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## Contents

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## **MINIREVIEWS**

Underrecognition and un-dertreatment of stress-related psychiatric disorders in physicians: Determinants, 131 challenges, and the impact of the COVID-19 pandemic

Huang CLC

141 Kynurenine pathway of tryptophan metabolism in pathophysiology and therapy of major depressive disorder

Badawy AAB, Dawood S, Bano S

- 149 Reducing psychiatric illness in the perinatal period: A review and commentary Rohr J, Vahidy FS, Bartek N, Bourassa KA, Nanavaty NR, Antosh DD, Harms KP, Stanley JL, Madan A
- 161 Neuroimmune, clinical and treatment challenges in multiple sclerosis-related psychoses Vesic K, Gavrilovic A, Mijailović NR, Borovcanin MM

## **ORIGINAL ARTICLE**

## **Observational Study**

171 Relationship between perceived social support and post-traumatic growth in coronavirus disease 2019 patients discharged from the hospital

Şirin Gök M, Çiftçi B

## SYSTEMATIC REVIEWS

Use of new technologies for the promotion of physical activity in patients with mental illness: A systematic 182 review

Guerrero-Jiménez M, Ruiz M, Gutiérrez-Rojas L, Jiménez-Muñoz L, Baca-Garcia E, Porras-Segovia A

191 COVID-19 pandemic in the intensive care unit: Psychological implications and interventions, a systematic review

Monti L, Marconi E, Bocci MG, Kotzalidis GD, Mazza M, Galliani C, Tranquilli S, Vento G, Conti G, Sani G, Antonelli M, Chieffo DPR



## Contents

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MINIREVIEWS

# Underrecognition and un-dertreatment of stress-related psychiatric disorders in physicians: Determinants, challenges, and the impact of the COVID-19 pandemic

## Charles Lung-Cheng Huang

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## Abstract

Medical practitioners' duties are highly stressful and performed in a particularly challenging and competitive work environment. Stress and burnout among physicians have emerged as a worldwide public health problem in recent years. A high level of distress and burnout can lead to clinically significant behavioral health problems, such as stress-related psychiatric disorders. Mounting evidence shows that physicians have higher risks of insomnia, anxiety, and depression than the general population, especially during the coronavirus disease 2019 pandemic. However, the behavioral health problems of these vulnerable healthcare professionals are noteworthy for being underrecognized and undertreated. In this minireview, we summarize the current progress of studies on the prevalence and determinants of distress and stress-related psychiatric disorders among physicians and their healthcare-seeking behaviors. We discuss future research directions and the clinical approach that may maximize self-awareness and promote prompt and adequate treatment for clinically significant behavioral health problems of physicians.

Key Words: Physician; Depression; Anxiety; Insomnia; Healthcare-seeking behavior; Undertreatment

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**Core Tip:** Physicians are experiencing unprecedented stress and distress. They face major risks of distress and burnout, which can subsequently cause stress-related psychiatric disorders, such as insomnia, anxiety, and depression. Nevertheless, many of these vulnerable healthcare professionals do not seek medical help. There is a clear need for further research to evaluate the determinants of underrecognition and undertreatment of stress-related psychiatric disorders, how to enhance early detection and management of these mental health problems, and how to eliminate obstacles to the use of mental health services in this population.

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## INTRODUCTION

Healthcare professionals are well known to bear a heavy burden of high job strain and workplace challenges<sup>[1]</sup>. High-pressured working environments, with excessive workloads, extended working hours, high levels of time pressure, limited resources, and restricted autonomy, have been acknowledged as factors causing mental health issues of healthcare professionals. In addition to these issues, medical practitioners may also have to deal with medical disputes and hospital evaluations in addition to the challenges of their clinical practice[2]. Distress and burnout, regarded as the exhaustion of emotional or physical strength as a result of prolonged frustration or stress, are common among physicians[3-6]. In a Medscape survey, 56% of physicians said they experienced burnout and attributed it to excessive bureaucracy combined with other causal factors, including long working hours, increasing computerization of practice, lack of respect from colleagues, lack of clinical autonomy, and insufficient compensation[7].

The issue of physicians' wellness has been gaining attention in recent years, and how to measure physicians' wellbeing and mental health is crucial<sup>[8]</sup>. A lot of literature reports physicians' distress or mental illness in terms of fatigue, burnout, emotional exhaustion or withdrawal, anxiety, depression, suicide, substance abuse, or functioning impairment. Additionally, there are existing instruments that can evaluate physician wellness. For instance, Arnetz<sup>[9]</sup> used a standardized questionnaire, *i.e.*, the quality of work competence survey, to evaluate core elements of organizational and staff wellbeing. These included mental energy, skills development, work-related exhaustion, work climate, work tempo, leadership, and organizational efficacy.

The high level of occupational stress, distress, and burnout of physicians affects not only their physical and mental well-being, but also the quality of patient care and the overall efficiency and costs of the healthcare system [8,10,11]. Firth-Cozens [11,12] called attention to stress, depression, alcoholism, and suicide among doctors in the United Kingdom in the 1990s. Since then, multiple epidemiological studies and several systematic reviews have been conducted worldwide[13-17]. Their findings are broadly similar as are the causal relationships between rates of stress and stress-related mental disorders, including anxiety, depression, insomnia, and substance use.

The distress, burnout, and subsequent behavioral health problems of healthcare professionals may be aggravated during special circumstances, such as pandemics. For instance, the coronavirus disease 2019 (COVID-19) pandemic has completely altered the lives of millions of people globally, putting an enormous strain on society and healthcare systems [18]. It is anticipated that the mental health problems of healthcare professionals would be exacerbated due to persistent stress and long-term sequelae following COVID-19[19-23].

Doctors' well-being and stress-related behavioral health problems are becoming a global public health issue. However, studies also show that healthcare professionals are passive seekers of help to deal with their mental health problems[24-26]. In this review, we focus on the distress and behavioral health problems of physicians. We extract data from the relevant literature and follow the progress of the latest studies on the prevalence and influential factors of distress and subsequent stress-related psychiatric disorders among physicians. Furthermore, we discuss physicians' healthcare-seeking behaviors and suggest strategies for intervention.

## EPIDEMIOLOGY OF STRESS-RELATED PSYCHIATRIC DISORDERS AMONG PHYSICIANS

An increasing body of literature shows that distress and burnout among medical practitioners can lead



to clinically significant behavioral health problems, especially stress-related psychiatric disorders, including depression[15-17,27,28], anxiety[29,30], insomnia[31], substance use[32,33], and even suicide [33-37]. In 2015, a landmark meta-analysis and systematic review analyzed data from 54 cross-sectional and longitudinal studies involving 17560 resident physicians from 18 countries[38]. Results showed that the overall pooled estimate of depression or depressive symptoms was 28.8% [95% confidence interval (CI) = 25.3-32.5]. A review by Yates<sup>[3]</sup> highlighted that 42% of United States physicians participating in a large-scale online survey in 2018 stated that they experienced burnout. The survey repeated in 2019 showed similar results, with 44% "feeling burned out" and 14% reporting suicidal thoughts. A recent survey of doctors in Hong Kong revealed that 16.0% of the respondents screened positive for depression and 15.3% reported suicidal ideation [28]. In the Canadian Physician Health Study, almost one quarter of physicians reported a period of depression lasting at least two weeks[15], and the rate of depression was higher among female physicians. A study evaluating the levels of an association between occupational stress and depression in Taiwanese physicians found a depression rate (13.3%), which was more than three times higher than that of the general population (3.7%) in Taiwan[16]. The authors also found that gender was not independently correlated with depression, but that the interaction between job control and gender was independent of depression. In a national crosssectional survey of Japanese physicians, depressive symptoms were noted in 8.3% of men and 10.5% of women[37], and 5.7% of men and 5.8% of women exhibited suicidal ideation. Another national study performed before the COVID-19 pandemic revealed that 6.5% of US doctors had suicidal thoughts in the previous year[36]; this rate exceeded the prevalence of suicidal ideation among United States workers in other fields.

Fewer studies have surveyed anxiety disorders in physicians, with early surveys using validated scales suggesting rates of anxiety disorder as high as 24%[39] and post-traumatic stress disorder ranging between 4% and 15%[39,40]. One Canadian study using the posttraumatic stress disorder (PTSD) Checklist-Civilian Version (PCL-C) found a prevalence of probable PTSD of 4.4%[40]. For probable PTSD, no gender differences were observed, but possible PTSD was more common in males (47.3% vs 20.4%, P = 0.001). Additionally, mean scores were higher for men than for women (30.4 vs 25.4, 95%CI = 1.4-8.5, P = 0.006). A recent systematic review by Pougnet *et al*[29] found that 7.8%-48.0% of hospital doctors had mood disorders, 2.2%-14.6% had post-traumatic stress disorder, and 10.5%-19.3% had anxiety disorders. In a study of sleep patterns of physicians in Japan, 21.0% of men and 18.1% of women [31] suffered from insomnia.

#### **RISK FACTORS**

Several factors are associated with the risks of distress and stress-related psychiatric disorders. Studies investigating the impact of gender on the mental health of physicians found that females were more vulnerable to stress-related psychiatric disorders and suicide[15,37,41,42]. For example, data from the Canadian Physician Health Study indicated that depression was more prevalent among female physicians[15]. Furthermore, more than a quarter of the physicians reported that mental health concerns made it difficult to manage their workload, a problem more common among female physicians. The Norwegian Physicians' Survey indicated that mental health problems were related to low work control (autonomy), time pressure, and demanding patients[24]. There is little gender difference early in the career, but more female doctors than male doctors seem to experience problems in the later years. Schernhammer and Colditz[42] web-based survey showed that female physicians' suicide rate was disproportionately higher than that of male physicians. They reported that the suicide rates of female and male physicians were 2.3 times (95%CI = 1.90-2.73) and 1.4 times (95%CI = 1.21-1.65) higher compared to that of the general population, respectively.

Age and work experience of doctors may also matter[36,41,43]. More experienced and older physicians report lower burnout or psychological distress than younger physicians[43]. This result may due to experienced and older physicians' independence afforded by experience accumulated over time and ever-changing work conditions and the development of protective defenses in their interaction with patients. A study by the British Medical Association revealed that junior physicians reported the highest rate of diagnosis of a mental health condition[41].

Other factors may also contribute to distress and stress-related psychiatric disorders in doctors. For instance, physicians working longer hours seem to be more vulnerable to psychological disturbance [41]. A narrative review found that distress and suicide risks are affected by a lack of positive feedback, emotional exhaustion to the brink of burnout, a lack of support networks, and workplace isolation[44]. Furthermore, risks may be aggravated by long working hours, strained family relationships, and poor work-life balance, as well as organizational and systemic issues. A recent systematic review by Saade *et al*[27] summarized the work-related risk factors of depression, including skill utilization; decision authority; physical and psychological demands; number of hours worked; work schedule (regular/ irregular; daytime/nighttime); social support from coworkers, supervisor, and the family; job promotion and recognition; job security; and bullying.

## THE IMPACT OF THE COVID-19 PANDEMIC

In several ways, the COVID-19 pandemic has profoundly altered social and occupational environments. There are many factors that influence the mental health of the general population as well as healthcare providers, including fear of infection, social distancing policies, mandatory lockdowns, and isolation periods, as well as suspension of production activity, loss of earnings, and anxiety about the future, together influence the mental health of the general population and healthcare providers. The possibility of high infection rates during the pandemic period added to the stress of healthcare professionals. This included using protective equipment, implementing new medical procedures, long working shifts, staying away from family, *etc*[20].

The distress, burnout, and stress-related psychiatric disorders of medical practitioners seemed to have been exacerbated during the COVID-19 pandemic[20,45-47]. A recent systematic literature review of the symptoms of burnout syndrome in physicians revealed that the overall burnout rate ranged from 14.7% to 90.4% during the outbreak of the COVID-19 pandemic[20]. In addition, the review highlighted that the high prevalence of burnout symptoms was associated with stress, anxiety, and depression; the factors that contributed to burnout included the violent issues related to organizational health as well as the lack of personal protective equipment.

An umbrella review of systematic reviews by Fernandez *et al*[47] found a 17.0%-19.8% rate of anxiety and a 40.4% rate of depression among physicians during the COVID-19 pandemic. In an umbrella review involved 44 meta-analyses[45], 26.7% (95%CI = 19.8-33.6) of hospital doctors reported anxiety and 30.9% (95%CI = 24.9-36.9) reported depression symptoms, while 37.2% (95%CI = 32.61-41.86) suffered from insomnia during the COVID-19 pandemic. In a recent systematic review and metaanalysis by Johns *et al*[46], the pooled prevalence of anxiety and depression was 25.8% (95%CI = 20.4%-31.5%) and 20.5% (95%CI = 16.0%-25.3%), respectively. The authors argued that a significant proportion of physicians experienced high levels of anxiety and depression symptoms during the COVID-19 pandemic, although not conclusively more so than before the pandemic.

A recent study of health professionals' help-seeking behavior during the COVID-19 pandemic in Spain reported a notable increase (29.4%) in the number of referrals to the special clinical unit during the pandemic, especially among physicians compared to nurses[48]. The most prevalent major diagnoses at admission remained similar before and during the pandemic: Adjustment disorders, mood disorders, anxiety disorders, and substance use disorders.

## HELP-SEEKING BEHAVIORS AND UNDERTREATMENT OF PHYSICIANS

Although evidence shows that medical practitioners are at high risk of clinically significant behavioral health problems that may require treatment, they tend to be reluctant to seek treatment for mental health problems [25,28,36,41,49]. A recent survey exploring United States doctors' suicidal ideation and attitudes to seeking help found that 1 in 15 doctors reported having suicidal thoughts in the previous 12 mo[36]. Most doctors (72.9%) disclosed that they would seek professional help if they had a serious emotional problem. However, doctors with suicidal ideation were less likely to state that they would seek help (64.2%) than those without suicidal ideation. Earlier research data from the Canadian Medical Association showed that of the 18% of physicians who were recognized as depressed, only a quarter considered seeking help and only 2% actually did[25]. A European study revealed that 78.3% of distressed physicians had never sought professional help for burnout or depression[49]. In a study conducted by the British Medical Association, junior doctors and medical students reported the highest rate of being formally diagnosed with a mental illness, but junior doctors were the least likely to know how to access support or help[41]. A recent survey of physicians in Hong Kong also found that among the cases positive for depression (16.0%), less than half reported having a formally diagnosed mood disorder[28].

Studies using objective data echo the findings of self-report surveys on the help-seeking behaviors of doctors[33,50]. Gold *et al*[33] used data from the National Violent Death Reporting System to explore suicide among United States physicians. They found that although mental illness was a critical comorbidity in doctors who committed suicide, postmortem toxicology testing showed low rates of antidepressants. We also conducted a study using a nationwide population-based database of the National Health Insurance program in Taiwan to explore the actual risk of stress-related psychiatric disorders among healthcare-seeking doctors[50]. A total of 15150 doctors and 45450 matched controls were included, and the results showed that the adjusted odds ratios for treated depression, anxiety, and insomnia in the physicians enrolled were 0.716 (95%CI = 0.630-0.813), 1.103 (95%CI = 1.020-1.193), and 2.028 (95%CI = 1.892-2.175), respectively. In other words, doctors have a higher likelihood of being treated for insomnia and anxiety but a lower likelihood of being treated for depression than the general population. Moreover, we found that undertreatment was more common in female doctors for anxiety; in age groups > 35 years for depression; in surgery and OBS/GYN specialties for anxiety; as well as in surgery and internal specialties for depression.

Doctors' own attitudes may be the reason for their hesitancy in seeking professional help for psychological or behavioral health problems. A survey of United States female physicians revealed that almost 50% believed that they fit the criteria for mental illness although they had not sought treatment[51]. The main reasons for avoiding care included limited time, the belief that diagnosis was embarrassing or shameful, fear of reporting to a medical licensing board, and a belief that they could independently manage their illness. A recent study of Australian physicians' help-seeking for depression found that the most common barrier to help-seeking was "confidentiality/privacy" [52]. In addition to the fear of professional consequences, e.g., the impact on the medical license<sup>[53]</sup>, physicians identified barriers such as limited time to seek medical treatment and the stigma attached to mental illness<sup>[54]</sup>. Previous studies have suggested that physicians are reluctant to see another professional, especially if the problem is psychological [26,55]. Doctors become used to coping with their distress or psychological problem through avoidance and denial, although the effect is doubtful[11,56,57]. Instead, most doctors tend to use self-prescribed medications and self-treatment for their own psychological distress or medical illness[24,49,58,59].

Doctors' attitudes can hinder their access to proper health care for themselves. Physicians are not used to the role of being the patient and fear that their need for help may be seen as a mark of their inability to cope or weakness[55,60,61]. Such a perceived stigma is associated with resistance to helpseeking. In an anonymous survey of 1401 academic physicians in the United States, 12% reported moderate to severe depressive symptoms in the previous two weeks[62], but of these, less than half reported that they were likely to seek treatment for a mental health problem. More than half the doctors endorsed survey items about the stigma attached to mental illness. It is worth noting that the fear of being stigmatized can develop as early as when the doctors are students[63-65]. In a survey of students at six medical schools in the United States, only a third of the respondents with burnout sought help for a mental health issue in the last 12 mo[63]. The authors concluded that negative personal experiences, perceived stigma, and the hidden curriculum may lead to the majority of students not seeking the help they needed.

#### RECOMMENDED MANAGEMENT AND INTERVENTION STRATEGIES

As physicians' mental health problems have been globally recognized as a health crisis, an increasing number of researchers have proposed action plans and intervention strategies in recent years, although not all of them are validated. Interventions to deal with this problem can be divided into two categories: Those focusing on the individual; and those addressing the work environment [3,66]. Individual-focused programs frequently comprise instruction in mindfulness, exercise, and nutrition, while programs on dealing with the work environment focus mainly on stressors such as productivity pressures, electronic health records, and the administrative burden.

In a recent review focusing on physician stress and burnout, Yates[3] proposed a number of solutions, including decreasing the amount of time physicians spend on non-clinical tasks, organizational changes to improve usability of electronic medical record systems, the adoption of scribes, personal resilience methods focused on self-care, and programmatic approaches to promoting physician well-being. Other authors also recommend specific interventions such as meditation, mindfulness training, and individualized professional coaching and groups for stress management[67-70]. Posluns and Gall[68] focused on the role of self-care in promoting well-being and suggested self-care practices including awareness, balance, flexibility, social support, physical health, and spirituality. Furthermore, they suggested integrating self-care practice into clinical training programs and the quality assurance courses of professional associations in the field of mental health.

A number of interventions have been established to improve the well-being of junior physicians and resident doctors[71-74]. For example, a recent study assessed an educational program, the Resident Physician Burnout and Peer Communication Curriculum, aimed at promoting a strong informational and emotional social support system[73]. The course used peer roleplaying to establish self-awareness and social support, enhance communication skills, and inform about available mental health resources, thus encouraging intervention. The author concluded that roleplaying provided an effective, low-cost method of destigmatizing via encouraging discussion of burnout, educating about signs and symptoms, and learning about available resources. In their recent review, Krishnan et al[71] identified three main types of interventions in the United Kingdom: Mentorship, clinical preparation interventions, and mindfulness. Most of the studies reviewed showed positive outcomes of interventions, suggesting them to be advantageous in reducing stress levels and anxiety, and thereby improving the well-being of young doctors. However, a study evaluating a suicide screening and treatment referral program for faculty and residents at an academic medical center in the United States highlighted the challenges of engaging the professionals in the program, although the minority who successfully participated in the treatment referral program were satisfied with the outcomes[74].

Medical residents and doctors often find it inconvenient to receive professional counseling owing to concerns about cost, time, confidentiality, and stigma. The distress and mental health problems of frontline physicians exacerbated by the COVID-19 pandemic emphasize the need for accessible psycho-



Table 1 Summary of recommended management and intervention strategies				
Individual	Work environment	Program	Ref.	
Personal resilience methods focused on self-care	Decreasing the amount of time physicians spend on non-clinical tasks, organizational changes to improve usability of electronic medical record systems, the adoption of scribes	Programmatic approaches to promoting physician well-being	[3]	
Meditation, mindfulness training, and individu- alized professional coaching and groups for stress management			[67- 70]	
Self-care practices including awareness, balance, flexibility, social support, physical health, and spirituality		Integrating self-care practice into clinical training programs and the quality assurance courses of profes- sional associations	[68]	
Peer roleplaying to establish self-awareness and social support, enhance communication skills, and inform about available mental health resources, thus encouraging intervention	A strong informational and emotional social support system	Resident physician burnout and peer communication curriculum	[73]	
Mindfulness	Mentorship	Clinical preparation interventions	[ <b>7</b> 1]	
	Providing confidential, free, and individual on-site counseling and medication management	RFWP	[ <mark>76</mark> ]	
	A novel smartphone app offering a digital-first mental health resource		[75]	
Normalizing depression as a medical disorder, decreasing the stigma of mental disorders, and encouraging faculty and physicians to seek treatment			[72]	

RFWP: Resident and Faculty Wellness and Peer Support Program.

logical support for medical professionals. There are novel approaches to reducing barriers [75,76]. For instance, the Resident and Faculty Wellness and Peer Support Program at Oregon Health and Science University has sought to reduce these obstacles by providing confidential, free, and individual on-site counseling and medication management<sup>[76]</sup>. During the COVID-19 pandemic, all appointments via this program were shifted to a telehealth service and many doctors were grateful for the opportunity to talk through their apprehensions and strengthen their coping ability. Another study investigated a novel smartphone app offering a digital-first mental health resource to young physicians<sup>[75]</sup>. It contained psychoeducational material, information on common work stressors, cognitive behavioral modules, guided meditation, and a section on help-seeking options for mental health problems through workplace and private routes. Results showed that anxiety and depressive symptoms significantly decreased between the pre- and post-assessment points; however, doctors' safety concerns about COVID-19 significantly increased.

In a special article aiming to reduce the stigma associated with mental illness and encourage medical students to seek treatment, Brower<sup>[72]</sup> suggested that faculty attitudes toward mental health problems, including unwillingness to acknowledge having such issues, may be transmitted to medical students educated by them and keep depression concealed via the hidden curriculum. In addition, the fear of mental illness is manifested as privileging applications and licensing under the guise of patient safety, leading to a culture of shame and silence. Brower[72] appealed to medical faculty and physicians, as founders and executors of this professional culture, to be the ones to start changing it. The article also provides suggestions for normalizing depression as a medical disorder, decreasing the stigma of mental disorders, and encouraging faculty and physicians to seek treatment (Table 1).

## CONCLUSION

Healthcare providers' mental wellness has become a worldwide public health concern. The literature on stress-related mental health conditions of these vulnerable professionals and their determinants was limited until a few years ago. Although recent research has begun to focus on action plans and intervention strategies, few mention the barriers to help-seeking and the impacts of doctors' mental health problems on patient care<sup>[77]</sup>. The present review highlights that physicians have high risks of distress, burnout, and subsequent stress-related psychiatric disorders, which may be further exacerbated during the COVID-19 pandemic. However, at-risk physicians are still notably underrecognized and undertreated. Doctors' reluctance to seek help may be largely due to their own attitudes,



especially the stigma attached to mental illness. Our review is limited by its focus on qualitative analysis without quantitative analyses, such as the effectiveness of mental health interventions in doctors.

We hope that this review encourages a number of future considerations. Firstly, improved awareness of the significance of physician wellness, both organizationally and individually, is needed by physicians, their employers, and their patients. Inclusion of physician wellness as an indicator of quality of organizations might be the first step that can lead to a shift in the culture of care for physicians' wellness. Thus, health systems and organizations should routinely measure physician wellness and the level of distress and burnout, establish evidence-based intervention strategies, and discuss the challenges related to their implementation. Secondly, educating physicians themselves, especially medical students and future doctors, about the impact of mental health problems, how to develop selfawareness and help-seeking, and how to eliminate the stigma is crucial. Finally, more prospective and longitudinal studies are needed to explore the causes, manifestations, impacts, and determinants of distress, burnout, and subsequent stress-related psychiatric disorders in physicians. Moreover, research on health care-seeking behaviors of physicians, as well as the possible barriers, both individual and organizational, to their use of mental healthcare resources is necessary. Accordingly, assessment of comprehensive management and novel intervention methods, such as telehealth, digital medicine, groups, and other outreach treatments, and their efficacy is also highly recommended.

## FOOTNOTES

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MINIREVIEWS

# Kynurenine pathway of tryptophan metabolism in pathophysiology and therapy of major depressive disorder

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## Abstract

Serotonin deficiency in major depressive disorder (MDD) has formed the basis of antidepressant drug development and was originally attributed to induction of the major tryptophan (Trp)-degrading enzyme, liver Trp 2,3-dioxygenase (TDO), by cortisol, leading to decreased Trp availability to the brain for serotonin synthesis. Subsequently, the serotonin deficiency was proposed to involve induction of the extrahepatic Trp-degrading enzyme indoleamine 2,3-dioxygenase (IDO) by proinflammatory cytokines, with inflammation being the underlying cause. Recent evidence, however, challenges this latter concept, as not all MDD patients are immune-activated and, when present, inflammation is mild and/or transient. A wide range of antidepressant drugs inhibit the activity of liver TDO and bind specifically to the enzyme, but not to IDO. IDO induction is not a major event in MDD, but, when it occurs, its metabolic consequences may be masked and overridden by upregulation of kynurenine monooxygenase (KMO), the gateway to production of modulators of immune and neuronal functions. KMO appears to be activated in MDD by certain proinflammatory cytokines and antidepressants with anti-inflammatory properties may block this activation. We demonstrate the ability of the antidepressant ketamine to dock (bind) to KMO. The pathophysiology of MDD may be underpinned by both the serotonin deficiency and glutamatergic activation mediated respectively by TDO induction and N-methyl-D-aspartate receptor activation. Inhibition of TDO and KMO should be the focus of MDD pharmacotherapy.

Key Words: Major depressive disorder; Indoleamine 2,3-dioxygenase; Kynurenine monooxygenase; Proinflammatory cytokines; Serotonin deficiency; Tryptophan 2,3dioxygenase



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**Core Tip:** Antidepressant drugs inhibit the activity of liver tryptophan 2,3-dioxygenase (TDO) and bind specifically to the enzyme, but not to indoleamine 2,3-dioxygenase (IDO). IDO induction is not a major event in the pathophysiology of major depressive disorder (MDD), but may be masked and overridden by upregulation of kynurenine monooxygenase (KMO), the gateway to production of modulators of immune and neuronal functions. The pathophysiology of MDD may be underpinned by both the serotonin deficiency and glutamatergic activation mediated respectively by TDO induction and N-methyl-Daspartate receptor activation. Inhibition of TDO and KMO should be the focus of MDD pharmacotherapy.

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## INTRODUCTION

#### Serotonin deficiency in major depressive disorder

Antidepressant drug development has been based on the monoamine hypothesis of affective disorders that postulates a deficiency of one or more monoamines and the need to develop agents that can inhibit either their breakdown (monoamine oxidase inhibitors) or their reuptake and subsequent degradation [tricyclic antidepressants (TCAs), serotonin-specific and serotonin-noradrenaline reuptake inhibitors]. The serotonin deficiency was originally suggested from observations by Curzon and Bridges[1] that patients with depression exhibit raised cortisol levels that can induce the synthesis of liver tryptophan 2,3-dioxygenase (TDO; formerly Trp pyrrolase) resulting in accelerated peripheral Trp degradation and hence a decrease in its availability to the brain for 5-HT synthesis. Brain (Trp) is the major determinant of 5-HT synthesis, because Trp hydroxylase exists partially ( $\leq 50\%$ ) saturated with its Trp substrate[2]. Depriving the brain of Trp by the acute Trp depletion test reverses antidepressant-induced remission in depressed patients[3].

#### Inhibition of liver TDO by antidepressant drugs

Curzon[4] suggested that TDO is a biochemical factor in depressive illness and Samsonova and Lapin were the first to demonstrate TDO inhibition by some TCAs[5]. Subsequently, a wide range of antidepressant drugs of various structures and pharmacological profiles were shown to inhibit TDO activity in rat liver in vitro and after administration[6-13]. TDO inhibition occurs with doses as small as 0.5 mg/kg body weight<sup>[7]</sup> and involves prevention of conjugation of the inactive apoenzyme with its heme activator and cofactor. TDO inhibition by antidepressants therefore depends on extent of the heme saturation of the apoenzyme and also of its glucocorticoid induction by cortisol, with some antidepressants being better inhibitors of heme-activated TDO, whereas others are better inhibitors of cortisolinduced TDO[13]. Ability of antidepressants to lower raised cortisol levels is another determinant of TDO inhibition[13].

Further evidence of the targeting of TDO by antidepressant drugs was provided by our group, using molecular docking in silico: A technique for screening potential inhibitors of target proteins[14,15], but is also useful to confirm known inhibitors. We demonstrated high docking scores (strong binding) of many antidepressants, including amoxapine, citalopram, fluoxetine, fluvoxamine, moclobemide, paroxetine, seproxetine, sertraline[16], tianeptine and venlafaxine, but not the non-antidepressant drugs pargyline and mefenamic acid<sup>[17]</sup> to the crystal structure of TDO, but no docking to that of the extrahepatic IDO. Thus, antidepressants target TDO and this could explain their ability to restore serotonin homeostasis, at least in part, by reversing the defective serotonin synthesis. As TDO is the first and rate-limiting enzyme of the kynurenine (Kyn) pathway (KP), a description of this pathway and its intermediates may be useful at this point (Figure 1).

#### The KP of Trp metabolism

The KP is the major pathway of Trp degradation, accounting for 95% of dietary Trp metabolism, with the hepatic pathway contributing 90% and the extrahepatic pathway the remaining 5%, though contribution of the latter pathway is significantly increased by immune activation of IDO by interferons and other proinflammatory cytokines[18]. The liver contains all the enzymes leading to NAD<sup>+</sup> synthesis, whereas other tissues express fewer enzymes [18]. Production of Trp metabolites in extrahepatic tissues including immune cells will therefore depend on the enzymes present. In the absence of TDO or IDO induction, the Kyn produced in liver or IDO-containing tissues can be transported elsewhere for further





**Figure 1 Tryptophan metabolism to serotonin and kynurenine metabolites.** AA: Anthranilic acid; ALAAD: Aromatic L-amino acid decarboxylase; ACMS: 2-amino-3-carboxymuconic acid-6-semialdehyde; FAMID: N-formylkynurenine formamidase; 3-HAA: 3-hydroxyanthranilic acid; 3HAAO: 3-hydroxyanthranilic acid; 3HAAO: 3-hydroxyanthranilic acid; 3-HAA: 3-hydroxygenase; 3-HK: 3-hydroxykynurenine; 5-HT: 5-hydroxytryptamine (serotonin); 5-HTP: 5-hydroxytryptophan; IDO: Indoleamine 2,3-dioxygenase; KX: Kynurenic acid; Kyn: Kynurenine; KAT: Kynurenine aminotransferase; KYNU: Kynureninase; KMO: Kynurenine monooxygenase (Kyn hydroxylase); NFK: N-formylkynurenine; QA: Quinolinic acid; Trp: Tryptophan; TDO: Tryptophan 2,3-dioxygenase; XA: Xanthurenic acid; TPH2: Tryptophan hydroxylase isoform 2.

metabolism. Activity of the KP controls plasma Trp availability for cerebral serotonin synthesis and results in production of a range of Kyn metabolites that influence immune and neuronal functions[18].

## Control of plasma Trp availability

Control of plasma Trp availability to tissues including the brain is primarily the function of liver TDO. Thus, deletion of the *tdo2* gene in mice increases plasma (Trp) by up to 12.7-fold[19,20] and brain (Trp) by 10.6-fold[21]. The increase in brain (Trp) is associated in increased 5-HT synthesis[21]. By contrast, deletion of the *IDO1* or *IDO2* gene does not alter Trp availability to the brain or 5-HT synthesis[21]. Trp availability for cerebral 5-HT synthesis is therefore determined by hepatic TDO activity in the first place, but also, secondarily, but more immediately, by 2 other determinants: albumin binding of plasma Trp and extent of competition for entry into the brain from a group of large neutral or competing amino acids (CAA), mainly Val Leu, Ile, Phe and Tyr. The best predictor of likely change in brain Trp and hence 5-HT synthesis is the ratio in plasma of Trp/CAA[13]. Plasma Trp exists largely (90%-95%) bound to albumin, with 5%-10% being freely available for tissue uptake. Binding is determined by levels of

albumin and of the physiological displacers of bound Trp, nonesterified fatty acids (NEFAs). Free Trp can therefore be easily altered by dietary, hormonal and pharmacological factors that influence Trp binding[22]. Under certain conditions wherein displacement of bound Trp is strong and sustained, the rise in free Trp will be associated with a decrease in total Trp, due to the rapid equilibration between the free and total fractions. Investigators should be careful in interpreting the changes in Trp disposition under these conditions<sup>[22]</sup>, and whereas most investigators measure the ratio of total Trp/CAA, the ratio of free Trp/CAA is a more accurate measure in situations other than after acute Trp depletion or loading, as these are associated with parallel changes in both free and total Trp.

## Neuronal and immune properties of KP metabolites

Neuronal activity is influenced by the cytoprotective kynurenic acid (KA) and excitotoxic quinolinic acid (QA) as antagonist and agonist respectively of the N-methyl-D-aspartate (NMDA) receptors of the excitatory amino acid glutamate[23], with the balance between QA and KA determining the level of neuronal excitability. Immune function is influenced by several Kyn metabolites. 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA) and QA are the main proinflammatory metabolites that undermine T-cell function[18], whereas picolinic acid (PA) is anti-inflammatory. KA is dually acting [24]. KMO is the gateway for production of these metabolites and the pathway favours Kyn oxidation by KMO to 3-HK and hydrolysis of the latter to 3-HAA by KYNU, because of the relatively high affinity of both enzymes towards their respective substrates [18]. 3-HAA 3,4-dioxygenase is the most active of KP enzymes, hence the rapid conversion of 3-HAA to an unstable intermediate that cyclises nonenzymically to QA[18]. Affinity of Kyn aminotransferase (KAT) towards its Kyn and 3-HK substrates is much weaker, hence the relatively low production of KA and xanthurenic acid, formation of both of which requires increased levels of the KAT substrates [18]. KMO gene deletion in mice decreases plasma 3-HK and QA by about 86% and 92% respectively and increases concentrations of Kyn, KA and AA by 15-, 133- and 4-fold respectively[25]. Thus, KMO inhibition diverts Kyn metabolism towards the cytoprotective KA. By contrast, activation of KMO can enhance the conversion of Kyn to 3-HK leading to decreased Kyn levels: An effect that will neutralise the rise in Kyn expected with TDO and/or IDO induction. This may explain the frequent observation that the reported increase in the Kyn/Trp ratio after mild immune activation is mostly due to the decrease in Trp, rather than an increase in Kyn[26]. These aspects may help explain some of the KP changes in MDD and their modulation by antidepressants (see below). Investigators use the plasma Kyn/Trp ratio to express indirectly IDO activity. While this may apply correctly in *in vitro* culture or cell systems, this ratio is not specific for IDO in *in* vivo situations, as other factors also alter it, including TDO activity, flux of plasma free Trp down the KP and activities of KMO and KYNU[26].

## Inflammation and glutamatergic activity in major depressive disorder

The involvement of inflammation in major depressive disorder (MDD) was first proposed following the observation [27] that hepatitis C patients treated with interferon-alpha (IFN- $\alpha$ ) become depressed. As this cytokine is an IDO inducer, the concept that serotonin deficiency in MDD is underpinned by IDO induction secondarily to inflammation was born. Extrapolating from hepatitis C to MDD was however unwise, given that Trp metabolism is already compromised by this virus and the use of IFN- $\alpha$  can only potentiate the effect of the virus on Trp metabolism, in particular IDO induction[17]. Although many studies of the immune status in MDD followed, recent studies suggested that not all MDD patients are immune-activated and, when present, inflammation is mild and/or transient and its reversal does not reflect clinical outcome [28,29]. Elevation of proinflammatory cytokines in some patients is not associated with an inflamed subgroup, but is due to a right shift of the immune marker distribution[30]. In MDD, reports of changes in the Kyn/Trp ratio used to express IDO activity are contradictory, partly because of the non-specificity of this ratio[26]. Whereas considerable evidence exists for liver TDO inhibition leading to elevation of plasma and brain Trp and enhanced serotonin synthesis in rats by a broad range of antidepressant drugs[6-8], and emerging evidence for inhibition of the accelerated Trp degradation in MDD by escitalopram causing an increase in plasma Trp[31], little is known about potential IDO inhibition by antidepressants. The absence of docking of antidepressants to IDO[17] suggests that this extrahepatic enzyme does not play a role in MDD antidepressant therapy and this notion is supported by the observations that the Kyn/Trp ratio does not link inflammation with depressive symptoms[32], and that IDO expression in monocytes of MDD patients is not different from that in healthy controls[33], though this may reflect patient heterogeneity.

#### Antidepressants and KP enzymes

As stated above, antidepressant drugs inhibit and target liver TDO, but not extrahepatic IDO[17]. Even when IDO is induced in some MDD patients by proinflammatory cytokines, it is most likely that the effect of this induction (as well as that of TDO) will be masked, superseded or overridden by changes in subsequent KP enzymes, notably KMO. KMO activation in MDD is gaining ground and may be another important biochemical event in the pathophysiology of this disorder. KMO activation can result in decreased levels of the Kyn substrate and consequently in the Kyn transamination product KA, as has been reported in unmedicated MDD patients[34,35]. While many antidepressants have previously been





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Figure 2 Molecular docking of kynurenine and ketamine to kynurenine monooxygenase. Docking was performed using the Molegro virtual Docker software as described previously[16,17], but with kynurenine monooxygenase. With kynurenine (top), the best scored docking solution of 5y66 with the reference ligand, amino acids in the active site are presented in ball and stick with element colour and ligand is presented in thick lines with element colour (where carbon is grey, oxygen is red, nitrogen is blue, sulphur is yellow and hydrogen is white). Blue lines represent the hydrogen bonds in between the ligand and the active site of 5y66. Docking parameters were as follows: Kynurenine: Molecular weight (207.206), docking score (-95.4662), re-rank score (-81.6652), root mean square deviation (RMSD) (2.19513), torsion (4), H-bond (-6.03152). Amino acid residues at the kynurenine monooxygenase (KMO) active site are: Gly321, Ile224, Phe319, Met373, His320, Ala56, Leu226, Phe319, ligand binding amino acid residues are: Tyr404, His320, and Leu226. With ketamine (bottom), molecular weight (237.725), docking score (-81.8059), re-rank score (-65.0284), RMSD (zero), torsion (2), H-bond (-0.0342033). Amino acid residues at the KMO active site are: Asp112, Arg39, Gly16, Ala15, Glu37, Phe131, Arg101, Arg100, ligand binding amino acid residues are: Asn 115, Arg111. KMO: Kynurenine monooxygenase; KYN: Kynurenine.

> proposed to act by reducing inflammation and hence inhibition of IDO induction, it is more likely that they act by inhibiting KMO activation by cytokines, notably, interleukin-1 $\beta$  and IFN- $\gamma$ [36], as has been demonstrated with ketamine<sup>[29]</sup>, escitalopram<sup>[31]</sup> and sertraline<sup>[37]</sup>. Additionally, whereas ketamine does not dock to either TDO or IDO and so is unlikely to inhibit either enzyme[17], we demonstrate here for the first time its strong docking to KMO (Figure 2), that is comparable with that of the reference ligand Kyn itself, and suggest that KMO inhibition is likely to be one mechanism of action of ketamine.

## The role of anti-inflammatory drugs in MDD therapy

Current evidence suggests that anti-inflammatory strategies have not met with the anticipated success in MDD therapy and that only MDD patients with chronic inflammation may benefit from such therapy, while other patients with low-grade inflammation may experience harm[38]. Of 6 non-steroidal antiinflammatory drugs tested, only salicylic acid (the active aspirin metabolite) docks to TDO[17] and aspirin appears to be an effective single or adjunctive therapy of MDD if given in relatively small doses and for short- to medium-term durations, but not for long-term use, which does not protect against depression and can actually induce it[18]. Mechanisms of these opposite effects of aspirin involve modulation by salicylate of Trp metabolism and disposition in opposite direction[17].

#### Serotonin and glutamate interactions

KMO activation leads to production of the excitotoxic Kyn metabolite and NMDA receptor agonist QA. Glutamatergic activity can therefore be enhanced in at least some MDD patients. Mutual interactions between serotonergic and glutamatergic activities are well established and may be important determinants of MDD pathophysiology. Thus, serotonin modulates glutamate neurotransmission in several brain regions, especially those involved in cognition, motor function and nociception, with raphe neurons being immune-positive for glutamate[39]. The cognitive and emotional disorders in MDD due to defective serotonin function can in part be due to disruption of the serotonin control over glutamate and gamma-aminobutyric acid neurotransmission[40,41]. On the other hand, NMDA receptors may regulate behavior by modulating serotonin and dopamine function[42,43]. Though complex in nature, this mutual interaction can be viewed simplistically as low serotonin losing control over glutamate neurotransmission and inhibition of the latter facilitating serotonin function (Figure 3).

## CONCLUSION

We hypothesized that the KP is at the center of MDD pathophysiology and a target of antidepressant therapy. Figure 3 outlines the potential role of the KP in MDD and emphasizes the importance of TDO and KMO, the inhibition of which is likely to become the focus of pharmacotherapy of MDD. Studies on the frequency of KMO enhancement and its mechanism(s) in MDD are needed. Effects of antidepressants other than ketamine and escitalopram on enzymes and metabolites of the KP should be investigated. KMO inhibition therapy could be explored in MDD. We suggest that lowering glutamatergic activity by KMO inhibition can restore serotonin function and should be recognized as a new mechanism of antidepressant action, perhaps exemplified by ketamine. The rapid and novel mode of action of ketamine should encourage the search for safer and longer-acting alternatives. The requirement of normal serotonin levels in the antidepressant-like efficacy of ketamine in rodent models





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Figure 3 Schematic representation of the proposed role of the kynurenine pathway in the pathophysiology of major depressive disorder. Mutual interactions between serotonergic and glutamatergic functions are indicated by the bidirectional arrows for increased or decreased function. MDD: Major depressive disorder; KMO: Kynurenine monooxygenase; Trp: Tryptophan; IDO: Indoleamine 2,3-dioxygenase; TDO: Tryptophan 2,3-dioxygenase; IFN: Interferon; IL: Interleukin.

[44] may explain in part the transient efficacy of the drug in humans. Furthermore, studies with the two ketamine enantiomers suggest that NMDA receptor antagonism is not the sole mechanism of the drug's antidepressant action[45]. KMO inhibition and blockade of progress of the KP to QA formation is thus far a potential mechanism of ketamine action. Addressing the above issues may provide a way forward in the search for the ideal MDD pharmacotherapy.

## FOOTNOTES

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MINIREVIEWS

## Reducing psychiatric illness in the perinatal period: A review and commentary

Jessica Rohr, Farhaan S Vahidy, Nicole Bartek, Katelynn A Bourassa, Namrata R Nanavaty, Danielle D Antosh, Konrad P Harms, Jennifer L Stanley, Alok Madan

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## Abstract

This brief overview highlights the global crisis of perinatal psychiatric illness (PPI). PPI is a major contributor to many adverse pregnancy, childbirth, and childhood development outcomes. It contributes to billions of dollars in spending worldwide each year and has a significant impact on the individual, their family, and their community. It is also highly preventable. Current recommendations for intervention and management of PPI are limited and vary considerably from country to country. Furthermore, there are several significant challenges associated with implementation of these recommendations. These challenges are magnified in number and consequence among women of color and/or minority populations, who experience persistent and negative health disparities during pregnancy and the postpartum period. This paper aims to provide a broad overview of the current state of recommendations and implementation challenges for PPI and layout a framework for overcoming these challenges. An equityinformed model of care that provides universal intervention for pregnant women may be one solution to address the preventable consequences of PPI on child and maternal health. Uniquely, this model emphasizes the importance of managing and eliminating known barriers to traditional health care models. Culturally and contextually specific challenges must be overcome to fully realize the impact of improved management of PPI.

Key Words: Perinatal psychiatric illness; Postpartum depression; Equity-oriented care; Minority populations; Maternal mortality; Pregnancy



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**Core Tip:** Perinatal psychiatric illness is a major contributor to maternal mortality and morbidity rates, especially among women of color. This paper explores the ways in which current standard of practice is failing to address these disparities and offers an alternative framework for consideration.

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## INTRODUCTION

Rates of maternal morbidity and mortality are a global health crisis. In 2017, 295000 women worldwide perished due to maternal causes [1]. Global maternal mortality rates are estimated at 211 maternal deaths per 100000 live births. The lifetime risk of maternal mortality for a 15-year-old girl is estimated at 1 in 190[1]. Mortality rates are more than 40 times higher in underdeveloped countries compared to developed geographic areas such as Europe and Australia<sup>[1]</sup>. There are major differences in rates of maternal mortality and morbidity. Differences can be seen between countries, with sub-Saharan Africa and Southern Asia accounting for approximately 86% of all estimated global maternal deaths in 2017[1]. Differences based on minority status can also be seen within countries. In the United States, Black women are 2.5 times more likely to die in childbirth than White women[2]. In the United Kingdom, Black and Asian women are more likely to die of maternal-related causes than White women[3]. Ethnic minorities (e.g., non-Han women) in China have higher maternal mortality rates than non-minority populations (e.g., Han women[4]). In Brazil, non-white women are 3.5 times more likely to die from obstetric deaths than White women<sup>[5]</sup>. In Australia, Indigenous women have a maternal mortality rate 4.6 times higher than non-Indigenous women[6]. These trends are consistent worldwide.

Maternal Mortality Review Committees have determined that 11% of pregnancy-related deaths are due to perinatal psychiatric illness (PPI), and these deaths are 100% preventable[7]. PPI is the most common morbidity in pregnancy and the leading cause of mortality during the perinatal period in developed nations[8]. PPI is a significant contributor to poor outcomes throughout pregnancy, childbirth, and postpartum. Rates of PPI in high-income countries range from 7%-15%, while the prevalence ranges from 19%-25% in low- and middle-income countries[9]. Women of color are especially at risk for PPI. In the United States, Black, Asian/Pacific Islander and Hispanic/Latinx women report experiencing PPI at 2-5 times the rates of White women[10,11]. In the United Kingdom, non-White (especially Asian) women experience PPI at higher rates than White women[12]. In Norway, the prevalence of PPI in women of underrepresented ethnicities was almost 3 times that of Western Europeans[13]. Research on racial disparities is limited. Many studies combine all racial and/or ethnic minorities together, which disregards important differences between races and cultures.

PPI refers to any psychiatric illness experienced from the beginning of pregnancy up to 1 year postpartum. A landmark study of 10000 mothers found that of women who screened positive for depression, 27% reported being depressed before pregnancy and 33% reported that their depression began during pregnancy<sup>[14]</sup>. Though many primarily think of postpartum depression when referring to PPI, there are several psychiatric illnesses that are prevalent and related to negative outcomes during the perinatal period. Perinatal depression is indeed common, occurring in around 25% of women[15]. It refers to the occurrence of a major depressive episode in the perinatal period, marked by low mood, low energy, sleep problems (apart from caring for the infant), and sometimes suicidal thoughts. This is differentiated from what has been called the "baby blues" or the "maternity blues", which refers to a transient affective disturbance that usually peaks within 5 d after childbirth[16]. PPI also refers to psychiatric symptoms beyond depression. Perinatal anxiety presents with symptoms such as excessive and uncontrollable worries about the baby and motherhood, fear of childbirth, and intrusive thoughts of the baby being harmed or dying [17]. It may occur at higher rates than perinatal depression [18]. Perinatal obsessive-compulsive disorder is more common than obsessive-compulsive disorder in the general population and is marked by obsessions and compulsions related to the baby [19]. Obsessions are generally related to fears of contamination and harming the baby and compulsions may include avoidance of child-rearing tasks and mental rituals<sup>[19]</sup>. Perinatal post-traumatic stress disorder (PTSD) refers either to a recurrence of PTSD brought on by major life changes during pregnancy and postpartum or to new onset PTSD secondary to traumas experienced during pregnancy or childbirth. Symptoms include nightmares, avoidance of stimuli associated with the trauma, and negative



appraisals of self and others related to the trauma<sup>[20]</sup>. Finally, perinatal psychosis, though relatively rare, is an emergent situation. It typically occurs within 2-3 d of childbirth, though emerging evidence suggests that some women may even experience it prenatally. It is most common in women with a history of bipolar disorder or with a first-degree relative with schizophrenia or bipolar disorder[21].

PPI is associated with a range of negative outcomes. Women experiencing PPI tend to initiate prenatal care later and miss more appointments. Both factors are highly associated with poor childbirth outcomes<sup>[22-24]</sup> and are targets for appropriate intervention like psychoeducation and enhanced awareness of PPI. PPI is also associated with pregnancy and delivery complications (such as high blood pressure, gestational diabetes premature labor, low infant APGAR score, low birth weight[25]). Specific findings stratifying risk by ethnicity and race are limited. One United States study found that non-Hispanic Black and Asian women have higher levels of risk for preterm birth while depressed than White women, and Hispanic women were not at higher risk for preterm birth when depressed[26].

Women with PPI and their babies also experience postpartum comorbidities associated with psychiatric illness. Women with PPI have more trouble bonding with their baby, and mental health concerns can be seen 4-5 years postpartum in 30%-40% of women [22,27,28]. The children of women with untreated psychiatric distress go on to have higher rates of psychiatric illness, behavioral problems, and academic difficulties<sup>[29]</sup>. To illustrate, a French study showed increased externalizing and internalizing behavior and poor motor and regulation skills in 1-year-old children of mother with perinatal depression[30]. These findings were replicated in a large (n = 2698) study out of the Netherlands examining internalizing behavior in 3-year-old children of women with perinatal anxiety and depression[31]. Studies of teenagers (aged 16 to 17-years-old) in Finland and the United Kingdom demonstrated increased risk for depression and low social competence when their mother had experienced perinatal depression[32,33].

Risk factors for PPI are myriad and many are quite common. Individual risk factors include unwanted pregnancy (50% of pregnancies), primiparity (i.e., first pregnancy), and fertility difficulties [34]. Social determinants of health related to PPI include childhood maltreatment, especially childhood sexual violence, which affects up to 25% of girls from low-income and middle-income countries[9]. Other social determinants that increase risk for PPI and are disproportionately experienced by women of color and underrepresented ethnicities are poverty, poor nutrition, lower levels of educational attainment, low social support, gender discrimination and gender-based violence, and previous mental health conditions[9,34,35]. Again, studies stratifying risk for PPI by race and ethnicity are extremely limited, though there is evidence for the deleterious impact of immigration and race-based discrimination on mental health (*i.e.*, increased risk for PPI) in the perinatal period[36]. Adversity more commonly observed in underrepresented populations, such as intimate partner violence, childhood trauma and military deployment, is also associated with greater risk for mental health outcomes[36].

Untreated PPI can have devastating consequences for mothers, their partners, their children, their workplaces, and their communities. At the population level, PPI is associated with increased healthcare costs, inappropriate use of healthcare (i.e., excess- and under-utilization as well as increased use of emergent care), child abuse, family dysfunction, and, at worst, suicide, homicide, and infanticide[22,37]. At the individual level, PPI impacts the mother's health, attachment with their child, the infant's health, and can lead to suicide or homicide [38,39]. At an economic level, the cost of PPI is significant. Though research on exact costs worldwide are limited, studies out of Canada and South Africa suggest that women with PPI utilize services costing roughly 2 times those of women without PPI[40,41]. In the United States, PPI costs an estimated \$14 billion per year, including cost estimates of loss of productivity and direct healthcare<sup>[42]</sup>. Even when strictly examining medical costs in the United States, PPI costs 5 times as much as other pregnancy concerns like gestational diabetes or postpartum hemorrhage[43].

Given the regular touchpoints between pregnant women and providers during the prenatal period and the onset of many psychiatric concerns during the prenatal period, pregnancy offers an optimal time for early detection and intervention for perinatal mental health problems[44]. The American College of Obstetricians and Gynecologists recommends 13 care appointments during the prenatal period<sup>[45]</sup>. Evidence suggests that prenatal mental health interventions are effective at improving health outcomes and preventing psychiatric distress, but PPI is significantly under-identified and largely under-treated[46].

## CURRENT RECOMMENDATIONS

In response to mounting concerns related to PPI and its impact on women and communities, initiatives to improve care have focused on universal screening. In the United States, the following organizations all recommend at least one screening for perinatal depression with a validated measure during the perinatal period: American College of Obstetricians and Gynecologists, American Academy of Pediatrics, United States Preventive Services Task Force (USPSTF), Centers for Medicare and Medicare Services, Council on Patient Safety in Women's Health Care[47-50]. The USPSTF specifies that screenings should only occur when there are significant resources for effective treatment and follow-up [51]. In the United Kingdom, universal screening is recommended by the National Institute for Health



and Care Excellence, though again, only when there are resources available for treatment and follow-up [52]. This is consistent with guidelines suggested by the World Health Organization in 2022[34] which suggested a stepped-care approach to the integration of perinatal mental health services into maternal health care. In Canada, universal screening is not recommended by the Canadian Task Force on Preventive Healthcare due to paucity of evidence for its benefits[53].

## FOUR CHALLENGES ASSOCIATED WITH CURRENT RECOMMENDATIONS

Though there are some benefits to universal screening, including the low cost and low provider burden of having patients complete the forms, at least four major challenges have arisen with the current recommendations for universal screening in the perinatal period. Each challenge impacts all pregnant women, and each is also uniquely impactful in the outcomes of women of color.

## Universal screening is not universally implemented

Unfortunately, screening has not been universally and systematically implemented in prenatal care, with estimates of screening by OB/GYN providers ranging from 39-72% [44,54,55]. Providers often do not assess for psychiatric illness for a number of reasons, including: (1) Lack of education regarding efficient measurement tools; (2) uncertainty regarding how to respond if a pregnant person endorses signs of perinatal psychiatric illness (PPI, and whether they will then be liable if negative outcomes occur); (3) lack of guidance regarding availability of appropriate treatment; (4) lack of time in short visits; and (5) lack of financial incentive for clinicians to screen [56,57].

There are notable racial disparities in the decision whether to screen for psychiatric distress. Women of color are 5%-10% less likely to be asked about psychiatric distress than White women[58,59], and without screening, women of color are less likely to spontaneously offer information regarding psychiatric distress due to discomfort and stigma[60].

#### Pregnant women underreport distress on psychiatric screenings

When screening does occur, many pregnant women underreport psychiatric distress. A qualitative review found that across several studies, many women reported that they did not have knowledge about PPI and were unaware that they would likely meet criteria given their current symptoms[61]. Other women who did recognize that they had symptoms of PPI reported being unable or unwilling to disclose feelings due to fear of burdensomeness, fear of giving their family a "bad name", and fear of losing their baby[61]. Many women had previously had symptoms dismissed or over-normalized (*i.e.*, described as normal aspects of the pregnancy period, a "rite of passage") and thus declined to disclose symptoms[62]. Other reasons to underreport symptoms include fear of disclosure outcomes, worry about being judged to be a bad mother, and lack of continuity of care[44,63]. Importantly, one study linked discomfort with being screened with higher scores on a depression scale, highlighting the relationship between experience of symptoms and discomfort with reporting them[64].

Limited data exist on differences in reporting of symptoms among pregnant women of different racial groups. However, women of color underreport psychiatric distress in non-pregnant samples, so it can be assumed they likely underreport symptoms during pregnancy[65].

#### Referrals are inconsistent

Women who do screen positive for psychiatric distress may or may not be given a referral to care, based on the clinic's access to resources and information. One program successfully engaged 80% of women who screened positive for depression symptoms in care, while another saw fewer referrals to care after universal screening was implemented than before[56,66].

Women of color who screen positive for psychiatric distress are not referred when appropriate as often as are White women. In one study, White women who disclosed psychiatric distress were referred for treatment twice as often as Asian and Black women[59]. In another, Hispanic/Latinx and Black women who met full criteria for depression were less likely to receive a depression diagnosis, limiting referrals[67]. Some studies show a 10% referral to treatment rate when women of color screen positive for psychiatric distress[68].

#### Follow-up after referrals is inconsistent

If they are given a referral to care, pregnant women do not follow up with treatment. In a study of referral rates, only approximately 40% of women referred attended even one visit[69]. Primary reasons for lack of follow-up include practical concerns (*e.g.*, perceived insufficient time, the inconvenience of attending appointments), perceived stigma (*e.g.*, feeling that needing help makes one a bad mother), and displeasure with how symptoms were handled by their provider (*e.g.*, feeling minimized, dismissed, or humiliated[61,62]). Pharmacological hesitancy is also noted in failure to follow-up, with many women worried about addiction, side effects, and stigma[62].

When resources might be available, women of color have significantly lower utilization rates of psychiatric services (e.g., attendance at appointments, continued care and follow-up, medication management) than White women, even when controlling for age, type of psychiatric condition, and socioeconomic status [70-74]. Some researchers identify mental illness stigma as a potential contributor to these differences [75], as Black women perceive greater overall depression stigma than White women, regardless of personal experience with depression[76]. Furthermore, prior experiences with mental health treatment likely play a role in the attitudes of Black women seeking treatment during periods of psychological distress<sup>[77]</sup>.

Though screening all women is the suggested standard of care in response to the mental health crisis in pregnant and postpartum women, these data demonstrate that universal screening is not sufficient for improving outcomes. Universal screening may even paradoxically serve as a barrier to care when delivered in its most common form (attached as a form to check-in paperwork). Without an explanation as to how the answers will be used, women (especially women of color) underreport symptoms to avoid negative outcomes[78].

In short and consistent with the Canadian Task Force on Preventive Healthcare, the current recommendations for universal screening are not effective for improving outcomes.

## EQUITY-ORIENTED CARE

The above-described challenges inherent to universal screening reflect profound health inequities for pregnant women and especially pregnant women of color. Current standards of care (e.g., universal screening and referral) were developed using the traditional medical framework, within which health inequities are increasing worldwide<sup>[79-81]</sup>. Even countries that provide universal health services to their citizens demonstrate major inequities based on race and ethnicity in their perinatal care. For example, in a large study in the United Kingdom examining over 600000 women who gave birth, Black African, Asian, and White non-British women had significantly lower access to outpatient mental health services than White British women [82]. Moving the needle on PPI and thus maternal mortality and morbidity will require approaches that are fundamentally aware of and responsive to health inequities in a way that traditional healthcare is not.

Equity-oriented care is positioned as an alternative to traditional care. It has been previously defined as "an approach that aims to reduce the effects of structural inequities, etc.; the impact of multiple and intersecting forms of racism, discrimination, and stigma (e.g., related to mental illness, chronic illnesses, non-conforming gender and sexual identities, etc.) on people's access to services and their experiences of care; and the frequent mismatches between dominant approaches to care, etc., and the needs of people who are most affected by health and social inequities" [83]. An equity-oriented framework is traumainformed (recognizing the higher rates of trauma and violence in communities of color), culturally safe (explicitly addressing power dynamics and historical mistrust in the medical system), and contextually tailored (highlighting skills and education relevant to the medical system and community)[84].

Therefore, a successful perinatal mental health intervention would deviate from the traditional model of screening to refer and would follow an equity-oriented model. This model would specifically address mental health stigmatization and work to reduce systemic racism in the medical context while addressing practical barriers to accessing care. A direct way to meet both needs is to move away from universal screening and toward universal intervention.

#### UNIVERSAL INTERVENTION IN THE PRENATAL PERIOD

A universal intervention approach to psychiatric distress in pregnancy may eliminate known barriers to appropriate psychiatric management, thus improving trajectories for all pregnant women, and especially for women of color. Rather than losing women at every step of the screening-to-referral pipeline, provision of a universal intervention in the prenatal period ensures that evidence-based tools for prevention of PPI are delivered. Providing this intervention to all women is a novel approach to management of PPI.

Based on the accumulation of evidence regarding the most impactful interventions in the perinatal period, equity-oriented prenatal universal intervention should be trauma-informed[85] and limited to one 45-min session. This model is consistent with research suggesting that even one childbirth educational session is effective for improving outcomes and that requiring more sessions creates a barrier to psychiatric care[86,87]. It should be delivered in the prenatal period as either an adjunct to a standing prenatal appointment or as a separate appointment. It can be delivered by a mental health professional (e.g., contracted, embedded, or other) or potentially by a trained OB/GYN provider (e.g., nurse, MA, or other). Based on previous research regarding barriers to effective care as well as what is most helpful for women during the prenatal period, the universal intervention should include the following components: (1) Brief education about pregnancy and the childbirth process; (2) brief discussion of perinatal psychiatric issues in plain language; (3) discussion of trust and potential



discomfort with providers; (4) explanation of skills for maximizing healthcare appointments; and (5) list of free and low cost resources available throughout pregnancy and after childbirth. Components 1-4 could be created and disbursed as relevant for all pregnant women while component 5 needs to be individualized to the clinic based on location and institutional/community resources.

## Brief education about pregnancy and the childbirth process

Various psychological techniques and theories suggest the importance of understanding stressors that lie ahead and managing them proactively (*i.e.*, stress inoculation training[88], dialectical behavior therapy[89]). Consistent with these theories, education should be provided regarding both the normal course of the pregnancy and childbirth process (including medically normal but potentially psychologically stressful situations such as transvaginal ultrasounds, manual cervical checks, and childbirth) as well as non-normal but still common situations (*e.g.*, gestational diabetes, preeclampsia, emergency c-sections). A respectful and informative overview of the pregnancy and childbirth phases will provide patients with an understanding of their course as well as allowing for prophylactic distress tolerance for the different situations.

#### Brief discussion of perinatal psychiatric issues in plain language

The average medical communication requires a level of health literacy (*i.e.*, ability to read and use medical information) that is higher than that of the average patient[90]. Improving mental health literacy, or knowledge about specific mental health conditions including early detection, has been suggested as a way to intervene earlier in the experience of psychiatric illness[91]. For this intervention, this would include providing patients with a plain language description of various PPI, including how they might experience them (in contrast to education for providers, which focuses more on how the provider might perceive symptoms).

## Discussion of trust and potential discomfort with providers

Because limitations to screening include the likelihood of underreporting symptoms due to discomfort with and lack of trust in providers, an intervention should include a candid and humble discussion of this issue. Discussing common barriers to effective collaboration with providers (*e.g.*, experience of racism, fear of how shared knowledge will be used, previous traumatic medical experiences) may elucidate individual biases and difficulties that can be managed.

## Explanation of skills for maximizing healthcare appointments

Patient empowerment is a crucial component of good medical care, and it is especially critical for vulnerable populations that tend to engage more passively in medical care[92]. Empowering women to utilize their medical appointments in the ways that they find most helpful can be done through providing simple skills and providing permission for their use. Skills should include bringing in questions written down ahead of time, recording appointments (with permission from provider), and asking for time for questions at the start of the appointment[93]. Skills also include emotion regulation skills to use when feeling anxious in the appointment.

#### List of free and low-cost resources available throughout pregnancy and after childbirth

A list of virtual and in-person options should be provided if the patient is interested in pursuing further behavioral health resources.

This method is equity-oriented in that it is trauma-informed, culturally safe (by explicitly addressing trust and discomfort with providers), and contextually tailored (discusses skills in plain language and ways to maximize healthcare appointments). It does not rely on women to overcome systemic barriers, fear and mistrust to risk disclosing painful experiences; rather, it offers information and education from a place of cultural humility and openness.

#### This method may confer a number of benefits over universal screening

**Reduction of stigma:** By delivering the intervention to all women, the information and education are considered standard components of prenatal care (similar to education about gestational diabetes) rather than specialized referrals based on problematic or unique disclosures. We expect that providers may see an increase in scores on screenings and in PPI diagnoses due to increased comfort with disclosing.

**Increased preparation:** The information provided within a universal psychological intervention should highlight events during the pregnancy and childbirth periods that may be uniquely stressful with an emphasis on identifying methods of coping in advance. This normalizes the potential reactions the pregnant person may have and allows them to prepare appropriately.

**Increased mental health literacy:** This intervention will provide general education about mental health concerns, which increases mental health literacy and reduces stigma.

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Table 1 Advantages and disadvantages of universal screening and universal intervention			
	Advantages	Disadvantages	
Universal screening	Low cost; low provider burden	Patients likely to under-disclose; disparities in referrals and follow- ups; disparities in who receives resources and psychoeducation; reflects traditional model of healthcare; higher levels of care not always available if needed	
Universal intervention	All patients receive psychoeducation and resources; mental healthcare is integrated into prenatal care; all patients have opportunity to discuss mental health concerns; will likely reduce costs long-term	Higher immediate cost; need for additional practitioners; higher levels of care not always available if needed	

Increased comfort with help-seeking: By destignatizing PPI and clearly explaining the importance of treating PPI, pregnant women may feel more comfortable seeking access to mental healthcare. These interventions should be standard of care for all pregnant women.

## CHALLENGES OF THIS MODEL

This model is not without its challenges. Systems-level barriers continue to exist, whether healthcare is privatized or nationalized. In low-, middle-, and high-income countries, challenges include low levels of funding afforded to mental health services, inequalities in levels of access to mental health care, and shortages of mental health providers [94,95]. Decisions will need to be made in clinic as to whether the intervention should be delivered by an embedded mental health professional (MHP) or by an OB/GYN provider. Benefits of delivery by an MHP are need for limited training, ability to provide ongoing care in clinic, and reduced burden on an already overburdened OB/GYN staff. Benefits of delivery by an OB/GYN provider are the low resources needed for implementation and reduction in the likelihood that the provider will divert responsibility for mental health management fully to the MHP, a frequent occurrence when MHPs are embedded in primary care[66]. Finally, this model does not address the major shortage of psychiatrists and mental health practitioners, both of whom are necessary when ongoing care is needed for more serious PPI management.

## **UNIVERSAL INTERVENTION VS UNIVERSAL SCREENING**

As discussed above, universal intervention may address many of the concerns with universal screening. In summary, Table 1 discusses the advantages and disadvantages of universal screening (current state in many countries) and universal intervention (proposed model).

## CONCLUSION

The application of a universal intervention model may de-stigmatize psychiatric care and address many of the barriers that continue to contribute to health disparities for women and especially women of color. Delivering a universal intervention to all patients, regardless of psychiatric distress within the context of prenatal care may improve individual and community outcomes for women by reducing stigma, increasing preparation, providing a connection to a psychiatric professional and improving mental health literacy. For women with psychiatric distress, a universal intervention may also provide a basic stress inoculation for pregnancy process, individualized referral to services if needed, and updated resources. If successful on a large scale, this intervention could contribute to changes in major international guidelines regarding the appropriate course of prenatal care.

## FOOTNOTES

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MINIREVIEWS

# Neuroimmune, clinical and treatment challenges in multiple sclerosis-related psychoses

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## Abstract

In recent years, epidemiological and genetic studies have shown an association between autoimmune diseases and psychosis. The question arises whether patients with schizophrenia are more likely to develop multiple sclerosis (MS) later in life. It is well known that the immune system plays an important role in the etiopathogenesis of both disorders. Immune disturbances may be similar or very different in terms of different types of immune responses, disturbed myelination, and/or immunogenetic predispositions. A psychotic symptom may be a consequence of the MS diagnosis itself or a separate entity. In this review article, we discussed the timing of onset of psychotic symptoms and MS and whether the use of corticosteroids as therapy for acute relapses in MS is unfairly neglected in patients with psychiatric comorbidities. In addition, we discussed that the anti-inflammatory potential of antipsychotics could be useful and should be considered, especially in the treatment of psychosis that coexists with MS. Autoimmune disorders could precipitate psychotic symptoms, and in this context, autoimmune psychosis must be considered as a persistent symptomatology that requires continuous and specific treatment.

Key Words: Multiple sclerosis; Psychosis; Schizophrenia; Corticosteroids; Antipsychotics

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**Core Tip:** Immunological perturbations in multiple sclerosis (MS) can lead to the development of psychotic symptoms. The use of corticosteroids and antipsychotics might prove beneficial and in patients with MSrelated psychosis and outweigh their adverse effects.

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## INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) that is characterized by neuroinflammation, demyelination, axonal loss and neurodegeneration[1]. It is one of the most common neurologic disorders and the most common cause of acquired neurological disability in young adults, that has an effect on 2.5 million people worldwide[2]. MS patients are two to three times more likely than the general population to suffer from mood and mental disorders[3,4].

Neurological and psychiatric diseases often overlap and co-occur [5,6]. Psychiatric symptoms may occur at any time during a neurological autoimmune disease, but they may also be an initial clinical manifestation and precede the onset of typical neurological symptoms [7]. The initial or early presence of these symptoms may complicate the establishment of a correct diagnosis, hinder the early recognition of the underlying brain disorder, and lead to inadequate treatment and a poorer prognosis[8,9]. Furthermore, the presence of various psychotic symptoms in neurological diseases additionally compromises these conditions and has an impact on individual functioning and overall disease burden [10]. The prevalence of psychosis/psychotic disorders is approximately 4.3%[11].

Mental disorders in neurological diseases may have different underlying causes<sup>[12]</sup>. In MS patients, the onset of psychiatric symptoms may be a consequence of the MS diagnosis itself[13]. Brain lesions, physical disabilities, symptoms of MS and pharmacological treatments may cause psychopathological manifestations<sup>[14]</sup>.

There is limited scientific evidence that could be useful for clinical decision-making in the resolution of psychotic symptoms in patients with MS. Recent data by Sabe and Sentissi have confirmed our clinical observations[15]. There is a lack of data considering MS and psychosis, especially schizophrenia (SCH), simultaneously. We might think that this is due to a lack of interest in the field, but it is also possible that these disorders do not exist at their full capacity simultaneously. In this mini-review, we aim to resolve some clinical dilemmas. First, we discuss the timing of the onset of psychotic symptoms and MS. Second, whether the use of corticosteroids is unfairly neglected and whether a more aggressive treatment approach is warranted. And third, whether antipsychotics may be of benefit as adjunctive therapy is discussed. Immune disturbances may be similar or very different in terms of different types of immune responses, disturbed myelination, and/ or immunogenetic predispositions.

This mini-review was conducted through a systematic electronic search of the PubMed, Cochrane, and Web of Science databases to identify cases of MS with psychotic symptoms. The terms used were "multiple sclerosis"; "psychosis"; "schizophrenia"; "neurodegeneration"; "neuroinflammation"; "corticosteroids"; and "antipsychotics." We searched for studies published in English, with no restriction on year of publication. Experimental studies, randomized or nonrandomized clinical trials, cohort studies, and case-control studies were included. We have assessed the abstracts of potentially relevant titles and reviewed the full text of potentially eligible studies. In this mini-review, we attempted to select and focus on only up-to-date and clinically relevant data.

## NEUROIMMUNOLOGICAL ASPECTS OF MS AND PSYCHOSIS

Genetic predisposition, individual and environmental factors, and specific immune responses had a significant impact on disease onset and clinical presentation. This suggests that the same etiological factors and pathophysiological pathways may influence the association between MS and psychosis. It raises the question of whether patients with SCH might also suffer from MS later in life. The genetic basis of MS is supported by the fact that the risk of disease is higher in MS family members than in the general population, that certain racial and ethnic groups have a lower illness tendency, and that the concordance rate is higher in monozygotic twins[16]. Previous genetic studies have shown that the predisposition to develop MS depends on several independent polymorphic genes and their interaction. No single gene variant is necessary or sufficient to cause MS, but each one increases the overall risk of the disease in an additive manner [17]. Genome-wide association studies (GWAS), which examine gene polymorphisms in the whole genome, suggest that over 200 gene loci that have different immune



functions are responsible for the development of MS[18,19]. The risk genes control the differentiation and state of these cells through their function in specific cellular processes in immune cells. In addition, recent evidence indicates that many immune cell populations are highly heritable, raising the possibility that MS risk genes define differences of immune cell populations that could also be involved in the pathogenesis of illness[18].

It is well known that the immune system plays an important role in the etiopathogenesis of MS and SCH[20,21]. Some authors assign them to the same group of neuroinflammatory and neurodegenerative properties, but with marked differences in the immune response. From the clinician's point of view, this fact could mean that these disorders are mutually exclusive. We have already considered confronting results of the prevalent immune responses in MS and SCH as prototypes of disorders of type 1 vs type 2 immune responses, respectively [22,23]. In recent years, growing epidemiological evidence has suggested a bidirectional association between autoimmune diseases and increased risks with SCH[24]. A family history of autoimmune disease has been shown to be related to an increased risk of psychotic disorders and vice versa<sup>[25]</sup>. In addition, having a first-degree relative with SCH increases the risk of autoimmune diseases by 6%[26]. Previous studies have found that patients with MS are at an increased risk of developing SCH[27]. SCH and other psychotic disorders have been associated with genetic markers of immune activation, suggesting a possible etiological link between MS and psychosis[28]. GWAS emphasized the significant overlapping of genes, noted the involvement of similar HLA alleles, and identified 21 independent loci associated with SCH and also associated with MS. In these diseases it seems that the major histocompatibility complex is responsible for the genetic overlap[29,30]. A possible additional role of genetics in this association could be an inherited susceptibility to common risk factors for infections or a predisposition to abnormal immune responses that further increases the risk of autoimmune reactions[31]. Despite the contrasting nature of these diseases, some common features have been identified. Risk factors for both MS and SCH include an interaction between genetic and environmental factors[32,33]. Infection is one of the most important triggers for the development of both diseases [34,35]. In the last decade, considerable attention has been paid to the gut microbiome as a possible etiological factor in the pathophysiology of MS and SCH[36]. It has been suggested that the composition of the intestinal flora plays an important role in CNS and immune system development [37]. Dysbiosis of the microbiome has been shown to affect the Th1/Th2 balance and the ratio of regulatory T cells to Th17 cells, which affects the immune response to pathogens<sup>[38,39]</sup>. Dysbiosis has been found to affect T cell-mediated inflammation in MS and SCH patients[40,41].

In SCH, it has been previously hypothesized that inflammation in the microvasculature persists as chronic, low-grade inflammation and does not disseminate in whole brain parenchyma as in acute encephalitis<sup>[21]</sup>. This organic substrate could be related to the soft neurological signs, observed in patients with SCH[42]. Similar to SCH, the clinical manifestations in MS may be the result of acute or chronic neuroinflammation. In the acute stage, the peripheral immune system is involved, and T cells, B cells, and macrophages enter into CNS and cause acute inflammation in the brain[21]. In addition, these mechanisms have no influence on the chronic phase. Recently, a concept of "compartmentalization" of the inflammatory process in the brain has been postulated, in which a local immune response in the CNS occurs separately from the peripheral immune system<sup>[43]</sup>. This hypothesis is supported by the fact that disseminated activation of microglial cells is the primary characteristic of the chronic phase of the illness[44]. There is ample evidence of biomarkers indicating a link between immunological processes, psychotic disorders and MS. Elevated levels of different inflammatory markers have been found in the blood and cerebrospinal fluid (CSF) of patients with psychosis and MS, with particularly high levels in patients with first-episode psychosis or acute relapse[45,46]. Dysregulation of regulatory T cells and Th17 cells may be essential for immunological homeostasis and play a role in the development of both diseases[47,48]. In recent years, much attention has been paid to B cells and their role in the autoimmune pathology of MS and psychosis[49,50]. Oligoclonal bands (OCBs) in CSF have been detected in approximately 90% of patients with MS<sup>[51]</sup>. In up 12.5% of patients with SCH were found OCBs[45]. It is important to keep in mind that there are other possible triggering and contributing factors besides the specifics of the immune response in MS and psychosis. Within the new concept of nomothetic network psychiatry and causal models, perhaps the identification of these transdiagnostic classes could even be presented as new nosological categories[52].

## CLINICAL ASPECTS OF MS AND PSYCHOSIS

In clinical practice, it is important to distinguish whether psychosis precedes the onset of MS, coincides with MS, or is observed in the later stages of this somatic disease. We remind that these psychotic symptoms could be integral to SCH, a schizoaffective disorder, affective disorders, or even delirium. Also, we must point out that psychosis should be considered as a much broader concept than SCH. This information is important for the choice of future MS treatment.

Symptoms and signs of MS include ataxia, loss of coordination, hyperreflexia, spasticity, loss of visual acuity, sphincter incontinence, fatigue, anxiety, depression, and cognitive deficits [53]. Most patients have a relapsing-remitting form of the disease which is characterized by progression of symptoms in


relapse and possible further deterioration over time[53].

Neuropsychiatric symptoms were previously reported as a rare manifestation of MS. Recently, the most commonly observed behavioural disturbances preceding the onset of MS have been summarized. Symptoms described include lack of insight, delusions, auditory and visual hallucinations, mood disturbances, behaviour disorder, and confusion[15]. Psychotic symptoms reported in MS patients also include irritability/agitation, sleep disturbances, grandiosity, blunted affect, and rare symptoms such as catatonia and transient catalepsy[4,14].

In a recent systematic review of case reports and case series, the authors pointed out that psychotic symptoms preceded or accompanied the MS diagnosis in half of the cases, with a mean time to MS diagnosis of 0.8 ± 1.4 years, whereas 15.1% of MS diagnoses were discovered after isolated psychiatric symptoms. They observed a significant delay considering MS treatment initiation between initial psychotic symptoms and MS diagnosis ( $2.73 \pm 3$  years), and in patients with the first episode of psychos and MS diagnosis  $(0.8 \pm 1.2 \text{ years})$  [15]. Another important observation in their analysis was that typical MS white matter lesions were found in a small group of patients with psychiatric disorders [54]. Finally, they pointed out that resistance or poor response to antipsychotics was associated with excellent improvement of both psychiatric and neurological symptoms with corticosteroids in most cases [15]. Autoimmune psychosis must be considered as a persistent symptomatology that requires continuous treatment[55].

Pathological changes in white and grey matter structures may play an important role in the pathogenesis of MS-related psychosis. Neuroimaging studies revealed that MS patients with psychotic symptoms have a higher total lesion score, especially in periventricular areas[56]. Psychotic symptoms in MS are correlated with a higher number or volume of lesions in the temporal or frontal lobes, cerebellum, and corpus callosum[57,58]. In addition, the presence of soft neurological signs in patients with sudden or acute psychotic symptoms without a prior personal or family history of psychosis is an indication for neurological exploration[15,59].

## KNOWN FACTS AND TREATMENT CHALLENGES IN MS-RELATED PSYCHOSIS

Immunomodulatory medications for the treatment of MS could be useful to achieve remission of the disease, but in some cases may have a direct effect on the development of psychotic symptoms, although the mechanisms are poorly understood. This effect also occurs after initiation of corticosteroids or could be related with interferon beta (IFN- $\beta$ ) treatment. The study of 11 cases confirmed severe depression with suicidality in patients with MS, who were taking IFN- $\beta$  and had no psychiatric history [60]. These patients also had phobic, aggressive, behavioural, psychotic, and manic symptoms, indicating the presence of a complex mood-behaviour disorder associated with IFN- $\beta$  use. Complete remission of psychiatric complications was observed after discontinuation of IFN-β. Glatiramer acetate was generally not associated with deterioration of mod[61]. Gasim *et al*[62] conducted a systematic review to investigate whether the use of disease-modifying therapies is associated with adverse psychiatric effects in MS patients. This study included natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab and showed that their use do not increase risk of adverse psychiatric effects in MS, and some of them, such as fingolimod, even reduced the incidence of depressive symptoms. In addition, Krivinko et al[63] recently demonstrated that fingolimod treatment attenuated psychosis-associated behavioural deficits in rodents.

The standard MS treatment for acute exacerbations is pulse therapy with systemic glucocorticoids. Intravenous methylprednisolone at a dose of 1000 mg/d for 3 or 5 days or oral prednisone with or without tapering dose is usually used[64]. Administration of high-dose corticosteroids (HDC) may be repeated, depending on the MS course and disease activity[65]. Pulsed regimens of corticosteroid administration in the short term in MS have been reported to be well tolerated and safe, with only minor transient and dose- dependent side effects such as palpitations, hot flashes, dyspepsia, insomnia, and virulent taste[65].

An important clinical question is whether the use of corticosteroids, which are regularly used to treat MS relapses, can induce psychiatric symptoms. Several reports suggest that psychiatric side effects may occur with HDC use, including hypomania/mania, depression, psychosis, and suicidal ideation[66-71]. Mood changes, particularly (hypo)mania and depressive symptoms could be potentiated by HDC treatment<sup>[72]</sup>. In patients with MS, depression and mood disorders have been associated with pulse steroid therapy, suggesting that the risk may be related to the patient's psychiatric history<sup>[73]</sup>.

Steroid-induced psychosis is a well-documented phenomenon[74]. In clinical practice, there are different approaches to corticosteroid treatment for MS-related psychosis. The literature on the treatment of corticosteroid-induced psychosis is very scarce and limited to MS reports and small-sample size studies. In our country, the prevailing opinion is that patients with psychosis should not be treated with corticosteroids because they may exacerbate psychosis. Moreover, nearly 30% of patients in the acute phase of their psychotic symptoms were successfully treated with corticosteroid therapies [75]. The question arises whether it is more beneficial for the patient to keep the psychosis under control or to treat the acute relapse, act on the inflammation, and prevent further disease progression and



neurological disability. The Maudsley guideline indicates that the benefits of corticosteroid therapy may outweigh its adverse effects [76]. To date, however, few studies have explored the impact of corticosteroid therapy on psychosis in people affected by MS, and the specific risk factors predictive of psychiatric changes remain unclear [72,77]. Chronic consumption of corticosteroids and increase in their dose and duration of treatment are associated with these adverse effects [78]. As frequently mentioned, a general therapeutic strategy for corticosteroid-induced psychiatric symptoms should begin with dose reduction or discontinuation of the drug whenever possible [69,79].

Corticosteroid-induced hypomania, mania, and mixed mania showed to be successfully treated with a typical antipsychotic or mood stabilizer, most commonly haloperidol, haloperidol plus lithium, quetiapine, risperidone, olanzapine, olanzapine with valproate, carbamazepine, lithium, lamotrigine plus clonazepam, or clonazepam alone when lithium was ineffective[68]. In some cases, a combination of an antipsychotic and a benzodiazepine was needed[68]. In the case of medication-induced psychosis, adjustment of the MS drug should be considered and treatment with an antipsychotic should be initiated. There are few practical guidelines for the choice of antipsychotic drug and dosage, but there is evidence of good results with the use of clozapine, risperidone, ziprasidone, low-dose chlorpromazine, or the prophylactic use of lithium along with corticosteroid therapy [80]. In patients with steroidinduced psychosis, use of the antipsychotic quetiapine resulted in decreased irritability, reduced psychological distress, and improved sleep[81]. Atypical antipsychotics remain the treatment of choice in these patients because they have a more favourable tolerability profile, as they are less likely to affect the extrapyramidal system and reduce the risk of developing pseudoparkinsonism and catalepsy[82, 83]. Researchers also presumed that patients with MS had an unexpected sensitivity to antipsychotic drugs[84]. MS is closely related to various movement disorders[85]. However, clinicians should be aware that movement disorders can also represent adverse drug reactions caused by chronic antipsychotic therapy<sup>[86]</sup>, especially in cases of polypharmacy.

The anti-inflammatory potential of antipsychotics could be useful and should be considered especially in the treatment of psychosis that coexists with MS. Patients with SCH have been found to have decreased intracortical myelination, whereas certain antipsychotic agents may restore this defect. Patergnani et al[87] showed that human and experimental MS induce a mitochondrial deficit leading to activation of autophagy and mycophagy. These phenomena play a causal role in MS as their inhibition by antipsychotic drugs such as haloperidol and clozapine may prevent demyelination, induce remyelination, and reverse MS behavioural deficits[87]. In addition, Stamoula et al[88] argued that the atypical antipsychotics clozapine, risperidone, quetiapine, and olanzapine dramatically reduce the severity of experimental autoimmune encephalomyelitis and delay its onset by downregulating the production of pro-inflammatory cytokines and chemokines and attenuating T-cell infiltration, myeloid cell activation, and upregulation of T regulatory cells.

## CONCLUSION

Psychotic symptoms could represent an acutisation of MS, considering the specific localization of the lesions. In this context, it can be assumed that causal therapy of MS also leads to resolution of psychosis. It is also important to exclude somatic comorbidities to make the diagnosis of SCH. Autoimmune disorders could precipitate psychotic symptoms, and in this context, special attention should be paid to patients with the first psychotic episode and soft neurological signs, sudden cognitive decline, and unsatisfactory response to antipsychotic treatment. Only when all of the previously mentioned facts have been ruled out can one conclude that psychosis is a separate entity (Figure 1). Physicians treating patients with MS and psychosis should assume, first and foremost, that the psychotic syndromes are related to MS and not triggered by medication. Based on the literature data, it is extremely important for clinicians to perform accurate screening of psychiatric status in patients with MS before initiating HDC treatment and to note that HDC should be used with caution in patients with an acute MS exacerbation. The properties and indications of available immunomodulatory drugs need to be better understood, and the therapeutic approach should be adjusted with careful consideration of the individual's unique constellation of symptoms. The mechanism of action and pharmacokinetics of the antipsychotic drug, the safety and efficacy profile from clinical trials, and knowledge of potential side effects should also be incorporated into the therapeutic strategy.



Vesic K et al. Psychoses in multiple sclerosis



Figure 1 Etiopathogenesis of multiple sclerosis, psychosis, and multiple sclerosis-related psychoses and potential treatment options. Environmental factors, genetics, and immune disturbances lead to different types of immune responses that cause neuroinflammation, which is an underlying mechanism in the development of multiple sclerosis (MS) and psychosis. Inflammatory changes that occur in MS may induce psychotic symptoms. Corticosteroids and antipsychotics may be beneficial in patients suffering from MS-related psychoses. Th: T helper; MS: Multiple sclerosis.

# FOOTNOTES

Author contributions: Vesic K has presented the idea; Vesic K and Borovcanin M structured the manuscript; All authors searched the literature in their scope of interest and competencies; Vesic K incorporated all parts of the manuscript and drew a figure; The authors gave final suggestions and approval for the final version of the manuscript.

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# Relationship between perceived social support and post-traumatic growth in coronavirus disease 2019 patients discharged from the hospital

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# Abstract

# BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has affected mental health and physical health negatively in some individuals. Examining perceived social support and post-traumatic growth (PTG) in COVID-19 patients could facilitate our understanding of how patients maintain their mental health.

## AIM

To examine the relationship between the level of perceived social support and PTG in COVID-19 patients discharged from the hospital.

# **METHODS**

This descriptive study was carried out between August and September 2022 with patients who were hospitalized due to COVID-19 in a university hospital in Erzurum and who were discharged at least 3 mo prior to the beginning of the study. The study was completed by 196 patients. Study data were collected faceto-face using a personal information form, multidimensional scale of perceived social support and PTG inventory.

# RESULTS

The total mean score of the multidimensional scale of perceived social support was  $63.82 \pm 15.72$ . The PTG inventory total mean score was  $47.77 \pm 19.85$ . In addition, a direct significant correlation was found between perceived social support in COVID-19 patients and PTG.

## **CONCLUSION**

The study results showed that perceived social support variables affected PTG



significantly. Therefore, it is recommended for healthcare professionals to implement interventions to promote social support from healthcare professionals and the patient's family and friends. Considering the negative effects of the ongoing COVID-19 pandemic, it is very important and necessary to implement effective public health interventions to promote PTG to reduce mental health problems.

Key Words: COVID-19 patients; Perceived social support; Post-traumatic growth; COVID-19

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**Core tip:** Since post-traumatic growth (PTG) includes development at the level of psychosocial functionality, it can contribute to personal development by positively affecting psychological and social factors after traumatic events. Social support positively affects an individual's mental health and PTG. The results of this study remarkably showed that there is a significant relationship between perceived social support and PTG. More studies are needed to confirm this observation.

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# INTRODUCTION

The symptoms are variable in individuals diagnosed with coronavirus disease 2019 (COVID-19). Some individuals were asymptomatic, while the disease may progress from mild pneumonia to severe and fatal acute respiratory failure[1]. This disease affects the physical, psychological and social well-being of individuals[2]. Fear of death, hospitalization in the intensive care unit, endotracheal intubation, pain, limited communication, environmental stress, insomnia, impaired comfort, quarantine measures, feeling of loneliness, loss of control and stigmatization are among the different stressors of the COVID-19 pandemic[3]. A diagnosis of COVID-19 and hospitalization are considered the greatest of these stressors and accepted as a traumatic life experience[4]. While traumatic events cause serious mental problems such as anxiety, depression and post-traumatic stress disorder in some individuals[5], they may result in post-traumatic growth (PTG) in some[6]. PTG is defined as positive psychological changes as a result of a major life crisis or struggle with a traumatic event[7]. These changes occur in areas of improved interpersonal relationships, new opportunities, a greater sense of personal power, a greater appreciation of life and spiritual change[7].

The rapid increase in the number of COVID-19 cases and deaths has been reported to cause stress, fear, anxiety and depression in many people[8]. However, as individuals try to understand negative experiences and adapt to difficulties, positive reactions may also occur[9]. After the diagnosis of a severe disease, most survivors experience various positive changes that reflect useful psychological adaptation and positive personal development processes that enable them to better cope with the disease[7]. In a qualitative study, it was found that patients with severe COVID-19 showed negative emotional reactions in the early periods of the disease, while the disease resulted in psychological growth over time. The patients met the problems gratefully by cherishing their lives and their families[3]. Since PTG includes development at a psychosocial functionality level, it may contribute to personal development by positively affecting psychological and social factors after traumatic events[10]. In this context, social support is a source of resilience that positively affects individual mental health and facilitates PTG[11-13].

Measures taken during the COVID-19 pandemic, such as quarantine and social distancing, have led to differentiation in many areas of life. For this reason, individuals could not socialize at desired levels, and they faced problems such as social isolation and loneliness[14]. Similarly, in one study, social support was determined to be a psychological factor that made patients stronger[3]. Social support often refers to the care or support individuals receive from others or the feeling of belonging to a social network that provides mutual help[13]. To date social support has been broadly construed in two ways: perceived social support and received social support[15]. Perceived social support concerns the subjective evaluation of how individuals perceive friends and family members as available to provide material, psychological and overall support during times of need, whereas received support relates to the actual quantity of support received. This distinction between these two types of support is important for two reasons[15].

Social support in the face of stress can act in two different ways. In the buffer effect model, it is reported that social support reduces or balances the damaging effects of stress on physical and mental health as a buffer, especially in protecting physical and psychological health of people who are exposed to stressful experiences. In the basic impact model, social support has an effect independent of the level of stress, and there is a direct relationship between social support and health[16]. According to this approach, social support can increase life satisfaction and prevent or reduce stressful life events by providing a sense of belonging. Thus, with this effect of social support, the person experiences fewer physical and psychological problems[17]. Looking at the models that explain the relationship between psychological problems and social support, it is emphasized in the social causality model that lack of social support causes psychological symptoms. According to the social choice model, the individual's psychological symptoms cause the sources of social support to change. Finally, in the mutual effect model, while social support is effective on psychological well-being, the psychological state of the individual is also effective on accessing adequate social support. In other words, there is a bidirectional relationship between social support and psychological symptoms[18].

During COVID-19 treatment, the importance of psychosocial intervention is emphasized in both recovery and reducing psychological problems[13]. Studies conducted have reported that social support has an effect on improving psychological problems[12]. Psychological effects of contagious diseases may continue or develop over time. It has been found that individuals with high social support perception have fewer negative psychological consequences[11]. Social support is thought to be important for mental health in the post-discharge follow-up of COVID-19 survivors. Nurses, who are continuous interacting with patients, have important responsibilities in identifying traumatized individuals, increasing the support they need and empowering them in this process. Since the COVID-19 pandemic has negatively affected mental health and physical health, examining PTG and social support in COVID-19 patients will facilitate our understanding of how patients protect their mental health[19].

On the other hand, it is widely believed that high perceived social support predicts high PTG[15,20, 21]. Given that several studies have reported that people often feel isolated and alienated and have difficulty accessing social support when diagnosed with COVID-19[22], there is a need to further clarify the role of perceived social support within PTG during COVID-19. In light of all this information, the aim of this study was to examine the relationship between the level of perceived social support and PTG in COVID-19 patients discharged from the hospital.

#### Research questions

What are the perceived social support levels of COVID-19 patients discharged from the hospital?

What are the PTG levels of COVID-19 patients discharged from the hospital?

Is there a relationship between perceived social support and PTG in COVID-19 patients discharged from the hospital?

## MATERIALS AND METHODS

#### Study design

This study was conducted with a descriptive and a cross-sectional design.

#### Place and time of the study

The study was conducted at Atatürk University Research Hospital between August 2022 and September 2022.

#### Population and sample of the study

The population of the study consisted of patients who were discharged after receiving COVID-19 treatment at Atatürk University Research Hospital. Before starting the study, a sufficient number of sample was calculated for correlation analysis with the G Power 3.1.9.7. Package program. Since no similar study was found in the literature, priori power analysis was performed based on a moderate effect size (0.3). In the power analysis based on alpha of 0.05 and power of 0.99, it was determined that the sample size should be 195. For this reason, the study was completed with 196 patients.

#### Inclusion criteria

(1) Patients who were treated in the hospital with a diagnosis of COVID-19 and who had been discharged at least 3 mo prior to study enrollment; (2) Patients older than 18 years of age; and (3) Patients who did not have cognitive disabilities.

#### Data collection tools

Study data were collected by using a personal information form, multidimensional scale of perceived social support and PTG inventory.



**Personal information form:** This form was prepared by the researchers to find out the demographic characteristics of discharged COVID-19 patients and COVID-19-related characteristics. This form consisted of questions such as age, sex, educational status, marital status, number of children and level of income.

**Multidimensional scale of perceived social support:** The scale was developed by Zimet *et al*[23]. A Turkish validity and reliability study of the scale was conducted by Eker *et al*[24]. The scale is a 7-point Likert type self-report consisting of 12 items and 3 subscales. The subscales are family support, friend support and significant other support. Each item is evaluated between 1 and 7. The minimum possible score from the scale is 12, while the maximum possible score is 84. A higher score means higher perceived social support. Internal consistency of the scale is between 0.80 and 0.95 for the total scale and the subscales[24]. Cronbach's alpha value was 0.93 for the present study.

**PTG inventory:** The inventory was developed by Tedeschi *et al*[5]. The scale consists of a total of 21 items and 5 factors. The scale factors are improved relationships, new possibilities, personal strength, spiritual growth and appreciation for life. Internal consistency coefficient of the original scale is 0.90, while internal consistency coefficients of the factors vary between 0.67 and 0.85[5]. PTG inventory was adapted into Turkish by Dürü *et al*[25]. The scale is a 6-point Likert type scale. Scoring system is between 0 (I did not experience this change) and 5 (I experienced this change to a very great degree). It was stated in the Turkish adaptation that the 5-factor structure was preserved, and this structure explained 67.84% of the total variance. Score range of the scale is between 0 and 105. Higher scores from the scale mean higher PTG. Cronbach's alpha was 0.93 in the Turkish adaptation study[25]. Cronbach's alpha was 0.94 in the present study.

#### Data collection

Study data were collected with the face-to-face interview technique. After the purpose of the study was explained, the questions in the data collection tools were asked one by one, and the answers of the patients were recorded. Data collection lasted approximately 15 min for 1 patient. Consent was given by the patient prior to data collection.

#### Data assessment

Data analysis was performed using SPSS version 22.0. Frequency, percentage, mean and standard deviation measurement were used for descriptive statistics. Normality distribution of the data was analyzed with skewness and kurtosis coefficients. Pearson's correlation analysis was used for the examination of the comparison between the two scales. Cronbach's alpha was evaluated to test the reliability of the scales. A *P* value of 0.05 was considered statistically significant. Post-traumatic effect of perceived social support was analyzed with a simple linear regression analysis.

#### Ethical considerations

Ethical approval was obtained from the Ethics Committee of Atatürk University Faculty of Medicine to conduct the study. Written institutional permission was also obtained from Atatürk University Research Hospital for data collection. Oral and written informed consent was obtained from the patients.

#### Limitations of the study

The first limitation of the study was the collection of data with self-report scales. Another limitation was that PTG symptoms were not evaluated by a mental health professional but by the self-reports of the patient. Since the results depended on data collected from COVID-19 patients discharged in the Eastern Anatolia region of Turkey, it is not suitable for the results to be generalized to COVID-19 patients from other regions.

# RESULTS

Mean age of the patients was  $50.05 \pm 19.19$ . It was found that 57.1% of the patients were male, 73.0% were married, 75.0% had children, 66.8% had nuclear family, 60.7% lived in a city center, and 59.2% were primary education graduates. It was found that 45.9% of the patients were unemployed and 57.7% had income equal to expenditure. It was found that 70.4% of the patients were treated in the COVID-19 clinic, treatment lasted for an average of  $13.22 \pm 10.46$  d, 52.6% received oxygen therapy, and an average of  $12.67 \pm 5.93$  mo passed after being discharged. We observed that 63.3% of the patients did not have a chronic disease, and 78.1% were not hospitalized for any other reason after discharge from COVID-19. In addition, it was found that 55.6% of the patients lost a close friend due to COVID-19, 93.3% did not receive psychological help from any expert due to COVID-19, and 87.2% had been vaccinated for COVID-19 (Table 1).

# Table 1 Sociodemographic characteristics of the patients, *n* (%)

Characteristics	
Sex	
Female	112 (57.1)
Male	84 (42.9)
Marital status	
Single	53 (73.0)
Married	143 (27.0)
Children	
Yes	147 (75.0)
No	49 (25.0)
Family type	
Nuclear family	131 (66.8)
Extended family	65 (33.2)
Living place	
Village	45 (23.0)
District	32 (16.3)
Province	119 (60.7)
Education status	
Primary education	116 (59.2)
High school	39 (19.9)
University or graduate	41 (20.9)
Income status	
Less than income	40 (20.4)
Income is equivalent to expenses	113 (57.7)
More than income	43 (21.9)
Working status	
Yes <sup>1</sup>	90 (45.9)
No <sup>2</sup>	106 (54.1)
Chronic disease	
Yes	72 (36.7)
No	125 (63.3)
Treatment place	
Intensive care unit	46 (23.5)
Clinic	138 (70.4)
Both	12 (6.1)
Form of treatment	
No support	89 (45.4)
Oxygen therapy	103 (52.6)
Noninvasive-invasive ventilation	4 (2.0)
Lost a loved one due to COVID-19	
Family	31 (15.8)
Relative	56 (28.6)

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#### Şirin Gök M et al. Perceived social support and PTG

Close friend	109 (55.6)
Hospitalization for another reason	
Yes	43 (21.9)
No	153 (78.1)
Received psychological support from a specialist due to COVID-19	
Yes	12 (6.1)
No	184 (93.9)
Availability of COVID-19 vaccine	
Yes	171 (87.2)
No	25 (12.8)
Age, mean ± SD	$50.05 \pm 19.19$
Treatment duration (d), mean ± SD	$13.22 \pm 10.46$
Time elapsed after COVID-19 treatment (mo), mean ± SD	$12.67 \pm 5.93$
Stress level related to COVID-19, mean ± SD	$7.14 \pm 2.58$

<sup>1</sup>Officer, self-employed, student.

<sup>2</sup>Housewife and those who do not work in another job. COVID-19: Coronavirus disease 2019.

The total mean score of the multidimensional scale of perceived social support was  $63.82 \pm 15.72$ . The mean subscale scores of the multidimensional scale of perceived social support were  $20.22 \pm 6.27$  for family support,  $20.85 \pm 5.80$  for friend support and  $22.74 \pm 4.71$  for significant other support.

PTG growth inventory total mean score was  $47.77 \pm 19.85$ . When the factors were examined, the mean scores were  $13.87 \pm 5.57$  for improved relationships,  $8.52 \pm 3.82$  for new possibilities,  $8.81 \pm 4.71$  for personal strength,  $9.20 \pm 4.35$  for spiritual growth and  $7.34 \pm 3.43$  for appreciation for life (Table 2).

A weak, yet significant, positive correlation was found between family support and improved relationships, new possibilities, personal strength and total PTG scale (P < 0.05). In the significant other subscale of perceived social support, no significant correlation was found between total PTG scale and subfactors (P > 0.05). A weak, yet significant, positive correlation was found between perceived social support total score of the patients and improved relationships, new possibilities, personal strength and total PTG scale (P < 0.05) (Table 3). According to the results of the simple linear regression analysis, it was found that perceived social support significantly and positively predicted the PTG levels of the discharged COVID-19 patients ( $\beta = 0.159$ , P < 0.05). According to the model, perceived social support explained 2.5% of the total variance in PTG ( $R^2 = 0.025$  F = 5.026, P < 0.05) (Table 4).

# DISCUSSION

In this study, which examined the relationship between the perceived social support level of COVID-19 patients discharged from the hospital and PTG, it can be seen that the patients had a good level ( $63.82 \pm 15.72$ ) of perceived social support (between 12 and 84) (Table 2). Social support was defined as the support available to the individual through social relationships with others. Social support from health professionals and health institutions is an effective factor in this regard[26]. A study by Moodi *et al*[27] showed that patients' perceived social support scores were high. Zhang *et al*[28] found increased support from friends and family during the COVID-19 outbreak. Thompson *et al*[29] found that social support increased in discharged COVID-19 patients. In the study of Kandeğer *et al*[30], COVID-19 patients were found to have high perceived social support. Alnazly *et al*[31] concluded that patients had high social support levels.

Health personnel became an important source of support for patients due to lack of direct communication between the patient and family members during their hospitalization. In addition to the support of family members, patients also receive support, such as education and counselling, from the health system. All these services may have played an important role in the formation of perceived social support. Increased perceived social support may subsequently positively influence PTG. Positive developments during the pandemic, such as the development and dissemination of the vaccine, may have helped to eliminate the negative emotions of COVID-19 patients and to create positive coping styles of the patients.

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# Table 2 Multidimensional scale of perceived social support and post-traumatic growth scale sub-scale and mean, minimum and maximum values of total score averages

Scales	Minimum and maximum scores that can be obtained from the scale	Minimum and maximum scores taken from the scale	mean ± SD
MSPSS			
Family support	4-28	4-28	$20.22 \pm 6.27$
Friend support	4-28	7-28	$20.85 \pm 5.80$
Significant other support	4-28	4-28	22.74 ± 4.71
Total MSPSS	12-84	24-84	63.82 ± 15.72
PTGS			
Relationships with others	0-30	0-30	13.87 ± 5.57
New possibilities	0-20	0-18	$8.52\pm3.82$
Personal strength	0-20	0-20	$8.81 \pm 4.71$
Spiritual change	0-20	0-20	$9.20 \pm 4.35$
Appreciate life	0-15	0-15	$7.34 \pm 3.43$
Total PTGS	0-105	0-100	$47.77 \pm 19.85$

MSPSS: Multidimensional scale of perceived social support; PTGS: Post-traumatic growth scale.

Table 3 Relationship between post-traumatic growth scale and multidimensional scale of perceived social support										
Palationahin	Family support		Friend support		Significant o	ther support	Total MSPSS			
Relationship	R	P value	R	P value	R	P value	R	P value		
Relationships with others	0.177	0.177	0.151	0.035 <sup>a</sup>	0.132	0.064	0.166	0.020 <sup>a</sup>		
New possibilities	0.163	0.023 <sup>a</sup>	0.155	0.030 <sup>a</sup>	0.125	0.08	0.16	0.025 <sup>a</sup>		
Personal strength	0.142	0.048 <sup>a</sup>	0.135	0.059	0.126	0.078	0.144	0.044 <sup>a</sup>		
Spiritual change	0.135	0.06	0.085	0.239	0.069	0.335	0.106	0.141		
Appreciating life	0.127	0.077	0.141	0.048 <sup>a</sup>	0.123	0.085	0.14	0.051		
Total PTGS	0.166	0.020 <sup>a</sup>	0.147	0.039 <sup>a</sup>	0.128	0.074	0.159	0.026 <sup>a</sup>		

<sup>a</sup>Correlation was significant at the 0.05 level (two-tailed).

R: Pearson's correlation; MSPSS: Multidimensional scale of perceived social support; PTGS: Post-traumatic growth scale.

Table 4 Perceived social support as predictors of post-traumatic growth										
Parameter	В	Standard error	β	t	P value	R <sup>2</sup>	Adjusted R <sup>2</sup>			
Total PTGS	34.969	5.880		5.947	0.000					
Total MSPSS	0.201	0.089	0.159	2.242	0.026	0.025	0.020			

R = 0.159,  $R^2 = 0.025$ , F = 5.026, P < 0.05, Durbin Watson: 2.100. MSPSS: Multidimensional scale of perceived social support; PTGS: Post-traumatic growth scale.

In this study, it was found that the individuals had moderate ( $47.77 \pm 19.85$ ) PTG (between 0 and 105) (Table 2). Although there are few studies on PTG in COVID-19 patients who have survived after admission to the intensive care unit, these results are in line with previous studies. Therefore, the present study showed that PTG may be important in patients treated in an intensive care unit for COVID-19. In another study, it was found that patients hospitalized in the intensive care unit with a

COVID-19 diagnosis experienced PTG close to a moderate level after treatment[32]. In a study conducted on discharged COVID-19 patients, Thompson *et al*<sup>[29]</sup> showed moderate PTG. The most important step for post-traumatic development is that individuals do not see themselves as trauma victims but as post-traumatic survivors. Tedeschi et al[5] suggested that initial stress is induced by traumatic events, which encourages individuals to challenge and rebuild (existing) schemas and assumptions, which then results in positive changes. However, one of the important points is that the evaluation of PTG symptoms by the patient's own reports, not by a mental health professional, may have affected this result. For this reason, the importance of the findings of this study will be emphasized, and the evaluation of the patient by both their own PTG and mental health experts will strengthen the results.

According to Tedeschi et al<sup>[5]</sup>, social support plays an important role in the transition from trauma to growth since it activates the cognitive processes that support PTG. It can be especially valuable for COVID-19 patients to have the opportunity to express themselves in a supportive environment and to get help in any adversity they experience. Social support is associated with better physical and psychological health. The correlation between patients' perceived social support and PTG and the factors of improved relationships, new possibilities and personal strength was found to be positive but weak (Table 3). In the study by Gökahmetoğlu et al[33], no correlation was found between perceived social support and PTG. In a study conducted by Hill et al[34] on cancer patients, it was concluded that social support was not a predictive variable in PTG. In a study conducted on patients with different traumatic experiences, Dürü et al[25] found that social support did not have an effect on PTG.

On the other hand, perceived social support and PTG were found to be positively correlated in our study. In the study by Sun et al[3], it was stated that during quarantine periods individuals benefited from the emotional support they received from their families as well as the support provided by their colleagues and neighbors. Similarly, in a study conducted with individuals diagnosed with COVID-19 and discharged in China, it was determined that social support systems were positively related to PTG [29]. In a study examining the quarantine experiences of COVID-19 patients, it was stated that the social support patients received from their families and friends made a significant contribution to coping with negative emotions[35]. In a study by Lohiniva et al[36], some patients mentioned some positive developments such as feeling closer to their spouses and spending more time as a family during the quarantine period. A high level of perceived social support affects the individual's ability to provide a sense of having a safe environment, to emphasize their sense of belonging, to act as a buffer against stress, to provide new meanings and to create more positive perceptions that support growth. While perceived social support facilitates adaptation to cognitive processes, it also supports individuals to effectively manage coping strategies in identifying positive situations for their personal development.

Being diagnosed with COVID-19, physical symptoms caused by the disease and quarantine practices can cause many changes in individuals, especially spiritually. It is thought that the uncertainty about the disease and the treatment process, the fact that the disease can be fatal and the restrictions on daily life cause personal changes in individuals. Especially in this process, it has been observed that individuals experience many personal changes such as changes in life philosophy and perspective, changes in life priorities, strengthening in self-perception and appreciating and being grateful for what they have. It is thought that the differences between study results are due to the scales used, inclusion criteria and the way individuals perceive and evaluate social support. This positive change experienced by individuals may have led them to emerge stronger from the crisis created by the pandemic. Findings showed that increasing perceived social support can contribute to PTG.

Another remarkable finding is that the most significant growth in PTG was in the spiritual subdimension (Table 2). A sample of parents in Portugal during the pandemic found high rates of PTG, particularly in the areas of appreciation for life and improved relationships<sup>[37]</sup>. In the study by Liu *et al* [38], some patients stated that COVID-19 supported their personal development and motivation for a better life in the future. It is thought that this difference is due to Turkish culture, religious differences and customs. In this context, COVID-19 diagnosis may cause an individual change and empowerment in patients. In the present study, it was suggested that patients' life priorities and philosophies have changed and that they will prioritize their health.

## CONCLUSION

In the present study, which examined the relationship between perceived social support level of COVID-19 patients discharged from the hospital and PTG, it was found that patients had a good level of perceived social support and a moderate level of PTG. A significant correlation was also shown between perceived social support of the patients and PTG. Since there are few studies examining the relationship between these variables in the literature, it is important to conduct more studies to confirm these findings. It may be useful to repeat the research with larger samples. Prospective and longitudinal studies are recommended to further confirm the versatility of the findings and to elucidate the factors influencing PTG. Since these findings include subjective evaluations of patients, it is recommended to plan new studies in which the results are also evaluated objectively by mental health professionals.



## Relevance for clinical practice

It is known that a large number of people have been affected by the COVID-19 pandemic, especially patients in the intensive care unit. The high impact of the traumatic event, although at least 3 mo have passed after being discharged from the intensive care unit due to COVID-19, may be associated with the continuation of the pandemic process and the increase in the number of patients. Therefore, considering the adverse mental health impacts of the ongoing COVID-19 pandemic, it is crucial to implement effective public health interventions to promote PTG and reduce mental health issues.

# ARTICLE HIGHLIGHTS

#### Research background

The coronavirus disease 2019 (COVID-19) pandemic has affected the mental health of individuals. There is a controversial relationship between perceived social support and post-traumatic growth (PTG).

#### Research motivation

There are few studies that show the relationship between perceived social support and PTG in COVID-19 patients.

## Research objectives

To examine the relationship between the level of social support perceived and PTG.

## Research methods

This descriptive study was carried out between August and September 2022 with patients who were hospitalized due to COVID-19 and who were discharged at least 3 mo prior to the beginning of the study. The study was completed by 196 patients. Study data were collected face-to-face using a personal information form, multidimensional scale of perceived social support and PTG inventory.

## **Research results**

It was found that patients had a good level of perceived social support and a moderate level of PTG.

#### Research conclusions

Perceived social support positively affects PTG.

#### Research perspectives

Further research is needed to confirm these results. In the future, mental health specialists should evaluate individuals for PTG.

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# FOOTNOTES

Author contributions: Şirin Gök M contributed to the data analysis; Şirin Gök M and Çiftçi B contributed to the study design, data collection, study supervision, manuscript writing and critical revisions for important intellectual content.

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SYSTEMATIC REVIEWS

# Use of new technologies for the promotion of physical activity in patients with mental illness: A systematic review

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# Abstract

#### BACKGROUND

Physical exercise is an underutilized tool for the management of mental disorders. New technologies have made a breakthrough in health care, and one of its possible applications (apps) could be that of customizing exercise programs for special populations, such as patients with mental disorders. However, the app of the so-called e-health to mental health care is still limited.

#### AIM

To know the efficacy of apps to promote physical activity in patients with mental disorders.

# **METHODS**

We conducted a systematic review of the PubMed and Embase databases with the aim of exploring the use of new technologies for the enhancement of physical exercise in patients with a psychiatric illness. Following the selection process, 10 articles were included in the review.

## RESULTS

The most commonly used devices in this type of intervention are wearable devices and web platforms. Good results in terms of effectiveness and acceptability were obtained in most of the studies.

## **CONCLUSION**



Our findings suggest that the use of new technologies in mental health represents a feasible strategy with great potential in clinical practice.

Key Words: e-health; m-health; Physical exercise; Mobile applications; Wearable device

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**Core Tip:** Physical exercise is an underutilized tool for the management of mental disorders. New technologies have made a breakthrough in health care, and one of its possible applications (apps) could be that of customizing exercise programs for special populations, such as patients with mental disorders. Apps that aim to improve and increase physical activity in patients diagnosed with the disease have shown good results in terms of efficacy and acceptability, so they should be known by clinicians in order to offer them to patients who meet a good profile.

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## INTRODUCTION

Mental illness is one of the major global public health problems[1]. People with severe mental disorders are in poorer health, with more cardiovascular risk factors and high morbidity and mortality rates. Factors associated with this poorer health status include a greater tendency to lead a sedentary lifestyle and high comorbidity with chronic physical illnesses[2-4]. Furthermore, mental disorders often do not access the health care they require and, even when they do, treatment is often inadequate[5].

The relationship between physical health and mental illness can also be harnessed to our advantage and contribute to closing the gap in the treatment of these disorders: Numerous studies show the benefits of physical exercise on mental state[6-14]. In a recent population-based survey in Spain, physical exercise was inversely associated with major depressive disorder (MDD), irrespective of body mass index[6]. Several studies have investigated the therapeutic potential of physical exercise in other mental disorders such as anxiety, post-traumatic stress disorder, or even psychotic disorders[7-12]. Finally, several randomised clinical trials agree on the antidepressant effect of physical exercise[13,14].

However, it is difficult to inculcate physical exercise habits in people with psychiatric symptoms, especially in the acute phases of the illness. New technologies can make this task easier. Digital medicine, also called e-health, is opening new horizons in the management of a multitude of diseases, including MDD[15]. The enhancement of physical activity is one of the most exploited functions by this type of technology that is based on applications (apps) and software programmes managed through various platforms, such as websites, wearable devices, smartphones, or social networks. Some of these devices have sensors that allow continuous measurement of physical activity, mainly through accelerometers[16].

Physical activity promotion programmes show better results when they take into account the particularities of each population. Apps and other electronic interventions therefore have been designed for focusing on promoting physical activity in different patient populations, such as people with diabetes or cancer[17,18]. However, the role played by digital medicine in the management of mental illness is more limited, despite the fact that these populations could benefit from the advantages of new technologies. Several studies demonstrate the interest shown by psychiatric patients in the use of mobile technology to improve their mental health[15,19-21]. It is therefore crucial that the large offer available on the digital market is screened by clinicians and researchers.

Nursing professionals have sown a prominent interest in e-health interventions and can play a key role in the app of new technologies to mental health care, as they are often the closest link to the patient [22]. For example, patients often prefer to ask nurses for advice on mobile apps they can use[23]. The continuous development of new technologies, however, is progressing significantly faster than the research conducted to empirically test these advances[24]. A review of the evidence on these tools is crucial to provide the best evidence-based knowledge conducive to good use of this technology. The aim of this paper is to systematically review the available evidence on mobile apps for physical activity enhancement in patients with mental illness.

## MATERIALS AND METHODS

#### Registration

This systematic review was conducted in accordance with the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses recommendations<sup>[25]</sup>. The protocol for this systematic review was registered in the PROSPERO database (registration number: CRD42021242258).

#### Search strategy

We conducted a systematic literature search in the PubMed and Embase databases to identify studies on e-health interventions for the enhancement of physical activity in people with mental illness. The concept of "enhancement" encompassed both the outcomes of increased physical activity and the results obtained because of this activity (such as weight loss or improvement in other health parameters).

The inclusion criteria were as follows: (1) Original articles; (2) Published in the last ten years 10 years (November 15, 2012 to November 15, 2022); (3) Peer-reviewed journals; (4) Language: English or Spanish; (5) Exploring mobile apps for physical activity promotion in individuals with mental illness; (6) Adult population; and (7) Providing measurable outcomes, either in terms of effectiveness or feasibility.

The search terms used in PubMed were as follows: (physical[Title/Abstract] OR exercise[Title/ Abstract]) AND (psychiatr\*[Title/Abstract] OR mental disorder\*[Title/Abstract] OR mental illness\* [Title/Abstract] OR schizophreni\*[Title/Abstract] OR anxiety[Title/Abstract] OR bipolar[Title/ Abstract] OR depressi\*[Title/Abstract]) AND (phone[Title/Abstract] OR device[Title/Abstract] OR app[Title/Abstract] OR web[Title/Abstract] OR social media[Title/Abstract] OR virtual reality[Title/ Abstract] OR new technologies[Title/Abstract] OR digital[Title/Abstract] OR e-health[Title/Abstract] OR m-health[Title/Abstract]).

A similar search strategy was employed for the Embase database, such as: "(physical OR exercise) AND (psychiatr\* OR mental disorder\* OR mental illness\* OR schizophreni\* OR anxiety OR bipolar OR depressi\*) AND (phone OR device OR app OR web OR social media OR virtual reality OR new technologies OR digital OR e-health OR m-health)".

#### Selection and extraction process

Two researchers (Guerrero-Jiménez M and Ruiz M) independently analysed the eligibility of the studies. Critical appraisal tools checklists were used to assess the quality of the articles [26]. When there was no agreement between the reviewers, the decision rested with the senior investigator. The variables of interest collected from the articles were: (1) Scientific content and technical characteristics of the apps; (2) Effectiveness; (3) Acceptability (level of approval by users); (4) Level of satisfaction; and (5) Outcome measures.

#### Quality assessment

Two reviewers (Guerrero-Jiménez M and Ruiz M) assessed independently the quality of the articles (this is described in Supplementary Table 1). Discrepancies between reviewers were resolved by discussing and reaching a consensus. We assessed several aspects, including methodological design, risk of bias, and reporting quality. For randomized clinical trials, Cochrane Collaboration's tool for assessing risk of bias was used.

## RESULTS

Figure 1 shows the flow chart of the literature search. The initial search yielded 6257 results (PubMed = 5970; EMBASE = 302) of which 9 were finally included in the review, characteristics and main findings of the studies are recorded (Table 1)[27-35]. With the exception of two studies[28,34], the reviewed articles worked with sample sizes of less than 50 participants. All studies had positive results following intervention with mobile technologies. Acceptability was generally high, as was participation in the studies. The different studies reviewed can be divided according to the intervention tool used. Our review includes about 400 participants with different psychiatric illness as bipolar disorder and MDD.

#### Mobile apps

The pilot study by Macias *et al*[30] found that the use of the app promoted longer walks in obese patients with mental illness, in addition to obtaining good adherence and user satisfaction with the platform (Table 2).

#### Wearables

Studies such as those by Macias et al[30] and Naslund et al[31] or Aschbrenner et al[27] used wearables in the intervention with patients with mental illness, obtaining positive results in weight loss, and in one of the studies, improvement in physical condition.



Table 1 Characteristics and main findings of the studies										
Ref.	Device	Features	Design	Sample	Measures and scales	Main findings				
Aschbrenner et al[27], 2016	Wearable device (Fitbit Zip)	Accelerometer, step and distance registration	Pilot study pre-post	13 patients with overweight and psychiatric disorders	Satisfaction questionnaire 6-MWT; weight (kg)	At 6 mo 45% of the participants were underweight and 45% improved their physical condition				
Haller <i>et al</i> [ <mark>28]</mark> , 2018	Internet platform	Heart rate monitor and resistance bands	RCT	20 patients with MDD (moderate and severe)	Depression scales: (1) QIDS; (2) Self-efficacy, quality of life and physical activity; and (3) General health status SF- 36	Feasible and effective in patients with moderate to severe depressive symptoms, improving quality of life and decreasing depressive symptoms				
Lambert <i>et al</i> [ <mark>29</mark> ], 2018	eMotion (Web)	Accelerometer. Weekly module course. Interactive worksheets	RCT	62 patients with at least moderate depressive symptoms and anxiety	PHQ-8. Vigorous physical activity	Depression levels were lower in the intervention group than in the control group				
Macias <i>et al</i> [ <mark>30</mark> ], 2015	WellWave	Digital library with readings, personal messages and a variety of activities	Pilot study	10 patients with obesity and mental illness (schizophrenia, MDD or BD)	Self-assessments. Number of steps and walking time	Seven of the ten participants increased the number and duration of weekly walks. High app participation				
Naslund <i>et al</i> [ <mark>31]</mark> , 2016	Wearable device (Fitbit Zip)	Accelerometer. Podometer. Progress Log	Prospective	34 patients with psychiatric disorders (various diagnoses)	Weight (kg). 6-MWT	Higher average daily steps were associated with greater weight loss				
Naslund <i>et al</i> [ <mark>32</mark> ], 2016	Wearable device (Fitbit Zip)	Accelerometer. Podometer. Progress Log	Exploratory study	11 patients with severe mental illness and obesity	Quantitative usability and satisfaction questionnaire. Interviews	The use of the app motivates participants to engage in physical exercise				
Naslund <i>et al</i> [ <mark>33]</mark> , 2018	Facebook	Messages, posting of posts, photos	Exploratory study	25 patients with mental illness (MDD, BD and schizophrenia, obesity under pharmacological treatment)	FB Interactions. 6-MWT. Weekly group attendance	Participants who actively contributed to the Facebook group have a higher weight loss				
Pfirrmann <i>et al</i> [34], 2018	Web	Forum, psychoedu- cation	Analysis of four clinical trials	5 participants with oesophageal carcinoma, 5 with liver disease, 5 with MDD and 5 with cystic fibrosis	-	Efficacy as an exercise enhancer in all pathologies				
Young and Morgan[35], 2018	SHED-IT	Measuring tape, pedometer	Pre-post study	209 male patients with overweight and depressive symptoms	PHQ-8. Weight (kg)	Reduction of weight and depressive symptoms, with a high level of engagement and satisfaction				

6-MWT: 6-minute walk test; BD: Bipolar disorder; FB: Facebook; MDD: Major depressive disorder; MINI: Mini international neuropsychiatric interview; PANSS: Positive and negative syndrome scale; SCID: Structured clinical interview for axis-I DSM-IV disorders; RCT: Randomized controlled trial; PHQ: Patient health questionnaire.

## Social networks

Naslund et al[32] explored the use of the social network Facebook in intervention with patients diagnosed with mental illness and obesity. They found that the use of this social platform prompted patients to greater motivation for weight loss, with participants with the highest number of interactions having lost the most weight.

## Other digital interventions

Other studies used web-based platforms, where their effectiveness was observed, both in various pathologies[33] and in the reduction of depressive symptomatology, which was greater in the intervention group compared to the control group[28].

# DISCUSSION

However, most of the studies focus their interventions on pathologies other than mental health, which is



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Table 2 User satisfaction with the different device										
Ref.	Device	Positive	Negative	Suggested improvements						
Macias et al <mark>[30]</mark> , 2015	WellWave	Personal messages, reading library	-	Test whether learning how to use the app can increase personal satisfaction						
Naslund <i>et al</i> [ <mark>31</mark> ], 2016	Wearable device	Self-monitoring	Difficulties of use	Make tutorials on the use of the device						
Naslund <i>et al</i> [ <mark>32</mark> ], 2016	Wearable device	Self-monitoring	Difficulties of use	Make tutorials on the use of the device. Participants are satisfied with the use of the app						
Aschbrenner <i>et al</i> [27], 2016	Wearabledevice	Self-monitoring	Difficulties of use	Make tutorials on the use of the device before. High level of satisfaction						
Haller <i>et al</i> [ <mark>28</mark> ], 2018	Web platform	Easy to use, self-monitoring	Does not include follow- up	Include monitoring as web-based apps show a trend towards non-use over time. Show a trend towards non-use over time						
Lambert <i>et al</i> [29], 2018	eMotion	Self-monitoring	Not assessed	Not assessed						
Naslund <i>et al</i> [33], 2018	Facebook	Accessibility, facilitates communication between people in the same condition. Allows information sharing and feedback	Not assessed	Not assessed						
Pfirrmann <i>et al</i> [ <mark>34], 2018</mark>	Web	Forum. Unspecific information	Not assessed	Not assessed						
Young and Morgan[ <mark>35</mark> ], 2018	SHED-IT	Self-monitoring	Not assessed	Longer-term programme of longer duration						

apps: Applications.





why, despite the large amount of literature published on the subject, only 9 studies were conducted on the population to be studied and included in this review [27-35].

#### Discussion of effectiveness

Our findings suggest that physical exercise may be a useful tool in the management of mental disorders, and that the delivery of these interventions through e-health platforms may increase adherence and accessibility to treatment. The therapeutic effect of physical exercise can be explained by several



mechanisms. Physical activity may have neuroregenerative properties and increase brain-derived neurotrophic factor (BDNF)[36,37] although a recent meta-analysis did not find that physical exercise significantly increased BDNF in patients with depression[38].

The immune system may also be involved in this association. Inflammatory pathways are thought to play a key role in the neurobiological basis of mental illnesses such as MDD, which would explain the bidirectional association that has been found between certain mental illnesses and inflammation[39,40]. Exercise has been shown to have anti-inflammatory properties[41], and this reduction in inflammation and oxidative stress may explain the beneficial effects of exercise on mental health. This effect may be mediated by changes in the neuroimmune system, such as induction of the release of interleukin-10 and other anti-inflammatory cytokines[42,43].

#### Comparisons with prior reviews

Many barriers to the adoption of e-health in clinical practice remain despite the great potential of new technologies. Qualitative survey results of investigation involving patients and professionals provide some insight into the challenges that remain to be overcome for the adoption of e-health[44]. While patients appear open to using e-health, their interest differs from actual use. A 2019 survey of veterans with depression found that while 73.1% of them were interested in mental health apps, only 10.7% actually used any of them [45].

Among the most important barriers is precisely the lack of integration in public health systems, which leads to mistrust between users and professionals. In this respect, the United Kingdom is a pioneer in trying to integrate new technologies into its healthcare system [46]. Another barrier is the concern for privacy when using tools with internet access, as there is a risk of dissemination of highly sensitive data [47,48]. The absence of privacy policies is a frequent drawback when creating and using apps. Privacy is an issue of concern to users, and one of the main features they value in this type of media is that there is a method of protecting sensitive information by passwords, for example[49].

Mental disorder may act as a barrier in itself, as shown by a study in which veterans with posttraumatic stress disorder (PTSD), despite demanding more mental health services, were less willing to participate in mental health apps than their peers without PTSD[50]. The lack of confidence of medical professionals themselves in the reliability of e-health interventions sometimes slows down the adoption of mental health in clinical practice. In addition, there is a markedly smaller number of studies evaluating these interventions than the number of devices and apps available on the market[51]. Users often seek advice from their healthcare professionals, such as doctors or nurses. Training doctors, nurses and other healthcare professionals in the use of new technologies is therefore a crucial element in accelerating the adoption of these interventions in clinical practice[52,53].

# CONCLUSION

Digital medicine represents a tool of great potential in clinical practice. Thanks to their great versatility and acceptance among users, new technologies can open up new fields in mental health care. In the specific case of physical exercise enhancement in mental health patients, new technologies can facilitate adherence to exercise programmes and increase their personalization. However, there are still wideranging barriers to the adoption of these interventions on a day-to-day basis. One of the steps needed to advance research is the development of new apps and tools, and their testing in exploratory articles with larger sample sizes.

Another of the fronts to be explored is the field known as machine learning. From the huge amount of data that these devices can collect, we can detect behavioural patterns characteristic of each person and thus optimise interventions to individual needs. This is a step towards participatory medicine, a paradigm shift that has been pursued for years[53], in which the integration of multidisciplinary treatment teams would also be an important point.

# **ARTICLE HIGHLIGHTS**

#### Research background

Mobile applications (apps) have proven to be very useful in improving physical health in numerous medical illnesses.

#### Research motivation

We want to know if apps have proven to be useful in patients with mental illness.

#### Research objectives

The main objective of the present systematic review is to know the efficacy of apps to increase physical



activity in patients suffering from mental illness.

## Research methods

We have carried out a systematic review, following the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses recommendations, of the last 10 years, selecting articles that have studied the efficacy of apps in increasing physical activity in patients with mental illness. The quality of the selected studies was also analyzed.

## **Research results**

From 6257 initial articles we included finally 9 articles that met the criteria for inclusion. We resume the principal studies that have showed an improvement in reduction of weight and depressive symptoms and an increase of level of satisfaction and physical exercise in patients that are suffering a mental disease.

## Research conclusions

Apps can be a good strategy to improve the physical health of patients with mental illness.

## Research perspectives

In the future, digital tools should be developed to analyze clinical efficacy using multivariate analysis, larger samples, including different psychiatric diseases and more specific treatments using artificial intelligence (machine learning).

# FOOTNOTES

Author contributions: Guerrero-Jiménez M and Ruiz M contributed equally to this work; Gutiérrez-Rojas L, Jiménez-Muñoz L, Baca-Garcia E and Porras-Segovia A designed the research study; Ruiz M, Jiménez-Muñoz L and Porras-Segovia A performed the research; Guerrero-Jiménez M and Ruiz M contributed analytic tools; Guerrero-Jiménez M, Ruiz M, Gutiérrez-Rojas L and Porras-Segovia A analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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SYSTEMATIC REVIEWS

# **COVID-19** pandemic in the intensive care unit: Psychological implications and interventions, a systematic review

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# Abstract

## BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic produced changes in intensive care units (ICUs) in patient care and health organizations. The pandemic event increased patients' risk of developing psychological symptoms during and after hospitalisation. These consequences also affected those family members who could not access the hospital. In addition, the initial lack of knowledge about the virus and its management, the climate of fear and uncertainty, the increased workload and the risk of becoming infected and being contagious, had a strong impact on healthcare staff and organizations. This highlighted the importance of interventions aimed at providing psychological support to ICUs, involving patients, their relatives, and the staff; this might involve the reorganisation of the daily routine and rearrangement of ICU staff duties.

## AIM

To conduct a systematic review of psychological issues in ICUs during the COVID-19 pandemic involving patients, their relatives, and ICU staff.

## **METHODS**

We investigated the PubMed and the ClinicalTrials.gov databases and found 65 eligible articles, upon which we commented.

#### RESULTS

Our results point to increased perceived stress and psychological distress in staff, patients and their relatives and increased worry for being infected with severe acute respiratory syndrome coronavirus-2 in patients and relatives. Furthermore, promising results were obtained for some psychological programmes aiming at improving psychological measures in all ICU categories.

#### CONCLUSION

As the pandemic limited direct inter-individual interactions, the role of interventions using digital tools and virtual reality is becoming increasingly important. All considered, our results indicate an essential role for psychologists in ICUs.

**Key Words:** COVID-19; Intensive care unit; Psychological interventions; Pandemic; Mental health; Health care professionals

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**Core Tip:** The coronavirus disease 2019 (COVID-19) pandemic produced changes in patient care and organization of intensive care units (ICUs). The pandemic event increased patients' risk of developing psychological symptoms during and after hospitalisation. We carried out a systematic review of the psychological issues raised in ICUs during the COVID-19 pandemic which concerned patients, their relatives, and the ICU staff. Our results point to increased perceived stress and psychological distress in staff, patients and their relatives and increased worry for being infected with severe acute respiratory syndrome coronavirus-2 in patients and relatives. Promising results were obtained for some psychological measures in all ICU categories.

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## INTRODUCTION

Intensive care unit (ICU) utilisation during the coronavirus disease 2019 (COVID-19) pandemic accounted for around 25% of patients hospitalised during the February 2020 to September 2021 period in 21 United States Healthcare systems[1]. The COVID-19 pandemic has produced changes in ICUs both in patient care and in hospital care organization. On the one hand, the high burden of stress that patients usually experience in the ICU, has been exacerbated by the fear of the virus and the need to isolate, especially from family members. The pandemic has consequently increased the patient's risk of developing important psychological symptoms during and after hospitalization[2-4]. In addition, family members also experienced psychological symptoms due to the lack of access to the hospital, as this keeps them away from their loved ones and made it more difficult to exchange information with health workers[5]. Psychological symptoms associated with the COVID-19 pandemic, despite being more severe in the patient population, match those of relatives[6]. Finally, the lack of knowledge about the virus and its management, the climate of fear and uncertainty, increased workload, and the risk of becoming infected and infecting loved ones, had a great impact on staff[7-9]. This highlighted the importance of interventions aiming to provide psychological support to the treatment team, to reorganise the daily routine, and to characterise the role of the professionals working in an ICU.

With the awareness that the COVID-19 emergency is not over, the aim of this review was to highlight the changes and developments occurring in ICUs during the pandemic, knowing that many of its characteristics and changes are still important and will probably be in the future. The need to monitor the psychological phenomena taking place in ICUs during the COVID-19 period and to implement adequate interventions in the same structures has already been stressed in neonatal/paediatric[9,10-13] and adult age[14]. A review focused on the role of the psychologist in paediatric ICUs[15], and other two in adults were systematic reviews, one on informational and educational interventions in ICUs[16], the other on bereavement support[17], while one study identified three areas of utility of a psychologist in an ICU, namely, attention to patients at the ICU, attention to family members or caregivers, and work with health personnel[18]. There are currently no studies collecting experiences and evidence of effectiveness of psychological interventions during the COVID-19 pandemic. Hence, through this review we intend to investigate the psychological characteristics of ICU admission during the pandemic, through the assessment of the perspectives of the various involved individuals, *i.e.*, patients, family members, and staff members, and on the interventions that the psychologist, along with the medical team, enforced to deal with the health emergency.

We will start by describing patients' most frequent psychological repercussions of ICU admission and stay. Subsequently, we will summarise the elements of the main psychological characteristics of patients, family members, and caregivers during the COVID-19 pandemic.

As the pandemic limited direct, person-to-person interindividual interactions, with a concomitant rise in the use of digital homework, we found it interesting to dedicate a section of this review to interventions with digital tools. During the pandemic, these tools proved to be very effective (besides being the only available) in facilitating communication at various levels. Within this framework, we also highlight the role of virtual reality (VR) used in intensive care to treat the psychological consequences and promote the well-being of patients hospitalised with COVID-19 (and their relatives).

## MATERIALS AND METHODS

To identify evidence of psychological issues and interventions in ICUs, we searched the PubMed database adopting the following search strategy: COVID-19 AND ("Intensive Care Unit" OR ICU) AND psychol\* AND (implicat\* OR intervent\*), which produced on September 30, 2022, 214 results. We also searched the ClinicalTrials.gov database using the strategy Condition or disease: COVID-19 and Other terms: intensive care unit AND psychological, which produced 41 results on the same date. Eligibility depended on being an experimental work having data, either epidemiological or interventional. Excluded were reviews (and meta-analyses as well as guidelines; n = 25), case reports and series (n = 5), opinion articles (n = 16, editorials, comments on other articles, and reports without data), protocols of future studies (n = 17), articles not reporting on psychological outcomes or interventions, not involving ICUs, or not involving COVID-9 (collectively labelled as outcome, n = 52), studies not providing results (n = 38), studies lumping ICU data with data from other wards without providing separate data for ICUs (n = 6), studies with overlapping populations (n = 1, in which case only the article with the higher sample size would have been selected, provided it was higher in quality than others), studies with inadequate design to obtain the desired results (n = 16), unfocused articles (n = 12), papers unrelated to the subject matter (n = 5), *post mortem* studies (n = 0), and animal studies (n = 0).

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## RESULTS

Reviews/meta-analyses and guidelines were excluded but we thoroughly searched their reference lists for studies that possibly eluded our database searches. Duplicates were also to exclude if occurring in both searched databases (n = 0). When adding records concerning ClinicalTrials.gov to those of PubMed, we took care to substitute those that had their NCT number published within PubMed with the published article and rate it as appropriately. One ClinicalTrials.gov record produced four additional articles published with its NCT number, thus amounting to a grand total of 259 records. ClinicalTrials.gov added 1 eligible article; the 64 identified by PubMed. PubMed results did not overlap with those of ClinicalTrials.gov. We found no duplicates in our searches. Of the records identified by our ClinicalTrials.gov search, 19 were completed, but only 1 of them had results (and was not eligible, record 29 in Supplementary Material), 9 were still recruiting, 7 were active, but not recruiting, 1 was not yet recruiting, 3 had unknown status, and 2 were terminated (one in Malaysia for logistical problems/ administrative issues, the other in Turkey, due to technical reasons). Most projects were based in France (n = 19, 1 in its extra-European territories), other 9 in Northern Europe and British isles (5 Belgium, 2 the Netherlands, 1 Denmark, and 1 United Kingdom), 6 in Southern Europe (3 Spain, 2 Turkey, and 1 Italy), 5 in the Americas (3 United States, 1 Brazil, and 1 Colombia), 1 in Asia (Malaysia), and 1 in Africa (Egypt) (Supplementary Material). The first was first-posted on June 19, 2019, the last on June 16, 2022, indicating early and enduring interest in the subject. Qualitative analyses were included if they adequately assessed psychological outcomes, but unfortunately, most did not. We assessed eligibility by reaching consensus among five authors (Monti L, Tranquilli S, Mazza M, Marconi E, and Kotzalidis GD) through Delphi rounds; no more than two were necessary to establish it. The results of the search are shown in Figure 1[19]. The list of studies considered is in the Supplementary Material in a Table, where reasons for exclusion are provided for each study (Supplementary Material). The final number of included studies was 65, spanning from July 2, 2020 to September 23, 2022. A summary of their results is provided in Table 1.

## DISCUSSION

#### Psychological implications of being hospitalised in an ICU: ICU admission

Admission to the ICU often has significant consequences for patients and their caregivers and family members<sup>[20]</sup>. It is an event with traumatic potential. In fact, it involves a high stress charge due to invasive and painful procedures, sleep deprivation, unnatural noises and lights, inability to communicate, feeling of helplessness, and especially imminent threat of death[21]. The most frequent negative experiences reported by patients were thirst, loss of control, and noise[22].

During the COVID-19 pandemic, patients reported increased stress, probably related to the increased preventive and personal protective measures and the increased isolation from family, friends, and caregivers[20]. Indeed, many patients recall traumatic and loneliness elements in their ICU experience and many of them were admitted to the ICU during the pandemic while family members were in critical, sometimes fatal, conditions[23]. ICU admission often renders patients psychologically vulnerable; in fact, patients frequently report high levels of anxiety and depression[24]. Such symptoms may affect treatment plans and outcomes[25]. Psychological distress and psychiatric symptoms should be taken into account to prevent worsening of the quality of life after leaving the ICU[26].

## Psychological implications of being hospitalised in an ICU: During ICU hospital stay

People who are admitted to ICUs may already have or not have psychological distress; ICU admission may worsen pre-existing psychological distressed, expressed as a variety of psychiatric symptoms which resemble post-traumatic stress disorder (PTSD), depression, excessive worrying, insomnia, and anxiety, or may induce newly developed psychological distress. An Italian study found that ICU admission may be associated with increased depression levels and suicidal ideation in a small, but clinically significant proportion of patients with COVID-19, and may worsen pre-existing depression [27]. A Turkish study showed depression may be mediated by restricted visits to the ICU patient, while anxiety was mediated by ICU admission itself[28]. In this study, ICU admission and visit restriction were independent risk factors; positive polymerase chain reaction for COVID-19 and female gender were associated with both anxiety and depression, as assessed with the Hospital Anxiety and Depression (HAD) scale. Another Turkish study examined the quality of sleep using the Pittsburgh Sleep Quality Index and depression and anxiety with the HAD in ICU patients with COVID-19; poor sleep quality was associated with depression and longer ICU hospitalisation[29]. The authors concluded that through improving sleep quality would help reducing duration of ICU stay.

Clozapine is a second-generation antipsychotic agent that is reserved to severe, treatment-resistant cases of schizophrenia and bipolar disorder due to potentially life-threatening agranulocytosis. Because of this, it is associated with worse pulmonary outcomes, namely pneumonia[30]. Although the use of second-generation antipsychotics is generally associated with reduced odds of getting a COVID-19 infection[31], it has been suggested that patients on clozapine may be at higher risk of COVID-19



Ref.	Туре	Population	Design	Outcomes and assessments	Results	Conclusions and observations	
Sayde <i>et al</i> [ <mark>138]</mark> , 2020	C-S survey	265 ICU patients recruited, 20 refused, 185 excluded, 35 included: 17: Intervention group, (16 female, 11 male); 18 patients control group (15 female,13 male)	Diary and questionnaire administered 1 (BL), 4, 12, and 24 wk after ICU discharge (September 2017 to September 2018) in New Orleans, Louisiana, United States	Psychological distress, (IES-R), Anxiety and Depression (PHQ-8; HADS; GAD-7)	Controls had a significantly greater decrease in PTSD, hyperarousal, and depression symptoms at week 4 compared to the intervention group. No significant differences in other measures, or at other follow-ups. Both study groups exhibited clinically significant PTSD symptoms at all timepoints after ICU discharge	Diary increased awareness of the psychological support available to ICU survivors and family members	
Huang <i>et al</i> [139], 2020	C-S online survey	6523 people with contact history, completed the survey, 260 were excluded, 6261 included. 3585 female (57.3%), 2676 male (42.7%)	Online questionnaire sent to participants of Hubei province and outside Hubei province, China, from February 10 to 15, 2020	Tested depression (PHQ-9) and public perceptions in response to the COVID-19 outbreak	Most people endorsed preventive and avoidance behaviours. People from Hubei, with contact history, and people who were infected or whose family members were infected by COVID-19, had a much higher prevalence of depression and anxiety	Assessing public response, perception, and psychological burden during the outbreak may help improving public health recommend- ations and deliver timely psychological intervention	
Leng <i>et al</i> [140], 2021	C-S survey	90 ICU nurses; 65 female (72.2%), 25 male (27.8%)	Tests administered to ICU Wuhan (China) nurses, from 11 to 18 March 2020	PTSD (PTSD Checklist- Civilian and PSS), related to demographic survey and 2 open questions	Nurses have elevated PTSD levels. Nurses' stress and PTSD symptoms were positively correlated. Isolated environment, concerns about personal protective equipment shortage and usage, physical and emotional exhaustion, intensive workload, fear of being infected, and insufficient work experiences with COVID-19 were a major stress source	Even highly skilled and resilient nurses experienced some degree of mental distress, such as PTSD symptoms and perceived stress	
Lasater <i>et al</i> [80], 2021	C-S analyses	ICU nurses and ICU patients: First sample 4298 medical-surgical nurses; second sample 2182 ICU nurses	Staffing data collected from registered nurses in New York and Illinois using HCAHPS and AHA, between 16-12- 2019-24-2-2020	Information on patient satisfaction, hospital characteristics	Over half the nurses experienced high burnout. Half gave their hospitals unfavourable safety grades and two-thirds would not definitely recommend their hospitals. One-third of patients rated their hospitals less than excellent and would not definitely recommend it to others	Hospital nurses had burn-out and were working in understaffed conditions in the weeks prior to the first wave of COVID- 19 cases, thus increasing public health risks	
Jain <i>et a</i> [ <mark>81],</mark> 2020	C-S online survey	512 Indian anaesthesiologists, 227 female (44.3%), 285 male (55.7%)	Online questionnaire sent to anaesthesi- ologists across India from 12-5-2020 to 22- 5-2020	Anxiety (GAD-7) and Insomnia (ISI)	Elevated COVID-19- related anxiety and insomnia levels of anaesthesiologists. Age < 35 yr, female sex, being married, resident doctors, fear of infection to self or family, fear of salary deductions, increase in working hours, loneliness due to isolation. food and	Anaesthesiologists on COVID-19 duty suffer from anxiety and insomnia	



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# Monti L et al. Psychological consequences of COVID-19 on ICUs

					accommodation issues and posting in COVID- 19 duty were risk factors for anxiety. < 35 yr, unmarried, those with stress due to COVID-19, fear of loneliness, issues of food and accommodation, increased working hours favour insomnia	
Kirolos <i>et al</i> [82], 2021	LS	41 families with a baby at NICU	Multicentre service evaluation in five United Kingdom neonatal care units, between July and November 2019	Surveys contained quantitative (9-point Likert scale, or closed- ended yes/no responses) and qualitative items (open comment boxes)	In post-implementation surveys ( $n = 42$ ), 88% perceived a benefit of the service on their neonatal experience. 71% ( $n = 55$ ) felt the service had a positive impact on relationships with families	Asynchronous video supports models of family integrated care and can mitigate family separation
Lasalvia <i>et al</i> [83], 2020	C-S online survey	2195 ICU HCWs; female 539 (24.7 %), male 1647 (75.3)	All healthcare and administrative staff of Verona University Hospital (Veneto, Italy) from April to May 2020	Psychological distress (IES-R), Anxiety (SAS) and mental health (PHQ-9)	63.2% of participants reported COVID- related traumatic experiences at work; 53.8% showed symptoms of post- traumatic distress; 50.1% showed symptoms of clinically relevant anxiety; 26.6% symptoms of moderate depression	The psychological impact of the COVID- 19 pandemic on healthcare staff working in a highly burdened north-east Italy is high and to some extent higher than that reported in China
Ou et al[84], 2021	C-S study	92 nurses in isolation ward, female 85 (92.4%); male 7 (7.6%)	Test was administered to nurses in isolation ward, the Guangdong Province of China, in February 2020	Resilience and psycho- pathological symptoms (CD-RISC2; SCL-90)	Total resilience score was $87.04 \pm 22.78$ . SCL- 90 score ranged 160-281 (202.5 ± 40.79). Only 8.70% of nurses ( $n = 8$ ) scored > 160 on the SCL-90, suggesting positive symptoms. Most nurses had 0 to 90 positive self-assessment items (median 14); 19.57% ( $n = 18$ ) had > 43 positive items to CD- RISC 2	High resilience promotes physical and mental health, and may be improved by training, psycho- logical interventions, and full use of hospital resources
Vlake <i>et al</i> [69], 2020	Case report	One COVID-19 patient (male), age: 57 yr	Test for evaluating COVID-19 ICU-VR intervention in one Dutch man with COVID-19	Anxiety and depression (HADS) and psycho- logical distress (IES-R)	One week after receiving ICU-VR, levels of PTSD, anxiety, and depression had normalised and stayed normal 6 mo after discharge	Virtual realty improved psycho- logical rehabilitation outcomes, hence they should be considered by clinicians for the treatment of ICU- related psychological sequelae after COVID-19
Fernández- Castillo <i>et al</i> [85], 2021	C-S survey	17 nurses: 6 male, 11 male	17 nurses of a tertiary teaching hospital in Southern Spain, from 12-30 April 2020	Semi-structured videocall interviews	Four main themes emerged from the analysis and 13 subthemes: "providing nursing care", "psychosocial aspects and emotional lability", "resources management and safety" and "profes- sional relationships and fellowship"	Nursing care has been influenced by fear and isolation, making it hard to maintain humanisation of health care
Writing Committee for the COMEBAC Study Group <i>et</i> <i>al</i> [86], 2021	C-S telephone survey	834 eligible COVID- 19 survivors: 478 evaluated (201 male, 277 female)	Survivors of COVID- 19 in France underwent telephone assessment 4 mo after discharge, between July and September 2020	Respiratory, cognitive, and functional symptoms (Q3PC cognitive screening questionnaire, symptom Checklist and 20-item Multidimensional	244 patients (51%) declared at least 1 symptom absent before COVID-19: Fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnoea in	4 mo after hospital- isation for COVID-19, a cohort of patients frequently reported previously absent symptoms



				Fatigue Inventory; SF- 36; cognitive impairment (MoCA)	16%. The median 20- item Multidimensional Fatigue Inventory score ( $n = 130$ ) was 4.5 for reduced motivation and 3.7 for mental fatigue. The median SF-36 score ( $n = 145$ ) was 25 for the subscale "role limited owing to physical problems". Among 94 former ICU patients, anxiety, depression, and PTSD symptoms were observed in 23%, 18%, and 7%, respectively. The left ventricular ejection fraction was < 50% in 8 of 83 ICU patients (10%)	
Stocchetti <i>et al</i> [87], 2021	C-S online study	Of 271 medical staff working in this ICU, 136 included: 84 nurses (62%) and 52 physicians (38%)	Nurses and physicians working in this ICU participated to online survey in January 2021	Burnout (MBI), anxiety (HADS); resilience (RSA) and Insomnia (ISI)	60% of participants show high burnout level: Nurses reported significantly higher scores of anxiety and insomnia levels. 45 % reported symptoms of depression, and 82.4% of the staff showed moderate-to-high levels of resilience	The COVID-19 pandemic can have a significant impact on ICU staff. Effective interventions needed to maintain healthcare profes- sionals' mental health and relieve burnout
Kirk et al <b>[12]</b> , 2021	C-S online study	430 of 458 paediatric HCWs, concluded the online survey	Online survey administered to paediatric HCWs in the emergency, ICU and infectious disease units from April 28 to May 5 2020	Depression and Anxiety symptoms (DASS-21)	168 (39.1%) of respondent showed depression, 205 (47.7%) anxiety and 106 (24.7%) symptoms of stress. Depression reported in the mild (47, 10.9%), moderate (76, 17.7%), severe (23, 5.3%) and extremely severe (22, 5.1%) categories. Anxiety (205, 47.7%) and stress (106, 24.7%) were reported in the mild category only	A high prevalence of depression, anxiety and stress was reported among frontline paediatric HCWs during the COVID-19 pandemic
Yang <i>et al</i> [ <mark>88]</mark> , 2021	C-S online study	Of 1075 contacted individuals, 1036 front-line HPCD completed the online survey: Female 755 (72.9%), male 288 (27.1). 874 (84.4%) nurses, 162 (15.6%) physicians	1036 front-line HPCDs exposed to COVID-19 were tested online from 5 to 9 March 2020 in Wuhan, China	Sleep, insomnia, emotional regulation (RESE)	543 (52.4 %) reported symptoms of sleep disorders. HPCD for patients with COVID- 19 in China reported experiencing sleep disturbance burdens, especially those having exposure experience and working long shifts	RESE is an important resource for alleviating sleep disturbances and improving sleep quality
Moradi <i>et al</i> [89], 2021	C-S survey	17 nurses in ICUs: 5 males and 12 females	Semi-structured face- to-face interviews were administered to nurses in ICUs of Urmia, Iran	Semi-structured face-to- face interviews	Four challenges throughout the provision of care for COVID-19 patients: 'organization's ineffi- ciency in supporting nurses', 'physical exhaustion', 'living with uncertainty' and 'psychological burden of the disease	A profound understanding of ICU nurses' challenges while caring for COVID-19 patients is needed to increase healthcare quality
Bruyneel <i>et al</i> [90], 2021	C-S online survey	1135 ICU nurses: Female 892 (78%); male 243 (22%)	Nurses in the French- speaking part of Belgium completed a web-based survey, April 21-May 4, 2020	Burnout (MBI)	68% burnout level. 29% of ICU nurses were at risk of depersonal- isation, 31% of reduced personal accomplishment, and 38% of emotional exhaustion	Burnout risk requires monitoring and implementation of interventions to prevent it and manage it



# Monti L et al. Psychological consequences of COVID-19 on ICUs

Shariati <i>et al</i> [91], 2021	LS online survey	67 family members of COVID-19 patients admitted to the ICU	Longitudinal pre- post intervention online survey of 67 family members of COVID-19 ICU patients in three hospitals in Iran; May to August 2020	Stress symptoms (PSS- 14)	Mean PSS-14 post- intervention significantly lower in the intervention group than in the control group ( $P < 0.001$ )	Use of web-based communication between nurses and family members was effective in reducing perceived stress
Kok et al[92], 2021	LS survey	Open cohort of ICUs professional: BL survey 252 respondents, response rate: 53%, male 66 (26.2%), female 186 (73.8%); and follow-up 233 respondents, response rate: 50%, male 65 (27.9%), female 168 (72.1%)	BL survey collected in October-December 2019 and follow-up survey sent in May- June 2020 to a university medical centre and a large teaching hospital in the Netherlands	Semi-structured interview form	The prevalence of burnout symptoms was 23.0% before COVID-19 and 36.1% after, with higher rates in nurses (38.0%) than in physicians (28.6%). Post-COVID-19 incidence rate of new burnout cases among physicians was higher (26.7%) than among nurses (21.9%). Higher prevalence of burnout symptoms after the beginning of the pandemic	Overburdening of ICU healthcare personnel during an extended period leads to burnout symptoms
Kürtüncü et al [93], 2021	C-S survey	18 COVID-19 patients: 4 females and 14 males	Telephone-conducted semi-structured interview of 18 ICU patients in Turkey; March-September, 2020	Semi-structured interview form	Interventions in ICUs are able to promote communication with patients and are essential for achieving positive circumstances	Families of missing patients may benefit from interventions of nurses aimed at working-through the loss and providing family support and care during their critical illness
Martillo et al [94], 2021	C-S online survey	45 COVID-19 ICU patients: Male 33 (73.3%), female 10 (22.2%)	Single-centre descriptive cohort study of ICU patients at Mount Sinai Hospital, New York; April 21 to July 7, 2020	Insomnia (ISI), mental health (PHQ-9), QoL (EQ-5D-3L), PTSD (PCL-5), telephone cognitive assessment (MoCA)	22 patients (48%) reported psychiatric impairment, and four (8%) had cognitive impairment. 38% at least mild depression, and 18% moderate-to- severe depression. 8% PTSD. 9% had impaired cognition	Severe COVID-19- related symptoms associated with high risk of developing PICS. Planning needed for appropriate post-ICU care
Donkers <i>et al</i> [95], 2021	C-S online survey	355 nurses, 108 supporting staff and 41 ICU physicians from 84 ICUs: 124 males, 380 females	Online questionnaire sent by email to Dutch ICU nurses and supporting staff from 7 April to 11 June, 2020	MD for HCWs (MMD- HP), Ethical Decision- Making (EDMCQ)	MD levels higher for nurses than others; "Inadequate emotional support for patients and their families" was the highest-ranked cause of MD for all participants; all participants; all positively the ethical climate regarding the culture of mutual respect, ethical awareness, and support	Targeted interventions on MD are important for improving the mental health of critical care professionals and the quality of patient care
Fteropoulli <i>et al</i> [96], 2021	C-S online survey	1071 healthcare personnel: 73% females, and 27% males	Anonymous online survey administered. May 25 to October 27, 2020, in Cyprus	QoL (WHOQOL-Brief), anxiety (GAD-7), depression (PHQ-8), burnout (CBI), and coping (Brief COPE)	27.6% moderate and severe anxiety, 26.8% depression. Being female, nurse or doctor, working in frontline units, perceptions of inadequate workplace preparation to deal with the pandemic and using avoidance coping were risk factors	There are several risk factors for psycho- logical distress during the pandemic, which may be individual, psychosocial, and organisational
Peñacoba et al [97], 2021	C-S online survey	308 intensive care nurses: Female 268 (87%) and male 40 (13%)	Online form used to collect data from surgical and general critical care units in a public Spain Hospital, March 2020 to June 2020	Stress subscale (depression, anxiety, and stress in Spanish DASS-21), physical and mental health-related QoL (SF-36), GSES, and resilience (RS-14)	Greater perception of self-efficacy related to lower perception of stress and greater resilience, while higher resilience was linked to greater physical and	Stress is related to physical and mental health factors which are linked to QoL through self-efficacy and resilience



					mental health	
Wozniak et al [98], 2021	C-S online study	3461 HCWs of 352 ICU	Online data collected from May 28 to July 7, 2020, at HUG, Switzerland	Socio-demographic data, lifestyle changes, anxiety (GAD-7; PHQ- 9), psychological distress (PDI; WHO-5)	145 (41%) reported poor well-being, 162 (46%) anxiety, 163 (46%) depression, 76 (22%) peritraumatic distress. Working in ICU more than other departments changes eating habits, sleeping patterns, and alcohol consumption ( $P$ < 0.01)	High prevalence of anxiety, depression, peritraumatic distress and poor well-being during the first COVID-19 wave among HCWs, especially in ICU
Li <i>et al</i> [99], 2021	C-S survey	78 ICUs nurses: Female 4 (17.95%), male 64 (82.05%)	Data from 78 ICU nurses in Beijing COVID-19 hospital during March 2020	Depression (SDS), stress (PPS)	44.9% (n = 35) reported depressive symptoms, stress perception; work experience in critical diseases, and education are risk factors for depression	Work experience in critical illness is linked to depression. Psychological intervention may reduce it
Manuela <i>et al</i> [100], 2021	C-S survey	34 females, mothers of premature infants born before 32 wk of gestational age; 20 pre-COVID-19 period <i>vs</i> 14 during COVID- 19 pandemic	20 mothers of premature infants recruited at HUG, CH, January 2018 to February 2020 before COVID-19 vs 14 mothers from November 2020 to June 2021	Postnatal depression (EPDS); (PSS:NICU), attachment (MPAS)	No significant differences for depression, stress, and attachment between the two groups; "trend" towards increase of depression symptoms in mothers during the COVID-19 pandemic; depression correlated with attachment and stress scores	Protective family- based actions and appropriate interventions to support parents during the COVID-19 pandemic can reduce depression and stress of mothers of premature infants
Nijland <i>et al</i> [76], 2021	LS survey	Of 326 ICU nurses, 138 (42.33%) participated; 86 VRelax users, male 13 (15%), female 73 (85%) and 52 non- users, male 9 (17%), female 43 (83%)	VRelax intervention investigated in Dutch ICU nurses in May, 2020	Single-question VAS- stress scale	VR reduced stress by 36% (mean difference = $14.0 \pm 13.3$ , $P < 0.005$ ). 62% of ICU nurses rated VRelax as helpful to reduce stress	VRelax is effective in reducing immediate perceived stress
Scheepers <i>et al</i> [101], 2021	LS survey	Of 203 ICU and internal medicine staff, 103 residents (50.1%) participated	ICU and Internal medicine staff of AMC, Amsterdam, The Netherlands tested during the first wave of COVID-19, March 15 to June 30, 2020	Explored residents' perceptions of well- being (well-being survey), and their perceived support of the well-being program during the COVID-19 pandemic	Residents working in the ICU reported significantly lower levels of mental well- being than internal medicine residents	Well-being programmes for ICU staff need to address ICU-specific stressors, enhancing supervision and peer support
Liu <i>et al</i> [102], 2021	Study 1: LS survey; study 2: LS survey	Study 1: Of 268 ICU nurses and 26 head nurses, 258 completed the survey: Female 220 (85.27%), male 38 (14.73%). Study 2: 64 ICU medical profes- sionals: Female 40 (65.57%), male 24 (34.43%)	Study 1: ICU nurses of major Chengdu hospital, China, recruited. Retested after 3 wk for work engagement and rated by head nurses for taking-charge behaviour after further 3 wk. Study 2: ICU medical staff of same Chinese hospital completed scales on early March, 2020 and 2 wk later	Studies 1-2: Perceived COVID-19 crisis strength and work meaningfulness assessed with 5-point Likert scales, and demographic data. Self- rating of work engagement and clinician rating of taking-charge behaviour	Study 1: Health worker'sperceived COVID-19 crisis strength exerted a more negative effect on his or her work engagement and taking charge at work. Study 2: The interventions significantly decreased perceived COVID-19 crisis strength and increased work meaningfulness for medical staff in an ICU	Study 1: Frontline health workers worldwide have regarded the COVID- 19 crisis as an extraordinarily stressful event. Study 2: Interventions are important for reducing stress during COVID-19 pandemic
Carmassi <i>et al</i> [103], 2021	C-S survey	265 frontline HCWs: Male 84 (31.7%), female 181 (68.3%)	Data was recruited in a sample of frontline HCWs at a major university hospital in Pisa, Italy, April 1 to May 1, 2020	PTSS (IES-R), anxiety (GAD-7), depression (PHQ-9), assess work and social Functioning (WSAS)	Subjects with acute PTSS have higher levels of PTSS, depressive symptoms, and moderate-to-severe anxiety symptoms	More long-term studies are needed to evaluate the impact of psychopathology on the socio-occupa- tional functioning of health professionals
Secosan <i>et al</i> [104], 2021	C-S survey	Of 200 frontline HCWs, 126, 63% (32 nurses and 94 physicians)	Data collected from Romanian frontline HCWs, March to April 2020	Psychological capital (PsyCap) (PCQ) related to anxiety and depression (DASS-21),	High anxiety predicts lower emotional exhaustion and a low level of mental health	PsyCap is may decrease the impact of anxiety and depression on


		participated; male 35.7%, female 64.3%; 42.8% single, 52.3% married, 4.7% divorced		burnout (MBI)	complaints about healthcare professionals when PsyCap is high	psychological outcomes in frontline HCWs. Psychological interventions can help ICUs staff
Scarpina <i>et al</i> [105], 2021	C-S survey	60 patients who survived COVID-19 infection: Male 58.3%, female 41.7%	Participants had been recruited at the COVID-19 post-ICU, from May 2020 to January 2021, in Italy	Fearful facial expressions recognition, perceived psychological functioning, Empathy (4-point Likert scale questionnaire)	Altered detection and recognition of fearful expressions and altered processing of fearful expressions in individuals who survived COVID-19 infection	Altered emotional face recognition could represent psychological distress; psycho- logical interventions in rehabilitative settings can be helpful
Kapetanos <i>et al</i> [106], 2021	C-S survey	381 HCWs: 72.7% nurses (202 males, 75 males) 12.9% physicians (28 males, 21 males), 14.4% other occupations (18 males; 7 males)	Data on mental health status of HCWs collected from healthcare profes- sionals from all over Cyprus from May to June 2020	64-item, self- administered questionnaire, which included DASS21 and MBI	Prevalence of 28.6% anxiety, 8.11% stress, 15% depression, and 12.3% burnout. Environmental changes included increased working hours, isolation, and separation from family	Also the second wave of the pandemic impaired psycho- logical health of HCWs
Manera <i>et al</i> [107], 2022	C-S survey	152 COVID-19 patients: 101 males, 51 females	Retrospective assessment of post- infectious SARS- CoV-2 patients at Maugeri Scientific Clinical Institutes, Northern Italy, May 2020 to May 2021	Cognitive measures (MMSE) as related to disease severity (at-risk <i>vs</i> not at-risk: Neuro+ <i>vs</i> Neuro-)	Mild-to-moderate patients (26.3%) showed impaired MMSE performances; ICU patients made less errors ( $P = 0.021$ ) on the MMSE than non-ICU patients. Age negatively influenced MMSE performance. For Neuro-patients, steroidal treatment improved MMSE scores ( $P = 0.025$ )	Mild-to-moderate patients, with mechanical ventilation who however are not admitted to an ICU, are more likely to suffer from cognitive deficits, independently from their aetiology
Mollard <i>et al</i> [108], 2021	C-S survey	885 postpartum women, 82.3% married	English-speaking adult postpartum women who gave birth in US hospitals from 1 March to 9 July 2020 participated in survey between 22 May to 22 July 2020	Demographic and health variables measured with self- report questionnaires; stress (PSS-10), Mastery (PM), and resilience (CD-RISC2)	Post-pandemic participants showed higher stress and lower resilience, high levels of depression, anxiety, and stress compared to a pre-pandemic normative sample. Women with an infant admitted to a NICU had higher stress. High income, full-time employment, and partnered relationships lowered stress. Lower stress increased mastery and resilience. Non-white women showed higher stress and lower resilience	Postpartum women are susceptible to stress, depression, and anxiety
Pappa <i>et al</i> [109], 2021	C-S survey	464 HCWs: Female 68%, male 32%; 43% nurses, 49% married	Six COVID-19 reference hospitals in Greece, from May 2020 to June 2020	Levels and risk factors of anxiety (GAD-7), Depression (PHQ-9), traumatic stress (IES-R), burnout (MBI) and fear (NFRS)	30% moderate/severe depression, 25% anxiety, 33% traumatic stress. 65% of respondents scored moderate-severe on EE, 92% severe on DP, and 51% low-moderate on PA. Predictors: Fear, perceived stress, risk of infection, lack of protective equipment and low social support	Need for immediate organisational and individual interventions to enhance resilience and psychological support for HCWs
Meesters <i>et al</i> [110], 2022	C-S online survey	25 parents (16 mothers, 9 fathers) of infants at NICU	Data collected at Rotterdam NICU from April to June 2020	Sociodemographic questions related to stressor (PSS:NICU) and COVID questionnaire	Most important sources of stress were being separated from, not being able to always hold their infant, and other family members	NICU staff can support psycholo- gically parents during hospital isolation and reduce the effect of



					not allowed to visit	restrictive measures
Piscitello <i>et al</i> [111], 2022	LS survey	Of 78 eligible, 33 ICU nurses (42%) completed survey: Female 29 (50.9%), male 28 (49.1)	Data collected November to December 2020 at Rush University	Nurse MD (MMD-HP)	Results pre and post intervention were not statistically different	Further research required to identify interventions that could improve nurses' MD
Sezgin <i>et al</i> [112], 2022	C-S online survey	10 ICU nurses: 2 males and 8 females	Data collected by online survey in 10 ICUs of 7 hospitals in İstanbul, Turkey, October to December 2020 using the snowball method to recruit	Followed the Consol- idated Criteria for Reporting Qualitative Research; 32-item checklist to identify major themes	'Death and fear of death', 'impact on family and social lives', 'nursing care of COVID-19 patients', 'changing perceptions of their own profession: empowerment and dissatisfaction', and 'experiences and perceptions of personal protective equipment and other control measures' are the major themes identified	There is need to improve working conditions and develop nursing standards in ICU
Rodriguez-Ruiz et al[113], 2022	LS online survey	HCW in ICU: 1065 in first time and 1115 in second time	Spanish ICUs in October to December 2019 and September to November 2020	MD (MMD-HP-SPA)	During the pandemic, nurses reported higher MD levels compared to the prepandemic period. ICU physicians reported significantly higher MD levels than ICU nurses during the prepandemic period, but not during the pandemic period	In Spain, during the COVID-19 pandemic, there is an increase of MD among ICU HCPs
Vlake <i>et al</i> [114], 2022	LS survey	89 post COVID patients: Male 63 (70%) and female 26 (39%)	VR efficacy data from Dutch post-ICU patients, June 2020 to February 2021; participants followed-up for 6 consecutive months	Psychological distress (IES-R) and QoL related to anxiety and depression (HADS)	High psychological distress levels in all groups. ICU-VR group showed improved ICU satisfaction with respect to the control group. 81% of patients reported a higher ICU quality, which was linked to virtual reality	ICU-VR is an innovative strategy to enhance satisfaction with ICU and improves ICU ratings aftercare, adding to its perceived quality
Fumis <i>et al</i> [115], 2022	C-S survey	Of 62 ICU physicians, 51 participated: Male 60.8%, female 39.2%; 76% married	Burnout investigated in ICU physicians during the second COVID-19 wave in São Paulo, Brazil, from December 10 to December 23, 2020	Questionnaire with demographic and occupational variables, and information on the impact of the COVID-19 pandemic on daily life (insomnia, lack of appetite, irritability, decreased libido, fear of being infected, fear of infecting loved ones, overspending) and MBI	19 (37.2%) showed high burnout, <i>i.e.</i> , 96.1% low PA, 51.0% high DP, and 51.0% high EE. Conflicts between the ICU physicians and other physicians were 50%	ICU staff have high burnout level
Levi and Moss [116], 2022	C-S survey	10 ICU nurses: 9 females and 1 male; 3 married and 7 single	ICU nurses completed psycho- logical stress survey during the COVID-19 pandemic in south- eastern United States from August to September 2020	Psychological Stress and PTSD Symptoms (PTSD Checklist), job satisfaction (a Likert- type scale), demographic information	The survey revealed 6 recurring themes: Change in Practice, Emotion, Patient's Family, Isolation, Job Satisfaction, and Public Reaction. 7 of 10 ICU nurses reported PTSD symptoms; 6 of 10 wanted to quit their jobs	Critical care nurses during the COVID-19 pandemic are highly subjected to PTSD; its early identification may prevent other related health deteri- orating problems
Righi et al[117], 2022	C-S survey	465 long COVID patients: 54% male and 46% female; 51 % hospitalised	Patients > 18 yr with SARS-CoV-2 infection at Verona University Hospital during February 29 to May 2 2020, followed for 9 mo	Duration and predictors of symptom persistence (symptom questionnaire), physical health and psycho- logical distress (K10)	37% of patients had at least 4 symptoms; 42% had symptom lasting more than 28 d. 19% showed psychological distress after 9 mo. Female and symptom persistence at day 28 were risk factors for psychological distress	Patients with advanced age, ICU stay, and multiple symptoms were more likely to suffer from long-term symptoms, with negative impact on both physical and mental wellbeing

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Gilmartin <i>et al</i> [118], 2022	C-S survey	22 post COVID-19 patients: Male 15 (68%), female 7 (32%)	A prospective cohort study through establishing a PICS follow-up clinic at Tallaght University Hospital in October 2020 for patients who had been admitted to their ICU	PICS investigated by psychological assessment for ICU (IPAT), PTSD (PCL-5), cognitive impairment (MoCA)	IPAT score was $6.6 \pm 4.6$ with a PCL-5 score of $21.1 \pm 17.5$ and a MoCA score of $24 \pm 8.4$ , suggestive of mild cognitive impairment	Patients have a high burden of physical and psychologic impairment 6 mo following ICU discharge for post- COVID-19 pneumonia
Guttormson <i>et al</i> [119], 2022	C-S online survey	485 ICU nurses: Female 430 (88.1%), male 56 (11.5%)	Participants recruited from national United States sample of ICU nurses, through AACCN newsletters and social media during the COVID-19 pandemic, October 2020 to January 2021	Measure of MD (MMD- HP), burnout (PROQOL-5), PTSD symptoms (TSQ), anxiety, and depression (PHQ-ADS)	Nurses reported moderate-high levels of MD and burnout; 44.6% reported depression symptoms and 31.1% had anxiety symptoms, while 47% of participants showed risk for PTSD	United States ICU nurses had high levels of anxiety and depression and higher risk for PTSD
Likhvantsev et al[120], 2022	C-S survey	Of 403 eligible COVID-19 patients in Russian ICUs (Moscow), 135 participated	Prospective cohort study investigated patients admitted in COVID-19 ICUs, March to June 2020	QoL (SF-36 questionnaire)	Heparin treatment in the ICU proved to be the only modifiable factor associated with an increase in the physical component of QoL	Heparin treatment enhanced QoL during COVID-19 patient recoveries at ICUs
Shirasaki <i>et al</i> [121], 2022	C-S survey	54 family members (68.5% female, 31.5% male) of 85 patients (16.7% female, 83.3% male) with COVID-19 admitted to ICU participated	PICS-F was invest- igated between March 23, 2020, and September 30, 2021, in Japan	PICS-F related to Psychological distress (IES-R), anxiety, and depression (HADS), and PTSD (FS-ICU)	Family members had 24% of anxiety, 26% depression and 4% PTSD	One-third of family members of COVID- 19 patients admitted to the ICU had symptoms of PICS-F
Amiri Gooshki et al[122], 2022	C-S survey	152 patients with COVID-19: Male 55 (36.2%), female 97 (63.8%); 98 (64.47%) married	Psychological consequences of COVID-19 were investigated at hospitals in south- eastern Iran in 2020	Demographic and background information, Depression, Anxiety (DASS-21), psycho- logical distress (IES-R)	73% of patients showed severe PTSD, 26.3% moderate depression and 26.3% severe anxiety	Higher psychological load is enhanced by ICU admission, divorce, illiteracy, and retirement
Omar et al [123], 2022	C-S survey	445 HCWs (physicians, nurses, and respiratory therapists): 171 ECMO-ICU, 274 non ECMO-ICU; male 239 (53.7%), female 206 (46.3%)	HCWs grouped by ECMO service (ECMO-ICU vs non- ECMO-ICU) and burnout status (burnout vs no burnout), in 8 tertiary-care hospital ICUs in Qatar, January 1 to June 30, 2021	General and demographic questions, burnout (MBI-HSS)	288 HCWs reported burnout and 158 did not. PA lower among ECMO-ICU personnel compared with those in a non-ECMO-ICU (42.7% vs 52.6%, P = 0.043)	High burnout in both ECMO-ICU and non- ECMO-ICU personnel
Arshadi Bostanabad <i>et al</i> [124], 2022	C-S online survey	207 ICU nurses: Male 60 (29%), female 147 (71%); 51.7% married	Psychological empowerment was investigated in Iran, from February 2021 through April 2021	Psychological empowerment questionnaire, demographic information	Positive relationship between clinical competencies and psychological empowerment ( $r = 0.55$ , P < 0.001) and between clinical competencies and work experiences ( $r$ = 0.17, $P = 0.01$ )	Clinical competency is linked to nurse health and quality of care
Zhang et al[9], 2022	C-S online survey	Of 3055 eligible PICUs HCWs, 2109 HCWs completed the survey: Female 1793 (85.2%) and male 316 (14.98%); 35.04% doctors and 64.96% nurses; 1456 (69.04%) married	Online survey was administered to HCWs in the paediatric ICUs of 62 hospitals in China on March 26, 2020	General information, PTSD (IES-R), anxiety and depression (DASS- 21)	970 HCWs (45.99%) reported PTSD symptoms; 39.69% had severe depression, 36.46% anxiety and 17.12% high level of stress. Married HCWs showed higher risk of PTSD than unmarried. PTSD was influenced by marital status, intermediate profes- sional titles and exposure history; while professional titles and going to work during the epidemic were a	During public health emergencies, HCWs need specialised support



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					risk factor for depression	
Kılıç and Taşgıt [125], 2023	C-S survey	93 parents who were not allowed to see their NICU babies as a response to the COVID-19 pandemic: 52 mothers (55.91%) and 41 fathers (44.09%)	Data collected between March and October 2021, in the NICU of a public hospital in Ankara, Turkey	Descriptive questionnaire, anxiety, depression, and stress (DASS-42), and Coping Style (CSS)	Depression subscale was $13.69 \pm 8.86$ , Anxiety subscale $12.11$ $\pm 8.37$ , and stress subscale $19.09 \pm 9.24$ . CSS "self-confident" scale was $2.71 \pm 0.65$ , "optimistic" $2.57 \pm 0.59$ , "helpless" $2.29 \pm 0.62$ , "submissive coping" $2.25 \pm 0.49$ , and "seeking of social support" $2.38 \pm 0.52$ . Participants who received information about their babies' condition by nurses had lower mean CSS "helpless" and "submissive" subscale scores than others	For parents of NICU patients need use psychological empowerment programs to help them adopt active coping strategies to deal with challenges in times of crisis
Pappa <i>et al</i> [126], 2022	C-S online survey	464 self-selected HCWs: 68% female, 32% male; nurses (43%), married (49%)	Online questionnaire sent to ICU HCWs in Greece, from May 2020, to June 2020	Depression (PHQ-9), anxiety (GAD-7) and traumatic stress (IES-R) related to burnout (MBI) and level of fear (NFRS)	Depression was 30%, anxiety 0 25% and traumatic stress 33%. Burnout was high: 65% of HCWs scored moderate-severe on EE, 92% severe on DP and 1% low-moderate on PA	Need for interventions to enhance resilience and support wellbeing in pandemic
Vranas <i>et al</i> [127], 2022	C-S survey	Of 36 eligible intens- ivists, 33 participated: Female 12 (36%), male 21 (64%)	Semi-structured interviews conducted on ICUs of six United states between August and November 2020	Four S (space, staff, stuff, and system) semi- structured interview, related to MD, Burnout and Fear of Becoming Infected	Restricted visitor policies and their perceived negative impacts on patients, families, and staff enhanced MD. Burnout symptoms in intens- ivists were enhanced by experiences with patient death, exhaustion, and perceived lack of support from colleagues and hospitals	COVID-19 pandemic reduced ICU workers' well-being, increased burnout and MD
Voruz et al [128], 2022	C-S survey	102 COVID-19 patients: 26 anosognosic, and 76 nosognosic patients	Tests administered by clinical psycho- logists and question- naires online to patients at HUG	Neuropsychological battery (TMT, Stroop task, verbal fluency and GREFEX, backward digit span43 and backward Corsi test, Test for Attentional Performance, Rey- Osterrieth Complex Figure test, BECLA battery, WAIS-IV, QPC, BRIEF-A), psychiatric (ERQ, BDI-II, STAI, API, PTSD Checklist, GMI, DES, PSS, ESS) olfactory (Sniffing Sticks test battery), dyspnoea (self- report questionnaire), and QoL (SF-36)	Patients with anosognosia for memory dysfunction scored significantly lower on objective cognitive and olfactory measures compared with nosognosic patients; but reported significantly more positive subjective assessments of their QoL, psychiatric status, and fatigue. The number of patients exhibiting a lack of consciousness of olfactory deficits was significantly higher in the anosognosic group. Significantly more patients with lack of consciousness of olfactory deficits were in the anosognosic group, as confirmed by connectivity analyses	Cognitive disorders like anosognosia are related to different COVID-19 symptoms
Green <i>et al</i> [129], 2023	LS survey	24 ICU HCWs: 67% female, 33% male; 79% nurses	At Cedars-Sinai Medical Center (CSMC) in Los	Administered tests were: SAQ, TC, resilience (BRS),	Positive feedback paradigm enhanced resiliency and improve	Need to improve TC and resiliency. A messaging interface



203

			Angeles, CA, United States, over a 6-wk period from June 2020 to July 2020	burnout (BSI)	attitudes toward a TC	to exchange mutual positivity can be a simple, low-cost intervention to provide an effective peer-to-peer support system
Wozniak <i>et al</i> [130], 2022	C-S survey	3461 HCWs. 352 ICU HCWs: Female 23 (66.5%), male 118 (33.5); 242 (68.7%) married. 3109 no-ICU HCWs: Female 2327 (74.9%), male 779 (25.1%); 1973 (63.5%) married	Mental health outcomes and lifestyles change in ICU HCWs and non- ICU HCWs; the study was carried out at HUG and 8 public hospitals in Switzerland, between May to July 2020	Anxiety (GAD-7), depression (PHQ-9), distress (PDI) and Well- Being (WHO-5)	ICU HCW: 41% showed low well-being, 46% symptoms of anxiety, 46% depression and 22% peritraumatic distress. ICU HCWs scored higher than non- ICU HCWs on all tests ( P < 0.01). Working in ICU rather than in other departments, being a woman, the fear of catching and transmitting COVID-19, anxiety of working with COVID-19 patients, work overload, eating and sleeping disorders can enhance worse mental health outcomes	High prevalence of anxiety, depression, peritraumatic distress and low well-being during the first COVID-19 wave among HCWs, especially ICU HCWs
Tariku <i>et al</i> [ <mark>131</mark> ], 2022	C-S survey	402 of 423 eligible participants, responded to survey: Male 233 (58.0%), female 169 (42.0%); 137 (34.1%) married	HCWs mental disease was investigate in Ethiopia, during the coronavirus disease 2019	Survey assessing the presence of common mental disorders (SRQ- 20)	22.6% of mental disorders in HCWs. Being female, married, having had direct contact with COVID-19 patients, working in COVID-19 treatment centres and ICU, having any symptoms of COVID-19, and poor social support were a risk factor for mental disorders in HCWs	On-fourth to one-fifth of Ethiopian HCWs have a mental disorder during COVID-19 pandemic
Wang et al [ <mark>132</mark> ], 2021	C-S telephone survey	Of 267 eligible patients, 199 COVID- 19 patients participated in the survey; male 93 (46.7%), and female 106 (53.3%); age 42.72 $\pm$ 17.53; 163 $\pm$ 81.9 married	PTSD symptoms in COVID-19 survivors investigated with telephone survey 6 mo after hospital discharge in 5 hospitals of 5 Chinese cities, August to September 2020	Somatic symptoms after discharge (PHQ-15), PTSD (PTSD-8)	7% of participants having PTSD; socio- demographic status, hospitalization experiences, post- hospitalization experiences, and psychological status enhanced PTSD symptom	Effects of COVID-19 on survivors can also involve psychological aspects and last for many months after recovery
Moll <i>et al</i> [133], 2022	LS survey	Pre-pandemic survey, 1233 HCWs, of which 572 responded (46.5%): Female 408 (71.3%), male 127 (24.9%). Pandemic survey: Of 1422 clinicians, 710 (49.9%) responded to survey; female 529 (74.5%), male 146 (20.5%)	Burnout data collected March to May 2017 and June to December 2020, during the pandemic at Emory University, Atlanta (Georgia)	Burnout (MBI)	46.5% (572 respondents) in 2017 and 49.9% (710 respondents) in 2020 shown higher burnout symptoms. Nurses' burnout prevalence increased with pandemic from 59% to 69% ( $P < 0.001$ ), with increased EE and DP, and decreased PA. Other HCWs showed no differences in burnout levels between 2017 and 2020	Nurses are more at risk for burnout after the beginning of the COVID-19 pandemic
Groenveld <i>et al</i> [134], 2022	LS survey	Of 48 post-COVID-19 patients, 40 completed the survey: Female 68%, male 32%; median age 54 yr	Feasibility of virtual reality exercises at home for post- COVID-19 condition was investigated, between July 2020 and February 2021, in the southeast of the Netherlands	VR platform to reduce stress and anxiety and promote cognitive functioning	70% of participant report an advertising event during VR, but only 25% recall these events. 75% reports VR as having a positive influence on their recovery	VR physical exercises at home is feasible and safe with good acceptance
Lovell et al	LS online	240 nursing staff, 8	A before-and-after	PERMA-Profiler,	Well-being scores after	Study findings may



[ <mark>135</mark> ], 2023	Survey	permanent ICU consultants, 32 rotational registrars, 10 allied health staff members, and a team of 10 administrative and 20 operational support staff members of ICUs	interventional online study was conducted over a 2-yr period, between 2019 and 2021, in a 30-bed level-3 ICU within an Australian metropolitan teaching hospital	questionnaire to assess overall well-being (1 item), negative emotions (3 items: Sadness, anger, and anxiety), loneliness (1 item), and physical health (3 items)	the intervention were not statistically different from BL. There are three key categories: Boosting morale and fostering togetherness, supporting staff, and barriers to well-being	inform strategies for improving ICU staff members' well-being
Sun <i>et al</i> [ <mark>136</mark> ], 2022	C-S online survey	524 ICU nurses provided 340 valid questionnaires (64.89% actual rate); 313 females, 27 males; 229 (67.35%) married	Online questionnaire sent to ICU nurses of 15 Chinese provinces, December 2020 to January 2021	Tested calling (BCS) and resilience (BRCS) as related to thriving at work (TWS) and ethical leadership (ELS)	All variables strongly and positively correlated with each other. The high resilience group was closely associated with calling after adjusting for age, gender, marital status, and other factors	Nurses' resilience underlies their promptness to stick to their duty and calling
Chommeloux <i>et al</i> [137], 2023	LS survey	Of 80 eligible patients, 62 patients supported by ECMO for severe ARDS were included in the study	Psychological disorders of ICU patients assessed at 6 and 12 mo after ECMO onset, March to June 2020 in 7 French ICUs	Anxiety, depression, PTSD, and QoL	Mental health is one of the most impaired domains: 44% of patients had significant anxiety, 42% had symptoms of depression and another 42% were at risk of PTSD, one year after admission to an ICU	Despite partial physical recovery one year after COVID-19, psychological function remains impaired

Calling, commitment to one's duties due to internal or external value system prompts (must serve society and others, because of a supreme entity recommends so or because of one's own beliefs). AACCN: American Association of Critical Care Nurses; AMC: Academisch Medisch Centrum; API: Apathy Motivation Index; ARDS: Acute respiratory distress syndrome; BCS: Brief Calling scale; BECLA: Batterie d'évaluation Cognitive du Language; BDI-II: Beck Depression Inventory Inventory-Second Edition; BL: Baseline; BRCS: Brief Resilient Coping Scale; BRIEF-A: Behaviour rating inventory of executive function; Brief COPE: Brief Coping Orientation to Problems Experienced; BRS: Brief Resilience Scale; BSI: Burnout Scale inventory; CBCL: Child Behaviour Checklist; CBI: Copenhagen Burnout Inventory; CD-RISC2: Two-item Connor-Davidson resilience index; CI: Confidence interval; C-S: Crosssectional; CSS: Coping Stress Scale; DASS-21: Depression, Anxiety, and Stress Scale; DES: Dissociative Experience Scale; DP: Depersonalisation scale of the Maslach Burnout Inventory; ECMO: ExtraCorporeal Membrane Oxygenation; EDMCQ: Ethical Decision-Making Climate Questionnaire; EE: Emotional exhaustion of the Maslach Burnout Inventory; ELS: Ethical leadership scale; EPDS: Edinburgh Postnatal Depression Scale; EQ-5D-3L: Euro quality of life; ERQ: Emotion Regulation Questionnaire; ESS: Epworth Sleepiness Scale; FS-ICU: Family satisfaction with the intensive care unit survey; GAD-7: General Anxiety Disorder-7 Item; GMI: Goldberg Mania Inventory; GREFEX: Groupe de Réflexion sur l'Évaluation des Fonctions Exécutives battery; GSES: General Self-Efficacy Scale; HADS: Hospital Anxiety and Depression Scale; HCAHPS: Hospital Consumer Assessment of Healthcare Providers e Systems; HCP(s): Healthcare professional(s); HCW(s): Healthcare worker(s); HPCD: Healthcare providers; HUG: Geneva University Hospitals; ICU: Inventory of Callous-Unemotional Traits; ICU(s): Intensive care unit(s); ICU-VR: Intensive care unit - virtual reality; IES-R: Impact of Event Scale-Revised; IPAT: Intensive Care Psychological Assessment Tool; ISI: Insomnia Severity Index; K10: Kessler Psychological Distress Scale; LS: Longitudinal survey; MBI: Maslach Burnout Inventory; MBI-HSS: Maslach Burnout Inventory Human Services Survey for Medical Personnel; MD: Moral distress; MMD-HP: Measure of Moral Distress for Healthcare Professionals; -SP: Spanish version; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; MPAS: Maternal Postnatal Attachment Scale; NICU: Neonatal intensive care unit; NFRS: Numerical fear rating scale; PA: Personal accomplishment of the Maslach Burnout Inventory; PCL-5: Post-Traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders-5th Edition; PCQ: Psychological Capital Questionnaire; PICS: Post-intensive care syndrome; PICS-F: Post-intensive care syndrome-Family; PICU: Paediatric intensive care units; PDI: Peritraumatic Distress Inventory; PHQ-9: Patient Health Questionnaire-9; PHQ-ADS: Patient Health Questionnaire Anxiety and Depression Scale; PM: Pearlin Mastery Scale; PROQOL-5: Professional Quality of Life Scale; PsyCap: Positive psychological state, psychological capital; PSS-10: Perceived Stress Scale-10; PSS:NICU: Parental Stressor Scale:Neonatal intensive care unit; PTSD: Post-traumatic stress disorder; PTSS: Post-traumatic stress symptoms; QPC: Cognitive Complaints Questionnaire; QoL: Quality of life; Q3PC: Cognitive Screening, European AIDS Clinical Society cognitive screening questions; RESE: Regulatory, Emotional Self Efficacy Scale; RS-14: 14-item Resilience Scale; RSA: Resilience Scale for Adults; SAQ: Safety Attitude Questionnaire; SAS: Self-rating Anxiety Scale; SCL-90: Symptom Checklist 90; SDS: Self-rating Depression Scale; SFSW: Finnish Strongest Families Smart Website; SF-36 Questionnaire: Short Form Health Survey-36 item questionnaire; SRQ-20: Self-Reporting Questionnaire; SRSS: Self-rating sleeping situation scaling; TC: Teamwork climate; TMT: Trial making test; TSQ: Trauma Screening Questionnaire; TWS: Thriving at work scale; VAS: Visual Analogue Scale; VR: Virtual reality; WHO-5: World Health Organization Well-Being Index; WAIS: Wechsler Adult Intelligence Scale-Fourth Edition; WSAS: Work and Social Adjustment Scale.

> infection[32]. However, ICU patients with COVID-19 on clozapine did not differ for outcome from those receiving other antipsychotics[33].

#### Psychological implications of being hospitalised in an ICU: ICU post-discharge

As previously mentioned, the ICU exposes patients to stressful experiences with potential long-term repercussions. People who overcome a critical phase of illness and ICU admission can develop a postintensive care syndrome (PICS), a cluster of physical, cognitive, and mental impairments observed after ICU hospitalisation; this shares clinical features with depression, anxiety, and PTSD[34]. The main risk factors for developing PICS can be classified as interventional, environmental, and psychological factors, including treatments such as mechanical ventilation, unfamiliar environment, and severe stress

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Figure 1 Results of our database searches for psychological consequences of the coronavirus disease 2019 pandemic on intensive care units and possible psychological interventions according to the recommendations of the Preferred Reporting Items for Systematic Reviews statement. <sup>1</sup>Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). <sup>2</sup>If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. COVID-19: Coronavirus disease 2019.

experienced during hospitalisation[26,35].

The emergence of the COVID-19 pandemic has increased the number of patients exposed to risk factors of PICS and who require intensive care and aftercare<sup>[20]</sup>. Furthermore, a COVID-19 patient in the ICU who develops acute respiratory failure, is likely to be exposed to increased use of sedation and limited physical therapy in addition to mechanical ventilation. Therefore, critically ill COVID-19 patients have high chances of developing PICS[23]. Patients with COVID-19 who were treated in the ICU and survived have higher risk due to visit restriction, prolonged mechanical ventilation, higher sedative exposure, and reduced availability of physical therapy [36], but they are also at risk of developing prolonged cognitive dysfunction[37]. Generally, after ICU hospitalisation, mental health problems are very common and often impact health-related quality of life. These include anxiety, depression, and PTSD, as well as guilt, reduced libido, social isolation, irritability, and low confidence [38].

During the pandemic, PTSD appears to have a high incidence, of about 30% [39], characterised by symptoms such as hypervigilance, avoidant behaviour, and re-living the traumatic experience. In particular, hypervigilance may result in panic responses, irritability, and altered sleep-wake cycle, or in overconfident behaviour or, as in the case of COVID-19 patients, with concern about contagion and reexposure[23]. Sometimes patients may present with disturbing and intrusive memories related to hospitalisation. Specific stimuli, such as smells, images, and sounds, may also activate memories. In addition, some patients may be inclined to avoid any medical environment after ICU admission[23].

COVID-19 and its complications, long hospital stay, and side effects of medications lead to reduced physical capacity that can affect mood. Recent literature has shown that both patients with COVID-19 and those without have high rates of post-hospitalisation depression[40], as well as anxiety and insomnia[41]. However, ICU patients with COVID-19 and ICU patients without COVID-19 did not differ on psychological distress, *i.e.*, cumulative symptoms of PTSD, anxiety, and depression three months after discharge, thus suggesting not to focus exclusively on COVID-19-positive patients[42].

During the COVID-19 pandemic, another major problem was social stigma<sup>[43]</sup>. In some cases, patients experienced guilt or shame for passing the disease on to others, with ensuing difficulty in



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returning to their customary daily lives<sup>[23]</sup>. Multidisciplinary critical care, in addition to preventing imminent death, lays the foundation for improving patients' overall long-term survival experience[44].

### Interventions aiming at addressing the psychological implications of COVID-19: Interventions with patients

In general, in patients admitted to the ICU, it is important to consider not only physical health but also mental health. This was especially important in COVID-19 patients, as high mortality and unpredictability had peculiar psychological meanings and consequences [45]. Attention is also due to patients with a previous history of mental disorder, as social isolation and estrangement can make the individual particularly vulnerable to psychopathological breakdown events. For this reason, during the pandemic, healthcare personnel has worked closely with psychologists to monitor the psychological condition of patients[45]. In this study, an in-person psychological intervention aimed at preventing unpleasant outcomes was encouraged in the most severe cases, which can result in aggression, self-injurious behaviour, and suicide attempts. Psychological support, taking care to use individual precautions aiming at reducing the risk of infection, was based on the assessment of the patient's prior state of mental health (traumas, previous episodes of self-harm, etc.) and his/her social and family environment. It is also important to take into account the potential impact of COVID-19 on the patient's socioeconomic status[45].

In some ICUs, interventions such as music therapy or meditation were performed to mitigate the anxiety and distress of patients[46]. The addition of available technological devices such as TV, laptop, or radio may alleviate the patient's sense of isolation[46]. Sometimes psychological support for COVID-19 patients in ICU has been conducted remotely, through the use of digital tools. In particular, phones and the internet have proven to be effective in treating psychological issues[45]. Technology has also allowed ICU patients to keep in touch with their relatives, with tablets and mobiles provided for this purpose[46]. As mentioned above, patients may experience psychological sequelae even after discharge from the ICU. Early psychological interventions can support the patient in regaining ordinary daily routine. To treat PTSD, anxiety, worry, and panic reactions the use of cognitive behavioural therapy or metacognitive therapy could be given a trial, as these techniques have shown some efficacy in all these conditions[47,48]. In this framework, psychoeducational interventions are used to teach the patient to manage possible stress reactions<sup>[49]</sup>. Online support groups led by a psychologist can help COVID-19 survivors to share emotions related to the period experienced in the ICU[23].

# Interventions aiming at addressing the psychological implications of COVID-19: Interventions with family members

Family members of patients admitted to the ICU are at high risk of developing psychological disorders. Anxiety, depression, PTSD, and other trauma-related reactions are the most common. In the literature, this clinical condition is called PICS-family [26,50]. During the COVID-19 pandemic, these symptoms can exacerbate due to the isolation family members suffer and the impossibility to get into direct contact with their loved ones. In addition, family members are often positive for COVID-19 and isolated at home, and this generates a sense of helplessness and loneliness in patients[45,51]. Relatives play a fundamental role, especially when the patient is dying because they have to make decisions for him, or to defend his/her interests[50].

For these reasons, it is important to design interventions that help preventing psychological dysfunctions among family members and support them in decision making during this difficult moment. In this frame, the psychologist is responsible for establishing clear criteria, that are shared with all health care professionals, to determine whether and how to intervene<sup>[52]</sup>. The psychological needs of family members to consider in the development of these interventions are the following: The need to be informed and updated about the medical condition of their loved one, the need to be emotionally supported by receiving reassurance and listening, the need to maintain a connection with the patient, even at a distance, and the need to receive support during the grieving process in case of death of their loved one[53]. In all these situations, it is important not to view as pathological any emotional reactions of family members but to consider them as being normal in the context of the difficult moment they are experiencing<sup>[52]</sup>.

Most interventions aimed at family members used digital tools to reduce the possibility of transmitting COVID-19. Phone and video calls were the preferred tools for addressing relatives' psychological needs [54,55]. However, in case of a high psychopathological risk, family members were allowed to access the ICU. For instance, in-person visits accompanied by the psychologist were encouraged to preserve the relationship between the patient and his/her relatives. Personal protective equipment was used to protect all those involved[53].

## Interventions aiming at addressing the psychological implications of COVID-19: Interventions with health workers

During the pandemic, intensive care workers, exposed to a high workload and high risk of infection, reported states of severe anxiety, insomnia, irritability, anxiety, and fear[56]. For this reason, ICU



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healthcare professionals also seemed to be at serious risk of developing a burnout syndrome. The main factors associated with this risk include weak communication among staff members as well as organisational difficulties<sup>[57]</sup>.

This highlighted the need to develop interventions aimed at ensuring ICU health care professionals' well-being and preventing emotional distress. These interventions must be designed on the basis of certain primary needs, *i.e.*, the need to feel safe, the need to belong to a unit group with clear, welldefined, and shared goals, the need to be listened to and, finally, the need to emotionally decompress [53]. The literature has confirmed the need for psychologists and psychological interventions in ICUs even during the pandemic; in fact, the applicability of psychological knowledge and skills to staff wellbeing before and during the pandemic were shown for example to promote teamwork and group cohesion and also to lead defusing activities<sup>[53]</sup>. Indeed, group defusing can allow for reframing the meaning of a traumatic event by reducing its emotional impact<sup>[58]</sup>. Defusing is the process of helping a disaster victim through the use of brief conversation and may help survivors in shifting from a survival mode to focusing on practical steps to reach stability again and to better understand the thoughts and feelings linked to their experience of the disaster[59]. Defusing involves professionals in three stages with different functions. Introduction is the general presentation of the intervention to clarify and engage participants. Exploration is the moment in which traumatic experiences related to working in ICU emerge or are extracted, through the recollection of particular thoughts and emotions. Information aims to normalise stress reactions by providing continuous support, reassurance, and coping strategies to address emotional distress<sup>[60]</sup>. As the pandemic is still persisting or returning under new forms, rapid, pandemic-specific assessment tools may be needed to allow better evaluation of patients' stress in the ICU[61].

It may also be useful to set up a room for the ICU healthcare professionals to allow them to offload tensions by promoting physical and psychological decompression[53]. Relaxation techniques showed efficacy in managing stress, preventing burnout, and increasing work motivation, in particular autogenic training[62]. Relaxation techniques during COVID-19 confirmed their effectiveness as procedures apt to improve quality of life, work motivation, burnout and stress perceptions within the emergency department team[63].

Psychological interventions in this field should be considered as preventive and proactive health interventions, rather than as treatments for psychopathological problems, helping individuals to effectively express their own resources. Emergency psychology has offered appropriate techniques to achieve this goal[64]. Summarising, COVID-19 pandemic has highlighted the importance of frontline workers' mental health and the need to support the presence of psychologists in ICUs; in this way, healthcare workers could experience more relief from the many responsibilities that hamper the effectiveness of their work[45].

#### Humanised technology during COVID-19 pandemic: Digital communication

During COVID-19 pandemic in ICUs, patients' possibilities to see their relatives were reduced[65]. In this context, digital communication proved to be a very effective tool for facilitating communication despite visitation restrictions [66]. Digital interactions can bring significant benefits in terms of emotional support and communication of information to family members, and also in terms of patient recovery and increased ICU staff moral[22].

Recent studies have mainly explored the impact of digital interventions on family members: COVID-19 pandemic has reduced the possibility to see the patient and directly interfacing with the medical teams to receive clinical updates. In general, allowing family members to use video calls to see their loved ones has proven to be a good way to alleviate the discomfort of physical distance[54]. Other studies show that family members report mixed feelings about video calls with the patient. For example, they wanted the opportunity to see the patient but reported that the images of their loved ones lying down were upsetting. This fact underlines the importance of assessing each individual family for burden and preferences[67].

Regarding communication between family members and the medical team, phone calls were used as a tool to communicate quick information [54]. Video calls, instead, were preferred to align doctors and family members' perspectives on the patient's condition. Doctors' doubts about their capacity to transmit empathy at a distance were denied by family members' opinions, who reported a sense of closeness when using a telephone or a video, despite the distance[66]. An Italian team developed ten statements and two checklists to enable medical teams to communicate effectively with family members, that could be also used as guidelines[68].

It is appropriate at this point to talk about the barriers limiting the use of digital tools in intensive care. In fact, family members do not always have the necessary skills to access the set video platforms or they not even possess a suitable technological device. Problems with the Wi-Fi connection and, in some cases, lack of time and of specific training in the staff add to the above-mentioned barriers[22].

#### Humanised technology during COVID-19 pandemic: VR interventions

Several ICUs during the COVID-19 pandemic used VR interventions to deal with patients' psychological symptoms such as anxiety, stress, PTSD, and depression[69]. VR bring the user into a "realistic, immersive multi-sensory environment" through computer-generated visuals[70] and this digital tool



proved to be effective in reducing anxiety and pain, by distracting the user and providing a relaxing experience[71]. In the presence of full-blown PTSD, VR can subsequently be used as 'exposure therapy'; it can promote deep involvement and activation of the user's traumatic memory of fearful stimuli[72], such as those experienced in an ICU[73]. For this reason, VR exposure therapy turned out to be also one of the most popular game-based digital interventions for the treatment of depression caused by fear [74], although in PTSD patients, it did not reduce the anxiety and did not differentiate from other standard treatments[75].

The use of VR as a therapy for the psychological sequelae of COVID-19 patients has some important advantages. First, it could be helpful for reconstructing the phases the patient experienced during the ICU hospitalisation, so to adjust to unpleasant memories, as proposed in a protocol[76]. Second, it can be used remotely to respect social distance needs. Third, it allows to manage more patients at the same time. However, VR implementation should overcome some barriers. These mainly concern the organization of VR interventions at home and remote support. For this purpose, it is necessary to design a toolkit that is safe, comfortable, and easily accessible[70].

Other possible applications of VR during COVID-19 pandemic in ICU include its use to rapidly upskill healthcare professionals and to reduce perceived interindividual stress[56], but also to improve communication of information about ICU treatment and ICU environment to patients' relatives (ICU-VR-F)[77].

#### Current and future perspectives

The present review identified 65 studies targeting COVID-19 in ICUs and the ensuing psychological problems, of which 43 focused on the role of the psychologist in increasing team cohesion, reducing distress of patients, relatives, and staff and preventing or reducing burnout in the latter, and highlighting that during the COVID-19 pandemic the psychologist is playing an increasingly important role within the ICU.

Special psychological needs emerged for the patient and his/her relatives, and also for healthcare professionals. Frequently psychologists acted promptly through interventions aimed at providing psychological support to all involved and facilitating communicative exchanges, despite the restrictions imposed. In this way, the medical team members were relieved of much workload and were free to focus mainly on the medical aspects of the cases inside the ICU[74].

As the coordinated interventions of the medical team and the psychologist has proven to be very effective in patient care and in promoting patient well-being, it is desirable that the presence of the psychologist becomes a structural feature of ICUs and other hospital areas that deal with emergencies. Based on the literature, digital tools were much used in ICUs during the COVID-19 pandemic to promote communication between patients, family members, and healthcare professionals[56,77]. The addition of new learning-based approaches, such as deep learning or machine learning[78] may help people overcoming this difficult moment by implementing psychological techniques[79]. Since the risk of contagion is still high, they can still be used - when in-person visitation is not strictly necessary - to make communication easier.

VR is a particular technological tool, which is useful in treating psychological sequelae of ICU inpatients. It is mostly used during the COVID-19 pandemic and can significantly improve the mental health of previously hospitalized patients. For their numerous benefits, digital tools, including VR, should be commonly used in ICUs. For this to be possible, however, it is necessary to overcome the previously outlined limitations and barriers.

#### Limitations

We did not include in our review other databases that could have accrued our results. The obtain results used diverse methodologies, leading to heterogeneity which did not allow us to perform sound statistical analyses such as meta-analyses or meta-regressions. We did not include specific distinctions regarding the target audience (geriatric patients, neonatal ICUs, or patients with disabilities), so we collected all studies independently from methodology. As a result, we cannot make generalizations regarding the efficacy or effectiveness of the mentioned interventions. Some of these interventions could be modified or adapted according to patients' needs.

#### CONCLUSION

In this review, we analysed the role of the psychologist in the ICU during the COVID-19 pandemic, focusing on the interventions with patients, family members, and healthcare professionals. We chose a narrative review of the literature because currently there is dearth of studies focusing on the psychologist's work in ICUs during the public health emergency represented by COVID-19. This fact, and the fact that the methodologies of the studies we were able to gather are heterogeneous, make the field not meta-analysable. Since the COVID-19 pandemic is not still over, we need further studies to support the standpoint that psychological support in the ICU is fundamental.

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# **ARTICLE HIGHLIGHTS**

#### Research background

Coronavirus disease 2019 (COVID-19) upset intensive care unit (ICU) function, increasing risk for psychological distress during and after hospitalisation. This paved the way for psychological interventions to support patients in ICUs.

## **Research motivation**

To alleviate the increased workload and burden of ICU staff through psychological interventions.

# **Research objectives**

We carried out a systematic review of the psychological issues raised in ICUs during the COVID-19 pandemic which concerned patients, their relatives, and the ICU staff (physicians, nurses, and auxiliary staff) as well as of the possible psychological treatments that could improve psychological measures.

#### **Research methods**

Search of PubMed and ClinicalTrials.gov databases, establishing inclusion/exclusion criteria and deciding eligibility through Delphi rounds among involved researchers.

## **Research results**

We found 65 eligible articles, which summarised. Results point to increased perceived stress and psychological distress in staff, patients and their relatives. Some psychological interventions hold promise.

#### **Research conclusions**

Psychological programmes to improve psychological measures in ICU patients, relatives, and staff may enhance ICU functional efficiency.

## **Research perspectives**

The role of interventions using digital tools and virtual reality may pave the way to a better work climate within ICUs, with psychologists gaining a liaison role within the staff.

# FOOTNOTES

**Author contributions:** Monti L and Marconi E contributed equally to this work and share first authorship. Monti L, Marconi E, and Bocci MG conceived the review; Kotzalidis GD, Mazza M, Galliani C, and Tranquilli S made literature searches and shaped the review; Vento G and Conti G implemented the database; Monti L, Marconi E, Bocci MG, Kotzalidis GD, Mazza M, Galliani C, and Tranquilli S provided the first draft; Sani G, Antonelli M, and Chieffo DPR supervised the writing of the manuscript; Monti L, Tranquilli S, and Kotzalidis GD provided the final draft; and all authors read and approved the final draft and revision.

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