui-Lan Sun, Sheng-Liang Yang, Ping Guo, Shan-Fei Cheng, Min-Cai Qian, Huan-Xin Chen

Shi-Kai Wang, Min Feng, Yu Fang, Liang Lv, Gui-Lan Sun, Sheng-Liang Yang, Ping Guo, Shan-Fei Cheng, Department of Psychiatry, The Third People's Hospital Affiliated to Huzhou University, Huzhou 313000, Zhejiang Province, China

Min-Cai Qian, Department of Neurosis and Psychosomatic Diseases, The Third People's Hospital Affiliated to Huzhou University, Huzhou 313000, Zhejiang Province, China

Huan-Xin Chen, Department of Key Laboratory, The Third People's Hospital Affiliated to Huzhou University, Huzhou 313000, Zhejiang Province, China

Corresponding author: Ping Guo, Doctor, MD, Associate Chief Physician, Deputy Director, Department of Psychiatry, The Third People's Hospital Affiliated to Huzhou University, No. 2088 Tiaoxi East Road, Wuxing District, Huzhou 313000, Zhejiang Province, China. gp12131997@126.com

Abstract

There are various types of traumatic stimuli, such as catastrophic events like wars, natural calamities like earthquakes, and personal trauma from physical and psychological neglect or abuse and sexual abuse. Traumatic events can be divided into type I and type II trauma, and their impacts on individuals depend not only on the severity and duration of the traumas but also on individuals' self-evaluation of the traumatic events. Individual stress reactions to trauma include posttraumatic stress disorder (PTSD), complex PTSD and trauma-related depression. Trauma-related depression is a reactive depression with unclear pathology, and depression occurring due to trauma in the childhood has gained increasing attention, because it has persisted for a long time and does not respond to conventional antidepressants but shows good or partial response to psychotherapy, which is similar to the pattern observed for PTSD. Because trauma-related depression is associated with high risk of suicide and is chronic with a propensity to relapse, it is necessary to explore its pathogenesis and therapeutic strategy.

Key Words: Psychological trauma; Trauma-related depression; Reactive depression; Posttraumatic stress disorder; Antidepressant; Psychotherapy

Core Tip: Exposure to psychological trauma may induce posttraumatic stress disorder (PTSD) and trauma-related depression. Major depression can be a progression secondary to PTSD. Both trauma-related depression and PTSD show good response to psychotherapy or prazosin, but a poor response to conventional antidepressants, suggesting that trauma-related depression should have different pathological mechanisms, like energy metabolism deficiency. It is necessary to explore the pathogenesis of and therapeutic strategy for PTSD and trauma-related depression.

INTRODUCTION

Psychological trauma is a stressful event that causes distress that exceeds an individual's ability to integrate the emotions and cognitions involved in the experience[1]. Its occurrence is unexpected and uncontrollable, often exceeding people's coping resources and making them feel powerless, helpless, and fearful. Besides natural disasters and wars, psychological trauma also encompasses various forms of physical and emotional abuse or neglect, sexual abuse, bullying, or household dysfunction experienced throughout one's entire lifespan[2].

Psychological trauma has attracted attention when the veterans returned from the Vietnam War. Although their lives have been restored, the scenarios on the battlefield always reappear and flash up in their brain every day accompanied by fragmentary memories, sleep disorders, nightmares, unstable moods, and anhedonia[3]. For the evaluation and intervention of the veterans' psychological crisis, posttraumatic stress disorder (PTSD) was first inserted in the third edition of Diagnostic and Statistical Manual of Mental Disorders in 1980[4].

Traumatic events increase not only the risk of PTSD but also depression. Trauma-related depression, which meets the criteria of major depressive disorder, can be caused directly or indirectly by psychological trauma. Previous studies showed that 61% of patients with first-episode depression and 51% with recurrent depression reported childhood or recent trauma, including adverse childhood experiences[5], recent life events[6], and occupational stressors[7]. While the pathological mechanism remains unclarified, trauma-related depression has attracted more attention because of its prolonged duration and resistance to conventional antidepressants. However, patients with trauma-related depression have a full or partial response to psychotherapy, like PTSD. Since trauma-related depression is at a high risk of suicide and is prone to relapse and be chronic, it is essential to explore the pathogenesis, therapeutic strategy, and causal relationships between psychological trauma, PTSD, and trauma-related depression. In this article, we will review the clinical characteristics of and relationship between PTSD and trauma-related depression, and their therapies.

TYPES AND CHARACTERICS OF TRAUMA

Terr[8] divided childhood trauma into type I and type II trauma (Table 1)[8,9] according to trauma characteristics. Type I trauma includes fully detailed memories, "omens", and misperceptions (such as a car accident) and has characteristics including: (1) The time of trauma formation is short or at one time; (2) trauma may occur in different stages of childhood and adulthood; (3) the duration of trauma is not long, usually within three months; and (4) some heal naturally, some benefit from treatment, and some transform into type II. Type I trauma may lead to acute stress disorder (ASD), PTSD, and adjustment disorders. Among these disorders, PTSD is the most harmful. The diagnostic requirements of PTSD include re-experiencing traumatic events, avoidance, increased sensitivity or alertness, and functional impairment.

Type II is complex trauma, including denial and numbing, self-hypnosis and dissociation, and rage, which repeatedly occurs in childhood and lasts for a long time, such as physical and emotional abuse and neglect. Its characteristics include a long time to form and a broad impact on an individual's body and mind. The trauma may occur in different stages of childhood development or adult life. In general, type II trauma presents complex and diverse symptoms and will not heal naturally. 25% to 30% of type II trauma may evolve from type I trauma[10]. Compared with type I, type II trauma has a more severe impact on individuals. It also significantly differs from type I trauma in terms of its symptoms, neuroimaging findings, treatments, and prognoses. Furthermore, it also often leads to complex PTSD (CPTSD)[11].

Table 1 Characteristics of Type I and Type II trauma

Characteristics	Type I	Type II
Resource	Disaster or accident	Abuse or violence or neglect
Onset	Acute onset	Acute or insidious onset in childhood
Duration	Sudden, transient	Repeated, long-lasting
Outcome	Be healed or develop to Type II	Be scarred or protracted
Manifestation	Re-experience, avoidance, alertness, *etc.* (take PTSD as an example)	PTSD symptoms, disorders in self-organization, disassociation
Mental disorders	Acute stress disorder, PTSD, adjustment disorder	CPTSD, adjustment disorder, Dissociative/conversive disorder

PTSD: Posttraumatic stress disorder; CPTSD: Complex posttraumatic stress disorder.

The term "complex PTSD" was proposed by Herman[11] to describe the repeated and long-term symptoms experienced by survivors of trauma, including changes in emotional regulation, consciousness, self-perception, and interpersonal relationships. This disorder can result from a single severe traumatic event or multiple chronic traumas that are difficult or impossible to escape, such as childhood abuse, domestic violence, torture, and imprisonment. The diagnosis of CPTSD in International Classification of Diseases 11th edition (ICD-11)[9] requires not only meeting the diagnostic criteria of PTSD but also evidence of disorders in self-organization, including affective dysregulation, negative self-concept, and disorders in relationships.

There is additional type of trauma called chronic unpredictable mild stress (CUMS), which has been used to model depressive symptoms in rodents[12]. Long-term (> 3 wk) exposure to a series of mild but unpredictable stressors can make animals depressive, which simulates a depressive state of human beings after encountering the stressors in the real world. However, there have been few clinical studies on CUMS thus far[13].

TRAUMA AND STRESS RESPONSE

The impact of trauma depends not only on the traumatic event itself but also on the individuals' perceptions, psychological defense mechanisms, and whether the support system is timely and sufficient. Although genetic heritability is one of the risk factors for the development of PTSD or major depressive disorder (MDD) in the population with traumas, a genetic factor may be less important as trauma exposure increases, that is, high levels of trauma are likely to lead to PTSD and MDD[14].

From the perspective of psychiatric phenomenology, traumatic events may lead to a series of nonspecific mental and behavioral symptoms of post-trauma reaction. The impact of trauma on an individual's mental state is mainly determined by the trauma's intensity, duration, and age. According to the theory of the classical response to stress[15], stress reaction can be roughly divided into alarm, resistance, and exhaustion stages[16]. In the alarm stage of post-trauma condition, a stress reaction may manifest a "fight or flight" response by activating the sympathetic nervous system to release catecholamine. If stress reaction is insufficient, ASD will occur. After the acute stage comes the resistance stage. This stage involves adjustment to the persistent trauma or the after-effects of traumatic events *via* the activation of the hypothalamus–pituitary–adrenal (HPA) axis and promotion of endogenous glucocorticoids function to maintain the internal environment. If the stress reaction is insufficient, the manifestations of PTSD will appear.

If the trauma is too intense or prolonged, Individuals will encounter the exhaustion stage by excessive mobilization of the sympathetic nervous system and HPA axis, and manifests maladjustment or trauma-related depression (reactive depression). Therefore, multiple traumatic events can have cumulative detrimental effects on mental health of the victims[17], manifesting depressive symptoms such as negative emotions, guilt, shame, self-blame, social withdrawal, or social isolation. They can also become irritable, aggressive, violent, and of self-injury or suicidal behaviors, or have persistent dissociative symptoms and acoustic and visual hallucinations similar to those that occur in psychosis[18, 19]. Individuals with post-trauma reactions are often diagnosed with depression or bipolar depression with or without psychotic symptoms or borderline personality disorder according to the ICD-11 or the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)[20].

PTSD AND TRAUMA-RELATED DEPRESSION

Relationship between PTSD and trauma-related depression

Studies have shown that collective trauma caused by earthquakes and plagues may lead to collective emotions accompanied by pro-social behaviors, thus reducing the adverse effects of traumatic events on individuals[21]. However, suffering from interpersonal trauma (individualized trauma) such as abuse, neglect, or sexual violence often brings negative consequences which are easily internalized, become chronic and gradually develop into "trauma mode" as Piaget referred to[22], which manifests as persistent depression, negative cognition, negative self-concept, and self-injury/suicide[23].

ASD usually occurs within minutes or hours after a severe traumatic event. The symptoms are transient, usually relieved within days or a week. Therefore, PTSD is the most common lasting and harmful stress response to trauma and it is dominated by negative emotions such as anxiety, fear, irritability, and depression. The onset of PTSD usually occurs one month or several years after traumatic events. PTSD and depression often occur comorbidly. As a result of a meta-analysis (k = 57 studies; n = 6670 participants), 52% of individuals with PTSD had comorbid MDD[23]. In addition, a number of overlapping symptoms were reported. Although it is sometimes challenging to differentiate, PTSD and MDD are two significantly different diseases.

Although the depressive symptoms present in PTSD can predict the occurrence and severity of depression, some scholars, such as Freedman *et al*[24] and Bleich *et al*[25] argue that there is no chronological progression from PTSD to MDD. However, many studies support the continuity between PTSD and MDD[26,27]. PTSD can lead to affective disorder[16], significantly increasing the risk for the first-onset of major depression[28].

The COVID-19 pandemic caused long-term psychological impacts on people, like insomnia, anxiety, depression, and burnout syndrome, which has raised public health concerns globally. Burnout is a state of physical or mental stress resulting from prolonged exposure to job stressors. Burnout prevalence differs in different specialties. Studies have shown that after a high workload or prolonged contact with patients, nearly one-third of healthcare workers met the clinical level of exhaustion and manifested anxiety, irritation, fatigue, depression, depersonalization, and PTSD[29,30]. A 1-year observational study showed that the prevalence of burnout and anxiety was similar at 3 mo (52% *vs* 51%) and 12 mo (23% *vs* 23%), while the prevalence of PTSD was higher than that of depression at both 3 mo (23% *vs* 11%) and 12 mo (11% *vs* 6%)[31].

The prevalence of depression and PTSD-like symptoms in adolescents increased significantly during the pandemic period of COVID-19[32,33]. During the COVID-19 pandemic, the comorbidity prevalence of PTSD and depression was about 50%[34]. However, a remote telephone interview revealed that the prevalence of PTSD and depression in patients who recovered from COVID-19 was 56.9% and 29.0%, respectively[35]. It indicates that PTSD symptoms are the main symptoms during or at the beginning of traumatic events.

In a survey of the elderly, the lifetime prevalence and 12-mo prevalence of sexual violence are 44% and 8%, respectively, while the lifetime prevalence of depression, anxiety, and PTSD are 27%, 26%, and 6%, respectively[36]. It indicates that the long-term effects of traumatic events on individuals are mainly depressive symptoms, and the patients might be diagnosed with major depressive disorder according to DSM-5 or ICD-10. Because this type of depression is associated with psychological trauma(s), it is often resistant to the treatment and much harmful.

Treatment and potential mechanism of PTSD and trauma-related depression

Trauma-related depression is caused by intense and persistent frustration or other psychological conflict factors. It may be considered reactive depression (stress-induced depression) and different from endogenous (biogenic) depression. Reactive depression and endogenous depression were proposed by the German psychiatrist Kurt Schneider in 1920[37] in trying to classify depression by its etiology. This classification enjoyed broad acceptance[38] up to the introduction of DSM-IV in 1994[39]. Since then, psychiatrists and scholars have returned to the principle of phenomenological description of mental disorders. For instance, if a patient has clinical manifestations that meet the descriptive criteria for depression, the patient will be uniformly diagnosed with depression without emphasizing its etiological classification, which makes the diagnosis and intervention much easier. The etiology of different depression types seemed less important, particularly since the discovery of tricyclic antidepressants and the establishment of a monoamine-based hypothesis[40].

However, since 1994 and even more since the COVID-19 pandemic, patients with reactive depression have increased markedly[41]. The poor efficiency of conventional antidepressants in reactive depression has again drawn attention to psychological trauma and "reactive depression", particularly depression with childhood trauma. Studies[42,43] have confirmed that depression related to trauma (especially childhood trauma) is very complex in clinical manifestations and many other aspects, such as neurobiological factors, treatment response and prognosis.

Childhood trauma or a recent traumatic event is an important precipitating and perpetuating factor of depression in adolescents and elderly patients[36,43]. Severe psychological trauma can also lead to PTSD or CPTSD with comorbid depression. For example, more than 50% of PTSD patients have

Table 2 Studies investigating the therapy on major depressive disorder patients with childhood trauma or recent trauma

Ref.	Study/review	Details	Tools	Results
Nemeroff *et al*[47], 2003	RCT	681 MDD patients with childhood trauma were assigned to nefazodone, CBASP, or combination	HRSD24	For those with childhood trauma, psychotherapy alone was superior to antidepressant monotherapy
Asarnow *et al*[52], 2009	RCT	334 youth failed in an adequate SSRI trial were randomized to 12 wk with an alternative SSRI, an alternative SSRI + CBT, venlafaxine, or venlafaxine + CBT	CDRS-R, CGI-I	The CBT or combined treatment was superior to medication alone
Nanni *et al*[50], 2012	meta-analysis	10 clinical trials of 3098 MDD subjects with childhood trauma were analyzed based on depression course: recurrence or persistence	CIDI, PSE, SCAN, MINI or HAMD	Childhood maltreatment was associated with lack of response to treatment and lack of remission (OR = 1.43, 95%CI: 1.11-1.83)
Williams *et al*[48], 2016	Cohort study	1008 MDD and 336 healthy controls were treated with escitalopram, sertraline or venlafaxine for 8 wk	QIDS_SR16, HRSD17	Below 7 yr of age predicted poorer outcomes, and 4-7 yr the poorest
Yrondi *et al*[51], 2019	Cohort study	In 291 TRD patients, 135 (52.7%) were available at 1-year follow-up	QIDS_SR, MADRS	Baseline CTQ scores had a significant influence on remission at 1 year [χ^2 (1) = 5.57; $P < 0.05$]
Christensen *et al*[6], 2020	Cohort study	61% of subjects (1113/1811) reported trauma history, and were treated with vortioxetine (5-20 mg/d) or placebo for 8 wk	MADRS, CGI-I	Subjects with trauma with placebo were more likely to relapse than with vortioxetine
Menke *et al*[55], 2021	Cohort study	150 in-patients of MDD were recruited in the 4-wk antidepressant trial, 68 with multiple childhood trauma (*i.e.* ≥ 3) and 59 with ≥ 3 severe recent life events	HRSD21	Severe recent life events were associated with a poor response to antidepressants ($F = 7.456$; df = 1; $P = 0.008$), These effects may not be observed with childhood trauma

RCT: Randomized controlled trial; MDD: Major depressive disorder; CBASP: Cognitive behavioral analysis system of psychotherapy; HRSD24: Hamilton rating scale for depression-24 items; SSRI: Selective serotonin reuptake inhibitor; CBT: Cognitive-behavioral therapy; CDRS-R: Children depression rating scale-revised; CGI-I: Clinical global impression–improvement; CIDI-C: Composite international diagnostic interview-core version; PSE: Present state examination; SCAN: Schedules for clinical assessment in neuropsychiatry; MINI: The MINI-international neuropsychiatric interview; HAMD: Hamilton depressive scale; OR: Odds ratio; 95%CI: 95% confidence interval; QIDS_SR16: The 16-item self-report versions of the quick inventory of depressive symptomatology; HRSD17: Hamilton rating scale for depression-17 items; TRD: Treatment-resistant depression; QIDS_SR: Self-report versions of the quick inventory of depressive symptomatology; MADRS: The Montgomery-Asberg depression rating scale; CTQ: The Childhood trauma questionnaire; HRSD21: Hamilton rating scale for depression-21 items.

comorbid depression[34]. Psychological trauma may affect the individual's response to antidepressants, clinical outcomes, and function. Regarding the treatment of PTSD, paroxetine, sertraline, fluoxetine, and venlafaxine are recommended, however, the efficiency of selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors in PTSD is comparably low (only about half as strong)[44]. Psychotherapy is the treatment of choice for PTSD, including cognitive behavior therapy (CBT), prolonged exposure, and eye movement desensitization and reprocessing (EMDR)[45].

The treatment of trauma-related depression, particularly in patients with childhood trauma, has been extensively studied (Table 2). Previous studies have shown that various childhood abuses is unfavorable to the treatment, and the poor response is significantly related to childhood abuse[46-48], particularly trauma that occurred before the age of 7 years. Even after 8 wk of therapy with antidepressants, there was no remission. Moreover, there was a high risk of recurrence[5,48]. Meanwhile, childhood trauma is also an important risk factor for suicidal ideation and the increased severity of refractory depression[49-51]. However, although patients with chronic depression after trauma have a comparatively good response to the psychotherapy with EMDR[47]. Asarnow *et al*[52] found that patients of refractory depression with a history of abuse have a significantly lower response to CBT than those without abuse. Shirk *et al*[53] believed that trauma-focused cognitive behavioral therapy (TF-CBT) could significantly improve depressive symptoms. A meta-analysis[54] showed that TF-CBT and EMDR are beneficial in alleviating the traumatic experience, depression, and anxiety of patients with PTSD. It was found that psychotherapy has better compliance than psychopharmacological therapy. Therefore, it is suggested that psychotherapy should be introduced in the early stage of the treatment of trauma-related depression[55].

Taken together, for the patients with trauma-related depression, the symptomatology is more complex; the suicide rate is higher[49]; the clinical condition is more prone to be chronic, and the response to antidepressant is poorer[5,42,47,48]. Therefore, it is speculated that trauma-related depression may have different biological mechanisms compared to other depressed patients[56,57].

Compared with classic depression, there are few studies on the underlying neurobiological mechanisms of trauma-related depression. It was previously thought that the occurrence of PTSD or chronic PTSD was related to noradrenergic dysfunction[58] or cytokines[57]. However, in recent years, we have learned by the CUMS model that energy metabolism disorder might play an important role[59-61].

Although the etiological mechanisms underlying PTSD or trauma-related depression are not known in detail, the efficacy of certain therapies may be indicative of existing pathomechanisms[62]. For example, in a case study, it was reported that low-dose prazosin led quickly to rapid improvement in depressive symptoms, including cognitive function in a therapy-resistant depressive patient with comorbid chronic PTSD[63]. The patient had previously received antidepressants that work *via* serotoninergic, noradrenergic, and dopaminergic mechanisms as well as several sessions of modified electroconvulsive therapy but did not benefit from these treatments, suggesting that prazosin may have acted by different pharmacological mechanisms from monoamine hypothesis[64]. This observation might turn out to be important in order to explore the pathogenesis of PTSD and trauma-related depression[65].

However, there is also a meta-analysis[50] has showed that, for adult depressive patients with childhood abuse, the effectiveness of antidepressant drugs alone, and psychotherapy alone, combined therapy is not satisfactory. In the same sense, some PTSD patients still have poor responses to psychotherapy. Therefore, we need to explore new treatment methods to improve the prognosis of PTSD patients with comorbid depression. For this purpose, it is necessary to expand our knowledge of the pathogenesis of trauma-related depression.

CONCLUSION

Exposure to psychological trauma may induce PTSD and trauma-related depression. Major depression can be a progression secondary to PTSD. Both trauma-related depression and PTSD show good response to psychotherapy or prazosin, but a poor response to conventional antidepressants, suggesting that trauma-related depression should have different pathological mechanisms, like energy metabolism deficiency. It is necessary to explore the pathogenesis of and therapeutic strategy for PTSD and trauma-related depression. Although we reviewed detailed features of trauma-related depression and PTSD, the relationship between them is ambiguous. In this article, one weakness is the limited discussion of the pathogenesis of trauma-related depression and PTSD, and the etiological roles in the pathogenesis.

FOOTNOTES

ORCID number: Shi-Kai Wang 0000-0002-2321-0524; Ping Guo 0000-0002-3735-1993.

REFERENCES

1   **Kolk BA**, Brown P, Hart O. Pierre Janet on post-traumatic stress. *J Trauma Stress* 1989; **2**: 365-378 [DOI:

10.1002/jts.2490020403]

2   **Teicher MH**, Gordon JB, Nemeroff CB. Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Mol Psychiatry* 2022; **27**: 1331-1338 [PMID: 34737457 DOI: 10.1038/s41380-021-01367-9]

3   **Horowitz MJ**, Solomon GF. A Prediction of Delayed Stress Response Syndromes in Vietnam Veterans. *J Soc Issues* 1975; **31**: 67-80 [DOI: 10.1111/j.1540-4560.1975.tb01012.x]

4   **Cooper AM**, Robert M. Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. *Am J Psychiatry* 1981 [DOI: 10.1176/ajp.138.1.128]

5   **Hovens JG**, Giltay EJ, Spinhoven P, van Hemert AM, Penninx BW. Impact of childhood life events and childhood trauma on the onset and recurrence of depressive and anxiety disorders. *J Clin Psychiatry* 2015; **76**: 931-938 [PMID: 25699690 DOI: 10.4088/JCP.14m09135]

6   **Christensen MC**, Florea I, Loft H, McIntyre RS. Efficacy of vortioxetine in patients with major depressive disorder reporting childhood or recent trauma. *J Affect Disord* 2020; **263**: 258-266 [PMID: 31818787 DOI: 10.1016/j.jad.2019.11.074]

7   **Petereit-Haack G**, Bolm-Audorff U, Romero Starke K, Seidler A. Occupational Risk for Post-Traumatic Stress Disorder and Trauma-Related Depression: A Systematic Review with Meta-Analysis. *Int J Environ Res Public Health* 2020; **17** [PMID: 33327657 DOI: 10.3390/ijerph17249369]

8   **Terr LC**. Childhood traumas: an outline and overview. *Am J Psychiatry* 1991; **148**: 10-20 [PMID: 1824611 DOI: 10.1176/ajp.148.1.10]

9   **Hyland P**, Murphy J, Shevlin M, Vallières F, McElroy E, Elklit A, Christoffersen M, Cloitre M. Variation in post-traumatic response: the role of trauma type in predicting ICD-11 PTSD and CPTSD symptoms. *Soc Psychiatry Psychiatr Epidemiol* 2017; **52**: 727-736 [PMID: 28194504 DOI: 10.1007/s00127-017-1350-8]

10   **Yehuda R**, Resnick H, Kahana B, Giller EL. Long-lasting hormonal alterations to extreme stress in humans: normative or maladaptive? *Psychosom Med* 1993; **55**: 287-297 [PMID: 8346336 DOI: 10.1097/00006842-199305000-00006]

11   **Herman JL**. Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. *J Trauma Stress* 1992; **5**: 377-391 [DOI: 10.1007/BF00977235]

12   **Markov DD**, Novosadova EV. Chronic Unpredictable Mild Stress Model of Depression: Possible Sources of Poor Reproducibility and Latent Variables. *Biology (Basel)* 2022; **11** [PMID: 36358321 DOI: 10.3390/biology11111621]

13   **Jin K**, Zhang S, Jiang C, Liu R, Chen B, Zhao H, Zhang Q, Shen Z, Xu P, Hu X, Jiao J, Lu J, Huang M. The role of reelin in the pathological mechanism of depression from clinical to rodents. *Psychiatry Res* 2022; **317**: 114838 [PMID: 36103758 DOI: 10.1016/j.psychres.2022.114838]

14   **Lipsky RK**, Garrett ME, Dennis MF; VA Mid-Atlantic MIRECC Workgroup, Hauser MA, Beckham JC, Ashley-Koch AE, Kimbrel NA. Impact of traumatic life events and polygenic risk scores for major depression and posttraumatic stress disorder on Iraq/Afghanistan Veterans. *J Psychiatr Res* 2023; **158**: 15-19 [PMID: 36542982 DOI: 10.1016/j.jpsychires.2022.12.014]

15   **Selye H**. The general adaptation syndrome and the diseases of adaptation. *J Clin Endocrinol Metab* 1946; **6**: 117-230 [PMID: 21025115 DOI: 10.1210/jcem-6-2-117]

16   **Ducrocq F**, Vaiva G, Cottencin O, Molenda S, Bailly D. Post-traumatic stress, post-traumatic depression and major depressive episode: literature. *Encephale* 2001; **27**: 159-168 [PMID: 11407268]

17   **Agyapong B**, Shalaby R, Eboreime E, Obuobi-Donkor G, Owusu E, Adu MK, Mao W, Oluwasina F, Agyapong VIO. Cumulative trauma from multiple natural disasters increases mental health burden on residents of Fort McMurray. *Eur J Psychotraumatol* 2022; **13**: 2059999 [PMID: 35599978 DOI: 10.1080/20008198.2022.2059999]

18   **Longden E**, Madill A, Waterman MG. Dissociation, trauma, and the role of lived experience: toward a new conceptualization of voice hearing. *Psychol Bull* 2012; **138**: 28-76 [PMID: 22082488 DOI: 10.1037/a0025995]

19   **Ross J**, Armour C, Kerig PK, Kidwell MC, Kilshaw RE. A network analysis of posttraumatic stress disorder and dissociation in trauma-exposed adolescents. *J Anxiety Disord* 2020; **72**: 102222 [PMID: 32272318 DOI: 10.1016/j.janxdis.2020.102222]

20   **Maercker A**, Cloitre M, Bachem R, Schlumpf YR, Khoury B, Hitchcock C, Bohus M. Complex post-traumatic stress disorder. *Lancet* 2022; **400**: 60-72 [PMID: 35780794 DOI: 10.1016/S0140-6736(22)00821-2]

21   **Gold SN**. Collective trauma: Terrain that challenges conventional wisdom on mental health. *Psyccritiques* 2014; **59** [DOI: 10.1037/a0036545]

22   **Allasio D**, Fischer H. Torture *vs* child abuse: what's the difference? *Clin Pediatr (Phila)* 1998; **37**: 269-271 [PMID: 9564579 DOI: 10.1177/000992289803700410]

23   **Rytwinski NK**, Scur MD, Feeny NC, Youngstrom EA. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress* 2013; **26**: 299-309 [PMID: 23696449 DOI: 10.1002/jts.21814]

24   **Freedman SA**, Brandes D, Peri T, Shalev A. Predictors of chronic post-traumatic stress disorder. A prospective study. *Br J Psychiatry* 1999; **174**: 353-359 [PMID: 10533555 DOI: 10.1192/bjp.174.4.353]

25   **Bleich A**, Koslowsky M, Dolev A, Lerer B. Post-traumatic stress disorder and depression. An analysis of comorbidity. *Br J Psychiatry* 1997; **170**: 479-482 [PMID: 9307701 DOI: 10.1192/bjp.170.5.479]

26   **Kessler RC**, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995; **52**: 1048-1060 [PMID: 7492257 DOI: 10.1001/archpsyc.1995.03950240066012]

27   **Perkonigg A**, Kessler RC, Storz S, Wittchen H -U. Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity. *Acta Psychiatr Scand* 2000; **101**: 46-59 [PMID: 10674950 DOI: 10.1034/j.1600-0447.2000.101001046.x]

28   **Breslau N**, Davis GC, Peterson EL, Schultz L. Psychiatric sequelae of posttraumatic stress disorder in women. *Arch Gen Psychiatry* 1997; **54**: 81-87 [PMID: 9006404 DOI: 10.1001/archpsyc.1997.01830130087016]

29   **Dimitriu MCT**, Pantea-Stoian A, Smaranda AC, Nica AA, Carap AC, Constantin VD, Davitoiu AM, Cirstoveanu C, Bacalbasa N, Bratu OG, Jacota-Alexe F, Badiu CD, Smarandache CG, Socea B. Burnout syndrome in Romanian medical

residents in time of the COVID-19 pandemic. *Med Hypotheses* 2020; **144**: 109972 [PMID: 32531540 DOI: 10.1016/j.mehy.2020.109972]

30   **Cotel A**, Golu F, Pantea Stoian A, Dimitriu M, Socea B, Cirstoveanu C, Davitoiu AM, Jacota Alexe F, Oprea B. Predictors of Burnout in Healthcare Workers during the COVID-19 Pandemic. *Healthcare (Basel)* 2021; **9** [PMID: 33803286 DOI: 10.3390/healthcare9030304]

31   **Cyr S**, Marcil MJ, Houchi C, Marin MF, Rosa C, Tardif JC, Guay S, Guertin MC, Genest C, Forest J, Lavoie P, Labrosse M, Vadeboncoeur A, Selcer S, Ducharme S, Brouillette J. Evolution of burnout and psychological distress in healthcare workers during the COVID-19 pandemic: a 1-year observational study. *BMC Psychiatry* 2022; **22**: 809 [PMID: 36539718 DOI: 10.1186/s12888-022-04457-2]

32   **Stewart TM**, Fry D, McAra L, Hamilton S, King A, Laurie M, McCluskey G. Rates, perceptions and predictors of depression, anxiety and Post Traumatic Stress Disorder (PTSD)-like symptoms about Covid-19 in adolescents. *PLoS One* 2022; **17**: e0266818 [PMID: 35476795 DOI: 10.1371/journal.pone.0266818]

33   **Zhou SJ**, Zhang LG, Wang LL, Guo ZC, Wang JQ, Chen JC, Liu M, Chen X, Chen JX. Prevalence and socio-demographic correlates of psychological health problems in Chinese adolescents during the outbreak of COVID-19. *Eur Child Adolesc Psychiatry* 2020; **29**: 749-758 [PMID: 32363492 DOI: 10.1007/s00787-020-01541-4]

34   **Karatzias T**, Shevlin M, Murphy J, McBride O, Ben-Ezra M, Bentall RP, Vallières F, Hyland P. Posttraumatic Stress Symptoms and Associated Comorbidity During the COVID-19 Pandemic in Ireland: A Population-Based Study. *J Trauma Stress* 2020; **33**: 365-370 [PMID: 32662129 DOI: 10.1002/jts.22565]

35   **Srivastava A**, Bala R, Devi TP, Anal L. Psychological trauma and depression in recovered COVID-19 patients: A telecommunication based observational study. *Trends Psychiatry Psychother* 2021 [PMID: 34967182 DOI: 10.47626/2237-6089-2021-0381]

36   **Nobels A**, Lemmens G, Thibau L, Beaulieu M, Vandeviver C, Keygnaert I. "Time Does Not Heal All Wounds": Sexual Victimisation Is Associated with Depression, Anxiety, and PTSD in Old Age. *Int J Environ Res Public Health* 2022; **19** [PMID: 35270496 DOI: 10.3390/ijerph19052803]

37   **Kasahara Y**. DSM-III (Diagnostic and Statistical Manual of Mental Disorders, the 3d edition), a new diagnostic criteria in the United States. *Seishin Shinkeigaku Zasshi* 1981; **83**: 607-611 [PMID: 7347819]

38   **Mendels J**, Cochrane C. The nosology of depression: the endogenous-reactive concept. *Am J Psychiatry* 1968; **124**: Suppl 1-Suppl 11 [PMID: 4872231 DOI: 10.1176/ajp.124.11S.1]

39   **Zimmerman M**, McGlinchey JB, Young D, Chelminski I. Diagnosing major depressive disorder introduction: an examination of the DSM-IV diagnostic criteria. *J Nerv Ment Dis* 2006; **194**: 151-154 [PMID: 16534430 DOI: 10.1097/01.nmd.0000202235.78441.53]

40   **Schildkraut JJ**. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 1965; **122**: 509-522 [PMID: 5319766 DOI: 10.1176/ajp.122.5.509]

41   **Bricka TM**, He Y, Schroeder AN. Difficult Times, Difficult Decisions: Examining the Impact of Perceived Crisis Response Strategies During COVID-19. *J Bus Psychol* 2022; 1-21 [PMID: 36531152 DOI: 10.1007/s10869-022-09851-x]

42   **Hazel NA**, Hammen C, Brennan PA, Najman J. Early childhood adversity and adolescent depression: the mediating role of continued stress. *Psychol Med* 2008; **38**: 581-589 [PMID: 18261247 DOI: 10.1017/S0033291708002857]

43   **Jaffee SR**, Moffitt TE, Caspi A, Fombonne E, Poulton R, Martin J. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Arch Gen Psychiatry* 2002; **59**: 215-222 [PMID: 11879158 DOI: 10.1001/archpsyc.59.3.215]

44   **de Moraes Costa G**, Ziegelmann PK, Zanatta FB, Martins CC, de Moraes Costa P, Mello CF. Efficacy, acceptability, and tolerability of antidepressants for sleep quality disturbances in post-traumatic stress disorder: A systematic review and network meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2022; **117**: 110557 [PMID: 35395322 DOI: 10.1016/j.pnpbp.2022.110557]

45   **Merians AN**, Spiller T, Harpaz-Rotem I, Krystal JH, Pietrzak RH. Post-traumatic Stress Disorder. *Med Clin North Am* 2023; **107**: 85-99 [PMID: 36402502 DOI: 10.1016/j.mcna.2022.04.003]

46   **Miller S**, McTeague LM, Gyurak A, Patenaude B, Williams LM, Grieve SM, Korgaonkar MS, Etkin A. Cognitionchildhood maltreatment interactions in the prediction of antidepressant outcomes in major depressive disorder patients: Results from the ispot-d trial. *Depress Anxiety* 2015; **32**: 594-604 [PMID: 25917683 DOI: 10.1002/da.22368]

47   **Nemeroff CB**, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, Ninan PT, McCullough JP Jr, Weiss PM, Dunner DL, Rothbaum BO, Kornstein S, Keitner G, Keller MB. Differential responses to psychotherapy *vs* pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci U S A* 2003; **100**: 14293-14296 [PMID: 14615578 DOI: 10.1073/pnas.2336126100]

48   **Williams LM**, Debattista C, Duchemin AM, Schatzberg AF, Nemeroff CB. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. *Transl Psychiatry* 2016; **6**: e799 [PMID: 27138798 DOI: 10.1038/tp.2016.61]

49   **Fuller-Thomson E**, Baird SL, Dhrodia R, Brennenstuhl S. The association between adverse childhood experiences (ACEs) and suicide attempts in a population-based study. *Child Care Health Dev* 2016; **42**: 725-734 [PMID: 27280449 DOI: 10.1111/cch.12351]

50   **Nanni V**, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am J Psychiatry* 2012; **169**: 141-151 [PMID: 22420036 DOI: 10.1176/appi.ajp.2011.11020335]

51   **Yrondi A**, Aouizerate B, Bennabi D, Richieri R, D'Amato T, Bellivier F, Bougerol T, Horn M, Camus V, Courtet P, Doumy O, Genty JB, Holtzmann J, Lancon C, Leboyer M, Llorca PM, Maruani J, Moirand R, Molière F, Samalin L, Schmitt L, Stephan F, Turecki G, Vaiva G, Walter M, Petrucci J; FondaMental Advanced Centers of Expertise in Resistant Depression (FACE-DR) Collaborators, Haffen E, El-Hage W. Childhood maltreatment and clinical severity of treatment-resistant depression in a French cohort of outpatients (FACE-DR): One-year follow-up. *Depress Anxiety* 2020; **37**: 365-374 [PMID: 31999402 DOI: 10.1002/da.22997]

52   **Asarnow JR**, Emslie G, Clarke G, Wagner KD, Spirito A, Vitiello B, Iyengar S, Shamseddeen W, Ritz L, Birmaher B,

Ryan N, Kennard B, Mayes T, DeBar L, McCracken J, Strober M, Suddath R, Leonard H, Porta G, Keller M, Brent D. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry* 2009; **48**: 330-339 [PMID: 19182688 DOI: 10.1097/chi.0b013e3181977476]

53   **Shirk SR**, Kaplinski H, Gudmundsen G. School-Based Cognitive-Behavioral Therapy for Adolescent Depression. *J Emot Behav Disord* 2008; **17**: 106-117 [DOI: 10.1177/1063426608326202]

54   **Coventry PA**, Meader N, Melton H, Temple M, Dale H, Wright K, Cloitre M, Karatzias T, Bisson J, Roberts NP, Brown JVE, Barbui C, Churchill R, Lovell K, McMillan D, Gilbody S. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis. *PLoS Med* 2020; **17**: e1003262 [PMID: 32813696 DOI: 10.1371/journal.pmed.1003262]

55   **Menke A**, Nitschke F, Hellmuth A, Helmel J, Wurst C, Stonawski S, Blickle M, Weiß C, Weber H, Hommers L, Domschke K, Deckert J. Stress impairs response to antidepressants *via* HPA axis and immune system activation. *Brain Behav Immun* 2021; **93**: 132-140 [PMID: 33422640 DOI: 10.1016/j.bbi.2020.12.033]

56   **Østergaard L**, Jørgensen MB, Knudsen GM. Low on energy? An energy supply-demand perspective on stress and depression. *Neurosci Biobehav Rev* 2018; **94**: 248-270 [PMID: 30145282 DOI: 10.1016/j.neubiorev.2018.08.007]

57   **Yang XJ**, Zhao BC, Li J, Shi C, Song YQ, Gao XZ, Jiang HL, Yu QY, Liang XC, Feng SX, Li X, Sun Y, Li YH, Wang YP, Bao T, Zhang ZJ. Serum NLRP3 Inflammasome and BDNF: Potential Biomarkers Differentiating Reactive and Endogenous Depression. *Front Psychiatry* 2022; **13**: 814828 [PMID: 35295780 DOI: 10.3389/fpsyt.2022.814828]

58   **Maity S**, Abbaspour R, Nahabedian D, Connor SA. Norepinephrine, beyond the Synapse: Coordinating Epigenetic Codes for Memory. *Int J Mol Sci* 2022; **23** [PMID: 36077313 DOI: 10.3390/ijms23179916]

59   **Linghu T**, Gao Y, Li A, Shi B, Tian J, Qin X. A unique insight for energy metabolism disorders in depression based on chronic unpredictable mild stress rats using stable isotope-resolved metabolomics. *J Pharm Biomed Anal* 2020; **191**: 113588 [PMID: 32927418 DOI: 10.1016/j.jpba.2020.113588]

60   **Lu S**, Li C, Jin X, Zhu L, Shen J, Bai M, Li Y, Xu E. Baicalin improves the energy levels in the prefrontal cortex of mice exposed to chronic unpredictable mild stress. *Heliyon* 2022; **8**: e12083 [PMID: 36531636 DOI: 10.1016/j.heliyon.2022.e12083]

61   **Zhang J**, Liu K, Zeng S, Chen C, Deng Y, Jing L, Wen G. Energy metabolism disorder and functional magnetic resonance imaging of the medial prefrontal cortex in mice with chronic unpredictable mild stress. *Nan Fang Yi Ke Da Xue Xue Bao* 2021; **41**: 521-528 [PMID: 33963710 DOI: 10.12122/j.issn.1673-4254.2021.04.06]

62   **Mizushima J**, Sakurai H, Mizuno Y, Shinfuku M, Tani H, Yoshida K, Ozawa C, Serizawa A, Kodashiro N, Koide S, Minamisawa A, Mutsumoto E, Nagai N, Noda S, Tachino G, Takahashi T, Takeuchi H, Kikuchi T, Uchida H, Watanabe K, Kocha H, Mimura M. Melancholic and reactive depression: a reappraisal of old categories. *BMC Psychiatry* 2013; **13**: 311 [PMID: 24237589 DOI: 10.1186/1471-244X-13-311]

63   **Guo P**, Fang Y, Feng M, Zhao X, Wang S, Qian M, Huang J, Chen H. Case report: Prazosin augmentation for treating comorbid treatment-resistant depression and chronic post-traumatic stress disorder. *Front Psychiatry* 2022; **13**: 803220 [PMID: 35935442 DOI: 10.3389/fpsyt.2022.803220]

64   **Simmering JE**, Welsh MJ, Liu L, Narayanan NS, Pottegård A. Association of Glycolysis-Enhancing α-1 Blockers With Risk of Developing Parkinson Disease. *JAMA Neurol* 2021; **78**: 407-413 [PMID: 33523098 DOI: 10.1001/jamaneurol.2020.5157]

65   **Linghu T**, Zhao Y, Wu W, Gao Y, Tian J, Qin X. Novel targets for ameliorating energy metabolism disorders in depression through stable isotope-resolved metabolomics. *Biochim Biophys Acta Bioenerg* 2022; **1863**: 148578 [PMID: 35640666 DOI: 10.1016/j.bbabio.2022.148578]

ORIGINAL ARTICLE

Basic Study

Acupuncture at Back-Shu point improves insomnia by reducing inflammation and inhibiting the ERK/NF-κB signaling pathway

Ming-Ming Zhang, Jing-Wei Zhao, Zhi-Qiang Li, Jing Shao, Xi-Yan Gao

Ming-Ming Zhang, Zhi-Qiang Li, Department of Pain Treatment, Luoyang Orthopedic Traumatological Hospital of Henan Province, Zhengzhou 471002, Henan Province, China

Jing-Wei Zhao, Jing Shao, Department of Geriatric Medicine, The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450046, Henan Province, China

Xi-Yan Gao, Department of Acupuncture and Moxibustion, The Third Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450046, Henan Province, China

Corresponding author: Xi-Yan Gao, MD, Professor, Department of Acupuncture and Moxibustion, The Third Affiliated Hospital of Henan University of Chinese Medicine, No. 156, Jinshui East Road, Zhengdong New District, Zhengzhou 450046, Henan Province, China. gaoxiyan26@126.com

Abstract

BACKGROUND
Insomnia is a disease where individuals cannot maintain a steady and stable sleep state or fail to fall asleep. Western medicine mainly uses sedatives and hypnotic drugs to treat insomnia, and long-term use is prone to drug resistance and other adverse reactions. Acupuncture has a good curative effect and unique advantages in the treatment of insomnia.

AIM
To explore the molecular mechanism of acupuncture at Back-Shu point for the treatment of insomnia.

METHODS
We first prepared a rat model of insomnia, and then carried out acupuncture for 7 consecutive days. After treatment, the sleep time and general behavior of the rats were determined. The Morris water maze test was used to assess the learning ability and spatial memory ability of the rats. The expression levels of inflammatory cytokines in serum and the hippocampus were detected by ELISA. qRT-PCR was used to detect the mRNA expression changes in the ERK/NF-κB signaling pathway. Western blot and immunohistochemistry were carried out to evaluate the protein expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB.

RESULTS
Acupuncture can prolong sleep duration, and improve mental state, activity, diet

volume, learning ability and spatial memory. In addition, acupuncture increased the release of 1L-1β, 1L-6 and TNF-α in serum and the hippocampus and inhibited the mRNA and protein expression of the ERK/NF-κB signaling pathway.

CONCLUSION

These findings suggest that acupuncture at Back-Shu point can inhibit the ERK/NF-κB signaling pathway and treat insomnia by increasing the release of inflammatory cytokines in the hippocampus.

Key Words: ERK/NF-κB signaling pathway; Acupuncture; Insomnia; Inflammation; Acupuncture at Back-Shu point; Traditional Chinese medicine

Core Tip: In this study, insomnia was a condition that was unable to maintain a stable sleep state or to sleep. Western medicine mainly uses sedative and hypnotic drugs to treat insomnia, which easy to produce drug resistance and some adverse reactions. Acupuncture has excellent efficacy and unique advantages in the treatment of insomnia. This study aimed to investigate the molecular mechanism of Back-Shu acupuncture for insomnia.

INTRODUCTION

Insomnia is a common clinical disease. Sleeping difficulty and short sleep time are typical clinical symptoms of insomnia. Insomnia not only seriously affects patients' daily activities and work, but also leads to a reduction in their living standards. Some patients also have anxiety, depression, and other negative psychological emotions. Long-term sleep disorders can easily induce immunity and memory loss, increase the risk of cardiovascular and cerebrovascular diseases, and threaten the life and health of patients[1]. At present, sedatives, hypnotics, antidepressants, and other psychiatric drugs are mainly used to treat insomnia. However, high drug dependence and a high incidence of adverse reactions limit their clinical application[2]. Traditional Chinese medicine believes that insomnia is a type of restlessness caused by liver qi stagnation and spleen damage. Traditional Chinese medicine prescriptions and external treatment with traditional Chinese medicine have remarkable effects on this disease[3].

The pathogenesis of insomnia is still unclear and may be related to the dysfunction of neurotransmitters, inflammatory cytokines, neuroendocrine factors, melatonin, signal transduction pathways, neurotrophic factors, and intestinal flora in the brain. The ERK pathway belongs to the MAPK family and mediates various physiological and pathological processes such as cell proliferation, differentiation, apoptosis, oxidative stress, and immune inflammation. It plays an essential regulatory role in tumor pathogenesis, various inflammatory diseases, mental disorders, insomnia, and other diseases[4,5]. The ERK signaling pathway can be activated after receiving stimulation signals, which activates the downstream transcription factor NF-κB, affects the secretion of inflammatory cytokines [interleukin (1L)-1β, 1L-6, tumor necrosis factor (TNF)-α], and induces functional changes, thereby leading to insomnia and increasing the risk of chronic inflammatory diseases[6-8]. Abnormal activation of the ERK signaling pathway can also aggravate apoptosis and inflammatory injury in cardiomyocytes, leading to cardiac diseases. The administration of corresponding inhibitors can enhance myocardial reoxygenation capacity, inhibit apoptosis and the inflammatory response, reduce myocardial ischemia, and promote the recovery of cardiomyocyte function[9,10]. Clinical studies have found that acupuncture at Back-Shu point has an excellent therapeutic effect on insomnia, effectively improving depression, anxiety, memory loss, immunity decline and other clinical symptoms caused by insomnia[11]. Experimental studies have confirmed that the pathogenesis of insomnia is closely related to the ERK/NF-κB signaling pathway[12]. We hypothesize that inhibition of ERK/NF-κB signaling pathway activation may be a potential target in the treatment of insomnia.

In this study, a rat model of insomnia was established by intraperitoneal injection of p-chlorophenylalanine (PCPA). The rats were treated with acupuncture at Back-Shu point and injection of the ERK/NF-κB pathway inhibitor U0126, respectively. The sleep status, learning and memory ability, body

weight, mental state, response to external interference and other general behaviors were observed before and after treatment. The secretion levels of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α in serum and the hippocampus, and the protein expression of ERK/NF-κB signaling pathway markers were detected to verify whether acupuncture at Back-Shu point could inhibit the ERK/NF-κB signaling pathway to relieve insomnia, providing new insights for the clinical treatment of insomnia.

MATERIALS AND METHODS

Forty male specific pathogen free (SPF) Sprague Dawley (SD) rats aged 12 wk weighing 200 ± 20 g were selected and were given water and food ad libitum. The rats, purchased from Henan Laboratory Animal Center, were housed at a room temperature of 20-24 °C, and relative humidity of 40%-60%. The 40 rats were randomly divided into 4 groups: Control group (Con), model group (Model), acupuncture group (Acupuncture), and U0126 group (U0126), with 10 rats in each group. Rats in the Model group were continuously injected with PCPA suspension (1 mL/kg) by intraperitoneal injection. Rats in the Con group were injected with the same amount of normal saline. Rats in the Acupuncture group received acupuncture 7 d in advance, which was performed continuously for 7 d. Rats in the U0126 group were injected with U0126 (0.2 mg/kg/d) (Alfa Chemical, Zhengzhou, Henan, China) *via* the tail vein 7 d in advance, once a day.

Drug treatment
Ultrapure water was heated to between 30-40 °C, sodium bicarbonate powder (Tianjin Hengxing Chemical Reagent, Tianjin, China) was slowly added to prepare a 5% $NaHCO_3$ aqueous solution, and 0.9% physiological saline was added to dilute to a weak alkaline solution (pH 7-8). PCPA was then added and sonicated for 10 h to obtain a PCPA suspension.

Evaluation of the insomnia model
Twelve hours after PCPA suspension injection on day 3, three rats were randomly selected from the Con and Model groups to receive pentobarbital sodium (45 mg/kg). The rats were placed in the supine position on the experimental table to observe the righting reflex. The disappearance of the righting reflex for 1 min was considered the sleep latency, the time to recovery was the sleep time, and the rats varus 3 times within 30 s was the end index. The sleep latency and sleep time of rats were recorded, respectively.

Acupuncture intervention
The acupoints on both sides were "Xin Yu," "Gan Yu," "PI Yu," "Fei Yu," and "Shen Yu." Xin Yu: The 5th thoracic vertebra on the lower intercostal side; Pi Yu: The 12th thoracic vertebra on the lower intercostal side; Gan Yu: The spinous process of the 9th thoracic vertebra is opened 3 mm below; Fei Yu: The 3rd thoracic vertebra on the lower intercostal side; Shen Yu: The lower side of the 2nd lumbar spine. After disinfection, the operator held a millimeter needle (0.25 mm × 15 mm) in the right hand, which was quickly inserted into the acupoint to 6 mm. The needle was retained for 10 min, and then removed. Acupuncture began at 9:00 a.m. every day for 7 consecutive days.

Morris water maze test
The rats in each group were placed into the water maze for adaptive training 1 d before the experiment. The positioning navigation experiment was used to train the learning and memory ability of the rats. The rats were placed in quadrants I, II, III, and IV daily. The test time for each quadrant was 70 s. The escape latency period was the time from placed in the water to finding the landing platform. If the platform was not found within the specified time, the animal was actively placed on the platform for 15 s to induce learning and memory ability. The SuperMaze software recorded the movement trajectory and escape latency using a camera. The spatial exploration experiment was used to evaluate the spatial memory ability of the rats. The rats were placed in the water from the contralateral side of quadrant III and allowed to freely explore for 60 s. The SuperMaze software recorded the movement trajectory of the rats using a camera.

Enzyme-linked immunosorbent assay (ELISA)
After the last behavioral experiment, the rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (30 mg/kg), placed supine on the rat board, blood was collected from the abdominal aorta, the animal was decapitated, and the hippocampus was isolated, homogenized, centrifuged, and the supernatant obtained. The expression levels of IL-1β, IL-6 and TNF-α in rat serum and the hippocampus were detected by ELISA according to the manufacturer's protocol (Multisciences, Hangzhou, Zhejiang, China). The absorption was measured at the wavelength of 450 nm.

Quantitative real-time PCR (qRT-PCR)

Total RNA in the hippocampus was extracted with Trizol reagent (Servicebio, Wuhan, Hubei, China). RNA concentration and purity were detected using a Nanodrop 2000 spectrophotometer. 1 μg RNA was reverse transcribed into cDNA according to the manufacturer's protocol (Servicebio, Wuhan, Hubei, China). The obtained cDNA was used as the template in qRT-PCR according to the instructions. The primer sequences were as follows:

GAPDH: F: CTGGAGAAACCTGCCAAGTATG; R: GGTGGAAGAATGGGAGTTGCT; Raf1: F: TGTTTGATGGCTCCAGTTGC; R: AGCGTGCTTTCTTACCTTTGTG; MEK2: F: TGAATGAGC-CACCTCCCAAG; R: ATAGCCAGCCAGCGAAGTCC; ERK1/2: F: TTCAGGACCTCATGGAGACGG; R: GCCACATACTCGGTCAGAAAGC; NF-κB: F: GGGACTATGACTTGAATGCGG; R: CAGCCAG-GTCCCGTGAAATA.

Western blot

Total protein in the hippocampus was extracted for Western blot detection. The protein samples were mixed with RAF-1, MEK-2, ERK1/2, NF-κB, and β-actin as an internal reference (all obtained from Servicebio, Wuhan, Hubei, China).

Immunohistochemistry

The paraffin sections were deparaffinized for antigen retrieval, washed three times with phosphate buffer saline (PBS), 5 min each time, and then serum-blocked and then added to primary antibody RAF-1 (1:200), primary antibody MEK-2 (1:200), primary antibody ERK1/2 (1:200), primary antibody NF-κB (1:200), and incubated overnight at 4 °C. The sections were washed 3 times with PBS, 5 min each time, diluted secondary antibody (1:1000) was added, incubated at room temperature for 50 min, washed 3 times with PBS, 5 min each time, DAB color developing solution (Servicebio, Wuhan, Hubei, China) was added dropwise, hematoxylin was used as the counterstain and returned to blue, then dehydrated and made transparent. After drying, the sections were mounted and observed under the microscope.

Statistical analysis

SPSS 24.0 software was used for statistical analysis of the experimental data, measurement data were expressed as mean ± SD, and the *t*-test (comparison between two groups) or LSD analysis of variance was used when normal distribution and homogeneity of variance were satisfied. For comparisons between multiple groups, the Dunnett's-T3 test was used to compare uneven variance, and $P < 0.05$ was considered statistically significant.

RESULTS

Acupuncture at Back-Shu point improved the general state and prolonged sleep time in rats

PCPA was injected intraperitoneally in rats to construct an insomnia model. Compared with the Con group, the sleep latency of rats in the Model group was prolonged and the sleep time was shortened, indicating that the insomnia rat model was successfully established (Figure 1). PCPA can cause general status and behavioral changes in rats[13]. Rats in the Model group showed a poor mental state, fighting and biting each other, with reduced food intake, increased drinking water, dull and damp hair, and poor hair glossiness. After acupuncture treatment, aggressive behavior in rats decreased, food intake increased, and water intake decreased (Table 1). Compared with rats in the Model group, the sleep latency of the Acupuncture group and the U0126 group was shortened and the sleep time was prolonged (Figure 1). In conclusion, acupuncture at Back-Shu acupoints improved cognitive behavioral changes and emotional disturbances caused by insomnia.

Effects of acupuncture at Back-Shu point on the behavior of insomnia rats

We carried out location experiments to evaluate the memory ability of rats. With the increase in training times, the average escape latency of rats in each group gradually shortened, showing that rats with increased training, remembered the platform. However, the trend in average escape latency in rats was basically the same. After treatment, compared with the Con group, the escape latency of the Model group was prolonged. Compared with the Model group, the escape latency of rats in the Acupuncture group and U0126 group was shortened (Figure 2A). The spatial exploration experiment was used to evaluate the spatial memory ability of rats. The movement trajectories of rats in the Model group showed that the movement trajectories of rats in the four quadrants were basically the same. In contrast, the trajectories of rats in the Con group and the Acupuncture group were primarily concentrated in quadrant III (Figure 2B). Compared with the Con group, the time taken to cross the original platform and the quadrants of the original platform were significantly reduced in the Model group. Compared with the Model group, the number of large crossings of the original platform and the quadrant of the original platform increased in the Acupuncture group and the U0126 group (Figure 2C). These results indicated that acupuncture treatment improved the learning and memory ability of rats and promoted

Table 1 General state of the rats (*n* = 10)						
Group	Dietary volume	Drinking volume	Mental state	Hair glossiness	Aggressive behavior	Sensitivity
Con						
Model	- - -	+ + +	- - -	- - -	+ + +	- - -
Acupuncture	-	+	-	- -	+	-
U0126	- -	+ +	-	- -	+	-

-: Represents the degree of reduction; +: Indicates the degree of increase.

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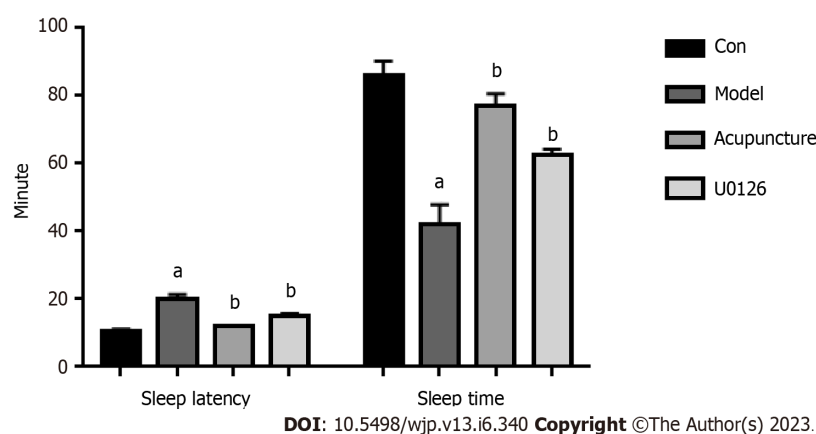
Figure 1 Effects of acupuncture at Back-Shu point on sleep latency and sleep duration in rats. [a]*P* < 0.05, compared to the Con group; [b]*P* < 0.05, compared to the Model group.

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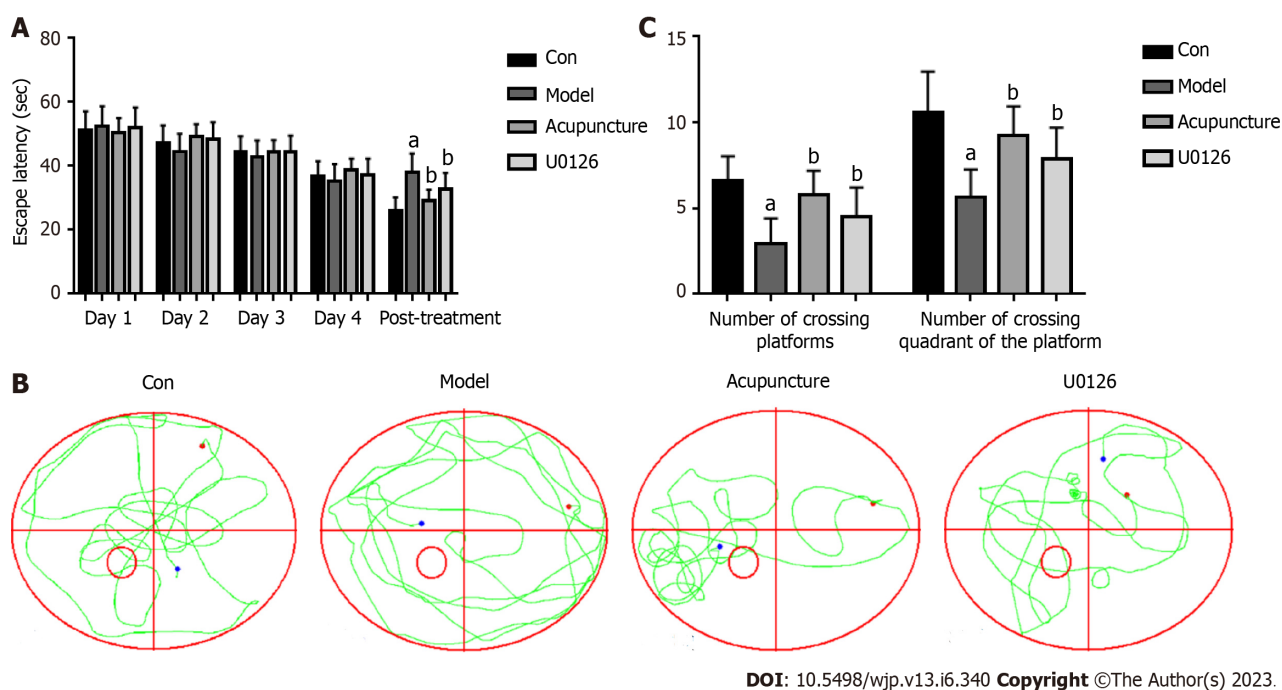
Figure 2 Effects of acupuncture at back-shu point on the behavior of rats. A: Average escape latency of rats; B: Spatial exploration movement trajectories of rats; C: Spatial exploration results of rats. [a]*P* < 0.05, compared to the Con group; [b]*P* < 0.05, compared to the Model group.

the recovery of learning and memory function.

Acupuncture at Back-Shu point increased inflammation in insomnia rats

Inflammatory cytokines act as mediating signals between the sleep-wake cycle and the immune system. Abnormal secretion of inflammatory cytokines can cause sleep-wake cycle disorder and lead to insomnia. As shown in Figure 3A-C, compared with the Con group, the secretion of inflammatory cytokines (IL-1β, IL-6 and TNF-α) in serum of the Model group was decreased. After acupuncture and U0126 treatment, the secretion of IL-1β, IL-6, and TNF-α in the serum of rats were significantly increased. In the rat hippocampus, we found the same trend in inflammatory cytokine secretion (Figure 3D-F).

Acupuncture at Back-Shu point inhibited the ERK/NF-κB signaling pathway

The ERK/NF-κB signaling pathway is closely related to the body's immune system. It plays an important role in the synaptic plasticity of neurons in brain regions, which mainly regulates learning and memory processes. U0126 is a highly potent inhibitor of ERK1/2, MEK-1, and MEK-2. The qRT-PCR results showed that compared with the Con group, the mRNA expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in the hippocampus of the Model group were increased. In addition, acupuncture and U0126 significantly inhibited the expression of these genes (Figure 4). The protein expression levels of the ERK/NF-κB signaling pathway related genes were detected by Western blot and immunohisto-chemistry, and the results were consistent with the trend in mRNA expression (Figure 5). In conclusion, we believe that acupuncture at Back-Shu point can improve insomnia in rats by inhibiting the ERK/NF-κB signaling pathway.

DISCUSSION

Insomnia is a common disease that not only reduces patients' life quality, but also causes other physical diseases, significantly impacting patients' lives[14]. Due to their reproductive ability, easy feeding, easy modeling and experimental operation, and similar sleep-wake cycle and biological regulatory function to humans, rats were selected to construct the insomnia model in this study. PCPA can inhibit sleep and affect the expression of serotonin (5-HT). As an inhibitor of tryptophan hydroxylase, an essential enzyme in the process of 5-HT biosynthesis, PCPA can reduce the concentration of 5-HT in the brain and serum by inhibiting it, thus causing disorder of the sleep-wake cycle[15]. After intraperitoneal injection of PCPA in rats for three consecutive days, the rats showed circadian rhythm disorder, frequent daytime activity, wet and dark hair, increased aggression during stimulation, and mutual fighting and biting behaviors, which lasted for one week, which was consistent with the clinical symptoms caused by insomnia, indicating that the insomnia model was successfully established.

In traditional Chinese medicine, insomnia belongs to the category of "sleepless" and the Back-Shu point is the acupoint on the bladder meridian, which is closely related to the brain. Currently, the five acupoints most commonly used in treating insomnia by acupuncture at Back-Shu point are Xin Yu, Gan Yu, PI Yu, Fei Yu, and Shen Yu[16]. This study found that continuous application of acupuncture at Back-Shu point for seven days can promote appetite, prolong sleep time and improve the mental state, activity, and excessive behavior. The results of the Morris water maze test showed that compared with the Model group, the ability of positioning navigation and space exploration of rats in the Acupuncture group and U0126 group improved to varying degrees, the latency in seeking platform escape was shortened, and the number of swims across the platform was increased. In conclusion, the results show that acupuncture at the Back-Shu point can improve the cognitive behavior changes and emotional disorders caused by insomnia, improve learning and memory ability in rats, and promote learning and memory function recovery.

The sleep-wake cycle is bidirectional in the immune system. Activation of the immune system will change the sleep state, which can lead to increased sleep duration, and lead to the occurrence of insomnia[17]. Cytokines in the sleep-wake cycle and immune system mediate between signals, and through the receptor act on the peripheral nervous system or the central nervous system neurons, astrocytes and microglia, through afferent nerve fibers and blood to the brain signals, cause inflammation and then insomnia[18]. In recent years, the role of inflammatory cytokines in maintaining the NREM sleep cycle has been extensively studied in animal experiments. Anti-inflammatory factors (IL-4, IL-10) can reduce the duration of NREM sleep, and proinflammatory factors (1L-1β, IL-2, IL-6, TNF-α) can promote the duration and depth of NREM sleep[19-21]. The results of the present study showed that compared with the Con group, the proinflammatory cytokines, IL-6, 1L-1β and TNF-α in the Model group rats' serum and hippocampus were significantly decreased ($P < 0.01$), suggesting that insomnia can result in a proinflammatory cytokine secretion imbalance, affect the body's immune system, resulting in sleep cycle disorder, consistent with previous research results. Compared with the Model group, the secretion of IL-1β, IL-6 and TNF-α in the Acupuncture group and U0126 group were significantly increased, suggesting that acupuncture at Back-Shu point may participate in the regulation of sleep and the immune system, improve the secretion of proinflammatory cytokines, maintain the balance of cytokines, and promote recovery of the body's immune system and the improvement of insomnia.
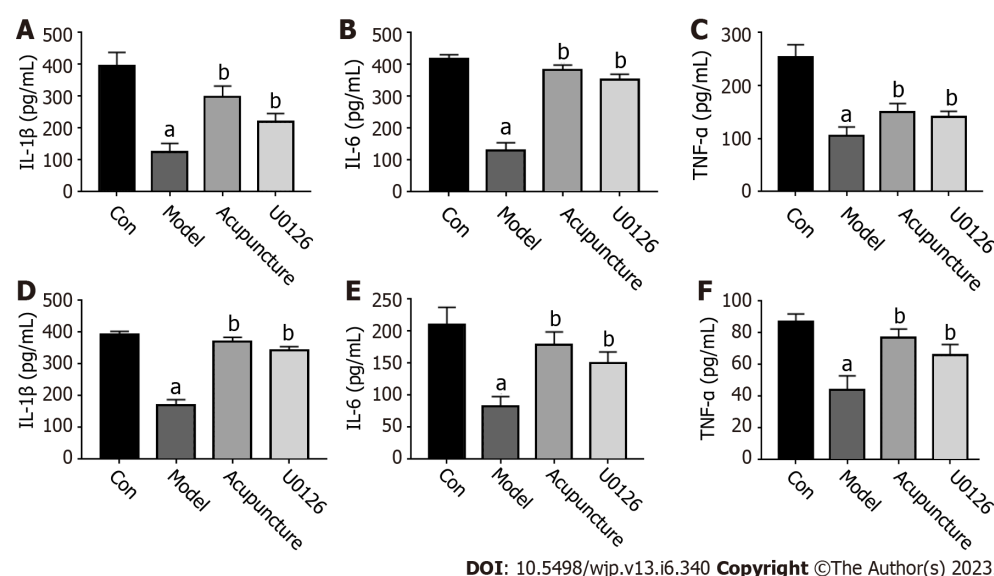
Figure 3 Acupuncture at Back-Shu point increased secretion of inflammatory cytokines in rats. A-C: Secretion of IL-1β, IL-6 and TNF-α in serum; D-F: Secretion of IL-1β, IL-6 and TNF-α in rat hippocampus. [a]$P < 0.05$, compared to the Con group; [b]$P < 0.05$, compared to the Model group.
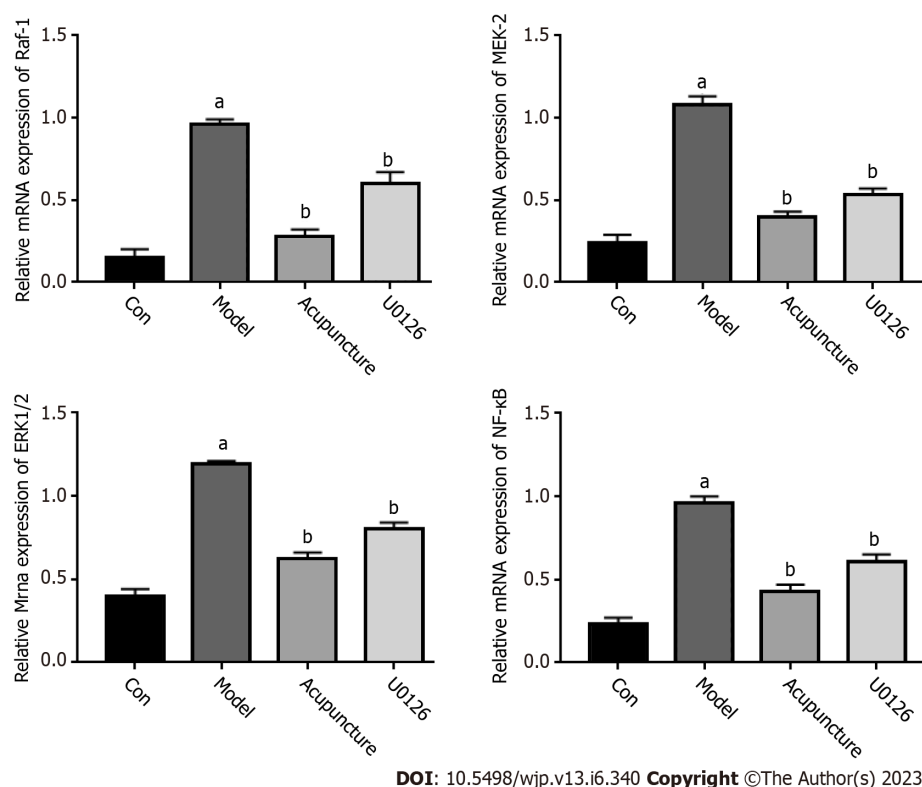
Figure 4 Relative mRNA expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in rat hippocampus. [a]$P < 0.05$, compared to the Con group; [b]$P < 0.05$, compared to the Model group.

The MAPK signaling family is divided into the ERK, JNK, ERK5/BMK1 and P38 MAPK signaling pathways, of which the ERK-mediated MAPK signaling pathway is considered a classical MAPK signal transduction pathway[22]. The ERK signaling pathway transfers extracellular signals into cells through the RAF-MEK-ERK cascade effect and then regulates the expression of downstream key target NF-κB, which affects the occurrence of diseases. RAF-1, MEK-2, ERK1/2 and NF-κB are essential targets in the RAF-MEK-ERK-NF-κB pathway, which regulate cell proliferation, apoptosis, differentiation and other physiological activities, and participate in the pathogenesis and clinical symptoms of insomnia[23-25]. This study showed that compared with the Con group, the mRNA and protein expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in the hippocampus of the Model group were significantly increased ($P < 0.01$), and the number of positive cells increased, suggesting that the pathogenesis of insomnia may
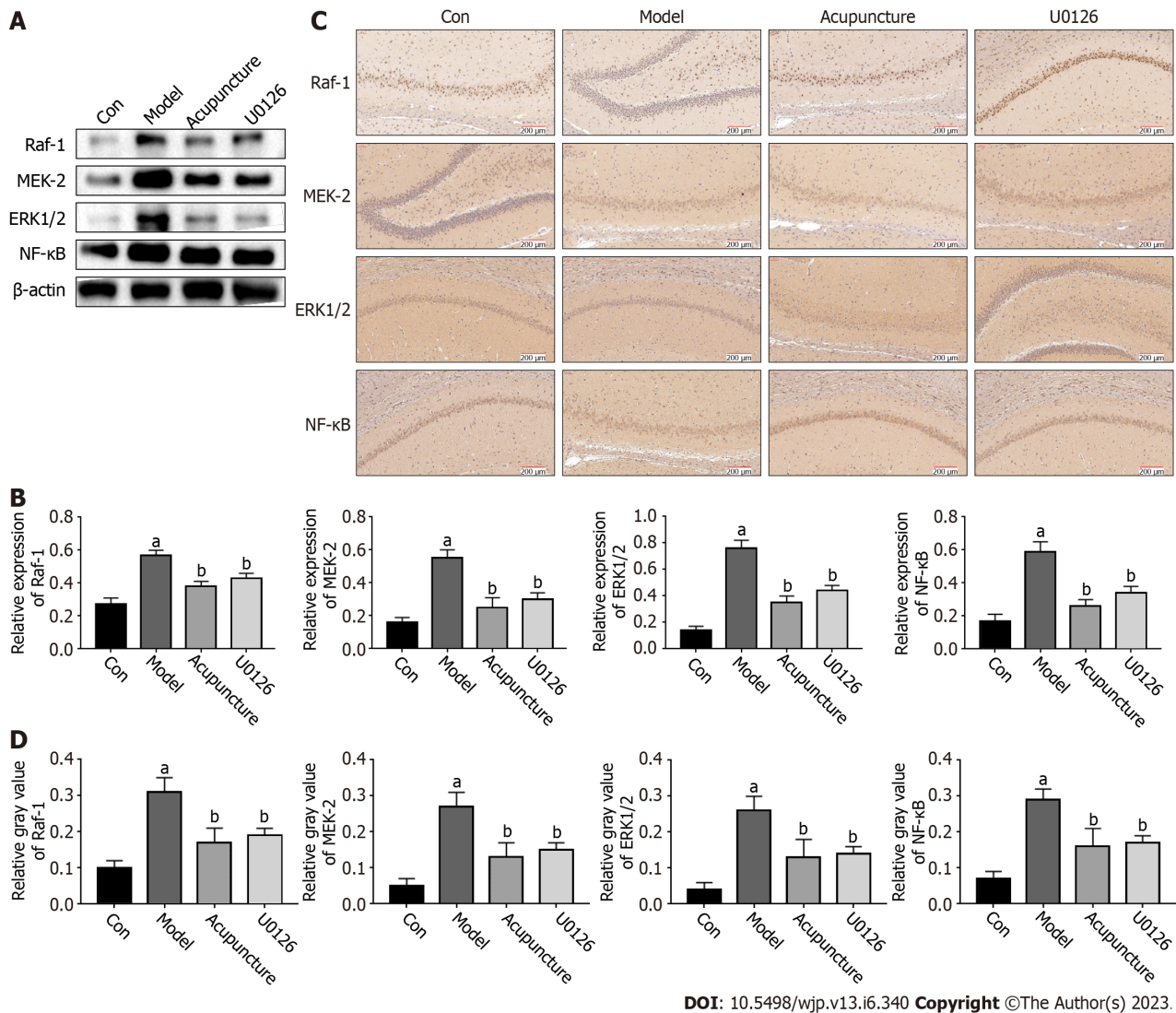
Figure 5 Acupuncture at Back-Shu point inhibited the ERK/NF-κB signaling pathway in rats. A: The expression of ERK/NF-κB pathway-related proteins in rat hippocampus was detected by western blot; B: The relative protein expression level of RAF-1, MEK-2, ERK1/2 and NF-κB in rat hippocampus; C: The expression levels of ERK/NF-κB pathway-related proteins in the hippocampus in rats were detected by immunohistochemistry, scale bars = 100 μm (× 200); D: The gray values of RAF-1, MEK-2, ERK1/2 and NF-κB. [a]$P < 0.05$, compared to the Con group; [b]$P < 0.05$, compared to the Model group.

be related to activation of the ERK/NF-κB pathway. To further investigate whether acupuncture at the Back-Shu point improves insomnia by inhibiting the ERK/NF-κB signaling pathway, U0126 was injected into the tail vein of rats. U0126, a highly efficient pathway inhibitor that selects ERK1/2, MEK-1, MEK-2 and other families, can simultaneously inhibit ERK and MEK through a non-competitive pathway, have an impact on the RAF-MEK-ERK cascade reaction, further inhibit cell apoptosis, migration, invasion, and regulate the expression of related proteins[25,26]. Studies have shown that U0126 can effectively inhibit the proliferation, migration and apoptosis of cancer cells *in vivo*, and antioxidant protection of neuronal cells; thus, it is widely used in the treatment of nerve damage, sleep disorders, decreased learning and memory ability, and cancer caused by hypoxia and ischemia[27-29]. Compared with the Model group, the mRNA and protein expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in the Acupuncture group and U0126 group were significantly down-regulated ($P < 0.01$), suggesting that acupuncture at Back-Shu point and injection of U0126 inhibited activation of the ERK/NF-κB signaling pathway.

CONCLUSION

In summary, acupuncture at Back-Shu point can promote appetite, prolong sleep time, improve learning and memory ability, maintain the balance of proinflammatory cytokine secretion, and improve rats' mental state, activity, and excessive behavior. We believe that the pathogenesis of insomnia may be related to activation of the ERK/NF-κB signaling pathway. Acupuncture at Back-Shu point may inhibit

conduction of the ERK/NF-κB signaling pathway, down-regulate the mRNA and protein expression of RAF-1, MEK-2, ERK1/2 and NF-κB in the pathway, increase the secretion levels of proinflammatory cytokines IL-1β, IL-6 and TNF-α, maintain the balance of cytokines, and protect nerve cells. Thus, acupuncture may promote the body's immune system recovery and play a role in the treatment of insomnia.

ARTICLE HIGHLIGHTS

Research background

The characteristics of insomnia are dissatisfaction with sleep, including difficulty beginning or maintaining sleep, waking up with/or early morning, accompanied by related daytime damage, such as fatigue and emotional disorders. Western medicine mainly uses sedatives and hypnotic drugs to treat insomnia, and long-term use is prone to drug resistance and other adverse reactions. Acupuncture has a good curative effect and unique advantages in the treatment of insomnia.

Research motivation

To explore the molecular mechanism of acupuncture at Back-Shu point for insomnia.

Research objectives

To provides a new insight into the treatment of insomnia by acupuncture at Back-Shu point from the perspective of traditional Chinese medicine.

Research methods

We first prepared a rat model of insomnia, and then carried out acupuncture for 7 consecutive days to explored the effect of acupuncture. The Morris water maze test was used to assess behavioral change. The detailed mechanism research was detected by RT-qPCR, ELISA, and Western blot.

Research results

Some Western drugs can improve insomnia symptoms, but their high drug dependence and adverse reactions limit their clinical application. Our study provides new insights into the treatment of insomnia symptoms from the perspective of traditional Chinese medicine. Our study fills a gap in the treatment of insomnia with acupuncture at Back-Shu point and provides a new treatment for insomnia.

Research conclusions

This study suggest that acupuncture at the Back-Shu point can improve the insomnia by inhibiting the ERK/NF-κB signaling pathway and increasing the release of inflammatory cytokines in the hippocampus. Acupuncture at the Back-Shu point has promoted the treatment of insomnia and benefited the public's sleep health.

Research perspectives

This paper provides new ideas for the treatment of insomnia from the perspective of acupuncture.

FOOTNOTES

Author contributions: Zhang MM and Zhao JW contributed equally to this work; Gao XY, Zhang MM and Zhao JW designed the study; Zhang MM, Zhao JW, and Li ZQ conducted the study; Zhang MM and Shao J contributed new reagents and analytical tools; Zhang MM analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Country/Territory of origin: China

ORCID number: Xi-Yan Gao 0009-0006-7012-0894.

REFERENCES

1 **Li O**, Wang F. [Acupuncture at back-shu points of five zang, Geshu (BL 17) and Shenmen (HT 7) for the treatment of menopausal insomnia]. *Zhongguo Zhen Jiu* 2018; **38**: 4693-4672 [PMID: 29797909 DOI: 10.13703/j.0255-2930.2018.05.005]

2 **Riemann D**, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, Espie CA, Garcia-Borreguero D, Gjerstad M, Gonçalves M, Hertenstein E, Jansson-Fröjmark M, Jennum PJ, Leger D, Nissen C, Parrino L, Paunio T, Pevernagie D, Verbraecken J, Weeß HG, Wichniak A, Zavalko I, Arnardottir ES, Deleanu OC, Strazisar B, Zoetmulder M, Spiegelhalder K. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* 2017; **26**: 675-700 [PMID: 28875581 DOI: 10.1111/jsr.12594]

3 **Tang Y**, Li Z, Yang D, Fang Y, Gao S, Liang S, Liu T. Research of insomnia on traditional Chinese medicine diagnosis and treatment based on machine learning. *Chin Med* 2021; **16**: 2 [PMID: 33407711 DOI: 10.1186/s13020-020-00409-8]

4 **Acuff NV**, Li X, Elmore J, Rada B, Watford WT. Tpl2 promotes neutrophil trafficking, oxidative burst, and bacterial killing. *J Leukoc Biol* 2017; **101**: 1325-1333 [PMID: 28356348 DOI: 10.1189/jlb.3A0316-146R]

5 **Du R**, Wang JL, Wang YL. Role of RhoA/MERK1/ERK1/2/iNOS signaling in ocular ischemic syndrome. *Graefes Arch Clin Exp Ophthalmol* 2016; **254**: 2217-2226 [PMID: 27538909 DOI: 10.1007/s00417-016-3456-1]

6 **Zhang Q**, Liu L, Hu Y, Shen L, Li L, Wang Y. Kv1.3 Channel Is Involved In Ox-LDL-induced Macrophage Inflammation Via ERK/NF-κB signaling pathway. *Arch Biochem Biophys* 2022; **730**: 109394 [PMID: 36100082 DOI: 10.1016/j.abb.2022.109394]

7 **Kim SY**, Han SD, Kim M, Mony TJ, Lee ES, Kim KM, Choi SH, Hong SH, Choi JW, Park SJ. Mentha arvensis Essential Oil Exerts Anti-Inflammatory in LPS-Stimulated Inflammatory Responses *via* Inhibition of ERK/NF-κB Signaling Pathway and Anti-Atopic Dermatitis-like Effects in 2,4-Dinitrochlorobezene-Induced BALB/c Mice. *Antioxidants (Basel)* 2021; **10** [PMID: 34943044 DOI: 10.3390/antiox10121941]

8 **Kim SO**, Park JY, Jeon SY, Yang CH, Kim MR. Saikosaponin a, an active compound of Radix Bupleuri, attenuates inflammation in hypertrophied 3T3-L1 adipocytes *via* ERK/NF-κB signaling pathways. *Int J Mol Med* 2015; **35**: 1126-1132 [PMID: 25672367 DOI: 10.3892/ijmm.2015.2093]

9 **Yan HJ**, Qi GQ, Ma Y. Effect of propofol on myocardial ischemia-reperfusion injury through MAPK/ERK pathway. *Eur Rev Med Pharmacol Sci* 2019; **23**: 11051-11061 [PMID: 31858577 DOI: 10.26355/eurrev_201912_19813]

10 **Ye HK**, Zhang HH, Tan ZM. MiR-328 inhibits cell apoptosis and improves cardiac function in rats with myocardial ischemia-reperfusion injury through MEK-ERK signaling pathway. *Eur Rev Med Pharmacol Sci* 2020; **24**: 3315-3321 [PMID: 32271449 DOI: 10.26355/eurrev_202003_20699]

11 **Li JJ**, Xie C, Zhao N, Wang C, Chen YF. [Regularity of Acupoint Selection in Treatment of Insomnia by Catgut Embedding Therapy]. *Zhen Ci Yan Jiu* 2018; **43**: 670-673 [PMID: 30365265 DOI: 10.13702/j.1000-0607.170578]

12 **Oh HK**, Park SJ, Bae SG, Kim MJ, Jang JH, Ahn YJ, Woo H, Kwon G, Ryu JH. Kami-ondam-tang, a traditional herbal prescription, attenuates the prepulse inhibition deficits and cognitive impairments induced by MK-801 in mice. *J Ethnopharmacol* 2013; **146**: 600-607 [PMID: 23376282 DOI: 10.1016/j.jep.2013.01.032]

13 **Lv YB**, Zhou Q, Yan JX, Luo LS, Zhang JL. Enzymolysis peptides from Mauremys mutica plastron improve the disorder of neurotransmitter system and facilitate sleep-promoting in the PCPA-induced insomnia mice. *J Ethnopharmacol* 2021; **274**: 114047 [PMID: 33753142 DOI: 10.1016/j.jep.2021.114047]

14 **Dopheide JA**. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. *Am J Manag Care* 2020; **26**: S76-S84 [PMID: 32282177 DOI: 10.37765/ajmc.2020.42769]

15 **Hong J**, Chen J, Kan J, Liu M, Yang D. Effects of Acupuncture Treatment in Reducing Sleep Disorder and Gut Microbiota Alterations in PCPA-Induced Insomnia Mice. *Evid Based Complement Alternat Med* 2020; **2020**: 3626120 [PMID: 33178314 DOI: 10.1155/2020/3626120]

16 **Chen Y**, Zhao Y, Tan RY, Zhang PY, Long T, Shi Y, Zheng HB. The Influence of Stomach Back-Shu and Front-Mu Points on Insular Functional Connectivity in Functional Dyspepsia Rat Models. *Evid Based Complement Alternat Med* 2021; **2021**: 2771094 [PMID: 34621320 DOI: 10.1155/2021/2771094]

17 **Sgro M**, Kodila ZN, Brady RD, Reichelt AC, Mychaisuk R, Yamakawa GR. Synchronizing our clocks as we age: the influence of the brain-gut-immune axis on the sleep-wake cycle across the lifespan. *Sleep* 2022; **45** [PMID: 34757429 DOI: 10.1093/sleep/zsab268]

18 **He S**, Chen XX, Ge W, Yang S, Chen JT, Niu JW, Xia L, Chen GH. Are Anti-Inflammatory Cytokines Associated with Cognitive Impairment in Patients with Insomnia Comorbid with Depression? A Pilot Study. *Nat Sci Sleep* 2021; **13**: 989-1000 [PMID: 34234602 DOI: 10.2147/nss.s312272]

19 **Brager AJ**, Ehlen JC, Castanon-Cervantes O, Natarajan D, Delisser P, Davidson AJ, Paul KN. Sleep loss and the inflammatory response in mice under chronic environmental circadian disruption. *PLoS One* 2013; **8**: e63752 [PMID: 23696854 DOI: 10.1371/journal.pone.0063752]

20   **Ballesteros-Zebadua P**, Custodio V, Franco-Perez J, Rubio C, González E, Trejo C, Celis MA, Paz C. Whole-brain irradiation increases NREM sleep and hypothalamic expression of IL-1β in rats. *Int J Radiat Biol* 2014; **90**: 142-148 [PMID: 24168236 DOI: 10.3109/09553002.2014.859767]

21   **Zielinski MR**, Gerashchenko D, Karpova SA, Konanki V, McCarley RW, Sutterwala FS, Strecker RE, Basheer R. The NLRP3 inflammasome modulates sleep and NREM sleep delta power induced by spontaneous wakefulness, sleep deprivation and lipopolysaccharide. *Brain Behav Immun* 2017; **62**: 137-150 [PMID: 28109896 DOI: 10.1016/j.bbi.2017.01.012]

22   **Lee S**, Rauch J, Kolch W. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *Int J Mol Sci* 2020; **21** [PMID: 32046099 DOI: 10.3390/ijms21031102]

23   **Sun Y**, Liu WZ, Liu T, Feng X, Yang N, Zhou HF. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. *J Recept Signal Transduct Res* 2015; **35**: 600-604 [PMID: 26096166 DOI: 10.3109/10799893.2015.1030412]

24   **Rai SN**, Dilnashin H, Birla H, Singh SS, Zahra W, Rathore AS, Singh BK, Singh SP. The Role of PI3K/Akt and ERK in Neurodegenerative Disorders. *Neurotox Res* 2019; **35**: 775-795 [PMID: 30707354 DOI: 10.1007/s12640-019-0003-y]

25   **Lavoie H**, Gagnon J, Therrien M. ERK signalling: a master regulator of cell behaviour, life and fate. *Nat Rev Mol Cell Biol* 2020; **21**: 607-632 [PMID: 32576977 DOI: 10.1038/s41580-020-0255-7]

26   **Wang T**, Wu J, Dong W, Wang M, Zhong X, Zhang W, Dai L, Xie Y, Liu Y, He X, Liu W, Madhusudhan T, Zeng H, Wang H. The MEK inhibitor U0126 ameliorates diabetic cardiomyopathy by restricting XBP1's phosphorylation dependent SUMOylation. *Int J Biol Sci* 2021; **17**: 2984-2999 [PMID: 34421344 DOI: 10.7150/ijbs.60459]

27   **Wang A**, Zhang H, Liang Z, Xu K, Qiu W, Tian Y, Guo H, Jia J, Xing E, Chen R, Xiang Z, Liu J. U0126 attenuates ischemia/reperfusion-induced apoptosis and autophagy in myocardium through MEK/ERK/EGR-1 pathway. *Eur J Pharmacol* 2016; **788**: 280-285 [PMID: 27343376 DOI: 10.1016/j.ejphar.2016.06.038]

28   **Ye H**, Zhang Y, Wang Y, Xia J, Mao X, Yu X. The restraining effect of baicalein and U0126 on human cervical cancer cell line HeLa. *Mol Med Rep* 2017; **16**: 957-963 [PMID: 28560420 DOI: 10.3892/mmr.2017.6648]

29   **Dumoulin MC**, Aton SJ, Watson AJ, Renouard L, Coleman T, Frank MG. Extracellular signal-regulated kinase (ERK) activity during sleep consolidates cortical plasticity *in vivo*. *Cereb Cortex* 2015; **25**: 507-515 [PMID: 24047601 DOI: 10.1093/cercor/bht250]

ORIGINAL ARTICLE

Observational Study

Psychological impact of cancer scale: Turkish validity and reliability study

Gülcan Bahçecioğlu Turan, Seda Karaman, Meyreme Aksoy

Gülcan Bahçecioğlu Turan, Department of Nursing, Faculty of Health Sciences, Fırat University, Elazığ 23100, Turkey

Seda Karaman, Faculty of Nursing, Atatürk University, Erzurum 25240, Turkey

Meyreme Aksoy, Department of Nursing, Faculty of Health Sciences, Siirt University, Siirt 56500, Turkey

Corresponding author: Gülcan Bahçecioğlu Turan, PhD, RN, Assistant Professor, Department of Nursing, Faculty of Health Sciences, Fırat University, Rectorate Campus, Exterior Door No. 2, Elazığ 23100, Turkey. glcnbah@hotmail.com

Abstract

BACKGROUND

In the diagnosis and treatment of cancer, it is important to evaluate the components of psychological adjustment. Considering the key role of nurses in providing care to patients, it is important to evaluate patients, to determine high-risk patients and to use tools with acceptable validity and reliability to develop care plans.

AIM

To analyze the Turkish validity and reliability of The Psychological Impact of Cancer Scale (PICS).

METHODS

This methodological study was conducted with 257 cancer patients admitted to the oncology-haematology clinic and outpatient clinic of a University Hospital between February and October 2021. After the translation process of the scale, content and construct validity were conducted. Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) was examined with construct validity, while item analyses and internal consistency analysis were conducted for reliability.

RESULTS

Analyses and assessment results showed that the content validity index of the scale was 0.96. In the exploratory factor analysis of the Turkish adaptation study, total variance rate explained was found as 84.98%. Factor loads of all items were between 0.82 and 0.94. It was found that Cronbach Alpha values were between

0.860 and 0.930 and total scale Cronbach Alpha value was 0.844. EFA and CFA showed that Turkish form of 12-item and 4-factor. The Psychological Impact of Cancer Scale was confirmed with no changes to the original scale. CFA revealed good fit indices.

CONCLUSION
Turkish PICS is a valid and reliable measurement tool for the evaluation of individual's psychological response to cancer diagnosis and treatment and for being used in clinical practice.

Key Words: Cancer; Patient; Psychological impact; Reliability; Validity

Core Tip: In the diagnosis and treatment of cancer, it is important to evaluate the components of psychological adjustment. Considering the key role of nurses in providing care to patients, it is important to evaluate patients, to determine high-risk patients and to use tools with acceptable validity and reliability to develop care plans. A valid and reliable intercultural adaptation of Turkish the Psychological Impact of Cancer Scale can be useful in making comparisons across settings and to be used in the psychological assessment of cancer in Turkish patients. Therefore, the aim of this study is to conduct validity and reliability of Turkish version of the scale. In this research, it was seen that the Turkish version of the 12-item and 4 sub-dimensional Cancer Psychological Impact Scale was confirmed without any change in the original scale form.

INTRODUCTION

Cancer is the second leading cause of death globally and it was evaluated as the cause of one in six deaths in 2020[1]. Cancer continues to grow globally by causing a huge physical, emotional and financial burden on individuals, families, societies and health systems. Survival rates in many cancer types continue to increase with early diagnosis, good treatment and quality care[1,2]. Cancer patients develop emotional, psychological and behavioural reactions before diagnosis, during diagnosis, during treatment, after treatment, during disease progression and during terminal/palliative periods. Due to the unexpected and difficult to control nature of cancer, it is known that the diagnosis and treatment process is disturbing and traumatic for the individual[3]. With this aspect, cancer, which can be associated with metaphors such as "war", "the angel of death", "winter" and "monster' by patients, may cause radical changes in the lives of individuals[4]. During the treatment phase, treatment methods such as examinations and surgery, chemotherapy and radiotherapy come to the fore according to the type of cancer[5]. It may cause a decrease in the quality of life during the treatment phase by disrupting many issues such as social life, activity, work life, sexual life, *etc*.[6-8]. These changes related to the process and treatment of cancer represent an important stress factor for any patient and create both physical and psychological threats to the patient[9,10]. Compared with the general population, studies have shown patients with malignancies to have higher rates of distress, anxiety and depression[11,12].

"The Psychological Impact of Cancer Scale (PICS)" which was developed by Hulbert-Williams *et al* [13] in 2019 for the evaluation of the components of psychological adjustment to cancer diagnosis and treatment is one of the measurement instruments with high validity and reliability. It is an easily applicable 12-item scale with which the psychological impact of cancer on patients can be evaluated [13]. Considering the key role of nurses in providing care to patients, it is important to use tools with acceptable validity and reliability to evaluate patients, to determine patients with high risk and to develop care plans[8]. A valid and reliable intercultural adaptation of Turkish the Psychological Impact of Cancer Scale can be useful in making comparisons across settings and to be used in the psychological assessment of cancer in Turkish patients. At the same time, the scale can be easily applied to cancer patients since it has a small number of items. The scale is expected to be useful in terms of evaluating the psychological impact of cancer on Turkish patients and will make it easier to decide whether patients need psychological support. For this purpose, the aim of the study is to conduct validity and reliability of Turkish version of the scale.

MATERIALS AND METHODS

Study design and sample

This methodological study was carried out at Oncology-Haematology clinic and outpatient clinic of a University between February and October 2021. Population of the study consisted of cancer patients receiving treatment between these dates. The sample included 257 volunteering patients who met the research criteria (having been diagnosed with cancer at least for 3 mo, being older than 18 years of age, not having any psychiatric problems and being able to communicate sufficiently) between the aforementioned dates. In scale adaptation studies, at least 5 individuals for each item should be reached for factor analysis. If it is not a problem to reach the sample, 10 individuals for each item should be reached. The Psychological Impact of Cancer Scale consists of a total of 12 items. Aiming to reach at least 10 cancer patients for each item, the study was completed with 257 patients[14].

Outcome Measurements

Personal Information Form: This form prepared by the researchers includes 9 questions to find out patients' socio-demographic and disease-related characteristics (age, gender, marital status, educational status, employment status, duration of disease, stage of disease, presence of another chronic disease and type of treatment).

PICS: It was developed by Hulbert-Williams *et al*[13] in 2019 to evaluate the psychological impact of the disease in cancer patients. 12-item PICS is used to evaluate the components of psychological compliance with cancer diagnosis and treatment. Each item is answered with "Totally suitable (1)", "Not suitable (2)", "Suitable (3)", "Totally suitable (4)". The scale is a 4-likert type scale. It consists of 4 factors: Cognitive distress (2, 6, 7); Cognitive avoidance (8, 10, 11); Emotional Distress (3, 5, 12); Spiritual Coping (1, 4, 9). Factor scores are calculated by adding the scores obtained from items in each scale. There are no reversely coded items[13].

Data Assessment: Study data were analysed with IBM SPSS (Statistical Package for Social Sciences) 22 and Scientific Software International, Inc. LISREL 8.8. In data analysis, number and percentage were used for evaluation of personal information. Content and construct validity were analysed with expert views, Barlett Tests, Kaiser-Meyer-Olkin Index (KMO), exploratory factor analysis (EFA), confirmatory factor analysis (CFA) and principle components analysis. In terms of reliability, internal consistency was determined with Cronbach's a coefficient, Pearson correlation analysis, item-total score correlation, composite reliability coefficient (CR) and average variance explained (AVE).

Ethical Considerations: Fırat University Non-Interventional Research Ethics Committee (2020/12 numbered) approved the study. Official permission was taken through e-mail from the researcher who developed the scale for adapting the scale into Turkish and using the scale in the study. Helsinki Declaration of Human Rights was adhered to while carrying out the study. Verbal consent was taken from study participants after the aim of the study was explained.

Stages in the adaptation of the scale to Turkish: Official permission was first obtained from the author *via* e-mail to adapt and use PICS in Turkish. Adaptation phase of the scale was carried out in five steps. Language validity was carried out in the first step; two linguists translated the scale into Turkish independently. Translation was followed with a form including the expressions in scale items, which was examined by two Turkish language experts. These experts examined whether scale items were suitable, checked Turkish language validity and cultural appropriateness and made corrections. Following the corrections, scale items were collected in a single form and they were back translated into the original language by a language expert[14]. Turkish form was found to be similar to the English form after the original scale and the translated form were compared.

In the second step, content validity was performed to prove both language and cultural equivalence and content validity of items with numerical values[15]. Content Validity Index (CVI) of the items was calculated with percentage of agreement between the opinions of at least 3 and at most 20 experts[16]. A pilot study was conducted in the third step. In scale adaptation studies, with the pilot study, a sample of about 30 should be reached, the scale should have an internal consistency value of ≥ 0.70 and it should be checked whether item total correlation is lower than 0.30[15]. In the present study, the pilot study was conducted with 30 cancer patients. With the pilot study, it was determined that the questions were understandable. The data of the pilot study were not included in study data. After the pilot study, the study was initiated without making any corrections in the light of this information. In the fourth step, EFA and CFA were conducted for construct validity[14,17]. Acceptable range of CFA goodness of fit values were found as $5 > \chi^2/df < 2$, RMSEA < 0.08, RMR < 0.08, SMR < 0.08, NFI > 0.80, CFI > 0.90, IFI > 0.90, GFI > 0.90, AGFI > 0.85, PGFI > 0.50, and PNFI > 0.50[14,18-20]. In the fifth step, to determine the reliability of the scale, test-retest reliability with an interval of two weeks in data collection stage, Cronbach alpha reliability coefficient Pearson Correlation analysis, item-total score correlation, composite reliability coefficient and mean explained variance were used[21-24].

RESULTS

Mean age of the patients was found as 59.32 ± 12.89 in the study. It was found that 51.4% of the patients were female, 53.7% were primary education graduates, 91.1% were married, 47.9% had a disease duration between 1-5 years, 40.5% were in stage 2, 86.4% were not employed, 67.3% were receiving only chemotherapy and 65.8% did not have another chronic disease.

Results on validity

Exploratory factor analysis: KMO value was 0.799 and χ^2 value was calculated as 2310.444 as a result of Barlett's Test of Sphericity analysis in the study. Test results were found to be significant at $P = 0.000$ Level of significance (Table 1). The sample size was found to be adequate and suitable for factor analysis and this showed that the analysis could be continued[14,20].

In the exploratory factor analysis, it was found that the scale explained 84.98% of total variance (Table 2). Due to the number of factors in the EFA, Varimax factor rotation method was applied and the scale items were checked in terms of items with cross-loading. The factors with an eigenvalue of > 1 were evaluated while determining the factors. It was found that the scale items were grouped under 4 factors with factor load values found as > 0.30 (0.82-0.94). Varimax rotation method results showed that. It was found that there were no items that had to be deleted from the scale[14,25]. The values obtained showed that the scale consisted of 12 items and 4 factors.

CFA: In Table 3, CFA fit index values were found as: χ^2 = 116.49, df = 47 ($P < 0.05$), χ^2/df = 2.47, RMSEA = 0.076, CFI = 0.97, NFI = 0.95, IFI = 0.97, RMR = 0.034, SRMR = 0.059, GFI = 0.92, AGFI= 0.88, PGFI= 0.56 and PNFI = 0.68. It was found that model fit was acceptable and some values showed perfect fit[14, 18-20]. Figure 1 shows PATH diagram obtained with CFA.

In the study, it was found as a result of EFA and CFA that Turkish form of 12-item and 4-factor "PICS'' was confirmed without any changes to the original scale form. All these results obtained show that the scale has high validity in Turkish culture.

Results regarding reliability

For reliability analysis, the data were reapplied two weeks later to 50 individuals from the sample on whom EFA was conducted. Test retest correlation coefficient was found as 0.923 for the whole scale, as .0951 for "Cognitive avoidance (F1)" factor, as 0.992 for "Cognitive distress (F2)" factor, as 0.904 for "Spiritual coping (F3)" factor and as 0.993 for "Emotional distress (F4)" factor (Table 4).

Cronbach Alpha coefficient was calculated to find out the internal reliability of the scale. It was found as 0.930 for "Cognitive avoidance" factor, as 0.0914 for "Cognitive distress" factor, as 0.899 for "Spiritual coping" factor and as 0.860 for "Emotional distress" factor. Total Cronbach Alpha coefficient was found as 0.844 (Table 4).

In this study, AVE value was found as 0.89 and CR value was 0.96 for cognitive avoidance factor; AVE value was 0.78 and CR value was 0.91 for cognitive distress factor; AVE value was 0.77 and CR value was 0.91 for spiritual coping factor, and AVE value was found as 0.67 and CR value was found as 0.86 for emotional distress factor. As a result, it was found that all CR values were higher than AVE values and AVE values were found to be higher than 0.50, which is the critical value (Table 4). When the item-total correlation coefficients of the scale were examined, it was found that all item total correlation coefficients were higher than 0.30 (0.41-0.63) (Table 2).

DISCUSSION

Content validity

Opinions of 5 experts were taken for content validity. CVI was used to evaluate expert opinions. The fact that CVI value was > 0.80 shows that there is agreement between expert opinions[26,27]. In the evaluation after expert opinions, CVI value was calculated as 0.96 in this study. This result shows that there is agreement among experts and the scale measures the subject sufficiently and content validity is met.

Construct validity

KMO and Bartlett's Sphericity test evaluated the appropriateness and sufficiency of the data for factor analysis. It is stated in literature that Bartlett's Sphericity test should be statistically significant and KMO value should be at least 0.60 for factor analysis[28]. In this study, Bartlett's Sphericity test value is 2310.444 and it is statistically significant ($P = 0.000$). KMO value was calculated as 0.799. These results show that data base and sample size are suitable for factor analysis[28]. The data base and sample size in this study are similar to those of Hulbert-Williams *et al*[13] who developed the original scale.

In order to determine the number of factors, eigenvalue was taken as ≥ 1 and it was found that the scale consisted of four factors (cognitive distress, cognitive avoidance, emotional distress, spiritual coping)[29,30]. The original scale also consists of four factors[13]. In the exploratory factor analysis, it

Table 1 Results of the Kaiser–Meyer–Olkin measure of sampling adequacy and Bartlett's test of Sphericity

Tests		Test results	
KMO		0.799	
Bartlett Sphericity Test	χ^2	2310.44	$P < 0.001$
	SD	66	
	P value	0	

Table 2 Exploratory factor analysis results of Psychological Impact of Cancer Scale

Scale items	Communality	Corrected item-total correlations	Cronbach's alpha if item deleted	Factor load values			
				F1	F2	F3	F4
Item 8	0.909	0.411	0.839	0.943			
Item 10	0.894	0.492	0.834	0.917			
Item 11	0.848	0.454	0.837	0.888			
Item 2	0.887	0.511	0.7		0.833		
Item 6	0.87	0.538	0.7		0.83		
Item 7	0.879	0.556	0.7		0.829		
Item 1	0.887	0.46	0.68			0.837	
Item 4	0.836	0.635	0.67			0.827	
Item 9	0.882	0.536	0.5			0.831	
Item 3	0.798	0.543	0.67				0.83
Item 5	0.764	0.51	0.66				0.833
Item 12	0.812	0.54	0.66				0.831
Eigenvalue	-	-	-	2.686	2.587	2.52	2.406
Total explained variance (%) = 84.98%	-	-	-	22.382	21.555	21.001	20.051

was found that the 4-factor scale explained 84.98% of the total variance. In multi-factor scales, explained variance is desired to be over 40% and the higher total variance, the stronger the construct validity is[29, 30]. In this study, high explained variance shows that construct validity is robust. It was decided in which factors the scale factors would be included by examining the factor loads. Factor load should be ≥ 0.30[25]. In this study, it was found that the factor loads of the items in the scale were between 0.82 and 0.94 and factor loads were very high. In this study, the fact that factor loads obtained from each scale were > 0.30 shows that the scale has a robust factor structure.

It is reported in literature that CFA should examine the construct revealed with exploratory factor analysis[31]. In this study, it was found with EFA that the scale has 4 factors, as in the original scale. For 4-factor CFA, factor loads of all factors were > 0.30 and goodness of fit indices were (GFI, NFI, CFI and IFI) > 0.90, RMSEA = 0.076. χ^2 value divided by degree of freedom was χ^2/df =2.47. A robust and significant correlation was found between the scale and factors. In literature, a model fit indicator of > 0.90, χ^2/df < 5 and a RMSEA value of < 0.08 are considered as good fit indicators[14,18-20]. CFA results of the present study are in parallel with the criteria reported in literature. In their study, Hulbert-Williams *et al*[13] calculated RMESA value as 0.083. CFA results show that the data are consistent with the model, the four factor construct is confirmed, factors are associated with the scale and the items in each factor define their own factor sufficiently. In this study, EFA and CFA results supported construct validity and showed that the scale is a valid tool.

Reliability analysis

Cronbach's alpha coefficient shows whether the scale items measure the same characteristics and whether the items are correlated with the subject to be measured. Cronbach's alpha value is expected to be as close to 1 as possible. Cronbach's alpha coefficients between 0.60 and 0.80 show that the scale is reliable, while those between 0.80 and 1.00 show that the scale is highly reliable[23,29,32]. In this study, both total and factor α values of the scale are > 0.90. These results show that PICS Turkish version is a reliable measurement tool in evaluating the psychological reactions of patients towards cancer. Hulbert-

Table 3 Confirmatory factor analysis results

Fit criteria	Found	Appropriate	Acceptable	Result
χ^2/df	2.47	< 2	< 5	Perfect fit
RMSEA	0.076	< 0.05	< 0.08	Acceptable fit
CFI	0.97	> 0.95	> 0.90	Perfect fit
NFI	0.95	> 0.95	> 0.80	Acceptable fit
IFI	0.97	> 0.95	> 0.90	Perfect fit
RMR	0.034	< 0.05	< 0.08	Perfect fit
SRMR	0.059	< 0.05	< 0.08	Acceptable fit
GFI	0.92	> 0.95	> 0.90	Acceptable fit
AGFI	0.88	> 0.95	> 0.85	Acceptable fit
PGFI	0.56	> 0.89	> 0.50	Acceptable fit
PNFI	0.68	> 0.89	> 0.50	Acceptable fit

CFI: Comparative fit index; RMSEA: Root mean square error of approximation; RMR: Root mean square residual; NFI: Normed fit index; IFI: Incremental fit index; SRMR: Standardized root mean square residual; GFI: Goodness of fit index; AGFI: Adjusted goodness of fit index; PGFI: Parsimony goodness of fit index; PNFI: Parsimony normed fit index.

Table 4 Correlations between factors, mean scores and reliability results

Factors	α	AVE	CR	mean ± SD	Test-retest (r)
F1	0.93	0.89	0.96	2.57 ± 0.66	0.951
F2	0.914	0.78	0.91	2.32 ± 0.85	0.992
F3	0.899	0.77	0.91	2.69 ± 0.71	0.904
F4	0.86	0.67	0.86	2.66 ± 0.80	0.993
PICS total	0.844	-	-	2.56 ± 0.50	0.923

α: Cronbach Alpha Coefficient; r: Correlation; AVE: Average variance extracted; CR: Construct Reliability; PICS: Psychological Impact of Cancer Scale.

Williams *et al*[13] found the total Cronbach alpha of the scale as > 0,62. In this study, AVE value was 0.89 and CR value was 0.96 for cognitive avoidance factor; AVE value was 0.78 and CR value was 0.91 for cognitive distress factor; AVE value was 0.77 and CR value was 0.91 for spiritual coping factor, and AVE value was 0.67 and CR value was 0.86 for emotional distress factor. The fact that AVE value is > 0.50 and CR value is > 0.80 shows that the scale has good reliability[33]. In addition, values of CR > AVE; AVE > 0.5 are required for convergent validity[24]. As a result, it was found that all CR values were found to be higher than AVE values and AVE values were > 0.50, which is the critical value.

Item-total score analysis is recommended to prove whether the items in the scale measure the variable to be measured. Item-total score analysis explains the correlation between the scores obtained from each item of a scale[34]. In item-total score analysis, it is expected of the correlation to be positive and the correlation value to be > 0.20. When item-total correlation coefficients were examined in the present study, all item total correlation coefficients were found to be > 0.30 (0.41-0.63). Item-total correlation coefficients of the original scale were between 0.33 and 0.73. These results show that the item-total correlation coefficients in the present study are similar to the original scale and item reliabilities are high.

One of the best ways to measure consistency of scales is test retest method[29,35]. No statistically significant difference was found between the two measurements obtained as a result of test-retest analysis (P > 0.01). Test-reliability coefficients of the scale items were found to be statistically significant in the evaluation of the correlation between first and second application scores of each item (P = 0.000).

Practical implications

The fact that the number of items is low will make implementation and evaluation stages easier. The scale can be easily administered to cancer patients. It is thought that using this scale will be beneficial in terms of evaluating the psychological impact of cancer on Turkish patients and will facilitate deciding

Chi-Square = 116.49, df = 47, *P* value = 0.00000, RMSEA = 0.076

Figure 1 Path diagram regarding the factor structure of the scale.

on whether patients require psychological support.

CONCLUSION

The present study shows that The Psychological Impact of Cancer Scale is a valid and reliable measurement tool in evaluating the psychological impact of cancer for Turkey sample. The scale can present new research opportunities for researchers who want to work in the field. In terms of researchers, it can be said that the scale is practical and economical since the number of items is low and the expressions are short in the scale.

ARTICLE HIGHLIGHTS

Research background

Cancer patients develop emotional, psychological and behavioural reactions before diagnosis, during diagnosis, during treatment, after treatment, during disease progression and during terminal /palliative periods.

Research motivation

Turkish scale adaptation.

Research objectives
To analyze the Turkish adaptation of The Psychological Impact of Cancer Scale (PICS).

Research methods
This methodological study was conducted with 257 cancer patients.

Research results
Cronbach Alpha value was 0.844. Exploratory factor analysis and Confirmatory factor analysis showed that Turkish form of 12-item and 4-factor.

Research conclusions
PICS Turkish version has acceptable validity. PICS is homogeneous and consistent for Turkish society. Healthcare professionals can use PICS.

Research perspectives
The use of the scale will be useful in evaluating the psychological impact of cancer on Turkish patients.

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FOOTNOTES

REFERENCES

1   **World Health Organization**. National Cancer Institute. *Qeios* 2020 [DOI: 10.32388/xo5awv]
2   **Fidler MM**, Bray F, Soerjomataram I. The global cancer burden and human development: A review. *Scand J Public*

Health 2018; **46**: 27-36 [PMID: 28669281 DOI: 10.1177/1403494817715400]

3   **Marziliano A**, Tuman M, Moyer A. The relationship between post-traumatic stress and post-traumatic growth in cancer patients and survivors: A systematic review and meta-analysis. *Psychooncology* 2020; **29** 604-616 [PMID: 31834657 DOI: 10.1002/pon.5314

4   **Körükcü Ö**. Bazı Yaşamsal Geçişler Zordur. Jinekolojik Kanser Tanısı Almak Gibi. *Acıbadem Üniversitesi Sağlık Bilimleri Dergisi* 2018; **9**: 248-254 [DOI: 10.31067/0.2018.22]

5   **Wang JJ**, Lei KF, Han F. Tumor microenvironment: recent advances in various cancer treatments. *Eur Rev Med Pharmacol Sci* 2018; **22**: 3855-3864 [PMID: 29949179 DOI: 10.26355/eurrev_201806_15270]

6   **Calver L**, Tickle A, Moghaddam N, Biswas S. The effect of psychological interventions on quality of life in patients with head and neck cancer: A systematic review and meta-analysis. *Eur J Cancer Care (Engl)* 2018; 27 [PMID: 29094780 DOI: 10.1111/ecc.12789]

7   **Van Beek FE**, Wijnhoven LMA, Holtmaat K, Custers JAE, Prins JB, Verdonck-de Leeuw IM, Jansen F. Psychological problems among cancer patients in relation to healthcare and societal costs: A systematic review. *Psychooncology* 2021; **30** 1801-1835 [PMID: 34228838 DOI: 10.1002/pon.5753

8   **Hasanvand S**, Rassouli M, Mandegari Z, Salmani N, Moghimkhan F. A Critical Review of Instruments Measuring the Quality of Life of Cancer Patients in Iranian Studies and Their Psychometrics Properties. *Asian Pac J Cancer Prev* 2019; **20**: 333-343 [PMID: 30803191 DOI: 10.31557/APJCP.2019.20.2.333]

9   **Cillessen L**, Johannsen M, Speckens AEM, Zachariae R. Mindfulness-based interventions for psychological and physical health outcomes in cancer patients and survivors: A systematic review and meta-analysis of randomized controlled trials. *Psychooncology* 2019; **28**: 2257-2269 [PMID: 31464026 DOI: 10.1002/pon.5214]

10   **Zhao C**, Lai L, Zhang L, Cai Z, Ren Z, Shi C, Luo W, Yan Y. The effects of acceptance and commitment therapy on the psychological and physical outcomes among cancer patients: A meta-analysis with trial sequential analysis. *J Psychosom Res* 2021; **140**: 110304 [PMID: 33248396 DOI: 10.1016/j.jpsychores.2020.110304]

11   **Pitman A**, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. *BMJ* 2018; **361**: k1415 [PMID: 29695476 DOI: 10.1136/bmj.k1415]

12   **Tsaras K**, Papathanasiou IV, Mitsi D, Veneti A, Kelesi M, Zyga S, Fradelos EC. Assessment of Depression and Anxiety in Breast Cancer Patients: Prevalence and Associated Factors. *Asian Pac J Cancer Prev* 2018; **19**: 1661-1669 [PMID: 29938451 DOI: 10.22034/APJCP.2018.19.6.1661]

13   **Hulbert-Williams NJ**, Hulbert-Williams L, Whelen L, Mulcare H. The Psychological Impact of Cancer (PIC) Scale: development and comparative psychometric testing against the Mini-MAC Scale in UK and Australian cancer survivors. *J Psychosoc Oncol Res Pract* 2019; 1 [DOI: 10.1097/or9.0000000000000008]

14   **Seçer İ**. Psikolojik test geliştirme ve uyarlama süreci: SPSS ve LISREL uygulamaları. Ankara: Ani Publishing, 2015

15   **Çapık C**, Gözüm S, Aksayan S. Intercultural Scale Adaptation Stages, Language and Culture Adaptation: Updated Guideline. *Florence Nightingale Hemşirelik Dergisi* 2018; 199-210 [DOI: 10.26650/fnjn397481]

16   **Morgado FFR**, Meireles JFF, Neves CM, Amaral ACS, Ferreira MEC. Scale development: ten main limitations and recommendations to improve future research practices. *Psicol Reflex Crit* 2017; **30**: 3 [PMID: 32025957 DOI: 10.1186/s41155-016-0057-1]

17   **Büyüköztürk Ş (2017) Data analysis handbook for social sciences statistics**, research pattern spss applications and ınterpretation.   Pegem Academy., Ankara [DOI: 10.1002/9781119183426.ch11]

18   **Byrne BM**.   Structural equation modeling with Mplus: Basic concepts, applications, and programming. New York: Routledge, 2013 [DOI: 10.4324/9780203807644]

19   **Kline P**.   An easy guide to factor analysis. New York: Routledge, 1994 [DOI: 10.4324/9781315788135]

20   **Aksu G**, Eser MT, Güzeller CO.   Açımlayıcı ve doğrulayıcı faktör analizi ile yapısal eşitlik modeli uygulamaları. Ankara: Detay Yayıncılık, 2017

21   **Güngör D**. Psikolojide ölçme araçlarının geliştirilmesi ve uyarlanması kılavuzu. *Türk psikoloji yazıları* 2016; **19**: 104-112

22   **Karasar N**.   Bilimsel Araştırma Yöntemi: Kavramlar İlkeler Teknikler. Ankara: Nobel Akademik Yayıncılık, 2019

23   **Özdamar K**.   Statistical Data Analysis with Package Programs. Eskişehir: Kaan Bookstore, 2004

24   **Yaşlıoğlu MM**. Sosyal bilimlerde faktör analizi ve geçerlilik: Keşfedici ve doğrulayıcı faktör analizlerinin kullanılması. *İstanbul Üniversitesi İşletme Fakültesi Dergisi* 2017; 46: 74-85

25   **Finch WH**.   Exploratory Factor Analysis. Thousand Oaks, CA: Sage Publications Inc., 2019 [DOI: 10.4135/9781544339900]

26   **Polit DF**, Beck CT, Owen SV. Is the CVI an acceptable indicator of content validity? Appraisal and recommendations. *Res Nurs Health* 2007; **30**: 459-467 [PMID: 17654487 DOI: 10.1002/nur.20199]

27   **Terwee CB**, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007; **60**: 34-42 [PMID: 17161752 DOI: 10.1016/j.jclinepi.2006.03.012]

28   **Boateng GO**, Neilands TB, Frongillo EA, Melgar-Quiñonez HR, Young SL. Best Practices for Developing and Validating Scales for Health, Social, and Behavioral Research: A Primer. *Front Public Health* 2018; **6**: 149 [PMID: 29942800 DOI: 10.3389/fpubh.2018.00149]

29   **Çam M**, Baysan-Arabacı L. Qualitative and quantitative steps on attitude scale construction. *Turkish J Res Dev Nurs* 2010; **2**: 65-68

30   **Hayran M**, Hayran M.   Sağlık araştırmaları için temel istatistik. Ankara: Art Ofset Matbaacılık, 2011: 403-416

31   **Xia Y**, Yang Y. RMSEA, CFI, and TLI in structural equation modeling with ordered categorical data: The story they tell depends on the estimation methods. *Behav Res Methods* 2019; **51**: 409-428 [PMID: 29869222 DOI: 10.3758/s13428-018-1055-2]

32   **32 Trevisan MS**. Book Review: Scale Development: Theory and Applications Robert F. DeVellis Newbury Park CA: Sage Publications Inc.. *Applied Psychological Measurement* 2016; **15**: 425-426 [DOI: 10.1177/014662169101500413]

33   **Netemeyer RG**, Bearden WO, Sharma S.   Scaling procedures: Issues and applications. Thausand Oaks, CA: Sage

Publication, Inc., 2013 [DOI: 10.4135/9781412985772]

34   **Jonhson RB**, Christensen L.   Educational research quantitative, qualitative, and mixed approach. Thausand Oaks, CA: Sage Publication, Inc., 2013

35   **Alpar C**.   Spor, Sağlık ve Eğitim Bilimlerinden Örneklerle Uygulamalı İstatistik ve Geçerlik-Güvenirlik. Ankara: Detay Yayıncılık, 2016

Observational Study

Relationship between depression, smartphone addiction, and sleep among Chinese engineering students during the COVID-19 pandemic

Wen-Juan Gao, Yan Hu, Jun-Lin Ji, Xin-Qiao Liu

Wen-Juan Gao, Yan Hu, Jun-Lin Ji, Institute of Higher Education, Beihang University, Beijing 100191, China

Wen-Juan Gao, Yan Hu, Jun-Lin Ji, School of Public Administration, Beihang University, Beijing 100191, China

Wen-Juan Gao, Yan Hu, Jun-Lin Ji, Research Center for Beijing Higher Education Development, Beihang University, Beijing 100191, China

Xin-Qiao Liu, School of Education, Tianjin University, Tianjin 300350, China

Corresponding author: Xin-Qiao Liu, PhD, Associate Professor, School of Education, Tianjin University, No. 135 Yaguan Road, Jinnan District, Tianjin 300350, China. xinqiaoliu@pku.edu.cn

Abstract

BACKGROUND
Existing research has demonstrated that depression is positively related to smartphone addiction, but the role of sleep has not been discussed thoroughly, especially among engineering undergraduates affected by the coronavirus disease 2019 pandemic.

AIM
To evaluate sleep as a mediator of the association between smartphone addiction and depression among engineering undergraduates.

METHODS
Using a multistage stratified random sampling method, a cross-sectional survey was conducted among 692 engineering undergraduates from a top engineering university in China, and data were collected by self-reported electronic question-naires. The data included demographic characteristics, such as age, gender, the Smartphone Addiction Scale-Short Version (SAS-SV), the 9-item Patient Health Questionnaire, and the Pittsburgh Sleep Quality Index. Pearson correlation and multiple linear regression analyses were used to examine the association between smartphone addiction and depression, while structural equation models were established to evaluate the possible mediating role of sleep.

RESULTS

Based on the cutoffs of the SAS-SV, the rate of smartphone addiction was 63.58 percent, with 56.21 percent for women and 65.68 percent for men, among 692 engineering students. The prevalence of depression among students was 14.16 percent, with 17.65 percent for women, and 13.18 percent for men. Smartphone addiction was positively correlated with depression, and sleep played a significant mediating effect between the two, accounting for 42.22 percent of the total effect. In addition, sleep latency, sleep disturbances, and daytime dysfunction significantly mediated the relationship between depression and smartphone addiction. The mediating effect of sleep latency was 0.014 [$P < 0.01$; 95% confidence interval (CI): 0.006-0.027], the mediating effect of sleep disturbances was 0.022 ($P < 0.01$; 95%CI: 0.011-0.040), and the mediating effect of daytime dysfunction was 0.040 ($P < 0.01$; 95%CI: 0.024-0.059). The influence of sleep latency, sleep disturbances, and daytime dysfunction accounted for 18.42%, 28.95%, and 52.63% of the total mediating effect, respectively.

CONCLUSION
The results of the study suggest that reducing excessive smartphone use and improving sleep quality can help alleviate depression.

Key Words: Smartphone addiction; Depression; Pittsburgh Sleep Quality Index; Engineering students; COVID-19; Mediating effect

Core Tip: This study described the prevalence of depression and smartphone addiction among engineering students during the coronavirus disease 2019 pandemic and analyzed the relationship between depression, smartphone addiction, and sleep. The results showed that there was an alarmingly high rate of smartphone addiction among engineering students, and they suffered from mild depression on average. Smartphone addiction and poor sleep were significant factors affecting depression, and sleep mediated the relationship between smartphone addiction and depression, including sleep latency, sleep disturbances, and daytime dysfunction.

INTRODUCTION

The prevalence of depression among college students has aroused broad public concern. A review of studies demonstrated that the pooled prevalence of depressive symptoms was 34%[1]. A recent study of American college students showed that 48.14% experienced moderate to severe levels of depression[2], and the prevalence rate of depression among Chinese college students from 1997 to 2015 reached 23.8% on average[3]. Furthermore, 41.8% of Chinese college students struggled with depressive disorders during the coronavirus disease 2019 (COVID-19) pandemic[4], especially those in places at high risk of COVID-19 spread who showed more severe depressive symptoms[5].

In particular, engineering undergraduates reported higher levels of depression than students in other majors[6]. The heavy academic burden and long study time create tremendous psychological pressure [7]. Previous studies noted that engineering students were under higher pressure than students with nonengineering majors[8,9]. They also had a higher prevalence of depression[10] and suffered from more severe depressive symptoms[8]. Given the importance of engineering education to national development and the adverse mental health of engineering students, it is crucial to identify the influencing factors of engineering students' depression in the context of the COVID-19 pandemic to develop interventions to improve their mental health.

Smartphone addiction is considered a behavioral addiction and refers to an excessive use of smartphones that interferes with users' daily life and has harmful effects[11]. Evidence from China indicated that the prevalence of smartphone addiction among college students ranges from 20% to 50% [12-14]. Notably, smartphone addiction is associated with mental health problems[15]. Smartphone addicts may suffer from social isolation and interpersonal relationship problems[16], musculoskeletal pain and neurological problems[17], emotion dysregulation[18], pressure, and anxiety[19], which may lead to depressive disorders. Previous empirical studies confirmed a positive correlation between

depression and smartphone addiction[20,21], and smartphone addiction exerted a significant effect on depression in different countries and regions[22,23]. However, the mechanism of smartphone addiction's relationship to depression has not been thoroughly discussed, so analyzing the pathway between smartphone addiction and depression is still an important area of study.

Sleep serves as the basis of personal emotional and physical health[24], and empirical studies have verified that poor sleep quality is significantly correlated with depression[25-28]. Some longitudinal studies have indicated that sleep disturbance triggers depression[29]. Lack of sleep makes individuals more sensitive to emotional and stressful stimuli[30], further increasing their risk of depression. According to the gratification theory of the internet, individuals extend their smartphone use time to obtain a sense of satisfaction[31]. Rich smartphone applications also cause addiction in people and make them lose their sense of time[31]. Therefore, problems such as sleep delay, lack of sleep, and poor sleep quality are very likely to occur among college students. Empirical studies have proven that smartphone addiction correlates significantly with poor sleep quality[32,33] and is considered a risk factor for poor sleep quality[34]. The literature in the field also implies that sleep plays a mediating role in smartphone addiction and depression; however, this has not been thoroughly discussed.

There are several research gaps according to the review of relevant studies. First, most of these studies are based on the general population of college students or medical students. More pertinent research needs to be explicitly explored for students of different majors, such as engineering students. Second, college students' mental health status has considerably changed since the outbreak of COVID-19, with a large proportion of students suffering from severe depression and anxiety. Therefore, it is necessary to explore the changes in depression, mobile phone addiction, and sleep status of college students under the influence of COVID-19 and investigate their relationship in this specific context. Third, the role of sleep in the relationship between mobile phone addiction and depression has been poorly analyzed. Although a few studies have confirmed that sleep mediates the relationship between smartphone addiction and depression[35], special attention has been given to engineering students, and the mediating role of sleep needs to be further discussed.

Therefore, this study carried out a cross-sectional survey among engineering students in the context of the COVID-19 pandemic. It adds to the literature mainly by analyzing the relationship between smartphone addiction, sleep, and depression among Chinese engineering students during COVID-19 and investigating the mediating role of sleep in the relationship between smartphone addiction and depression. Based on the extant empirical evidence, the present study hypothesized that there is a significant positive correlation between smartphone addiction and depressive symptoms (Hypothesis I) and that sleep significantly mediates the relationship between smartphone addiction and depression (Hypothesis II). Specifically, engineering students with higher levels of smartphone addiction in the context of the pandemic are more likely to struggle with sleep disorders, which further results in more severe depressive symptoms.

MATERIALS AND METHODS

Participants and procedure

The data were collected from an online survey of 692 engineering undergraduates at a top university in China in December 2021. This study adopted a multistage stratified random sampling method; first, five engineering schools were randomly selected from 25 engineering schools in the university, and then the respondents were randomly chosen according to the size of each school and the number of students in different years. Given the pandemic limiting the face-to-face investigation, the survey team sent electronic questionnaire links to the selected participants' mobile phone numbers or email accounts. All participants were notified of the purpose of the study and gave informed consent to participate. It took approximately 20 min on average to complete the questionnaire, after which students received a cash reward ranging from 8 CYN to 15 CNY. To avoid duplications or fraud in the online survey, the links were exclusive to each student and automatically became invalid after students completed and submitted the questionnaire. Participants were required to complete all questions before submitting the questionnaire. The participants in the study were Chinese engineering undergraduates aged 18-24. The study was reviewed by the ethics committee of Tianjin University and used the STROBE cross-sectional reporting guidelines.

The final sample comprised 153 females (22.11%) and 539 males (77.89%). The age of students ranged from 18 to 24 years old, and the mean age was 20.804 years old (SD = 1.109). Students were distributed evenly from freshmen to seniors, with 76 (10.98%), 242 (34.97%), 231 (33.38%), and 143 (20.67%), respectively. Among them, 608 (87.86%) were of Han nationality, and 84 (12.14%) were ethnic minorities. There were 439 (63.44%) only children and 253 (36.56%) with siblings. In terms of home location, 122 students (17.63%) were from rural areas, and 570 students (82.37%) were from towns. There were 343 (49.57%) students whose fathers completed tertiary education and 349 (50.43%) students whose fathers never received higher education. Regarding the types of high schools, 524 students (75.72%) attended the best local high schools, and 168 (24.28%) attended other high schools.

Measures

Depression: Students' depression was measured using the Patient Health Questionnaire-9 (PHQ-9), a part of the PHQ measuring depressive mood. The PHQ is a 3-page questionnaire self-assessed by patients[36], among which the 9-item depression module is used to measure depressive symptoms. Each item in the PHQ-9 ranges from 0 (no) to 3 (almost every day), and the total score ranges from 0 to 27, with higher scores representing more severe depression[37]. Most studies divide depression scores into five categories based on the severity of depression for practical applications, namely, minimal depressive symptoms (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27), and use a total score of no less than 10 as a reasonable threshold for screening depression[38].

Smartphone addiction: This study used the Smartphone Addiction Scale-Short Version (SAS-SV) to measure participants' smartphone addiction levels. The SAS-SV was adapted by Kwon *et al*[39] based on the SAS. They invited at least 6 experts to select 10 questions from the 33 questions in the SAS and verified that the CVI was greater than 0.78, and the average I-CVI and S-CVI/UA were 0.943 and 0.60. Kwon *et al*[39] verified a Cronbach's alpha correlation coefficient of 0.91 for the SAS-SV in Korea; thus, it was regarded as a suitable tool for assessing smartphone addiction. In this study, experts were invited to translate English SAS-SV questions into Chinese, and appropriate adaptations were made according to the actual situation. For example, in the original item, "constantly checking my smartphone so as not to miss conversations between other people on Twitter or Facebook", "Twitter or Facebook" was changed to "QQ or WeChat" to adapt to the Chinese context. The answers were reported on a 7-point scale, with 1 meaning "strongly disagree" and 7 meaning "strongly agree". The total SAS-SV scale ranges from 10 to 70. Previous studies confirmed that the critical values of male and female smartphone addiction were 31 and 33, respectively[40]. Since the original SAS-SV is a six-point scale with a score range of 10-60, the critical values of male and female smartphone addiction in the study are 36.2 and 38.5, respectively. SAS-SV has been proven reliable and valid in mainland China and Hong Kong. Luk *et al*[40] used the Chinese version of the SAS-SV to measure the smartphone use addiction of adults in Hong Kong and found that the SAS-SV had good internal consistency, with an α coefficient of 0.844. Cheung *et al*[41] tested the SAS-SV scale among Hong Kong children and adolescents, and the α coefficient was 0.86, indicating that the scale had good reliability and validity when applied to Chinese students.

Sleep quality: Sleep quality in the study was measured by the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-assessment questionnaire. It included seven components: Sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The seven components, each scoring 0-3 points, constituted the sleep index, with higher scores denoting worse sleep quality[42].

Statistical analysis

First, descriptive statistical analysis was conducted to demonstrate the general situation of smartphone addiction, overall sleep quality, and depression among engineering students and to compare differences in gender subgroups with the t test. Second, the correlation between smartphone addiction, sleep, and depression was explored with Pearson's correlation analysis. Third, the influence of smartphone addiction on depression among engineering students was examined with multiple linear regression. Depression level was the outcome variable in the regression models, while smartphone addiction level and sleep quality were the core independent variables. It controlled for confounding variables such as students' age, gender, ethnicity, political status, only child status and family socioeconomic status. To identify the effects of different variables, we successively included control variables, smartphone addiction, and sleep in the multiple regression model. Specifically, Model 1, $Y = \beta_0 + \beta_1 x' + \varepsilon$, was developed first to include control variables on engineering students' depression. Mobile phone addiction was further included in Model 2, $Y = \beta_0 + \beta_1 x' + \beta_2 SA + \varepsilon$. The seven sleep index components were then incorporated into Model 3, $Y = \beta_0 + \beta_1 x' + \beta_2 SA + \beta_3 SleepQuality + \beta_4 SleepLatency + \beta_5 SleepDuration + \beta_6 HabitualSleepEfficiency + \beta_7 SleepDisturbances + \beta_8 SleepMedication + \beta_9 DaytimeDysfunction + \varepsilon$. Y denotes the level of depression of engineering students at college. SA represents the degree of smartphone addiction. "x'" represents the control variables, including students' age, gender, ethnicity, political status, only child status, family socioeconomic status, and whether their father received higher education. "ε" defines the error. Finally, a structural equation model was built to examine the mediating role of sleep in the relationship between smartphone addiction and depression. Data analysis was performed by Stata SE 15.

RESULTS

Descriptive statistics and correlations of variables

Table 1 shows the mean and SD of depression, smartphone addiction, and overall sleep quality. The

Table 1 Descriptive statistics of depression, smartphone addiction and sleep (*n* = 692)

Variables	All		Female		Male		Test statistic	*P* value
	Mean	SD	Mean	SD	Mean	SD		
Depression	5.082	4.971	5.425	4.656	4.985	5.056	-0.966	0.335
Smartphone addiction	39.126	11.252	39	10.668	39.161	11.422	0.157	0.876
Pittsburgh Sleep Quality Index	5.496	2.827	5.856	3.023	5.393	2.763	-1.790	**0.074**
Sleep quality	0.990	0.731	1.059	0.771	0.970	0.718	-1.323	0.186
Sleep latency	0.906	0.858	0.928	0.897	0.900	0.848	-0.360	0.719
Sleep duration	1.009	0.766	1.052	0.768	0.996	0.766	-0.797	0.426
Habitual sleep efficiency	0.201	0.542	0.190	0.483	0.204	0.558	0.293	0.770
Sleep disturbances	0.883	0.574	0.915	0.584	0.874	0.571	-0.784	0.434
Sleep medication	0.104	0.441	0.111	0.467	0.102	0.434	-0.224	0.823
Day dysfunction	1.403	1.007	1.601	1.009	1.347	1.000	-2.771	**0.006**

Bold represents statistically significant.

mean score of depression among engineering students was 5.082 (± 4.971); the average score of females was 5.425 (± 4.656), and the average score of males was 4.985 (± 5.056). In general, engineering students experienced mild depression at college, and there was no statistically significant difference in the mean level of depression between female and male students. Regarding the prevalence of depression (Figure 1), 54.91%, 30.92%, 8.82%, 3.61%, and 1.73% of the students exhibited minimal, mild, moderate, moderately severe, and severe depression, respectively. For female students, 82.36% had minimal or mild depression, while 3.92% had moderate or severe depression. For males, 86.83% had minimal or mild depression, whereas 5.76% struggled with moderately severe or severe depression. Given that the extant literature usually uses a PHQ-9 total score of no less than 10 to distinguish whether the participants suffer from depression, 14.16% of students experienced depression disorders (depression ≥ 10), and female and male students who suffered from depressive disorders accounted for 17.65% and 13.18%, respectively (Table 1, Figure 1).

The mean value of mobile phone addiction was 39.126 (± 11.252); the score for females was 39.000 (± 10.668), and the score of males was 39.161 (± 11.422). There was also no significant gender difference in the average mobile phone addiction level. It should be noted that 63.58% of engineering students were addicted to mobile phones, with 56.21% of females and 65.68% of males being addicted to mobile phones. The mean sleep quality score was 5.496 (± 2.827), with female students scoring 5.856 (± 3.023) and males scoring 5.393 (± 2.763). The sleep quality of females was significantly worse than that of males (*P* = 0.074). Specifically, among the seven components of the sleep quality index, day dysfunction showed a significant gender difference, with girls having higher perceived day dysfunction than boys (*P* < 0.010).

In sum, smartphone addiction among engineering students was alarming, with more than 60% exhibiting smartphone addiction, which is higher than that reported by most studies in other countries [43-46]. In addition, engineering students suffered from mild depression on average, and female students had more serious sleep problems than males.

The correlation analysis shown in Table 2 demonstrated that depression was positively correlated with mobile phone addiction, with a coefficient of 0.330 (*P* < 0.01). There was also a positive correlation between depression and PSQI, with a coefficient of 0.503 (*P* < 0.01). Mobile phone addiction and PSQI were significantly positively correlated with a coefficient of 0.250 (*P* < 0.01). In addition, depression was positively correlated with the seven components of the sleep index, among which daytime dysfunction had the strongest correlation with a coefficient of 0.414. Mobile phone addiction had a statistically significant positive correlation with sleep quality, sleep latency, sleep disturbances, and daytime dysfunction, among which the strongest correlation was also with daytime dysfunction, with a coefficient of 0.246. The results revealed that depression, smartphone addiction, and sleep index were closely related. The increased risk of smartphone addiction might not only predict the deterioration of sleep quality but also lead to an increase in depressive mood (Table 2).

Multivariate regression of depression on smartphone addiction and sleep
The regression model sequentially included the control variables, mobile phone addiction, and sleep index (Table 3). Model 1 shows the influence of engineering students' age, gender, nationality, political status, household registration, and other factors on depression (R^2 = 0.011). Model 2 further displays the

No.	Variable	1	2	3	4	5	6	7	8	9	10
	Table 2 Correlation analyses among depression, smartphone addiction, and sleep (*n* = 692)										
1	Depression	1.000									
2	Smartphone addiction	0.330[a]	1.000								
3	Pittsburgh Sleep Quality Index	0.503[a]	0.250[a]	1.000							
4	Sleep quality	0.315[a]	0.153[a]	0.738[a]	1.000						
5	Sleep latency	0.334[a]	0.203[a]	0.676[a]	0.483[a]	1.000					
6	Sleep duration	0.164[a]	0.027	0.470[a]	0.204[a]	0.072[c]	1.000				
7	Habitual sleep efficiency	0.090[b]	0.060	0.378[a]	0.151[a]	0.156[a]	0.226[a]	1.000			
8	Sleep disturbances	0.369[a]	0.182[a]	0.539[a]	0.311[a]	0.351[a]	0.091[b]	0.104[a]	1.000		
9	Sleep medication	0.232[a]	0.036	0.373[a]	0.219[a]	0.194[a]	-0.007	0.076[b]	0.191[a]	1.000	
10	Daytime dysfunction	0.414[a]	0.246[a]	0.664[a]	0.425[a]	0.272[a]	0.179[a]	0.016	0.210[a]	0.140[a]	1.000

[a]$P < 0.01$.

[b]$P < 0.05$.

[c]$P < 0.10$.
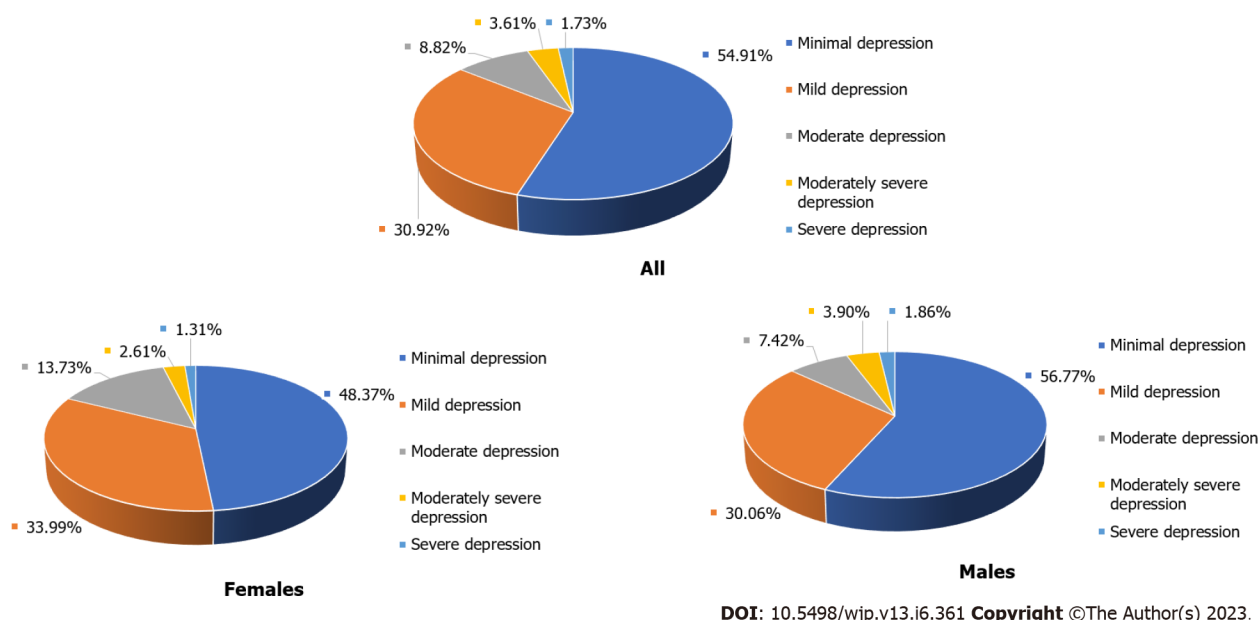
Figure 1 Prevalence of depression among engineering students, *n* = 692.

impact of smartphone addiction and control variables on depression (R^2 = 0.116). For every one-point increase in the mobile phone addiction score, the average depression score increased significantly by 0.141 among engineering students. Model 3 depicts the influence of the seven components of the sleep index, mobile phone addiction, and control variables (R^2 = 0.352). Sleep latency, sleep duration, sleep disturbance, sleep medication, daytime dysfunction, and smartphone addiction significantly affected the depressive mood of students, among which sleep disturbances had the most considerable effect. For every additional point scored by the sleep disturbances, the average depression score of students increased significantly by 1.817. The regression coefficient of smartphone addiction on depression in Model 3 was lower than that in Model 2, indicating that smartphone addiction may indirectly affect depressive mood by affecting sleep quality (Table 3).

Path analysis

This study further established a structural equation model of mobile phone addiction, sleep index, and depression based on correlation and regression analyses to explore possible mediating effects (Figure 2). According to the results in Table 4, the total effect of smartphone addiction on depression was 0.180 (*P* < 0.01; 95%CI: 0.134-0.233), with the direct effect of smartphone addiction on depression being 0.104 (*P* <

Table 3 Multiple linear regression of depression (*n* = 685)			
Variables	**Model 1**	**Model 2**	**Model 3**
Sleep quality	-	-	0.158
Sleep latency	-	-	**0.587**[a]
Sleep duration	-	-	**0.471**[b]
Habitual sleep efficiency	-	-	0.185
Sleep disturbances	-	-	**1.817**[a]
Sleep medication	-	-	**1.436**[a]
Daytime dysfunction	-	-	**1.304**[a]
Smartphone addiction	-	**0.141**[a]	**0.082**[a]
Age	-0.130	-0.113	-0.066
Gender	0.526	0.602	0.112
Nationality	-0.524	-0.570	-0.292
Political status	0.435	-0.035	-0.102
Only child	-0.279	-0.047	0.092
Home location	-0.557	-0.668	-0.392
Family socioeconomic status	-0.170	-0.153	-0.181
Father' education	-0.115	-0.152	0.228
Observations	685	685	685
Adjusted R^2	0.011	0.116	0.352

[a]$P < 0.01$.

[b]$P < 0.05$.

[c]$P < 0.10$.

Bold represents statistically significant. Gender: 0 = male, 1 = female. Nationality: 0 = minority nationality, 1 = Han nationality. Political status: 0 = nonparty member, 1 = Communist Party member; only child: 0 = having siblings; 1 = only child. Home location: 0 = rural, 1 = town. Family socioeconomic status: 1 = lower, 2 = lower middle, 3 = middle, 4 = upper middle, 5 = upper. Father's educational level: 0 = never receiving higher education, 1 = completing higher education.

Table 4 Bootstrapping indirect effect and 95% confidence interval for mediation model (*n* = 692)				
Effect path	**Estimated effect**	***P* value**	**Standard errors**	**95%CI**
Total effects	0.180	**0.001**	0.025	0.134-0.233
Smartphone addiction-depression	0.104	**0.001**	0.022	0.063-0.149
Smartphone addiction-sleep latency/sleep; disturbances/daytime dysfunction-depression	0.076	**0.001**	0.012	0.053-0.102
Smartphone addiction-sleep latency-depression	0.014	**0.001**	0.005	0.006-0.027
Smartphone addiction-sleep disturbances-depression	0.022	**0.000**	0.007	0.011-0.040
Smartphone addiction-daytime dysfunction-depression	0.040	**0.001**	0.009	0.024-0.059

Bold represents statistically significant. 95%CI: 95% confidence interval.

0.01; 95%CI: 0.063-0.149), accounting for 57.78% of the total effect. The mediating effect of sleep on the relationship between mobile phone addiction and depression was 0.076 ($P < 0.01$; 95%CI: 0.053-0.102), accounting for 42.22% of the total. Specifically, the mediating effect of sleep latency was 0.014 ($P < 0.01$; 95%CI: 0.006-0.027), the mediating effect of sleep disturbances was 0.022 ($P < 0.01$; 95%CI: 0.011-0.040), and the mediating effect of daytime dysfunction was 0.040 ($P < 0.01$; 95%CI: 0.024-0.059). The influence of sleep latency, sleep disturbances, and daytime dysfunction accounted for 18.42%, 28.95%, and 52.63% of the total mediating effect, respectively (Figure 2, Table 4).
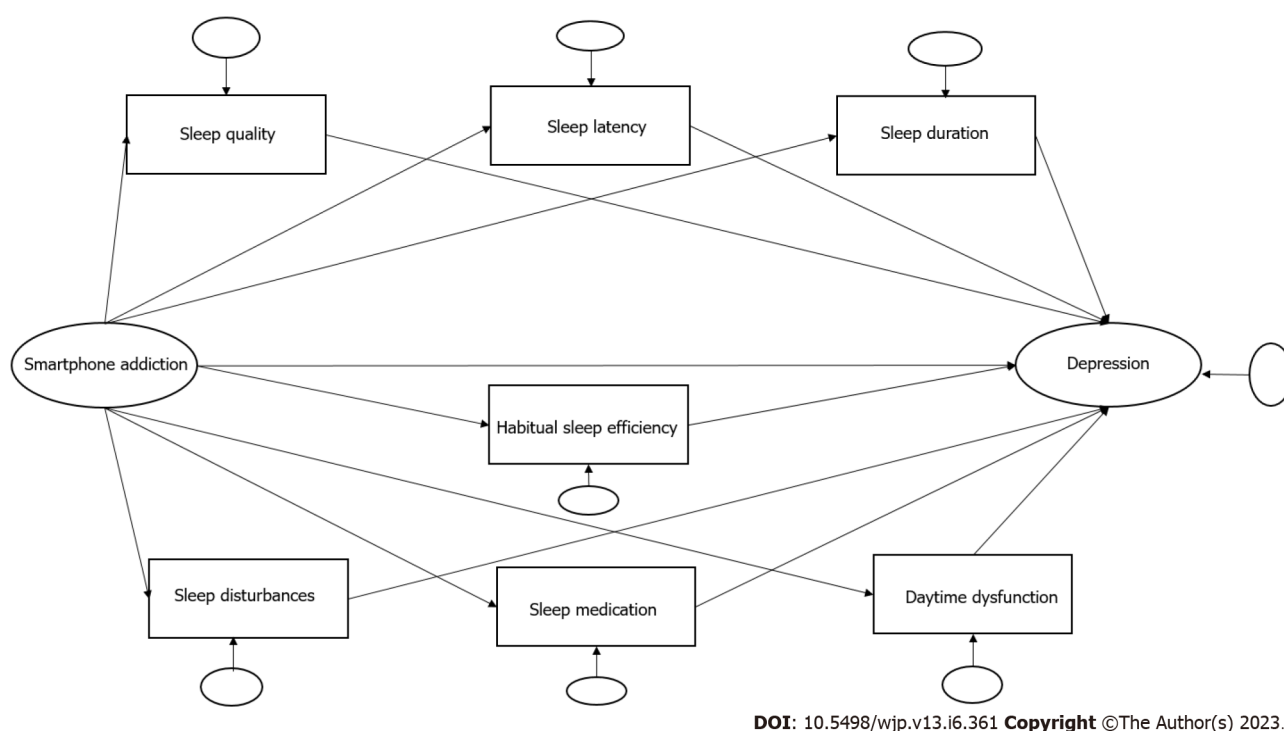
Figure 2 Structural equation model of depression, *n* = 692.

DISCUSSION

This study analyzed the relationship between smartphone addiction and depression among engineering students, which has been extensively discussed in the extant literature, yet the underlying mechanisms need to be further explored and verified in diverse contexts and among different populations. The results generally support the hypotheses that smartphone addiction is a significant predictor of depression and that sleep mediates the effect of smartphone addiction on depression. Therefore, alleviating smartphone addiction and improving sleep quality could be an effective strategy to reduce the incidence of depression among engineering students.

The study found a high prevalence rate of smartphone addiction of 63.58% among engineering students in China, with that of male students at 65.68% and female students at 56.21%. The addiction rate appeared to be much higher than in other regions or populations, such as 11.8% in Taiwan[47], 36.8% in Nepal[48], and 41.93% of medical students in Asian countries[49]. There are two reasons for our study's high prevalence of smartphone addiction apart from different cultural backgrounds or various measurement tools. First, given that engineering students usually confront heavy learning tasks and relatively poor face-to-face communication, smartphones might be essential for them to release pressure and maintain social networking. Second, the survey was conducted amid the coronavirus pandemic, which may have exacerbated smartphone addiction among college students. Indeed, the risk of smartphone addiction increased due to the fear of contracting the disease, reduced social interactions due to lockdowns, and long hours of online education. Previous empirical studies confirmed that the smartphone addiction rate of college students in the beginning and fading periods of the pandemic was significantly lower than that in the severe period[50]. It should also be noted that the gender difference in mobile phone addiction in this study was insignificant, inconsistent with existing research findings [24]. This may be due to the small percentage of female engineering students and the widespread influence of online teaching on engineering students.

The prevalence of depression among engineering students in the study was 14.16%, and most students (85.83%) experienced minimal or mild depression during COVID-19. Relevant research found that the prevalence rate of depression among college students was 9.0% in China one month after the outbreak of COVID-19[51] and 34.19% in Spain in March 2020[52]. Forty-four percent of students experienced some depressive thoughts during the COVID-19 pandemic in the United States[53]. The prevalence of depression among engineering students in this study was within the rate range of previous studies, which may be related to the time of the survey. The study was conducted in December 2021, when the pandemic spread was effectively contained, and college students returned to school. The general situation had improved at this stage, and relevant fear and worries had been alleviated, although their study life was still partially affected by the pandemic.

Pearson correlation and multiple regression analysis verified Hypothesis I that smartphone addiction was a significant influencing factor of depression and that high levels of smartphone addiction caused more serious depressive symptoms among engineering students. The result was consistent with most previous studies that there was a positive correlation between mobile phone addiction and depression [21,22,54,55]. The influence of smartphone addiction on depression can be explained by the effect on physiological health and social relations. First, smartphone addiction may result in individuals' unhealthy states, including physical pain, sleep disorders, and inattention, leading to mental health problems such as depression[56]. Second, the overuse of smartphones may increase social isolation and aggravate social anxiety due to the reduction of face-to-face communication and the narrowing of social circles, thus increasing the risk of depression, according to displacement theory and Sullivan's interpersonal theory[57]. The longitudinal study by Herrero *et al*[58] strongly confirmed that smartphone addiction negatively affected college students' social support over time and generated high levels of depression.

For smartphone addiction as a predictor of poor sleep outcomes, the findings agree with most relevant research[59,60]. The overuse of smartphones may expose individuals to blue light from screens for a long time, affecting melatonin levels and thus normal circadian rhythm[61]. Furthermore, when users browse social networking sites through smartphones, the intensity of emotional synchronization may be amplified, resulting in emotional contagion[62]. Smartphone addiction affects the emotions of mobile phone users[35] and increases their psychological pressure[63], thus affecting their normal sleep procedure. In particular, the continuous use of smartphones may lead to bedtime procrastination[31]. The study also found that smartphone addiction was related to sleep quality but not sleep duration, which is consistent with the findings of relevant studies in this field[21,64,65].

Poor sleep positively predicted depressive symptoms in engineering students, especially the components of sleep latency, sleep duration, sleep disturbances, sleep medication, and daytime dysfunction. This finding partially coincides with prior studies[66,67]. Hypothesis II confirms that sleep plays a mediating role in the effect of smartphone addiction on depression, especially sleep latency, sleep disturbances and daytime dysfunction. In fact, poor sleep may affect the emotional regulation ability of the individual through a physiological mechanism[68], and a lack of sleep increases the threat across multiple domains of dysfunction[69]. Sleep is associated with depression at the molecular and neurophysiological levels, and abnormalities in these neurotransmitter systems associated with sleep disorders may contribute to the exacerbation of depression[70]. In addition, sleep disorders affect students' daytime function, resulting in daytime sleepiness, drowsiness, and inattention. This interferes with students' daily tasks and reduces their interest in activities, exposing them to stress and irritability and worsening depressive symptoms[67].

The role of daytime dysfunction was noticeable in both the direct and indirect effects of depression. The influence of daytime dysfunction on depression has been partially confirmed by studies[71,72]. Daytime dysfunction can be regarded as the primary link between night sleep and depression[73]. In fact, daytime dysfunction is closely related to fatigue and burnout[74]. People with high levels of daytime dysfunction tend to be more tired and therefore more vulnerable to depressive moods.

This study suggests that colleges and universities can alleviate depression among students by intervening in smartphone addiction and improving sleep. Studies have discussed effective interventions to reduce smartphone addiction, such as self-awareness and self-control, involuntary restriction, and peer support[75]. College students in adulthood should be soberly aware of the harm of smartphone addiction and seek scientific interventions when necessary. For instance, cognitive behavioral therapy (CBT) was proven effective in a meta-analysis of treatment interventions for adolescents with internet addiction[76]. The group mindfulness-based cognitive-behavioral intervention [77] and mind-body exercise (ME)[78] have been shown to be helpful in the intervention of smartphone addiction among Chinese college students. Thus, cognitive behavioral interventions and MEs (*e.g.*, QigongBaduanjin) should be encouraged. For involuntary restraint, using technology against it, a new mode of intervention for treating smartphone addiction, focuses on monitoring and limiting the use of smartphones with functionalities built into the smartphone and third-party apps. Empirical studies have found that ways to limit notifications and reduce screen time are becoming more widely accepted[79, 80]. Social support, such as favorable peer relationships and harmonious family relationships, is also a protective factor against smartphone addiction[81]. In addition, colleges and universities should also make efforts to expand the accessibility of mental health services to alleviate smartphone addiction.

In addition, physical exercise is the most common way to enhance sleep quality, and sleep therapy training is also practical in improving the sleep situation of college students[82]. For example, sleep training programs for university students with sleep problems proved feasible to significantly enhance students' sleep quality[83]. Psychological interventions such as cognitive behavior therapy for insomnia (CBT-I) have also been recommended to improve sleep[84]. Other interventions, such as improving sleep hygiene, relaxation, mindfulness and hypnotherapy, also play a role in improving sleep quality [85]. Therefore, college students should be encouraged to strengthen their physical exercise, improve their sleeping conditions and restrict mobile phone use to ensure sleep time and quality. For students with serious sleep problems, necessary psychological intervention and medical treatment should be carried out in time to avoid deterioration of the problem and more severe sleep disorders and psychological problems.

The study has several limitations. First, the self-reported data by students may have measurement errors. For example, students may underestimate their smartphone addiction tendency, sleep disorders, and depressive symptoms. Second, other possible influencing factors of depression, such as stress and self-esteem, were not included in this study's analysis framework for assessment. Third, there may exist sample selection bias in the analysis results since written informed consent was obtained before students entered the questionnaire, and those who refused to consent were not included in the sample of this study. Fourth, the cross-sectional data used in this study make it difficult to identify the causal relationship between smartphone addiction and depression. Future studies may investigate the causal relationship between smartphone addiction and depression based on longitudinal data and incorporate more factors into the theoretical mechanisms to discover more effective measures.

CONCLUSION

This cross-sectional study investigated the relationship between smartphone addiction and depression and examined the mediating role of sleep among engineering students in China. First, there was an alarmingly high rate of smartphone addiction among engineering students with no significant gender difference, which has become an urgent issue requiring attention from all parties. In addition, engineering students suffered from mild depression on average, and female students had more severe sleep problems than males. Second, smartphone addiction and sleep deterioration were significant factors affecting depression among engineering students, which might increase the risk of their depressive disorders. Third, sleep latency, sleep disturbances, and daytime dysfunction mediated the relationship between smartphone addiction and depression, among which daytime dysfunction had the most pronounced mediating effect.

The effects of smartphone addiction and sleep on depression may be complicated. Existing literature has confirmed that smartphone addiction could increase the risk of individual depression not only through social reasons (such as social difficulties and task conflicts) but also by affecting physiological functions (such as insomnia and physical pain). In addition, the mediating role of sleep should be considered thoroughly. Sleep disorders can increase the risk of depression by influencing students' emotional control and regulation function or affecting their learning behaviors. Therefore, depression can be alleviated by reducing the use of smartphones and improving sleep quality. Colleges and universities can take measures to relieve depressive problems and improve engineering students' mental health, such as enhancing their self-control ability, restricting mobile phone use, creating a soothing sleep environment, developing a daily routine, and improving physical fitness.

ARTICLE HIGHLIGHTS

Research background

It has been reported that engineering students have severe depressive symptoms, especially during the epidemic. Published research confirms a positive correlation between smartphone addiction and depression. Sleep may play a mediating role in the relationship between smartphone addiction and depression. However, this hypothesis has not been carefully studied in the engineering student population.

Research motivation

Although it is reasonable that sleep plays a mediating role in the relationship between smartphone addiction and depression, this hypothesis has not been discussed in detail. The motivation of this study is to explore the mediating role of sleep in the relationship between smartphone addiction and depression among engineering students.

Research objectives

To investigate whether sleep plays a significant mediating role in the relationship between smartphone addiction and depression among engineering students.

Research methods

During the coronavirus disease 2019 pandemic, we conducted an online survey of 692 engineering students from an engineering university in Beijing, China. The Smartphone Addiction Scale-Short Version was used to assess smartphone addiction. Depression was measured using the 9-item Patient Health Questionnaire. The Pittsburgh Sleep Quality Index was used to measure sleep. We used multivariate regression models and structural equation model analysis to evaluate sleep as a mediator.

Research results

Among 692 engineering students, the rate of smartphone addiction was 63.58%, and the prevalence of depression was 14.16%. According to a multivariate regression model, smartphone addiction and sleep significantly affect depression. Sleep plays a significant mediating role in the relationship between smartphone addiction and depression.

Research conclusions

Current research shows that sleep is a mediator between smartphone addiction and depression. Controlling smartphone use and improving sleep quality can help alleviate depression.

Research perspectives

Future longitudinal studies need to verify the mediating role of sleep in the association between smartphone addiction and depression. In addition, more variables (such as stress and anxiety) need to be controlled for and considered.

FOOTNOTES

REFERENCES

1   **Deng J**, Zhou F, Hou W, Silver Z, Wong CY, Chang O, Drakos A, Zuo QK, Huang E. The prevalence of depressive symptoms, anxiety symptoms and sleep disturbance in higher education students during the COVID-19 pandemic: A systematic review and meta-analysis. *Psychiatry Res* 2021; **301**: 113863 [PMID: 33984824 DOI: 10.1016/j.psychres.2021.113863]

2   **Wang X**, Hegde S, Son C, Keller B, Smith A, Sasangohar F. Investigating Mental Health of US College Students During the COVID-19 Pandemic: Cross-Sectional Survey Study. *J Med Internet Res* 2020; **22**: e22817 [PMID: 32897868 DOI: 10.2196/22817]

3   **Lei XY**, Xiao LM, Liu YN, Li YM. Prevalence of Depression among Chinese University Students: A Meta-Analysis. *PLoS One* 2016; **11**: e0153454 [PMID: 27070790 DOI: 10.1371/journal.pone.0153454]

4   **Xiang MQ**, Tan XM, Sun J, Yang HY, Zhao XP, Liu L, Hou XH, Hu M. Relationship of Physical Activity With Anxiety and Depression Symptoms in Chinese College Students During the COVID-19 Outbreak. *Front Psychol* 2020; **11**: 582436 [PMID: 33329238 DOI: 10.3389/fpsyg.2020.582436]

5   **Zhang Y**, Bao X, Yan J, Miao H, Guo C. Anxiety and Depression in Chinese Students During the COVID-19 Pandemic: A Meta-Analysis. *Front Public Health* 2021; **9**: 697642 [PMID: 34485228 DOI: 10.3389/fpubh.2021.697642]

6   **Asghar M**, Minichiello A, Iqbal A. Perceived Factors Contributing to the Subjective Wellbeing of Undergraduate Engineering Students: An Exploratory Study. *Int J Environ Res Public Health* 2022; **19** [PMID: 36498354 DOI: 10.3390/ijerph192316284]

7   **Liu Z**, Li M, Ren C, Zhu G, Zhao X. Relationship Between Physical Activity, Parental Psychological Control, Basic Psychological Needs, Anxiety, and Mental Health in Chinese Engineering College Students During the COVID-19 Pandemic. *Front Psychol* 2022; **13**: 802477 [PMID: 35350737 DOI: 10.3389/fpsyg.2022.802477]

8   **Jensen KJ**, Cross KJ. Engineering stress culture: Relationships among mental health, engineering identity, and sense of inclusion. *J Eng Educ* 2021; **110**: 371-392 [DOI: 10.1002/jee.20391]

9   **Foster C**, Spencer L. Are Undergraduate Engineering Students at Greater Risk for Heart Disease than Other Undergraduate Students? *J Eng Educ* 2003; **92**: 73-77 [DOI: 10.1002/j.2168-9830.2003.tb00740.x]

10   **Siddiqui NA**, Fatima S, Taj FB, Shahid A, Moosa ZA. Depression among undergraduate medical and engineering students: A comparative study. *Pak J Med Sci* 2020; **36**: 1096-1099 [PMID: 32704296 DOI: 10.12669/pjms.36.5.1858]

11   **Rathakrishnan B**, Bikar Singh SS, Kamaluddin MR, Yahaya A, Mohd Nasir MA, Ibrahim F, Ab Rahman Z. Smartphone Addiction and Sleep Quality on Academic Performance of University Students: An Exploratory Research. *Int J Environ Res Public Health* 2021; **18** [PMID: 34444042 DOI: 10.3390/ijerph18168291]

12   **Xin C**, Ding N, Jiang N, Li H, Wen D. Exploring the connection between parental bonding and smartphone addiction in Chinese medical students. *BMC Psychiatry* 2022; **22**: 712 [PMID: 36384567 DOI: 10.1186/s12888-022-04355-7]

13   **Chen B**, Liu F, Ding S, Ying X, Wang L, Wen Y. Gender differences in factors associated with smartphone addiction: a cross-sectional study among medical college students. *BMC Psychiatry* 2017; **17**: 341 [PMID: 29017482 DOI: 10.1186/s12888-017-1503-z]

14   **Long J**, Liu TQ, Liao YH, Qi C, He HY, Chen SB, Billieux J. Prevalence and correlates of problematic smartphone use in a large random sample of Chinese undergraduates. *BMC Psychiatry* 2016; **16**: 408 [PMID: 27855666 DOI: 10.1186/s12888-016-1083-3]

15   **Wacks Y**, Weinstein AM. Excessive Smartphone Use Is Associated With Health Problems in Adolescents and Young Adults. *Front Psychiatry* 2021; **12**: 669042 [PMID: 34140904 DOI: 10.3389/fpsyt.2021.669042]

16   **Kim YJ**, Jang HM, Lee Y, Lee D, Kim DJ. Effects of Internet and Smartphone Addictions on Depression and Anxiety Based on Propensity Score Matching Analysis. *Int J Environ Res Public Health* 2018; **15** [PMID: 29693641 DOI: 10.3390/ijerph15050859]

17   **Ratan ZA**, Parrish AM, Zaman SB, Alotaibi MS, Hosseinzadeh H. Smartphone Addiction and Associated Health Outcomes in Adult Populations: A Systematic Review. *Int J Environ Res Public Health* 2021; **18** [PMID: 34832011 DOI: 10.3390/ijerph182212257]

18   **Rozgonjuk D**, Elhai JD. Emotion regulation in relation to smartphone use: Process smartphone use mediates the association between expressive suppression and problematic smartphone use. *Curr Psychol* 2021; **40**: 3246-3255 [DOI: 10.1007/s12144-019-00271-4]

19   **Elhai JD**, Dvorak RD, Levine JC, Hall BJ. Problematic smartphone use: A conceptual overview and systematic review of relations with anxiety and depression psychopathology. *J Affect Disord* 2017; **207**: 251-259 [PMID: 27736736 DOI: 10.1016/j.jad.2016.08.030]

20   **Rozgonjuk D**, Levine JC, Hall BJ, Elhai JD. The association between problematic smartphone use, depression and anxiety symptom severity, and objectively measured smartphone use over one week. *Comput Hum Behav* 2018; **87**: 10-17 [DOI: 10.1016/j.chb.2018.05.019]

21   **Demirci K**, Akgönül M, Akpinar A. Relationship of smartphone use severity with sleep quality, depression, and anxiety in university students. *J Behav Addict* 2015; **4**: 85-92 [PMID: 26132913 DOI: 10.1556/2006.4.2015.010]

22   **Mohamed SM**, Mostafa MH. Impact of smartphone addiction on depression and self-esteem among nursing students. *Nurs Open* 2020; **7**: 1346-1353 [PMID: 32802355 DOI: 10.1002/nop2.506]

23   **Volungis AM**, Kalpidou M, Popores C, Joyce M. Smartphone Addiction and Its Relationship with Indices of Social-Emotional Distress and Personality. *Int J Ment Health Addict* 2020; **18**: 1209-1225 [DOI: 10.1007/s11469-019-00119-9]

24   **Dong L**, Xie Y, Zou X. Association between sleep duration and depression in US adults: A cross-sectional study. *J Affect Disord* 2022; **296**: 183-188 [PMID: 34607059 DOI: 10.1016/j.jad.2021.09.075]

25   **Peng M**, Mo B, Liu Y, Xu M, Song X, Liu L, Fang Y, Guo T, Ye J, Yu Z, Deng Q, Zhang X. Prevalence, risk factors and clinical correlates of depression in quarantined population during the COVID-19 outbreak. *J Affect Disord* 2020; **275**: 119-124 [PMID: 32658813 DOI: 10.1016/j.jad.2020.06.035]

26   **Wolf MR**, Rosenstock JB. Inadequate Sleep and Exercise Associated with Burnout and Depression Among Medical Students. *Acad Psychiatry* 2017; **41**: 174-179 [PMID: 26976402 DOI: 10.1007/s40596-016-0526-y]

27   **Zhai K**, Gao X, Wang G. The Role of Sleep Quality in the Psychological Well-Being of Final Year UndergraduateStudents in China. *Int J Environ Res Public Health* 2018; **15** [PMID: 30558301 DOI: 10.3390/ijerph15122881]

28   **Roberts RE**, Duong HT. The prospective association between sleep deprivation and depression among adolescents. *Sleep* 2014; **37**: 239-244 [PMID: 24497652 DOI: 10.5665/sleep.3388]

29   **Lovato N**, Gradisar M. A meta-analysis and model of the relationship between sleep and depression in adolescents: recommendations for future research and clinical practice. *Sleep Med Rev* 2014; **18**: 521-529 [PMID: 24857255 DOI: 10.1016/j.smrv.2014.03.006]

30   **Vandekerckhove M**, Cluydts R. The emotional brain and sleep: an intimate relationship. *Sleep Med Rev* 2010; **14**: 219-226 [PMID: 20363166 DOI: 10.1016/j.smrv.2010.01.002]

31   **Geng Y**, Gu J, Wang J, Zhang R. Smartphone addiction and depression, anxiety: The role of bedtime procrastination and self-control. *J Affect Disord* 2021; **293**: 415-421 [PMID: 34246950 DOI: 10.1016/j.jad.2021.06.062]

32   **Kaya F**, Bostanci Daştan N, Durar E. Smart phone usage, sleep quality and depression in university students. *Int J Soc Psychiatry* 2021; **67**: 407-414 [PMID: 32969293 DOI: 10.1177/0020764020960207]

33   **Sanusi SY**, Al-Batayneh OB, Khader YS, Saddki N. The association of smartphone addiction, sleep quality and perceived stress amongst Jordanian dental students. *Eur J Dent Educ* 2022; **26**: 76-84 [PMID: 33527620 DOI: 10.1111/eje.12674]

34   **Ozcan B**, Acimis NM. Sleep Quality in Pamukkale University Students and its relationship with smartphone addiction. *Pak J Med Sci* 2021; **37**: 206-211 [PMID: 33437278 DOI: 10.12669/pjms.37.1.3130]

35   **Liu M**, Lu C. Mobile phone addiction and depressive symptoms among Chinese University students: The mediating role of sleep disturbances and the moderating role of gender. *Front Public Health* 2022; **10**: 965135 [PMID: 36203678 DOI: 10.3389/fpubh.2022.965135]

36   **Spitzer RL**, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; **282**: 1737-1744 [PMID: 10568646 DOI: 10.1001/jama.282.18.1737]

37   **AlHadi AN**, Alhuwaydi AM. The mental health impact of pandemic COVID-19 crisis on university students in Saudi Arabia and associated factors. *J Am Coll Health* 2021; 1-9 [PMID: 34437818 DOI: 10.1080/07448481.2021.1947839]

38   **Kroenke K**, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606-613 [PMID: 11556941 DOI: 10.1046/j.1525-1497.2001.016009606.x]

39   **Kwon M**, Kim DJ, Cho H, Yang S. The smartphone addiction scale: development and validation of a short version for adolescents. *PLoS One* 2013; **8**: e83558 [PMID: 24391787 DOI: 10.1371/journal.pone.0083558]

40   **Luk TT**, Wang MP, Shen C, Wan A, Chau PH, Oliffe J, Viswanath K, Chan SS, Lam TH. Short version of the Smartphone Addiction Scale in Chinese adults: Psychometric properties, sociodemographic, and health behavioral correlates. *J Behav Addict* 2018; **7**: 1157-1165 [PMID: 30418073 DOI: 10.1556/2006.7.2018.105]

41   **Cheung T**, Lee RLT, Tse ACY, Do CW, So BCL, Szeto GPY, Lee PH. Psychometric Properties and Demographic Correlates of the Smartphone Addiction Scale-Short Version Among Chinese Children and Adolescents in Hong Kong. *Cyberpsychol Behav Soc Netw* 2019; **22**: 714-723 [PMID: 31621411 DOI: 10.1089/cyber.2019.0325]

42   **Buysse DJ**, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193-213 [PMID: 2748771 DOI: 10.1016/0165-1781(89)90047-4]

43   **Alimoradi Z**, Lotfi A, Lin CY, Griffiths MD, Pakpour AH. Estimation of Behavioral Addiction Prevalence During COVID-19 Pandemic: A Systematic Review and Meta-analysis. *Curr Addict Rep* 2022; **9**: 486-517 [PMID: 36118286 DOI: 10.1007/s40429-022-00435-6]

44   **Lee YS**, Joo JH, Shin J, Nam CM, Park EC. Association between smartphone overdependence and generalized anxiety disorder among Korean adolescents. *J Affect Disord* 2023; **321**: 108-113 [PMID: 36283537 DOI: 10.1016/j.jad.2022.10.018]

45   **Meng SQ**, Cheng JL, Li YY, Yang XQ, Zheng JW, Chang XW, Shi Y, Chen Y, Lu L, Sun Y, Bao YP, Shi J. Global prevalence of digital addiction in general population: A systematic review and meta-analysis. *Clin Psychol Rev* 2022; **92**: 102128 [PMID: 35150965 DOI: 10.1016/j.cpr.2022.102128]

46   **Mescollotto FF**, Castro EM, Pelai EB, Pertille A, Bigaton DR. Translation of the short version of the Smartphone Addiction Scale into Brazilian Portuguese: cross-cultural adaptation and testing of measurement properties. *Braz J Phys Ther* 2019; **23**: 250-256 [PMID: 30249438 DOI: 10.1016/j.bjpt.2018.08.013]

47   **Chao CS**, Li MH, Chang SP, Chen YH. Multiple Logistic Regression Analysis of Smartphone Use in University Students. *Front Psychol* 2022; **13**: 821345 [PMID: 35422734 DOI: 10.3389/fpsyg.2022.821345]

48   **Karki S**, Singh JP, Paudel G, Khatiwada S, Timilsina S. How addicted are newly admitted undergraduate medical students to smartphones?: a cross-sectional study from Chitwan medical college, Nepal. *BMC Psychiatry* 2020; **20**: 95 [PMID: 32122328 DOI: 10.1186/s12888-020-02507-1]

49   **Zhong Y**, Ma H, Liang YF, Liao CJ, Zhang CC, Jiang WJ. Prevalence of smartphone addiction among Asian medical students: A meta-analysis of multinational observational studies. *Int J Soc Psychiatry* 2022; **68**: 1171-1183 [PMID: 35422151 DOI: 10.1177/00207640221089535]

50   **Hu Q**, Liu Q, Wang Z. Meaning in life as a mediator between interpersonal alienation and smartphone addiction in the context of Covid-19: A three-wave longitudinal study. *Comput Human Behav* 2022; **127**: 107058 [PMID: 34690416 DOI: 10.1016/j.chb.2021.107058]

51   **Tang W**, Hu T, Hu B, Jin C, Wang G, Xie C, Chen S, Xu J. Prevalence and correlates of PTSD and depressive symptoms one month after the outbreak of the COVID-19 epidemic in a sample of home-quarantined Chinese university students. *J Affect Disord* 2020; **274**: 1-7 [PMID: 32405111 DOI: 10.1016/j.jad.2020.05.009]

52   **Odriozola-González P**, Planchuelo-Gómez Á, Irurtia MJ, de Luis-García R. Psychological effects of the COVID-19 outbreak and lockdown among students and workers of a Spanish university. *Psychiatry Res* 2020; **290**: 113108 [PMID: 32450409 DOI: 10.1016/j.psychres.2020.113108]

53   **Son C**, Hegde S, Smith A, Wang X, Sasangohar F. Effects of COVID-19 on College Students' Mental Health in the United States: Interview Survey Study. *J Med Internet Res* 2020; **22**: e21279 [PMID: 32805704 DOI: 10.2196/21279]

54   **Li Y**, Li G, Liu L, Wu H. Correlations between mobile phone addiction and anxiety, depression, impulsivity, and poor sleep quality among college students: A systematic review and meta-analysis. *J Behav Addict* 2020; **9**: 551-571 [PMID: 32903205 DOI: 10.1556/2006.2020.00057]

55   **Alhassan AA**, Alqadhib EM, Taha NW, Alahmari RA, Salam M, Almutairi AF. The relationship between addiction to smartphone usage and depression among adults: a cross sectional study. *BMC Psychiatry* 2018; **18**: 148 [PMID: 29801442 DOI: 10.1186/s12888-018-1745-4]

56   **Zhang M**, Zhou Z, Tao X, Huang L, Zhu E, Yu L, Liu H. Prevalence of subhealth status and its effects on mental health and smartphone addiction: a cross-sectional study among Chinese medical students. *Rev Assoc Med Bras (1992)* 2022; **68**: 222-226 [PMID: 35239886 DOI: 10.1590/1806-9282.20210977]

57   **Chen L**, Yan Z, Tang W, Yang F, Xie X, He J. Mobile phone addiction levels and negative emotions among Chinese young adults: The mediating role of interpersonal problems. *Comput Hum Behav* 2016; **55**: 856-866 [DOI: 10.1016/j.chb.2015.10.030]

58   **Herrero J**, Urueña A, Torres A, Hidalgo A. Socially Connected but Still Isolated: Smartphone Addiction Decreases Social

Support Over Time. *Soc Sci Comput Rev* 2019; **37**: 73-88 [DOI: 10.1177/0894439317742611]

59   **Chatterjee S**, Kar SK. Smartphone Addiction and Quality of Sleep among Indian Medical Students. *Psychiatry* 2021; **84**: 182-191 [PMID: 33856961 DOI: 10.1080/00332747.2021.1907870]

60   **Sohn SY**, Krasnoff L, Rees P, Kalk NJ, Carter B. The Association Between Smartphone Addiction and Sleep: A UK Cross-Sectional Study of Young Adults. *Front Psychiatry* 2021; **12**: 629407 [PMID: 33737890 DOI: 10.3389/fpsyt.2021.629407]

61   **Oh JH**, Yoo H, Park HK, Do YR. Analysis of circadian properties and healthy levels of blue light from smartphones at night. *Sci Rep* 2015; **5**: 11325 [PMID: 26085126 DOI: 10.1038/srep11325]

62   **Coviello L**, Sohn Y, Kramer AD, Marlow C, Franceschetti M, Christakis NA, Fowler JH. Detecting emotional contagion in massive social networks. *PLoS One* 2014; **9**: e90315 [PMID: 24621792 DOI: 10.1371/journal.pone.0090315]

63   **Liu H**, Zhou Z, Huang L, Zhu E, Yu L, Zhang M. Prevalence of smartphone addiction and its effects on subhealth and insomnia: a cross-sectional study among medical students. *BMC Psychiatry* 2022; **22**: 305 [PMID: 35488216 DOI: 10.1186/s12888-022-03956-6]

64   **Lee JE**, Jang SI, Ju YJ, Kim W, Lee HJ, Park EC. Relationship between Mobile Phone Addiction and the Incidence of Poor and Short Sleep among Korean Adolescents: a Longitudinal Study of the Korean Children & Youth Panel Survey. *J Korean Med Sci* 2017; **32**: 1166-1172 [PMID: 28581275 DOI: 10.3346/jkms.2017.32.7.1166]

65   **Selçuk KT**, Ayhan D. The relationship between smartphone addiction risk and sleep duration and psychosocial comorbidities in health professional candidates. *Perspect Psychiatr Care* 2020; **56**: 541-546 [PMID: 31859383 DOI: 10.1111/ppc.12465]

66   **Davis JC**, Falck RS, Best JR, Chan P, Doherty S, Liu-Ambrose T. Examining the Inter-relations of Depression, Physical Function, and Cognition with Subjective Sleep Parameters among Stroke Survivors: A Cross-sectional Analysis. *J Stroke Cerebrovasc Dis* 2019; **28**: 2115-2123 [PMID: 31129108 DOI: 10.1016/j.jstrokecerebrovasdis.2019.04.010]

67   **Kurtovic A**, Hnojcik A. Early bird catches the worm? The relation between school schedule, sleep quality, and depression in Croatian adolescents. *Psychol Sch* 2021; **58**: 2361-2373 [DOI: 10.1002/pits.22597]

68   **Gruber R**, Cassoff J. The interplay between sleep and emotion regulation: conceptual framework empirical evidence and future directions. *Curr Psychiatry Rep* 2014; **16**: 500 [PMID: 25200984 DOI: 10.1007/s11920-014-0500-x]

69   **Roberts RE**, Roberts CR, Duong HT. Sleepless in adolescence: prospective data on sleep deprivation, health and functioning. *J Adolesc* 2009; **32**: 1045-1057 [PMID: 19361854 DOI: 10.1016/j.adolescence.2009.03.007]

70   **Li M**, Cui J, Xu B, Wei Y, Fu C, Lv X, Xiong L, Qin D. Sleep Disturbances and Depression Are Co-morbid Conditions: Insights From Animal Models, Especially Non-human Primate Model. *Front Psychiatry* 2021; **12**: 827541 [PMID: 35145441 DOI: 10.3389/fpsyt.2021.827541]

71   **Plante DT**, Finn LA, Hagen EW, Mignot E, Peppard PE. Longitudinal associations of hypersomnolence and depression in the Wisconsin Sleep Cohort Study. *J Affect Disord* 2017; **207**: 197-202 [PMID: 27723544 DOI: 10.1016/j.jad.2016.08.039]

72   **Becker SP**, Jarrett MA, Luebbe AM, Garner AA, Burns GL, Kofler MJ. Sleep in a large, multi-university sample of college students: sleep problem prevalence, sex differences, and mental health correlates. *Sleep Health* 2018; **4**: 174-181 [PMID: 29555131 DOI: 10.1016/j.sleh.2018.01.001]

73   **Ji XW**, Ng SM, Chan CLW, Chan JSM, Chan CHY, Chung KF. Integrative body-mind-spirit intervention for concurrent sleep and mood disturbances: sleep-specific daytime functioning mediates sleep and mood improvements. *J Sleep Res* 2018; **27**: 56-63 [PMID: 28744938 DOI: 10.1111/jsr.12583]

74   **Pagnin D**, de Queiroz V, Carvalho YT, Dutra AS, Amaral MB, Queiroz TT. The relation between burnout and sleep disorders in medical students. *Acad Psychiatry* 2014; **38**: 438-444 [PMID: 24683060 DOI: 10.1007/s40596-014-0093-z]

75   **Chun J**. Conceptualizing effective interventions for smartphone addiction among Korean female adolescents. *Child Youth Serv Rev* 2018; **84**: 35-39 [DOI: 10.1016/j.childyouth.2017.11.013]

76   **Chun J**, Shim H, Kim S. A Meta-Analysis of Treatment Interventions for Internet Addiction Among Korean Adolescents. *Cyberpsychol Behav Soc Netw* 2017; **20**: 225-231 [PMID: 28263660 DOI: 10.1089/cyber.2016.0188]

77   **Lan Y**, Ding JE, Li W, Li J, Zhang Y, Liu M, Fu H. A pilot study of a group mindfulness-based cognitive-behavioral intervention for smartphone addiction among university students. *J Behav Addict* 2018; **7**: 1171-1176 [PMID: 30418075 DOI: 10.1556/2006.7.2018.103]

78   **Lu C**, Zou L, Becker B, Griffiths M, Yu Q, Chen S-T, Demetrovics Z, Jiao C, Chi X, Chen A, Yeung A, Liu S, Zhang Y. Comparative Effectiveness of Mind-Body Exercise Versus Cognitive Behavioral Therapy for College Students with Problematic Smartphone Use: A Randomized Controlled Trial. *IJMHP* 2020; **22**: 271-282 [DOI: 10.32604/IJMHP.2020.014419]

79   **Aboujaoude E**, Vera Cruz G, Rochat L, Courtois R, Ben Brahim F, Khan R, Khazaal Y. Assessment of the Popularity and Perceived Effectiveness of Smartphone Tools That Track and Limit Smartphone Use: Survey Study and Machine Learning Analysis. *J Med Internet Res* 2022; **24**: e38963 [PMID: 36264627 DOI: 10.2196/38963]

80   **Liu XQ**, Guo YX, Xu Y. Risk factors and digital interventions for anxiety disorders in college students: Stakeholder perspectives. *World J Clin Cases* 2023; **11**: 1442-1457 [PMID: 36926387 DOI: 10.12998/wjcc.v11.i7.1442]

81   **Zhao G**, Xie F, Li S, Ding Y, Li X, Liu H. The relationship between perceived social support with anxiety, depression, and insomnia among Chinese college students during the COVID-19 pandemic: The mediating role of self-control. *Front Psychiatry* 2022; **13**: 994376 [PMID: 36276317 DOI: 10.3389/fpsyt.2022.994376]

82   **Barber LK**, Cucalon MS. Modifying the Sleep Treatment Education Program for Students to include technology use (STEPS-TECH): Intervention effects on objective and subjective sleep outcomes. *Stress Health* 2017; **33**: 684-690 [PMID: 28156049 DOI: 10.1002/smi.2746]

83   **Schlarb AA**, Friedrich A, Claßen M. Sleep problems in university students - an intervention. *Neuropsychiatr Dis Treat* 2017; **13**: 1989-2001 [PMID: 28794633 DOI: 10.2147/NDT.S142067]

84   **Saruhanjan K**, Zarski AC, Bauer T, Baumeister H, Cuijpers P, Spiegelhalder K, Auerbach RP, Kessler RC, Bruffaerts R, Karyotaki E, Berking M, Ebert DD. Psychological interventions to improve sleep in college students: A meta-analysis of randomized controlled trials. *J Sleep Res* 2021; **30**: e13097 [PMID: 32672865 DOI: 10.1111/jsr.13097]

85   **Friedrich A**, Schlarb AA. Let's talk about sleep: a systematic review of psychological interventions to improve sleep in college students. *J Sleep Res* 2018; **27**: 4-22 [PMID: 28618185 DOI: 10.1111/jsr.12568]

ORIGINAL ARTICLE

Observational Study

Prevalence of posttraumatic stress disorder following acute coronary syndrome and clinical characteristics of patients referred to cardiac rehabilitation

Ivana Sopek Merkaš, Nenad Lakušić, Zdenko Sonicki, Barbara Koret, Sandra Vuk Pisk, Igor Filipčić

Ivana Sopek Merkaš, Nenad Lakušić, Department of Cardiology, Special Hospital for Medical Rehabilitation Krapinske Toplice, Krapinske Toplice 49217, Croatia

Nenad Lakušić, Department of Clinical Medicine, Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

Nenad Lakušić, Department of Internal Medicine, Family Medicine and History of Medicine, Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

Zdenko Sonicki, Department of Medical Statistics, Epidemiology, and Medical Informatics, School of Public Health Andrija Stampar, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Barbara Koret, Sandra Vuk Pisk, Igor Filipčić, Department of Psychiatry, Clinic for Psychiatry "Sveti Ivan", Zagreb 10000, Croatia

Sandra Vuk Pisk, Igor Filipčić, Department of Psychiatry and Neurology, Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

Igor Filipčić, Department of Psychiatry and Psychological Medicine, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Corresponding author: Nenad Lakušić, PhD, Full Professor, Department of Cardiology, Special Hospital for Medical Rehabilitation Krapinske Toplice, Gajeva 2, Krapinske Toplice 49217, Croatia. nenad.lakusic@post.t-com.hr

Abstract

BACKGROUND
Studies have demonstrated that patients who have experienced acute coronary syndrome (ACS) have an increased risk of developing posttraumatic stress disorder (PTSD) and experiencing worse survival outcomes than those who do not develop PTSD. Nevertheless, the prevalence rates of PTSD following ACS vary widely across studies, and it is noteworthy that in most cases, the diagnosis of PTSD was based on self-report symptom questionnaires, rather than being established by psychiatrists. Additionally, the individual characteristics of patients who develop PTSD after ACS can differ widely, making it difficult to

identify any consistent patterns or predictors of the disorder.

AIM
To investigate the prevalence of PTSD among a large sample of patients undergoing cardiac rehabilitation (CR) after ACS, as well as their characteristics in comparison to a control group.

METHODS
The participants of this study are patients who have experienced ACS with or without undergoing percutaneous coronary intervention and are enrolled in a 3-wk CR program at the largest CR center in Croatia, the Special Hospital for Medical Rehabilitation Krapinske Toplice. Patient recruitment for the study took place over the course of one year, from January 1, 2022, to December 31, 2022, with a total of 504 participants. The expected average follow-up period for patients included in the study is about 18 mo, and currently ongoing. Using self-assessment questionnaire for PTSD criteria and clinical psychiatric interview, a group of patients with a PTSD diagnosis was identified. From the participants who do not have a PTSD diagnosis, patients who would match those with a PTSD diagnosis in terms of relevant clinical and medical stratification variables and during the same rehabilitation period were selected to enable comparability of the two groups.

RESULTS
A total of 507 patients who were enrolled in the CR program were approached to participate in the study. Three patients declined to participate in the study. The screening PTSD Checklist-Civilian Version questionnaire was completed by 504 patients. Out of the total sample of 504 patients, 74.2% were men (n = 374) and 25.8% were women (n = 130). The mean age of all participants was 56.7 years (55.8 for men and 59.1 for women). Among the 504 participants who completed the screening questionnaire, 80 met the cutoff criteria for the PTSD and qualified for further evaluation (15.9%). All 80 patients agreed to a psychiatric interview. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders criteria. Among the variables analyzed, there was a noticeable difference in the percentage of theoretical maximum achieved on exercise testing between the PTSD and non-PTSD groups. Non-PTSD group achieved a significantly higher percentage of their maximum compared to the PTSD group (P = 0.035).

CONCLUSION
The preliminary results of the study indicate that a significant proportion of patients with PTSD induced by ACS are not receiving adequate treatment. Furthermore, the data suggest that these patients may exhibit reduced physical activity levels, which could be one of the possible underlying mechanisms in observed poor cardiovascular outcomes in this population. Identifying cardiac biomarkers is crucial for identifying patients at risk of developing PTSD and may derive benefits from personalized interventions based on the principles of precision medicine in multidisciplinary CR programs.

Key Words: Cardiac rehabilitation; Acute coronary syndrome; Posttraumatic stress disorder; Psychiatric interview; Multidisciplinary team; Cardiac biomarkers

Core Tip: The preliminary results of the first large-scale study on a sample of cardiac rehabilitation (CR) patients with posttraumatic stress disorder induced by acute coronary syndrome indicate a significant number of patients who have a persistently increased risk of adverse events, and yet are still insufficiently recognized and treated. The study demonstrates that one possible mechanism of poorer outcomes is the avoidance of physical activity. A multidisciplinary approach involving cardiologists, psychiatrists, and psychologists is required for the identification and early intervention in these patients, and CR and comprehensive social support play a critical role.

INTRODUCTION

There is evidence to suggest that mental health disorders such as chronic stress, anxiety, and depression are linked to adverse cardiovascular outcomes[1,2]. In particular, stress-related disorders, especially posttraumatic stress disorder (PTSD)[3,4], have been identified as independent risk factors for acute cardiac events[5-7]. There are presumed different interaction mechanisms through which PTSD is associated with cardiovascular diseases. These include psychological (ability to adapt to stress, personality profile, personal traits, social interactions), behavioral (smoking, alcohol, diet, sleep disorders, adherence to prescribed therapy), and biological factors (neuroendocrine dysfunction involving metabolic syndrome, hypothalamic-pituitary-axis dysfunction, inflammation, renin-angiotensin system dysregulation, autonomic nervous system dysfunction)[7-9].

Furthermore, there is a growing recognition of acute coronary syndrome (ACS) as a potential precipitating event for PTSD[10-12], which is now increasingly acknowledged as a medical issue, prompting questions about its prevalence and clinical implications. It has been observed that patients who develop PTSD following an ACS have a higher risk of experiencing recurrent myocardial infarction (MI) and higher mortality rates[5,11,13]. A meta-analysis from 2012 reported a 12% prevalence of significant PTSD symptoms following ACS[11], while a 2021 systematic review found a prevalence range of 3% to 19%[13]. It's worth noting that the higher prevalence rates were observed when PTSD was assessed through self-report questionnaires compared to clinical diagnostic interviews conducted by a psychiatrist who made the diagnosis.

Reports on the characteristics of individuals who develop PTSD after ACS vary greatly, and there is no consensus on the specific demographic or biological risk factors that contribute to its development. In the systematic review from 2021 the authors reported several risk factors for PTSD following MI, including female gender, younger age and prior history of psychiatric disorders[13]. However, the individual characteristics of those who develop PTSD after ACS can differ widely, making it difficult to identify any consistent patterns or predictors of the disorder. Identifying patients at risk for persistent and severe ACS-induced PTSD based on demographic, biological and psychological factors could facilitate the implementation of early preventive measures[14].

While there is a significant correlation between PTSD and acute cardiac events, research on PTSD development following ACS is not as advanced. As a result, mechanisms of interaction are poorly understood. ACS-induced PTSD is associated with an increased risk of recurrence, but this risk is most prominent during the first year after the cardiovascular event, which is much shorter than the time frame required for many of the potential mechanisms linking PTSD to cardiovascular diseases[5]. Early identification and intervention are crucial, especially during this first year, when patients participate in cardiac rehabilitation (CR), which offers a unique opportunity for timely recognition and management of high-risk patients, potentially leading to improved outcomes.

MATERIALS AND METHODS

Study design

This ongoing observational, prospective, analytical case-control study presents preliminary findings on the number of patients who developed PTSD diagnosed by a psychiatrist after an ACS in a sample of patients undergoing CR, and their demographic, behavioral and biological characteristics compared to the control group.

Study subjects

This study enrolled patients who experienced ACS, with or without undergoing percutaneous coronary intervention (PCI), and who were participating in a 3-wk CR program at the at the Special Hospital for Medical Rehabilitation Krapinske Toplice, the largest CR center in Croatia. Patient recruitment for the study spanned a year (from January 1, 2022 to December 31, 2022), and the study ultimately included 504 participants. The expected follow-up period is approximately 18 mo and is currently ongoing. Inclusion criteria: Patients who have completed one month after an ACS (stressful event) before arriving at rehabilitation, both sexes, aged between 18 and 70 years. Exclusion criteria: Patients with a history of cardiac surgery, repeated MI, active psychiatric treatment, diagnosed psychiatric disorder or previously diagnosed PTSD from another cause, active malignancy, clinically unstable patients (acute heart failure, unstable coronary disease, acute infection), and patients who do not wish to participate in the study. Exclusion criteria are also applied to those who develop conditions that are defined as exclusion criteria during data collection, or those who no longer wish to participate in the study.

To identify patients with PTSD, a combination of self-assessment questionnaires and clinical psychiatric interviews were used. The initial screening of patients who agreed to participate in the study involved the use of the PTSD Checklist-Civilian Version (PCL-C) questionnaire[15,16]. For the purposes of this study, the recommended cutoff score for suggesting the possibility of PTSD based on the questionnaire was 30-35 points, given the civilian population. A combination of both scoring methods was employed, using a higher threshold score (35 points) and the requirement of a symptom pattern to

minimize the number of false positives. Participants who met the criteria based on the questionnaire underwent a clinical psychiatric interview, and those who were diagnosed with PTSD in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification[17] by the psychiatrist were included in the group of patients with PTSD (Figure 1).

From the pool of study participants who did not receive a PTSD diagnosis, a subset of individuals was selected for further analysis based on clinically and medically relevant stratification variables such as age, gender, type of ACS [ST-elevation MI (STEMI), non-STEMI (NSTEMI), or unstable angina (UA)], who underwent rehabilitation during the same period. They form a second group of participants that matches the characteristics of those with a PTSD diagnosis, in order to enable comparability of the two groups.

Data collection
The study obtained medical data through a patient's anamnesis, including their age, gender, lifestyle habits such as smoking and alcohol consumption, family history of cardiovascular disease (positive or negative), comorbidities such as hypertension, dyslipidemia, diabetes, and body mass index (BMI). Additionally, diagnostic tests were conducted during the three-week rehabilitation period to obtain data on important biological characteristics [laboratory testing, exercise stress test (ergometry), echocardiogram].

Follow-up
The expected average follow-up period of patients in the study is approximately 18 mo and is currently ongoing. Both groups of patients will be contacted (letter sent by post along with questionnaires and subsequently contacted by phone). They will complete the PCL-C scale again, a questionnaire on quality of life, medication adherence, and report any adverse cardiovascular events. In case it is not possible to contact the patient, data will be obtained from family members or primary care physician. After the end of the study, further analysis of the collected data will follow, and the obtained results and conclusions should direct attention to a subpopulation of patients in terms of precision medicine (identification of specific groups of patients).

Statistical analysis
We used the SPSS 29.0.0.0 statistical software package, setting significance level at $P < 0.05$ (2-tailed). For clarity, we present all data in original units (mean ± SD, ranges). For calculations of differences between groups, the student' t test, χ^2 test, Fisher's exact test and Mann Whitney test were used.

Ethical considerations
The study protocol was approved by the ethics committee of the Special Hospital for Medical Rehabilitation Krapinske Toplice. Data regarding patients were extracted from routine medical and treatment records. Patient identities have not been revealed. Written informed consent was obtained from every patient who agreed to participate in the study. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

RESULTS
A total of 507 patients who were enrolled in the CR program were approached to participate in the study, out of which 3 patients refused to participate. The PCL-C questionnaire was completed by 504 patients. Of these, 74.2% ($n = 374$) were men and 25.8% ($n = 130$) were women. The mean age of all participants was 56.7 years (55.8 years for men and 59.1 years for women). Out of the 504 participants, 80 individuals met the cutoff criteria for PTSD on the screening questionnaire and qualified for further evaluation, representing 15.9% of the total sample. All 80 patients agreed to psychiatric interview. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to DSM-5 criteria (Figure 1, Table 1).

From 51 PTSD patients, 32 were male (62.7%) and 19 female (37.3%). The average age of male participants diagnosed with PTSD was 52.8 years (range 42-65), and for female it was 56.5 years (range 42-66). Of these PTSD patients, 39 suffered STEMI (76.5%), 12 NSTEMI (23.5%), and there were no cases of PTSD following UA (Table 2).

Patients' characteristic
This preliminary report of the study presents findings on the investigation of demographic, behavioral, and particularly biological factors, and examines the differences in individual characteristics between PTSD and non-PTSD group (which was formed based on clinically and medically relevant variables such as age, gender, type of ACS), and the results are summarized in the table (Table 3).

Among the variables included, the PTSD group had a significantly lower percentage of maximum exercise capacity achieved compared to the non-PTSD group ($P = 0.03$). No significant differences were

Table 1 All patients included in the study

General data	Value
Patients	504
Age	56.68 ± 7.82 (27-70)
Male patients	374 (74.21%)
Male patients age	55.85 ± 8.04 (27-70)
Female patients	130 (25.79%)
Female patients age	59.05 ± 6.6 (44-70)
PTSD patients after PCL-C questionnaire	80 (15.87%)
Diagnosed PTSD patients	51 (10.12%)

Data are given as mean ± SD (ranges) or values (percentages). PTSD: Posttraumatic stress disorder; PCL-C: Posttraumatic stress disorder Checklist-Civilian Version.

Table 2 Posttraumatic stress disorder/pairs included in the study

General data	Value
Patients in each group	51
Age	54.16 ± 6.64 (42-66)
Male patients	32 (62.75%)
Male patients age	52.78 ± 6.53 (42-65)
Female patients	19 (37.25%)
Female patients age	56.47 ± 6.32 (42-66)
STEMI	39 (76.47%)
NSTEMI	12 (23.53%)
UA	0 (0.0%)

Data are given as mean ± SD (ranges) or values (percentages). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; UA: Unstable angina.

found in commonly observed comorbidities in cardiology patients such as hypertension, diabetes, dyslipidemia, and BMI.

In the study, there were participants who underwent a second PCI as an elective procedure after an acute event and those who experienced cardiorespiratory arrest and other complications following MI. Within the PTSD group, 7 participants (13.7%) underwent an elective PCI during hospitalization due to MI, while in the non-PTSD group, the number was 12 (23.5%). Acute heart failure was reported as a complication of MI in one male participant from each group. Within the PTSD group, one participant had a complication of surgically treated ventricular septal defect, while in the non-PTSD group, one female participant experienced post-procedural atrial fibrillation that was successfully converted to sinus rhythm using amiodarone. In both groups, two patients experienced cardiac arrest and were successfully resuscitated. Complications occurring during the acute phase of ACS and repeated PCI did not prove to be significant risk factors for developing PTSD.

DISCUSSION

To our knowledge, this is the first study on a large sample of CR patients that investigates the prevalence of PTSD after ACS, characteristics of these patients, and possible factors important for clinicians to recognize such patients in a timely manner. Consistent with prior research, it has been demonstrated that the prevalence of PTSD is lower when diagnosed by a psychiatrist rather than relying solely on self-administered questionnaires. The results confirm that the diagnosis of PTSD after ACS made by a psychiatrist is approximately 10%, which exceeds the prevalence reported in meta-analysis

Table 3 Characteristics of patients

Variable	PTSD	Non-PTSD	*P* value
BMI	29.09 ± 4.15 (21.9-41.9)	28.58 ± 4.15 (20.5-36.4)	0.5373
Smoking	31 (60.78%)	26 (50.98%)	0.3187
Alcohol use	0 (0.0%)	2 (3.92%)	0.495
Family history of cardiovascular diseases	23 (45.1%)	30 (58.82%)	0.1654
History of hypertension	26 (50.98%)	31 (60.78%)	0.3187
History of dyslipidemia	18 (35.29%)	19 (37.25%)	0.8368
History of diabetes	10 (19.61%)	7 (13.73%)	0.4254
LDL	2.15 ± 0.8 (1.1-4.5)	2.28 ± 0.64 (0.9-3.3)	0.3481
LVEF	53.27 ± 10.81 (25-75)	55.78 ± 9.12 (30-76)	0.2078
LVDd	52.2 ± 10.81 (43-66)	50.78 ± 9.12 (41-68)	0.2462
Theoretical maximum percentage in exercise test	88.55 ± 13.35 (46-114)	94.24 ± 13.58 (44-124)	0.0354
WATT in exercise test	126.96 ± 39 (50-200)	132.65 ± 47.83 (50-225)	0.512
METs in exercise test	6 ± 1.36 (2.8-9.89)	6.3 ± 1.45 (3.5-9.29)	0.2754
MPRH percentage in exercise test	76.76 ± 11.02 (54-103)	79.04 ± 9.76 (54-103)	0.2726
PCI in second act	7 (13.73%)	12 (23.53%)	0.2035
Positive exercise test	4 (7.84%)	4 (7.84%)	-
Acute complications	2 (3.92%)	2 (3.92%)	-
Arrest	2 (3.92%)	2 (3.92%)	-

Data are given as mean ± SD (ranges) or values (percentages). BMI: Body mass index; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; LVDd: Left ventricular diastolic diameter; METs: Metabolic equivalents; MPHR: Maximal predicted heart rate; PCI: Percutaneous coronary intervention.

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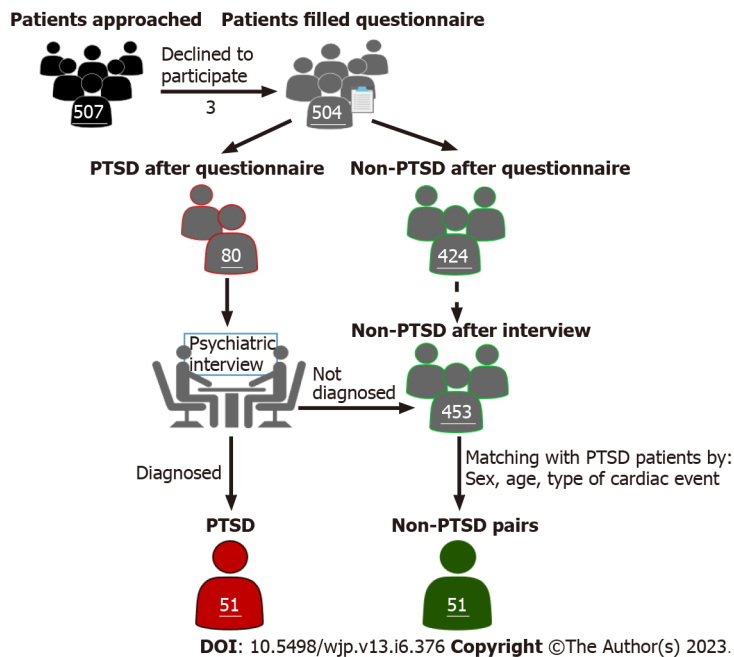
Figure 1 Algorithm for patient selection. PTSD: Posttraumatic stress disorder.

[11] and literature review[13], but similar prevalence has been reported[18]. If only a self-reported questionnaire is used to assess the PTSD symptoms, reported prevalence can be up to 16%. These findings highlight the significant impact of this clinical disorder on a substantial group of patients who

are often underdiagnosed and at increased risk for poor clinical outcomes.

The biological mechanisms in PTSD have been extensively reviewed and could potentially contribute to the modification of cardiac and vascular functions, ultimately leading to the development of cardiovascular events[19,20]. These mechanisms involve a complex set of pro-inflammatory, pro-atherogenic, pro-ischemic, neuro-hormonal, metabolic, and immune reactions. As presented in the table, numerous biological factors were examined regarding the ACS-induced PTSD (Table 3). While no significant differences were found in commonly observed comorbidities (hypertension, diabetes, dyslipidemia, BMI) as well as in left ventricular ejection fraction, the study introduced a novel approach by using results from an exercise stress test which showed a significant difference between the two groups. A standardized protocol is used to measure the maximum amount of oxygen an individual can consume during exercise (VO_2max) and to estimate the maximum watts a patient should attain during the exercise test[21]. The non-PTSP group achieved a significantly higher percentage of their theoretical maximum compared to the PTSP group. Recent research shows that patients with PTSD following ACS may avoid physical activity if they experience cardiac symptoms such as dyspnea and tachycardia, which can be reminiscent of the traumatic event[22]. Our study further confirms that this could be an underlying mechanism that contributes to the negative prognosis of patients with ACS-induced PTSD.

Complications related to ACS, repeated PCI, and even cardiac arrest during the acute phase did not show a significant association with the development of PTSD. However, previous study demonstrated that cardiac arrest-induced posttraumatic symptoms are linked to an increased risk of mortality and cardiovascular disease[23].

A recent meta-analysis provides further support evidence that the presence of PTSD is a risk factor for the subsequent development recurrent cardiac events, such as MI[24]. Due to the significant prevalence of PTSD after ACS, which was confirmed in this study, further research is needed to identify the mediating factors involved in the direct association between PTSD and the subsequent occurrence of adverse cardiovascular events in more precise medical terms.

The latest study highlights the increasing acknowledgement of the importance of social support and the role of CR, emphasizing comprehensive, multidisciplinary approach and early intervention has the potential to exert a favorable effect on the outcomes of these patients[25]. Early psychological assessment and intervention in ACS patients is important, and the inclusion of psychological interventions can improve patients' attendance and adherence to CR programs[26,27]. Therefore, it is essential not to downplay the role of such interventions following ACS. Recent studies suggest that mental health conditions may not be a barrier to CR and that CR may provide an opportunity for greater mental health care and support[28]. Therefore, a CR program with a multidisciplinary team including cardiologists, psychiatrists, and psychologists could be considered as a potential early intervention site, and by combining medical treatment, lifestyle modifications, and psychosocial support, patients may benefit from a more holistic approach to their care, which could lead to improved quality of life, reduced morbidity, and better long-term adherence to lifestyle changes.

Study advantages

The present study is the first large-scale study among rehabilitation patients, excluding patients with a preexisting psychiatric diagnosis (which is not the case in most previous studies, and it is important in explaining pathophysiology) or a history of MI, focusing on a more precise description of PTSD as a secondary risk factor in cardiology patients and revealing possible mechanism of interactions. One of the strengths of the study is also the use of psychiatrist-based diagnosis. By identification of potentially important biomarkers, it may be possible to predict which subgroup of patients is at a higher risk for developing PTSD after an ACS.

Study limitations

This is a preliminary report of an ongoing study, with patients still under follow-up. Some biological markers have not yet been included in the analysis, and comprehensive data analyses will be performed once all data is collected. We do not yet have information on whether all enrolled patients will remain in the follow-up and if we will have complete data for all patients by the end of the study.

CONCLUSION

This study is one of the largest cohorts to investigate the incidence of PTSD after ACS, and it is the first to consider the role of CR in this context, with the diagnosis made by a psychiatrist using the DSM-5 classification system. The preliminary findings of the study reports on substantial group of patients with PTSD induced by ACS (10.1%) and suggest that they may avoid physical activity, which could be one of the underlying mechanisms of the worse cardiovascular outcomes observed in this population. It is imperative to identify potential cardiac biomarkers that could aid in detecting increased cardiac risk in patients with secondary risk factor - ACS-induced PTSD, as current research in this area is limited. Further research is necessary, as there is significant potential value in identifying prognostically useful cardiac biomarkers to predict and prevent the onset of recurrent cardiovascular events and higher

morbidity and mortality rates in this group of patients.

After completing the follow-up period of the present study and conducting complex statistical analyses of all collected data, it may be possible to identify a specific subset of patients who are at risk of developing PTSD and may derive benefits from personalized interventions based on the principles of precision medicine. In this individualized approach, CR with a multidisciplinary team and the development of specific therapeutic and rehabilitation strategies can play a key role in improving quality of life and reducing overall mortality of this vulnerable and previously under-recognized subgroup of patients.

ARTICLE HIGHLIGHTS

Research background
Acute coronary syndrome (ACS) can be a stressor in the development of posttraumatic stress disorder (PTSD). Patients with PTSD after ACS have worse survival outcomes, and studies report different prevalence rates of PTSD following ACS. It is challenging to identify these patients and prevent their unfavorable outcomes.

Research motivation
Clinicians and cardiologists who deal with cardiac rehabilitation (CR) are increasingly noticing patients with elements of PTSD after ACS. The problem is their poorer outcomes, and CR with a multidisciplinary team (cardiologist, psychiatrist, psychologist) can be a place for early detection and intervention in these patients.

Research objectives
In this study we aim to investigate the prevalence of PTSD after ACS in patients undergoing CR and their demographic, behavioral, and biological characteristics. Identifying patients at risk for persistent and severe ACS-induced PTSD based on these characteristics could facilitate the implementation of early preventive measures.

Research methods
This is an ongoing prospective analytical case-control study. The study includes patients who have experienced ACS and are enrolled in a 3-wk CR program. A group of patients with PTSD diagnosis was identified using self-assessment questionnaires for PTSD criteria and clinical psychiatric interviews, and a control group was formed based on clinically relevant variables to enable comparison of these patient groups. Medical data were collected, and diagnostic tests were conducted to obtain data on important biological characteristics [laboratory testing, exercise test (ergometry), echocardiogram]. The expected average follow-up period for patients included in the study is approximately 18 mo.

Research results
Of 504 patients completed PTSD Checklist-Civilian Version questionnaire and 80 (15.9%) met the cutoff criteria for the PTSD and qualified for further evaluation by psychiatrists. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders criteria. Among the variables analyzed, there was a noticeable difference in the percentage of theoretical maximum achieved on exercise testing between the PTSD and non-PTSD groups. Non-PTSD group achieved a significantly higher percentage of their maximum compared to the PTSD group (P = 0.035).

Research conclusions
This study found a significant proportion of patients with PTSD induced by ACS (10.1%), and these patients are under-recognized and not appropriately treated. The study also found that patients with PTSD achieved a lower theoretical maximum on exercise testing, suggesting that they may avoid physical activity, which could be one of the underlying mechanisms for the worse cardiovascular outcomes observed in this subpopulation of patients.

Research perspectives
Early identification of patients with ACS-induced PTSD and intervention are crucial, and CR provides a unique opportunity for timely recognition and management of high-risk patients, potently leading to improved outcomes. Future research could focus on identifying possible cardiac biomarkers to detect patients at risk of developing PTSD after ACS and apply personalized interventions based on the principle of precision medicine. Multidisciplinary CR programs may be particularly effective in addressing the complex needs of patients with ACS induced PTSD.

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FOOTNOTES

ORCID number: Ivana Sopek Merkaš 0000-0002-0888-5005; Nenad Lakušić 0000-0002-2329-2582; Zdenko Sonicki 0000-0002-4143-5620; Sandra Vuk Pisk 0000-0001-9690-1265; Igor Filipčić 0000-0002-3283-8786.

REFERENCES

1   **Li J**, Ji F, Song J, Gao X, Jiang D, Chen G, Chen S, Lin X, Zhuo C. Anxiety and clinical outcomes of patients with acute coronary syndrome: a meta-analysis. *BMJ Open* 2020; **10**: e034135 [PMID: 32647021 DOI: 10.1136/bmjopen-2019-034135]

2   **Meneghetti CC**, Guidolin BL, Zimmermann PR, Sfoggia A. Screening for symptoms of anxiety and depression in patients admitted to a university hospital with acute coronary syndrome. *Trends Psychiatry Psychother* 2017; **39**: 12-18 [PMID: 28403318 DOI: 10.1590/2237-6089-2016-0004]

3   **Song H**, Fang F, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, Fall K, Lichtenstein P, Thorgeirsson G, Valdimarsdóttir UA. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *BMJ* 2019; **365**: l1255 [PMID: 30971390 DOI: 10.1136/bmj.l1255]

4   **Edmondson D**, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J* 2013; **166**: 806-814 [PMID: 24176435 DOI: 10.1016/j.ahj.2013.07.031]

5   **Edmondson D**, von Känel R. Post-traumatic stress disorder and cardiovascular disease. *Lancet Psychiatry* 2017; **4**: 320-329 [PMID: 28109646 DOI: 10.1016/S2215-0366(16)30377-7]

6   **Akosile W**, Colquhoun D, Young R, Lawford B, Voisey J. The association between post-traumatic stress disorder and coronary artery disease: a meta-analysis. *Australas Psychiatry* 2018; **26**: 524-530 [PMID: 30113869 DOI: 10.1177/1039856218789779]

7   **Sumner JA**, Cleveland S, Chen T, Gradus JL. Psychological and biological mechanisms linking trauma with cardiovascular disease risk. *Transl Psychiatry* 2023; **13**: 25 [PMID: 36707505 DOI: 10.1038/s41398-023-02330-8]

8   **O'Donnell CJ**, Schwartz Longacre L, Cohen BE, Fayad ZA, Gillespie CF, Liberzon I, Pathak GA, Polimanti R, Risbrough V, Ursano RJ, Vander Heide RS, Yancy CW, Vaccarino V, Sopko G, Stein MB. Posttraumatic Stress Disorder and Cardiovascular Disease: State of the Science, Knowledge Gaps, and Research Opportunities. *JAMA Cardiol* 2021; **6**: 1207-1216 [PMID: 34259831 DOI: 10.1001/jamacardio.2021.2530]

9   **Hargrave AS**, Sumner JA, Ebrahimi R, Cohen BE. Posttraumatic Stress Disorder (PTSD) as a Risk Factor for Cardiovascular Disease: Implications for Future Research and Clinical Care. *Curr Cardiol Rep* 2022; **24**: 2067-2079 [PMID: 36306020 DOI: 10.1007/s11886-022-01809-y]

10   **Vilchinsky N**, Ginzburg K, Fait K, Foa EB. Cardiac-disease-induced PTSD (CDI-PTSD): A systematic review. *Clin Psychol Rev* 2017; **55**: 92-106 [PMID: 28575815 DOI: 10.1016/j.cpr.2017.04.009]

11   **Edmondson D**, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. *PLoS One* 2012; **7**: e38915 [PMID: 22745687 DOI: 10.1371/journal.pone.0038915]

12   **Abbas CC**, Schmid JP, Guler E, Wiedemar L, Begré S, Saner H, Schnyder U, von Känel R. Trajectory of posttraumatic stress disorder caused by myocardial infarction: a two-year follow-up study. *Int J Psychiatry Med* 2009; **39**: 359-376 [PMID: 20391858 DOI: 10.2190/PM.39.4.b]

13   **Jacquet-Smailovic M**, Tarquinio C, Alla F, Denis I, Kirche A, Brennstuhl MJ. Posttraumatic Stress Disorder Following Myocardial Infarction: A Systematic Review. *J Trauma Stress* 2021; **34**: 190-199 [PMID: 33007150 DOI: 10.1002/jts.22591]

14   **von Känel R**, Meister-Langraf RE, Barth J, Schnyder U, Pazhenkottil AP, Ledermann K, Schmid JP, Znoj H, Herbert C, Princip M. Course, Moderators, and Predictors of Acute Coronary Syndrome-Induced Post-traumatic Stress: A Secondary Analysis From the Myocardial Infarction-Stress Prevention Intervention Randomized Controlled Trial. *Front Psychiatry* 2021; **12**: 621284 [PMID: 34108894 DOI: 10.3389/fpsyt.2021.621284]

15   **Weathers FW**, Litz BT, Herman DS, Huska JA, Keane TM.   The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. Proceedings of the 9th Annual Meeting of the International Society for Traumatic Stress Studies; 1993; San Antonio, Texas. United States: International Society for Traumatic Stress Studies, 1993

16   **Ruggiero KJ**, Del Ben K, Scotti JR, Rabalais AE. Psychometric properties of the PTSD Checklist-Civilian Version. *J Trauma Stress* 2003; **16**: 495-502 [PMID: 14584634 DOI: 10.1023/A:1025714729117]

17   **American Psychiatric Association**.   Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). Arlington: American Psychiatric Publishing. 2013

18   **Guler E**, Schmid JP, Wiedemar L, Saner H, Schnyder U, von Känel R. Clinical diagnosis of posttraumatic stress disorder after myocardial infarction. *Clin Cardiol* 2009; **32**: 125-129 [PMID: 19301284 DOI: 10.1002/clc.20384]

19   **Wentworth BA**, Stein MB, Redwine LS, Xue Y, Taub PR, Clopton P, Nayak KR, Maisel AS. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? *Cardiol Rev* 2013; **21**: 16-22 [PMID: 22717656 DOI: 10.1097/CRD.0b013e318265343b]

20   **Wolf EJ**, Schnurr PP. PTSD-Related Cardiovascular Disease and Accelerated Cellular Aging. *Psychiatr Ann* 2016; **46**: 527-532 [PMID: 27990033 DOI: 10.3928/00485713-20160729-01]

21   **Uth N**, Sørensen H, Overgaard K, Pedersen PK. Estimation of VO2max from the ratio between HRmax and HRrest--the Heart Rate Ratio Method. *Eur J Appl Physiol* 2004; **91**: 111-115 [PMID: 14624296 DOI: 10.1007/s00421-003-0988-y]

22   **Monane R**, Sanchez GJ, Kronish IM, Edmondson D, Diaz KM. Post-traumatic stress disorder symptoms and aversive cognitions regarding physical activity in patients evaluated for acute coronary syndrome. *Eur J Prev Cardiol* 2018; **25**: 402-403 [PMID: 29198138 DOI: 10.1177/2047487317746255]

23   **Agarwal S**, Presciutti A, Cornelius T, Birk J, Roh DJ, Park S, Claassen J, Elkind MSV, Edmondson D. Cardiac Arrest and Subsequent Hospitalization-Induced Posttraumatic Stress Is Associated With 1-Year Risk of Major Adverse Cardiovascular Events and All-Cause Mortality. *Crit Care Med* 2019; **47**: e502-e505 [PMID: 30889030 DOI: 10.1097/CCM.0000000000003713]

24   **Jacquet-Smailovic M**, Brennsthul MJ, Denis I, Kirche A, Tarquinio C. Relationship between Post-traumatic Stress Disorder and subsequent myocardial infarction: a systematic review and meta-analysis. *J Affect Disord* 2022; **297**: 525-535 [PMID: 34715167 DOI: 10.1016/j.jad.2021.10.056]

25   **von Känel R**, Meister-Langraf RE, Barth J, Znoj H, Schmid JP, Schnyder U, Princip M. Early Trauma-Focused Counseling for the Prevention of Acute Coronary Syndrome-Induced Posttraumatic Stress: Social and Health Care Resources Matter. *J Clin Med* 2022; **11** [PMID: 35407601 DOI: 10.3390/jcm11071993]

26   **Fernandes AC**, McIntyre T, Coelho R, Prata J, Maciel MJ. Brief psychological intervention in phase I of cardiac rehabilitation after acute coronary syndrome. *Rev Port Cardiol* 2017; **36**: 641-649 [PMID: 28882655 DOI: 10.1016/j.repc.2017.01.005]

27   **Abreu A**. Brief psychological intervention in patients admitted after acute coronary syndrome: Essential or secondary? *Rev Port Cardiol* 2017; **36**: 651-654 [PMID: 28838567 DOI: 10.1016/j.repc.2017.07.004]

28   **Krishnamurthi N**, Schopfer DW, Shen H, Whooley MA. Association of Mental Health Conditions With Participation in Cardiac Rehabilitation. *J Am Heart Assoc* 2019; **8**: e011639 [PMID: 31115253 DOI: 10.1161/JAHA.118.011639]

ORIGINAL ARTICLE

Observational Study

Abnormal volumetric brain morphometry and cerebral blood flow in adolescents with depression

Yu-Jia Fu, Xiao Liu, Xing-Yu Wang, Xiao Li, Lin-Qi Dai, Wen-yu Ren, Yong-Ming Zeng, Zhen-Lin Li, Ren-Qiang Yu

Yu-Jia Fu, Xiao Liu, Xing-Yu Wang, Wen-yu Ren, Ren-Qiang Yu, Department of Radiology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Xiao Li, Lin-Qi Dai, Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Yong-Ming Zeng, Department of Radiology, Chongqing HongRen Yi Hospital, Chongqing 408400, China

Zhen-Lin Li, Department of Radiology, West China Hospital, Chengdu 610041, Sichuan Province, China

Corresponding author: Ren-Qiang Yu, Doctor, Doctor, Department of Radiology, the First Affiliated Hospital of Chongqing Medical University, Yixueyuan Road, Yuzhong District, Chongqing 400016, China. yurenqiang@hospital.cqmu.edu.cn

Abstract

BACKGROUND
Prior research has demonstrated that the brains of adolescents with depression exhibit distinct structural alterations. However, preliminary studies have documented the pathophysiological changes in certain brain regions, such as the cerebellum, highlighting a need for further research to support the current understanding of this disease.

AIM
To study brain changes in depressed adolescents.

METHODS
This study enrolled 34 adolescents with depression and 34 age-, sex-, and education-level-matched healthy control (HC) individuals. Structural and functional alterations were identified when comparing the brains of these two participant groups through voxel-based morphometry and cerebral blood flow (CBF) analysis, respectively. Associations between identified brain alterations and the severity of depressive symptoms were explored through Pearson correlation analyses.

RESULTS

The cerebellum, superior frontal gyrus, cingulate gyrus, pallidum, middle frontal gyrus, angular gyrus, thalamus, precentral gyrus, inferior temporal gyrus, superior temporal gyrus, inferior frontal gyrus, and supplementary motor areas of adolescents with depression showed an increase in brain volume compared to HC individuals. These patients with depression further presented with a pronounced drop in CBF in the left pallidum (group = 98, and peak t = - 4.4324), together with increased CBF in the right percental gyrus (PerCG) (group = 90, and peak t = 4.5382). In addition, 17-item Hamilton Depression Rating Scale scores were significantly correlated with the increased volume in the opercular portion of the left inferior frontal gyrus (r = - 0.5231, P < 0.01).

CONCLUSION
The right PerCG showed structural and CBF changes, indicating that research on this part of the brain could offer insight into the pathophysiological causes of impaired cognition.

Key Words: Voxel-based morphometry; Cerebral blood flow; Arterial spin labeling; Adolescent; Depression; The right percental gyrus

Core Tip: In this study, we first combined cerebral blood flow (CBF) and voxel-based morphometry (VBM) to study brain alterations in adolescent depression. We also found that the brain function (CBF) changes were mainly in the left pallidum and right precentral gyrus. Meanwhile, we detected alterations in the cerebellum. Our finding about a wide range of brain structure (VBM) changes in adolescent depression contributes to better treatment and prevention strategies for depression.

INTRODUCTION

Adolescents suffer from high rates of depression that contribute to adverse outcomes, including academic difficulties, substance abuse, behavioral issues, parental conflict, impaired peer interactions, and suicidality[1-3]. Depression rates are exceptionally high among children in middle school, with an incidence of up to 24.3%[4]. Clinical symptoms of depression include feelings of sadness, hopelessness, cognitive impairments, and reductions in motivation and pleasure. Overcoming depression can be particularly challenging among adolescents, with treatment failing to have any pronounced effect in 30%-50% of cases[5]. Recurrence rates are also very high[6], with most adolescents experiencing relapses multiple times in adulthood[7,8]. Adolescence is also a critical period for brain growth[9], and this disease can have a profound negative impact on such development[10]. Despite this fact, many studies have focused on the mental health of adults rather than exploring outcomes in vulnerable adolescent populations[11,12]. As a result, there is an urgent need for in-depth neurobiological research that investigates the pathophysiology of depression to develop effective treatments that can help free adolescents from the symptoms of this debilitating condition.

The results of imaging studies suggest that adolescents suffering from depression exhibit severe structural changes within their brains[13-15]. However, these reported findings have been inconsistent with some studies documenting the thinning of brain regions[16], whereas others note the thickening of certain areas[17]. These inconsistencies may result from a range of patient-specific confounding factors or pharmacological treatment effects. While cerebellar dysfunction has been documented in many disease states[18], changes in the cerebellum in depression remain overlooked mainly[19]. Recent research supports the cerebellum's function in the processing of emotion and its widely recognized role in the context of motor control[20]. Reductions in the gray matter volume in the cerebellum and anterior cerebellar vermis have been documented among adults with depression[21], and some evidence suggests the ability of cerebellar neurons to regulate depression-like behavioral development actively [22].

Given the poorly understood nature of the pathophysiological basis for depression among adolescents, efforts to detect and clarify morphological alterations associated with functional changes provide an opportunity to define these underlying pathogenic processes better. In a previous publication, we used cerebral blood flow (CBF) to assess Major Depressive Disorder(MDD) in adolescents and reported CBF alterations after treatment[22]. Voxel-based morphometry (VBM) is a

technique that is frequently applied to detect structural changes within the brain[23], allowing for the voxel-by-voxel classification of brain volumes in different regions to enable the systematic, reproducible comparison of regions among multiple individuals more effectively than the traditional region of interest (ROI)-based strategies. VBM can assess anatomical differences throughout the brain with a short execution time[23,24] and is widely used in studies of alterations in depressed brains[25-27]. Still, there are also conflicting and heterogeneous results reported by VBM and magnetic resonance imaging (MRI) whole brain analysis[16,17]. These examples encourage the further development of VBM in MDD investigations. CBF can also be detected noninvasively and quantitatively through arterial spin labeling (ASL), in which arterial blood magnetic labeling is leveraged as an endogenous tracer[28]. Investigations have utilized VBM and voxel-based pathophysiology to analyze MDD[29]. Because structural alterations are usually accompanied by functional abnormalities[30,31], we decided to extend our study approach to incorporate VBM with CBF. The current study's findings are consistent with the high repetitive rate of change obtained so far regarding depression[32-34]. The cerebellum's role in depressive symptoms was confirmed in a recent study[35], and elevated pallidum CBF was also detected in patients with mild traumatic brain injury that may lead to cognitive decline[36]. These repeats suggest a potential association between the changes we detected using VBM combined with CBF and MDD dysfunction. Accordingly, in the present study, VBM and CBF strategies were used to evaluate changes in the brains of adolescents with depression.

Regular examinations of a broader range of brain regions are required to understand the pathophysiology of depression in adolescents properly, and unmedicated young people diagnosed with first-episode depression are the perfect model for studies of disease-related brain alterations. For the present analysis, these patients were thus the primary subjects of interest in hopes of detecting previously unrecognized yet clinically significant abnormalities present in depressed adolescents that have yet to undergo pharmacological treatment. These approaches offer a promising means of exploring the pathophysiology of adolescent depression while also validating and expanding upon previously published results[37].

Through the application of VBM and CBF techniques, a series of complex structural and functional alterations were documented within the brains of adolescent patients with depression compared to a healthy control (HC) population. The cerebellum was expected to undergo alterations because of its crucial involvement in developmental processes, and depression-related structural and functional changes were anticipated to coincide in several brain regions. These were the two primary outcomes that were expected from the present research.

MATERIALS AND METHODS

Participants

From August 2020 to July 2022, adolescents with depression were recruited from the Department of Psychiatry at Chongqing Medical University's First Affiliated Hospital. The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) was used by senior psychiatrists to confirm the diagnosis of depression in all cases, and symptom severity was assessed with the 17-item Hamilton Depression Rating Scale (HAMD-17). Patients eligible for study participation were individuals of Han ethnicity who were right-handed, exhibited a HAMD score ≥ 17, had no history of antidepressant treatment, were experiencing first-episode depression, had no history of psychotropic drug use, and had no history of anesthetic or sedative, or analgesic drug use within 1 mo before the study initiation. Patients were excluded if they had a history of prior mental health conditions, including schizophrenia or bipolar disorder, a history of drug abuse or dependence, exhibited MRI contraindications, or had been diagnosed with organic brain diseases or severe physical ailments.

Participants in the HC trial were selected from age-, gender-, and education-level-matched subjects with no personal history of mental illness or psychosis among first-degree relatives. The same exclusion criteria were applied for both patients with depression and HCs. In total, 34 treatment-naive first-episode adolescent depression patients and 34 HCs from 12-17 years of age were recruited for study participation.

The First Affiliated Hospital of Chongqing Medical University approved this study (NO. 2017-157). The legal guardians of all participants provided written informed consent, and all participants were provided with a comprehensive overview of the details of the study.

General data collection

Sociodemographic data were collected using a questionnaire regarding participant age, sex, and educational status. For the MINI-KID, the parents of eligible study participants were contacted and informed about this study, after which questionnaire and interview responses were obtained electronically. One professional interviewer conducted the interview processing, which was completed in under two days[38].

HAMD-17 surveys were administered by two psychiatrists with similar levels of training to assess symptom severity based on appropriate guidelines. Two examiners blinded to participant details independently performed all subsequent scoring to ensure the absence of subjectivity.

MRI data collection

MRI scanning was performed with a Signa 3.0 Tesla MRI instrument (GE Medical Systems, WI, United States), yielding T1-weighted, T2-weighted, and T2-fluid-attenuated inversion recovery (T2-Flair) imaging sequences. T2-Flair data were used to detect any evidence of potential brain disorders, with patients exhibiting such conditions being eliminated from further study inclusion.

Structural images were acquired with no gap using the following settings: the number of axial slices = 156, time repetition (TR) = 8.4 ms, echo time (TE) = 3.3 ms, flip angle (FA) = 12°, slice thickness = 1.0 mm, the field of view (FOV) = 240 mm × 240 mm, matrix = 240 × 240, and voxel dimension = 1 mm × 1 mm× 1 mm. Parameters used for ASL image acquisition were as follows: NEX 3, TE 9.8 ms, TR 4639 ms, FOV 240 mm × 240 mm, slice thickness 4.0 mm, post label delay time 1525 ms, 3D spiral k-space filling, points 512, arms 8, acquisition scan slices 40. During imaging, participants were directed to remain awake with their eyes closed, and foam padding was employed to restrict head movement.

Image processing

FSL-VBM was used to analyze structural images[39]. After the initial recovery of these images, they were segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid regions, followed by nonlinear registration-based alignment of these images to the Montreal Neurological Institute (MNI) standard space. Native GM images were then re-registered nonlinearly to the resultant averaged images to produce a template specific to the present study. Native GM images were then registered to this template and modified as appropriate based on local contraction or expansion associated with nonlinear spatial transformation. The altered GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (FWHM = 6.9 mm) as per FSL recommendations[39].

ASL images were analyzed following the earlier reported studies[22,28].

Statistical analysis

SPSS 22.0 (IL, United States) was used to analyze all data. Data are reported as means ± SD and were compared between groups with two-way ANOVA, while comparisons between males and females were made using chi-square tests.

Analyses of GM and WM volumes included group-based comparisons of larger and smaller volumes in HC individuals relative to adolescents with depression. These analyses employed grand mean scaling and absolute threshold masking. Voxel-level GM and WM density were compared between these groups with two-sample t-tests using SPM5. Random Gaussian field theory was used to estimate significant differences among groups using a familywise error-corrected alpha of 0.05. Clusters were displayed as statistical parametric maps in standard anatomical space. Participant age, education status, and total intracranial volume were utilized as covariates when conducting two-way ANOVA analyses of smoothed CBF images, with an initial $P < 0.001$ thresholds for cluster-level false discovery rate (FDR) multiple comparison correction ($P < 0.05$). Regions of the brain affected by sex or group interactions for CBF perfusion were then acquired with the xjview software (https://www.alivelearn.net/xjview). Brain areas with interactive effects were selected as ROIs, and the CBF values for these ROIs were extracted using DPABI[40].

Relationships between brain alterations and depressive symptom severity were explored through Pearson correlation analyses with $P < 0.05$ as the significance threshold.

RESULTS

Participant characteristics

Table 1 provides details regarding the characteristics of the study participants. No differences in age, sex, or education level were detected between depressed adolescents and HCs ($P > 0.05$), whereas HAMD-17 scores differed significantly between these groups ($P < 0.001$).

Depression-related changes in VBM

FSL-VBM analyses exploring differences between groups highlighted increases in the volume of several regions of the brain following correction for multiple testing ($P < 0.05$), including the cerebellum, superior frontal gyrus, cingulate gyrus, pallidum, middle frontal gyrus, angular gyrus, thalamus, precentral gyrus, inferior temporal gyrus, superior temporal gyrus, inferior frontal gyrus, and supplementary motor area (Table 2, Figure 1). No regions of the brain exhibited depression-related decreases in brain volume.

Table 1 Participant demographic and clinical characteristics

Item	depressed adolescents (*n* = 34)	healthy controls (*n* = 34)	*t*/χ^2	*P* value
Gender (F/M)	23/11	23/11	0[a]	1.00
Age (yr)	15.26 ± 0.99	15.68 ± 1.77	- 1.18[b]	0.24
Education (yr)	10.06 ± 1.98	10.44 ± 1.97	- 0.80[b]	0.43
HAMD-17	26.12 ± 4.43	1.03 ± 1.70	30.84[b]	< 0.001

[a]χ^2 test.

[b]Two sample *t*-test.

The values are illustrated as mean ± SD. F: Female; M: Male; HAMD-17: 17-item Hamilton Depression Rating Scale.

Table 2 Whole-brain group statistics for healthy controls and adolescents with depression

Brain sub-region	Peak (MNI)			Number of voxels	*P* value (FWE corrected)
	X	Y	Z		
HCs > depressed adolescents					
Cerebellum_6_L	73	64	56	973	0
Frontal_sup_medial_L	81	16292	101106	925	0.01
Cingulum_mid_R	103	120	67	221	0.02
Pallidum_R	113	-6	49	211	0.02
Cingulum_mid_L	-4	168	92	146	0.04
Frontal_mid_L	67	70	118	113	0.03
Angular_R	119	116	92	88	0.03
Thalamus_L	85	136	102	74	0.03
Precentral_R	151	134	27	57	0.04
Temporal_inf_R	127	142	46	55	0.04
Temporal_Pole_Sup_L	61	130	98	42	0.04
Frontal- Inf_Oper_L	51	66	105	25	0.04
Occipital_Mid_L	63	126	148	24	0.04
Supp_Motor_Area_L	79	88	52	14	0.04
Cerebellum_3_R	101			13	0.04

HCs: Healthy controls; MNI: Montreal Neurological Institute; FWE: Family wise error.

Depression-related changes in CBF

Adolescents with depression exhibited pronounced decreases in CBF in the left pallidum as compared to HCs (group = 98, and peak *t* = -4.4324), together with an increase in the right percental gyrus (PerCG) (group = 90, and peak *t* = 4.5382) (Figure 2). This analysis was performed using a cluster cut-off *P*-value < 0.001.

Correlations between brain alterations and depression severity

In patients with depression, HAMD-17 scores were significantly correlated with the increased volume of the opercular part of the left inferior frontal gyrus (IFG) (r = - 0.5231, *P* < 0.01). No correlations were detected between HAMD-17 scores and other changes in brain volume or CBF (*P* > 0.05).

DISCUSSION

The current findings showed that, in contrast to HCs, treatment-naive first-episode depression in adolescents is associated with CBF and brain volume modifications. Notably, increased volume of many
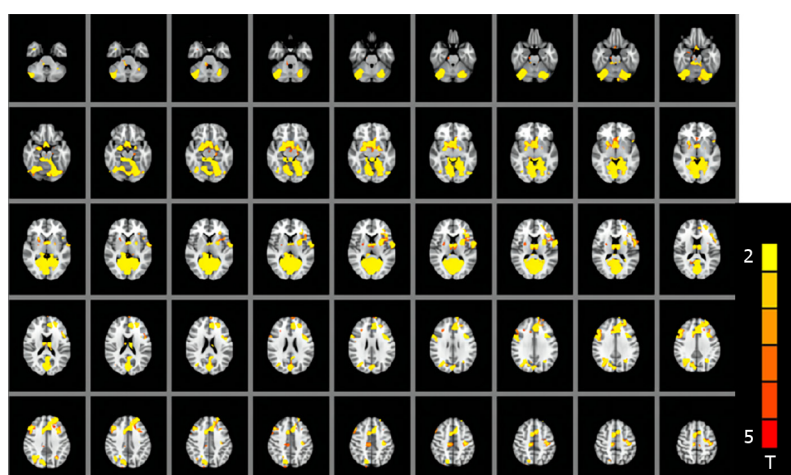
Figure 1 Two-sample tests comparing healthy controls and adolescents with depression based on a whole-brain mask.
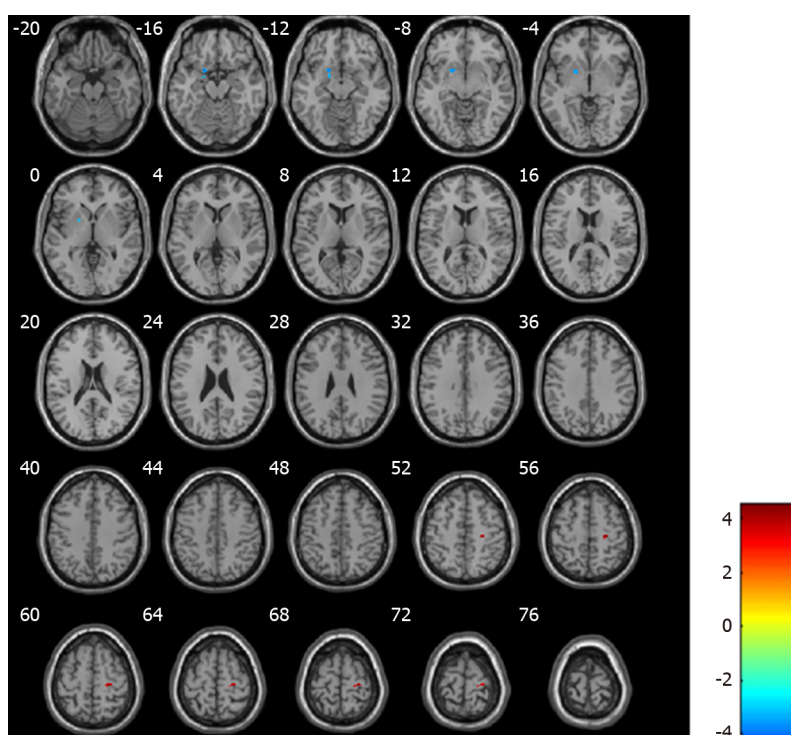
Figure 2 Differences in cerebral blood flow when comparing healthy controls and adolescents with depression. Blue and red indicate reductions and increases in cerebral blood flow, respectively.

brain regions was observed in adolescent depression patients, with increased CBF in the PerCG and decreased CBF in the left pallidum. HAMD-17 scores in these patients were also negatively correlated with the volume of the opercular portion of the left IFG. In particular, decreases in both volume and CBF were observed in the right PerCG, suggesting that this region may be an important area for future research to understand the pathophysiological bases of depression.

The PreCG regulates primary motor behaviors and has been reported to exhibit alterations in individuals with movement-related disorders, including amyotrophic lateral sclerosis[41] and akinetic-rigid Parkinson's disease[42]. Increased PreCG CBF is correlated with increased reaction time[43], pure apraxia of speech and other forms of impaired verbal fluency[44], and autism[45]. Several studies suggest a relationship between PreCG and emotion[46]. Depression can impair neural plasticity in the motor cortex, contributing to behavioral and cognitive alterations in affected patients[47]. Pathological alterations in the PreCG may thus be functionally linked to depression. An increase in PreCG GM volume has been reported[48,49], with the present results confirming these prior reports and

highlighting a link between these changes and altered CBF.

The left IFG plays a crucial role in the functional and structural brain network that underlies language in neurocognitive models of language perception[50]. The opercular portion of the left IFG is a crucial node connected to multiple cerebellar, cortical, and subcortical structures within the language network [51]. In the present study, adolescents with depression exhibited a correlation between HAMD-17 scores and the volume of this opercular portion of the left IFG, consistent with its potential association with depression severity.

The cerebellum is thought to be closely related to movement, with additional experimental evidence highlighting its association with attention and motor systems[52], as well as with cognition[53]. This link could explain depression-related symptoms, such as cognitive impairment, disinterest, and poor attention. Adolescent depression may affect the cerebellum, contributing to frequent episodes in adulthood. However, it is essential to highlight that the reported increase in the cerebellum in the present study contradicts other published studies in which cerebellar volume was shown to be reduced [54,55]. These differences may be attributable to variations in disease severity, assessment methodology, diagnoses, or treatment approaches.

Other regions exhibiting abnormal findings included the cingulate gyrus, an essential component of the pathophysiological basis for depression related to the makeup of the default mode network[56]. In clinical research, cingulate gyrus abnormalities have been reported in various psychiatric disorders[57]. Altered WM connectivity in adolescent depression patients has also been described[58], contributing to reduced default mode network connectivity closely related to depression incidence[59-61].

There are various drawbacks to this study. Firstly, the number of participants was relatively small, partly due to parental reservations about fMRI examinations. Secondly, the effects of resting state physiological noise derived from the heart and respiratory rhythms cannot be eliminated from these analyses. Lastly, this cross-sectional analysis could not detect disease progression-related changes in brain morphological characteristics, underscoring a need for future longitudinal research with multiple follow-up visits per patient to monitor better such changes and how they respond to treatment.

CONCLUSION

In summary, the present results demonstrate that adolescent depression patients exhibited various structural changes in the brain and altered CBF in the left pallidum and right PerCG. Considering the finding that the right PerCG demonstrated structural and CBF changes associated with depression in these adolescent subjects, research on the right PerCG may provide fresh perspectives on the pathophysiology of this devastating psychological disorder. This identification of novel evidence regarding changes in the cerebellum and other brain areas provides robust imaging evidence supporting the hypothesis that these regions are involved in cognition and disease-related pathogenesis. The future application of these findings has the potential to guide the better prevention and treatment of depression among adolescents.

ARTICLE HIGHLIGHTS

Research background
The prevalence of depression in adolescents is high and research is scarce. Therefore, it is urgent to investigate depressed adolescents.

Research motivation
In-depth neurobiological studies investigating the pathophysiology of depression are urgently needed to develop effective treatments to help adolescents escape the symptoms of this debilitating illness. Several studies have documented the role of the cerebellum in psychiatric disorders, which is rarely mentioned in the imaging of depression, emphasizing the need for further research on the depressed brain.

Research objectives
We aimed to detect structural and functional changes in depressed adolescents. These changes may be relevant to better prevention and treatment of adolescent depression. We found that adolescents with depression exhibit various structural changes in the brain and alter cerebral blood flow in the left syphilitic spiral and right percent gyrus.

Research methods
This study recruited 34 adolescents with depression and 34 matched healthy control (HC) individuals. Voxel-based morphometry (VBM) discovers structural changes in the brain; Cerebral blood flow (CBF)

explore functional changes in the brain; 17-item Hamilton Depression Rating Scale (HAMD-17) measures depression; *t*-test assess statistical differences.

Research results

We found that patients with adolescent depression exhibit various structural changes in the brain and altered CBF in the left pallidum and right percental gyrus. These findings may provide new insights into the pathophysiology of this disruptive psychological disorder and provide strong imaging evidence to support the hypothesis that these regions are involved in cognition and disease-related pathogenesis. Future applications of these findings have the potential to guide better prevention and treatment of depression in adolescents.

Research conclusions

New theory: Our study provides imaging evidence that supports the hypothesis that cerebellum is involved in cognition and disease-related pathogenesis. New method: We first combined VBM and CBF to examine the brains of depressed adolescents.

Research perspectives

Incorporating imaging data into the diagnosis of psychiatric disorders.

FOOTNOTES

REFERENCES

1   **Hauenstein EJ**. Depression in adolescence. *J Obstet Gynecol Neonatal Nurs* 2003; **32**: 239-248 [PMID: 12685676 DOI: 10.1177/0884217503252133]

2   **Frankish H**, Boyce N, Horton R. Mental health for all: a global goal. *Lancet* 2018; **392**: 1493-1494 [PMID: 30314858 DOI: 10.1016/S0140-6736(18)32271-2]

3   **Stringaris A**, Vidal-Ribas P. Probing the Irritability-Suicidality Nexus. *J Am Acad Child Adolesc Psychiatry* 2019; **58**: 18-

19 [PMID: 30577933 DOI: 10.1016/j.jaac.2018.08.014]

4   **Tang X**, Tang S, Ren Z, Wong DFK. Prevalence of depressive symptoms among adolescents in secondary school in mainland China: A systematic review and meta-analysis. *J Affect Disord* 2019; **245**: 498-507 [PMID: 30439677 DOI: 10.1016/j.jad.2018.11.043]

5   **Liu FF**, Adrian MC. Is Treatment Working? Detecting Real Change in the Treatment of Child and Adolescent Depression. *J Am Acad Child Adolesc Psychiatry* 2019; **58**: 1157-1164 [PMID: 30825497 DOI: 10.1016/j.jaac.2019.02.011]

6   **Thapar A**, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet* 2012; **379**: 1056-1067 [PMID: 22305766 DOI: 10.1016/S0140-6736(11)60871-4]

7   **Clayborne ZM**, Varin M, Colman I. Systematic Review and Meta-Analysis: Adolescent Depression and Long-Term Psychosocial Outcomes. *J Am Acad Child Adolesc Psychiatry* 2019; **58**: 72-79 [PMID: 30577941 DOI: 10.1016/j.jaac.2018.07.896]

8   **Johnson D**, Dupuis G, Piche J, Clayborne Z, Colman I. Adult mental health outcomes of adolescent depression: A systematic review. *Depress Anxiety* 2018; **35**: 700-716 [PMID: 29878410 DOI: 10.1002/da.22777]

9   **Fuhrmann D**, Knoll LJ, Blakemore SJ. Adolescence as a Sensitive Period of Brain Development. *Trends Cogn Sci* 2015; **19**: 558-566 [PMID: 26419496 DOI: 10.1016/j.tics.2015.07.008]

10   **Sacchet MD**, Ho TC, Connolly CG, Tymofiyeva O, Lewinn KZ, Han LK, Blom EH, Tapert SF, Max JE, Frank GK, Paulus MP, Simmons AN, Gotlib IH, Yang TT. Large-Scale Hypoconnectivity Between Resting-State Functional Networks in Unmedicated Adolescent Major Depressive Disorder. *Neuropsychopharmacology* 2016; **41**: 2951-2960 [PMID: 27238621 DOI: 10.1038/npp.2016.76]

11   **Rice F**, Eyre O, Riglin L, Potter R. Adolescent depression and the treatment gap. *Lancet Psychiatry* 2017; **4**: 86-87 [PMID: 28087200 DOI: 10.1016/S2215-0366(17)30004-4]

12   **Coles ME**, Ravid A, Gibb B, George-Denn D, Bronstein LR, McLeod S. Adolescent Mental Health Literacy: Young People's Knowledge of Depression and Social Anxiety Disorder. *J Adolesc Health* 2016; **58**: 57-62 [PMID: 26707229 DOI: 10.1016/j.jadohealth.2015.09.017]

13   **Pagliaccio D**, Alqueza KL, Marsh R, Auerbach RP. Brain Volume Abnormalities in Youth at High Risk for Depression: Adolescent Brain and Cognitive Development Study. *J Am Acad Child Adolesc Psychiatry* 2020; **59**: 1178-1188 [PMID: 31634568 DOI: 10.1016/j.jaac.2019.09.032]

14   **Redlich R**, Opel N, Bürger C, Dohm K, Grotegerd D, Förster K, Zaremba D, Meinert S, Repple J, Enneking V, Leehr E, Böhnlein J, Winters L, Froböse N, Thrun S, Emtmann J, Heindel W, Kugel H, Arolt V, Romer G, Postert C, Dannlowski U. The Limbic System in Youth Depression: Brain Structural and Functional Alterations in Adolescent In-patients with Severe Depression. *Neuropsychopharmacology* 2018; **43**: 546-554 [PMID: 29039414 DOI: 10.1038/npp.2017.246]

15   **Wu B**, Li X, Zhou J, Zhang M, Long Q. Altered Whole-Brain Functional Networks in Drug-Naïve, First-Episode Adolescents With Major Depression Disorder. *J Magn Reson Imaging* 2020; **52**: 1790-1798 [PMID: 32618061 DOI: 10.1002/jmri.27270]

16   **Fan S**, Lippard ETC, Sankar A, Wallace A, Johnston JAY, Wang F, Pittman B, Spencer L, Oquendo MA, Blumberg HP. Gray and white matter differences in adolescents and young adults with prior suicide attempts across bipolar and major depressive disorders. *J Affect Disord* 2019; **245**: 1089-1097 [PMID: 30699851 DOI: 10.1016/j.jad.2018.11.095]

17   **Straub J**, Brown R, Malejko K, Bonenberger M, Grön G, Plener PL, Abler B. Adolescent depression and brain development: evidence from voxel-based morphometry. *J Psychiatry Neurosci* 2019; **44**: 237-245 [PMID: 30720261 DOI: 10.1503/jpn.170233]

18   **Stoodley CJ**. The Cerebellum and Neurodevelopmental Disorders. *Cerebellum* 2016; **15**: 34-37 [PMID: 26298473 DOI: 10.1007/s12311-015-0715-3]

19   **Konarski JZ**, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *J Psychiatry Neurosci* 2005; **30**: 178-186 [PMID: 15944742]

20   **Huang M**, de Koning TJ, Tijssen MAJ, Verbeek DS. Cross-disease analysis of depression, ataxia and dystonia highlights a role for synaptic plasticity and the cerebellum in the pathophysiology of these comorbid diseases. *Biochim Biophys Acta Mol Basis Dis* 2021; **1867**: 165976 [PMID: 33011198 DOI: 10.1016/j.bbadis.2020.165976]

21   **Arnone D**, Job D, Selvaraj S, Abe O, Amico F, Cheng Y, Colloby SJ, O'Brien JT, Frodl T, Gotlib IH, Ham BJ, Kim MJ, Koolschijn PC, Périco CA, Salvadore G, Thomas AJ, Van Tol MJ, van der Wee NJ, Veltman DJ, Wagner G, McIntosh AM. Computational meta-analysis of statistical parametric maps in major depression. *Hum Brain Mapp* 2016; **37**: 1393-1404 [PMID: 26854015 DOI: 10.1002/hbm.23108]

22   **Yu RQ**, Zhang ZJ, Chen RS, Wang XY, Li X, Dai LQ, Li ZL. Electroconvulsive therapy-induced neuroimaging alterations measured by cerebral blood flow in adolescents with major depressive disorder. *J Affect Disord* 2023; **327**: 385-390 [PMID: 36758871 DOI: 10.1016/j.jad.2023.02.027]

23   **Ashburner J**, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000; **11**: 805-821 [PMID: 10860804 DOI: 10.1006/nimg.2000.0582]

24   **Matsuda H**. MRI morphometry in Alzheimer's disease. *Ageing Res Rev* 2016; **30**: 17-24 [PMID: 26812213 DOI: 10.1016/j.arr.2016.01.003]

25   **Serra-Blasco M**, Radua J, Soriano-Mas C, Gómez-Benlloch A, Porta-Casteràs D, Carulla-Roig M, Albajes-Eizagirre A, Arnone D, Klauser P, Canales-Rodríguez EJ, Hilbert K, Wise T, Cheng Y, Kandilarova S, Mataix-Cols D, Vieta E, Via E, Cardoner N. Structural brain correlates in major depression, anxiety disorders and post-traumatic stress disorder: A voxel-based morphometry meta-analysis. *Neurosci Biobehav Rev* 2021; **129**: 269-281 [PMID: 34256069 DOI: 10.1016/j.neubiorev.2021.07.002]

26   **Zhao W**, Zhang X, Zhou X, Song X, Zhang Z, Xu L, Zhou F, Kendrick KM. Depression mediates the association between insula-frontal functional connectivity and social interaction anxiety. *Hum Brain Mapp* 2022; **43**: 4266-4273 [PMID: 35596617 DOI: 10.1002/hbm.25952]

27   **Du M**, Liu J, Chen Z, Huang X, Li J, Kuang W, Yang Y, Zhang W, Zhou D, Bi F, Kendrick KM, Gong Q. Brain grey matter volume alterations in late-life depression. *J Psychiatry Neurosci* 2014; **39**: 397-406 [PMID: 24949867 DOI: 10.1503/jpn.130275]

28   **Xiong Y**, Chen RS, Wang XY, Li X, Dai LQ, Yu RQ. Cerebral blood flow in adolescents with drug-naive, first-episode major depressive disorder: An arterial spin labeling study based on voxel-level whole-brain analysis. *Front Neurosci* 2022; **16**: 966087 [PMID: 35968369 DOI: 10.3389/fnins.2022.966087]

29   **Gray JP**, Müller VI, Eickhoff SB, Fox PT. Multimodal Abnormalities of Brain Structure and Function in Major Depressive Disorder: A Meta-Analysis of Neuroimaging Studies. *Am J Psychiatry* 2020; **177**: 422-434 [PMID: 32098488 DOI: 10.1176/appi.ajp.2019.19050560]

30   **Albajara Sáenz A**, Villemonteix T, Massat I. Structural and functional neuroimaging in attention-deficit/hyperactivity disorder. *Dev Med Child Neurol* 2019; **61**: 399-405 [PMID: 30276811 DOI: 10.1111/dmcn.14050]

31   **Lenka A**, Jhunjhunwala KR, Saini J, Pal PK. Structural and functional neuroimaging in patients with Parkinson's disease and visual hallucinations: A critical review. *Parkinsonism Relat Disord* 2015; **21**: 683-691 [PMID: 25920541 DOI: 10.1016/j.parkreldis.2015.04.005]

32   **Wise T**, Radua J, Via E, Cardoner N, Abe O, Adams TM, Amico F, Cheng Y, Cole JH, de Azevedo Marques Périco C, Dickstein DP, Farrow TFD, Frodl T, Wagner G, Gotlib IH, Gruber O, Ham BJ, Job DE, Kempton MJ, Kim MJ, Koolschijn PCMP, Malhi GS, Mataix-Cols D, McIntosh AM, Nugent AC, O'Brien JT, Pezzoli S, Phillips ML, Sachdev PS, Salvadore G, Selvaraj S, Stanfield AC, Thomas AJ, van Tol MJ, van der Wee NJA, Veltman DJ, Young AH, Fu CH, Cleare AJ, Arnone D. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Mol Psychiatry* 2017; **22**: 1455-1463 [PMID: 27217146 DOI: 10.1038/mp.2016.72]

33   **Li J**, Wang Z, Hwang J, Zhao B, Yang X, Xin S, Wang Y, Jiang H, Shi P, Zhang Y, Wang X, Lang C, Park J, Bao T, Kong J. Anatomical brain difference of subthreshold depression in young and middle-aged individuals. *Neuroimage Clin* 2017; **14**: 546-551 [PMID: 28331801 DOI: 10.1016/j.nicl.2017.02.022]

34   **Ramasubbu R**, Brown EC, Marcil LD, Talai AS, Forkert ND. Automatic classification of major depression disorder using arterial spin labeling MRI perfusion measurements. *Psychiatry Clin Neurosci* 2019; **73**: 486-493 [PMID: 31077500 DOI: 10.1111/pcn.12862]

35   **Baek SJ**, Park JS, Kim J, Yamamoto Y, Tanaka-Yamamoto K. VTA-projecting cerebellar neurons mediate stress-dependent depression-like behaviors. *Elife* 2022; **11** [PMID: 35156922 DOI: 10.7554/eLife.72981]

36   **Xiong F**, Li T, Pan Y, Liu Y, Zhang J, Bai L. [Arterial spin labeling magnetic resonance evaluates changes of cerebral blood flow in patients with mild traumatic brain injury]. *Zhongnan Daxue Xuebao Yixueban* 2022; **47**: 1016-1024 [PMID: 36097769 DOI: 10.11817/j.issn.1672-7347.2022.210754]

37   **Müller VI**, Cieslik EC, Serbanescu I, Laird AR, Fox PT, Eickhoff SB. Altered Brain Activity in Unipolar Depression Revisited: Meta-analyses of Neuroimaging Studies. *JAMA Psychiatry* 2017; **74**: 47-55 [PMID: 27829086 DOI: 10.1001/jamapsychiatry.2016.2783]

38   **McDonald E**, Whitney S, Horricks L, Lipman EL, Ferro MA. Parent-Child Agreement on the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *J Can Acad Child Adolesc Psychiatry* 2021; **30**: 264-272 [PMID: 34777509]

39   **Douaud G**, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J, James S, Voets N, Watkins K, Matthews PM, James A. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain* 2007; **130**: 2375-2386 [PMID: 17698497 DOI: 10.1093/brain/awm184]

40   **Yan CG**, Wang XD, Zuo XN, Zang YF. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics* 2016; **14**: 339-351 [PMID: 27075850 DOI: 10.1007/s12021-016-9299-4]

41   **Mezzapesa DM**, D'Errico E, Tortelli R, Distaso E, Cortese R, Tursi M, Federico F, Zoccolella S, Logroscino G, Dicuonzo F, Simone IL. Cortical thinning and clinical heterogeneity in amyotrophic lateral sclerosis. *PLoS One* 2013; **8**: e80748 [PMID: 24278317 DOI: 10.1371/journal.pone.0080748]

42   **Wang J**, Shen Y, Peng J, Wang A, Wu X, Chen X, Liu J, Wei M, Zou D, Han Y, Cheng O. Different functional connectivity modes of the right fronto-insular cortex in akinetic-rigid and tremor-dominant Parkinson's disease. *Neurol Sci* 2021; **42**: 2937-2946 [PMID: 33236247 DOI: 10.1007/s10072-020-04917-1]

43   **Iacoboni M**, Woods RP, Lenzi GL, Mazziotta JC. Merging of oculomotor and somatomotor space coding in the human right precentral gyrus. *Brain* 1997; **120 (Pt 9)**: 1635-1645 [PMID: 9313645 DOI: 10.1093/brain/120.9.1635]

44   **Silva AB**, Liu JR, Zhao L, Levy DF, Scott TL, Chang EF. A Neurosurgical Functional Dissection of the Middle Precentral Gyrus during Speech Production. *J Neurosci* 2022; **42**: 8416-8426 [PMID: 36351829 DOI: 10.1523/JNEUROSCI.1614-22.2022]

45   **Anderson JS**, Druzgal TJ, Froehlich A, DuBray MB, Lange N, Alexander AL, Abildskov T, Nielsen JA, Cariello AN, Cooperrider JR, Bigler ED, Lainhart JE. Decreased interhemispheric functional connectivity in autism. *Cereb Cortex* 2011; **21**: 1134-1146 [PMID: 20943668 DOI: 10.1093/cercor/bhq190]

46   **Chen XF**, He P, Xu KH, Jin YH, Chen Y, Wang B, Hu X, Qi L, Wang MW, Li J. Disrupted Spontaneous Neural Activity and Its Interaction With Pain and Emotion in Temporomandibular Disorders. *Front Neurosci* 2022; **16**: 941244 [PMID: 36090263 DOI: 10.3389/fnins.2022.941244]

47   **Player MJ**, Taylor JL, Weickert CS, Alonzo A, Sachdev P, Martin D, Mitchell PB, Loo CK. Neuroplasticity in depressed individuals compared with healthy controls. *Neuropsychopharmacology* 2013; **38**: 2101-2108 [PMID: 23676792 DOI: 10.1038/npp.2013.126]

48   **Wehry AM**, McNamara RK, Adler CM, Eliassen JC, Croarkin P, Cerullo MA, DelBello MP, Strawn JR. Neurostructural impact of co-occurring anxiety in pediatric patients with major depressive disorder: a voxel-based morphometry study. *J Affect Disord* 2015; **171**: 54-59 [PMID: 25285899 DOI: 10.1016/j.jad.2014.09.004]

49   **Long X**, Li L, Wang X, Cao Y, Wu B, Roberts N, Gong Q, Kemp GJ, Jia Z. Gray matter alterations in adolescent major depressive disorder and adolescent bipolar disorder. *J Affect Disord* 2023; **325**: 550-563 [PMID: 36669567 DOI: 10.1016/j.jad.2023.01.049]

50   **Schell M**, Zaccarella E, Friederici AD. Differential cortical contribution of syntax and semantics: An fMRI study on two-word phrasal processing. *Cortex* 2017; **96**: 105-120 [PMID: 29024818 DOI: 10.1016/j.cortex.2017.09.002]

51   **Bulut T**. Meta-analytic connectivity modeling of the left and right inferior frontal gyri. *Cortex* 2022; **155**: 107-131 [PMID:

35985123 DOI: 10.1016/j.cortex.2022.07.003]

52   **Allen G**, Buxton RB, Wong EC, Courchesne E. Attentional activation of the cerebellum independent of motor involvement. *Science* 1997; **275**: 1940-1943 [PMID: 9072973 DOI: 10.1126/science.275.5308.1940]

53   **Diedrichsen J**, King M, Hernandez-Castillo C, Sereno M, Ivry RB. Universal Transform or Multiple Functionality? Understanding the Contribution of the Human Cerebellum across Task Domains. *Neuron* 2019; **102**: 918-928 [PMID: 31170400 DOI: 10.1016/j.neuron.2019.04.021]

54   **Moberget T**, Alnæs D, Kaufmann T, Doan NT, Córdova-Palomera A, Norbom LB, Rokicki J, van der Meer D, Andreassen OA, Westlye LT. Cerebellar Gray Matter Volume Is Associated With Cognitive Function and Psychopathology in Adolescence. *Biol Psychiatry* 2019; **86**: 65-75 [PMID: 30850129 DOI: 10.1016/j.biopsych.2019.01.019]

55   **Gur RE**, Moore TM, Rosen AFG, Barzilay R, Roalf DR, Calkins ME, Ruparel K, Scott JC, Almasy L, Satterthwaite TD, Shinohara RT, Gur RC. Burden of Environmental Adversity Associated With Psychopathology, Maturation, and Brain Behavior Parameters in Youths. *JAMA Psychiatry* 2019; **76**: 966-975 [PMID: 31141099 DOI: 10.1001/jamapsychiatry.2019.0943]

56   **Smallwood J**, Bernhardt BC, Leech R, Bzdok D, Jefferies E, Margulies DS. The default mode network in cognition: a topographical perspective. *Nat Rev Neurosci* 2021; **22**: 503-513 [PMID: 34226715 DOI: 10.1038/s41583-021-00474-4]

57   **Bubb EJ**, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. *Neurosci Biobehav Rev* 2018; **92**: 104-127 [PMID: 29753752 DOI: 10.1016/j.neubiorev.2018.05.008]

58   **Cullen KR**, Klimes-Dougan B, Muetzel R, Mueller BA, Camchong J, Houri A, Kurma S, Lim KO. Altered white matter microstructure in adolescents with major depression: a preliminary study. *J Am Acad Child Adolesc Psychiatry* 2010; **49**: 173-83.e1 [PMID: 20215939 DOI: 10.1097/00004583-201002000-00011]

59   **Höflich A**, Michenthaler P, Kasper S, Lanzenberger R. Circuit Mechanisms of Reward, Anhedonia, and Depression. *Int J Neuropsychopharmacol* 2019; **22**: 105-118 [PMID: 30239748 DOI: 10.1093/ijnp/pyy081]

60   **Zhou HX**, Chen X, Shen YQ, Li L, Chen NX, Zhu ZC, Castellanos FX, Yan CG. Rumination and the default mode network: Meta-analysis of brain imaging studies and implications for depression. *Neuroimage* 2020; **206**: 116287 [PMID: 31655111 DOI: 10.1016/j.neuroimage.2019.116287]

61   **Dutta A**, McKie S, Downey D, Thomas E, Juhasz G, Arnone D, Elliott R, Williams S, Deakin JFW, Anderson IM. Regional default mode network connectivity in major depressive disorder: modulation by acute intravenous citalopram. *Transl Psychiatry* 2019; **9**: 116 [PMID: 30877271 DOI: 10.1038/s41398-019-0447-0]

Digital interventions empowering mental health reconstruction among students after the COVID-19 pandemic

Xin-Qiao Liu, Yu-Xin Guo, Xin-Ran Zhang, Lin-Xin Zhang, Yi-fan Zhang

Xin-Qiao Liu, Yu-Xin Guo, Xin-Ran Zhang, Lin-Xin Zhang, Yi-fan Zhang, School of Education, Tianjin University, Tianjin 300350, China

Corresponding author: Xin-Qiao Liu, PhD, Associate Professor, School of Education, Tianjin University, No. 135 Yaguan Road, Jinnan District, Tianjin 300350, China. xinqiaoliu@pku.edu.cn

Abstract

With the gradual end of the coronavirus disease 2019 (COVID-19) pandemic, the reconstruction of students' mental health is urgently necessary. Digital interventions offer advantages such as high accessibility, anonymity, and accurate identification, which can promote the reconstruction of students' mental health through the provision of psychological support platforms, psychological assessment tools, and online mental health activities. However, we recognize that digital interventions must undergo many adjustments, and corresponding ethical norms require further clarification. It is crucial for different stakeholders to collaborate and work toward maximizing the effectiveness of digital interventions for the reconstruction of mental health after the COVID-19 pandemic.

Key Words: Digital interventions; Artificial intelligence; Big data; Students; Mental health

Core Tip: As the coronavirus disease 2019 (COVID-19) pandemic has gradually come to an end, a challenge that has emerged is how to restore the mental health of students after the pandemic. This paper contends that digital interventions are cutting-edge and that effective approaches should be fully utilized to address the impact of the COVID-19 pandemic on the mental health of students.

TO THE EDITOR

We have read the observational study titled "Investigating adolescent mental health of Chinese students during the coronavirus disease 2019 (COVID-19) pandemic: Multicenter cross-sectional comparative investigation" authored by Huang *et al*[1] and published in the 11th issue of the *World Journal of Psychiatry* in 2022. In this paper, the impact of the COVID-19 pandemic on the daily life and learning of adolescents was analyzed from four aspects: Time distribution, cohabitation groups, and positive and negative effects. The Patient Health Questionnaire-9 and the Generalized Anxiety Disorder Questionnaire- 7 were used to measure the impact of the COVID-19 pandemic on the mental health of adolescents. The results of the study indicated that there were significant differences in the time distribution of daily activities and cohabitation groups for adolescents before and after the COVID-19 pandemic. The academic performance of adolescents from different grades was negatively impacted by the pandemic, with distinct features observed for students at different grade levels; in particular, there was a significant increase in the rate of severe anxiety among junior high school students[1].

We believe that the conclusion of the article is highly valuable for discussion. The COVID-19 pandemic has greatly impacted the daily lives and learning of adolescents, and the mental health status of this population deserves more attention. Our previous research also showed that the prevalence rates of depression and anxiety among Asian university students range from approximately 20% to 40%[2,3], which are relatively high rates and have various negative effects on the daily lives of these students. Given the uniqueness of the COVID-19 pandemic, most studies suggest that the mental health of adolescents has shown a deteriorating trend during the pandemic[4,5]. Other studies have also reported results consistent with the findings of Huang *et al*[1], indicating that the incidence of mental disorders among adolescents, such as depression, anxiety, and stress, has decreased during the COVID-19 pandemic[6-8]. However, the mental health status of adolescents remains concerning. During the COVID-19 pandemic, the improvement of mental health among adolescents is often accompanied by an increase in attachment security and communication with parents, continuous optimization of organizational structures within schools, and gradual adaptation to daily life changes[7,9]. In our study, family, school, and individual factors were considered to be influencing factors of individual depression and anxiety levels, such as family relationships, parental education level, school environment, peer relationships, and lifestyle factors[2,3]. Therefore, general intervention measures should start from these three aspects, namely, enhancing family support for the mental state of adolescents, providing various forms of psychological counseling in schools, and adolescents themselves making efforts to maintain a positive attitude. These measures would improve the mental health status of adolescents during and after the COVID-19 pandemic.

Currently, there are abundant research findings on the impact of the COVID-19 pandemic on students' mental health. However, as the pandemic ends, it remains challenging to effectively address the mental health crisis caused by the pandemic and reshape positive mindsets in individuals. Digital therapy is emerging rapidly and gradually becoming a hot topic in the research and practice of mental health interventions. Digital interventions, carried out *via* the internet, big data, and artificial intelligence, provide a new form for screening, assessing, intervening and treating mental health problems[10,11]. Several studies have confirmed the effectiveness of digital interventions in the treatment of mental health[12-15]. Their advantages are mainly reflected in the following three aspects. First, digital interventions are highly accessible, which can alleviate the imbalance between the supply and demand of mental health services[16,17]. The COVID-19 pandemic was characterized by a sudden onset, long duration, and broad impact. The resulting mental health problems have become increasingly prominent, and many professional psychologists are needed to provide targeted mental health services. In fact, the public health system has a limited capacity to respond to emergencies, and mental health resources are limited[18]. In the context of the intelligence era, students can access various forms of digital intervention services through the internet and mobile platforms to address potential mental health problems in a timely manner[19]. Second, digital interventions are anonymous, which can reduce the risk of stigmatization. Due to concerns about stigmatization, many students have low willingness to seek psychological help, and their anxiety and depression may not be relieved in a timely manner[20]. With the use of digital interventions, students can access services anonymously at any time[21]. Third, digital interventions can accurately identify psychological health problems and provide effective solutions. Through health data tracking and intelligent analysis systems, digital interventions can accurately screen students with potential psychological health problems, making it easier to provide psychological counseling in a timely manner. In addition, based on the different needs of students, digital interventions can also provide personalized psychological support, making them more flexible and convenient to use[16,22].

It is worth noting that there are still some challenges in more extensive and efficient mining and application of digital psychological health interventions. First, students inevitably face the risk of information leakage when using applications and other mobile platforms. Various countries have not established an effective supervision and management system, and the corresponding ethical norms need to be further clarified[23,24]. Second, digital interventions are essential tools. Psychological health practitioners should combine their professional literacy and fully utilize the characteristics of digital technology to maximize the potential of digital interventions[25]. Finally, technology changes rapidly,

and digital psychological health interventions have not kept up with the pace[18]. Different stakeholders need to work together to inject new vitality into digital psychological health interventions using the latest artificial intelligence and virtual reality technologies.

The rapid development of artificial intelligence provides powerful support for the improvement and popularization of mental health services. In response to the challenges encountered in the application of digital psychological interventions, the latest research proposes suggestions from three aspects: Theory, practice, and future development trends. First, the theoretical foundation for the development of digital intervention needs to transform good clinical practice standards (such as CBT) into key components of mental health services[26]. Second, to improve the effectiveness of digital psychological interventions, a participatory design approach should be widely adopted[27], and cultural relevance should be integrated into mobile applications or online platforms[28,29]. Finally, future digital psychological interventions should fully utilize the latest developments in artificial intelligence, applying algorithms such as machine learning and deep learning to automatically identify and analyze emotional states and establish a mental health database. In addition, protecting user data privacy, reducing costs, and improving usability are also key issues that need to be addressed in the future[30,31]. Regarding the protection of user privacy, we believe that students' information literacy should be given attention. In the digital environment, students are vulnerable to data malfunctions and the unethical use of their data. To prevent this situation, students should be aware of the risks they may face in digital media, improve their digital literacy and safety awareness, effectively use and manage their digital archives, and have a healthy online/offline social life.

In conclusion, after the outbreak of the COVID-19 pandemic, restoring the mental health of students is urgently necessary. Digital interventions can promote the reconstruction of students' mental health by providing a platform for psychological support, offering psychological assessment tools, and facilitating online mental health activities. We believe that digital interventions should be actively adopted to support students' mental health and enhance social welfare.

FOOTNOTES

ORCID number: Xin-Qiao Liu 0000-0001-6620-4119; Yu-Xin Guo 0000-0001-7823-3195; Yi-fan Zhang 0000-0002-8870-9983.

REFERENCES

1   **Huang BW**, Guo PH, Liu JZ, Leng SX, Wang L. Investigating adolescent mental health of Chinese students during the COVID-19 pandemic: Multicenter cross-sectional comparative investigation. *World J Psychiatry* 2022; **12**: 1323-1334 [PMID: 36438680 DOI: 10.5498/wjp.v12.i11.1323]

2   **Liu XQ**, Guo YX, Xu Y. Risk factors and digital interventions for anxiety disorders in college students: Stakeholder perspectives. *World J Clin Cases* 2023; **11**: 1442-1457 [PMID: 36926387 DOI: 10.12998/wjcc.v11.i7.1442]

3   **Liu XQ**, Guo YX, Zhang WJ, Gao WJ. Influencing factors, prediction and prevention of depression in college students: A literature review. *World J Psychiatry* 2022; **12**: 860-873 [PMID: 36051603 DOI: 10.5498/wjp.v12.i7.860]

4   **Fruehwirth JC**, Biswas S, Perreira KM. The Covid-19 pandemic and mental health of first-year college students: Examining the effect of Covid-19 stressors using longitudinal data. *PLoS One* 2021; **16**: e0247999 [PMID: 33667243 DOI: 10.1371/journal.pone.0247999]

5   **Hawes MT**, Szenczy AK, Klein DN, Hajcak G, Nelson BD. Increases in depression and anxiety symptoms in adolescents

and young adults during the COVID-19 pandemic. *Psychol Med* 2022; **52**: 3222-3230 [PMID: 33436120 DOI: 10.1017/S0033291720005358]

6   **Foster S**, Estévez-Lamorte N, Walitza S, Dzemaili S, Mohler-Kuo M. Perceived stress, coping strategies, and mental health status among adolescents during the COVID-19 pandemic in Switzerland: a longitudinal study. *Eur Child Adolesc Psychiatry* 2022; 1-13 [PMID: 36515772 DOI: 10.1007/s00787-022-02119-y]

7   **Hussong J**, Möhler E, Kühn A, Wenning M, Gehrke T, Burckhart H, Richter U, Nonnenmacher A, Zemlin M, Lücke T, Brinkmann F, Rothoeft T, Lehr T. Mental Health and Health-Related Quality of Life in German Adolescents after the Third Wave of the COVID-19 Pandemic. *Children (Basel)* 2022; **9** [PMID: 35740717 DOI: 10.3390/children9060780]

8   **Shi W**, Zhao L, Liu M, Hong B, Jiang L, Jia P. Resilience and mental health: A longitudinal cohort study of Chinese adolescents before and during COVID-19. *Front Psychiatry* 2022; **13**: 948036 [PMID: 36061276 DOI: 10.3389/fpsyt.2022.948036]

9   **Yang B**, Chen BB, Qu Y, Zhu Y. The positive role of parental attachment and communication in Chinese adolescents' health behavior and mental health during COVID-19. *J Adolesc* 2022; **94**: 1081-1095 [PMID: 35971991 DOI: 10.1002/jad.12085]

10   **Harith S**, Backhaus I, Mohbin N, Ngo HT, Khoo S. Effectiveness of digital mental health interventions for university students: an umbrella review. *PeerJ* 2022; **10**: e13111 [PMID: 35382010 DOI: 10.7717/peerj.13111]

11   **Yosep I**, Hikmat R, Mardhiyah A. Types of Digital-Based Nursing Interventions for Reducing Stress and Depression Symptoms on Adolescents During COVID-19 Pandemic: A Scoping Review. *J Multidiscip Healthc* 2023; **16**: 785-795 [PMID: 37006343 DOI: 10.2147/JMDH.S406688]

12   **Harrer M**, Adam SH, Baumeister H, Cuijpers P, Karyotaki E, Auerbach RP, Kessler RC, Bruffaerts R, Berking M, Ebert DD. Internet interventions for mental health in university students: A systematic review and meta-analysis. *Int J Methods Psychiatr Res* 2019; **28**: e1759 [PMID: 30585363 DOI: 10.1002/mpr.1759]

13   **Lattie EG**, Adkins EC, Winquist N, Stiles-Shields C, Wafford QE, Graham AK. Digital Mental Health Interventions for Depression, Anxiety, and Enhancement of Psychological Well-Being Among College Students: Systematic Review. *J Med Internet Res* 2019; **21**: e12869 [PMID: 31333198 DOI: 10.2196/12869]

14   **Rith-Najarian LR**, Boustani MM, Chorpita BF. A systematic review of prevention programs targeting depression, anxiety, and stress in university students. *J Affect Disord* 2019; **257**: 568-584 [PMID: 31326690 DOI: 10.1016/j.jad.2019.06.035]

15   **Bolinski F**, Boumparis N, Kleiboer A, Cuijpers P, Ebert DD, Riper H. The effect of e-mental health interventions on academic performance in university and college students: A meta-analysis of randomized controlled trials. *Internet Interv* 2020; **20**: 100321 [PMID: 32382515 DOI: 10.1016/j.invent.2020.100321]

16   **Sugarman DE**, Meyer LE, Reilly ME, Rauch SL, Greenfield SF. Exploring Technology-Based Enhancements to Inpatient and Residential Treatment for Young Adult Women with Co-Occurring Substance Use. *J Dual Diagn* 2021; **17**: 236-247 [PMID: 34261413 DOI: 10.1080/15504263.2021.1940412]

17   **Li J**. Digital technologies for mental health improvements in the COVID-19 pandemic: a scoping review. *BMC Public Health* 2023; **23**: 413 [PMID: 36859184 DOI: 10.1186/s12889-023-15302-w]

18   **Philippe TJ**, Sikder N, Jackson A, Koblanski ME, Liow E, Pilarinos A, Vasarhelyi K. Digital Health Interventions for Delivery of Mental Health Care: Systematic and Comprehensive Meta-Review. *JMIR Ment Health* 2022; **9**: e35159 [PMID: 35551058 DOI: 10.2196/35159]

19   **Baños RM**, Herrero R, Vara MD. What is the Current and Future Status of Digital Mental Health Interventions? *Span J Psychol* 2022; **25**: e5 [PMID: 35105398 DOI: 10.1017/SJP.2022.2]

20   **Reavley NJ**, McCann TV, Cvetkovski S, Jorm AF. A multifaceted intervention to improve mental health literacy in students of a multicampus university: a cluster randomised trial. *Soc Psychiatry Psychiatr Epidemiol* 2014; **49**: 1655-1666 [PMID: 24797396 DOI: 10.1007/s00127-014-0880-6]

21   **Sorkin DH**, Janio EA, Eikey EV, Schneider M, Davis K, Schueller SM, Stadnick NA, Zheng K, Neary M, Safani D, Mukamel DB. Rise in Use of Digital Mental Health Tools and Technologies in the United States During the COVID-19 Pandemic: Survey Study. *J Med Internet Res* 2021; **23**: e26994 [PMID: 33822737 DOI: 10.2196/26994]

22   **Bolinski F**, Kleiboer A, Karyotaki E, Bosmans JE, Zarski AC, Weisel KK, Ebert DD, Jacobi C, Cuijpers P, Riper H. Effectiveness of a transdiagnostic individually tailored Internet-based and mobile-supported intervention for the indicated prevention of depression and anxiety (ICare Prevent) in Dutch college students: study protocol for a randomised controlled trial. *Trials* 2018; **19**: 118 [PMID: 29458407 DOI: 10.1186/s13063-018-2477-y]

23   **Lattie EG**, Lipson SK, Eisenberg D. Technology and College Student Mental Health: Challenges and Opportunities. *Front Psychiatry* 2019; **10**: 246 [PMID: 31037061 DOI: 10.3389/fpsyt.2019.00246]

24   **Wykes T**, Lipshitz J, Schueller SM. Towards the Design of Ethical Standards Related to Digital Mental Health and all Its Applications. *Curr Treat Options Psychiatry* 2019; **6**: 232-242 [DOI: 10.1007/s40501-019-00180-0]

25   **Drerup ML**, Ahmed-Jauregui S. Online Delivery of Cognitive Behavioral Therapy-Insomnia: Considerations and Controversies. *Sleep Med Clin* 2019; **14**: 283-290 [PMID: 31029194 DOI: 10.1016/j.jsmc.2019.02.001]

26   **Rauschenberg C**, Schick A, Hirjak D, Seidler A, Paetzold I, Apfelbacher C, Riedel-Heller SG, Reininghaus U. Evidence Synthesis of Digital Interventions to Mitigate the Negative Impact of the COVID-19 Pandemic on Public Mental Health: Rapid Meta-review. *J Med Internet Res* 2021; **23**: e23365 [PMID: 33606657 DOI: 10.2196/23365]

27   **Malla A**, Joober R. COVID-19 and the Future with Digital Mental Health: Need for Attention to Complexities. *Can J Psychiatry* 2021; **66**: 14-16 [PMID: 32885686 DOI: 10.1177/0706743720957824]

28   **Mindu T**, Mutero IT, Ngcobo WB, Musesengwa R, Chimbari MJ. Digital Mental Health Interventions for Young People in Rural South Africa: Prospects and Challenges for Implementation. *Int J Environ Res Public Health* 2023; **20** [PMID: 36674209 DOI: 10.3390/ijerph20021453]

29   **Naslund JA**, Aschbrenner KA, Araya R, Marsch LA, Unützer J, Patel V, Bartels SJ. Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. *Lancet Psychiatry* 2017; **4**: 486-500 [PMID: 28433615 DOI: 10.1016/S2215-0366(17)30096-2]

30   **Cao XJ**, Liu XQ. Artificial intelligence-assisted psychosis risk screening in adolescents: Practices and challenges. *World J*

Psychiatry 2022; **12**: 1287-1297 [PMID: 36389087 DOI: 10.5498/wjp.v12.i10.1287]

31   **Choudhury A**, Kuehn A, Shamszare H, Shahsavar Y. Analysis of Mobile App-Based Mental Health Solutions for College Students: A Rapid Review. *Healthcare (Basel)* 2023; **11** [PMID: 36673640 DOI: 10.3390/healthcare11020272]

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