**ISSN** 2220-3206 (online)

# World Journal of *Psychiatry*

*World J Psychiatr* 2015 December 22; 5(4): 352-438

Published by Baishideng Publishing Group Inc

WJP World Journal of Psychiatry

A peer-reviewed, online, open-access journal of psychiatry

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WJP World Journal of Psychiatry

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Quarterly Volume 5 Number 4 December 22, 2015

## SYSTEMATIC REVIEWS

NAME OF JOURNAL
*World Journal of Psychiatry*

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Quarterly

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PUBLICATION DATE
December 22, 2015



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DOI: 10.5498/wjp.v5.i4.352

*World J Psychiatr* 2015 December 22; 5(4): 352-361
ISSN 2220-3206 (online)


EDITORIAL

# Conceptualization and treatment of negative symptoms in schizophrenia

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Author contributions: Sarkar S, Hillner K, and Velligan DI conceived the issues which formed the content of the manuscript and wrote the manuscript.

Supported by The Patient-Centered Outcomes Institute (2012-2015).

Conflict-of-interest statement: Dawn I Velligan has received fees for serving as consultant and/or advisory board member for Otsuka Pharmaceuticals, Lundbeck Pharmaceuticals, Abbvie, Forum Pharmaceuticals, Reckitt Benckiser Pharmaceuticals, and Janssen Pharmaceuticals and as a speaker for Otsuka Pharmaceuticals and Janssen Pharmaceuticals. Sonali Sarkar and Kiley Hillner have no conflicts of interest.



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Received: May 26, 2015
Peer-review started: May 28, 2015
First decision: June 18, 2015
Revised: July 7, 2015
Accepted: October 12, 2015
Article in press: October 13, 2015
Published online: December 22, 2015

## Abstract

Negative symptoms of schizophrenia including social withdrawal, diminished affective response, lack of interest, poor social drive, and decreased sense of purpose or goal directed activity predict poor functional outcomes for patients with schizophrenia. They may develop and be maintained as a result of structural and functional brain abnormalities, particularly associated with dopamine reward pathways and by environmental and psychosocial factors such as self-defeating cognitions and the relief from overstimulation that accompanies withdrawal from social and role functioning. Negative symptoms are more difficult to treat than the positive symptoms of schizophrenia and represent an unmet therapeutic need for large numbers of patients with schizophrenia. While antipsychotic medications to treat the symptoms of schizophrenia have been around for decades, they have done little to address the significant functional impairments in the disorder that are associated with negative symptoms. Negative symptoms and the resulting loss in productivity are responsible for much of the world-wide personal and economic burden of schizophrenia. Pharmacologic treatments may be somewhat successful in treating secondary causes of negative symptoms, such as antipsychotic side effects and depression. However, in the United States there are no currently approved treatments for severe and persistent negative symptoms (PNS) that are not responsive to treatments for secondary causes. Pharmacotherapy and psychosocial treatments are currently being developed and tested with severe and PNS as their primary targets. Academia, clinicians, the pharmaceutical industry, research funders, payers and regulators will need to work together to pursue novel treatments to address this major public health issue.

**Key words:** Motivation; Functional outcomes; Negative symptoms; Schizophrenia; Treatment

**Core tip:** Negative symptoms of schizophrenia including social withdrawal, diminished affective response, lack of interest, poor social drive, and decreased sense of purpose or goal directed activity predict poor functional outcomes for patients with schizophrenia. Negative symptoms and the resulting loss in productivity are responsible for much of the world-wide personal and economic burden of schizophrenia. We describe current theories of negative symptom development and maintenance and address the data regarding current and emerging treatments. Negative symptoms represent an unmet therapeutic need for large numbers of patients. Academia, clinicians, the pharmaceutical industry, research funders, payers and regulators will need to work together to pursue novel treatments to address this public health issue.

Sarkar S, Hillner K, Velligan DI. Conceptualization and treatment of negative symptoms in schizophrenia. *World J Psychiatr* 2015; 5(4): 352-361 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/352.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.352

## INTRODUCTION

Schizophrenia is one of the top 10 disabling mental conditions and impacts 1% of the adult population worldwide[1]. Patients suffering from schizophrenia struggle with cognitive and functional impairment. Due to the often chronic course of illness, patients with schizophrenia have poor educational attainment, reduced quality of life, impairment in independent living and major socio-occupational dysfunction[2,3]. Impairment arising from schizophrenia is so severe that only 10%-20% of patients work full time or part time[4]. The majority of patients suffering from schizophrenia require some form of public funding for support. The loss of productivity associated with schizophrenia is a major driver of cost which is estimated to be over 60 billion dollars annually; or more than $1000 for every man, woman, and child in the United States[5-9]. There is an additional burden on the family members and relatives who care for such patients[10].

Much of the burden of schizophrenia is due to what are called the negative symptoms. This manuscript will review the definition of negative symptoms, describe the onset and maintenance of these symptoms and identify potential treatments.

## DESCRIPTION OF NEGATIVE SYMPTOMS

Negative symptoms are defined as absence or reduction of behaviors that are normally present in the general population[11]. Negative symptoms of schizophrenia include social withdrawal, diminished affective response, lack of interest, poor social drive, and decreased sense of purpose or goal directed activity[11]. DSM-V emphasizes two negative symptom domains: expressive deficits and avolition[12]. Expressive deficits include blunted facial expression, few changes in voice tone, and a paucity of expressive gestures which are normally present in conversation. Avolition refers to a lack of initiative for daily activity and interaction with others. Individuals with avolition may have difficulty even generating an idea to do something, and have low levels of productive activity during the day[13]. They may spend a lot of time sitting or lying around, have few interests and relate little to others[12-15].

Negative symptoms of schizophrenia persist longer than positive symptoms and are more difficult to treat[16,17]. In addition, negative symptoms of schizophrenia serve as better predictors of concurrent and future socio-occupational functioning than do positive symptoms[18-20]. A large number of studies have found attenuated negative symptoms in patients with at risk mental states[21]. In fact, the severity of negative symptoms rather than positive symptoms has been found to predict conversion to psychosis in patients with at risk mental states[22]. Persistent negative symptoms (PNS) are present in about one third to one-half of first episode psychosis (FEP) patients[23,24].

Moreover, those FEP patients who demonstrate negative symptoms at baseline show significantly worse functioning when assessed again at 12 mo in comparison to FEP patients without negative symptoms[23]. Therefore, decreasing negative symptoms and improving functional outcomes among individuals with schizophrenia is an important public health issue. Effectively treating negative symptoms could help to prevent long term disability in first episode patients with schizophrenia.

## TYPES OF NEGATIVE SYMPTOMS

Approximately 20%-40% of patients with schizophrenia have persistent or deficit negative symptoms[25]. Primary (deficit) negative symptoms are defined as symptoms that are idiopathic to schizophrenia, arising from a distinct yet ultimately mysterious underlying pathologic process. These symptoms are present during and between episodes of symptom exacerbation and are not always dependent on whether the patient is taking medication[11,26,27].

Secondary (non-deficit) symptoms are defined as those that are caused by factors other than the illness of schizophrenia[11]. Secondary causes of negative symptoms can include medication side effects, notably extrapyramidal side effects (EPS) of antipsychotic medication, neuroleptic akinesia, or drug withdrawal from Central Nervous System stimulants[11,15]. Secondary negative symptoms can also be due to depression, social deprivation or personality disorders[11]. Secondary negative symptoms may be non-persistent or appear for a shorter duration when compared to primary negative symptoms[16].

Data suggest that individuals with deficit syndrome

have poor premorbid functioning prior to their first episode of psychosis than individuals without deficit syndrome, and are less likely to be married[28-35]. In addition, some studies report more severe cognitive impairments, and distinct neuroimaging findings in deficit syndrome[34-38]. The differences between deficit and non-deficit forms of negative symptoms may suggest that deficit syndrome represents a separate disease entity. However, it has also been argued that the deficit syndrome lies on a continuum of severity within schizophrenia and does not characterize a distinctly separate subgroup[39]. In practice, it can be difficult to distinguish the primary *vs* secondary negative symptoms of schizophrenia and they may coexist.

The NIMH-MATRICS consensus statement on negative symptoms suggests that treatment development should focus on PNS[40]. PNS are defined as either primary or secondary negative symptoms that are present for a minimum of 6 mo duration, and are not responsive to any potential treatments for secondary negative symptoms[11]. The NIMH-MATRICS consensus statement on negative symptoms indicated that PNS represent an unmet therapeutic need for patients suffering from schizophrenia[40,41].

## MECHANISMS IN THE DEVELOPMENT OF NEGATIVE SYMPTOMS

Alterations in neurotransmitter systems which could be either neurodevelopmental in origin or develop secondary to dopaminergic blocking medications may predispose a person to develop negative symptoms of schizophrenia[42,43]. Prior studies have indicated that disruptions in ventral striatal reward systems are associated with the development of negative symptoms[44,45]. Some studies have highlighted dopaminergic and noradrenergic circuitry involved with reward as neural substrates for the negative symptoms of schizophrenia[46,47]. Alterations in normal connectivity among brain regions have been implicated. Even individuals at high risk for psychosis have demonstrated alterations in functional brain connectivity. Dandash *et al*[48] have demonstrated that conversion to psychosis from an at risk mental state is mediated by alterations in both dorsal and ventral corticostriatal systems. Moreover, studies of brain structure have shown negative symptoms to be associated with subtle tissue decrements in the frontal lobes[38,49-56]. A correlation has also been found between severity of negative symptoms specifically and the right posterior superior temporal gyrus, with the greater severity of negative symptoms being correlated with larger volumes of gray matter in this region[57]. While many of these abnormalities are clearly present prior to the development of a full blown psychotic disorder, it is difficult to say whether these structural and functional changes are causally related to the development of negative symptoms in particular[58].

In addition to brain structure and functioning, negative symptoms may also develop during early stages of psychosis as a psychosocial defense mechanism for dealing with distress beyond one's capacity to cope[59]. In this model, exposure to overwhelming social and environmental stimuli leads to shutting down of various psychological systems, presenting as negative symptoms. This removal of distressing stimuli by shutting down is negatively reinforcing as the person experiences relief. This contributes to a dependence on negative symptoms like social isolation, apathy, and avolition to reduce exposure to and the impact of aversive or over stimulating experiences[59]. Thus, the mechanisms involved in the development of negative symptoms are multifactorial and may include structural, neurobiological, environmental and psychosocial factors.

## MAINTENANCE OF NEGATIVE SYMPTOMS

Velligan *et al*[60] proposed a negative symptom maintenance loop. According to their model, dysfunctional brain reward systems and/or the onset of psychotic symptoms and associated psychosocial withdrawal leads to a maintenance loop wherein decreased initiation and withdrawal lead to a series of self-perpetuating outcomes including decreased responsiveness to environmental stimuli, a lower level of interest in the world, little to discuss in conversations with others, a low level of reinforcement from the person's surroundings, lower levels of overall stimulation, loss of skills previously attained for work or socializing with others, and decreased planning for the future such that everyday looks very much the same.

Moreover, when someone with negative symptoms is asked to participate with others or attempt something new, self-defeating cognitions about failure or ridicule may prevent the person from trying activities[59,61]. Repeated negative consequences and failures following the initiation of various tasks and behaviors may further prevent initiation of activities[59]. This negative feedback loop persists and makes it difficult to break the cycle leading to maintenance of negative symptoms[61,62].

Additionally, a study conducted by Gard *et al*[63] indicated that individuals with schizophrenia are less able than others to anticipate enjoyment (anticipatory pleasure) in spite of experiencing enjoyment to a similar extent (consummatory pleasure) when engaging in activities. This reduced ability to anticipate pleasure may lead the individual to perceive that the effort required to engage in behaviors, interact with people or pursue interests will not be worth the benefits achieved. This situation ultimately leads to reduced planning of activities that actually may be pleasurable[60].

The onset and maintenance of negative symptoms is described in the figure below adapted from Velligan *et al*[60].

**Table 1 Negative Symptom Assessment scales**

| Assessment name | Scale | Negative symptom domains measured |
|---|---|---|
| Negative Symptom Assessment (NSA-16) | Score of 1 (normal)-6 (severe)<br>Each symptom within the 5 domains is scored separately | Five domains (each domain has several specific symptoms listed): Communication, Emotion/Affect, Social Involvement, Motivation, Retardation |
| Positive and Negative Syndrome Scale | Score of 1-7 on each item. Score of 7 indicates higher symptom severity | Seven domains: Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive/apathetic Social Withdrawal, Difficulty in Abstract Thinking, Lack of spontaneity and Flow of Conversation, Stereotyped Thinking |
| Scale for Assessment of Negative Symptoms | Score of 0 (absent) -5 (severe)<br>Each symptom within the 5 domains is scored separately | Five domains (each domain has several specific symptoms listed): Affective Flattening or Blunting, Alogia, Avolition-Apathy, Anhedonia-Asociality, Attention |
| Brief Negative Symptom Scale | Score of 0 (absent) - 6 (severe)<br>Each domain is scored | Six Domains (each domain has several symptoms listed): Anhedonia, Distress, Asociality, Avolition, Blunted Affect, Alogia |
| Clinical Assessment Interview for Negative Symptoms | Score 0 (no impairment) -4 (severe)<br>Each symptom within the 5 domains is scored separately | Five Domains (each domain has several specific symptoms listed): Asociality, Avolition, Anhedonia, Affective Flattening, Alogia |
| Brief Negative Symptom Assessment | Score 1 (normal)-6 (severe) | Four Domains: Prolonged Time to Respond, Emotion, Reduced Social Drive, Grooming and Hygiene |
| Four item Brief Negative Symptom Assessment | Score 1 (normal)-6 (severe) | Four Domains: Restricted Speech Quantity, Reduced Emotion, Reduced Social Drive, Reduced Interests |

## NEGATIVE SYMPTOM ASSESSMENT IN SCHIZOPHRENIA

Patients with negative symptoms of schizophrenia are frequently brought in for an assessment by their close relatives as part of family conflict with the chief complaint of poor social functioning[64,65]. Instruments developed to measure the negative symptoms are primarily used for research purposes[66-69]. Rating scales used to measure the negative symptoms of schizophrenia include the Negative Symptom Assessment (NSA-16)[66], Positive and Negative Syndrome Scale[68], Scale for Assessment of Negative Symptoms[70], the Brief Negative Symptom Scale[69] and the Clinical Assessment Interview for Negative Symptoms (CAINS)[67]. The majority of these scales provide definitions of each negative symptom domain, a semi-structured interview to obtain needed information and a series of behavioral anchor points to help the rater identify the frequency, severity and intensity of each symptom type. A brief description of these scales, item scoring, and domains assessed appear in Table 1. Studies have demonstrated very high correlations among negative symptom measures averaging around 80, which suggesting that they are all tapping the same construct[66,67,69,71]. These instruments form the basis for determining the presence of PNS according to the NIMH-MATRICS consensus guidelines[40]. Guidelines require that a patient must have at least moderate scores on at least two negative symptom domains which persist for a minimum of 6 mo, along with low levels of positive symptoms, depression and EPS[40].

Unfortunately, the scales listed above are too lengthy for use in typical community mental health centers treating large numbers of patients. In fact, for clinicians, negative symptoms are often not a focus of assessment or treatment because they are rarely a reason for patients to be in crisis or pose a need to go to the hospital. However, assessing negative symptoms will become increasingly important as medications are developed specifically to target these symptoms. In clinical interviews, it is important to assess daily activities, social relationships within and outside of the family, and work or school involvement and performance. Several brief 4-item measures of negative symptoms for use in clinical situations are available[66,72]. Some items on each scale require no questioning as they are based upon observation of the patient. Such scales have been used reliably in busy community mental health departments seeking to promote outcomes-based treatment[72].

## PHARMACOLOGICAL TREATMENT OF NEGATIVE SYMPTOMS

Treatment of negative symptoms depends upon their causes. If negative symptoms such as social withdrawal are secondary to a patient's positive symptoms then increasing the dosage of antipsychotic medication or switching to a different antipsychotic medication may be helpful[73]. Alternatively, if negative symptoms are associated with depressed affect, then treatment for depression should be considered[74]. A recent Cochrane review of the literature indicated that antidepressants may have a positive impact on negative symptoms, however additional prospective studies are needed on a larger-scale to reach this definitive conclusion[75]. Moreover, it is not clear from the existing literature whether antidepressants improve negative symptoms in the long term, as most randomized blinded trials have been brief. If the occurrence of negative symptoms are secondary to EPS of antipsychotic medications, these can be potentially decreased by reducing the dosage of antipsychotic medication to a level that does not

produce EPS or by prescribing atypical antipsychotics with lower potential for EPS side effects[76]. Of course problems with increasing positive symptoms may result from lowering the dose of antipsychotic medications.

Currently there are no approved treatment options for PNS that are not responsive to treatments for secondary causes in the United States. Some evidence for efficacy of second generation antipsychotics has been reported, and Amisulpride (not available in the United States) is approved for treatment of negative symptoms in Europe and Asia[77-79]. However, none of the studies mentioned above included design features established by expert consensus as necessary to prove efficacy for PNS[11]. The design features deemed necessary include documentation for persistence of negative symptoms for a minimum duration of 6 mo, relatively low and stable positive symptoms, low levels of depression, and stable medication side effects. Such studies cannot rule out pseudospecificity in which negative symptoms improve secondary to improvement in positive symptoms, depression or EPS[11].

According to the Patient Outcomes Research Team (PORT) U.S. schizophrenia guidelines, no pharmacologic treatment for negative symptoms has proven to have sufficient evidence to support a recommendation, indicating a significant unmet need for important treatment in this area[80].

Novel compounds exerting action on the glutamate system have demonstrated some initial efficacy in negative symptoms. For example, a phase Ⅱ randomized controlled trial with bitopertin (RG1678), a glycine transporter inhibitor when added to standard antipsychotic therapy for 8 wk demonstrated statistically significant improvement on negative symptoms when compared to antipsychotic treatment plus a placebo[81]. In this trial, a positive trend for functional outcome was also observed in the Bitopertin group. Unfortunately, these results were not replicated in larger scale trials. Phase Ⅲ trials of Bitopertin did not support its efficacy for the treatment of negative symptoms[82]. There is limited evidence supporting alpha 7 nicotinic acetylcholine receptor co-agonists as treatments for negative symptoms[83]. In a placebo controlled, randomized double-blind study, folic acid and B12 significantly improved the negative symptoms, but the treatment response was related to genetic variation in folate absorption[84]. Clinical trials of medications for treating negative symptoms have been described in depth by Arango *et al*[85]. A continued effort to find viable pharmacologic options for the treatment of negative symptoms is needed.

## PSYCHOSOCIAL TREATMENTS FOR NEGATIVE SYMPTOMS

Adjunctive psychosocial therapies (cognitive remediation, social cognition training, family intervention, social skills) have been found to be effective in the treatment of schizophrenia[86,87]. Among these psychosocial treatments, cognitive behavioral therapy (CBT) has demonstrated some improvement in negative symptoms of schizophrenia[88,89]. In addition, in a small study, body-oriented psychotherapy directed towards getting the individual moving around and developing self-awareness with environmental boundaries was successful in reducing the negative symptoms of schizophrenia[90]. Some studies suggest that negative symptoms may improve in cognitive remediation (CR), a treatment targeting attention, memory and planning[91-93]. However, the most successful CR studies are imbedded in larger psychosocial treatment programs, which makes the impact of CR alone unclear for negative symptoms. Social skills training targets social adaptation, improves social skills and functioning in patients with schizophrenia[94,95]. Cognitive Adaptation Training (CAT) is a home based manual-driven treatment that involves the use of environmental supports and cues (signs, alarms, checklist) to bypass the cognitive impairments characteristic of schizophrenia with the goal of improving community functioning[96,97]. In multiple studies CAT has improved targeted behaviors (medication adherence, grooming socializing) and functional outcomes in patients with schizophrenia[97-100]. CAT has been found to improve one negative symptom dimension, the motivation factor of the NSA, with moderate effect sizes in published studies[101].

None of the studies mentioned above included design features established by expert consensus as necessary to prove efficacy for PNS[40]. Studies that do not include these design features may reduce only secondary causes of negative symptoms rather than addressing the primary or PNS of schizophrenia.

Motivation and Engagement Training (MOVE) is a novel home based, multi-modal, integrated psychosocial treatment developed by Velligan *et al*[60] to specifically address all negative symptoms domains. MOVE is designed to break the negative feedback maintenance loop described in Figure 1 and incorporates 5 components: Antecedent control, Anticipatory pleasure alteration, Emotional processing, CBT for negative cognition, and Skill building[60].

Antecedent control refers to external cues (signs, checklist) along with the placement of supplies in the home with the goal of cuing behavior and increasing the initiation of activity, establishing habits and increasing automaticity[96-99]. When behaviors are externally cued, the individual does not have to generate a plan[97-100]. Decreasing the steps required for completing each task through organization and task analysis also increases the probability that a task will be attempted and completed successfully[60].

MOVE also targets deficits in anticipatory pleasure. These deficits may prevent an individual from perceiving that he will enjoy an activity or that the activity will be worth the effort needed to pursue it[63]. In MOVE treatment, anticipated pleasure is elicited prior to participating in a pleasurable activity and again during

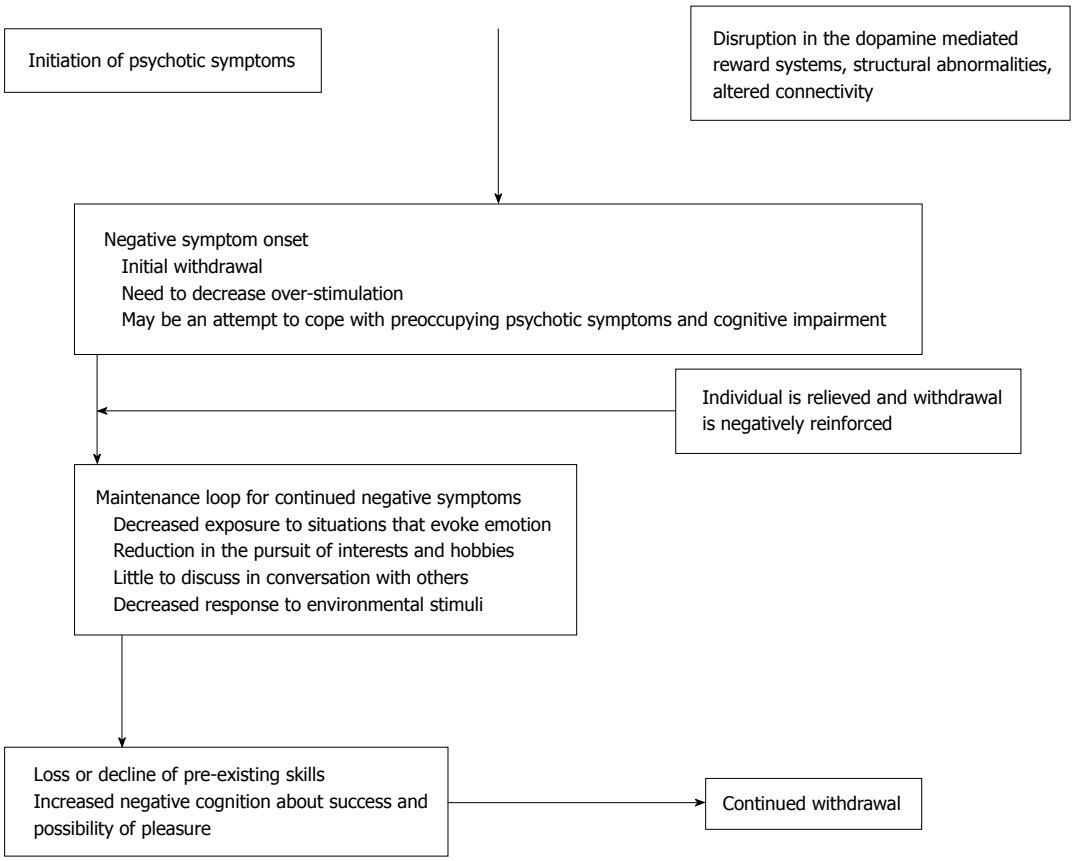


**Figure 1 Maintenance loop for the negative symptoms of schizophrenia.**

that activity[60,63]. This information is used to teach the individual about the discrepancy between anticipated and experienced pleasure. The MOVE therapist discusses with the individual how problems in anticipatory pleasure may interfere with planning recreational and social activities. Statements about the level of enjoyment an individual actually experiences during the activity are recorded and replayed for cueing future activities. Photographs of this enjoyment may be placed on the person's wall to remind the person of their pleasure and increase the probability of planning similar events in the future[60].

Emotional processing targets both the identification of emotion and its expression. Individuals with schizophrenia often experience difficulty identifying their own feeling states[60]. MOVE therapists use graded check-ins with errorless learning methods that enable the individual to identify or label their own emotions. Multiple techniques including voice and visual recording are used to help individuals learn to successfully convey these emotions with appropriate facial expression, voice modulation and gestures. Computer exercises based upon Social Cognition Interaction Training are utilized to improve identification of the emotions of others[102].

CBT techniques are used in MOVE to address self-defeating negative thoughts that prevent initiation of and participation in social activities[59]. Cognitive distortions ("No one will like me, I will be alone all night at the party.") are identified and the person is helped to come up with more accurate self-assessments[59].

Skill training is a final component of MOVE. Behavioral techniques (shaping, modeling) are used to coach the individual to perform various social and independent living tasks (*e.g.,* returning an item to a store). Trainers assist the patient with these tasks not in a group at a clinic but *in vivo* in relationship to situations the person needs to address in their daily lives[60].

In MOVE, positive reinforcement initially encourages behavioral attempts. Successful completion of activities is thought to improve the individual's self-efficacy[60]. A sense of self-efficacy leads to increased willingness to try new behaviors[60]. Higher productivity provides an opportunity for the individual to share new activities in conversation with others[60]. Skills building strategies can help to increase success in social interactions and improve enjoyment[102,103].

A recent study of 50 patients randomized to MOVE *vs* treatment as usual (medication follow-up and case management only) found that MOVE improved negative symptoms as assessed on the CAINS and the NSA-16[71]. Effect sizes were moderate and suggest that larger studies of MOVE may be warranted.

## CONCLUSION

Negative symptoms are devastating for patients and families. They contribute to the high levels of disability observed in schizophrenia. Negative symptoms are

difficult to treat with currently available pharmacotherapies. While some improvements have been noted with psychosocial treatments, few have been studied with design features needed to establish their efficacy in the treatment of PNS. Brief reliable and valid assessments of negative symptoms are available but need to be made widely available to clinicians. Treatments of secondary causes of negative symptoms are important to attempt. Despite these challenges, continued work on treatment development involving a concentrated effort from academia, clinicians, the pharmaceutical industry, payers, research funders, and regulators is needed to address these devastating symptoms.

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**P- Reviewer**: Durgam S, Maniglio R, Serafini G, Zhou X
**S- Editor**: Tian YL **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Psychiatry

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DOI: 10.5498/wjp.v5.i4.362

*World J Psychiatr* 2015 December 22; 5(4): 362-365
ISSN 2220-3206 (online)


EDITORIAL

# Early psychological interventions for psychosis

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Author contributions: Ochoa S and López-Carrilero R have contributed equally in the revision and the writing of this work.

Supported by The PI014/0044, of the Plan Nacional de I+D+I and co-funded by ISCIII – Subdirección General de Evaluación y Formento de la Investigación Sanitaria; and Fondo Europeo de Desarrollo Regional (FEDER).

Conflict-of-interest statement: There is no conflict of interests.



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Received: April 16, 2015
Peer-review started: April 21, 2015
First decision: July 6, 2015
Revised: August 4, 2015
Accepted: September 16, 2015
Article in press: September 18, 2015
Published online: December 22, 2015

## Abstract

The manuscript correspond to an editorial in order to assess the most important and effective interventions for people with psychosis in the early stages.

**Key words:** Schizophrenia; Psychological interventions; Psychosis; Early psychosis; Cognitive behavioral therapy



**Core tip:** The present manuscript is an editorial that tries to describe the most important results found regarding early psychological interventions in psychosis. A description of the main results found in this area is discussed.

Ochoa S, López-Carrilero R. Early psychological interventions for psychosis. *World J Psychiatr* 2015; 5(4): 362-365 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/362.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.362

## INTRODUCTION

Schizophrenia and other psychotic disorders cause severe levels of disability, leading to a considerable burden for caregivers and health systems. At present, the most commonly used treatments rely on antipsychotic medication; however this approach is not sufficient for the improvement of functional outcomes, and approximately 50%-75% of the patients discontinue medication. In recent decades an interest in psychological therapies addressed to people with psychosis has emerged[1]. Psychological therapies for treating people with psychosis have been shown to be beneficial[2]; more than 40% of patients show clear improvement in symptoms, even in the absence of medication[3]. However, implementation in routine services is still poor despite the inclusion of these therapies in clinical guidelines. Haddock *et al*[4] reported that only 6.9% of services offer psychological interventions, although psychological treatments have been found to be cost-effective[5]. Treatment costs can be reduced to a

limited extent not only by the prevention of psychotic symptoms and relapse but also by the improvement of role-functioning capacities. According to the Global Burden of Disease Study, schizophrenia causes a high degree of disability, which accounts for 1.1% of the total disability-adjusted life years (DALYs) and 2.8% of years lived with disability (YLDs). In the World Health Report, schizophrenia is listed as the 8th leading cause of DALYs worldwide[6]. In this context the present editorial aims to revise the most effective psychological interventions for people with first-episode of psychosis and those developed for early interventions to prevent psychosis.

## PSYCHOLOGICAL INTERVENTIONS FOR FIRST-EPISODE PSYCHOSIS

Early psychological interventions have been developed in recent decades in order to treat people with psychosis once the first symptoms appear.

Several clinical trials have tested the effectiveness of psychological interventions. Cognitive behavioral therapy (CBT) was one of the most used, and it has been adapted for specific areas of treatment. In the study of Lewis *et al*[7], CBT showed transient advantages over routine care alone or supportive counselling in speeding remission from acute symptoms in early schizophrenia. In contrast, Jackson *et al*[8] performed a clinical trial comparing CBT *vs* Befriending; the results showed that both groups improved in symptoms, but no specific effect of CBT was demonstrated. Specially addressed to cannabis consumption, Edwards *et al*[9] performed a clinical trial with a cannabis-focused intervention (based on CBT) which found significant changes regarding the consumption of cannabis. On the other hand, the cognitive orientated therapy for early psychosis based on cognitive therapy showed a greater average improvement in a measure of suicide ideation[10]. Other types of psychological treatment such as assertive community treatment in an intensive early-intervention program showed improved clinical outcome after 2 years (OPUS study)[11]. Moreover, psychological therapy based on Adherence Coping Education has been found to be useful in decreasing symptoms[12].

In a review by Barlati *et al*[13], the authors found several results that showed the efficacy of cognitive remediation therapy (CRT) in the early course of psychosis. Randomized controlled studies[14] demonstrated that a cognitive remediation program might have beneficial effects for some specific aspects of cognition. Wykes *et al*[15] carried out a single-blind randomized controlled trial with two groups, one receiving CRT and the other standard care, in patients with a recent diagnosis of early onset schizophrenia. Compared to standard care, CRT produced significant additional improvements in cognitive flexibility as measured by the Wisconsin Card Sort Test.

In summary, although the literature on psychological therapies in the early stages of the psychosis is still scarce, the results suggest that they could be beneficial in reducing several domains, such as symptoms, relapses, suicide, cannabis consumption and in improving cognitive functioning. These studies suggest that psychological treatment in these stages of the illness should be included in the clinical resources.

## PSYCHOLOGICAL INTERVENTIONS AS EARLY STRATEGIES TO PREVENT PSYCHOSIS

Effective psychological interventions for early stages are needed due to the importance of early intervention in reducing chronicity. In this context, most studies have assessed the effectiveness of CBT in preventing transition to psychosis[16-21] as well as integrated therapies that combine individual cognitive-behavioural therapy, group skills training, cognitive remediation and multifamily psychoeducation[22]. Two meta-analyses have been performed regarding the effectiveness of early interventions in psychosis. The first one by Marshall *et al*[23] found that there was inconclusive evidence that interventions could help in the prodromal phase. In the second meta-analysis of Stafford *et al*[24] the authors explored the effectiveness of psychological interventions in preventing psychosis. The conclusions of the study point out that five of the clinical trials of CBT had a moderate effect on transition to psychosis at both 12 and 18 mo. Moreover, the authors suggested that integrated psychological therapies could reduce transition to psychosis.

## LIMITATIONS AND CLINICAL IMPLICATIONS

Several studies have indicated the effectiveness of psychological therapies in the treatment of early psychosis, especially those centered on CBT and CRT treatment. However, the meta-analysis noted above[23,24] pointed up the difficulty of assessing the effectiveness of psychological interventions due to the small number of cases of patients that transit to psychosis. Moreover, Stafford *et al*[24] suggested that a limitation in the assessment of effectiveness of psychological therapies lies in the difficulty in blinding the intervention to patients. Nevertheless, all the clinical trials analyzed in the meta-analysis included a comparing group (supported counseling and monitoring). Several advantages arise in the use of psychological therapies for people with psychosis in several phases of the illness. First, the importance of addressing symptoms from the onset of the illness will improve the course of the illness. In recent years there has been interest in focusing attention on this population, creating specific programs for people with a first-episode psychosis. In this context,

the implementation of psychological therapies should be necessary. Second, evidence of positive results regarding the implementation of CBT and CRT therapies has been demonstrated in early intervention in the care of people with psychosis. Considering these results, psychological therapies could be added to medication treatment for the improvement of symptoms, adherence, insight and information about the illness. Moreover no evidence was found regarding the potential disadvantages or risks of the implementation of psychotherapy. However, further studies are needed to better identify the specific domains in which psychological therapies will help people with psychosis.

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**S- Editor**: Song XX **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5498/wjp.v5.i4.366

*World J Psychiatr* 2015 December 22; 5(4): 366-378
ISSN 2220-3206 (online)


REVIEW

# Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches

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Author contributions: Coplan JD and Kim Y contributed to the psychopharmacological approaches; Aaronson CJ contributed to the psychosocial approaches; Coplan JD and Aaronson CJ both contributed to the review of literature, discussion and conclusion of this paper; Panthangi V contributed specifically to the psychosocial approaches.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.



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Received: August 20, 2014
Peer-review started: August 24, 2014
First decision: September 28, 2014
Revised: September 26, 2015
Accepted: November 3, 2015
Article in press: November 4, 2015

Published online: December 22, 2015

## Abstract

Comorbid anxiety with depression predicts poor outcomes with a higher percentage of treatment resistance than either disorder occurring alone. Overlap of anxiety and depression complicates diagnosis and renders treatment challenging. A vital step in treatment of such comorbidity is careful and comprehensive diagnostic assessment. We attempt to explain various psychosocial and pharmacological approaches for treatment of comorbid anxiety and depression. For the psychosocial component, we focus only on generalized anxiety disorder based on the following theoretical models: (1) "the avoidance model"; (2) "the intolerance of uncertainty model"; (3) "the meta-cognitive model"; (4) "the emotion dysregulation model"; and (5) "the acceptance based model". For depression, the following theoretical models are explicated: (1) "the cognitive model"; (2) "the behavioral activation model"; and (3) "the interpersonal model". Integration of these approaches is suggested. The treatment of comorbid anxiety and depression necessitates specific psychopharmacological adjustments as compared to treating either condition alone. Serotonin reuptake inhibitors are considered first-line treatment in uncomplicated depression comorbid with a spectrum of anxiety disorders. Short-acting benzodiazepines (BZDs) are an important "bridging strategy" to address an acute anxiety component. In patients with comorbid substance abuse, avoidance of BZDs is recommended and we advise using an atypical antipsychotic in lieu of BZDs. For mixed anxiety and depression comorbid with bipolar disorder, we recommend augmentation of an antidepressant with either lamotrigine or an atypical agent. Combination and augmentation therapies in the treatment of comorbid conditions vis-à-vis monotherapy may be necessary for positive outcomes. Combination

therapy with tricyclic antidepressants, gabapentin and selective serotonin/norepinephrine reuptake inhibitors (*e.g.*, duloxetine) are specifically useful for comorbid chronic pain syndromes. Aripiprazole, quetiapine, risperidone and other novel atypical agents may be effective as augmentations. For treatment-resistant patients, we recommend a "stacking approach" not dissimilar from treatment of hypertension In conclusion, we delineate a comprehensive approach comprising integration of various psychosocial approaches and incremental pharmacological interventions entailing bridging strategies, augmentation therapies and ultimately stacking approaches towards effectively treating comorbid anxiety and depression.

**Key words:** Generalized anxiety disorder; Cognitive behavioral therapy; Treatment-resistant mood disorders; Bipolar disorder comorbid with anxiety; Augmentation strategies; Major depressive disorder



**Core tip:** A comprehensive diagnostic assessment is a critical first step in treating patients with mixed anxiety and depression. Practitioners should be alert to the possibility that this may be a concealed bipolar disorder since misdiagnoses rates can be 70%. Treatment in the patient with uncomplicated non-substance-abusing unipolar disorder may be quite straight forward. However patients are in all likelihood treatment-resistant with probable bipolarity and substance abuse. In the latter instance, more complex regimen of medications with combinations of pharmacotherapy are required. Finally, a "stacking" approach, to cover the full spectrum of available receptors targeted by current pharmacotherapy regimens is recommended.

Coplan JD, Aaronson CA, Panthangi V, Kim Y. Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches. *World J Psychiatr* 2015; 5(4): 366-378 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/366.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.366

## INTRODUCTION

The article reviews the comorbidity of anxiety and mood disorders, with a primary focus on treatment. For the psychosocial component, we will only focus on the comorbidity of generalized anxiety disorder and major depressive disorder, as a focus on each anxiety disorder would exceed the scope of the current article. However, for the psychopharmacological component, we focus on mood disorders comorbid with the gamut of anxiety disorders. It should be noted that for psychosocial treatments, many of the principles are common to treatment of a spectrum of disorders whereas in psychopharmacology a precise choice of medications may be required for specific presentations.

## PSYCHOSOCIAL APPROACHES TO COMORBIDITY OF GENERALIZED ANXIETY DISORDER AND MAJOR DEPRESSIVE DISORDER

Generalized anxiety disorder (GAD) is the most common anxiety disorder in primary care[1] and has a lifetime prevalence of 5.1% or possibly higher[2]. Major depressive disorder (MDD) has, by certain estimates, a lifetime prevalence of 16.2%[3]. The prevalence of the comorbidity of GAD and MDD is as follows; 62% of individuals with GAD also had an MDD episode in their lifetime[4], while 59% had the episode of MDD in the past year[5] and comorbidity of GAD and MDD predicts a poor outcome[6].

## THEORETICAL MODELS

In the current article, we describe a range of alternative yet complementary theoretical models of the comorbidity of GAD and MDD. The theoretical models of GAD include: (1) the Avoidance Model of GAD first advanced by Borkovec *et al*[7]; (2) the intolerance of uncertainty (IU) model[8]; (3) the metacognitive therapy model (MCT)[9]; (4) the emotion dysregulation model[10]; and (5) the acceptance-based model[11]. The theoretical models of MDD include: (1) the cognitive model[12]; (2) the behavioral activation model[13]; and (3) the interpersonal model[14].

## THE AVOIDANCE MODEL OF GAD

In the Avoidance Model of GAD, worry is considered a language- and thought-based activity, which activates somatic and emotional sensations at the same time inhibiting mental images. According to this model, when somatic and emotional experiences are inhibited, emotional processing of fear and avoidance is poorly achieved; which is important for habituation and extinction. This model proposes that worry is "a poor attempt to solve problems and deal with a perceived threat while avoiding the aversive somatic and emotional experiences that occur when confronting the feared stimulus"[15]. On the contrary, "worry becomes negatively reinforced as less distressing thoughts replace catastrophic mental images reducing somatic and emotional experiences"[15]. Here, "worry is maintained by positive beliefs about worrying"[15].

Treatment models that were developed based on the Avoidance Model focus on "self-monitoring of situations, thoughts, feelings, physiological reactions and behaviors"[15]. In addition, the other components include "progressive muscle relaxation exercises and breathing retraining; self-control desensitization such as imaginal practice to develop different, more effective ways of

coping; specific "worry time" which leads to gradual stimulus control; monitoring of worries including what situations are feared, what outcome is feared and what outcome actually occurs; present moment focus and expectancy-free living (realistic expectations)"[15].

The integrative therapy component[16] is associated with the interpersonal problems that are frequently involved in the content of worry which were not included in previous cognitive behavioral therapy (CBT) protocols. This added component to the therapy specifically focuses on interpersonal problems and avoidance of emotions. The results of a comparative study show an effect size of 2.80 for the avoidance CBT model alone and 3.15 for CBT + I/EP (Interpersonal and emotional processing therapy). The response percentage after treating with CBT + SL (supportive listening) was 67% whereas it was 83% with CBT + I/EP.

### *IU model*

The IU model is based on the hypothesis that in individuals with GAD, "uncertain or ambiguous situations are very stressful or uncomfortable and can lead to chronic worry"[15]. According to this model, beliefs about worry include "the idea that worry will prevent some dreaded outcome or prepare the individual in some way for the dreaded outcome"[15]. This model also suggests that individuals have a "negative problem orientation" and engage in "cognitive avoidance" both of which maintain the worry. In negative problem orientation, individuals have "lack of confidence in the ability to solve problems"[15] and, moreover, "problems were perceived as threats and individuals have low frustration tolerance when dealing with problems and become pessimistic about the outcome"[15]. Cognitive avoidance is associated with thought replacement, thought distraction and thought suppression.

The treatment methods that were developed based on the IU model include components like self-monitoring; psycho-education about problem orientation; evaluating worry beliefs; cognitions about core fears that underlie worries; restructuring and exposure and improving problem orientation by cognitive restructuring (CR). The results of IU studies showed that 77% of individuals did not meet criteria for GAD at 6 and 12 mo post-treatment[17].

Dupuy *et al*[18] examined whether comorbid GAD/MDD individuals experienced significantly more IU compared to GAD only individuals. In this sample, the comorbid group differed in severity of GAD symptoms; in addition, they demonstrated greater IU, poorer problem orientation, and higher levels of cognitive avoidance. There was no difference in the level of beliefs about worry (both had similar positive beliefs about worry). This study demonstrates that the comorbid condition adds to the severity of symptoms compared to the GAD only condition.

### *MCT*

The MCT makes distinction between two types of worries known as type 1 and type 2. Type 1 worry is related to "positive beliefs about worry, which helps to cope with, prevent or prepare for dreaded events"[15]. Type 2 worry is related to beliefs about worry that are negative where there is "worry about worry" and here, worry is uncontrollable, and/or considered dangerous. The "ineffective strategies associated with type 2 worry are checking behaviors, thought suppression, distraction, avoidance and reassurance seeking"[15]. These strategies interfere with questioning the validity of beliefs which will increase symptoms of anxiety thus maintaining the worry. The treatment methods that were developed based on the MCT involve exploring worry triggers, and reactions as well as efforts to control/suppress worry; socialization involving psycho-education which focuses on altering beliefs about worry instead of lessening worry directly and thought correction of beliefs about worry, both negative and positive.

The results of an open trial utilizing MCT show that at post-treatment 87% recovered and 75% of individuals maintained symptom recovery after 12 mo of treatment[19]. In a randomized trial, Wells *et al*[20] treated GAD patients with either MCT or applied relaxation (AR) with similar results: 80% recovered at post-treatment compared to 10% in AR; 70% maintained MCT response after 6 mo compared to 10% in the AR condition.

### *The emotion dysregulation model*

The emotion dysregulation model is based on the premise that "individuals with GAD experience their emotions more intensely and/or more easily and quickly and have poor understanding of their emotions, negative attitudes about emotions and maladaptive emotional regulation and management strategies"[15]. The treatment methods that were developed based on the emotion dysregulation model seeks to improve emotional regulation as a means to improve GAD symptoms. The components include: relaxation exercises; reframing of beliefs; education about emotions; emotion skills training and experiential exposure exercises. An open label study results have demonstrated 66.7% of participants ($n$ = 21) achieved high end state functioning while 81%-95% experienced significant reduction in mood, worry and other GAD symptoms[21].

### *The acceptance based model*

The Acceptance based model is based on Hayes' model of experiential avoidance[22] and Borkovec's avoidance model[7], both of which deal with a problematic relationship with internal experiences and experiential avoidance and behavioral restriction. In this model, worry is defined as behavioral and cognitive avoidance of internal experiences. Whereas avoidance reduces short-term distress, it reinforces long-term behavioral restriction. The treatment methods that were developed based on the acceptance model comprises psycho-education about worry, avoidance, the reduction in valued

action, how emotions function and how to promote valued actions; mindfulness and acceptance exercises along with present moment awareness with the ultimate goal of behavioral change and valued actions. The results of a study demonstrate that 75% show response to treatment, whereas 62.5% of individuals meet "end-state high functioning" post-treatment[23].

## CONSIDERATION OF PSYCHOLOGICAL CONSTRUCTS

Regarding psychological constructs of comorbid GAD and MDD, Fresco *et al*[24] have compared the scores of Penn State Worry Questionnaire (PSWQ), Response Style Questionnaire and Mood and Anxiety Symptom Questionnaire in college students and developed a four-factor solution comprised of two worry factors and two rumination factors which have a significant positive correlation to anxiety and depression. According to that study, excessive and/or pathological worry is not exclusive to anxiety disorders. The GAD group experienced higher levels of worry, including co-morbid GAD/MDD, than MDD alone group. However, the MDD group alone had higher PSWQ scores than a group comprised of non-GAD anxiety disorders[25]. In contrast, rumination is a cognitive, verbal activity associated with MDD[26]. Thus, both worry and rumination factors are separate and distinct cognitive processes but both have significant relationships to depression and anxiety[24].

Clark *et al*[27] propose their own model which is a modified cognitive neurophysiological model of anxiety and depression in which maladaptive schemas of the self, the surrounding environment and the future are activated through life experiences that lead to biases in information processing and negative, pessimistic or threat-related thoughts, images or interpretations.

## MDD MODELS

### *The cognitive model*

The cognitive model of MDD pioneered by Beck[12] is based on the "cognitive triad of defective, inadequate, diseased or deprived (worthless)"[15] thoughts; the "tendency to interpret experiences in a negative way and the pessimistic future with hopelessness"[15]. The treatment methods that were developed based on the cognitive model focus on the use of rating scales: to monitor mood as well as to record thoughts; and the use of techniques such as CR of dysfunctional thoughts, progressive muscle relaxation exercise, role playing and assertiveness training. The treatment was designed to be short-term, from 12 to 16 wk, beginning with an explanation of the rationale (cognitive triad), awareness of the connection between thoughts, feelings and actions, active engagement in correcting cognitive distortions and encouraging the reinstatement of previously avoided activities.

A meta-analysis of randomized controlled studies of CBT for depression has demonstrated an effect size of 0.90 when compared to a wait-list group, 0.40 when compared to treatment as usual or attention placebo[28]. When compared to medication, CBT was just as effective[29].

### *The behavioral activation model*

The behavioral activation (BA) model of MDD is based on the early work by Lewinsohn *et al*[30], which demonstrates that depressed individuals have decreased access to pleasant events. The avoidance of positive activity leads to further low mood. The treatment method includes mood and event monitoring (daily pleasant/unpleasant), scheduling of activities, with an emphasis on development of social and time management skills. Patients are encouraged to pursue pleasant activities and to tell themselves that if they do the activity they will feel better, bringing the reward more proximal. They also tell themselves how much worse they will feel if they do not engage in the activity. There is also discussion of problem behaviors with an emphasis on problem solving.

The BA model was tested for efficacy compared to cognitive therapy (CT) and paroxetine and pill placebo in a 16-wk trial. The BA group did just as well as the paroxetine group, but better than the CT group in severely depressed participants[31]. A meta-analysis of activity scheduling[32], a major component of BA, found an effect size of 0.87 compared to a control condition after treatment for depression, but in the same analysis found no significant difference when compared to CT.

### *The interpersonal psychotherapy model*

The interpersonal psychotherapy (IPT) model of MDD is based on Sullivan's interpersonal theory[33] in which "interpersonal relationships play an important role in onset and maintenance of MDD"[15]. This model focuses on interpersonal functioning, which includes unresolved grief, interpersonal disputes, role transitions and social isolation or withdrawal.

IPT, initially a time-limited, weekly outpatient treatment for depressed patients, focuses on the connection between onset of symptoms and current interpersonal problems in the treatment. The first of the three phases of IPT treatment, usually during sessions 1-3, includes diagnostic evaluation and psychiatric history and sets the framework for the treatment. In the middle phase, strategies specific to the interpersonal problem area are pursued. During the final phase, usually the last few sessions, the patient is encouraged to recognize and consolidate therapeutic gains and to develop ways of identifying and countering depressive symptoms should they arise in the future.

The NIMH Treatment of Depression Collaboration Research Program (TDCRP) compared the effectiveness of CBT, IPT and imipramine[34]. Amongst those who completed treatment, 65% responded to CBT, 70% responded to IPT, 69% responded to imipramine while

**Table 1 Descriptions of studies conducted in support of theoretical model**

| | *n* | Treatments | Diagnosis | Response rates |
|---|---|---|---|---|
| Avoidance model | | | | |
| Integrative therapy | 24 | CBT + SL *vs* CBT + I/EP | GAD | CBT + SL = 66.7% |
| Newman *et al*[16] | | 14 sessions | | CBT + I/EP = 83.3% |
| Intolerance of uncertainty model | | | | |
| Ladouceur *et al*[81] | 26 | CBT *vs* wait list | GAD | CBT = 77% |
| Metacognitive model | | | | |
| Wells and King[19] | 10 | MCT | GAD | 87.5% |
| | | | | MCT = 80% |
| Wells *et al*[20] | 20 | MCT *vs* AR | GAD | AR = 10% |
| Acceptance based model | | | | |
| Roemer *et al*[23] | 31 | ABBT *vs* wait list | GAD | ABBT = 78% |
| | | | | Wait list = 17% |
| TDCRP | | | | |
| Elkin *et al*[34] | 50 | CBT | | CBT = 40%; 58% |
| | 56 | IPT | MDD | IPT = 47%; 60% |
| | 49 | IMI-CM | | IMI = 49%; 61% |
| | 50 | PLA-CM | | PLA = 26%; 50% |
| Cognitive model | | | | |
| Thoma *et al*[28] (meta-anlaysis) | 29 | CBT *vs* wait list | MDD/minor depression/dysthymia | ES = 0.90 |
| | 18 | CBT *vs* TAU | | ES = 0.40 |
| | 26 | CBT *vs* other[1] | | ES = 0.05 |
| | 23 | CBT *vs* medication | | ES = 0.10 |
| Behavioral activation | | | | |
| Dimidjian *et al*[31] | 45 | CT | | High severity |
| | 43 | BA | MDD | CT = 56%; 48% |
| | 100 | ADM | | BA = 60%; 76% |
| | 53 | PLA | High and low severity | ADM = 40%, 49% |
| Interpersonal psychotherapy model | | | | 26 wk |
| Peeters *et al*[37] | 63 | CT | MDD | CT = 41%; ES = 1.3 |
| | 56 | IPT | Nonrandomized trial | IPT = 39%; ES = 1.5 |
| | 34 | CT-PHT | | CT-PHT = 35%; ES = 1.0 |
| | 21 | IPT-PHT | | IPT-PHT = 33%; ES = 1.0 |

First percentage refers to response rates using Hamilton Rating Scale of Depression while second refers response rates using Beck Depression Inventory. [1]Other treatments include psychodynamic, behavior, humanistic and interpersonal psychotherapy. CBT: Cognitive behavior therapy; SL: Supportive listening; I/EP: Interpersonal and emotional processing; MCT: Metacognitive therapy; AR: Applied relaxation; ABBT: Acceptance-based behavior therapy; IPT: Interpersonal therapy; IMI-CM: Imipramine plus clinical management; PLA-CM: Placebo plus clinical management; TAU: Treatment as usual; ADM: Antidepressant medication; PHT: Pharmacotherapy.

51% responded to placebo. Amongst those who were in the "intent to treat" group, 49% responded to CBT, 56% responded to IPT, 53% responded to imipramine while only 40% responded to placebo. Imipramine demonstrated greater efficacy for severe MDD rather than IPT in this sample, whereas in less severe MDD, all the groups were equivalent. When comparing medication discontinuation to both cognitive approaches and BA, both are effective in relapse prevention[35], however, BA was more effective than cognitive therapies in severe MDD[36].

A Dutch study[37] offered MDD patients the choice of treatment: CT or IPT with or without antidepressant medication with the collaboration of their clinician. Treatment duration was up to 26 wk. At 8 wk, only 20% remitted based on Beck Depression Inventory, but by 26 wk 35% remitted. All the treatments were similarly effective, even the combination of antidepressants and therapy with effect sizes ranging from 1.3 to 1.5.

DeRubeis *et al*[29], after concerns about how well the CT was administered in the TDCRP trial, tested the effectiveness of CT and antidepressant medication (paroxetine or desipramine) *vs* placebo for 16 wk in a group of depressed individuals. The results showed that both active treatments were superior to placebo at 8 wk and at 16 wk and were equivalently effective.

A listing of all the research studies conducted on the various theoretical modals can be found in Table 1.

## COMPARISON OF PSYCHOSOCIAL MODELS

There are differences and similarities in all the models described above. The most notable differences include: the emotional dysregulation and the acceptance models focuses on emotional experience and exposure respectively, the CBT and the intolerance model focuses on cognitions (worries), the BA model focuses on behavior but not on CR whereas the IPT model focuses on relationships *via* behavior without any emphasis on CR. In contrast, the most notable similarities for all the models described above include the components: psycho-education, homework, CR, progressive muscle relaxation exercises and exposure.

There are many studies comparing the effectiveness

of two different types of psychosocial treatments as well as meta-analyses for response in specific disorders, such as major depression. A full inclusion of all such studies is beyond the scope of this article, but a few salient studies will be covered. Hofmann and Smits[38] conducted a meta-analysis of CBT randomized controlled studies for all adult anxiety disorders which revealed that those who completed any form of CBT were four times more likely to respond than those who were given a placebo treatment (usually a sham treatment). Hunot *et al*[39] conducted a meta-analysis of CBT treatment for GAD and found that in comparison to treatment as usual or waiting list, CBT was more effective; but when CBT was compared to supportive psychotherapy, both were equally as effective suggesting that active treatment is more effective than no treatment but good treatment is generally similarly effective.

Arch *et al*[40] compared CBT *vs* acceptance and commitment therapy (ACT) in a randomized controlled trial of 128 individuals for mixed anxiety and depression demonstrating that both were effective in reducing anxiety and improving mood with similar gains maintained at 12-mo follow-up. Although both were effective, the authors concluded that the treatments targeted different mechanisms; namely that CBT improved quality of life and ACT improved psychological flexibility.

In a study of relapse prevention[41], participants who had remitted from at least three previous episodes of MDD, were randomized to mindfulness-based cognitive therapy (MBCT), an active comparison treatment similar to MBCT except without meditation called cognitive psychological education or treatment as usual (continuing on medication and regular clinical visits). The follow-up period was 12-mo with the results that both active treatments were effective in preventing relapse but the MBCT group was most effective for individuals with significant trauma history.

Yovel *et al*[42] compared the core components of CBT and ACT in an attempt to understand how each of the treatments work. CR in CBT and cognitive diffusion (CD) in ACT are the core elements that target rumination and worry in both GAD and MDD. CR works to logically evaluate each thought and change the thought while CD works to accept the thoughts and not change them. In this study of 142 individuals, subjects were asked to identify a distressing thought through the recall of a sad, autobiographical event. After an induction task for rumination regarding the thought, they completed one of four brief interventions using either analogue CR, CD or a control intervention that included either distraction from the distressing thought or an exploration of different aspects of the thought. Results demonstrated improvement in mood about equally in both CR and CD - neither was superior to the other.

Thoma *et al*[28] conducted a meta-analysis comparing CBT to a second treatment, *e.g.*, psychodynamic or medication for major depression and/or dysthymia, with an added focus on quality of research conducted. This meta-analysis employed a rating system to evaluate methodological quality of the trials. The authors were surprised to discover that certain CBT studies, especially early ones, had "poor" quality which clearly detracted from the effect size. From 120 studies, in the regression analysis, there were four groups: CBT *vs* waiting list; CBT *vs* attention control or treatment as usual; CBT *vs* another treatment; CBT *vs* medication. They found that there was no significant difference in outcome between CBT and another treatment (*e.g.*, psychodynamic treatment) with the caveat that many of the studies were of poor quality.

## CHOOSING A MODALITY

In general terms, we would advocate BA and medication as the first-line treatment for severe MDD/GAD or other mixed anxiety and mood states. For moderate to mild MDD/GAD there is no evidence supporting an intervention order. Depending on what clients describe as their primary problem (*i.e.*, anxiety or depression), we would advise focusing on interventions targeting that particular aspect of the comorbid condition. Since most of the studies comparing head-to-head modalities for anxiety or depression have demonstrated fairly similar effectiveness, we are not recommending any particular modality. Often the choice is based on what modality the clinician is most proficient or comfortable conducting. What is yet missing from the research literature is which treatment method is most effective for a particular patient. Until that is known, any of the modalities detailed in this article have demonstrated effectiveness when conducted by a knowledgeable clinician. Medication may be combined with psychotherapy and the discussion of those approaches follows.

## PHARMACOLOGICAL APPROACHES TO COMORBID MOOD AND ANXIETY DISORDERS

### *Treating anxiety and depression*

Treating anxiety comorbid with mood disorders requires an adjustment of pharmacological approaches when compared to treating only anxiety or only depression. We discuss how anxiety disorders may manifest with variations of depression and how we should adapt pharmacotherapy for a range of situations that may be encountered. Conversely, when patients are being treated for bipolar disorder or major depression, anxiety disorders commonly go unnoticed. For instance, data obtained from the first 500 participants in the systematic treatment enhancement program for bipolar disorder indicated that lifetime comorbid anxiety disorders were extremely common, occurring in over one-half of the sample. Bipolar disorder comorbid with anxiety disorders was associated with younger age at onset, decreased likelihood of recovery, poorer quality of life, less time euthymic, and greater likelihood of suicide attempts[43]. In one study, panic disorder (PD) occurred

at higher rates in patients with bipolar compared to unipolar mood depression[44]. Similarly, in cross-national epidemiological surveys, patients with major were shown to be at increased risk for comorbidity with substance abuse and anxiety disorders at all sites[45].

### *Diagnostic considerations*

First, we need to pay attention to the evidence for major depression comorbid with significant anxiety. Sub-syndromal symptoms of either anxiety or depression should be noted. Not all anxiety falls into diagnostic categories but may be non-specific[46]. Positive family history of anxiety and/or depression will corroborate the diagnosis. Bipolar disorder commonly causes anxiety and depression symptoms. Therefore, a family history of bipolar disorder should raise a red flag for covert bipolarity in the patient. Non-response to previous treatments should also serve as an alert for covert bipolarity. Finally, comorbid substance abuse needs independent treatment but will also direct pharmacotherapy[47].

## PHARMACOTHERAPY FOR THE ANXIETY DISORDER COMPONENT

### *Addressing initial anxiety*

For uncomplicated cases, to achieve rapid control of anxiety symptoms in patients without substance abuse, use of a benzodiazepine (BZD) may still constitute the best option. Long half-life BZDs such as clonazepam or alprazolam XR are favored and reduce the likelihood of "mini-withdrawal" symptoms. Careful titration is always necessary, so we recommend starting at a dose of 0.5 -1.0 mg/d (or lower) for each of the aforementioned medications and double following 3 d. Night time dosing is preferred because it minimizes side effects. We advocate use of immediate release BZDs, such as alprazolam, on an as needed basis (PRN), for panic attacks or panic-inducing social situations. BZDs are an important "bridge strategy" since antidepressant onset of action will generally take 3-4 wk; (perhaps the duration of onset may be shorter for vilazodone, although studies are conflicting). The extent of use of PRN dosing serves as an indicator of the extent of increase necessary for the standing BZD dose[48].

For patients whose course is complicated by substance abuse, instead of using a BZD, we advise using an atypical antipsychotic for comorbid anxiety. Quetiapine is the only atypical antipsychotic, to our knowledge, to be shown effective in GAD as monotherapy at 50 mg QD[31]. Lower doses can be used (start at 25 mg QHS, go to 75 mg QHS over 5 d, or even lower). Doses may have to be raised to 400 or even 600 mg in certain patients. Other atypical agents require further study. Weight "neutral" atypical agents, for example, lurasidone, are in need of further investigation. Quetiapine XR shows, to our knowledge, no advantage over the generic form of quetiapine[49].

### *Antidepressant strategies*

The selective serotonin reuptake inhibitors (SSRIs) are probably the treatment of choice in treating depression and a gamut of comorbid anxiety disorders. The most used SSRI is escitalopram. Long-term problematic side effects include sexual side effects and weight gain. Although sexual side effects were initially viewed as uncommon with SSRI's, certain critical reviews have cited rates of > 80% of subjects experiencing some form of sexual side effect[50]. In another independent study, paroxetine showed the highest incidence rate of overall sexual dysfunction (64.71%) which was followed by fluvoxamine (58.94%)[51]. Although weight gain is frequently observed with prolonged SSRI treatment in clinical practice, a paucity of systematic data gathered over an extended period are available. In over 20000 adult patients who began receiving a medication of interest with available weight data over a 12 mo period, compared with citalopram, when adjusting for sociodemographic and clinical features, significantly decreased rate of weight gain was observed among individuals treated with bupropion, amitriptyline and nortriptyline; the latter two tricyclics have long been associated with weight gain, suggesting SSRI's are associated with greater weight gain than the older tricyclics antidepressants[52]. A meta-analysis of available studies suggested weight gain with paroxetine but not other SSRIs although only short-term data were available on certain SSRIs (*e.g.*, fluoxetine[53]). There is now a restriction by the FDA on citalopram doses above 40 mg per day due to QT interval prolongation although the relevance of this warning to escitalopram is unclear. We recommend starting at 5-10 mg/d and aim for a final dose of 10-30 mg/d with escitalopram. All anxiety disorders, with the exception of specific anxiety disorder, respond to SSRIs and SSRIs have been FDA approved for their treatment[54].

Vilazodone is a novel compound - an SSRI + 5-HT1$_A$ partial agonist. The 5-HT1$_A$ partial agonist binding is reportedly seven times more potent than buspirone[55]. Although the mechanisms are unknown, data to date indicate weight neutrality and much lighter burden for male and female sexual side effects. For this reason, Vilazodone may conceivably displace SSRIs as a first line. The dosing starts at 10 mg/d and is raised to 40 mg/d although lower doses may be effective. Vilazodone is only approved for depression, but in our hands it has worked as an excellent anxiolytic in GAD and PD with comorbid MDD[56].

Serotonin norepinephrine reuptake inhibitors (SNRIs) as a first line choice for comorbid GAD and MDD are a perfectly legitimate choice. We specifically recommend the use of duloxetine for comorbid fibromyalgia, osteoarthritic back pain or, for that matter, any other form of pain. The starting dose is 20-30 mg/d and the prescriber should aim for 60-120 mg. Other SNRIs, such as venlafaxine acts like an SSRI up to a dose of 150 mg/d and only then manifests noradrenergic reuptake properties. Des-venlafaxine may have fewer side

effects[57].

### *Pharmacotherapy of the bipolar patient with mixed anxiety/depression*

Frequently a patient with bipolar disorder presenting with mixed anxiety and depression is on an antidepressant. Bipolar disorder can be comorbid with any of the anxiety disorders and is frequently comorbid with substance abuse (approximately 70%)[58]. Approximately 70% of bipolar disorders are misdiagnosed[59] and if it is not appreciated that a patient has bipolar disorder, the patient will, in all likelihood, remain treatment-resistant. Although controversial, we generally recommend not discontinuing the antidepressant, but rather recommend augmentation of the antidepressant with a medication with mood-stabilizing properties. Bipolar patients are less likely to respond to psychotherapy including CBT, yet psychotherapy is an integral part of stabilization[60].

## LAMOTRIGINE

Lamotrigine works especially well for a hypomanic/anxious or depressed presentation although data for this position is scant. Slow dosage increase, a major disadvantage, is recommended to avoid maculopapular rashes and Steven-Johnson syndrome. For example, increasing dose from 25 mg/d up to 200 mg/d at weekly increases of 25 mg is recommended which takes a total of 8 wk. Bridging strategies include using BZDs and use of concomitant atypical antipsychotics is frequently indicated. Lamotrigine does not show any evidence of efficacy for any specific anxiety disorder. A major drawback of lamotrigine is the remote risk of a rash secondary to Steven-Johnson's syndrome but low weight gain or sexual side effects have been documented[61].

### *Atypical antipsychotics*

The risks *vs* benefits of atypical antipsychotics need to be weighed whenever using this class of drug in patients with mood and anxiety disorders. We have reviewed the risk of tardive dyskinesia in a long-term follow-up study of patients treated with atypical antipsychotics for mood and/or anxiety disorders[62]. Although the risk was significant, in most instances it resolved following cessation of the offending agent.

### *Aripiprazole augmentation*

Aripiprazole is FDA approved for augmentation of an antidepressant for partially responsive depression. Aripiprazole can be effectively used in a unipolar mixed anxiety/mood disorder patient who is not doing adequately well and is FDA-approved for the maintenance of bipolar disorder should a bipolar component be suspected. Aripiprazole works well for patients with bipolar mixed anxiety/depression, especially while waiting for lamotrigine to work. The onset of aripiprazole action is rapid (1-2 wk). Starting with low dosages (1-2 mg) is recommended, to avoid intolerable akathisia. The dosage goal is 5-10 mg per day, but is not imperative. The major downfall is weight gain; even at mini-doses (few are spared). Weight gain is associated with metabolic complication such diabetes mellitus. However, aripiprazole is known to cause less weight increase and metabolic burden than other second-generation antipsychotics[63]. The anxiolytic effects of aripiprazole as an augmentation are not, to our knowledge, specific to any anxiety disorders[64].

## QUETIAPINE AUGMENTATION

Quetiapine is FDA approved as a monotherapy for bipolar depression and has also been shown to be equivalently effective to duloxetine in unipolar depression[65]. Efficacy for GAD has been demonstrated but was rejected by the FDA for unclear reasons. We previously presented an abstract that quetiapine was effective for PD as an add-on. Sedation, an important side effect due to potent anti-histaminergic ($H_1$) effects, can be handled by careful titration. The sedating side effect of quetiapine and also olanzapine can be beneficial to patients who suffer from insomnia. Quetiapine also is reported to show less extra pyramidal effect. If one maintains low doses (< 200 mg/d), metabolic consequences and weight gain can be significantly averted in certain patients[66].

## OTHER ATYPICALS AGENTS USED FOR BIPOLAR DISORDER, ANXIETY DISORDERS AND MDD

Risperidone, a potent $D_2$ receptor antagonist, is a treatment option for augmenting SSRIs for obsessive compulsive disorder (OCD) but is an "unforgiving" weight-gainer even at low doses. Ziprasidone is approved for maintenance of bipolar disorder and its utility remains limited. Olanzapine is FDA approved for bipolar depression and is used as an add-on in GAD studies. Olanzapine has amongst the worst metabolic profiles but can be considered if choices are limited. Paliperidone has been better tolerated than risperidone in specific cases and has excellent antimanic properties[67].

### *Newer atypicals agents*

Lurasidone, along with $D_2$ and $5HT_{2a}$ antagonist properties, is a $5HT_7$ antagonist and has a favorable metabolic profile. Lurasidone does not need to be titrated and is useful if an additional atypical is necessary. It has recently been approved for bipolar depression. Anxiolytic effects of $5HT_7$ antagonists have been documented preclinically and a role for mixed anxiety/depression is envisaged. Asenapine is also a $5\text{-}HT_7$ antagonist and $5\text{-}HT_{1A}$ partial agonist. Asenapine has to be given sublingually BID and is approved for bipolar disorder. Iloperidone is a basic $D_2/5HT_{2a}$ antagonist but also has $D_3$ antagonist properties. It is only approved for schizophrenia but bears similarity to sulpiride in its

receptor binding profile; the latter has been used for decades for mood disorders[68]. Its future role is unexplored.

### *Anticonvulsant agents - gabapentin*

Gabapentin is useful in patients with anxiety disorders comorbid with substance abuse disorders but does not have antidepressant properties. Gabapentin, effective for GAD and social anxiety disorder (SAD), may have modest mood stabilizing properties, improves sleep quality, and me be very useful for comorbid chronic pain syndromes such as irritable bowel syndrome, fibromyalgia, interstitial cystitis, prostatitis and vuvlvodynia. Gabapentin necessitates combination with a high potency BZD or SSRI for PD or combined with an SSRI for OCD[69].

### *Buspirone*

Buspirone is only effective in GAD. Buspirone does not have antidepressant effects or efficacy for any other anxiety disorders. In fact, buspirone is useful as a "placebo" prescription, with attendant ethical implications, and perhaps has some value as an augmenting agent to an antidepressant. Buspirone, moreover, has minimal side effects and minimal withdrawal[70].

### *Antidepressants- tricyclic antidepressants*

Tricyclic antidepressants (TCAs) cover both depression and certain anxiety disorders including GAD and PD. However, TCAs are ineffective in SAD and post traumatic stress disorder where SSRIs are required. OCD can be treated with clomipramine which is a TCA with selective serotonin and norepinephrine reuptake inhibitor properties.

Side effects of TCAs stem from its anticholinergic and antimuscarinic properties. TCAs are also dangerous in overdose and produce cardiac conduction defects in patients with differing degrees of heart block. However, TCAs are especially useful in patients with functional pain syndromes such as irritable bowel syndrome, fibromylagia and neuropathic pain, probably by virtue of their noradrenergic reuptake blockade effects. In addition, TCAs promote sleep integrity which is key to treating disorders such as fibromyalgia and chronic fatigue syndrome[71]. Functional pain syndromes are especially comorbid with mixed anxiety and depression and can be comorbid with bipolar disorders.

### *Monoamine oxidase inhibitors*

Monoamine oxidase inhibitors (MAOIs) are now generally outmoded. They have become unpopular because of dietary restrictions and the risk of tyramine-induced hypertensive crisis. They can cause significant weight gain, especially phenelzine. However, prior to SSRIs, MAOIs were uniquely effective for SAD and atypical depression. Newer agents (selegiline patch) do not require diet restriction but are restricted by the low dosage recommendations. A major downfall of the MAOIs is that, because of the risk of serotonin syndrome, patients have to undergo a 2-wk washout (4 wk with fluoxetine) of other antidepressants[72]. Nevertheless, MAOIs may serve as the treatment of choice for treatment-resistant depression in its later stages and might be suitable for certain subtypes of depression such as atypical depression, anergic bipolar depression and anxious/phobic-associated depression[73]. It has been advised that the risk-benefit ratio is optimally managed not by avoiding MAOIs but rather, by assessing and discussing safety measures in a direct and continuous manner. Careful attention to medication storage and administration and securely controlling dosages and quantities of pills is recommended. Certain authors have opined that there may well be a greatly less occurrence of treatment-resistant depression if more practitioners were willing to prescribe optimal therapeutic doses of MAOIs[74].

### *Buproprion*

Buproprion is an effective antidepressant but it does not have specific anti-anxiety effects for PD, OCD or SAD. Buproprion may have a non-specific anxiolytic effect, but it has an excellent side effect profile by not inducing weight gain or sexual side effects. Thus, the weight gain and sexual side effects that are implicit to SSRI treatment, is obviated. Treating depression with buproprion can be performed, but for GAD, PD or SAD, concomitant high-potency long-acting BZDs are necessary[75].

## SPECIFIC SCENARIOS

### *The treatment resistant mixed patient*

If patients are resistant to treatment and show mixed anxiety/depression symptoms, patients may well suffer from a bipolar disorder. Then, having patients on a combination of an SSRI, lamotrigine and aripiprazole can be considered. In our experience, many treatment-resistant patients will respond to this combination of therapies. Regarding the use of antidepressants in bipolar disorder has been controversial. The 2002 American Psychiatric Association (APA) guidelines for the treatment of bipolar disorder recommended a more conservative use of antidepressants, including discontinuation because of the risk of mood cycling. The Munich group published a critique of the recommendations of the APA guidelines indicating that anticonvulsants when used as monotherapy in the absence of antidepressants have not been demonstrated to exhibit antidepressant properties[76]. Certain authors, including experts such as Ghaemi *et al*[77], argue that conceptually and empirically, there is a strong rationale for a cautious approach to antidepressant use in bipolar disorder, consistent with the APA guidelines. Certainly, antidepressant treatment of bipolar depression has been associated with manic switch and cycle acceleration. However, it has been argued that

many clinicians continue to employ antidepressants, especially in the management of severe depression that is unresponsive to mood stabilizers alone[78]. Certainly, in our experience, if antidepressants can be avoided, they should not be used. But in the context of more treatment-resistant mood disorders with comorbid anxiety they may well be necessary although a high level of vigilance for mood cycling is warranted. If the patient is still unresponsive, adding quetiapine without subtracting any medications, which is called a "stacking approach", is advised[79]. Many patients will respond but the side effect load may well become higher, especially weight gain. It is recommended to reserve lithium, because of nephrotoxicity risk, for the most treatment-resistant. If the patient is lithium treatment-resistant, a discussion of ECT should be initiated.

### *Mixed anxiety/depression patient with hypomania from an SSRI*

Frequently, patients with OCD, SAD or PD with comorbid depression may have become manic or hypomanic in the past because SSRIs can induce a mania, a bipolar type Ⅲ pattern. If SSRIs can be avoided, using lamotrigine plus gabapentin for GAD or SAD is encouraged. Otherwise, one has to "cover" for the possibility of a manic occurrence and an example is administering lamotrigine 200 mg/d. Many of these patients will require SSRIs for OCD as no alternatives are available. Vigorous treatment with concomitant CBT is required.

### *The bipolar mixed anxiety/depression patient with ADHD*

Many patients with a bipolar or unipolar mixed anxiety/depression have a childhood history of ADHD that has continued into adulthood. Many of the patients with these diagnoses may have undiagnosed ADHD. ADHD also may contribute to anxiety symptoms. Stimulants may serve as augmenters of antidepressants. However, the practitioner should make sure that comorbid bipolarity is stabilized before using stimulants. For substance-abusing patients, using the prodrug lisdexamfetamine, atomoxetine or guanfacine is recommended[80].

## CONCLUSION

In summary, a careful and comprehensive diagnostic assessment is a critical first step in treating the patient with mixed anxiety and depression. The practitioner should be alert to the possibility that this may be a concealed bipolar disorder since misdiagnoses rates can be 70%. Treatment in the patient with uncomplicated, non-substance-abusing unipolar disorder may be quite straight forward entailing the use of SSRIs and BZDs. However, the norm is far more complex. Patients are in all likelihood, treatment-resistant with probable bipolarity and substance abuse. In the latter instance a much more complex regimen of medications has to be used with careful attention being played to pros and cons of side effects and other comorbidities. Therefore, not infrequently, combinations of pharmacotherapy are required. Finally, a "stacking" approach, as is used in hypertension, to cover the full spectrum of available receptors targeted by current pharmacotherapy regimens is recommended.

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**P- Reviewer**: Castle D, El-Hage W
**S- Editor**: Gong XM **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Psychiatry

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DOI: 10.5498/wjp.v5.i4.379

*World J Psychiatr* 2015 December 22; 5(4): 379-386
ISSN 2220-3206 (online)


REVIEW

# Who says this is a modern disorder? The early history of attention deficit hyperactivity disorder

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Author contributions: Martinez-Badía J has contributed substantially to the conception and design of the study, acquisition of data from historical sources, drafting the article, and final approval of the manuscript; Martinez-Raga J has contributed substantially to the conception and design of the study, acquisition of data from medical sources, drafting the article, and final approval of the manuscript.

Conflict-of-interest statement: Martinez-Badía J reports no conflict of interest. Martinez-Raga J has received fees for serving as a speaker and as an advisory board member for Janssen, Shire, Juste, and Rovi Pharmaceuticals. No sources of funding were used in the preparation, review or approval of this manuscript.



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Received: September 2, 2015
Peer-review started: September 8, 2015
First decision: October 16, 2015
Revised: October 21, 2015
Accepted: December 9, 2015
Article in press: December 11, 2015

Published online: December 22, 2015

## Abstract

Attention-deficit hyperactivity disorder (ADHD) is a complex, heterogeneous and multifactorial neurodevelopmental disorder characterized by persistent symptoms of inattention, hyperactivity and impulsivity. Although the first clinical description of a constellation of symptoms highly resembling to what currently could be diagnosed as ADHD is generally attributed to George F Still in 1902, there are scattered but significant published historical medical, scientific and non-scientific reports, much prior to Still's lectures, of what is currently conceptualized as ADHD. The present report aimed at exploring the early history of ADHD, prior to the 20th century in the medical literature and in other historical sources, to provide clinicians, researchers and other professionals with a better understanding of the roots and current conceptualization of this disorder. It is possible to find clues and highly suggestive descriptions of individuals presenting symptoms resembling what is currently defined as ADHD in the literature, in paintings or in the Bible. However, the earliest medical reports of individuals with abnormal degrees of inattention, distractibility and overactivity date from the last quarter of the 18th century, included in two of the first textbooks specifically on the subject of mental diseases, published by the German Melchior Adam Weikard and the Scottish Sir Alexander Crichton. During the 19th century some eminent physicians from Germany, France or Great Britain, such as Charles West, Thomas C Albutt, Thomas S Clouston, William W, Ireland, John Haslam, Heinrich Neumann, or Désiré-Magloire Bourneville, among others provided clinical depictions of patients that most likely presently would be diagnosed as having ADHD. Whilst some of the children described by Still and his predecessors may have suffered from a variety of neurological and psychiatric disorders, many of these patients showed clear symptoms of ADHD and may present

with comorbid disorders, as it is commonly the case in clinical practice.

**Key words:** Attention-deficit disorder; Hyperactivity; Attention-deficit hyperactivity disorder; Hyperkinetic disorders; History; Concept; 18th century history; 19th century history



**Core tip:** Attention-deficit hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder in children and in adults. Although the conceptualization and diagnosis of this disorder is often controversial it is not a modern invention. There are significant published historical medical, and non-scientific reports of individuals with symptoms of inattention, distractibility and over-activity, prior to the 20th century, since the last quarter of the 18th century. The present paper explores the early history of ADHD in the medical literature and in other historical sources, to gain better understanding of the roots and evolution of the conceptualization of this disorder.

Martinez-Badía J, Martinez-Raga J. Who says this is a modern disorder? The early history of attention deficit hyperactivity disorder. *World J Psychiatr* 2015; 5(4): 379-386 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/379.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.379

## INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder in childhood and highly prevalent in adults, as well[1,2]. Over the recent three decades this complex and heterogeneous disorder, with clearly outlined neurobiological substrates, has been conceptualized as a chronic multifactorial disorder characterized by symptoms of inattention, hyperactivity and impulsivity[3,4]. Along the 20th century, "minimal brain damage", "minimal brain dysfunction", "minimal brain disorder", "hyperkinesis" or simply the "hyperactive child syndrome" are among the many different terms used to refer to what is currently known as ADHD[5-7]. Likewise, the Diagnostic and Statistical Manual of Mental Disorders (DSM) in its third edition, published in 1980[8], introduced the term "Attention-Deficit Disorder with or without hyperactivity", the contemporary term ADHD is relatively new, following the publication of DSM-Ⅲ-R[9]. The other major diagnostic system, the International Statistical Classification of Diseases and Related Health Problems in its current 10th Revision (ICD-10)[10] (World Health Organization, 1992), relies on the term "hyperkinetic disorders" to refer to a group of disorders of an early onset and characterized by disturbance of activity and attention with or without conduct disorder. Partly due to the different terminology used to coin this disorder which actually refer to various entities, but also due to that for decades there has been no unified conceptualization of the disorder, it has existed great controversy in the understanding and even the acceptance of this disorder[11-14].

The first clinical description of a constellation of symptoms highly resembling to what currently could be diagnosed as ADHD is generally attributed to George F Still in 1902[15], many years before the disorder entered the official diagnostic nomenclature. Sir George Frederic Still, a pediatrician who became England's first professor of childhood medicine at King's College Hospital London[6], is particularly acknowledged for his findings and reports of a form of chronic joint disease in children[16], which is currently known as "Still's disease"[17] In his Goulstonian lectures on "some abnormal psychical conditions in children", delivered in March 1902, before the Royal College of London, he described a group of 43 children, which he reported as having what he labelled as an "abnormal defect of moral control"[15] (Table 1). He described these children as often being aggressive, defiant, resistant to discipline, as well as excessively emotional or passionate. These children had problems with concentration and sustained attention, as well, and could not learn from the consequences of their actions. The Goulstonian Lectures are commonly considered as the scientific starting point of ADHD history[18-21]. However, there are scattered but significant published historical medical, scientific and non-scientific reports, much prior to Still's lectures, of what is currently termed as ADHD. Moreover, it is quite likely that Still's observations and clinical descriptions might have been influenced by the different medical depictions published during the 19th century.

In the present report we aimed to comprehensively review the historical and medical evidence of the on children, adolescents and adult individuals with symptoms resembling to what is currently acknowledged as ADHD throughout history, but focusing on the reports prior to the publication in 1902 by George Still of his seminal paper[15], thus prior to the 20th century. Exploring the roots of this neurodevelopmental disorder, not only in the medical literature, but also in other historical sources, can aid clinicians, researchers, and other professionals gaining a better understanding of its current conceptualization.

### *ADHD in the art and literature*

In order to appreciate and understand the present conceptualization of ADHD, it is important to consider the portrayal of the symptoms of inattention and hyperactivity not only in medical books, but also in other historical accounts, including in classical literary texts or in painting masterpieces. Indeed, although for the most part, disruptive behaviors we would now acknowledge as symptoms of ADHD, historically could be attributed to youthful exuberance or a simple lack of discipline

**Table 1 Terminology used in medical reports and textbooks in the 18th and 19th century to describe symptoms of inattention or hyperactivity resembling to the current concept of attention deficit hyperactivity disorder leading to Sir George F Still clinical descriptions**

| Ref. | Year | Term |
|---|---|---|
| Melchior Adam Weikard[39,41] | 1775 | Attention Deficit ("Mangel der Aufmerksamkeit" or "Attentio Volubilis") |
| Alexander Crichton[46] | 1798 | Disease of attention |
| Benjamin Rush[53] | 1812 | A syndrome involving inability to focus attention |
| Charles West[55] | 1848 | The nervous child |
| Heinrich Neumann[67] | 1859 | Hypermetamorphosis |
| Désiré-Magloire Bourneville[69,70] | 1885 | Mental instability |
| Thomas Clifford Albutt[57] | 1892 | Unstable nervous system |
| Thomas Smith Clouston[63] | 1899 | Simple hyperexcitability |
| George F Still[15] | 1902 | Abnormal defect of moral control |

or intellect, the different historical and artistic clues may provide solid clues of inattentive and hyperactive individuals throughout history.

Scientists, clinicians and historians have attempted to find examples in the literature, in historical accounts and in retrospective assessments of historical figures of hyperactivity, inattention and other behavioral problems akin to what is currently identified as ADHD. Indeed, albeit the difficulties of retrospective assessments, several reports have suggested that key figures such as Cromwell[22], Mozart[23,24], or Lord Byron[25] could have had ADHD. It has been even hypothesized, from descriptions of his disruptive behavior as recorded in the Scriptures that the Apostle Peter might have suffered from ADHD[26]. Likewise, Merzon *et al*[27] recently suggested that Esau, the first son of Isaac and Rebecca (Genesis, 25:36), Samson, one of the Judges of Israel (Judges, 13:16) and Saul, the first King of Israel (Samuel 1, 9:31) had clear symptoms of executive dysfunction and possibly ADHD in a study that correlated behavioral patterns of biblical characters with symptoms of ADHD and executive dysfunction. Another likely example of what could be identified as a possible ADHD can be found in the Deuteronomy, within the Old Testament, were it advised parents troubled by a stubborn and unruly son to denounce him to the city fathers, so that he might be stoned (Deuteronomy 21: 18-21)[28].

It is common to attribute one of the first medical descriptions of a hyperactive child to Heinrich Hoffmann's story book "Struwwelpeter" or "Slovenly Peter, Straw Peter"[7,29]. Indeed, the eponym "Straw Peter syndrome" has been used to refer to ADHD[30]. Hoffmann, born in Frankfurt am Main in Germany, was a prolific poet and children's author, as well as a psychiatrist. Among the didactic tales included in his children's book "Struwwelpeter", Hoffmann included the story of "Zappel-Philipp" or "Fidgety Phillip" where he portrayed the case of a child with disruptive behavioral problems who presently could easily be diagnosed as having ADHD, predominantly hyperactive/impulsive presentation, using DSM-5 criteria[3]. The author also included the tale of "Hans Guck-in-die-Luft" or "Johnny Look-in-the-Air", where he provided the description of another boy with what nowadays might be diagnosed as ADHD, predominantly inattentive presentation, using DSM-5 criteria[3], as he described a young boy constantly distracted by external stimuli and highly inattentive over a broad range of activities[31]. However, Hoffman's descriptions of impaired children cannot be acknowledged as a medical description of illness, neither his book as a psychiatric text, but rather a collection of 15 stories with colorful drawings for the amusement and mild admonition of ill-behaving children[28]. Hoffman actually wrote these stories for a children's book he designed as a Christmas present for his 3-year-old son[29]. In any case, Hoffman was a physician, who later founded the first mental hospital in Frankfurt and became a successful psychiatrist[6,29].

Much before Hoffman wrote his children's book, William Shakespeare, the great dramaturge and certainly a unique observer of human nature and behavior, alluded to an individual with serious problems with inattention in his play "King Henry Ⅷ" (Shakespeare, circa, 1613). In the play he made reference to a "malady of attention" by one of his characters[32]. It is interesting to note, as well, that he was speaking of an adult individual, not a child.

Another depiction of ADHD is allegedly to be found in Johann Wolfgang von Goethe's masterpiece Faust[33]. In the second part of Faust, published in 1832, Goethe described a very peculiar character of a boy, Euphorion, suggestive of presenting ADHD diagnosis, predominantly hyperactive, as he portrayed a persistent pattern of excessive motor activity, constantly coupled with impulsive actions, without any attention to his parents' warnings or any adverse consequences[33].

Additional indirect hints suggesting that children with attention and hyperactive problems existed throughout history can be found in paintings from renowned artists. Indeed, it has been suggested that one of the earliest examples of ADHD can be found in the masterpiece "The Village School" (c. 1670), by the Dutch master Jan Steen. As suggested by Kast and Altschuler (2008)[34] in their historical report, the painter portrayed several children who allegedly might be diagnosed as having what currently could be diagnosed with the predominantly hyperactive/impulsive presentation of ADHD. It is possible that Steen solely was reflecting a relatively normal scene of children being children, exaggerating

in play, but the painting contrasts with another piece by Steen known as well as "The Village School", where children obey and behave impeccably[34].

## THE HISTORY OF CLINICAL DESCRIPTIONS OF INATTENTION AND HYPERACTIVITY/IMPULSIVITY DURING OR PRIOR TO THE 19th CENTURY

### *Early history of inattention and hyperactivity*

The current conceptualization and clinical characterization of ADHD has evolved through a complex and diverse historical trajectory dating back to Greek times[35]. Prior to the distinct personality types described by Galen (131-201 AD), which are only vaguely related to the current definition of ADHD[32], Hippocrates (460-375 BC), almost universally considered the father of modern medicine, provided the earliest report of a condition that appears to be comparable with what is currently identified as ADHD[36]. Approximately in 493 BC, he described patients who had "... quickened responses to sensory experience, but also less tenaciousness because the soul moves on quickly to the next impression"[37]. Hippocrates attributed the condition to an "overbalance of fire over water" in the patients bodily humors and prescribed as a remedy for such "overbalance" lots of water and a bland diet, barley rather than wheat bread, fish instead of meat, water drinks, and many natural and diverse physical activities[36].

### *Medical descriptions of inattention and hyperactivity in the 18th century*

Although there are scattered historical reports of over-active and unruly children, the first medical reports on individuals, children and adults, with abnormal levels of attention, distractibility, and hyperactivity date from the last quarter of the 18th century, when the German Melchior Adam Weikard and the Scottish physician Sir Alexander Crichton published two of the first textbooks specifically on the subject of mental diseases. Both treatises included a conceptualization of attention and descriptions of individuals with abnormal degrees of attention, distractibility and overactivity. However, over a century before Weikard and Chrichton published their works, in the 17th century, the English philosopher and physician John Locke, who published the earliest modern essay on child education[38], although he did not directly address ADHD-symptoms, Locke actually described a perplexed group of young students who, try as hard as they could, would not keep their mind from straying[35].

The German physician Melchior Adam Weikard (1742-1803) studied physics, philosophy and medicine in the University of Würzburg, and in 1763[39]. He began his practice as a physician in Fulda, where he was a prominent physician and eventually became Professor of Medicine at the University of Fulda. Weikard, who was considered a progressive physician at his times, published numerous works on medical topics as well as on philosophy and psychology[40]. Among different relevant posts he held, in 1784 he was appointed as physician-in-ordinary to the Russian Tsarina Catherine Ⅱ, also known as Catherine the Great at the imperial court in St. Petersburg[39,40].

Between 1773 and 1775 Dr. Weikard published the first edition of his textbook "Der Philosophische Artz"[41], where he broke with prevailing opinion in suggesting that disorders of emotion and behavior arose from medical and physiological causes, not from astrological or other unscientific and outdated medieval hypotheses, such as witchcraft[42]. The book included a chapter on "Attention Deficit" ("Mangel der Aufmerksamkeit" or "Attentio Volubilis") (Table 1), that provided what possibly is the earliest description of ADHD-like behaviors in the medical literature[39], anticipating and strongly resembling the predominantly inattentive presentation of ADHD, as outlined in DSM-5[3].

Weikard described adults and children suffering from a lack of attention as being easily distractible by anything, even by his or her own imagination, as well as lacking perseverance and persistence, overactive and impulsive generally characterized as unwary, careless, flighty and bacchanal. Furthermore, he indicated that inattentive individuals "will be shallow everywhere", they are "mostly reckless", imprudent, and most inconstant in execution[41].

Weikard speculated that the ADHD-like behaviors depicted in his textbook were caused by either a general lack of discipline and stimulation, poor upbringing or child-rearing early in childhood or, more notably for his times, dysregulation of cerebral fibers resulting from over- or under stimulation[39,42]. Weikard made the observation that inattention was more common among younger than among older individuals, as is well-known nowadays[4,43]. However, contrary to what has been demonstrated in the last 100 years[3,4], he also noted that women were more inattentive than men.

Sir Alexander Crichton (1763-1856) was a Scottish physician and obtained his M.D. from the University of Leiden in The Netherlands, and then completed his studies in Paris, Stuttgart, Vienna, Halle, Berlin and Göttingen[6,44]. In addition to a well-known physician, he also became a prestigious chemist and mineralogist, with original contributions to all these fields[45]. Between 1804 and 1819 he lived in Russia, becoming the royal physician to the tsar Alexander.

In 1798 he published his influential book "An inquiry into the nature and origin of mental derangement: Comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects"[46]. In the second of the three volumes of his inquiry, he included a chapter "On Attention and its Diseases", where he provided a definition of attention and emphasized that the intensity of healthy attention varies within a normal range both between individuals and even within a person at different times[46]. Crichton described a disorder characterized by

abnormal degrees of inattention and distractibility and the incapacity to attend with the necessary degree of constancy to any object, and that was associated with unusual levels of impulsivity, restlessness and emotional reactivity[46], almost entirely consistent with the diagnosis for the predominantly inattentive presentation of ADHD[3,35,47]. Furthermore, he indicated that the condition "can be born with a person" and that may become evident "at a very early period of life"[46]. This feature also appears to be consistent with the current construct of ADHD, as outlined in DSM-5, that among its diagnostic features it includes the requirement that several symptoms have to be present before age 12 years[3].

In accordance with Weikard's hypotheses, Chrichton believed that attentional problems were a consequence of dysregulated "sensibility of the nerves"[42,44]. He also reported that these ADHD-behaviors interfered with education, suggesting as well that children with such problems needed special education intervention, as nowadays is recognized and recommended by consensus and treatment guidelines[48,49]. In addition, as suggested earlier by Weikard[41] and has been demonstrated in the 20th century[4,43,50], Chrichton reported that problems of inattention and distractibility diminished with age. He also indicated that problems with attention were associated with many other mental and physical disorders[47].

The different examples of patients with great distractibility, incapacity of attending, mental restlessness and overactivity provided by Chrichton to describe what he called a "disease of attention"[46] (Table 1) could be caused by a variety of etiologies, including a metabolic or an endocrine illness, a head injury or neurological disorders such as epilepsy. However, all symptoms observed and depicted by Chrichton[46], as did earlier Weikard[41] can be associated with ADHD diagnostic criteria as defined in the current DSM-5[3].

## HYPERACTIVITY AND INATTENTION IN THE MEDICAL LITERATURE IN THE 19th CENTURY

Several descriptions of what can be presently identified as hyperactive children, mostly in the form of case reports, can be found in the psychiatric literature along the 19th century. However, as was the case of earlier reports by Weikard[41] and Chrichton[46], the predominant feature of psychiatric descriptions of children resembling what is currently conceptualized as ADHD was uncontrollability. Indeed, references to behavioral disturbances in childhood of a similar nature to that seen in hyperactivity disorders can be found in several key psychiatric texts of Maudsley (1867), Ireland (1877), or Clouston (1899), among others.

By 1809, the English physician John Haslam, provided in his book "Observations on madness and melancholy" the description of a young child who from the age of two was indulged, mischievous and uncontrollable, with a tendency to break things, very oppositional, both at school and at home, and cruel to animals; in addition, the child also had limited attention span[51]. This case history has been pointed out as an early example of ADHD, although conduct disorder[7,35], and specific learning difficulties are among the differential diagnoses or comorbidities that may have exhibited the child[35]. Only three years later, in 1812, the American physician Benjamin Rush, who was among the members of Congress that signed the Declaration of Independence, and considered to be the "father of American psychiatry"[52], published his book "Medical inquiries and observations upon the diseases of the mind"[53]. Rush described "a syndrome involving inability to focus attention"[32] (Table 1). Furthermore, he provided the observations on uncontrollable children and adults and speculated on the "defective organization in those parts of the body which are occupied by the moral faculties of the mind"[53].

Sir Henry Maudsley, the British psychiatrist described in his book "The physiology and pathology of the mind" the case of a child "driven by an impulse of which it can give no account, to a destructive act, the real nature of which it does not appreciate: a natural instinct is exaggerated and perverted by disordered nerve centers, and the character of its morbid manifestation is often determined by accidents of external circumstances"[54]. This was consistent with reports by Charles West, the eminent pediatrician based in the Great Ormond Street Hospital, who in his Lectures on the Diseases of Infancy and Childhood[55] mentioned the emergence of a new type of a difficult child, the "nervous child", one that is neither an idiot nor insane, although in subsequent editions, he did not develop the topic[56]. Moreover, Thomas Clifford Albutt reported such children as having "an unstable nervous system"[57]. Likewise, the Scottish physician William W Ireland provided a further description of behavioral disturbance in childhood of a similar nature to that seen in hyperactivity disorders[58].

William James, the prominent American philosopher, psychologist and physician centered some of his extensive work on the study of attention and its characteristics. In his book, the "Principles of Psychology", he provided the description of what he called "the explosive will", which may resemble the difficulties experienced by those who today are described as having ADHD[32]. He also indicated that "effort of the attention is the essential phenomenon of will", which inspired Still and other mental health specialists in the 20th century[59], and to a certain extent provided the philosophical foundation of what later became ADHD[60].

Another important figure is Sir Thomas Smith Clouston, an eminent Scottish psychiatrist, who served as Physician Superintendent of the Royal Edinburgh Asylum and became the first official lecturer on mental diseases at the University of Edinburgh[61]. He was also a prolific writer on the nature of mental illness and theories of treatment. Whilst generally ignored when exploring the history of ADHD, only three years

before Still's description of children with hyperactive behaviors[15], in 1899, he elegantly depicted symptoms of hyperactivity, impulsivity and distractibility that characterize the diagnostic definition of ADHD over the last 50 years[62]. Clouston reported in a pivotal paper three cases of what he described as neurotic children who presented, hyper-excitability, hypersensitiveness and mental explosiveness[63]. Furthermore, he described the hyper-excitable child as someone who "becomes ceaselessly active, but ever-changing in its activity" and suffers from "undue brain reactiveness to mental and emotional stimuli". Such descriptions of what he termed "simple hyperexcitability" (Table 1) show greater resemblance to the current conceptualization of the hyperactive child than the observations of Sir George Still[62]. He believed that such conditions were due to an overactivity of the nerve cells in the cerebral cortex, as was demonstrated almost 100 years later[64-66]. In addition, Clouston[63] outlined a multimodal therapy that included a pharmacological intervention consisting of carefully dosed grains of potassium bromides to treat these children (Table 1).

German and French psychiatrists provided additional examples of disruptive behavior in individuals, resembling what currently is identified as ADHD during the 19th century. The German psychiatrist Heinrich Neumann, born in Breslau (now Wroclaw in Poland) introduced in 1859 the term "hypermetamorphosis" to refer to some children with inability to stay focused, but also highly volatile in their inclinations, restless, in perpetual motion, unable to sit still, with difficulties to get to sit down[67] (Table 1). Neumann also described eloquently the ambiguous feelings these children in their parents[28]. The term was later adopted by Wernicke, who was one of his assistants, but exclusively for psychotic children[68].

The emergence in France of the concept of ADHD according to modern terminology may stem from the concept of "mental instability" (Table 1) introduced in 1885 by Désiré-Magloire Bourneville at the Hospital Bicêtre in Paris, following his observations of children and adolescents who had been labeled "abnormal" and placed in medical and educational institutions[69]. Dr. Bourneville, who was a pioneer in the medico-pedagogical management of children and adolescents, developed what he termed as a medico-pedagogical approach for children with significant cognitive deficits, psychomotor restlessness, inattentiveness, as well as disobedient and lacking discipline[70]. Indeed, some of the descriptions of a heterogeneous population of "mentally unstable" children with an array of behavioral problems provided by Bourneville and subsequently by his disciple Charles Boulanger in his thesis published in 1892 were very much resembling to what us currently identified as ADHD[69]. Furthermore, in the early twentieth century, following the notions introduced by Bourneville two other French physicians, Georges Paul-Boncour and Jean Philippe identified the presence of a subgroup of "abnormal" school-children who suffered from a disease entity in its own right that included symptoms of hyperactivity, impulsivity and inattention[71], that would presently correspond to a diagnosis of ADHD associated with a comorbid oppositional defiant disorder or other conduct disorders[69].

## CONCLUSION

Sir George Still's descriptions in the Goulstonian lectures and the subsequent publication in The Lancet[15] clearly constitute a significant milestone in the conceptualization of what today is identified as ADHD. Of course, the writings of authors such as Alfred F Tredgold, Franklin G. Ebaugh, Franz Kramer and Hans Pollnow, among many other eminent physicians of the early 20th century have laid the foundation and are equally influential in our present understanding and definition of ADHD. However, this highly prevalent neurodevelopmental disorder cannot be fully understood without all the different previous contributions and medical description particularly those from eminent physicians and psychiatrists from the 18th and 19th century. This highlights that by no means it is modern disorder and as some critics suggest, an invention of pharmaceutical companies[12,72]. Indeed, the first pharmacological trials with stimulants for hyperactive children were conducted in 1937[73], almost four decades after Still published his seminal paper. ADHD is the childhood and neurodevelopmental disorder and overall one of the psychiatric disorders best and more thoroughly investigated, but it remains a controversial diagnosis. Critics argue that it is a diagnosis used to label difficult children who rather than ill, present behavioral problems at home and particularly at school that are at the extreme end of the normal spectrum[6,11,12]. It is certain that the history of ADHD and ADHD-like behaviors has to be viewed within a broader context, considering not only the medical descriptions, but also the concept of children and the educational status throughout history, particularly in the second half of the 18th century. Not only the conceptualization of the child as an individual in its own right emerged during the 18th century, but schooling began to be compulsory in many parts of the world during the 19th century. So, for instance, in 1870 the Parliament in Britain passed an important Education Act that made school compulsory.

Whilst some of the children described by Still, as is probably the case of some the earlier descriptions included in the present report, may have suffered from a variety of neurological and psychiatric disorders, including conduct disorder, oppositional defiant disorder, learning disabilities, autism spectrum disorders, epilepsy, chorea, among many others, many of these children showed clear symptoms of ADHD and may present with these comorbid disorders, as it is commonly the case in clinical practice. Moreover, as we now fully comprehend, the existence of other comorbid disorders not only does not exclude a diagnosis of ADHD, but often makes the diagnostic process of this neurodevelopmental disorder more difficult[74]. In any case, although many of the symptoms and diagnostic criteria of inattention,

hyperactivity and impulsivity are not exclusive to this neurodevelopmental disorder, the characteristic presentation of these symptoms, are typical of the disorder currently known as ADHD, as indicated not only in the solid neurobiological research on this disorder, but on the broad and diverse clinical descriptions published during the 20th century and, as outlined in the present report, in the various medical descriptions during the 18th and 19th centuries.

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**P- Reviewer**: Balazs J, Gazdag G, Hounie AG, West D
**S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Psychiatry

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DOI: 10.5498/wjp.v5.i4.387

*World J Psychiatr* 2015 December 22; 5(4): 387-396
ISSN 2220-3206 (online)


REVIEW

# Animal models for posttraumatic stress disorder: An overview of what is used in research

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Author contributions: Borghans B wrote and Homberg JR critically revised the manuscript.

Supported by The Netherlands Organisation for Scientific Research (NWO), No. 864.10.003 (awarded to Judith R Homberg).

Conflict-of-interest statement: The authors have no conflict of interest to report. Funding organisations had no further role in the design of the study, nor in the collection, analysis and interpretation of data.



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Received: June 9, 2015
Peer-review started: June 11, 2015
First decision: August 25, 2015
Revised: August 27, 2015
Accepted: October 23, 2015
Article in press: October 27, 2015
Published online: December 22, 2015

## Abstract

Posttraumatic stress disorder (PTSD) is a common anxiety disorder characterised by its persistence of symptoms after a traumatic experience. Although some patients can be cured, many do not benefit enough from the psychological therapies or medication strategies used. Many researchers use animal models to learn more about the disorder and several models are available. The most-used physical stressor models are single-prolonged stress, restraint stress, foot shock, stress-enhanced fear learning, and underwater trauma. Common social stressors are housing instability, social instability, early-life stress, and social defeat. Psychological models are not as diverse and rely on controlled exposure to the test animal's natural predator. While validation of these models has been resolved with replicated symptoms using analogous stressors, translating new findings to human patients remains essential for their impact on the field. Choosing a model to experiment with can be challenging; this overview of what is possible with individual models may aid in making a decision.

**Key words:** Post-traumatic stress disorder; Physical stressors; Animal models; Social stressors; Psychological stressors; Validity; Individual differences



**Core tip:** There are currently several widely accepted animal models being used in fundamental posttraumatic stress disorder (PTSD) research, and many publications using them have made valuable contributions to the collective knowledge on the subject. Still, the difference between models indicates that their suitability depends on the situation; each model has shown different amounts of success in replicating individual criteria or aspects of PTSD. Accordingly, the selection of the most suitable model for each experiment is important for optimally reliable results. This review offers relevant information to aid in that decision.

Borghans B, Homberg JR. Animal models for posttraumatic

stress disorder: An overview of what is used in research. *World J Psychiatr* 2015; 5(4): 387-396 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/387.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.387

## INTRODUCTION

Anxiety disorders are a common problem world-wide. One of them is posttraumatic stress disorder (PTSD), characterised by hyper-arousal, disturbing flashbacks and numbing or avoidance of memories of an event[1]. Ultimately only a subset of people experiencing trauma will develop PTSD, signifying the importance of individual variation. Treatment exists, but the psychological behavioural therapy lacks efficacy in many patients and medication is often no more than a temporary suppression of symptoms. PTSD is listed in the DSM-5 manual for mental disorders as a trauma or stressor-related trauma. The 8 criteria of PTSD according to DSM-5, labelled A through H, are: (1) A stressor must initiate the syndrome and symptoms; (2) Intrusive symptoms must be present; (3) Subjects must display increased avoidance; (4) Negative changes in cognition and mood must be present; (5) Changes in arousal and reactivity must occur; (6) Displayed symptoms must be persistent over time; (7) Symptoms must significantly affect the individual's functioning; and (8) Other factors that may cause the symptoms must be excluded.

### *Neurobiology*

Despite the wide variety of symptoms found in PTSD, essentially all important hallmarks can be traced back to changes in the brain. Systematic reviews have analysed individual publications over the years, yet the causative process of PTSD remains far from understood. A literature study comparing findings regarding the brain volumes of patients and controls found several significant differences: PTSD was associated with reduced hippocampal and bilateral anterior cingulate cortex (ACC) volume, and a medium effect size reduction. However, no significant difference in amygdala volume was found[2]. From these results it was proposed that the volume reductions in ACC underlie the attention and emotion modulation deficits found in PTSD. Another study found a volume reduction in the cornu ammonis 3 and dentate gyrus hippocampus subfields[3]. Examining brain connectivity using resting state fMRI in PTSD patients and controls after an earthquake found decreased path length and increased clustering coefficient, global efficiency and local efficiency in patients. They displayed increased centrality in nodes involved in the default-mode and salience networks including posterior cingulate gyrus, precuneus, insular cortex, putamen, pallidum, and temporal regions. The study suggested that patients exhibit a shift towards a small-world network rather than towards randomisation[4].

When children with PTSD caused by sexual assault and controls were tested for cortisol levels [output of the hypothalamus-pituitary-adrenal (HPA)-axis], it was found that cortisol levels increased with time after trauma[5]. Blunted circadian cortisol oscillations are common in PTSD, and associated with hippocampal volume loss[6]. The disrupted oscillations are thought to be driven by reduced circadian peaks and decreased overall cortisol secretion[7]. This is consistent with animal models indicating that circadian cortisol cycling is needed for proper synaptic formation and pruning[8]. PTSD patients having experienced the 2001 World Trade Center attack were found to have reduced circulating levels of endocannabinoid 2-arachidonoylglycerol (2-AG) than controls. Moreover, it was found that anandamide (AEA), another endocannabinoid, positively correlated with circulating cortisol content in PTSD patients. These findings support the hypothesis that deficient endocannabinoid signalling forms a component of PTSD's glucocorticoid dysregulation[9]. While it is generally accepted that HPA function is altered, often assessed as increased cortisol suppression with the dexamethasone challenge, the exact relationship between PTSD and HPA function remains under discussion[10]. Hyper-responsiveness of glucocorticoid receptors is also suggested by the increased circulating and cerebrospinal fluid concentrations of corticotropin releasing factor (CRF) neurotransmitter in PTSD patients, as well as depression and other mood disorders[11].

Also neurotransmitter system functions are altered in PTSD. For instance PTSD patients exhibit increased dopamine transporter density[12] and an association with serotonin transporter-linked polymorphic region (5-HTTLPR) genotype has been reported in cases of severe trauma exposure[13]. Furthermore, the levels of chief inhibitory neurotransmitter gamma-aminobutyric acid (GABA) are decreased significantly in the right anterior insula of PTSD patients, and associated with increased state-trait anxiety inventory psychological classification[14]. Glutamic acid decarboxylase (GAD65) is involved in memory consolidation, and consequently important for fear memory development[15] as an enzyme essential for the production of GABA. Adrenergic receptors play an important role in stress response, and alpha-2B (ADR2B) receptor gene polymorphism was found to interact with childhood trauma in predicting adult symptoms of PTSD[16]. The deletion variant selectively predicts enhancement of long-term memories induced by stress, in females at least[17]. As a result, (Liberzon, 2014, Interaction of the *ADRB2* gene polymorphism with childhood trauma in predicting adult symptoms of PTSD) adrenergic receptors are popular targets for drug development. For instance, prazosin has been suggested to improve PFC function PTSD patients by blocking alpha-1 adrenoceptors[18]. Similarly, alpha-2 adrenergic agonist guanfacine (extended release, GXR) has been shown to significantly alleviate symptoms of PTSD in children and adolescents[19]. Yohimbine, another alpha-2 adrenergic agonist, is being

used successfully in clinical trials as an enhancer of exposure therapy[20]. However, a clear consensus about the role of neurotransmitters in PTSD does not seem to be available yet.

An extremely extensive list of risk factors for PTSD has been found over the years, of which many fall within the genetics category. More recently the influence on epigenetics has been established as well. Given that epigenetic mechanisms are considered as an important channel by which the environment influences gene expression, and PTSD is a gene × environment disorder, epigenetics may be even more interesting than genetic factors in understanding PTSD's neurobiological underpinnings[21].

In sum, stress-based disorders obviously affect many different mechanisms in the brain, and more examples can be found whenever the effect of a new pathway on PTSD risk and treatment is observed. This forms a gradually improving model by which the workings and severity of the disorder can be assessed, as well as providing new targets for the development of pharmaceutical therapies.

## MODELLING PTSD

PTSD-related research is performed on many levels, and many groups focus on fundamental aspects of the disorder. Using human patients to research human diseases is an effective way to learn. However, the acquisition of PTSD in humans is incidental thus rarely observed in real-time. Also the nature of the trauma is highly variable. Furthermore, inducing PTSD in healthy volunteers is not ethically viable. Because of these reasons using human subjects is less suitable to identify the factors that are related to brain mechanisms involved in (failure of) recovery after trauma exposure.

With the human hallmarks of PTSD in mind, multiple research groups set out to find more practical ways to learn about this complex disorder. With laboratory animals already in use within many branches of science, it did not take long before several PTSD models were being used. Now several animal models, usually involving rats or mice, are used ubiquitously and successfully instead. What makes animal models for psychological disorders like PTSD useful is disease symptoms and the underlying cause can be introduced - with individual differences - to animal populations large enough to grant statistical reliability. Relevant fundamental understanding can be generated in animals and be translated to human subjects for validation and implementation in treatment design. The consensus of what is known in humans has to be linked to animal studies continuously, in order to make sense of findings in animal models. Before animal models can be used for this, however, there must be convincing evidence for the model's validity.

### *Face, construct and predictive validity*

As the high number of separate symptoms that PTSD can cause indicates, the disorder is extremely variable among patients. Since it originates in the brain, arguably the most complex part of the (human) body, the diversity of aspects found in PTSD is far from easy to recreate in models. This is an important reason for many scientists to look for a select group of symptoms. All models are expected to display phenomenological resemblance, critical aspects of PTSD symptoms (face validity), causality or theoretical explanatory basis (construct validity) and a response to treatment similar to what is seen in humans (predictive validity). Since the human response to trauma is strongly dependent on a variety of risk factors and interpersonal variation, models that focus too much on exposure alone tend to miss an important part of the disorder. Good models should inherently display similar variation in response in a predictable way, not only depending on the strength of the inflicted stress. Determining the vital criteria and what is clinically relevant for a valid model is what makes this process so challenging.

Face validity is often tested using a variety of classical behavioural experiments. These include the plus maze, open field and startle response tests mainly for the assessment of anxiety. Construct and predictive validity are usually judged by following up on stress with measurements of hormone or drug responses, (endocrine) stress response, neurological changes and comorbidity[22]. Several animal models have been developed to meet these requirements and mimic PTSD over the years, hoping to cover all the symptoms with face, construct and predictive validity. While it is practically impossible to recreate all features of a human psychiatric disorder in small animals with limited mental capacity, numerous models have been successful in reproducing key features. These validated models for PTSD are now being used to extrapolate knowledge to aid in finding a personalised treatment for humans.

### *Yehuda and Antelman's criteria for rationally evaluating PTSD animal models*

Before the current availability of several valid animal models, there were no systematic approaches for evaluating stress models for their relevance to PTSD. Yehuda and Antelman[23] devised a list for this purpose in 1993, which remains a useful way to compare different stressors. According to this list, at least 5 different criteria can be used to grade how comparable a model is to PTSD: (1) Even very brief stressors should induce biological or behavioural symptoms of PTSD; (2) The stressor should be capable of producing symptoms in a dose-dependent manner; (3) Produced biological alterations should persist or become more pronounced over time; (4) Alterations should have potential for bidirectional expression of biobehavioural changes; and (5) Interindividual variability in response is present as function of experience and/or genetics.

While this list was originally created to assess stress models for the use in PTSD research, it may now be equally useful for the comparison of existing models for

replicating specific aspects of PTSD.

## STRESSORS IN ANIMAL MODELS

Several animal models have been developed over the years. Due to the variety of methods used in these models to mimic PTSD-inducing trauma, it is useful to divide them into physical, psychological and social stressors.

### *Physical stressors*

Physical stressors are relatively basic strategies that use aversive stimuli to directly stress subjects, comparable to the near-death experiences or accidents such as those experienced by the soldiers that make up a large part of PTSD patients.

**Single-prolonged stress:** The single-prolonged stress (SPS) model is mainly rat-based, and set up around the development of PTSD resulting from one traumatic experience. The standard paradigm restrains rats for 2 h, subsequently subjecting them to 20 min forced swim and 15 min later to ether until unconsciousness. Failure to retain extinction memory, which is often observed in PTSD[24] has been reproduced with the SPS model[25]. The model also found increased fast negative feedback of the HPA-axis[26,27], mimicking the neuroendocrine indicator of PTSD[28]. SPS animals display reduced hippocampal synaptic plasticity which may be linked to decreased hippocampal function in PTSD, as well as increased acoustic startle[29], which may signify the psychological hyperarousal that is considered to be an important attribute of PTSD as one of the DSM-5 criteria[30]. Fear extinction was found to be linked to increased expression of glucocorticoid receptors in the hippocampus and prefrontal cortex[31].

**Restraint stress:** Besides the restraint stress (RS) often used as part of the SPS procedure, restraint by itself is also used to generate PTSD-like anxiety in the RS model. Animals generally either have their head and limbs attached to a wooden board or are placed in a plastic restraint device, for a duration between 15 min and 2 h at a time[32]. Afterwards immobility is often assessed using the forced swim test[26], a combination that has shown sensitisation to the latter forced swim stressor following the time-dependent sensitisation or stress-restress model. Studies using this model demonstrated increased negative HPA feedback similar to that observed in PTSD[23]. Acute and chronic restraint both generate significantly increased behavioural anxiety and nociception[33], but the effects of chronic restraint stress can be protected against by stimulating alpha-2A adrenoceptors with guanfacine[34].

**Foot shock:** Some groups use electrical shocks as a stressor. Although shocks can be given through the animal's tail, the most common choice in the footshock stress (FS) model is by the use of a floor of metal rods[35]. This shock-based strategy usually couples the aversive electrical stimulus to non-harmful factors, according to the classical fear conditioning procedure. Auditory cues are often used together with shocks in order to elicit post-shock fear recall using only sound[36]. The environment in which the shocks are delivered also tends to get associated with a fear response, by using a contextual difference between this setup and a place considered safe such as the animal's home cage[37]. Models based on this principle regularly include tests for fear extinction, which is impaired in PTSD[38] and of a large part of non-pharmaceutical PTSD treatment such as exposure therapy[39]. Rodents exposed to this procedure display reduced locomotion in new environments and reliable conditioned fear responses when confronted with cues associated with the shocks[40]. Repeated footshock exposure increases anxiety-like behaviour in the elevated plus maze test[41]. Returning the animals to the shock context weekly was found to increase their acoustic startle response, indicative of hyperarousal[42]. Reduced baseline cortisol levels and enhanced negative HPA feedback are PTSD hallmarks[43] not reflected reliably in inescapable shock models, where the expected HPA change was only found in female rats[44]. The FS model remains useful in researching individual differences in recovery from traumatic fear, modelling the variation in human susceptibility to PTSD[45]. Other risk factors such as variation in 5-HTTLPR in humans, that affects the prevalence of several anxiety disorders including PTSD, can be assessed in this model as well[46-48]. 5-HTT knockout rats, displaying increased freezing and impaired fear extinction[49-51] or fear extinction recall[52-54], have been used as model for the more PTSD-susceptible 5-HTTLPR genotype. The polymorphism results in differences in serotonin regulation that play an important role in anxiety disorders.

**Stress-enhanced fear learning:** Stress-enhanced fear learning (SEFL) relies on electrical shocks as well, utilising a single shock in a second environment (day 2) 24 h after unpredictable shocks on day 1, *vs* a control group that did not receive shocks on either day. Before any shocks are given in the second context on day 2, the animals' freezing is assessed as a measure of learned fear. On day 3 this is repeated once more in context 2 to evaluate fear memory[55]. Subsequent shocks were shown to improve the resulting fear response lasting several months[56]. Even mild stressors can be used to generate learned fear, and the strength of the sensitising shock affects the extent of sensitisation[57]. Mice subjected to the SEFL model show several PTSD-like symptoms including hypervigilance, insomnia, impaired attention and risk assessment and attenuated corticosterone levels. This behaviour is mediated by CRF receptors in the stria terminalis, where upregulation of CRF receptor type 2 mRNA corresponded with PTSD-like behaviour, and lentiviral knockdown reduced susceptibility to the symptoms[58]. Overexpression of

this receptor improves PTSD-like symptoms in rats as well[59].

**Underwater trauma:** Underwater trauma (UT), not to be confused with the forced swim test, induces traumatic stress by placing animals in water that is too deep to stand, leading to 30 s of forced swimming before submerging the subjects for 30 s[60]. The procedure has been proven to significantly increase anxiety-like behaviour in rats[61], and reminders of UT trigger several memory-related changes in rats' dentate gyrus[62] as well as the amygdala and hippocampus[63].

### *Social stressors*

Instead of relying on direct aversive stimuli, social stressors make use of the natural social behaviour of animals. Since humans are responsive to traumatic social experiences and have been known to develop PTSD in instances such as rape and (childhood) abuse, it makes sense that the same is true for other species.

**Housing instability:** The housing instability (HI) model pairs individual animals with different cage cohorts frequently, for instance each day[64]. This model makes sense considering PTSD is affected by HI of patients[65,66]. Animals subjected to this model are often first exposed to cats, following the predator-based psychosocial stress (PPS) model. After this combined procedure, mice displayed impaired acclimation to new environments[67]. Effects found in rats are increased corticosterone suppression and lowered baseline levels (as assessed by dexamethasone suppression test) indicative of HPA dysfunction, as well as increased freezing to stressor context and heightened elevated plus maze anxiety[68].

**Social instability:** Just like the random cage cohort HI model, PTSD-like symptoms can be created using social isolation (SI). Isolation for at least 1 d in adult mice leads to more contextual freezing and impaired fear extinction during FS-like fear conditioning[69]. Overlap with the prior HI model was found in the form of increased anxiety and HPA changes, although the latter is formed by impaired suppression and higher baseline levels of corticosterone in the SI model[70]. GAD65 haplodeficiency was found to grant stress resilience to mice, most likely through the maturation of GABAergic transmission[71].

**Early life stress:** Early life stress (ELS) plays an important role in the development of PTSD during adulthood. Inducing social instability through maternal isolation of rats generates similar results as the SI model on adult animals[72]. Traumatising events experienced by children were found to influence the chance to develop PTSD-like symptoms later in life, as well as their complexity[73]. Maternal separation of animals mimics childhood trauma by separating mother and pups for 1 or several hours, usually from postnatal day 2 to 14. Studies using this strategy found sex dependency in acoustic startle response, anxiety-like behaviour and HPA function[74]. Both male and female adults display increased anxiety[75], but studies regarding hyperarousal find conflicting evidence, possibly due to the use of different ways to test arousal[76]. When ELS is followed by other stress models once subjected animals are adult, it increases the response to another stressor. SPS after ELS through maternal separation leads to increased contextual freezing and anxiety-like behaviour[72].

**Social defeat:** In the social defeat (SD) model, subjects are exposed to and suppressed by a single aggressor animal[77,78]. Suppressed animals can be categorised as either susceptible or resilient, and while both express anxiety-like behaviour, only the susceptible population shows increased avoidance[79]. Susceptible animals display blunted corticosterone levels, while the resilient group increased concentrations 39 d after the stressor[80]. SD is regularly used for bidirectional behavioural symptoms, and suitable for examining the neurobiological mechanisms of PTSD[76].

### *Psychological stressors*

While both physical and social stressors generate PTSD-like responses by using potent stimuli, most of the involved models that rely on population averages do not take into account that humans display varied vulnerability to trauma, individuals being susceptible or resilient to the development of PTSD. This aspect is better reproduced with psychological stressors, which generally make use of the instinctual response to natural predators.

**PPS:** PPS model relies on a lack of control during threats, disruptive reminders of stressful experiences and limited social interaction that are also features of human PTSD[81-83]. The PPS model periodically immobilises rodents, followed by confrontations with a predator they naturally fear, and chronic social instability over an extended period of time[84]. This procedure causes increased anxiety, impaired cognition, cardiovascular reactivity and startle response, as well as an exaggerated response to yohimbine similar to that of human PTSD patients[64]. The idea that epigenetic DNA modification plays a fundamental role in anxiety disorders such as PTSD has been around for a while, and long-term traumatic memory expression is considered to be important in this process[85]. The brain-derived neurotrophic factor gene has been found to be selectively methylated in the hippocampus of rats that underwent the PPS paradigm, which supports the theory that traumatic stress causes (epigenetic) changes in brain regions regulating cognition and stress regulation. The PPS model also mimics the reduction of basal glucocorticoids found in humans[68,86]. PPS models are also used to predict responsiveness to new drugs

**Table 1 A list of posttraumatic stress disorder animal models and the separate criteria according to DSM-5 that each model has been reported to meet (according to PubMed literature search, individual references not listed)**

| Animal model for PTSD | DSM-5 criteria[1] |
|---|---|
| Single-prolonged stress | A, B, C, D, E, F, G, H |
| Restraint stress | A, B, C, D, E, F, G, H |
| Foot shock | A, B, C, E, F, G, H |
| Stress-enhanced fear learning | A, B, C, E, F, G, H |
| Underwater trauma | A, B, E, F, G, H |
| Predator-based psychosocial stress/predator scent stress | A, B, C, D, E, F, G, H |
| Housing instability | A, B, E, G, H |
| Social instability | A, B, E, F, G, H |
| Early life stress | A, B, C, D, E, F, G, H |
| Social defeat | A, B, C, E, F, G, H |

[1]The listed criteria are: Presence of a stressor (A), intrusive symptoms (B), avoidance (C), negative changes in cognition and mood (D), changes in arousal and reactivity (E), persistence of symptoms (F), functional significance (G) and exclusion of other factors that may cause the displayed symptoms (H). PTSD: Posttraumatic stress disorder.

**Table 2 A comparison of animal models based on Yehuda and Antelman's criteria and available publications**

| Criterion | Most suitable models per criterion[1] |
|---|---|
| Even brief stressors induce biological/behavioural effects | All models are comparably suitable |
| Intensity-dependent responses | FS, SEFL, RS, PPS/PSS |
| Persistence of alterations over time | All except HI |
| Bi-directional expression of behavioural changes | SPS, SD |
| Reliable production of interindividual variability | FS, PPS/PSS, SD |

[1]The animal models listed here are: Foot shock (FS), stress-enhanced fear learning (SEFL), restraint stress (RS), predator-based psychosocial stress (PPS)/predator scent stress (PSS), housing instability (HI), single-prolonged stress (SPS) and social defeat (SD).

for PTSD. A study found that post-trauma treatment, with several therapeutics, prevented the development of PTSD-like symptoms in PPS rats[87].

**Predator scent stress:** Predator scent stress (PSS) is a model suitable for recreating the variation that humans display in responding to trauma, inducing a stressor by confronting animals with the scent of one of their natural predators. It is more practical than the previously mentioned PPS in that it removes the need for actual predator exposure, and instead suffices with functional cues. For instance, rats can be brought into contact with used cat litter for 10 min, with the control group exposed to clean cat litter only[88]. Just like the part of humans that are susceptible to permanent psychological trauma, rats in the PSS model can be grouped in ranks of sensitivity. Using elevated plus maze, acoustic startle and freezing to cues it was determined that only 25% of subjected animals developed PTSD-like behavioural changes, 25% responding minimally and 50% intermediately[89]. The results found using the PSS model show a genotype dependency also seen in human PTSD[90]. The involvement of cytoarchitectural changes in rats' amygdala and hippocampus has also been demonstrated on behavioural disruption following PSS[91].

## CONCLUSION

Animal models are a widely used method to research PTSD without the need for actual victims. Any finding in a model provides a prediction for humans, giving scientists a valuable idea of what to expect mechanistically and in treatment response. When looking at the validity of the listed animal models, one finds that they all display enough symptoms of PTSD to have face validity. Since all stressors work at least roughly *via* the same fear pathways as PTSD-inducing traumas, it is not hard for them to meet the construct validity criterion. Predictive validity, however, is best considered for each individual discovery, because the symptoms of PTSD and individual human responses are too diverse to be judged for each model as a whole. Accordingly, the DSM-5 criteria for PTSD can be used to list the (behavioural) effect of the symptoms that individual animal models reproduce (Table 1).

The fact that all of the listed models are currently being used already indicates they display a decent amount of validity, their relevance for PTSD determined by replication of symptoms *via* comparable stress mechanisms. A number of DSM-5 criteria for PTSD have to be met for any animal model in order to qualify, criterion A, B, G and H. The remaining criteria show that not all models have been proven to mimic all symptoms of

PTSD. However, since different animal models are not only used to experiment with all or the same symptoms, it remains useful to judge individual models based on what they excel at. While individual symptoms are effectively assessed using DSM-5 criteria, Yehuda and Antelman provide a more suitable way to compare different stressors (Table 2).

The amount of publications of each model is mainly a measure for its popularity among researchers but also implies reliability, offering further proof that the model grants viable results. This does not automatically mean that less ubiquitous ones are worse, and new models can still prove better than the current ones. A model not meeting one of the DSM-5 criteria for PTSD does not necessarily mean it cannot be met, but rather has not yet been proven sufficiently. It should not be forgotten that new experiments and knowledge may work best with new models instead of those that are known now, and obtaining the optimal reflection of the human disorder is only achieved when the findings of all models are combined. Consequently, translation of individual discoveries in animal models to human patients must be fulfilled in order to maximise the practical impact on the field.

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**P- Reviewer**: Santarcangelo EL
**S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Psychiatry

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DOI: 10.5498/wjp.v5.i4.397

*World J Psychiatr* 2015 December 22; 5(4): 397-403
ISSN 2220-3206 (online)




# Does mindfulness meditation improve attention in attention deficit hyperactivity disorder?

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Author contributions: Modesto-Lowe V and Chaplin M wrote the majority of the first draft; Farahmand P wrote the majority of the second draft including an addition on the effects of mindfulness on attention; Sarro L wrote the clinical section, helped rewrite the subsequent drafts and edited each version.

Conflict-of-interest statement: The senior author and coauthors of this paper have no conflicts of interest to disclose.



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Received: June 12, 2015
Peer-review started: June 15, 2015
First decision: August 25, 2015
Revised: September 8, 2015
Accepted: October 16, 2015
Article in press: October 19, 2015
Published online: December 22, 2015

## Abstract

Attention deficit hyperactivity disorder (ADHD) manifests by high levels of inattention, impulsiveness and hyperactivity. ADHD starts in childhood and results in impairments that continue into adulthood. While hyperactivity declines over time, inattention and executive function difficulties persist, leading to functional deficits. Adolescents and adults with ADHD have pervasive impairment in interpersonal and family relationships. They may develop addiction, delinquent behavior and comorbid psychiatric disorders. Despite advances in diagnosis and treatment, persistent residual symptoms are common, highlighting the need for novel treatment strategies. Mindfulness training, derived from Eastern meditation practices, may improve self-regulation of attention. It may also be a useful strategy to augment standard ADHD treatments and may be used as a potential tool to reduce impairments in patients with residual symptoms of ADHD. Clinically, this would manifest by an increased ability to suppress task-unrelated thoughts and distractions resulting in improved attention, completion of tasks and potential improvement in occupational and social function.

**Key words:** Attention deficit hyperactivity disorder; Mindfulness; Treatment adjunct; Inattention; Meditation; Attention



**Core tip:** Attention deficit hyperactivity disorder (ADHD) is a chronic and potentially handicapping developmental disorder that affects both children and adults. Recent advances in research have led to improved screening,

diagnostic algorithms, pharmacologic and psychosocial treatment for patients with ADHD. However, impairing residual symptoms persist for most affected individuals. This article explores empirical evidence supporting the use of meditation for inattention in ADHD. The results of the study have found evidence for mindfulness training as a potentially effective treatment for residual inattention after pharmacological treatment of ADHD. Adequately powered prospective studies are needed to firmly establish efficacy.

Modesto-Lowe V, Farahmand P, Chaplin M, Sarro L. Does mindfulness meditation improve attention in attention deficit hyperactivity disorder? *World J Psychiatr* 2015; 5(4): 397-403 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/397.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.397

## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) affects 5% of children and 4% of adults. It is characterized by inattention, hyperactivity and impulsivity inconsistent with age. These characteristics result in dysfunctional social, academic and occupational environments[1-3]. Children are at risk for a range of problems including low self-esteem, peer rejection, physical injuries and poor adaptive functioning[2]. Similarly, adolescents with ADHD have significant difficulties with executive function and behavioral inhibition. They tend to make decisions impulsively and are prone to use alcohol, tobacco and other substances in comparison to adolescents without ADHD[4-6]. Furthermore, early onset of sexual activity, accidents, delinquency and reckless driving is heightened in adolescents with ADHD[7]. ADHD symptoms may also cause impairment in adult patients[8]. Similar to younger groups, adults with ADHD experience difficulties in academics, work, interpersonal areas and life skills, such as driving and parenting. They tend to have high rates of substance use, unemployment, divorce, antisocial behaviors and psychiatric comorbidities[9]. Overall, available data suggests that ADHD is a chronic handicapping condition associated with negative outcomes across the life span.

Recent advances in research have led to improved screening, diagnostic algorithms, as well as pharmacologic and psychosocial treatment for patients with ADHD[2,3,10]. In the United States, stimulants remain the first line pharmacotherapy and are associated with a remarkable response rate; however, despite the use of stimulants, impairing residual symptoms persist for most affected individuals[11]. Behavioral training for parents of affected children and cognitive behavioral therapy in older groups to augment the effects of medications has shown some promise[9]. Unfortunately, most studies in this area only evaluate the short-term outcomes of these therapies, and the long-term benefits remain unclear[5,10]. The interest in developing sustainable, non-pharmacological options to augment ADHD treatments has led to interest in mindfulness training (MT). MT is an intervention derived from Buddhist practices that may enhance attention and reduce impulsive responses[12]. The core aspects of mindfulness involve paying attention on purpose in the present moment and with nonjudgmental acceptance. Over the past few years MT has been adapted for use in clinical populations including adolescents and adults who have difficulties regulating their emotions and behaviors[13,14]. This article outlines the clinical presentation and neurobiology of ADHD and explores empirical evidence supporting the use of meditation for inattention in ADHD.

## CLINICAL FEATURES OF ADHD

ADHD is a neurodevelopmental disorder that typically presents in childhood and is characterized by troubles with inattention, hyperactivity and/or impulsivity[1,15]. According to the DSM-5, the diagnosis requires at least six symptoms of either inattention or hyperactivity/impulsivity, several of which must be present prior to the onset of adolescence. For individuals over the age of seventeen, only five symptoms are necessary for diagnosis. These symptoms must be present for at least 6 mo, occur in at least two settings, and hinder social, academic and/or occupational functioning[15]. ADHD is often thought of as a disorder of childhood; however, the reality is that it often persists into adolescence and adulthood[16].

The symptom presentation of ADHD differs across the lifespan. As individuals reach adolescence, the hyperactivity tends to abate somewhat while the inattention persists and often becomes more disabling[16,17]. In adolescence, impulsivity often presents as recklessness, unpremeditated actions and impatience. Similarly, the characteristic rambunctiousness of children with ADHD recedes and is replaced by motor restlessness. Adolescents with ADHD report feeling on edge and often choose activities that are physical in nature in order to avoid sedentary tasks. Despite the significant presence of restlessness, a study conducted by Sibley *et al*[16] found the symptoms of inattention to far outweigh those of hyperactivity/impulsivity in adolescence. Inattention is manifested by distractibility, carelessness, forgetfulness and organizational difficulty. Adolescents with ADHD have difficulty focusing during lectures or while reading; they complain of their mind "wandering" and often have difficulty listening, following through on instructions or finishing tasks. They frequently lose or misplace items and characteristically work in cluttered and disorganized environments. Additionally, there is a penchant to procrastinate and avoid activities that require prolonged attention. The difficulty with sustaining attention leads to marked school difficulties. Struggles with studying or paying attention in class can lead to academic decline and failure[18]. Adults often run the risk of unemployment due to ADHD jeopardizing job performance and acceptable attendance records. Socially, relationships

with others are threatened as inattention is seen as laziness, irresponsibility and unwillingness to cooperate[15]. While current pharmacological and behavioral treatments can reduce debilitating symptoms significantly, partial remission is common and residual difficulty with focus, impulse control and emotional regulation cause significant dysfunction for many adolescents and adults with ADHD.

## NEUROBIOLOGY OF ADHD

Neurobiological research has tied ADHD symptoms to structural-functional brain abnormalities and delayed development of the neocortex[19]. As children develop, brain maturation progresses in a posteroanterior fashion. Initially, myelination takes place in the visual pathway and then progresses to anterior areas such as the prefrontal cortex (PFC). The brain development that occurs during adolescence primarily involves changes in the frontal and parietal cortices, the sites responsible for executive function. A peak in gray matter volume at puberty is followed by a gradual decline, as the cortex undergoes synaptic pruning in areas that play a role in impulse control, planning and emotion regulation. The evolutional path of the brain in children with ADHD follows a parallel course with controls, but always with significantly smaller gray matter volumes[20]. Traditional magnetic resonance imaging (MRI) studies in children with ADHD have shown reduced volume in the frontal cortex, anterior cingulate cortex (ACC), basal ganglia and cerebellum[21]. Similarly, structural MRI studies in adults with ADHD have found overall reductions in cortical gray matter volume in the ACC, orbitofrontal cortex (OFC), inferior frontal cortex, dorsolateral prefrontal cortex (DLPFC), temporoparietal, cerebellar and occipital regions[22-25]. While volumetric reductions in subcortical areas have also been reported in adults with ADHD, most research focused on the frontal striatum circuit including the ACC, OFC and DLPFC.

Early research implicates dysfunction of the PFC and fronto-striatal circuitry in ADHD, including the OFC, DLPFC and ACC. The ACC modulates the peripheral nervous system (PNS) and the central locus ceruleus (LC), both norepinephrine (NE)-driven systems. For the most part, the ACC is activated by novel or salient stimuli as part of a neural circuit that serves to regulate cognitive and emotional processing. By rapidly modulating the activity levels of both principal NE systems, the ACC is able to adapt the state of the whole organism to optimize attention and support complex behavior. It is also responsible for selective attention and conflict monitoring. Furthermore, the ACC is the primary structure responsible for salience and detection of executive PFC networks. These networks integrate input from the internal and external environments to maximize adaptive processes[26]. The PFC provides top-down (cerebral-to-limbic) regulation of attention and behavioral inhibition through connections with posterior cortical and subcortical structures[27]. The OFC is involved in decision-making and impulsivity. The function of the DLPFC is to sustain attention, problem solve and organize information[28]. It has also been implicated in activating the brain mechanisms necessary for working memory and task completion. Overall, these PFC structures act in concert as well as communicate with subcortical structures (*e.g.*, basal ganglia, cerebellum) to optimize attention and executive function[29]. The catecholamine neurotransmitters, dopamine and NE, are critical for communication between the PFC and other brain structures[27]. Concentrations of these neurotransmitters in the PFC follow a bimodal curve: too much or too little disrupts its functioning. In persons afflicted with ADHD, poor connectivity among these brain areas may underlie the pathology associated with impaired goal setting, organization and planning.

Functional MRI (fMRI) technology has been used to map out brain-symptom correlations in ADHD. It assesses brain activity by measuring hemodynamic response in different regions of the brain under various cognitive tasks. In ADHD studies, fMRI findings have suggested that individuals with ADHD have hypoactivity in the PFC areas, superior parietal areas, caudate nucleus and thalamus[30]. These changes that result in impairment with tasks requiring attention and response inhibition have been show to normalize with appropriate treatment.

Overall efforts to delineate the neural systems underlying attention control in individuals with ADHD do not suggest a simple locus of neural dysfunction, but rather a deficit in integration of information across numerous brain areas[31]. Generally, the literature indicates that ADHD is characterized by multiple functional and structural neural network abnormalities beyond the classical fronto-striatal model, including fronto-parietal-temporal, fronto-cerebellar and even fronto-limbic networks.

## MINDFULNESS MEDITATION

Mindfulness is a technique of focusing attention that is derived from Eastern meditation practices. It has been defined as "bringing one's complete attention to experience the present moment"[32]. The basic elements of MT are intention, attitude and attention. The ability to direct one's attention can be developed through the practice of intentional self-regulation of attention from moment to moment[13]. Mindfulness has been conceptualized as a fundamental way of being, and is a learned skill involving non-judgmental observation of thoughts, emotions and somatic sensations that arise in one's awareness[33]. Over the past several years, researchers have been exploring the therapeutic potential of MT[34]. These efforts have included development of manuals that apply MT principles to Western psychotherapy. In the United States, the most frequently cited method of MT is mindfulness-based stress reduction, which was first used for the treatment of chronic pain[35]. The use of MT has since been extended to other clinical populations, and

has garnered acceptance as a legitimate psychotherapy modality[36]. Although research in ADHD is limited, some studies have documented improvements in attention skills in adolescents, as well as adults with ADHD[13,37].

When considering the various types of practices, two types of meditation are broadly recognized: focused and receptive attention. As the name implies, focused or concentrative meditation entails focusing on a specific thought, such as an image or body sensation, while distracting events are disregarded[26]. This allows the meditator to concentrate on one thing at a time rather than allowing attention to split among tasks. One example is the mindfulness of breathing, where a participant is trained to focus on his/her breathing and sustain attention on this sensation for the practice duration. The training includes explicit instructions to notice mind wandering and respond by redirecting attention. If the participant notices his/her attention wander away from the breath, he or she must notice the drift in attention and return to the breath. This practice leads to less distractibility and better ability to stay on task.

Another type of meditation, called open monitoring or receptive attention, includes observing the content of one's experience (*e.g*., sensations, thoughts and emotions) from moment to moment without reacting. In the open monitoring meditation, attention is extended to the whole field of awareness. It involves being alert to any stimuli that arise in the moment rather than a steady focus on one specific object. This type of meditation enhances attention switching, the ability to purposefully shift the attention focus between stimuli[38]. By directing attention to the experience of the moment, subjects learn to identify and dismiss unhelpful automatic reactions. This improvement in receptive attention can improve self-regulation and impulse control.

## MT AND ATTENTION

By enhancing attention, MT can potentially improve several core symptoms of ADHD, namely task completion, self-regulation and impulse control. Given its low cost and sustainability, it is of interest to clinicians to empirically validate the positive effect of MT on attention. Early research has studied the benefits of concentrative meditation using the Posner model of attention. According to Posner[39], the attention system is supported by three components: alerting, orienting and conflict monitoring. The alerting network attains and sustains a state of vigilance and is subserved by the reticular activating system. The orienting subsystem involves the parietal lobe. Its function is to select relevant environmental information and enable one to react quickly to a situation. The conflict monitoring subsystem prioritizes competing stimuli to regulate thoughts, emotions and actions. The ACC plays an important role in conflict monitoring by anticipating what to do next in situations. It has been proposed that MT's capacity to influence attention relates to its ability to act on these three attention processes[40].

In a study by Jha *et al*[41], the effects of focused MT on the elements of attention, including alerting, orienting, and conflict monitoring, were examined. Participants were divided into three groups - a novice group, who received 8 wk of training in MT, an experienced MT group and a meditation naïve control group. The novice participants were taught to focus attention, detect distraction, then disengage their attention from the source of distraction, and flexibly redirect and engage attention to an intended object. The experienced MT group participated in a 4-wk meditation retreat. On the first evaluation, the participants in the retreat group demonstrated improved conflict monitoring performance relative to those in the novice MT groups and controls. At follow up, those in the novice MT groups demonstrated significantly improved orienting in comparison with the other groups. These results suggest that MT may improve certain aspects of attention[41]. Another study by Tang *et al*[42], focused on the effects of short-term meditation on attention. Participants included forty Chinese college students randomly assigned to 5 d of either MT or relaxation. Results showed that there was an advantage of MT in conflict monitoring relative to the group that received relaxation. Apart from these studies, additional data supports that focused MT practice improves conflict monitoring and orienting[43,44].

A study by Chiesa *et al*[36] reviewed research evaluating the effects of MT on measures of cognitive function. This review supports the notion that focused MT may be associated with significant improvements in conflict monitoring. One proposed theory suggests that the mechanism underlying the effect of MT on conflict monitoring functions *via* activation of the attention-related cortices such as the PFC and ACC[36,45]. Efforts to elucidate the meditation-attention link have measured brain activation before and after variable periods of MT using fMRI[36]. One of the most frequently observed changes in response to meditation is the activation of the PFC and the ACC[26]. Activation of the ACC is typically accompanied by a widespread activation of other brain areas such as the LC and the autonomic nervous system. The LC is thought to optimize behavioral performance by modulating arousal and adaptively responding to environmental demands[46]. There is an inverse relationship between cortical arousal and peripheral sympathetic nervous system (SNS) arousal. It is believed that meditation acutely activates the ACC, which in turn inhibits the SNS, and decreases peripheral NE drives. The result is parasympathetic activation and relaxation promotion. At the same time, the ACC signals LC activation and an increase in cortical NE release, which results in enhanced attention processes.

Additional research has explored the effects of cognitive behavioral therapy and MT (CBT/MT) on attention in incarcerated adolescents. In this study, by Leonard *et al*[47], the investigators randomly assigned dormitories of incarcerated youth, ages 16-18, to a CBT/

MT intervention ($n$ = 147) or a control intervention ($n$ = 117). Both arms received about 750 min of training in small groups over a 3-5 wk period. Youth in the CBT/MT arm also reported on the amount of homework practicing MT exercises. The Attention Network Test was employed to measure attention performance at baseline and at 4-mo follow-up. The results of the study found that multi-session CBT/MT interventions had a protective effect on the incarcerated youths' attention capabilities[47]. Overall, there is emerging evidence that MT has an impact on attention capacity, which encourages its adaptation and application to patients with ADHD.

## MT IN ADHD PATIENTS

The use of meditation with ADHD populations is in its nascence[48]. In 2008, Zylowska *et al*[32] conducted a feasibility study, which adapted MT for adolescents and adults with ADHD. Subjects consisted of 24 adults and eight adolescents with ADHD who were treated with 8 wk of MT along with homework assignments. The curriculum, called Mindful Awareness Program, adapted to the specific requirements of persons with ADHD and included education in practices that ameliorate self-regulation and MT exercises. Participants began by meditating for 5 min at a time and gradually increased to 20 min. Each session lasted 2.5 h and was supplemented with daily at-home practice (CD's with guided meditations). The results were promising with 78% completing the study and 30% reporting a greater than 30% reduction in symptoms of ADHD (*i.e.*, set shifting and conflict attention)[13]. The authors concluded that an 8-wk MT adapted for adolescents and adults with ADHD was feasible; however, without a control group it is not clear whether the improvement in attention was due to the MT or non-specific factors.

Mitchell *et al*[49] also completed a study of the feasibility and acceptability of mindfulness meditation for adults with ADHD[49]. They compared a sample of 11 adults against a control group of 11, and found MT without additional ADHD treatment modalities was both feasible and acceptable to the participants. Sixty-three point six percent in the treatment group also rated a $\geqslant$ 30% reduction in inattention and hyperactivity symptoms compared to 0% reduction in the control group in self-rating scales. These results paralleled the in the clinician rating assessments (inattention and hyperactivity reductions of 81.8% and 72.7% in the treatment group *vs* 0% and 11% reductions respectively in the control group). Overall, these studies show evidence of acceptability and feasibility in MT[50]. However, controlled trials exploring MT as an attention enhancing strategy in the treatment of adult ADHD are needed to strengthen the evidence for MT's usefulness.

## CONCLUSION

ADHD is characterized by inattention, hyperactivity and impulsivity. It is a common developmental disorder that can persist throughout life and cause significant impairment in social, academic and occupational functioning. Although various treatment approaches exist, including pharmacologic and psychosocial treatments, residual symptoms persist for most affected individuals. In recent years, MT has been explored in ADHD populations to address ongoing distractibility, emotional dysregulation and impulsivity. Evidence suggests that certain meditative practices improve attention and may ameliorate the symptoms of ADHD by activating brain regions implicated in both sustaining and directing attention. There is much to gain from an improved understanding of the possible role of MT in enhancing attention. Overall, these findings support the idea that deliberate cultivation of attention using MT may prove to be a useful strategy to ameliorate residual inattention after pharmacological treatment of ADHD. However, adequately powered prospective studies of the relationship between meditation and inattention in ADHD populations are needed to firmly establish efficacy.

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**P- Reviewer**: Yew DT
**S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5498/wjp.v5.i4.404

*World J Psychiatr* 2015 December 22; 5(4): 404-411
ISSN 2220-3206 (online)


ORIGINAL ARTICLE

Case Control Study

# Comprehensive neurocognitive assessment of patients with anorexia nervosa

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**Supported by** The Jack Brockhoff Foundation (3410); the Dick and Pip Smith Foundation; Australian Postgraduate Award; and the David Hay Memorial Fund Award.

**Institutional review board statement:** The study was granted independent ethics approval by the Human Research Ethics committees at St Vincent's Hospital [Human Research Ethics Committee A (HREC-A)] (057/12), Austin Health [Non Drug Study Advisory Committee (NDSAC)] (H2012/04646) and The Melbourne Clinic [The Melbourne Clinic Research Ethics Committee (TMC REC)] (235). In addition, the study received expedited ethics approval from Swinburne's Human Research Ethics Committee (SUHREC) (2012/277) and was registered with The University of Melbourne Health Sciences Human Ethics Sub-Committee (HESC) (1239068), on the basis of the prior St Vincent's Hospital review.

**Informed consent statement:** All participants gave written informed consent prior to study inclusion.

**Conflict-of-interest statement:** Professor Castle reports grants and personal fees from Eli Lilly, grants and personal fees from Janssen-Cilag, Roche, Allergen, Bristol-Myer Squibb, Pfizer, Lundbeck, AstraZeneca and Hospira during the conduct of the study, outside the submitted work; and personal fees from Eli Lilly, Bristol-Myer Squibb, Lundbeck, Janssen-Cilag, Pfizer, Organon, Sanofi-Aventis, Wyeth, Hospira and Servier, outside the submitted work. Associate Professor Abel reports personal fees from Actelion Pharmaceuticals, Switzerland, outside the submitted work. Dr. Phillipou, Professor Rossell and Dr. Gurvich report no conflicts of interest.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the lead author at ap@unimelb.edu.au. No additional data are available.



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**Received:** June 24, 2015
**Peer-review started:** June 29, 2015
**First decision:** August 26, 2015
**Revised:** August 31, 2015
**Accepted:** October 1, 2015
**Article in press:** October 8, 2015
**Published online:** December 22, 2015

## Abstract

**AIM:** To utilise a comprehensive cognitive battery to gain a better understanding of cognitive performance in anorexia nervosa (AN).

**METHODS:** Twenty-six individuals with AN and 27 healthy control participants matched for age, gender and premorbid intelligence, participated in the study. A standard cognitive battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery, was used to investigate performance on seven cognitive domains with the use of 10 different tasks: speed of processing [Brief Assessment Of Cognition In Schizophrenia: Symbol Coding, Category Fluency: Animal Naming (Fluency) and Trail Making Test: Part A], attention/vigilance [Continuous Performance Test - Identical Pairs (CPT-IP)], working memory [Wechsler Memory Scale (WMS®-Ⅲ): Spatial Span, and Letter-Number Span (LNS)], verbal learning [Hopkins Verbal Learning Test - Revised], visual learning [Brief Visuospatial Memory Test - Revised], reasoning and problem solving [Neuropsychological Assessment Battery: Mazes], and social cognition [Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions]. Statistical analyses involved the use of multivariate and univariate analyses of variance.

**RESULTS:** Analyses conducted on the cognitive domain scores revealed no overall significant difference between groups nor any interaction between group and domain score [$F(1,45) = 0.73$, $P = 0.649$]. Analyses conducted on each of the specific tasks within the cognitive domains revealed significantly slower reaction times for false alarm responses on the CPT-IP task in AN [$F(1,51) = 12.80$, $P < 0.01$, Cohen's d = 0.982] and a trend towards poorer performance in AN on the backward component of the WMS®-Ⅲ Spatial Span task [$F(1,51) = 5.88$, $P = 0.02$, Cohen's d = -0.665]. The finding of slower reaction times of false alarm responses is, however, limited due to the small number of false alarm responses for either group.

**CONCLUSION:** The findings are discussed in terms of poorer capacity to manipulate and process visuospatial material in AN.


**Key words:** Cognition; Eating disorder; Body image; Spatial processing; Short-term memory



**Core tip:** The findings of this study suggest that individuals with anorexia nervosa (AN) have largely intact cognitive performance, which notably differs to the cognitive profile of other psychiatric illnesses, such as schizophrenia, bipolar disorder and major depressive disorder, which are all associated with significant cognitive deficits. However, a trend for AN participants to perform poorer on the backward component of a spatial span task was revealed. This suggests a poorer capacity to process and manipulate visuospatial information in AN, which may be related to the distortions of body image experienced by these individuals.

Phillipou A, Gurvich C, Castle DJ, Abel LA, Rossell SL. Comprehensive neurocognitive assessment of patients with anorexia nervosa. *World J Psychiatr* 2015; 5(4): 404-411 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/404.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.404

## INTRODUCTION

Anorexia nervosa (AN) is a serious psychiatric condition with a mortality rate among the highest of any mental illness[1,2]. Yet, the factors involved in the genesis and maintenance of the illness remain unclear. A common feature of AN is perfectionism, which has been identified as a significant risk factor for the illness, and is a feature found to persist following long-term recovery[3,4]. Thus, cognitive assessments reported in the AN literature often focus on tasks related to perfectionism and rigid thinking patterns, such as cognitive set shifting tasks[5]. Individuals with AN have been found to perform significantly more poorly than healthy individuals during tasks of cognitive set shifting such as the Wisconsin Card Sort Test and certain target detection tasks, displaying stereotyped behaviours with rigid approaches to changing rules[6-8]. However, unlike other psychiatric illnesses, there is a paucity of research employing more comprehensive assessments of cognitive profile in AN.

Studies of cognition in AN have tended to use a range of cognitive assessments rather than utilising a standard cognitive battery; they have consequently reported conflicting findings[9-18]. Therefore, the use of a standard neurocognitive battery, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)[19], would be advantageous and would also allow for direct comparisons to be drawn between AN and other clinical populations. The MCCB was originally designed to assess cognitive domains most relevant to schizophrenia but has since been applied to assess cognitive impairments in other psychiatric illnesses, including bipolar disorder[20], posttraumatic stress disorder[21] and major depressive disorder[22]. With the use of 10 different tasks, the MCCB assesses the following 7 cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.

Although cognitive batteries have been compiled in past research to assess cognition in AN[12,13], a standardised cognitive battery has rarely been used[23]. Furthermore, although each of the cognitive domains in the MCCB has been investigated in past research in AN, the findings are largely inconsistent. Under the speed of processing domain, intact fluency and symbol

coding performance has typically been found[15,24]. Poorer performance on trail making tasks on the other hand have been reported by some researchers[25], but not by others[8]. In relation to the attention/vigilance domain, performance on a continuous performance task has not been found to differ from healthy individuals[26], though performance on a similar task requiring rapid visual information processing has been found to result in poorer performance in AN patients[27]. Performance on tasks assessing verbal and visuospatial working memory, on the other hand, have also been found to not differ from healthy individuals by some investigators[10,27], whilst others have reported poorer visuospatial working memory in AN[28]. In relation to visual learning, performance has typically been found to be intact in AN[9,29]. Furthermore, although performance on reasoning and problem solving tasks such as mazes has also been found to be largely intact in AN[23], other tasks assessing this domain such as object assembly and block design, have been found to result in poorer performance in AN[11,28]. Finally, studies assessing social cognition in AN also show inconsistent findings, with some reporting poorer performance[30] and others failing to find a significant difference from healthy individuals[31].

Therefore, the aim of this study was to utilise a comprehensive battery of tasks to investigate cognitive performance in AN. We hypothesised that individuals with AN would show poorer performance on tasks assessing each of the cognitive domains, except the tasks assessing speed of processing and visual learning, where the literature has reported intact performance to date. We further completed exploratory analyses of performance of each of the tasks in AN given that the MCCB was originally designed to examine cognitive profile in people with schizophrenia, who are reported to show substantial cognitive problems. Individuals with AN are not expected to show such extreme deficits, and thus may only show impairment at the individual task level rather than at the level of domains overall. As cognitive performance is significantly affected by malnutrition[32] and this is a likely factor in the inconsistent findings to date in AN, we sought to investigate AN participants who were at a uniform phase of their illness trajectory [medically stable but below the healthy body mass index (BMI) range].

## MATERIALS AND METHODS

This study was approved by the Human Research Ethics Departments at the University of Melbourne, Swinburne University of Technology, the Melbourne Clinic, the Austin Hospital and St Vincent's Hospital; all in Melbourne, Australia. Informed written consent was obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

### *Participants*

Participants were 26 right-handed females with AN and 27 healthy controls (HC). Groups were matched for age and premorbid intelligence quotient (IQ). HCs were recruited through public advertisements, whereas AN participants were recruited through public advertisements; the Body Image and Eating Disorders Treatment and Recovery Service at the Austin and St Vincent's Hospitals; and The Melbourne Clinic; all in Melbourne, Australia. All patients were required to be medically stable (*i.e.*, not requiring medical attention due to their physical state) prior to inclusion in the study.

All participants were English speaking and had no history of significant brain injury or neurological condition. Controls were required to have no history of an eating disorder or other mental illness; they were also required to not be taking any medications apart from hormonal contraceptives (11 HC participants were taking medications). AN participants were instructed to continue with their normal medications, which were: selective serotonin reuptake inhibitors (11), atypical antipsychotics (12), benzodiazepines (6), serotonin-noradrenaline reuptake inhibitors (SNRIs) (3), hormonal contraceptives (3), melatonergic antidepressants (3), noradrenergic and specific serotonergic antidepressant (1) and cyclopyrrolones (1).

The Mini International Neuropsychiatric Interview, 5.0.0[33] was used to screen all participants for major Axis I psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-Ⅳ). It was also used to confirm diagnoses of AN, with the exception of the amenorrhea criterion which is no longer included in the current DSM-5. AN was required to be the primary diagnosis of the AN group. AN participants with comorbid psychiatric conditions, other than psychotic conditions, were not excluded as this would not have represented a typical AN sample.

Premorbid intelligence was estimated using the Wechsler Test of Adult Reading[34]. Eating disorder symptomatology was investigated with the Eating Disorders Examination Questionnaire[35] (Table 1).

### *Cognitive battery*

With the use of 10 different tasks, the MCCB assesses 7 cognitive domains. Scores on each task are entered into the MATRICS scoring program which produces cognitive domain scores.

**Speed of processing:** Speed of processing is assessed with three different tasks. The Brief Assessment of Cognition in Schizophrenia: Symbol Coding task requires participants to use a key to correctly match and report as many digits that correspond to nonsense symbols as they can within 90 s; the number of correctly matched symbols constitutes the score. The Category Fluency: Animal Naming (Fluency) task requires participants to orally report as many animals as they can in 60 s, which constitutes the task score. The Trail Making Test: Part

**Table 1 Clinical characteristics**

| | AN M (SD) | HC M (SD) | F | *P* | Cohen's d |
|---|---|---|---|---|---|
| Age | 22.81 (6.67) | 22.46 (3.16) | 0.06 | 0.81 | 0.07 |
| WTAR | 104.77 (8.11) | 106.19 (7.11) | 0.46 | 0.50 | 0.19 |
| BMI | 16.63 (1.19) | 22.60 (3.53) | 67.08 | < 0.01 | 2.27 |
| Illness duration | 6.42 (7.43) | - | - | - | - |
| Age of illness onset | 16.04 (3.40) | - | - | - | - |
| EDE-Q restraint | 3.93 (1.42) | 0.58 (0.63) | 116.84 | < 0.01 | 3.05 |
| EDE-Q eating concern | 3.78 (1.24) | 0.25 (0.31) | 188.56 | < 0.01 | 3.91 |
| EDE-Q shape concern | 5.01 (0.90) | 1.17 (0.84) | 236.44 | < 0.01 | 4.41 |
| EDE-Q weight concern | 4.50 (1.41) | 0.66 (0.82) | 136.11 | < 0.01 | 3.33 |
| EDE-Q global score | 4.30 (1.12) | 0.67 (0.54) | 211.44 | < 0.01 | 4.13 |

AN: Anorexia nervosa; HC: Healthy control; WTAR: Wechsler Test of Adult Reading; BMI: Body mass index; Age: Illness duration and age of illness onset reported in years; EDE-Q: Eating disorders examination questionnaire.

A task requires participants to draw a line connecting consecutive numbers from 1 to 25 irregularly placed on a sheet of paper as quickly as possible. The score is equivalent to the amount of time in seconds required to complete the task.

**Attention/vigilance:** Attention/vigilance is assessed with the Continuous Performance Test - Identical Pairs (CPT-IP). In this task, trials of 2-, 3- and 4-digit numbers are flashed briefly on a computer monitor and participants are required to click the mouse when the same number appears consecutively. The total number of possible hits is 90, the total number of possible false alarms is also 90, and total number of possible random responses is 270.

**Working memory:** Non-verbal working memory is assessed with the Wechsler Memory Scale (WMS®-Ⅲ): Spatial Span, a visual analogue of the digit span task. The Spatial Span task involves the administrator tapping a series of cubes in a specified sequence and participants are required to reproduce this sequence in the same order ("forward" component). Following the "forward" component, the "backward" component is administered in the same manner except participants are now required to reproduce the sequence in the reverse order. The number of correct sequences reproduced constitutes the task score.

The Letter-Number Span (LNS) task is a task of verbal working memory which requires the mental reordering of orally presented lists of intermixed letters and numbers. In this task, a list of letters and numbers is read out to respondents. The respondent is required to mentally reorder the sequence and verbally report the sequence beginning with the numbers from smallest to largest, followed by the letters in alphabetical order. The number of correct reordered sequences constitutes the score on the task.

**Verbal learning:** Verbal learning is tested with the Hopkins Verbal Learning Test - Revised. A list of 12 words from 3 semantic categories (four-legged animals, precious stones and human dwellings) is read out and respondents are required to report as many words as they can remember, in any order. The task comprises 3 trials, enabling a maximum score of 36. Following a period of 20-25 min, participants are asked to recall as many words as they can (trial 4). A retention score is also calculated by dividing the score for trial 4 by the higher score of trials 2 and 3, multiplied by 100. A longer list of 24 words is also read out to participants containing the original 12 words, as well as 6 semantically-related words and 6 semantically-unrelated words. A delayed recognition score is calculated by the total number of true positives minus the total number of false positives.

**Visual learning:** Visual learning is assessed with the Brief Visuospatial Memory Test - Revised which requires participants to reproduce 6 geometric figures following a 10 s presentation. The task comprises 3 trials, with one point each awarded for accuracy and correct placement of the figure, resulting in a maximum score of 36.

**Reasoning and problem solving:** Reasoning and problem solving is examined with the Neuropsychological Assessment Battery: Mazes task. In this task, a set of 7 mazes of increasing difficult is administered to participants. The score received for each maze is determined by the speed in which it is completed. A maximum score of 26 is achievable.

**Social cognition:** Social cognition is assessed with the Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions. The tasks involve the respondent rating the effectiveness of alternative actions or responses in achieving a certain result in situations where an individual must regulate their emotions. Lower scores indicate poorer performance.

### *Statistical analysis*

Following normality checking and the removal of outliers, a multivariate analysis of variance (MANOVA) was first

**Table 2 Cognitive domain scores**

| | AN M (SD) | HC M (SD) | F | *P* | Cohen's d |
|---|---|---|---|---|---|
| Speed of processing | 57.42 (9.75) | 59.85 (7.80) | 1.01 | 0.32 | 0.28 |
| Attention/vigilance | 43.42 (8.08) | 46.85 (8.47) | 2.27 | 0.14 | 0.41 |
| Working memory | 56.12 (9.68) | 58.56 (9.33) | 0.87 | 0.36 | 0.26 |
| Verbal learning | 53.38 (10.33) | 50.33 (8.19) | 1.42 | 0.24 | 0.33 |
| Visual learning | 54.85 (6.25) | 56.59 (9.77) | 0.60 | 0.44 | 0.21 |
| Reasoning and problem solving | 55.15 (8.29) | 58.11 (7.11) | 1.95 | 0.17 | 0.38 |
| Social cognition | 49.42 (6.93) | 48.07 (10.86) | 0.29 | 0.59 | 0.15 |
| Overall composite | 54.31 (7.97) | 56.19 (7.03) | 0.83 | 0.37 | 0.25 |

AN: Anorexia nervosa; HC: Healthy control.

conducted on the seven cognitive domain scores across groups. Secondly, one way analysis of variance was used on each of the task variables to compare group performance, with alpha set at 0.01 to account for multiple comparisons. Statistical review of the study was performed by a biomedical statistician.

## RESULTS

A MANOVA conducted on the cognitive domain scores revealed no overall significant difference between groups nor any interaction between group and domain score [$F(1,45) = 0.73$, $P = 0.649$] (Table 2). Analyses conducted on each of the specific tasks within the cognitive domains revealed significantly slower reaction times for false alarm responses on the CPT-IP task in AN [$F(1,51) = 12.80$, $P < 0.01$, Cohen's d = 0.982] and a trend towards poorer performance in AN on the backward component of the WMS®-Ⅲ Spatial Span task [$F(1,51) = 5.88$, $P = 0.02$, Cohen's d = -0.665] (Table 3). The finding of slower reaction times of false alarm responses is, however, limited due to the small number of false alarm responses for either group.

## DISCUSSION

Overall, the results from this study suggest intact cognitive performance in AN on the majority of the measures studied, despite significantly low BMIs and the potential long- and short-term effects of starvation. The only cognitive measure which showed a trend toward impairment in the AN group was visuospatial working memory. Poorer performance in AN was specifically found during the backward component of the task and not the forward component of the task, or the task overall. A study by Fowler *et al*[27] also reported intact overall spatial span performance in AN, but did not report whether AN and healthy individuals differed in the forward or backward components of the task. The forward component is thought to represent the capacity of the visuospatial sketchpad, whereas the backward component of this task is thought to represent a measure of executive function as it requires additional manipulation within temporary storage[36], suggesting that individuals with AN have specific working memory difficulties when the cognitive demand is high. This deficit appears to be specific to visuospatial working memory as LNS performance was intact in this cohort. Working memory deficits specific to visuospatial working memory have also been reported by Kemps *et al*[28], who found AN participants were poorer at recalling object locations, but did not differ in the recall of object names compared to healthy individuals. This finding is also in keeping with several studies reporting impairments in immediate recall on visuospatial memory tasks such as the Rey Complex Figure Test[37]. Poorer capacity to manipulate and process visuospatial material may also be related to the specific visuospatial processing deficits experienced in AN, in which patients overestimate the size of their own body[38]; though, this relationship would require specific investigation.

Contrary to expectations, individuals with AN did not differ from healthy individuals in performance on any other task. Though the AN group were found to make false alarm responses of longer reaction time than the control group, this finding is limited due to the small number of false alarm responses for either group, thereby not allowing accurate statistical analyses to be undertaken. The existing research utilising the same or similar tasks is particularly inconsistent with many studies reporting no cognitive deficits, while others report significantly poorer cognitive performance in AN. The inconsistency in findings may be largely related to differences in methodology, particularly the participants examined. Malnutrition certainly effects cognitive function as reported in studies of induced starvation[32]. Studies in AN patients often recruit individuals currently undergoing inpatient treatment as they are often easily accessible to researchers. The primary role of most inpatient treatment services is medical stabilisation. Therefore, patients admitted to such services are typically very physically unwell. The majority of patients in this study were outpatients at the time of testing. Furthermore, the few inpatients included were required to be medically stable. Despite all patients recruited for this study being medically stable, their BMIs were significantly below normal and their eating disorder symptomatology significantly high, suggesting that they were in an acute phase of the illness but were physically well enough to function. Therefore, the sample recruited

**Table 3 Specific task scores**

| | AN M (SD) | HC M (SD) | F | *P* | Cohen's d |
|---|---|---|---|---|---|
| Speed of processing | | | | | |
| BACS SC | 63.23 (9.80) | 68.11 (9.19) | 3.50 | 0.07 | 0.51 |
| Fluency | 28.19 (6.43) | 27.19 (5.54) | 0.37 | 0.54 | 0.17 |
| TMT-A | 23.62 (57.50) | 21.30 (4.83) | 2.54 | 0.12 | 0.44 |
| Attention/vigilance | | | | | |
| CPT-IP | | | | | |
| Hits proportion | 0.82 (0.10) | 0.86 (0.09) | 1.65 | 0.21 | 0.42 |
| Hits reaction time | 550.25 (60.43) | 533.05 (51.08) | 1.26 | 0.27 | 0.31 |
| False alarms proportion | 0.11 (0.05) | 0.09 (0.06) | 1.04 | 0.31 | 0.36 |
| False alarms reaction time | 508.08 (147.39) | 369.98 (133.55) | 12.80 | < 0.01 | 0.98 |
| Random responses proportion | 0.01 (0.01) | 0.01 (0.01) | 1.96 | 0.17 | 0.00 |
| DPRIME score | 2.55 (0.54) | 2.78 (0.56) | 2.37 | 0.13 | 0.42 |
| Working memory | | | | | |
| WMS®-Ⅲ | | | | | |
| Forward score | 9.65 (2.30) | 10.3 (1.88) | 1.25 | 0.27 | 0.31 |
| Backward score | 9.12 (1.80) | 10.3 (1.75) | 5.88 | 0.02 | 0.67 |
| Total score | 18.77 (3.54) | 20.59 (2.94) | 4.18 | 0.05 | 0.56 |
| LNS | 17.38 (2.82) | 16.74 (2.97) | 0.66 | 0.42 | 0.22 |
| Verbal learning | | | | | |
| HVLT-R™ | | | | | |
| Total recall | 29.38 (4.01) | 28.07 (3.82) | 1.48 | 0.23 | 0.34 |
| Delayed recall | 13.42 (17.74) | 9.96 (1.63) | 1.02 | 0.32 | 0.23 |
| Delayed retention | 92.80 (14.13) | 91.98 (14.59) | 0.04 | 0.84 | 0.06 |
| Delayed recognition | 11.04 (0.96) | 10.93 (1.33) | 0.12 | 0.73 | 0.10 |
| Visual learning | | | | | |
| BVMT-R™ | 28.62 (3.98) | 29.78 (6.23) | 0.65 | 0.42 | 0.22 |
| Reasoning and problem solving | | | | | |
| NAB®: Mazes | 22.46 (3.43) | 23.70 (2.63) | 2.20 | 0.14 | 0.41 |
| Social cognition | | | | | |
| MSCEIT™: Managing emotions | 96.98 (5.92) | 95.41 (9.57) | 0.51 | 0.48 | 0.20 |

AN: Anorexia nervosa; HC: Healthy control; BACS SC: Brief Assessment of Cognition in Schizophrenia: Symbol Coding; Fluency: Category Fluency: Animal Naming; TMT-A: Trail Making Task Part A reported in seconds; CPT-IP: Continuous Performance Test - Identical Pairs; WMS®-Ⅲ: Wechsler Memory Scale (WMS®-Ⅲ): Spatial Span; LNS: Letter Number Span; HVLT-R™: Hopkins Verbal Learning Test - Revised; NAB®: Mazes: Neuropsychological Assessment Battery Mazes task; MSCEIT™: Managing Emotions: Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions; reaction times on the CPT-IP reported in milliseconds.

is a significant strength of this study, especially as they were age, gender and IQ matched to the HC cohort, resulting in a homogenous sample which is often not achieved in research in AN.

The study is, however, not without its limitations. The MCCB is a standard cognitive battery originally compiled to assess the areas of cognition most relevant to schizophrenia and related disorders. Therefore, cognitions often associated with AN, such as cognitive set shifting[8,39,40], were not investigated. As the aim of the study was to investigate general cognition in AN, and the existing cognitive battery was already lengthy, an additional cognitive set shifting task was not considered feasible. Future research in AN would benefit from including set shifting tasks. Although the MCCB provides a comprehensive profile of basic cognitive tasks, a battery also including tasks related to the specific cognitive traits commonly associated with AN, and tasks allowing more detailed exploration of executive function would be beneficial in future research. Furthermore, the modest sample size may have contributed to the lack of significant differences between groups. Thus, further research utilising the same measures in a larger sample may reveal statistically significant group differences, rather than the trends reported in the current study. A further potential limitation is that the majority of patients were on medication at the time of testing, which may have influenced the findings.

The findings of this study suggest a cognitive profile in AN different to that of other psychiatric illnesses, such as schizophrenia, bipolar disorder and major depressive disorder, which are all associated with significant cognitive deficits on the MCCB[20,22,41]. Similar findings to the current study have, however, been reported in obsessive compulsive disorder (OCD). Intact performance on a range of cognitive tasks have been reported in OCD. Similarly to the current study, poorer performance on tasks of spatial working memory[42], but not specifically spatial span[43], have been reported in OCD patients. Similarly, poor visuospatial working memory has also been reported in body dysmorphic disorder (BDD), another psychiatric illness within the OCD-spectrum with prominent body image disturbance[44,45]. Though, unlike the current findings, poorer performance on tasks of verbal working memory and executive function have also been reported in BDD[45,46]. Unlike the current

study, however, the spatial span task components in these studies were not separated to better investigate visuospatial working memory. The deficits in visuospatial working memory and otherwise intact cognitive performance in OCD illustrates the overlap in clinical presentation that is often reported in AN, and may provide support for the long-proposed hypothesis that AN and OCD share overlapping psychopathology[47].

Overall, visuospatial working memory was the only cognitive measure that groups were found to differ on in this study, and this may be related to AN patients' difficulties in evaluating their own bodies. As cognitive functioning in general appears to remain largely unaltered in AN, it may suggest that the limited cognitive deficits observed may arise from quite restricted brain regions which may also be involved in the psychopathology of AN.

## ACKNOWLEDGMENTS

The authors would like to thank Charlotte Keating for administering the clinical interview. The authors would also like to thank Chia Huang, Richard Newton, Lynley Gervasoni, Michelle Snell, Helen Shepherd, Philippa Harrison and Felicity Lawrence for their assistance in recruiting participants. Finally, the authors would like to thank everyone who took the time to participate in the study.

## COMMENTS

### *Background*

Anorexia nervosa (AN) is a psychiatric condition associated with perfectionism and rigid thinking patterns. Investigations of cognitive performance in AN have often focused on related measures. However, comprehensive assessments of cognition in AN have rarely been undertaken and findings have been inconsistent. Therefore, this study utilised a comprehensive cognitive battery to gain a better understanding of cognitive performance in AN.

### *Research frontiers*

Individuals with AN appear to have largely intact cognitive function, but demonstrate difficulties with complex visuospatial processing.

### *Innovations and breakthroughs*

Findings in acute AN have rarely utilised a comprehensive set of cognitive tasks and have consequently tended to report conflicting findings. Employing a comprehensive set of cognitive assessments in a group of medically stable patients with acute AN suggests that AN may not be associated with significant cognitive deficits, but with subtle difficulties in manipulating visuospatial information.

### *Applications*

As only limited cognitive deficits were observed, they may arise from relatively restricted brain regions which may also be involved in the psychopathology of AN.

### *Peer-review*

The research is interesting and the manuscript is well written.

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*World J Psychiatr* 2015 December 22; 5(4): 412-424
ISSN 2220-3206 (online)


ORIGINAL ARTICLE

Retrospective Study

# Risk for emerging bipolar disorder, variants, and symptoms in children with attention deficit hyperactivity disorder, now grown up

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**Author contributions:** Elmaadawi AZ and Jensen PS designed research; Elmaadawi AZ and Jensen PS performed research; Jensen PS contributed to the new reagents or analytic tools; Elmaadawi AZ, Jensen PS, Arnold LE, Molina BSG and Swanson JM analyzed data; Elmaadawi AZ, Jensen PS, Arnold LE, Molina BSG, Hechtman L, Abikoff HB, Hinshaw SP, Newcorn JH, Greenhill LL, Swanson MJ and Galanter CA wrote the paper.

**Institutional review board statement:** IRB approval by the Mayo Clinic IRB board with IRB number 12-007481 last approval date 10/31/2014 and active till 10/30/2015.

**Informed consent statement:** Informed consent statement and data transfer agreements were obtained during the original MTA study design in 1995.

**Conflict-of-interest statement:** Dr. Ahmed Elmaadawi, the corresponding author, has no conflict of interest to disclose. Dr. Peter Jensen received funds from the followings: REACH Institute Employee, Mayo Clinic Consultant, Shire Pharmaceuticals, Inc., Grant Support and Honorarium for participation in another meeting and CATCH Services Member, Board of Governors and Stock or Equity. Dr. L Eugene Arnold Dr. Arnold has received research funding from Curemark, Forest, Lilly, Neuropharm, Novartis, Noven, Shire, and YoungLiving (as well as NIH and Autism Speaks) and has consulted with or been on advisory boards for Arbor, Gowlings, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Roche, Seaside Therapeutics, Sigma Tau, Shire, and Tris Pharma and received travel support from Noven. Dr. Brooke Molina has no conflict of interest to disclose. Dr. Lily Hechtman has funds from Eli Lilly and Company Advisory Board and Research Support, Shire Pharmaceuticals, Inc. Advisory Board and Research Support Purdue Pharma L.P. Advisory Board and Research Support Janssen Pharmaceuticals, Inc. Advisory Board and Research Support. Dr. Howard B. Abikoff has no conflict of interest to disclose. Dr. Stephen P. Hinshaw has no conflict of interest to disclose. Dr. Jeffrey H. Newcorn has no conflict of interest to disclose. Dr. Laurence Lee Greenhill has following funds: Shire Pharmaceuticals, Inc. Research Support, BioBehavioral Diagnostics Company Advisory Board National Institute on Drug Abuse Grant Support. Dr. James M. Swanson has no conflict of interest to disclose. Dr. Cathryn A. Galanter has following conflict of interest to disclose The REACH Institute Consultant, American Psychiatric Publishing Royalties.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at aelmaada@iupui.edu. Consent was not obtained but the presented data are anonymized and risk of identification is low.



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Received: April 14, 2015
Peer-review started: April 24, 2015
First decision: June 3, 2015
Revised: September 2, 2015
Accepted: October 12, 2015
Article in press: October 13, 2015
Published online: December 22, 2015

## Abstract

**AIM:** To determine the prevalence of bipolar disorder (BD) and sub-threshold symptoms in children with attention deficit hyperactivity disorder (ADHD) through 14 years' follow-up, when participants were between 21-24 years old.

**METHODS:** First, we examined rates of BD type Ⅰ and Ⅱ diagnoses in youth participating in the NIMH-funded Multimodal Treatment Study of ADHD (MTA). We used the diagnostic interview schedule for children (DISC), administered to both parents (DISC-P) and youth (DISCY). We compared the MTA study subjects with ADHD ($n$ = 579) to a local normative comparison group (LNCG, $n$ = 289) at 4 different assessment points: 6, 8, 12, and 14 years of follow-ups. To evaluate the bipolar variants, we compared total symptom counts (TSC) of DSM manic and hypomanic symptoms that were generated by DISC in ADHD and LNCG subjects. Then we sub-divided the TSC into pathognomonic manic (PM) and non-specific manic (NSM) symptoms. We compared the PM and NSM in ADHD and LNCG at each assessment point and over time. We also evaluated the irritability as category A2 manic symptom in both groups and over time. Finally, we studied the irritability symptom in correlation with PM and NSM in ADHD and LNCG subjects.

**RESULTS:** DISC-generated BD diagnosis did not differ significantly in rates between ADHD (1.89%) and LNCG 1.38%). Interestingly, no participant met BD diagnosis more than once in the 4 assessment points in 14 years. However, on the symptom level, ADHD subjects reported significantly higher mean TSC scores: ADHD 3.0; LNCG 1.7; $P < 0.001$. ADHD status was associated with higher mean NSM: ADHD 2.0 *vs* LNCG 1.1; $P < 0.0001$. Also, ADHD subjects had higher PM symptoms than LNCG, with PM means over all time points of 1.3 ADHD; 0.9 LNCG; $P = 0.0001$. Examining both NSM and PM, ADHD status associated with greater NSM than PM. However, Over 14 years, the NSM symptoms declined and changed to PM over time (df 3, 2523; F = 20.1; $P < 0.0001$). Finally, Irritability (BD DSM criterion-A2) rates were significantly higher in ADHD than LNCG ($\chi^2$ = 122.2, $P < 0.0001$), but irritability was associated more strongly with NSM than PM (df 3, 2538; F = 43.2; $P < 0.0001$).

**CONCLUSION:** Individuals with ADHD do not appear to be at significantly greater risk for developing BD, but do show higher rates of BD symptoms, especially NSM. The greater linkage of irritability to NSM than to PM suggests caution when making BD diagnoses based on irritability alone as one of 2 (A-level) symptoms for BD diagnosis, particularly in view of its frequent presentation with other psychopathologies.

**Key words:** Multimodal treatment study of attention deficit hyperactivity disorder; Irritability; Attention deficit hyperactivity disorder; Diagnostic interview schedule for children; Bipolar disorder



**Core tip:** Despite its formal DSM delineation, alternative pediatric bipolar disorder (BD) definitions have been debated for decades. Some research suggests that attention deficit hyperactivity disorder (ADHD) poses a risk for BD and that pediatric BD presents differently as non-episodic, greater chronicity, and more frequent irritability. In our study, we found the ADHD status is not a risk factor for developing BD over 14 years of follow-ups. When we controlled for overlapping ADHD/BD, nonspecific symptoms showed decreasing rates of BD in ADHD-diagnosed children. Clinicians are encouraged to pay greater attention to specific symptoms of mania in order to establish an accurate BD diagnosis. Furthermore, irritability (DSM criteria A2), was a nonspecific symptom of mania and linked to common psychopathologies in the early development of these children.

Elmaadawi AZ, Jensen PS, Arnold LE, Molina BSG, Hechtman L, Abikoff HB, Hinshaw SP, Newcorn JH, Greenhill LL, Swanson JM, Galanter CA. Risk for emerging bipolar disorder, variants, and symptoms in children with attention deficit hyperactivity disorder, now grown up. *World J Psychiatr* 2015; 5(4): 412-424 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/412.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.412

## INTRODUCTION

Bipolar disorder (BD) is a chronic mental illness affec-

ting approximately 5.7 million United States children and adults, with adult prevalence rates about 2.6% of the United States population[1]. Pediatric bipolar disorder (PBD) has been surrounded by considerable debate[2] with experts divided about applying the adult -based DSM-IV criteria to children and adolescents[3]. Proponents for different criteria[4,5] argue that children are less likely to show clear episodes, more likely to demonstrate more chronic mania-like symptoms, and more often meet Criterion A principally *via* Irritability, not Euphoria[3]). If these arguments are correct then BD not otherwise specified (rather than BP type Ⅰ with mania or BP type Ⅱ with hypomania) might be the most accurate diagnostic "label" to characterize these children[5-7]. Yet many of these same children could also be appropriately diagnosed with attention deficit hyperactivity disorder (ADHD), comorbid with Oppositional Defiant Disorder (ODD), anxiety, depression, and/or intermittent explosive disorder. This lack of clarity and agreement among researchers and clinicians on the diagnostic criteria may have contributed to the forty-fold rise in reported prevalence of PBD over the last two decades[8].

Additional difficulties in PBD diagnostic clarity may be due to the overlap in some of the (mania) symptom criteria with ADHD criteria, such as "inattention" (ADHD) and "distractibility" (BD); "often talks excessively" (ADHD) and "more talkative than usual" (BD); and is often "on the go" or often acts as if "driven by a motor" (ADHD) and "increased goal directed activity or psychomotor agitation" (BD). In addition, many symptoms commonly occurring within children with ADHD (even though not currently part of the symptom criteria), but explicitly identified within BD (mania) criteria include "decreased need for sleep" and "irritability". Because this latter symptom is common in ADHD and most other mental disorders, researchers have tried to distinguish whether irritability is (or should be) a major Criterion A for BD[9,10].

Although the co-occurrence of ADHD and BD is well documented, has a distinct phenotype, and evinces more unfavorable outcomes than either disorder alone[11,12], identifying each disorder in the context of the other remains a challenging task for clinicians. Though some research suggests that children with ADHD are at increased risk of developing BD[13], the actual proportion of ADHD children who eventually develop BD remains controversial[14-16]. The Longitudinal Assessment of Manic Symptoms (LAMS) study ($n$ = 707, aged 6-12)[11] reported that ADHD and BD comorbidity was no greater than chance considering the rate of each disorder in the sample. Moreover, ADHD was not a significant risk for earlier BD; there was no difference in age of BD onset between the "BD alone" and "comorbid BD and ADHD" groups, and there was no cross-diagnosis familial loading[17]. In addition, Mannuzza *et al*[18] in a review of comorbidity in ADHD, identified both limitations and gaps in the current literature with regard to the estimates of comorbidity in both adult and childhood ADHD. Their 33-year follow-up study revealed no significantly greater risk for emergence of BD within ADHD than found in the general population.

Investigators attempting to understand the degree of risk conferred by the presence of one condition to develop the other have adopted several strategies, including analyses that attempt to control for, or remove, confounding (or overlapping) ADHD/BD symptoms[16]. Such analyses lead to substantial reductions (24%-53%) in the proportions of ADHD/BD-dually diagnosed children, who continue to meet BD diagnostic criteria[19,20]. Even when the issue of overlapping symptoms is accounted for, studies have generated different estimates concerning the likelihood that children with ADHD manifest BD, either cross-sectionally or longitudinally, with estimates ranging from 28%[21] to as low as 1.5%[18,22], leading critical reviewers to call for additional research, especially longitudinal studies that might clarify the exact nature of the relationship between ADHD and BD[23]. Another strategy Brotman *et al*[24] utilized to recognize bipolar variants which identified youths with chronic irritability phenotype that lacked the pathognomonic symptoms of euphoria and grandiosity, thereby creating the clinical syndrome called severe mood dysregulation or (SMD). Interestingly, in comparison to the episodic narrow band BD, youngsters with SMD have a higher rate of ADHD comorbidity. Such intermediate phenotypes' of child bipolar diagnoses has been a significant advance for the field. Therefore, following Leibenluft's research, investigators were interested to differentiate subtypes of BD and its relationship with ADHD.

Moreover, given the possible overlap of some ADHD and BD symptoms, including some clinically challenging symptoms that often complicate the course and management of both conditions (irritability, aggression)[25], as well as the genetic characteristics shared between them[26], researchers have increasingly called for a strategy of studying children with ADHD, in order to better understand the prevalence of bipolar symptomatology and the BD diagnosis[7].

For researchers striving to obtain unbiased estimates of the likelihood of a child diagnosed with ADHD concurrently meeting criteria for or eventually developing full symptoms of BD, epidemiologically ascertained, prospectively followed samples are required. In the absence of such data (usually the case within the continental United States), one viable strategy might be to study the emergence of BD within an ADHD sample, assuming that the ADHD sample has been identified early (before BD onset), rigorously-defined, longitudinally followed, and is generally representative of children with ADHD[6,27].

The longitudinal database now available from the NIMH Multimodal Treatment Study of Children with ADHD (MTA)[28-30] might be used to better understand the emergence of BD, given the early diagnosis of ADHD. Although the MTA's principal aim was to evaluate different treatment approaches for ADHD, the study employed a rigorous assessment strategy, large sample size, geographic diversity and heterogeneity, and all

of the diagnostic advantages afforded by following participants into young adulthood, when BD most often emerges[31]. We analyzed BD and ADHD at the symptom level from baseline through the 14-year follow-up data, in order to determine whether or not participants demonstrate BD and BP-NOS variants over follow-up.

## MATERIALS AND METHODS

### Study Sample

At study outset, MTA investigators recruited 579 children (ages 7.0-9.9 years) with DSM-IV ADHD-Combined Type across 6 sites. Eighty percent of the sample was males and 20% were females (M = 465, F = 114). Sixty one percent of ADHD subjects were white Caucasian, 20% were African American and 8% were Hispanics. For comparison purposes, a "local normative comparison group" (LNCG, *n* = 289) was added to the study at 24 mo from the original baseline. LNCG children were matched with the initially selected children with ADHD, in order to reflect the same community, school, sex (Males = 235, Females = 54), and age composition as original participants. Children with presumed BD were meant to be excluded. Also, children on anti-psychotic agents or hospitalized within the last 6 mo were excluded. The institutional review board at the Mayo Clinic, Rochester, Minnesota approved the study, last approval date 10/31/2014; IRB number 12-00748. The study was determined as minimal risk retrospective chart review.

### Assessment points

ADHD participants were evaluated at baseline, 14, 24, 36 mo, and then at 6, 8, 10, 12, and 14 years. LNCG participants completed the same assessments at 24 mo (LNCG baseline) and beyond.

### Diagnostic assessments

The Diagnostic Interview Schedule for Children (DISC), developed by NIMH to assess more than 30 mental disorders, was administered to both parents (DISC-P) and youth (DISC)[32]. Through 3-year follow-up the DISC-P was used, followed by DISC Ver. 2.3/3.0 with both child and parent at the 6 years follow-up, then the DISC4 for parents at 8 years follow-up, and finally, a young adult self-report version of the DISC (DISC-YA) at the 12- and 14-year follow-ups. For this study, we focus on the DISC mania and hypomania assessments at 6, 8, 12, and 14 years. At those four follow-up assessments, retention rate of study participants with completed mania and hypomania assessments were: ADHD: 76%, 62%, 65%, and 73%; LNCG: 85%, 76%, 82%, and 84%, respectively.

### DISC bipolar diagnoses

Computer programs were used to generate the DSM diagnoses of Mania or hypomania within the last year's timeframe covered within DISC interviews. Diagnoses were based on the DISC-YA (self-report), since parents rarely completed these diagnostic data at the final 2 time points, once youth reached ages > 18 years.

### DISC bipolar symptoms

In addition to generating Mania or Hypomania diagnoses, the DISC assesses each of the individual symptoms that are required in order to meet BD diagnostic criteria. Thus, the DISC mania module inquires about 13 symptoms that are used to establish the presence or absence of the 9 DSM-IV A and B criteria of mania or hypomania. Thirteen questions are required because a) "inflated self-esteem or grandiosity" is broken into 2 questions; and "increased goal directed activity (social, work or sexual) or agitation" is broken into 4 questions. Within the DISC, when a specific symptom is endorsed, additional questions were asked to determine if that symptom is truly positive, according to the DSM criteria (*e.g.*, does that symptom meet the additional criteria for symptom duration, associated impairment, co-occurrence with other symptoms, *etc.*). Those symptoms that met these stringent criteria were counted in a "Total Symptom Count" (TSC).

### Identifying DISC-derived bipolar variants

Following previous investigators[16] we computed TSC-modified (TSC-M) scores, by subtracting 3 BD symptoms that could be considered to overlap with the ADHD symptoms of talkativeness, distractibility, and "on the go" (restlessness).

Besides these three symptoms, many others that occur in children with ADHD are also important for bipolar diagnosis, *e.g.*, irritability. Therefore, we decided to examine BD symptomology by separating symptoms more specific to mania (pathognomonic) from non-specific symptoms. Pathognomonic Manic (PM) symptoms included elevated mood, grandiosity, inflated self-esteem, and increased goal directed activity (socially, sexually, and at work) (*n* = 6); and Non-Specific Manic (NSM) symptoms included irritability, decreased need for sleep, impulsive behavior, racing thoughts, pressured speech, distractibility, and restlessness (*n* = 7) (total = 13).

### Evaluating irritability criteria

Irritability was evaluated at the symptom level to determine if it was more likely to correlate with elevated PM or NSM (excluding irritability) scores, and whether this differed between ADHD and LNCG.

### Statistical analysis

Descriptive analyses were performed for all symptom and diagnosis frequency rates, comparing differences in frequency between MTA and LNCG subjects $\chi^2$ (and Fishers Exact Tests when appropriate). Subsequent analyses examined TSC across all subjects and compared group TSC means between ADHD and LNCG subjects. Second, given the longitudinal nature

**Table 1 Diagnostic interview schedule for children-computed bipolar diagnoses in attention deficit hyperactivity disorder group and local normative comparison group at 6, 8, 12, and 14 years follow-ups**

| | ADHD | | | LNCG | | |
|---|---|---|---|---|---|---|
| | Mania | Hypomania | Prevalence (%) | Mania | Hypomania | Prevalence (%) |
| 6 yr | 1 | 1 | 0.45 | 0 | 0 | 0 |
| 8 yr | 2 | 3 | 1.38 | 1 | 1 | 0.93 |
| 12 yr | 1 | 2 | 0.79 | 1 | 0 | 0.42 |
| 14 yr | 1 | 0 | 0.24 | 0 | 1 | 0.41 |
| Total | 5 | 6 | 1.89 | 2 | 2 | 1.38 |

ADHD: Attention deficit hyperactivity disorder; LNCG: Local normative comparison group.

**Table 2 Diagnostic interview schedule for children-bipolar diagnosis consistency at 6, 8, 12, and 14 years follow-ups**

| | | 6 yr | 8 yr | 12 yr | 14 yr | Total |
|---|---|---|---|---|---|---|
| LNCG | Manic | Missing | Yes | No | No | 2 |
| | | No | No | Yes | No | |
| | Hypomanic | No | Yes | No | No | 2 |
| | | No | No | No | Yes | |
| ADHD | Manic | Yes | No | No | No | |
| | | No | Yes | Missing | No | |
| | | No | Yes | No | No | 5 |
| | | No | No | Yes | No | |
| | | No | No | No | Yes | |
| | Hypomanic | Yes | No | No | No | |
| | | No | Yes | No | No | |
| | | No | Yes | No | No | 6 |
| | | No | Yes | No | No | |
| | | No | Missing | Yes | No | |
| | | No | No | Yes | No | |

ADHD: Attention deficit hyperactivity disorder; LNCG: Local normative comparison group.

of the study and availability of multiple values for key outcomes (TSC, NSM, PM, *etc.*) within and across individuals over time, we used mixed-effects random regression methods (RRM) to examine the effects of group status (ADHD *vs* LNCG) or Irritability (Y/N), time, and group × time across all time points. The entire model tests the effect of the 3 variables interacting with each other. Now the preferred approach over traditional repeated measures ANOVAs for longitudinal studies, RRM allows all cases (even those with missing data) to contribute to the overall analysis, and may be less subject to selection/attrition biases.

## RESULTS

### *DISC bipolar diagnosis*

No significant differences were found between ADHD and LNCG groups in the frequency of mania/hypomania clinical diagnoses at any assessment point of 6, 8, 12, or 14 years ($\chi^2$ = 0.024, $P$ = 0.8). In fact, the prevalence rates, 0.24%-1.38% at different times for the ADHD subjects and 0%-0.93% at different times for the LNCG subjects, were very close to estimated bipolar prevalence rates in the general (adult) population. Fifteen subjects were diagnosed with DISC-Mania ($n$ = 7) and Hypomania ($n$ = 8). Their demographic differences from the whole sample were: 60% *vs* 80% males; 53% *vs* 62% Caucasian; one third *vs* 18% African-American (Table 1). Interestingly, the total of 15 participants (4 LNCG and 11 ADHD), met the DISC computed BD only once in all assessment points in 6-, 8-, 12- and 14-years (Table 2).

### *Bipolar symptom level*

At all assessment points (6-, 8-, 12- and 14-years), ADHD subjects reported significantly more of the 13 symptoms of the DISC mania/hypomania module (TSC) with means of 3.0 (ADHD) and 1.7 (LNCG) symptoms (Table 3). RRM confirmed significant effects of the overall model (df 3, 2538; F = 63.9; $P$ < 0.0001), as well as all specific factors within the model: group status (ADHD *vs* LNCG) (F = 177.1; $P$ < 0.0001), time (F = 5.1; $P$ < 0.02), and change of symptoms in groups over time (F = 5.4; $P$ < 0.02). Thus, although ADHD subjects did not show higher rates of BD diagnoses, they did have almost twice the rates of bipolar-mania symptoms at the 4 assessment points, and over time. They did have almost twice the rates of bipolar-mania symptoms at the 4 assessment points, and over time.

### *Bipolar variants*

In order to explore the possible ADHD - mania sym-

**Table 3 Diagnostic interview schedule for children bipolar mania total symptoms count in attention deficit hyperactivity disorder and local normative comparison group**

| Assessment point | ADHD | | LNCG | | DF | F ratio | *P* values |
|---|---|---|---|---|---|---|---|
| | *n* | Mean ± SD | *n* | Mean ± SD | | | |
| 6 yr | 441 | 3.38 ± 2.54 | 246 | 1.85 ± 1.93 | 1687 | 68.58 | < 0.0001 |
| 8 yr | 360 | 2.89 ± 2.3 | 219 | 1.45 ± 1.69 | 1578 | 63.70 | < 0.0001 |
| 12 yr | 378 | 3.05 ± 2.85 | 236 | 1.77 ± 2.07 | 1613 | 35.80 | < 0.0001 |
| 14 yr | 420 | 2.64 ± 2.59 | 242 | 1.72 ± 2.00 | 1661 | 22.51 | < 0.0001 |
| TSC Over Time | 579 | 3.0 ± 0 | | | 32538 | 63.9 | < 0.0001 |

ADHD: Attention deficit hyperactivity disorder; LNCG: Local normative comparison group; TSC: Total symptoms count.

ptom confounds, as well as symptom specificity, we proceeded in the following three steps:

After applying the Wozniak adjustment to remove bipolar symptoms that overlapped with ADHD diagnostic criteria[16], we calculated modified TSC scores (TSC-M) for both groups. RRM analysis revealed that ADHD group subjects continued to endorse significantly more symptoms, with TSC-M means of 2.2 (ADHD) and 1.4 (LNCG) (df 3, 2538; F = 38.8; $P < 0.0001$). ADHD *vs* LNCG group status was the only factor linked to higher TSC-M (F = 114.8; $P < 0.0001$), and neither time nor group x time factors contributed significantly.

Likewise, overall RRM analyses of PM were significant (df 3, 2524; F = 30.5; $P = 0.0001$), with PM means over all time points of 1.3 (ADHD) and 0.9 (LNCG). Both ADHD *vs* LNCG group status and time were significant factors for PM decreasing with time (F = 71.2; $P < 0.0001$; and F = 17.6; $P < 0.0001$, respectively) but not group × time).

Finally, the RRM analyses of NSM comparing groups over time yielded significant overall model effects (df 3, 2537; F = 69.3; $P < 0.0001$); with means of 2.0 (ADHD) and 1.1 (LNCG), and with significant ADHD *vs* LNCG group status: F = 194.7; $P < 0.0001$ and group × time: F = 12.1; $P = 0.0005$. These NSM differences in means between the ADHD and LNCG groups appeared twice as large as differences found above in PM scores, raising the possibility of a group (ADHD *vs* LNCG) × symptom type (PM *vs* NSM) interaction.

To examine this possible interaction, and to provide a sensitive test of the differential association of the relative proportions of PM *vs* NSM symptoms in ADHD *vs* LNCG subjects, we divided each subjects' total PM by the total possible number of PM symptoms, thereby generating for each one a specific ratio (0.0 to 1.0) of PM symptoms; we also computed similar ratios for NSM for each subject (again, 0.0 to 1.0). Then, to test the interaction, *i.e.*, differences in their relative proportions of PM *vs* NSM symptoms, we constructed a new variable by subtracting the NSM ratio from the PM ratio for each subject at each time point, thus generating *rPM* - rNSM difference scores, yielding a possible range of differences from -1.00 to +1.00 for each subject (positive score 0 to +1.0 is associated with PM and negative score -1.0 to 0 with NSM). Upon testing ADHD *vs* LNCG subjects on these difference scores, groups differed significantly, with disproportionately higher NSM ratios in subjects with ADHD, and significant change of ADHD group, shifting from NSM to PM over time. The entire RRM was significant (df 3, 2523; F = 20.1; $P < 0.0001$). All Variables were significantly linked to *rPM* - rNSM difference scores, including group status, time, and group × time (Figure 1).

Finally, we sought to examine the role of irritability across both ADHD and LNCG, and to assess its possible specificity/non-specificity as a key mania symptom criterion (Criteria A2), following 3 steps:

First, we calculated irritability criterion frequencies across the 2 groups. As expected, ADHD subjects reported significantly higher irritability compared to LNCG subjects, with relative risk of irritability 2.01 in ADHD subjects compared to the LNCG across the entire study ($\chi^2 = 122.2$, $P < 0.0001$).

We then assessed the relationship between irritability and the 2 mania symptom subscales (PM and NSM), after adjusting NSM values to remove irritability from its totals. The RRM model revealed that irritability was associated with both scales (PM: df 3, 2524; F = 86.5; $P < 0.0001$; NSM: df 3, 2524; F = 114.6; $P < 0.0001$).

Because irritability was associated with both PM and NSM, we created difference score ratios as described in paragraph 3 above, allowing us to examine any differences in irritability associations between PM and NSM across LNCG and ADHD subjects. Findings revealed that compared to LNCG subjects, ADHD subjects' likelihood of manifesting irritability significantly increased over time as the PM-NSM difference score decreased (became more negative) towards a greater preponderance of NSM symptoms (Overall Model RRM: df 3, 2538; F = 43.2 $P \leqslant 0.0001$). All variables were linked to PM-NSM difference scores (irritability status, time, and irritability × Time (see Figure 2).

## DISCUSSION

Our prevalence analyses of PBD and adult BD from DISC-computed mania and hypomania diagnoses among subjects with and without ADHD (MTA *vs* LNCG subjects) revealed no significant differences in the small numbers and proportions of individuals meeting DSM BD criteria, paralleling the results of Mannuzza[33].

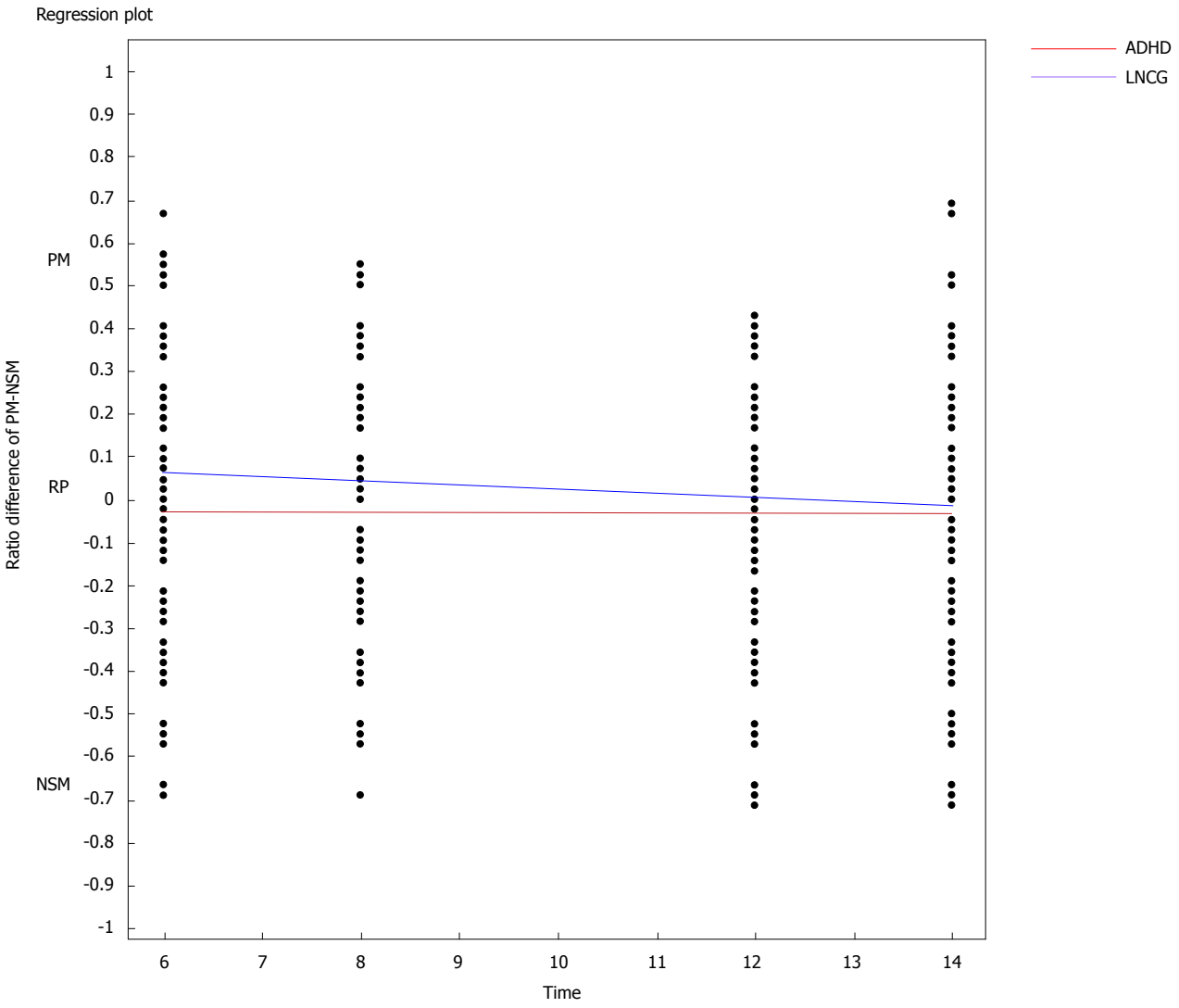


**Figure 1 Attention deficit hyperactivity disorder and local normative comparison group in relation to the relative proportion which represents the ratio of pathognomonic mania - the ratio of non- specific mania across all study subjects.** Positive score 0 to +1.0 is associated with more PM than NSM. Negative score -1.0 to 0 is as associated with more NSM than PM. Entire Model was significant RRM (df 3, 2523; F = 20.1; $P \leqslant 0.0001$). All Variables (Group status, assessments time, and the changes of group status over time) were linked to RP changes (effect of Groups Status: F = 39.9; $P \leqslant 0.0001$- effect of Time: F = 14.7; $P \leqslant 0.0001$, and the interaction of Group × Time: F = 12.1 $P \leqslant 0.0005$). ADHD patients started with a preponderance of NSM over PM symptoms and the LNCG with a preponderance of PM over NSM symptoms, but the ratios converged over time. RP: Relative proportion; PM: Pathognomonic mania; NSM: Non- specific mania; ADHD: Attention deficit hyperactivity disorder; LNCG: Local normative comparison group.

Interestingly, despite the fact that all subjects who were diagnosed with mania or hypomania by the DISC were evaluated at least 3 times, and 80% of them were evaluated in all 4 assessment points (6-14 years), none received mania or hypomania diagnoses more than once (Table 1). These findings raise questions about the stability of BD diagnoses over time, especially during early development - assuming reliability of the DISC, DIS, and DISC-YA[32]. After Shaffer *et al*[32] developed the DISC, many researchers widely evaluated the reliability and validity of the DISC, in comparison to other diagnostic tools. The results were consistent with high test-retest reliability across the study sample[34,35].

Various large epidemiological studies over the last 3 decades both in the United States and Europe have also noted that the diagnostic stability of all affective disorders (BP Ⅰ, BP Ⅱ, and major depressive disorder) varied depending on socioeconomic and even cultural factors[36,37]. Knowledgeable commentator-skeptics have raised concerns that both clinicians and clinical investigators alike are prone to succumb to the "Clinician's Illusion" as observed in psychosis[38]. Almost 30% of individuals who suffered from a psychotic episode never re-experience further episodes after the first one - a finding that is likely only observable within community-wide, diagnostically rigorous longitudinal studies. Nonetheless, these concerns must be tempered by the realization that BD is by definition episodic, so that varying presence of diagnostic symptoms over time is to be expected.

Given the lack of significant differences found here between subjects with ADHD and local normative

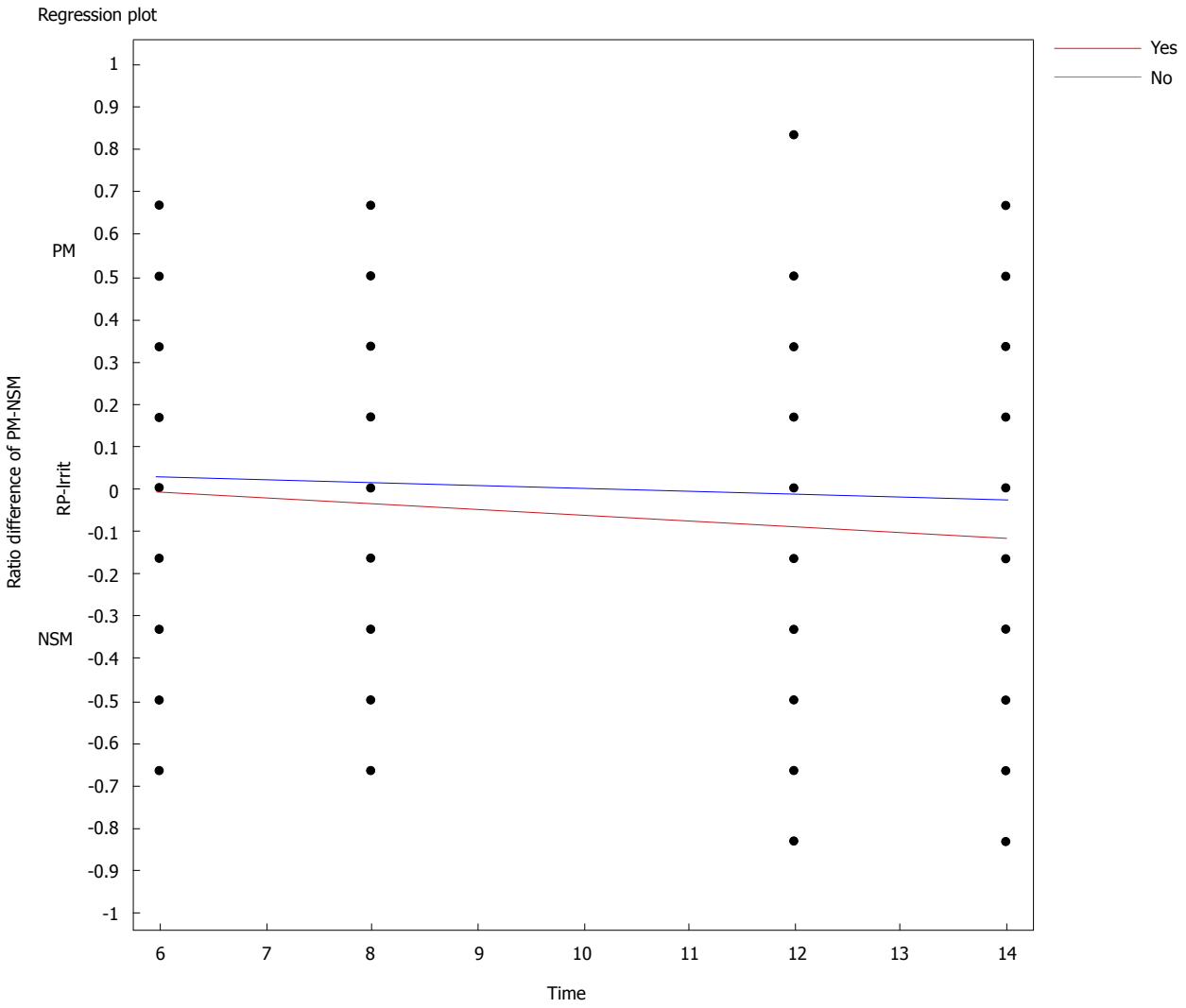


**Figure 2 Group (The Irritability Criterion with irritability *vs* No irritability) in relation to relative proportion of Pathognomonic Mania Ratio - Non-Specific Mania Ratio: Positive score 0 to +1.0 links irritability to pathognomonic mania rather than non- specific mania and negative score -1.0 to 0 links the irritability status with non- specific mania rather than pathognomonic mania: Entire Model Random Regression Methods (df 3, 2523; F = 17.7; *P* < 0.0001).** All Variables (Group status, assessments time, and the changes of group status over time) were linked to RP changes (effect of Irritability Status: F = 27.3; *P* < 0.0001; effect of Time: F = 32.5; *P* < 0.0001, and interaction of Irritability × Time: F = 4.3; *P* < 0.04). Irritability is linked at all time points with greater NSM than PM, and the linkage increases over time. Yes: Irritability present; No: Irritability not present. RP: Relative proportion; PM: Pathognomonic mania; NSM: Non- specific mania; ADHD: Attention deficit hyperactivity disorder; LNCG: Local normative comparison group; RRM: Random regression methods.

comparison subjects in BD diagnoses, we sought to determine if individuals from the ADHD group had more sub-threshold BD symptoms compared to the LNCG group. These analyses revealed that in fact, ADHD study subjects had higher BD symptoms (TSC scores) than LNCG subjects. Higher TSC in children with ADHD may count for the 40 folds increase in the BD diagnosis in the community. Although some authors have indicated that childhood ADHD may pose risks for developing BD over time; these 14-year longitudinal findings call this conclusion into question. We found an interesting decline of the TSC score over time in ADHD subjects. Eventually the TSC scores of young adults with ADHD were more similar to LNCG subjects by 14 years (though still significantly greater). Although childhood ADHD was unrelated to full BD diagnosis, it did pose a significant risk for BD symptoms (TSC) over time. However, the presence of an interaction effect (time × group) indicated that these symptom elevations (*vs* LNCG) decreased from 6 to 14 years' follow-up. It is possible that these decreases in TSC counts might continue their declines over time.

These results are compatible with cross-sectional baseline analyses from the LAMS study[11,17]. This sample was clinically recruited to be enriched with high levels of manic symptoms, but more of the children (age 6-12) had ADHD than bipolar spectrum disorder, illustrating the overlap of NSM. Considering the possibility of Berkson bias (independent psychiatric disorders may associated in clinical sample due to the higher chance of seeking medical attention)[39], yet the overlap of diagnoses (comorbid ADHD and BD) was no greater than expected by chance from the prevalence of each disorder in the sample. The ADHD-alone children

had fewer manic symptoms than those with BD alone but more than those with neither diagnosis (those with other psychiatric diagnoses), while the BD-alone children had more ADHD symptoms than those with neither diagnosis but less than those with ADHD alone. The ADHD-alone children had the same frequency of irritability as those with neither ADHD nor BD, which was half the rate in those with BD (with or without comorbid ADHD).

One possible interpretation is that the confounding of ADHD-associated symptoms with BD diagnoses may result in differences between ADHD subjects' *vs* normal comparison children's TSC scores during earlier development, and over time these confounding symptoms dissipate. Thus, the application of developmental considerations within DSM-5 in the classification of mental illness may help clinicians and researchers to be more careful making the BD diagnosis in the earlier stages of development[40].

Seeking to understand these differences in TSC scores, we like previous investigators (15), evaluated BD at the symptom level, eliminating DSM ADHD/BD overlapping symptoms (distractibility, on the go-restlessness, and talkativeness). Taking further steps to "unpack" and better understand BD symptoms, we separated those BD symptoms that might be a part of a non-specific presentation with ADHD (NSM) from those that were more specific to BD (PM). We found that ADHD-diagnosed subjects who presented with one or more BD symptoms were more likely than LNCG subjects (with one or more BD symptoms) to show elevated NSM (*vs* PM) symptoms. Thus, the 6 PM symptoms as we defined them (expansive or euphoric mood, inflated self-esteem, grandiosity, and increased goal directed activity) were relatively less likely to be present among ADHD subjects with a BD symptom than comparison subjects with a BD symptom.

Although later follow-ups may raises the question of self-report bias in ADHD subjects that lean to under report, however our analyses of PM and NSM changes over time among ADHD *vs* control subjects showed a time × diagnostic status (ADHD *vs* LNCG) effect for NSM only, revealing a gradual greater diminution of non-specific mania symptoms among ADHD than among LNCG subjects. Moreover, children with ADHD had persistently stable PM differences from LNCG subjects. The gradual abatement of NSM symptoms may facilitate distinguishing between ADHD and BD in older adolescents and adults; conversely the distinction may be obfuscated at earlier ages. The clinical implication is to observe over time in doubtful cases, as recommended by the LAMS group[41].

Although the differences in PM and NSM counts between ADHD and LNCG subjects were small, they appeared twice as large for NSM as for PM (mean symptom difference between ADHD and LNCG was 0.4 for PM and 0.9 for NSM) with both counts higher in ADHD than LNCG subjects. ADHD subjects had proportionally more NSM and PM symptoms, compared to LNCG subjects, with the difference diminishing over time. One might speculate that ADHD subjects tend to be "messy", *i.e.*, have many associated non-specific symptoms) during earlier childhood years, and these non-specific symptoms (if they overlap with BD criteria) might result in ADHD subjects being misdiagnosed with Bipolar disorder (NOS or even Ⅰ or Ⅱ), despite their lacking most PM symptoms. It is unclear if such children/youth carry some bipolar genes or have a sub-threshold bipolar variant, or perhaps a different disorder altogether. However, the fact that the symptom counts decrease over time makes this unlikely. One way to guard against early over diagnosis is to require episodicity and at least 3 of the pathognomonic symptoms, as done in the COBY and LAMS longitudinal studies. We may also hypothesis association of the paradigm shift of BD symptoms and the decline in impulsivity-hyperactivity symptoms of ADHD over time.

To further understand these elevations in NSM symptomatology in ADHD *vs* LNCG subjects, we examined the irritability criterion, particularly in view of its inclusion as one of A criteria in DSM for BD, and given its common phenotypical presentation in child psychopathology, including ADHD. Our results were compatible with findings from other studies[42]: children with ADHD are more irritable than the normal population, and over time, fewer young adults with ADHD report the irritability symptom, in contrast to a more stable but lower-level presence in LNCG subjects (significant group × time effects). However, due to the increasing linkages over time of irritability with NSM symptoms (*vs* PM symptoms) in both ADHD and LNCG groups, our final PM-NSM difference score analysis vis-à-vis irritability suggests that irritability may be a non-specific component of chronic psychopathology, not only for BD, but also for unipolar depression, anxiety, ADHD and other forms of psychopathology. In their study of patients with a subtype of SMD, Stringaris *et al*[43] also reported such conclusions. If irritability is indeed increasingly linked to NSM symptoms over time, the question might be raised, should we reconsider irritability as an A criterion for the diagnosis of BD? It is possible that the new DSM-5 disruptive mood dysregulation disorder diagnosis may help clinicians find a more fitting diagnosis for children with chronic, severe irritability, although initial studies of its reliability raise concerns about its viability[44].

Future BD diagnostic criteria might need to eliminate symptom confounds and overlaps. For example an exclusionary clause might be created - *i.e.*, in the presence of childhood ADHD, more symptoms might be required, or "irritability" might be excluded as an A criterion. More longitudinal research is required, both of patients first identified by manic symptoms (*e.g.,* LAMS), and of those first identified with ADHD, if we are to fully understand what symptoms should characterize "true" BD or its variants across development, in view of longitudinal studies of high-risk children from parents with BD[45]. These studies indicate that emerging BD

is not characterized by early onset irritability or ADHD, but instead by unfolding anxiety symptoms and sleep disturbances, before the first manic or hypomanic episode.

The limitation of our study involves the confining use of using a structure interview (DISC) that does not interpret invalid responses or atypical presentations, despite the fact that the assessment was conducted by experienced trained interviewers. There is also the possibility of positive illusionary bias in the ADHD group from self- reporting[46]. Moreover, like most retrospective studies, we were subject to recall bias, especially with relatively long follow-up over 14 years, and lengthy assessment intervals. The retention rate over 14 years was 75%, which also created a possible differential dropout in subjects with severe symptoms. With such limitations, we attempted to overcome the under-sample bias with RRP analysis.

Our findings suggest that individuals with childhood ADHD followed into early adulthood (ages 21-24) do not appear to be at a significantly greater risk for developing the full diagnostic picture of BD than comparison subjects. Although adolescents/young adults with ADHD do report modestly higher BD symptoms (*e.g.*, TSC scores) over time than comparison subjects, one might expect higher symptoms of many different types among patients who have been ascertained on the basis of having at least one disorder (ADHD, in this case), compared to non-clinical community subjects. These BD symptom elevations tend to be non-specific rather than pathognomonic, and they decline over time in adolescence and young adulthood. Further, BD diagnosis was not persistent at early stages of development. Irritability, one of the A criteria for BD diagnosis, was more associated with NSM than PM symptoms. Our findings suggest caution when making BD diagnoses in youth and young adults with histories of childhood ADHD. Moreover, because the irritability criterion was linked to increases in the percentage of non-specific rather than pathognomonic bipolar symptoms, future BD classification attempts should consider whether its continued inclusion as one of 2 alternative essential (A-level) criteria for BD diagnosis is warranted in children. A possible solution is to require more PM symptoms when irritability is used for the A criterion, as was done for bipolar-NOS in the LAMS and COBY studies.

## ACKNOWLEDGMENTS

The Multimodal Treatment Study of Children with ADHD (MTA) was a National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial, continued under an NIMH contract as a follow-up study and finally under a National Institute on Drug Abuse (NIDA) contract. Collaborators from NIMH: Benedetto Vitiello, M.D. (Child and Adolescent Treatment and Preventive Interventions Research Branch), Joanne B. Severe, M.S. (Clinical Trials Operations and Biostatistics Unit, Division of Services and Intervention Research), Peter S. Jensen, M.D. (currently at REACH Institute and Mayo Clinic), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Kimberly Hoagwood, Ph.D. (currently at Columbia); previous contributors from NIMH to the early phases: John Richters, Ph.D. (currently at National Institute of Nursing Research); Donald Vereen, M.D. (currently at NIDA). Principal investigators and co-investigators from the sites are: University of California, Berkeley/San Francisco: Stephen P. Hinshaw, Ph.D. (Berkeley), Glen R. Elliott, Ph.D., M.D. (San Francisco); Duke University: Karen C. Wells, Ph.D., Jeffery N. Epstein, Ph.D. (currently at Cincinnati Children's Hospital Medical Center), Desiree W. Murray, Ph.D.; previous Duke contributors to early phases: C. Keith Conners, Ph.D. (former PI); John March, M.D., M.P.H.; University of California, Irvine: James Swanson, Ph.D., Timothy Wigal, Ph.D.; previous contributor from UCLA to the early phases: Dennis P. Cantwell, M.D. (deceased); New York University: Howard B. Abikoff, Ph.D.; Montreal Children's Hospital/McGill University: Lily Hechtman, M.D.; New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill, M.D. (Columbia), Jeffrey H. Newcorn, M.D. (Mount Sinai School of Medicine). University of Pittsburgh: Brooke Molina, Ph.D., Betsy Hoza, Ph.D. (currently at University of Vermont), William E. Pelham, Ph.D. (PI for early phases, currently at Florida International University). Follow-up phase statistical collaborators: Robert D. Gibbons, Ph.D. (University of Illinois, Chicago); Sue Marcus, Ph.D. (Mt. Sinai College of Medicine); Kwan Hur, Ph.D. (University of Illinois, Chicago). Original study statistical and design consultant: Helena C. Kraemer, Ph.D. (Stanford University). Collaborator from the Office of Special Education Programs/US Department of Education: Thomas Hanley, Ed.D. Collaborator from Office of Juvenile Justice and Delinquency Prevention/Department of Justice: Karen Stern, Ph.D.

## COMMENTS

### Background

Pediatric bipolar disorder (PBD) is one of the most debatable mental illnesses of our time. Experts have been divided about whether the adult-based DSM criteria apply to children and adolescents. Interestingly, the diagnosis of PBD has risen 40-fold over the last two decades with bipolar-NOS being the most common diagnostic type. The prevalence of PBD ranges from 2.6% to a higher prevalence of 6.4%, which was reported when the subthreshold cases were included rather than classic Bipolar Disorder (BD). The differences in rates and difficulties of capturing PBD are related to many factors. First of all, BD presents in children and adolescents differently from adult BD, as children are less likely to show clear, (*i.e.*, more chronic), episodes. Also, unlike adult bipolar, the most common Criteria A of mania in PBD is irritability, not euphoria. However, irritability is also a common symptom in many psychiatric disorders in children and adolescents. More importantly, there are notable overlaps in many of the specific symptom criteria for both PBD and more common disorders, such as attention deficit hyperactivity disorder (ADHD), thus making differentiating diagnosis challenging.

### Research frontiers

Misdiagnosing PBD would have detrimental consequences to children, if

ADHD treatments for such children prove to be harmful, or would delay more appropriate PBD treatments. Hence, the relation between PBD comorbid phenotype, and ADHD, has continued to be the source of considerable study and debate for many years. Thus, the new DSM-5 disruptive mood dysregulation disorder, is an attempt to reduce over-diagnosing pediatric BD.

### Innovations and breakthroughs

The auhors careful evaluation of bipolar symptoms suggests future revisions of the DSM may be necessary to re-evaluate the special status of irritability as one of two required (A criterion) symptoms for making a BD diagnosis.

### Applications

Findings suggest that individuals with carefully diagnosed ADHD may not be at a significant risk for developing BD, *vs* controls. Given the lack of meaningful diagnostic differences and only modest differences in PBD symptom counts, the auhors were surprised to find that childhood ADHD diagnostic status predicted a greater likelihood of non-specific mania symptoms, rather than more pathognomonic symptoms. This suggests that such elevations might reflect general psychopathology rather than BD, *per se*. Even irritability, one of the 2 "A" criteria required for BD diagnosis, was more associated with non-specific mania than specific symptoms. Findings suggest that clinicians should be cautious when making a PBD diagnosis with individuals with histories of childhood ADHD. Such individuals with elevated non-specific BP symptoms, (sometimes called "messy" ADHD), may in fact be just that - "messy ADHD". However, it is also possible that they may have a different disorder altogether, a question thus requiring more research and study.

### Terminology

MTA is the Multimodal Treatment Study of Children with ADHD (MTA). NIMH funded the study in the 90$^{th}$ of the last century. The main principal aim was to evaluate different treatment approaches for ADHD; the study employed a rigorous assessment strategy, large sample size, geographic diversity and heterogeneity of study subjects. DISC is a highly structured diagnostic interview assessment. NIMH to diagnose over 30 mental illnesses created it. TSC: Total symptoms count, which represents the total 13 questions that generated by the DISC to establish the diagnosis of Mania or Hypomania. PM: is the pathogmonic manic symptoms, included elevated mood, grandiosity, inflated self-esteem, and increased goal directed activity (socially, sexually, and at work), total of 6 DISC questions. NSM: Nonspecific manic symptoms included irritability, decreased need for sleep, impulsive behavior, racing thoughts, pressured speech, distractibility, and restlessness; total of 7 DISC questions.

### Peer-review

The present findings raise questions about the stability of BD diagnoses over time, in particular during early development. However, it is also important to state that the authors adopted in their study a structure interview (DISC) that does not consider invalid responses or atypical presentations.

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**P- Reviewer**: Hosak L, Serafini G, Yang YK
**S- Editor**: Tian YL **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Psychiatry

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DOI: 10.5498/wjp.v5.i4.425

*World J Psychiatr* 2015 December 22; 5(4): 425-431
ISSN 2220-3206 (online)


ORIGINAL ARTICLE

Observational Study

# Prevalence of substance use among moroccan adolescents and association with academic achievement

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Author contributions: All authors contributed to this manuscript.

Institutional review board statement: This study was reviewed and approved by the Moroccan Ministry of Education, who acted as effective institutional review board.

Informed consent statement: Passive parental consent was provided as approved by the Moroccan Ministry of Education.

Conflict-of-interest statement: The authors report no conflicts of interest.

Data sharing statement: Original data can be obtained by emailing Dr. El Omari at fatima_elomari@hotmail.com.



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Received: May 7, 2015
Peer-review started: May 8, 2015
First decision: July 10, 2015
Revised: August 26, 2015
Accepted: September 25, 2015
Article in press: September 28, 2015
Published online: December 22, 2015

## Abstract

**AIM:** To investigate rates of drug and alcohol use and their association with academic performance in Moroccan youth.

**METHODS:** An adapted version of the European School Project on Alcohol and Other Drugs survey was administered to 2139 10[th]-12[th] graders in 36 Moroccan public high schools. Two multiple logistic regressions were completed, one for male and one for female subjects. Grade average was used as a two-part outcome variable, and drug use was used as a four-level categorical independent variable. Parents' education levels and socioeconomic status were included as covariates.

**RESULTS:** Of the subjects, 181 girls (16%) and 390 boys (40%) reported ever having used alcohol, hashish, or psychotropic drugs. Girls who had used any of those substances in the past 30 d demonstrated an adjusted odds ratio (AOR) of 2.62 (95%CI: 1.31-5.22) of having average or below-average grades, and those with any lifetime use showed an AOR of 1.72 (95%CI: 1.07-2.77). Among the boys, use in the past 30 d was associated with an AOR of 2.08 (95%CI: 1.33-3.24) of average or below average grades, and use in the last 12 mo with an AOR of 1.74 (95%CI: 1.00-3.05). Any lifetime use among male and previous 12 mo use among female subjects were not significantly associated with academic achievement.

**CONCLUSION:** Among Moroccan adolescents, drug use is substantially different between boys and girls. In both genders, lower academic achievement was associated with alcohol, hashish, or psychotropic drug use in the last 30 d.

**Key words:** Morocco; Academic performance; Drug and alcohol use; Adolescence



**Core tip:** Adolescent drug and alcohol use in Morocco is insufficiently documented. This study investigates its prevalence, its association with academic achievement, and different use patterns between genders in the country. We obtained these data using an adapted form of the European School Project on Alcohol and Other Drugs survey administered to 2139 high school students at urban public schools. Of those subjects, 181 girls (16%) and 390 boys (40%) reported use of alcohol, hashish, or psychotropic drugs at some point in their lifetime. Lower grades in both genders were associated with use of any substance in the last 30 d.

El Omari F, Salomonsen-Sautel S, Hoffenberg A, Anderson T, Hopfer C, Toufiq J. Prevalence of substance use among moroccan adolescents and association with academic achievement. *World J Psychiatr* 2015; 5(4): 425-431 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/425.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.425

## INTRODUCTION

Drug and alcohol use is associated with a high level of worldwide morbidity and mortality. In 2010, an analysis of the World Health Organization's Global Burden of Disease survey showed that, after high blood pressure, the 2 top risk factors for global disease burden were tobacco smoking and alcohol consumption[1]. The health burden of drugs and alcohol is particularly severe in low- and middle-income countries, where alcohol and drug use disorders account for 19.5 million and 6.5 million disability-adjusted life years (DALYs), levels several times higher than those in the developed world[2]. This is particularly true for adolescents, among whom drug and alcohol use is the top risk factor for DALYs worldwide[3].

Despite this, epidemiological data for adolescent drug and alcohol use in the developing world is sparse[4], especially among Arab countries. Studies from the Middle East seldom focus on adolescents[5,6] and rarely examine both boys and girls[7].

This is the case in Morocco, a North African Arabic country with a population of over 30 million[8]. Although illegal and forbidden by Islam, alcohol and drugs are available in the country, and it is currently considered one of the largest exporters of cannabis in the world[9]. One of the few epidemiologic studies conducted in Morocco demonstrated that the population-based lifetime prevalence of alcohol and drug dependence is comparable to that in other countries[10]. The World Health Organization estimates the 12-mo prevalence of alcohol dependence to be somewhat lower than that of other countries, at 0.78% in men and 0% in women[8]. However, neither of these studies report data specific to adolescent drug and alcohol use.

In addition to its significant contribution to adolescent mortality and morbidity, drug and alcohol use has also associated with lower academic performance; however, these studies have primarily been conducted in developed countries. For example, low academic performance has been shown to correlate with tobacco and marijuana use in adolescents[11]. Maggs *et al*[12] reports that low academic performance is a predictor of cocaine and alcohol use among adolescent students. Again, the majority of the academic performance and substance use correlational studies have been performed in developed countries, with few in countries with emerging economies[13,14].

Male and female adolescents have distinct drug use characteristics and risk factors that contribute to their development of substance use disorders. Adolescent boys typically are at a greater risk of dangerous drinking behaviors than girls[15]. Gender differences in adolescent drug use characteristics also have important implications for designing effective treatment strategies[16].

In light of these factors, the present study was designed to investigate three items of interest: the prevalence of drug and alcohol use among high school students in Morocco, the gender differences in that prevalence, and the association of substance use and academic performance. This study uses a validated survey instrument that was translated and culturally adapted for use in Moroccan high schools.

## MATERIALS AND METHODS

### *Participants*

Participants ($n$ = 2139) were part of the Mediterranean School Survey Project on Alcohol and Other Drugs (MedSPAD), which is supported by the Pompidou Group at the Council of Europe[17,18]. The purpose of the MedSPAD project is to improve knowledge about drug use in the non-European Countries of the Mediterranean region.

Data were collected in 36 public urban high schools in two Moroccan cities: 20 high schools in Rabat and 16 in Salé. In February 2006, the surveys were distributed in the last 3 grades (10$^{th}$, 11$^{th}$, and 12$^{th}$ grades) in the 36 high schools. Seventy-three classes, including 24 in the 10$^{th}$ grade, 22 in the 11$^{th}$ grade, and 27 in the 12$^{th}$ grade, completed the survey.

Authorization for this study was obtained from the Moroccan Ministry of Education and all students gave verbal consent to participate. The survey was anonymous and voluntary; students were informed that they did not have to answer any questions, if they did not want to; however, there were no refusals. Only researchers, including a senior psychiatrist and seven resident psychiatrists, were in the classroom while the students completed the survey.

### *Measure*

The survey was developed by the European School Project on Alcohol and Other Drugs (ESPAD), which is a validated questionnaire on student substance use and related risk and protective factors in Europe[19]. The questionnaire was translated into Arabic and adapted to the Moroccan social and cultural context. In 2003, a pilot survey of 400 students was completed in Rabat High schools[17]. The 2006 questionnaire consisted of 57 items (53 multiple choice questions and 4 open ended questions). The questionnaire took less than 30 min, on average, to complete. Questionnaire items included demographic information, relationship with parents, parent education, family socioeconomic level, onset age of drug use, lifetime drug use, past year drug use, past month drug use, risk perceptions of drug use, and attitudes about drug use.

### *Statistical analysis*

Data were edited and analyzed in SPSS, version 20.[43] Pearson $\chi^2$ analyses and independent *t* tests were completed to examine the association between variables of interest including *ad hoc* independent variables, covariates, and the outcome variable: grade average in the last trimester. These analyses were completed separately by males and females. The outcome variable grade average in the last trimester was created by dichotomizing the original variable. The original categories for grade average in the last trimester was less than 5, 5-9, 10-12, 13-14, and more than 15. There were very few students in the last two categories (3.4% total) while half of the students had a grade average of 10-12. Moroccan grades 16 and above are roughly equivalent to a United States grade of A+, 15.9-14.1 to an A, 14.0-12.1 to a B+, 12.0-11.1 to a B, 11.0-10.1 to a C, and the remaining grades are below average. Therefore, academic performance was recoded into two groups; the first group of students with grades of 12 and below were collapsed into the average and below average student group and the second group of students with grades 13 and above were collapsed into the above average student group (reference group).

Based on our *ad hoc* hypothesis that substance use would be associated with lower academic performance, two multiple logistic regressions were completed with the dichotomous outcome variable, grade, and an independent variable, drug use. The independent variable measuring drug use was a four level categorical variable: 3 = used alcohol, hashish, or psychotropic drugs in the past 30 d; 2 = used alcohol, hashish, or psychotropic drugs in the past 12 mo; 1 = ever used alcohol, hashish, psychotropic, or other drugs in lifetime; and 0 = never used any drug, except possibly tobacco (reference group). Each multiple logistic regression included 3 covariates; father's education level, mother's education level, and socioeconomic status in comparison to other families in country. Separate multiple logistic regression models were completed by gender. Alpha levels of 0.05 and two-sided tests were used to determine significance.

## RESULTS

Demographic information for the study participants is recorded in Tables 1 and 2. A little over half of the sample (53.2%) was female and a small percent (0.5%) did not report their sex. On average, participants were 17.5 (SD = 1.5) years old. Most of the participants (72.1%) described their socioeconomic status as the same as other families, 21.9% as above other families, and 6.0% as below other families in Morocco. Twenty-eight percent of the sample reported ever using alcohol, hashish, psychotropic drugs, or other drugs, 13.5% reported using alcohol, hashish, and psychotropic drugs in the past 12 mo, and 9.1% reported using alcohol, hashish, and psychotropic drugs in the past 30 d. Of those who ever used alcohol, hashish, or psychotropic drugs, they were 15.5 years old on average (SD = 2.4) when they first tried these substances. As seen in Table 1, all the variables, except using alcohol, hashish or psychotropic drugs in the past 12 mo, are significantly related to or trend towards significance in predicting girls' grade average in the last trimester. Girls who had above average grades were younger when they first used alcohol, hashish, or psychotropic drugs compared with girls who had average and below average grades [xbar age 14.7 (2.5) *vs* xbar age 15.7 (2.6), $t_{142}$ = -2.30, $P$ = 0.023].

As seen in Table 2, all the variables are significantly related to boys' grade average in the last trimester. Boys who had above average grades were on average a year younger than boys who had average and below average grades when they first used alcohol, hashish, or psychotropic drugs [xbar age 15.0 (2.4) *vs* xbar age 16.0 (2.0), $t_{310}$ = -3.66, $P$ = 0.0005].

Differences in use patterns between boys and girls are recorded in Table 3. Significantly, 40.5% of boys report ever having used, compared to 16.3% of girls. Twelve-month and 30-d use also varied highly between the genders (20.9% and 14.6% among boys and 6.9% and 4.1% among girls, respectively).

Table 4 reveals the results of the multiple logistic regression predicting girls' grade average in the last trimester, after adjusting for mother's and father's education and comparison socioeconomic status. When compared to girls who never used, girls who ever used alcohol, hashish, psychotropic, or other drugs were 1.72 times more likely to have average and below average grades, while girls who used alcohol, hashish, or psychotropic drugs in the past 30 d were 2.62 times more likely to have average and below average grades.

Table 5 reveals the results of the multiple logistic regression predicting boys' grade average in the last trimester, after adjusting for mother and father' s education and comparison socioeconomic status. Compared with boys who never used, boys who used

**Table 1 Bivariate analyses comparing grade average in the last trimester for girls only**

| Variable | Grades 13 and above (above average grades) *n* = 568 % (*n*) or mean (SD) | Grades 12 and below (average and below average grades) *n* = 541 % (*n*) or mean (SD) | Statistic | *P* value |
|---|---|---|---|---|
| Age | 17.0 (1.4) | 17.6 (1.4) | $t_{1107} = -7.71$ | 0.0005 |
| Days absent in the last 30 d | | | | |
| Not absent | 65.8% (374) | 53.2% (285) | | |
| 1 d | 16.0% (91) | 20.1% (108) | | |
| 2 d | 8.5% (48) | 9.5% (51) | $\chi_5^2 = 24.24$ | 0.0005 |
| 3-4 d | 3.9% (22) | 9.0% (48) | | |
| 5-6 d | 2.6% (15) | 3.2% (17) | | |
| 7 or more days | 3.2% (18) | 5.0% (27) | | |
| | | *n* = 536 | | |
| Father's education level | | | | |
| Not educated | 11.4% (58) | 22.4% (109) | | |
| Elementary school | 19.9% (101) | 23.2% (113) | | |
| Middle school | 10.5% (53) | 14.8% (72) | $\chi_4^2 = 56.59$ | 0.0005 |
| High school | 19.7% (100) | 20.9% (102) | | |
| College and beyond | 38.5% (195) | 18.7% (91) | | |
| | *n* = 507 | *n* = 487 | | |
| Mother's education level | | | | |
| Not educated | 30.9% (167) | 49.1% (255) | | |
| Elementary school | 15.2% (82) | 18.7% (97) | | |
| Middle school | 9.4% (51) | 9.2% (48) | $\chi_4^2 = 61.97$ | 0.0005 |
| High school | 22.0% (119) | 12.9% (67) | | |
| College and beyond | 22.6% (122) | 10.0% (52) | | |
| | *n* = 541 | *n* = 519 | | |
| Socioeconomic status compared with other families in country | | | | |
| Above other families | 25.7% (146) | 20.1% (108) | | |
| Same as other families | 71.0% (403) | 72.5% (390) | $\chi_2^2 = 12.57$ | 0.002 |
| Below other families | 3.3% (19) | 7.4% (40) | | |
| | | n = 538 | | |
| Ever used alcohol, hashish, psychotropic, or other drugs | 13.9 (79) | 18.9 (102) | $\chi^2 = 4.96$ | 0.026 |
| Age first used alcohol, hashish, or psychotropic drugs | 14.7 (2.5) | 15.7 (2.6) | $t_{142} = -2.30$ | 0.023 |
| | *n* = 65 | *n* = 79 | | |
| Used alcohol, hashish, or psychotropic drugs in the last 12 mo | 6.0 (34) | 7.9 (43) | $\chi^2 = 1.65$ | 0.199 |
| Used alcohol, hashish, or psychotropic drugs in the past 30 d | 3.0 (17) | 5.2 (28) | $\chi^2 = 3.39$ | 0.066 |

alcohol, hashish, or psychotropic drugs in the past 12 mo were 1.74 times more likely to have average and below average grades, and boys who used alcohol, hashish, or psychotropic drugs in the past 30 d were 2.08 times more likely to have average and below average grades.

## DISCUSSION

This study is one of the first to examine the use of drugs and alcohol by Moroccan adolescents, with the major findings being that among high school students 28% reported experimentation with alcohol, hashish, or psychotropic drugs, with 13.5% and 9.1% having used in the last 12 mo and 30 d, respectively. Lifetime substance use prevalence was much higher among boys (40.5%) than girls (16.3%). Girls with any lifetime use of drugs or alcohol and use in the last 30 d were about 1.7 and 2.6 times as likely, respectively, to have of having average lower grades compared to non-users. Boys' grades showed significant association with use in the past 30 d (2.1 times more likely to have lower grades than non-users) and in the past 12 mo (1.7 times more likely). Use in the last 12 mo in girls and any previous use in boys showed similar associations but were not statistically significant.

Data regarding substance use among high school students in Morocco from this study is comparable to that in other countries in the region. A study of high school students in Shiraz, Iran reported the prevalence of lifetime drug and alcohol use to be 30.23%[20]. In 2005, 30-d prevalence of alcohol use in Lebanon was reported to be 20%[4].

This study shows an association between use and one negative outcome: lower grades. The strongest association was seen with most recent use; neither use in the last 12 mo for boys nor lifetime use for girls was statistically significant. Research has shown drug and alcohol use to have multiple adverse effects on teens[11,12]. However, the cross-sectional nature of this study does not allow for a causal interpretation, and further research should be done to assess the effects of drug and alcohol use on Moroccan adolescents.

The gender difference in substance use prevalence is striking. Though Morocco is considered a more secular and Westernized country than others in the region, the difference in use among adolescent boys and girls is similar to that of countries with more religiously

**Table 2 Bivariate analyses comparing grade average in the last trimester for boys only**

| Variable | Grades 13 and above (above average grades) *n* = 377 % (*n*) or mean (SD) | Grades 12 and below (average and below average grades) *n* = 587 % (*n*) or mean (SD) | Statistic | *P* value |
|---|---|---|---|---|
| Age | 17.2 (1.6) *n* = 371 | 18.0 (1.6) *n* = 580 | $t_{949}$ = -7.74 | 0.0005 |
| Days absent in the last 30 d | | | | |
| Not absent | 56.1% (211) | 39.4% (230) | | |
| 1 d | 13.8% (52) | 17.6% (103) | | |
| 2 d | 12.5% (47) | 12.7% (74) | $\chi^2_5$ = 31.15 | 0.0005 |
| 3-4 d | 7.4% (28) | 11.3% (66) | | |
| 5-6 d | 2.9% (11) | 5.7% (33) | | |
| 7 or more days | 7.2% (27) *n* = 376 | 13.4% (78) *n* = 584 | | |
| Father's education level | | | | |
| Not educated | 19.5% (66) | 27.5% (142) | | |
| Elementary school | 16.3% (55) | 18.2% (94) | | |
| Middle school | 6.2% (21) | 11.8% (61) | $\chi^2_4$ = 28.09 | 0.0005 |
| High school | 21.6% (73) | 20.7% (107) | | |
| College and beyond | 36.4% (123) *n* = 338 | 21.9% (113) *n* = 517 | | |
| Mother's education level | | | | |
| Not educated | 36.3% (127) | 46.0% (251) | | |
| Elementary school | 14.3% (50) | 15.0% (82) | | |
| Middle school | 7.7% (27) | 9.0% (49) | $\chi^2_4$ = 22.22 | 0.0005 |
| High school | 16.9% (59) | 17.0% (93) | | |
| College and beyond | 24.9% (87) *n* = 350 | 13.0% (71) *n* = 546 | | |
| Socioeconomic status compared with other families in country | | | | |
| Above other families | 26.1% (98) | 17.2% (101) | | |
| Same as other families | 68.5% (257) | 74.8% (439) | $\chi^2_2$ = 12.40 | 0.002 |
| Below other families | 5.3% (20) *n* = 375 | 8.0% (47) | | |
| Ever used alcohol, hashish, psychotropic, or other drugs | 33.7 (127) | 44.8 (263) | $\chi^2$ = 11.78 | 0.001 |
| Age first used alcohol, hashish, or psychotropic drugs | 15.0 (2.4) *n* = 98 | 16.0 (2.0) *n* = 214 | $t_{310}$ = -3.66 | 0.0005 |
| Used alcohol, hashish, or psychotropic drugs in the last 12 mo | 17.0 (64) | 23.3 (137) | $\chi^2$ = 5.63 | 0.018 |
| Used alcohol, hashish, or psychotropic drugs in the past 30 d | 10.9 (41) | 17.0 (100) | $\chi^2$ = 6.98 | 0.008 |

**Table 3 Reported substance use by gender**

| Use pattern | Girls *n* = 1109 *n* (%) | Boys *n* = 964 *n* (%) |
|---|---|---|
| Ever used alcohol, hashish, psychotropic, or other drugs | 181 (16.3) | 390 (40.5) |
| Used alcohol, hashish, or psychotropic drugs in the last 12 mo | 77 (6.9) | 201 (20.9) |
| Used alcohol, hashish, or psychotropic drugs in the past 30 d | 45 (4.1) | 141 (14.6) |

**Table 4 Multiple logistic regression predicting girls' grade average in the last trimester, after adjusting for mother and father's education and comparison socioeconomic status (*n* = 970)**

| Combined drug use | B (SE) | AOR | 95%CI for AOR | *P* value |
|---|---|---|---|---|
| Used alcohol, hashish, or psychotropic drugs in the past 30 d | 0.96 (0.35) | 2.62 | 1.31, 5.22 | 0.006 |
| Used alcohol, hashish, or psychotropic drugs in the past 12 mo | 0.27 (0.38) | 1.3 | 0.63, 2.72 | 0.479 |
| Ever used alcohol, hashish, psychotropic, or other drugs | 0.54 (0.24) | 1.72 | 1.07, 2.77 | 0.026 |
| Never used | - | - | - | - |

AOR: Adjusted odds ratio.

conservative societies. A rapid study assessment of adolescent alcohol and drug use in Lebanon did not

**Table 5 Multiple logistic regression predicting boys' grade average in the last trimester, after adjusting for mother and father's education and comparison socioeconomic status ($n$ = 831)**

| Combined drug use | B (SE) | AOR | 95%CI for AOR | *P* value |
|---|---|---|---|---|
| Used alcohol, hashish, or psychotropic drugs in the past 30 d | 0.73 (0.23) | 2.08 | 1.33, 3.24 | 0.001 |
| Used alcohol, hashish, or psychotropic drugs in the past 12 mo | 0.55 (0.29) | 1.74 | 1.00, 3.05 | 0.052 |
| Ever used alcohol, hashish, psychotropic, or other drugs | 0.19 (0.20) | 1.21 | 0.82, 1.79 | 0.335 |
| Never used | - | - | - | - |

AOR: Adjusted odds ratio.

find gender difference in use of most substances to be significant. The reported lifetime prevalence of alcohol use among boys was reported at 69.1%; among girls it was 62.9%[21]. However, a study from Iran shows a gender gap similar to that in this Moroccan study: 15% prevalence of lifetime alcohol use among boys, 3.5% among girls[20]. Gender roles are broadly delineated in Morocco, and different socialization patterns between the genders may explain some of this difference in substance use. However, more research is required to further define the issue. This may have important ramifications for adolescent treatment and prevention programs. It has been reported that different gender use patterns are associated with different risk factors[22,23]. If different risk factors for drug and alcohol use exist among adolescent boys and girls in Morocco, gender-specific prevention and treatment strategies may prove more efficacious than a single approach[15]. Further research is indicated to identify those risk factors.

We found earlier age of onset of substance use to be associated with higher grades, a somewhat counterintuitive result. Previous research has shown an association between the onset of alcohol use before age 13 and lower high school grade average[24], as well as a relationship between early drug use and future truancy[25]. The finding in this study could relate to sampling bias, as lower-performing students who began using at an earlier age may have been truant when the survey was administered. Alternatively, there may be an unidentified factor that protected the high-achieving students who first used substances at an early age from developing a use disorder. As this study was cross-sectional and did not assess for substance-use disorders, additional research would help to ascertain the relationship in this finding.

The nature of this study leaves it with some limitations. Because the survey was administered at school, the data may have some response bias as truant students were not included in the study. As with all self-reported drug and alcohol use, the survey response reliability is difficult to ensure. In addition, the cross-sectional nature of the study makes it difficult to establish a causal relationship between substance use and academic performance. There was some delay in publication due to limited resources to analyze the data; however, this study remains the first and most recent report of adolescent substance use in Morocco.

Though adolescent drug and alcohol use has been studied in other North African and Middle Eastern countries, little research has been done on the subject in Morocco. This study is one of the first to provide a glimpse of the fairly high prevalence of adolescent substance use in the country, and it provides important implications for future treatment and prevention strategies.

## COMMENTS

### Background

Adolescent drug and alcohol use is associated with significant morbidity and mortality worldwide, including decreased academic performance. Epidemiological studies in Middle Eastern and Mediterranean countries show large variation in use patterns, both within the region and between genders. However, adolescent substance use has not been well-documented in Morocco.

### Research frontiers

Current research involves interventions to prevent and limit the harm from adolescent drug and alcohol use.

### Innovations and breakthroughs

This study is, to the authors' knowledge, the first to report data regarding adolescent drug and alcohol use in Morocco.

### Applications

By showing drug and alcohol use to be highly prevalent among urban Moroccan adolescents, particularly males, this study provides an argument for treatment and intervention strategies to help with substance use disorders.

### Terminology

Hashish: A cannabis extract in which its psychoactive chemicals are concentrated; Psychotropic drugs: A drug that can alter the mind, mood, and behavior.

### Peer-review

This is a very important topic among adolescents.

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**P- Reviewer**: Richter J
**S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5498/wjp.v5.i4.432

*World J Psychiatr* 2015 December 22; 5(4): 432-438
ISSN 2220-3206 (online)




# Impact of social isolation on behavioral health in elderly: Systematic review

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Author contributions: Choi H and Cho HJ developed the study concept and design; Choi H acquired the data; Choi H and Cho HJ analyzed and interpreted the data; Choi H, Irwin MR and Cho HJ drafted and critically reviewed the manuscript.

Conflict-of-interest statement: The authors have no conflict of interest related to the manuscript.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author.



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Received: June 12, 2015
Peer-review started: June 14, 2015
First decision: August 25, 2015
Revised: September 23, 2015
Accepted: November 10, 2015

Article in press: November 11, 2015
Published online: December 22, 2015

## Abstract

**AIM:** To examine and compare the effects of subjective and objective social isolation on behavioral health in elderly adults.

**METHODS:** A systematic search of PubMed was performed for original research articles from peer-reviewed journals examining one of the following topics: "Social isolation and sleep disturbance", "social isolation and depression", or "social isolation and fatigue in older adults". Studies were selected following the criteria established based on the aim of this review. Data were extracted from the articles by two independent reviewers. Due to the heterogeneity in study designs and outcome measures of the included studies, qualitative and narrative analyses were conducted.

**RESULTS:** The set criteria were used to select a total of 16 studies for the review. Of the 16, 13 were cross-sectional studies. The characteristics of study populations were identified as follows. A total of 12 studies randomly selected subjects irrespective of pre-existing health conditions. Consequently, an unspecified number of the study subjects had chronic diseases in the studies compared. In addition, cultural and ethnic backgrounds of studies in this review were diverse, and included subjects living in North America, South America, Asia, Europe, and Oceania. Both subjective and objective types of social isolation increased behavioral symptoms, such as sleep disturbance, depressive symptoms, and fatigue in older adults. Furthermore, a few recent studies reported stronger effects of subjective social isolation than objective social isolation on sleep disturbance and depressive symptoms.

**CONCLUSION:** Social isolation affects behavioral

health in older adults. Compared to the objective social isolation, subjective social isolation contributes more significantly to sleep disturbance and depression.

**Key words:** Older adults; Depression; Subjective social isolation; Objective social isolation; Sleep disturbance; Fatigue; Systematic review



**Core tip:** Older adults often experience social isolation which may have a profound negative effect on their behavioral health. However, to date, no systematic review has addressed this issue. Furthermore, few studies have distinguished the effects of subjective *vs* objective social isolation on behavioral health in this population. The findings of this systematic review suggest that social isolation in late life may indeed increase behavioral symptoms such as sleep disturbance, depression, and fatigue. Moreover, the effects of subjective social isolation, compared to objective social isolation, may contribute more significantly to sleep disturbance and depressive symptoms.

Choi H, Irwin MR, Cho HJ. Impact of social isolation on behavioral health in elderly: Systematic review. *World J Psychiatr* 2015; 5(4): 432-438 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i4/432.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i4.432

## INTRODUCTION

Older adults frequently report social isolation. In turn, social isolation in the aging population has been shown to have a profound negative effect on longevity and physical and mental health[1]. There are two types of social isolation, subjective and objective. In the recent literature, subjective social isolation has been characterized as "a perceived shortage in one's social resources, such as companionship or social support"[2]. Objective social isolation has been explained as "lack of contact with others due to situational factor, such as small size of social network, infrequent social interaction, or lack of participation in social activity"[2]. Therefore, the effects of social isolation could be due to an objective deprivation of social network and/or subjective experience of social isolation.

Several studies consistently demonstrated that both subjective and objective types of social isolation positively correlate with sleep disturbance, depression, and fatigue. Subjective social isolation, such as emotional loneliness coming from low support from coworkers, was associated with poor quality of sleep[3,4]. Studies on breast cancer survivors also suggest that those who feel lonelier experience more pain, symptoms of depression, and fatigue[5,6]. Friedman *et al*[7] studied objective social isolation and concluded that individuals who had a positive social relationship reported better sleep quality. An interventional study also showed that 4-8 wk of internet chatting with volunteer students who study psychology reduced loneliness and depressive symptoms by increasing the perception of social support[8].

Fewer data are available on older adults, even though older adults are more likely to face social isolation and its impact on behavioral health may be more robust. Furthermore, behavioral symptoms, such as sleep disturbance, depression and fatigue, are highly prevalent among older adults and may impair functioning, quality of life, and physical health[9-11]. However, to date, no systematic review has addressed this topic. Furthermore, few studies have distinguished the effects of subjective *vs* objective social isolation on behavioral health in older adults. Therefore, this systematic review aimed to: (1) Examine whether social isolation is associated with behavioral symptoms (sleep disturbance, depression, and fatigue) among older adults; and (2) Compare the effects of subjective *vs* objective social isolation on the same behavioral symptoms. The study hypotheses were: (1) Older adults with social isolation are more likely to experience sleep disturbance, depression, and fatigue; and (2) Compared to objective social isolation, subjective social isolation has a stronger impact on sleep disturbance, depression, and fatigue among older adults.

## MATERIALS AND METHODS

### Search strategy

A systematic literature search was performed using PubMed as the primary search engine, from its inception to April 2015. The PubMed search for social isolation research was conducted on three different topics: sleep disturbance, depression, and fatigue. For the topic "social isolation and sleep disturbance", search terms used were as follows: (feeling of seclusion OR loneliness OR social withdrawal OR social network OR social isolation) AND (sleep disorder OR insomnia OR sleep disturbance OR sleeplessness OR poor sleep quality OR somnolence OR altered sleep pattern OR sleep disruption). For the topic "social isolation and depression", a more focused and efficient search, using Medical Subject Headings (MeSH), was conducted given that there were a much larger number of references on this topic compared to the other two topics. Search terms were as follows: ["social isolation" (MeSH) OR "social network" (MeSH) OR "loneliness" (MeSH)] AND ["depression" (MeSH) OR "depressive" (MeSH)]. For the topic "social isolation and fatigue," search terms were used as follows: (loneliness OR social network OR social isolation) AND (fatigue OR weakness OR malaise). In the subsequent step, selection of abstracts was conducted based on the relevance of titles to the topics. After reading selected abstracts, selection of full articles was conducted based on how much the content of abstracts was significant in supporting the hypotheses of this review. All search results were filtered by "humans" for the species section of the PubMed website search tool.

### *Study selection*

Study selection was conducted by two independent reviewers. The inclusion criteria for the articles were as follows: (1) Type of studies: original research studies including observational and interventional studies; (2) Participants: older adults broadly defined as subjects older of than 50 years; when the exact age distribution was unavailable, studies involving subjects whose average age was greater than 55 years were included; (3) Independent variables: subjective and/or objective social isolation; and (4) Dependent variables: symptoms of sleep disturbance, depression, or fatigue.

### *Data extraction*

Data extraction was focused on the review aims. The following data were extracted by the two independent reviewers: (1) Authors and year of publication; (2) Study design; (3) Age range of subjects; (4) Health status of subjects; (5) Cultural/ethnic background of subjects; (6) Assessment methods; and (7) Outcomes (significance).

### *Data synthesis*

Due to the heterogeneity of the study designs and outcome measures, no meta-analysis was conducted. Instead, a narrative data synthesis was performed.

The statistical methods of this study were reviewed by a statistician for the University of California-Los Angeles (Los Angeles, CA, United States).

## RESULTS

### *Characteristics of study populations*

Most studies selected participants randomly, regardless of pre-existing medical or mental conditions. As a result, there were a varying number of participants with chronic diseases in the reviewed studies. In addition, this review evaluated studies that were conducted among subjects from diverse cultural and ethnic backgrounds, including those who live in North America, South America, Asia, Europe, and Oceania.

### *Social isolation and sleep disturbance*

For the topic "social isolation and sleep disturbance", the PubMed search identified 2625 references. Out of 2625 articles, 95 abstracts with a title relevant to the topic were selected. Out of the 95 abstracts, 21 articles were selected based on their abstract being deemed appropriate for testing of the hypotheses of this review paper. Out of the 21 articles, 6 articles specifically focused on the older adult population and evaluated the relationship between social isolation and sleep disturbance (Table 1).

Costa *et al*[12] suggested that older adults with a lower score on the Interpersonal Support Evaluation List had increased sleep onset latency or non-restorative sleep. A longitudinal study also found older adults, who felt subjectively lonely in the past, complained of more severe insomnia[13]. On the other hand, a cross-sectional study found that a group of people with higher social interaction had shorter sleep latency[14]. A study on the elderly with dementia also reported that lack of social support or not having a partner negatively affected sleep quality[15]. Yao *et al*[16] found that having a good relationship with friends and family predicted a better quality of sleep.

McHugh and Lawlor[17] found that both "emotional loneliness" (*e.g.*, subjective social isolation - the feeling of missing an intimate relationship) and "social loneliness" (*e.g.*, objective social isolation or missing a wider social network) - as defined by the De Jong Gierveld Loneliness Scale[18] - predicted sleep disturbance. However, subjective social isolation was a stronger predictor of sleep disturbance, and in fact when both measures were simultaneously included in the same multivariable regression model, only subjective social isolation remained a significant predictor[17].

### *Social isolation and depression*

For the topic "social isolation and depression", the PubMed search identified 1045 references. Out of 1045 articles, 82 abstracts with a title relevant to the topic were selected. Out of the 82 abstracts, 22 articles were selected based on their abstract being deemed appropriate for testing of the hypotheses of this review paper. Out of the 22 articles, 8 articles specifically focused on the older adult population and examined social isolation and depression (Table 1).

A study on Mexican Americans age 80 years or older concluded that high loneliness score was significantly correlated with the symptoms of depression[19]. This finding was further supported by several recent cross-sectional studies that also reported significant correlations between loneliness and symptoms of depression[20-23]. Bekhet and Zauszniewski[24] found that, in two different retirement communities, people who reported feeling lonely had a higher rate of symptoms of depression. Park *et al*[25] examined social isolation from a different angle, that is, the level of social engagement, which is a representation of an objective social isolation. They showed that low level of social engagement caused loneliness that was associated with depressive symptoms. A recent study suggested rumination as a mediator of the relationship between loneliness and depression[26].

An article comparing two forms of loneliness: "emotional loneliness" (*e.g.*, subjective social isolation - the feeling of missing an intimate relationship) and "social loneliness" (*e.g.*, objective social isolation or missing a wider social network) - as defined by the De Jong Gierveld Loneliness Scale[18] - showed that emotional loneliness was strongly associated with depressive symptoms, whereas social loneliness had a very weak association[27].

### *Social isolation and fatigue*

For the topic "social isolation and fatigue," the PubMed search identified 2891 references. Out of the 2891

**Table 1 Summary of 16 articles on older adults**

| Ref. | Outcome | Study design | Age in years (*n*) | Health status | Cultural/ethnic characteristics | Assessment method | Relevant results (significance) |
|---|---|---|---|---|---|---|---|
| Costa *et al*[12] | Sleep disturbance | Cross-sectional | ⩾ 65 (497) | Random selection; Unspecified number of subjects had chronic diseases | Brazilian | Questionnaire, NHP, MLAQ, ISEL | Elderly with sleep problem had lower score on ISEL ($P < 0.05$) |
| Jensen *et al*[13] | Insomnia | Longitudinal | 80 (212) | Random selection; Unspecified number of subjects had chronic diseases | Swedish | Questionnaire (graded sociological data) | Severity of insomnia associated with having felt lonely in the past ($P < 0.05$) Severity of insomnia associated with believing that future would bring loneliness ($P < 0.01$) |
| Troxel *et al*[14] | Insomnia | Cross-sectional | ⩾ 60 (119) | Study Group: Presence of insomnia; Unspecified stable medical and psych condition Control Group: Absence of insomnia | Pittsburg, PA, United States | Questionnaire, Pittsburgh sleep diary, PSQI, actigraphy | Wakefulness after sleep; onset is lower in people with higher social support ($P < 0.01$) In group with insomnia, shorter sleep latency in higher social interaction group ($P < 0.01$) |
| Eshkoor *et al*[15] | Sleep disturbance | Cross-sectional | ⩾ 60 (1210) | Dementia | Malaysian | SNSL, Mini-mental examination | Social support, marital status, having partner significantly affect sleep disturbance ($P < 0.05$) |
| Yao *et al*[16] | Sleep disturbance | Cross-sectional | 65-75 (187) | Random selection; Three-fourths of subjects had chronic illness | Taiwanese | Questionnaire, PSQI (Chinese version) | Good relationship with friends and family is negatively correlated with poor sleep quality ($P < 0.001$) |
| McHugh *et al*[17] | Sleep disturbance | Longitudinal observational | ⩾ 60 (447) | Random selection; Unspecified number of subjects had chronic diseases | Irish | DJGLS, PSQI | Emotional loneliness (subjective social isolation) rather than social loneliness (objective social isolation) is a stronger predictor of poor sleep quality ($P < 0.001$) Emotional loneliness increases stress ($P < 0.001$) Stress affects sleep quality ($P < 0.0001$) |
| Gerst-Emerson *et al*[19] | Depressive symptoms | Cross-sectional | 80-102 (3050) | Random selection; Unspecified number of subjects had chronic diseases | Mexican American in 5 states in the United States (TX, CA, AZ, CO, and NM) | Three-item loneliness scale, 20-item CES-D | Scores on depressive symptoms are positively associated with loneliness ($P < 0.001$) |
| Aylaz *et al*[20] | Depressive symptoms | Cross-sectional | ⩾ 60 (913) | Random selection; Unspecified number of subjects had chronic diseases | Turkish | GDS, ULS | ULS score and GDS score correlation ($r$) is 0.608 ($P < 0.001$) |
| Theeke *et al*[21] | Depressive symptoms | Cross-sectional | ⩾ 65 (60) | All subjects had chronic illnesses | Appalachians | ULS, CES-D, GDS | ULS score and depression has correlation coefficients value ($r$) of 0.388 ($P < 0.01$) |
| Adams *et al*[22] | Depressive symptoms | Cross-sectional | 60-98 (234) | Random selection; Subjects had 1.7 chronic diseases on average | Northeast United States (Retirement community affiliated with Methodist Church) | ULS, GDS | ULS score and GDS score correlation ($r$) is 0.458 ($P < 0.005$) |
| Alpass *et al*[23] | Depressive symptoms | Cross-sectional | ⩾ 65 (217) | Random selection; 61% of subjects had chronic illness or disability | New Zealand | ULS, GDS | ULS score and GDS score correlation ($r$) is 0.625 ($P < 0.01$) |
| Bekhet *et al*[24] | Depressive symptoms | Cross-sectional | 65-84 (314) | Random selection; Unspecified number of subjects had chronic diseases | Cleveland, OH, United States (Retirement community) | Questionnaire, CES-D | Elderly who reported feeling lonely had higher depressive symptom ($P < 0.001$) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Park *et al*[25] | Depressive symptoms | Cross-sectional | ⩾ 60 (674) | Random selection; Unspecified number of subjects had chronic diseases | Korean Americans in Tampa and Orlando, FL, United States | SNSL, 20-item ULS, GDS-short form | Loneliness mediates the relationship of social engagement related variables with depressive symptom ($P < 0.05$)<br>Social engagement related variables: not living alone, social network, activity participation<br>Exception: the relationship of social network and loneliness in men |
| Wan Mohd Azam *et al*[27] | Depressive symptoms | Cross-sectional | ⩾ 60 (161) | Random selection; Unspecified number of subjects had chronic diseases | Malaysian (Rural/ agricultural settlement) | DJGLS, GDS, MOSSS | When perceived social support decreases, feeling of loneliness increases ($P < 0.01$)<br>Social support mediates between loneliness and depression ($P < 0.05$)<br>Social loneliness and depression: Pearson correlation ($r$) is -0.189 ($P < 0.05$)<br>Emotional loneliness and depression: Pearson correlation ($r$) is 0.403 ($P < 0.01$) |
| Jason *et al*[28] | Fatigue | Interventional | 57.6 on average (30) | Individuals who were diagnosed with chronic fatigue syndrome in the past | Chicago, IL, United States | Buddies (intervention), questionnaire, MOSSF-36, FSS, PSS | After 4 mo of intervention (supportive interaction), severity of fatigue of experimental group decreased compared to control group based on FSS ($P < 0.05$) |
| Riemsma *et al*[29] | Fatigue | Cross-sectional | 51-75 (229) | All subjects were diagnosed with rheumatoid arthritis | Dutch | Double-anchored VAS, SSL12-I | Problematic social support and fatigue correlation ($r$) is 0.28 ($P < 0.001$) |

CES-D: Center for Epidemiological Studies-Depression Scale; DJGLS: De Jong Gierveld Loneliness Scale; FSS: Fatigue Severity Scale; GDS: Geriatric Depression Scale; ISEL: Interpersonal Support Evaluation List; MLAQ: Minnesota Leisure Activity Questionnaire; MOSSS: Medical Outcomes Survey Social Support; MOSSF-36: Medical Outcomes Survey Short Form – 36; NHP: Nottingham Health Profile; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; SAST: Short Anxiety Stress Test; SNSL: Social Network Scale of Lubben; SSL12-I: Social Support List Interaction; ULS: University of California-Los Angeles Loneliness Scale; VAS: Visual Analogue Scale.

articles, 15 abstracts with titles relevant to the topic were selected. Out of the 15 abstracts, 6 articles were selected based on their abstract being deemed appropriate for the testing of the hypotheses of this review. Out of the 6 articles, 2 articles specifically focused on the old adult population and examined social isolation and fatigue (Table 1).

An intervention study had student buddies help subjects (mean age, 57.6 years) with household tasks for 2 h per week for 4 mo. The control group did not have student buddies for the same period. All subjects in both the experiment and control groups completed a post-intervention questionnaire. Results showed that the experiment group was less fatigued and more energetic than the control group[28]. Having a supportive relationship with others appeared to lessen the severity of fatigue. A study focusing on fatigue in rheumatoid arthritis patients further supported this finding, with a significant correlation between problematic social support and level of fatigue[29]. The authors argued that problematic social supports, such as lack of sympathy or lack of understanding from a social network, played an important role in explaining fatigue[29]. No article comparing two forms of social isolation (subjective and objective) with fatigue was available from the PubMed search.

## DISCUSSION

In accordance with the initial hypotheses of this systematic review, both subjective and objective types of social isolation were associated with symptoms of sleep disturbance, depression, and fatigue in older adults. Furthermore, a few recent studies showed stronger effects of subjective social isolation than objective social isolation on sleep disturbance and depressive symptoms. The findings of this review suggest that social isolation may indeed increase behavioral symptoms in older adults, and that the effects of subjective social isolation, compared to objective social isolation, may contribute more significantly to sleep disturbance and depressive symptoms.

This review is meaningful because it has comprehensively reviewed the relationship between social isolation and behavioral symptoms that frequently affect older adults and impair their functioning, quality of life, and physical health. Furthermore, this review examined an important but poorly explored topic regarding the distinctive effects of subjective *vs* objective social isolation on behavioral symptoms. The effects of subjective isolation (*vs* objective social isolation) on behavioral symptoms were more robust. Additionally, when both were measured and simultaneously included in the

analyses, only the effects of subjective social isolation remained significant, suggesting that the effects of objective social isolation on behavioral symptoms may be dependent upon and explained by those of subjective social isolation. Thus, it can be speculated that older adults with objective social isolation may experience sleep disturbance, depression, and fatigue more often not only because they are deprived of social networks but also because they also feel socially isolated.

However, the following limitations should be considered in the interpretation of these findings. First, there was a significant heterogeneity in the design, outcome measures, and population characteristics of the included studies, and thus the meta-analytical approaches could not be employed. Of note, while this heterogeneity is certainly a limitation and does not allow for a meta-analysis, diverse cultural backgrounds and health status of the study populations may broaden the generalizability of the findings. More specifically, the inclusion of diverse cultures demonstrating similar results supports the present review that there is an association between social isolation and behavioral symptoms regardless of one's ethnic or cultural background. Second, each of the individual studies included in this review had their inherent limitations that could not be remedied in this review. In particular, most of the included studies were cross-sectional in design, and thus no causal or temporal directions could be established for the observed associations between social isolation and behavioral symptoms. Third, the literature search for the topic "social isolation and depression" was performed using MeSH terms. This focused search was an efficient way to search literature given that there were a much larger number of references on this topic compared to the other two topics. However, this focused approach could have compromised the comprehensiveness of the search.

To evaluate the causal link between social isolation and behavioral symptoms, future studies are needed to test interventions that target social isolation as potential treatments for improving behavioral health of older adults. Furthermore, the findings of this review suggest that, in testing such interventions, subjective social isolation may need to be the primary target rather than objective social isolation.

The findings of this systematic review suggest that social isolation increases sleep disturbance, depression, and fatigue in older adults. Moreover, the effects of subjective social isolation, compared to objective social isolation, contribute more significantly to sleep disturbance and depressive symptoms.

## COMMENTS

### Background

Behavioral symptoms such as sleep disturbance, depression, and fatigue are highly prevalent among older adults. Studies have shown that there are relationships between social isolation and behavioral symptoms that frequently affect older adults and impair their functioning, quality of life, and physical health. However, to date, no systematic review has addressed this issue. Furthermore, a few studies have distinguished the effects of subjective *vs* objective social isolation on the behavioral health in this population. The primary aim of this review was to examine whether social isolation was associated with symptoms of sleep disturbance, depression, and fatigue in older adults. The second aim was to compare the effects of subjective *vs* objective social isolation on these symptoms.

### Research frontier

Several studies consistently demonstrated that both subjective and objective types of social isolation are positively correlated with sleep disturbance, depression, and fatigue. Subjective social isolation, such as emotional loneliness coming from low support from co-workers, was associated with poor quality of sleep. Studies on breast cancer survivors suggest that those who experience loneliness have more pain, symptoms of depression, and fatigue. It has been shown that individuals who had a positive social relationship reported better sleep quality. Furthermore, chatting over the internet for 4-8 wk reduced loneliness and depressive symptoms by increasing the perception of social support.

### Innovations and breakthroughs

Based on the results of this systemic review, effects of subjective social isolation may have a more significant effect on sleep disturbance and depressive symptoms then objective isolation. Retrieved manuscripts related to this topic were reviewed by the authors, and data were extracted and synthesized in a narrative form.

### Applications

When treating depression or insomnia, clinicians should consider helping patients get social support by assessing the level of social connection. This is especially important for those individuals who feel lonely despite having a decent objective social network. In these cases, psychotherapy should be considered in the management of their subjective rather than the objective social isolation.

### Terminology

Subjective social isolation is defined as "perceived shortage in one's social resources, such as companionship or social support". Objective social isolation is defined as "a lack of contact with others due to situational factor, such as a small size of social network, infrequent social interaction, or lack of participation in social activity."

### Peer-review

This paper is concise and is written in a manner which is easy to follow. The authors use good theoretical reasoning for questioning the relationship of social isolation and the chosen symptoms of study. Additionally, the limitations of their study are well explicated.

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**P- Reviewer**: Sassoon SA, Surani S
**S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

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