# World Journal of

# *Psychiatry*

# World Journal of Psychiatry

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# Electroconvulsive therapy: 80 years old and still going strong

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## Abstract

Electroconvulsive therapy (ECT), which is among the oldest and most controversial treatments in the field of psychiatry, has its 80th birthday this year. In this brief historical overview, the discovery of the therapeutic effects of convulsive therapy by Laszló Meduna, and the circumstances that motivated Ugo Cerletti and Lucio Bini to use electricity as a means of seizure induction are described. Meduna's original theory about the antagonism between epilepsy and schizophrenia has been replaced by hypotheses on the mechanism of action of ECT. The position of ECT in modern psychiatry is also discussed with special attention to its most important clinical indications, including catatonia, and pre- and postpartum affective and psychotic states that are responsive to ECT and in which ECT may even be lifesaving. Adverse effects and comparison of ECT with recently developed brain stimulation methods are also reviewed. The negative media portrayal of ECT and its earlier misuse may have contributed to its negative professional and public perceptions indicated repeatedly in attitude surveys. This negative attitude has played an important role in the decreasing use of ECT in the developed world and a reduction in access to ECT, which constitutes a violation of psychiatric patients' right to an effective treatment.

**Key words:** Electroconvulsive therapy; History; Indications; Utilization; Attitudes

**Core tip:** Electroconvulsive therapy (ECT), which is among the most controversial psychiatric treatments, has its 80th birthday this year. The introduction of convulsive therapy to psychiatry and changes in seizure induction from chemical to electrical are

outlined. The place of ECT in contemporary psychiatry, particularly its most important clinical indications, is briefly discussed. Negative media representation and historical misuse are likely to have contributed to negative professional and public attitudes towards ECT and, consequently, it decreased use. Recent limitations of access to effective treatment in many parts of the world constitute a violation of patients' rights.

## INTRODUCTION

### Brief historical overview

Electroconvulsive therapy (ECT), one of the oldest treatment methods in the field of psychiatry, was first introduced 80 years ago in Rome when Ugo Cerletti and Lucio Bini used an electric current to elicit an epileptic seizure for therapeutic purposes[1]. However, this was not the first use of an epileptic fit to treat mental illness. The idea of inducing epileptic seizures to treat patients was first proposed by Meduna[2], a Hungarian neuropathologist and psychiatrist.

### History of chemical convulsive therapy

The idea that a disease could be cured by inducing another disease was proposed by Wagner-Jauregg, who observed that high fever caused symptomatic improvement in general paresis of the insane and infected syphilitic patients with malaria to induce repeated bouts of high fever. In 1927, Wagner-Jauregg was awarded the Nobel Prize for developing the first effective biological treatment in the field of psychiatry[3]. In the late 1920s, Meduna[4], a researcher at the beginning of his professional career in the psychiatric department of the University in Budapest, was interested in the histopathology of epilepsy. Meduna[4] observed that in the brains of epileptic patients, glial cells occupied the spaces left by lost neurons. In 1931, Hechst *et al*[5], his departmental colleague who studied the histopathology of schizophrenia, described a reduction in the number of glial cells in the brains of schizophrenia patients. This finding strongly contrasted Meduna[4]'s observations in the brains of patients with epilepsy.

Besides these neuropathological findings, clinical observations also appeared to indicate antagonism between epilepsy and schizophrenia. Nyírö *et al*[6] reported that the rate of schizophrenia was significantly lower among patients with epilepsy than in the general population. Meduna[4] was also intrigued by a report about two schizophrenia patients whose conditions remitted following episodic epileptic seizures[7]. A report in which only 8 of 6000 schizophrenia patients suffered from epilepsy also appeared to support the antagonism theory[8]. By then, Meduna[4] had become convinced of an antagonism between schizophrenia and epilepsy, as he concluded in his autobiography: "...if I can stimulate epileptic seizures in schizophrenics then these... will alter the chemical and humoral processes in the body in a way... that the abatement of the disease will be made physiologically possible"[9].

Meduna[10] planned to induce a seizure using a chemical agent and proceeded to test the safety and effectiveness of several epileptogenic compounds for this purpose. Finally, Meduna[10] identified camphor as the compound that satisfied his requirements. On January 2, 1934, he conducted the first human experiment involving intramuscular camphor injections[11]. In the 2 subsequent years, Meduna[12] treated more than 100 patients, of whom half recovered or significantly improved.

### Introduction of electrically induced seizures

Although camphor was later replaced with intravenous cardiazol, chemical seizure induction remained somewhat unpredictable, with considerable interpersonal variance. Furthermore, the time interval between the injection and seizure was extremely stressful for the patients. These difficulties led Ugo Cerletti and his colleagues at the university psychiatric clinic in Rome to search for an alternative means of seizure induction.

Prior to his arrival in Rome, Cerletti already had some experience with electricity, as he had used an electric current in animal studies of epilepsy in Genoa[13]. In Rome,

Cerletti continued these studies with the involvement of his assistant, Lucio Bini. The idea of using electricity to induce seizure first occurred to Cerletti and Bini when they witnessed cardiazol therapy in Vienna[14]. After defining the parameters of a safe electric stimulus through animal studies, they performed the first electric seizure induction in a psychotic patient named Enrico X on April 11, 1938. Although the initial stimulation did not result in an epileptic seizure, stimulation at a higher voltage induced an eighty seconds tonic-clonic seizure on April 20. After 11 further treatments, Enrico recovered and was released from the university psychiatry clinic[14]. Although the technical details of electric seizure induction were published shortly after the first treatment[1], their results with electroshock therapy were not summarized until 2 years later, which attests to the careful attitudes of the inventors[15].

## MECHANISM OF ACTION

Subsequent research could not confirm Meduna[12]'s hypothesis on antagonism between epilepsy and schizophrenia, and the mechanism of action of ECT remains to be elucidated. In response to frequent criticism regarding the latter point, significant efforts have been made to clarify the mechanism underlying ECT. One theory explains the therapeutic effects of ECT by referring to its effects on neurotransmitters, particularly the serotonin and dopamine systems[16]. Another theory conceptualizes depression as a pro-inflammatory state wherein ECT acts on cytokines, thereby treating the inflammation and normalizing mood[17]. Furthermore, clinical evidence indicates a hypertensive surge during ECT that causes transient blood-brain barrier permeability which may also play a role in its therapeutic effect[18]. Animal studies suggest that electrically induced seizures have epigenetic effects that may also add to the clinical effectiveness of ECT[19]. Finally, the most promising new findings appear to involve ECT-induced changes in structural brain plasticity. Recent studies also identified ECT as a strong stimulator of neurogenesis by promoting the proliferation of stem cells[20].

## PLACE OF ELECTROCONVULSIVE THERAPY IN MODERN PSYCHIATRY

Notwithstanding major advances in psychopharmacology and several recently introduced brain stimulation methods, ECT is not a closed chapter in the history of psychiatry but is rather a treatment modality used widely throughout the world[21]. ECT has well-defined indications[22,23] and remains one of the most effective treatment methods in psychiatry[24].

### ECT in the treatment of affective disorders
Meduna[12] considered convulsive therapy as a treatment for schizophrenia. However, it was soon found to be even more effective for the treatment of affective disorders[25]. Currently, major depression is the first indication for ECT[22,23,26]. Between the 1960s and 1980s, several studies investigated the efficacy of ECT. The majority of randomized controlled studies confirmed the superiority of ECT relative to sham ECT or antidepressants for the treatment of affective disorders, and these findings were supported by meta-analyses[24,27-29].

Independent of its antidepressant effects, ECT also has a clear anti-suicidal effect[30]. Therefore, ECT is recommended as the first choice of treatment for patients at a high risk of suicide[31].

In pharmacotherapy-resistant patients, maintenance ECT proved to be an effective alternative in relapse prevention[32].

### ECT in psychosis and schizophrenia
In several developing countries, including India[33] and China[34], the two most populous nations, schizophrenia remains the first indication for ECT. Although antipsychotics are equally effective for schizophrenia[35], financial reasons may explain the common use of ECT in this patient population[36]. Unmodified ECT is still practiced in the developing world due to limited financial resources[34].

Resistance to pharmacotherapy remains a serious problem in the treatment of schizophrenia[37]. ECT could be an augmentation strategy to enhance the effects of antipsychotic drugs[38]. ECT could also augment clozapine in clozapine-resistant patients[39]. Psychotic conditions that respond well to ECT include catatonia and pre- and postpartum psychotic states[40]. Combining maintenance ECT with antipsychotic

medications is an effective strategy for relapse prevention in schizophrenia[41].

### Adverse effects of ECT

From the beginning, psychiatrists' intentions was to make ECT as safe as possible by decreasing its side effects to the minimum. As a result of these efforts, muscle relaxation[42] and anaesthesia[43] were introduced by the early 1950s. The importance of minimizing cognitive side-effects was recognized early and unilateral stimulation technique was introduced as early as 1954[44]. Recent efforts to further reduce cognitive side effects focus on changing from brief to ultra brief pulse stimulation[45]. While a few individual testimonies reported longlasting and severe memory disturbances after ECT[46], extensive psychological tests could not detect significant memory deficits beyond six months following a course of ECT[47].

## ATTITUDES TOWARDS ECT

ECT is probably the most controversial form of treatment in medicine. It has been banned in certain parts of the world[48] while remaining widely practiced in other countries[49]. Besides economic and socio-cultural factors, historical contexts, such as the misuse of ECT during the Nazi era[50], might have contributed to the negative perceptions of this form of therapy. Misleading media representations of ECT have contributed further to this negative image. For example, the portrayal of ECT in the film "One Flew over the Cuckoo's Nest" by Milos Forman, has had a huge and long-lasting effect on perceptions, although other movies and social media have also presented a grossly distorted image[51]. Recently, however, a slow tendency towards a more objective depiction of ECT has been observed[52]. In contrast to its negative image in the media and the public misperception[53,54], attitudes towards ECT in patients, relatives and the mental health professionals are mainly positive[55,56].

## COMPARISON OF ECT WITH RECENTLY DEVELOPED BRAIN STIMULATION METHODS

In the last two decades several new neurostimulation methods have been introduced in psychiatry mainly from the field of neurology. These include transcranial magnetic stimulation (TMS), vagus nerve stimulation, deep brain stimulation, transcranial direct current stimulation. Most of these new techniques were introduced to treat major depression. To date, only TMS has been compared with ECT in randomized controlled trials, which consistently proved the superior efficacy of ECT in the treatment of major depression[57]. No other neurostimulation technique has a firm place in the treatment algorithm for major depression[58].

## CONCLUSION

After 80 years, electroconvulsive therapy remains one of the most effective treatment modalities in psychiatry. However, the popular image of ECT is controversial and mainly negative. This perception can sometimes hinder its use, thereby violating the rights of patients to access to an effective and sometimes lifesaving treatment.

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*REVIEW*

# Comorbidity of bipolar and anxiety disorders: An overview of trends in research

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## Abstract

Over the last three decades burgeoning research has shown that anxiety disorder comorbidity is not only highly prevalent in bipolar disorder (BD), but it also adversely impacts the course, outcome, and treatment of BD. The present review provides an overview of the current trends in research on comorbid anxiety and BDs based on prior reviews and meta-analyses (*n* = 103), epidemiological surveys, and large-scale clinical studies. The results reiterated the fact that at least half of those with BD are likely to develop an anxiety disorder in their lifetimes and a third of them will manifest an anxiety disorder at any point of time. All types of anxiety disorders were equally common in BD. However, there was a wide variation in rates across different sources, with most of this discrepancy being accounted for by methodological differences between reports. Comorbid anxiety disorders negatively impacted the presentation and course of BD. This unfavourable clinical profile led to poorer outcome and functioning and impeded treatment of BD. Despite the extensive body of research there was paucity of data on aetiology and treatment of anxiety disorder comorbidity in BD. Nevertheless, the substantial burden and unique characteristics of this comorbidity has important clinical and research implications.

**Key words:** Comorbidity; Bipolar disorder; Anxiety disorders; Correlates; Impact; Aetiology; Treatment

**Core tip:** This review of existing research shows that about half of those with bipolar disorder (BD) are likely to develop anxiety disorders in their lifetimes and a third of them will manifest these disorders at any point of time. Anxiety disorder comorbidity negatively impacts almost all aspects of the presentation and course of BD and makes for a much poorer treatment-response and outcome. Though research data on aetiology and management of such comorbidity is limited, clinicians need to screen patients with BD

for anxiety disorders and provide comprehensive and on-going treatment to prevent the deleterious consequences of anxiety disorder comorbidity in BD.

## INTRODUCTION

Comorbidity is defined as the 'presence of more than one disorder in a person in a defined period of time'[1]. Prior to the 1990s the focus was mostly on the link between anxiety disorders and unipolar depression, while substance-use disorders (SUDs) were the focus of research on comorbidity in bipolar disorder (BD). However, accumulated evidence over the last three decades has conclusively established that comorbidity with anxiety disorders is the rule rather than the exception among patients with BD[2-5]. In general, about a half to two thirds or even more of the patients with BD have a comorbid psychiatric condition. Anxiety disorders, SUDs, and behavioural disorders are the most common comorbid psychiatric disorders associated with BD. Very high lifetime and current rates of anxiety disorder comorbidity have been found in both epidemiological[5-9] and clinical studies of BD[5,6,8,10,11]. Additionally, multiple anxiety disorder comorbidity has been reported in a third of the patients with BD[12-16]. Despite differing widely across studies, rates of individual anxiety disorders comorbid with BD appear to be largely similar[11,17-20]. The presence of comorbid anxiety disorders in patients with BD has several adverse consequences including a negative impact on almost all aspects of the presentation and course of BD[10,15,21-23]. This unfavourable clinical profile leads to poorer outcome and functioning and impedes treatment of BD[16,17,20,24,25].

The increased awareness of the substantial burden of comorbid bipolar and anxiety disorders over the years has propelled research in this area[5,26]. Moreover, it gave rise to the hope that examination of anxiety disorder comorbidity in BD could provide clues to underlying etiopathogenetic mechanisms of BD[3,6,9]. Consequently, the existing literature now contains a sizeable body of research evidence on the subject[6,8,16,18]. However, there are several unresolved issues as well. This review intends to highlight both the well-known facts and the deficiencies in research concerning anxiety disorder comorbidity in BD. A major problem hampering research in this area has been the widely varying methodology of individual studies[20,26,27]. To obviate these methodological concerns to whatever extent possible, the current review is based on three of the relatively more reliable sources of evidence including prior reviews and meta-analyses, as well as epidemiological surveys and large-scale clinical studies of comorbid anxiety disorders and BD.

## OBJECTIVES

The principal objective of this review was to provide an overview of the current trends in research on comorbidity of bipolar and anxiety disorders. The main areas examined included rates of anxiety disorder comorbidity in BD, its demographic and clinical correlates, the impact of such comorbidity on the course and outcome of BD, and research on management and aetiological mechanisms of comorbid anxiety and BDs.

## LITERATURE SEARCH

A comprehensive literature search was undertaken using six English-language databases: MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane, and Google to identify published articles on anxiety disorders comorbid with BD from inception until August 2018. Search terms included BD, or bipolar depression, or mania AND comorbid, or comorbidity AND anxiety, or generalized anxiety disorder (GAD), or panic disorder, or phobia, or phobic disorder, or social anxiety disorder, or obsessive-compulsive disorder (OCD), or post-traumatic stress disorder (PTSD). Reviews,

editorials and original research articles were examined for their relevance to the subject. Reference lists of these articles were searched manually to locate other relevant reports.

## SELECTION OF ARTICLES

All articles that provided information on prevalence, clinical features, aetiology, and treatment of anxiety disorder comorbidity in BD were chosen initially. However, for the purposes of the current review only three sources of evidence including earlier reviews (meta-analytic, systematic, and open), epidemiological investigations, and large-scale (usually multi-centric) clinical studies were included. Other original research articles were considered only when they provided additional information not present in these three principal sources.

## DATA EXTRACTION AND SYNTHESIS

Data on different aspects of anxiety disorder comorbidity in BD were extracted from each source. Results were organized by identifying common patterns and trends so that logical conclusions could be drawn from the findings of the articles included.

## EVIDENCE-BASE FOR THE CURRENT REVIEW

The electronic search yielded 1294 articles, 249 of which were reviews about anxiety disorder comorbidity in BD. Relevant reviews were extracted from this initial list of 249 articles. A manual search was also conducted to identify any other reviews on the topic. After excluding duplicate publications, 103 reviews on the subject were finally included. The final selection contained 14 meta-analytic reviews, 29 systematic reviews, and 60 open (non-systematic) reviews. Incidentally, the literature search also yielded over 350 relevant studies on comorbid bipolar and anxiety disorders. However, only a selected list of articles pertaining to epidemiological and large-scale clinical studies was included in this review.

## OVERALL PREVALENCE OF ANXIETY DISORDERS IN BD

Data from meta-analytic and systematic reviews are included in Table 1, while Table 2 depicts the rates obtained as a part of non-systematic reviews. Prevalence rates from epidemiological studies are shown in Table 3 and from selected large-scale clinical studies in Table 4.

The first notable finding across all sources included in this review was the wide variation in prevalence rates between different reviews, epidemiological surveys, and clinical studies. The obvious reason for this discrepancy was differences in designs and methodologies of reviews and individual studies. However, despite these differences there appeared to be some consistency in the rates reported from different sources.

### Reviews

Four meta-analyses of lifetime prevalence rates of anxiety disorders among adult patients with BD yielded very similar rates of 41% to 47% from both community and clinical populations[11,18-20]. Current rates of anxiety disorder comorbidity among adult patients ranged from 35% to 38% in two meta-analyses of epidemiological and clinical studies of BD[20,35]. Mean prevalence rates in children/adolescents were found to be 27% (range 15% to 43%) in one meta-analysis[29] and 44% in another[34], which was in keeping with the adult rates. There was a greater variation in rates (11% to 93%) derived from systematic reviews depending on the number and type of studies included in each review. Nevertheless, systematic reviews among adult patients have also reported lifetime anxiety comorbidity in about half and current comorbidity in about a third of those with BD. Incidentally, the systematic review with the largest number of studies (*n* = 167) has been conducted among those with child/adolescent BD[43]. The mean prevalence rate of any anxiety disorder in BD was found to be 54% in this review (range 41% to 80%). A much greater disparity in rates was found in the non-systematic reviews, but even in these reviews the average lifetime prevalence was close to 50% and the average current prevalence was about 30% for anxiety disorders in BD. Rates for prevalence among the elderly appeared to be lower (mean

| Table 1 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from meta-analytic and systematic reviews | | |
| --- | --- | --- |
| **Details** | **Any anxiety disorder** | **Individual anxiety disorders** |
| Meta-analytic reviews | | |
| Kowatch *et al*[29], 2005. 7 studies of child and adolescent BD (*n* = 362) | Mean prevalence of any anxiety disorder in BD 27% (range 14%-43%) | |
| Vázquez *et al*[18], 2014. 46 studies of anxiety comorbidity in BD | Lifetime prevalence in epidemiological and clinical studies - mean 47% (range 24%-88%) | Mean prevalence: PD 22% (1%-40%), PHOBIAS 22% (2%-59%), GAD 20% (7%-42%), PTSD 16% (3%-39%), OCD 13% (5%-48%) |
| Amerio *et al*[30], 2015. 46 studies of comorbid BD and OCD | | Pooled prevalence of OCD in BD 17.0%; pooled prevalence of BD in OCD 18.0% |
| Nabavi *et al*[11], 2015. 52 interview-based studies of outpatients and inpatients | Lifetime prevalence of any anxiety disorder in BD 43% | Lifetime prevalence of: PD 17%, GAD 14%, SAD 13%, PTSD 11%, SP PHOBIA 11%, OCD 11%, AGORA 8% |
| Pavlova *et al*[19], 2015. 40 studies (*n* = 14914) of community and clinical population | Lifetime prevalence of anxiety disorder in BD 45% | Lifetime prevalence of: GAD 20%, SOC PHOBIA 20%, PD 19%, PTSD 17%; no differences between BP I and BP II |
| Tonna *et al*[31], 2015. 4 studies of adolescent BD-OCD (*n* = 345) | | Pooled prevalence of comorbid OCD in BD among adolescents 23%; greater than adults (14%) |
| Amerio *et al*[32], 2016. 14 studies of comorbid BD and OCD in BP I and BP II | | Pooled prevalence of OCD in BP I 22%; pooled prevalence of BP I in OCD 4% and of BP II in OCD 13.5% |
| Preti *et al*[33], 2016. 28 studies of comorbid BD and GAD (*n* = 7894) | | Current prevalence 12% and lifetime prevalence 15% of GAD in BD |
| Taskiran *et al*[34], 2016. 33 studies of child and adolescent BD | Prevalence of any anxiety disorder in BD 44% | Prevalence of: GAD 25%, SEP ANX 22%, OCD 17%, SOC PHOBIA 15%, PD 10% |
| Pavlova *et al*[35], 2017. 10 studies of euthymic BD (*n* = 2120) | Current prevalence of any anxiety disorder in BD 35% | Current prevalence of: GAD 12%, SAD 10%, SP PHOBIA 10%, OCD 7% |
| Yapici Eser *et al*[20], 2018. 135 studies of comorbid BD and anxiety disorders | Lifetime prevalence 41% and current prevalence 38% of anxiety disorder in BD; lifetime prevalence 38% in BD I and 34% in BD II; current prevalence 31% in BD I and 37% in BD II | Lifetime prevalence: PD 18%, GAD 13%, SAD 13%, OCD 10%; current prevalence: GAD 15%, PD 13%, SAD 12%, OCD 10%; prevalence PD and SAD significantly affected by proportion of BD I patients |
| Preti *et al*[36], 2018. 15 studies of comorbid BD and PD (*n* = 3391) | | Lifetime prevalence: PD 16%; current prevalence: PD 13%; no difference between BP I and BP II |
| Systematic reviews | | |
| Strakowski *et al*[37], 1994. 4 studies of anxiety comorbidity in BD | | Mean prevalence: PD 7%-16%, OCD 8%-13% |
| Krishnan[38], 2005. 10 studies of anxiety comorbidity in BD | Mean rate 71% (range 49%-92%) | Mean rates: SOC PHOBIA 47%, PTSD 39%, PD 11%, OCD 10% |
| McIntyre *et al*[8], 2006. 17 studies of anxiety comorbidity in BD | Lifetime rates 16%-79% in 11 studies; usually 30%50%; current prevalence 15%-56% in 8 studies | AGORA lifetime 22%-62%; current 6%-7%; SP PHOBIA lifetime 2%-67%; current 8% SOC PHOBIA lifetime 4%-47%; current 13%-19% GAD lifetime 3%-43%; current 2%-25% PTSD lifetime 7%-37%; current 4%-40% PD lifetime 2%-38%; current 8%-26% OCD lifetime 2%-31%; current 6%-8% |
| Tamam[9], 2007. 15 studies of anxiety comorbidity in BD | Lifetime prevalence in epidemiological and clinical studies 24%-93% | Lifetime prevalence of: SOC PHOBIA 5%-47%, PD 6%-43%, OCD 7%-39%, GAD 3%-43%, PTSD 7%-21% |
| Kauer-Sant'Anna *et al*[15], 2009. 9 studies of anxiety comorbidity in BD | Lifetime prevalence in epidemiological studies 48%-93% | SP PHOBIA 10%-67%, SOC PHOBIA 8%-47%, PTSD 7%-39%, GAD 3%-42%, PD 5%-33% |
| Quarantini *et al*[39], 2009. PTSD prevalence in BD | | Lifetime rates of PTSD in BD 16%-39% |
| Maina *et al*[16], 2011. 11 studies of anxiety comorbidity in BD | Lifetime prevalence in epidemiological studies 63%-89%; in clinical samples 11%-79% | PD 4%-39%, OCD 3%-35%, GAD 3%-32%, SOC PHOBIA 2%-31%, PTSD 5%-29% |
| Pallanti *et al*[40], 2011. 10 studies of comorbid BD and OCD | | Lifetime prevalence in epidemiological and clinical studies 15%-35% |
| Lala *et al*[41], 2012. 7 studies of elderly patients | | PTSD 5%-11%, PD -current 22%, GAD-current 16%, OTHERS 10%-11% |
| Schaffer *et al*[10], 2012. 9 studies of anxiety comorbidity in BD | Lifetime prevalence in epidemiological studies 52%-75% | Lifetime prevalence: OCD 10%-25%, PD 14%-27%, PTSD 16%-39% |
| Latalova *et al*[22], 2013. 12 studies of anxiety comorbidity in BD | Lifetime prevalence in epidemiological studies 75%; in clinical samples 27%-56% | Lifetime prevalence: SOC PHOBIA 47%-52%, SAD 38%, SP PHOBIA 35%, GAD 30%, PTSD 24% (16%-39%), PD 20%, OCD 14% (3%-35%) |
| Amerio *et al*[42], 2014. 64 articles of comorbid BD and OCD | | Lifetime prevalence of OCD in BD 11%-21% (mean BP I 15%, BP II 13%); lifetime prevalence of BD in OCD 6%-10% (mean BP I 4%, BP II 9%) |

| Frías *et al*[43], 2015. 167 studies of child and adolescent BD | Mean prevalence of any anxiety disorder in BD 54% (range 41%-80%) | GAD and SEP ANX rates higher than other disorders; OCD 36%-39%, PD 18%-23%, PTSD 8% |
| Sharma[44], 2017. 8 studies of post-partum BD comorbidity | | Anecdotal reports of simultaneous onset of comorbid BD-OCD in the postpartum period |

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; AGORA: Agoraphobia; GAD: Generalized anxiety disorder; OCD: Obsessive compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; SEP ANX: Separation anxiety disorder; SOC PHOBIA: Social phobia; SP PHOBIA: Specific phobia.

23%)[54], while average rates among children/adolescents seemed to be higher (range 14% to 77%) than adult rates[56,58,59].

### Epidemiological and clinical studies

Some of the highest rates of anxiety disorder comorbidity in BD have been reported in epidemiological surveys. In these studies, a minimum of one third of the patients with BD appeared to have a lifetime comorbid anxiety disorder[88], with some epidemiological studies reporting exceptionally high lifetime rates of 89% to 100%[76,78,90]. However, most epidemiological investigations have found lifetime rates of about 50% to 60% in those with BD. Current rates were lower and ranged from 7% to 52% in three studies[97-99]. The high rates obtained in epidemiological studies could be explained by the large number of patients examined, many of whom may have never sought treatment. Alternatively, they could be due to the high rates of false positive diagnoses made by lay interviewers who are usually employed to carry out these population surveys[26]. In contrast, while diagnostic ascertainment may be more reliable in clinical settings, clinical samples are also more likely to include severely ill patients with higher chances of having comorbid disorders (the so called Berkson's bias)[8,16,26]. Still, lifetime rates of anxiety comorbidity in BD were about 40% to 50%, while current rates were about 30% across several large-scale clinical studies. Thus, though rates in community samples were somewhat higher than clinical populations[26], these differences were not significant as indicated by two meta-analytic reviews[19,35].

### Remitted patients

Although some evidence suggested that anxiety disorder comorbidity was higher during acute, particularly depressive episodes[8,35], reviews of studies of remitted patients with BD have found that about a third to half of such patients (range 7% to 61%) have a comorbid anxiety disorder[16,35,119]. A recent meta-analysis of remitted BD found that the current prevalence rate for any anxiety disorder was 35%, thus confirming that anxiety disorder comorbidity extends beyond the acute to the inter-episodic period[35].

### Multiple comorbidity

About a third of the patients with BD also develop more than one anxiety disorder during their lifetimes[8,10,27,60]. Rates of such multiple anxiety disorder comorbidity have ranged from 10% to 47% in different studies of BD[9,13-16].

### BD in anxiety disorders

The prevalence of BD in anxiety disorders has been examined less often. Though some reviews have reported low rates of BD in primary anxiety disorders[18,40], the majority of reviews and studies have found that the prevalence of BD in anxiety disorders is equivalent to the rates of anxiety disorders in patients with BD[7,8,66,80,128]. This appears to be mainly true for OCD[30,32,128,129], but a similar trend has also been found for social phobia and panic disorder[7,8,46,66,128].

## PREVALENCE OF INDIVIDUAL ANXIETY DISORDERS IN BD

Not surprisingly, the greatest discrepancy was found in the prevalence of individual anxiety disorders in BD. Nonetheless, some uniform trends were evident from the three different sources of evidence of this review.

The four meta-analytic reviews among adults have reported highest lifetime rates for panic disorder (17% to 22%), GAD (13% to 20%), and social phobia (20%), followed by PTSD (11% to 17%), social anxiety disorder (13%), OCD (10% to 13%), specific phobias (11%), and agoraphobia (8%)[11,18-20]. A similar trend was also apparent in a meta-analysis of remitted patients[35]. Among children/adolescents the mean prevalence of GAD (25%) was very high, as were the rates of separation anxiety disorder (22%), OCD (17%), and social phobia (15%)[34]. Reviews of individual

**Table 2 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from open reviews**

| Ref. | Any anxiety disorder | Individual anxiety disorders |
| --- | --- | --- |
| Himmelhoch[45], 1998 | | Lifetime prevalence of PD in BD 21%; prevalence of BD in PD 14%-34% |
| Hantouche *et al*[46], 2002 | | Prevalence of BD in OCD 11%-16%, cyclothymia 50%-56% |
| Freeman *et al*[6], 2002 | Lifetime and current rates 32%-79% | SOC PHOBIA lifetime 8%-47%; PTSD lifetime 39%; current 40%-43%; PD lifetime 11%-21%; current 2%-9%; OCD lifetime 9%-21%; current 35% |
| McIntyre *et al*[47], 2003 | Lifetime rate 92% | Lifetime rates SP PHOBIA 67%, SOC PHOBIA 47%, GAD 42%, PTSD 39%, PD 33% |
| Sasson *et al*[12], 2003 | Lifetime rate 60%-65% | SOC PHOBIA 10%-40%, OCD 7%-35%, SP PHOBIA 10%, PTSD 7%, GAD 3% |
| Ghaemi[48], 2004 | Lifetime rate > 90% | GAD 50%, PD 20%, OCD 20% |
| Goldberg *et al*[2], 2004 | Epidemiological studies > 90%; clinical 4%-50% | |
| Issler *et al*[13], 2004 | Lifetime rate 24% to 79% | |
| McIntyre *et al*[49], 2004 | Lifetime rate 42%-90%; current rate 30% | PD 9%-20%, SOC PHOBIA 13%-16%, SP PHOBIA 8%-10%, GAD 3%, OCD 8%-9%, PTSD 4%-7% |
| Otto *et al*[50], 2004 | | Mean prevalence of PTSD in BD 16% |
| Bauer *et al*[14], 2005 | Lifetime rate 16%-42% and current rate 30%-31% in clinical studies | PTSD lifetime 7%-50%; current 4%-40% PD lifetime 4%-38%; current 8% OCD lifetime 3%-35%; current 6%-8% GAD lifetime 3%-32%; current 2%-3%; SOC PHOBIA lifetime 0%-31%; current 13% SP PHOBIA lifetime 10%-20%; current 8% |
| Hirschfeld *et al*[24], 2005 | Lifetime rate 42%-92% | PD 21% OCD 21% |
| Simon *et al*[51], 2005 | Lifetime rate 50%; current rate 30% | PD lifetime rates 14%-38%; PD current rates 4%-9% |
| Baldassano[52], 2006 | Lifetime rate 51%-65%; current rate 7% | |
| Keller[27], 2006 | Lifetime rates 51%-65% | |
| MacKinnon *et al*[53], 2006 | | Prevalence PD - community studies 12%-35%; clinical studies 5%-63%; family studies 11%-21% |
| Sajatovic *et al*[54], 2006 | Prevalence 23% among elderly patients | Prevalence PTSD 44%, others 43%, GAD 23%, PD 6%, OCD 5%, AGORA 3%, SOC PHOBIA 0.5%, SP PHOBIA 0.2% |
| Singh *et al*[55], 2006 | Mean prevalence 55% | Mean prevalence SOC PHOBIA 47%, PTSD 16%, PD 11%, OCD 10% |
| Dineen Wagner[56], 2006 | Prevalence in community studies 29%-50% and clinical samples 14%-76% of anxiety comorbidity in child and adolescent BD | Prevalence: OCD 9%-49%, SOC PHOBIA 3%-33%, GAD 19%-20%, SEP ANX 13%-57%, AGORA 15%-27%, PD 6%-11%, PTSD 18% |
| Bhagwagar[21], 2007 | Lifetime rate > 50% | |
| MacKinnon[57], 2007 | | Prevalence PD 15%-20% |
| Mantere[28], 2007 | Lifetime rate 42%-56%; current rate 30% | |
| El-Mallakh *et al*[17], 2008 | Lifetime rate 87%-92% in epidemiological studies | Lifetime rates: SAD 5%-52%, GAD 30%-42%, PTSD 16% -39%, OCD 17%-21,% PD 21% |
| Jolin *et al*[58], 2008 | Mean prevalence 14%-77%% in childhood and adolescent BD | Mean prevalence: SEP ANX 18%-22%, PHOBIA 4%-11%, PD 3%-11%, OCD 3% |
| Joshi *et al*[59], 2009 | Prevalence in adults and children 12%-76% | Prevalence OCD 15-35% |
| Sagman *et al*[60], 2009 | Lifetime rate 50%-65%; current rate 30% | |
| Simon[61], 2009 | Lifetime rate 51% | Lifetime rate GAD 18% |
| Bowden[62], 2010 | Lifetime rate 92% | |
| Saunders *et al*[4], 2010 | Lifetime rate 65% | Lifetime rate OCD 21% |
| Andrade-Nascimento *et al*[63], 2012 | | Current 15% and lifetime prevalence 16% of GAD in euthymic patients |
| Jana *et al*[64], 2012 | | Mean prevalence of OCD 0%-54% in childhood and adolescent BD |
| McIntyre *et al*[65], 2012 | Lifetime rate 63%-87% | |
| Perugi *et al*[66], 2012 | Lifetime rate 30%-93%; current rate 30% | Lifetime rate SP PHOBIA 67%, PD 33% |
| Cazard *et al*[67], 2013 | Mean prevalence 5%-33% | Mean prevalence: SOC PHOBIA 0.5%-47%, PTSD 2%-44%, GAD 3%-42%, OCD 1%-14% |
| Amerio *et al*[68], 2015 | Mean prevalence 50% | OCD 17%-18% |
| Chang *et al*[69], 2016 | Lifetime rate 51%-90%; current rate 31% | |
| Ketter[23], 2015 | Lifetime prevalence mean 48% (range 17%-79%) | |

| Shi[70], 2015 | Prevalence rate of OCD in BD 11%-21% |
| Tonna *et al*[71], 2015 | Prevalence rate of OCD in BD 21% |

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; AGORA: Agoraphobia; GAD: Generalized anxiety disorder; OCD: Obsessive compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; SEP ANX: Separation anxiety disorder; SOC PHOBIA: Social phobia; SP PHOBIA: Specific phobia.

disorders have usually confirmed these rates. The prevalence of OCD in BD was about 17% (range 11% to 23%) among adults and children/adolescents in three meta-analyses and one systematic review[30-32,42]. The lifetime prevalence of GAD was found to be 15% and that of panic disorder 16% in two separate meta-analyses[36], while a systematic review estimated the lifetime rates of PTSD to vary from 16% to 39%[39].

Epidemiological studies, on the other hand have found very high lifetime rates of comorbid phobias in BD including specific phobias, agoraphobia, social phobia, and social anxiety disorder. This is understandable given that phobic disorders are among the most common disorders found in general population surveys[131-134]. Lifetime rates of GAD were also very high while rates of other disorders were more variable. Consequently, most systematic as well as non-systematic reviews based on both epidemiological and clinical studies have found a similar pattern of prevalence of individual anxiety disorders in BD[8-10,22]. While some clinical studies have also found a comparable distribution of anxiety disorders, the more usual finding has been that panic disorder, PTSD, and OCD are about as common as phobic disorders and GAD.

## DEMOGRAPHIC CORRELATES OF ANXIETY DISORDER COMORBIDITY IN BD

Correlates of anxiety disorders among patients with BD are depicted in Table 5. Few studies have examined demographic correlates of comorbid bipolar and anxiety disorders. The association with age has yielded conflicting results[8,9,40,70], except for OCD comorbidity in BD, where younger patients have been found to have higher rates in a series of meta-analyses and systematic reviews[20,30,32,40,42]. In contrast, gender seemed to make a significant difference to the prevalence of comorbid anxiety disorders in BD in some studies. Higher prevalence of anxiety disorders has been reported among women, particularly from large-scale clinical studies such as those conducted by the Stanley Foundation[104]. However, the Systematic Treatment Enhancement Program for Bipolar Disorder and other studies have not been able to reproduce these gender differences[52]. There was similar inconsistency among epidemiological studies with some reporting higher prevalence of anxiety disorders in women with BD[74,85] and others finding equivalent rates between the two genders[76,99]. One meta-analysis found a significant excess of anxiety disorders among women with BD based on pooled prevalence rates from several studies[18], but many other meta-analyses and reviews have concluded that there are no gender differences in rates of anxiety disorder comorbidity in BD. The association of anxiety disorders with other demographic variables such as marital status, education, or socioeconomic class has been similarly characterized by inconsistent and contradictory results. On the other hand, there was some preliminary evidence of cross-national and ethnic differences in the prevalence of anxiety disorder comorbidity in BD. Geographical variations in rates of anxiety disorders have been found in several meta-analyses and systematic reviews[11,19,30,42]. Ethnic differences have also been noted in epidemiological studies[74]. Notably, some reviews have found lower rates of anxiety disorders among Asian patients with BD; genetic differences have been proposed to account for this finding[69,122,135].

## CLINICAL CORRELATES OF ANXIETY DISORDER COMORBIDITY IN BD

Unlike demographic variables, there appeared to be considerably more uniformity regarding clinical correlates of anxiety comorbidity in BD.

### *Age of onset*
Joslyn *et al*[136] examined the effects of age of onset of BD on the clinical profile and outcome of BD in a meta-analysis of 15 studies including 7370 patients. An earlier age of onset was found to be significantly associated with comorbid bipolar and anxiety

**Table 3  Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from epidemiological studies**

| | Any anxiety disorder | Individual anxiety disorders |
| --- | --- | --- |
| **Lifetime prevalence rates** | | |
| ECA[72-74] | | OCD 21%, PD 21% |
| NCS[75-77] | BD 93% | SP PHOBIA 67%, AGORA 62%, SOC PHOBIA 47%, GAD 43%, PTSD 39%, PD 33%, OCD 21% |
| NCS-R[78-80] | ANY BD 75%, BP I 87%, BP II 83%-89%, ST-BD 63%-72% | SOC PHOBIA 38%, SP PHOBIA 35%, SAD 35%, GAD 30%, PTSD 24%, PD 20%, OCD 14%-23%, AGORA 6% |
| WMH[81] | Bipolar spectrum 63%, BP I 77%, BP II 75%, ST-BD 53% | [1]SP PHOBIA 30%, [1]SAD 29%, SOC PHOBIA 26%, GAD 20%, PTSD 19%, OCD 12%, PD 11%, AGORA 6% |
| NESARC[82-84][2] | BD 60%, BP I 65%, BP II 45% | PD 53%, GAD 51%, SAD 48%, SP PHOBIA 21%-34%, PD 19%-33%, GAD 18%-32%, SOC PHOBIA 18%-26%, AGORA 0.2%-1% |
| Edmonton, Alberta, Canada[87] | | PHOBIA 54%, PD 18%, OCD 15% |
| OADP study[88] | 33% among adolescents with BD | SEP ANX 18%-22%, PHOBIA 4%-11%, PD 3%-11%, OCD 3% |
| Zurich Cohort Study[89] | Hypomania - any anxiety disorders 46%- 78% | SOC PHOBIA 10%-36%, AGORA 7%-29%, SP PHOBIA 10%-23%, PD 12%-22%, OCD 5%-6% |
| National Epidemiologic Survey, Hungary[90] | BD 39% | GAD 14%, SP PHOBIA 13%, PD 11%, AGORA 9%, SOC PHOBIA 8%, OCD 3% |
| Population-based study from Hungary[91] | BP I 54%, BP II 100% | AGORA 22%-37%, GAD 10%-21%, SP PHOBIA 9%-17%, PD 7%-12%, SOC PHOBIA 4%-12% |
| Sesto Fiorentino Study, Italy[92] | | In BD and ST-BD: GAD 28%-39%, SOC PHOBIA 13%-20%, OCD 16%-17%; PD 6%-16%, SP PHOBIA 4% |
| EDSP study[93] | BP I 55%, BP II 59%, ST-BD 53% (in 14-24-year-olds with BD) | SP PHOBIA 19%-38%, GAD 10%-18%, SOC PHOBIA 14%-16%, AGORA 5%-16%, OCD 3%-16%, PD 3%-12%, PTSD 9%-11% |
| Canadian Community Health Survey[94,95] | BD 52%-61% | |
| Singapore Mental Health Study[96] | | In BD: OCD 26%, GAD 18% |
| **Current prevalence rates** | | |
| Australian National Survey[97] | BD 52% | PD 26%, GAD 25%, SOC PHOBIA 19%, PTSD 11%, OCD 9%, AGORA 6% |
| Australian National Survey[98] | BD 7%-9% | SOC PHOBIA 5%-7%, PTSD 4%-7%, GAD 4%-6%, PD 4%-5%, OCD 4%-5%, AGORA 2%-3% |
| Canadian Community Health Survey[99] | BD 29% | SOC PHOBIA 17%, PD 13%, AGORA 3% |

[1]Only for bipolar spectrum disorders; [2]National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) prevalence among elderly-generalized anxiety disorder (GAD): lifetime 2.5%; current 1%, and panic disorder (PD)-lifetime 2.5%; current 2%-NESARC prevalence among youth-lifetime anxiety disorder 15%; GAD 29%-PD 22%-Social phobia 14%[85,86]. BD: Bipolar disorder; BP I; Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; ST-BD: Sub-threshold bipolar disorder; ECA: Epidemiologic Catchment Area Study; NCS: National Comorbidity Survey; NCS-R: National Comorbidity Survey-Replication study; WMH: World Mental Health surveys; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions; OADP: Oregon Adolescent Depression Project; EDSP: Early Developmental Stages of Psychopathology study; AGORA: Agoraphobia; GAD: Generalized anxiety disorder; OCD: Obsessive compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; SEP ANX: Separation anxiety disorder; SOC PHOBIA: Social phobia; SP PHOBIA: Specific phobia.

disorders with an odds ratio of more than two. The association with early onset has been replicated by other meta-analytic reviews of total anxiety disorder comorbidity and meta-analyses of individual anxiety disorders including comorbid GAD, OCD, and panic disorders[18,20,30,33,36]. This relationship has been further endorsed by several systematic reviews of comorbid anxiety disorders in BD[9,10,16,17,22]. Higher prevalence of anxiety disorders among those with a younger age of onset has also been found in epidemiological surveys[73,80,86,93,132] as well as large-scale clinical studies of BD[100,106,107,110,113]. Moreover, earlier age of onset has been associated with poorer outcome in patients with BD and comorbid anxiety disorders[8,17].

### *Predominance of depression*

A depressive onset, *i.e.* the first lifetime episode being a depressive one, has been reported more commonly among those with anxiety disorder comorbidity. Comorbid anxiety disorders have also been linked to more frequent and severe episodes of depression in BD. Impaired functioning, poor quality of life, and higher risk of suicide have been attributed to the predominance depressive pathology in comorbid anxiety disorders and BD[15,16,18,36,42]. In contrast, the relationship of this comorbidity with mania

| Table 4 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from selected large-scale clinical studies | | |
| --- | --- | --- |
| | Any anxiety disorder | Individual anxiety disorders |
| Stanley foundation studies | | |
| McElroy *et al*[100], 2001 (*n* = 288) | Lifetime rate 42%; Current rate 30% | PD lifetime 20%, current 9%; SOC PHOBIA lifetime 16%, current 13%; SP PHOBIA lifetime 10%, current 8%; OCD lifetime 9%, current 8%; PTSD lifetime 7%, current 4%; GAD lifetime 3%, current 3% |
| Suppes *et al*[101], 2001 (*n* = 261) | Lifetime rate 44% | |
| Dittmann *et al*[102], 2002 (*n* = 152) | Lifetime rate 12% | |
| Levander *et al*[103], 2007 (*n* = 350) | Lifetime rate BD 46%; BP I 45%-48%; BP II 38%-58% | |
| Altshuler *et al*[104], 2010 (*n* = 711) | Lifetime rate: women 46%, men 29% | Lifetime rates: PD women 21%, men 14%; SOC PHOBIA women 12%, men 10%; SP PHOBIA women 12%, men 4%; OCD women 12%, men 7%; PTSD women 11%, men 3%; AGORA women 3%, men 2% |
| STEP-BD | | |
| Kogan *et al*[105], 2004 (*n* = 1000) | Lifetime rate 47% | |
| Perlis *et al*[106], 2004 (*n* = 983) | Prevalence rate 38%-69% | SOC PHOBIA 13%-31%, GAD 13%-29%, PD 14%-27%, PTSD 11%-27%, OCD 8%-13%, AGORA 5%-11% |
| Simon *et al*[107], 2004 (*n* = 475) | Lifetime rate BD 51%; BP I/BP II 53%/46%; Current BD 30%; BP I/BP II 34%/19%; | Lifetime BD: SAD 22%, GAD 18%, PD 17%, PTSD 17%, OCD 10%, AGORA 8%; current BD: SAD 13%, PD 8%, OCD 6%, PTSD 5%, AGORA 4%, GAD 2% |
| Simon *et al*[108], 2004 (*n* = 919) | Current rate 32% | GAD 13%, SAD 13%, PD 8%, OCD 7%, PTSD 5%, AGORA 4% |
| Otto *et al*[109], 2006 (*n* = 1000) | Current rate 32% | Current rates: SAD 13%, GAD13%, PD 8%, OCD 7%, PTSD 5%, AGORA 4% |
| Simon *et al*[110], 2007 (*n* = 120) | Lifetime rate 62%; current rate 29% | GAD lifetime 31%, current 13%; SAD lifetime 27%, current 14%; PD lifetime 22%, current 5%; PTSD lifetime 27%, current 11%; OCD lifetime 11%, current 6%; AGORA lifetime 9%, current 2% |
| Other studies | | |
| Vieta *et al*[111], 2001 (*n* =129) | | PD 2%, SOC PHOBIA 2%, SP PHOBIA 2%, OCD 2% |
| MacKinnon *et al*[112], 2002 (*n* = 192) | | Prevalence PD 14% |
| Henry *et al*[113], 2003 (*n* = 318) | Lifetime rates 24% | Lifetime rates: PD 16%, PHOBIAS 11%, OCD 3% |
| Boylan *et al*[114], 2004 (*n* = 138) | Prevalence 56% | |
| Bauer *et al*[14], 2005 (*n* = 328) | Lifetime rate 43%; current rate 38% | PTSD lifetime 28%, current 25%; PD lifetime 20%, current 17%; OCD lifetime 11%, current 8% |
| Mantere[28], 2007 (*n* = 191) | Lifetime rate: BD 53%, BP I 46%, BP II 60%; current rate: BD 45%, BP I 36%, BP II 52% | PD lifetime 32%, current 24%; SOC PHOBIA lifetime 26%, current 18%; PTSD lifetime 16%, current 10%; GAD lifetime 15%; SP PHOBIA lifetime 8%, current 8%; OCD lifetime 5%, current 2%; AGORA lifetime 3%, current 2% |
| Azorin *et al*[115], 2009 (*n* = 1090) | Lifetime rate 27% | Lifetime rates: GAD 20%, PD 5%, AGORA 4%, SOC PHOBIA 2%, PTSD 2%, OCD 1.5% |
| Coryell *et al*[116], 2009 (*n* = 259) | | Lifetime rates: PHOBIA 3%-6%, GAD 1%-5%, PD 1%-4%, OCD 2% |
| Gao *et al*[117], 2010 (*n* = 564) | Prevalence in RCBD 46% | |
| Guo *et al*[118], 2010 (*n* = 136763) | Prevalence 36%-37% | |
| Mantere *et al*[119], 2010 (*n* =191) | Current rate 31%-44% | |
| Fracalanza *et al*[120], 2011 (*n* = 186) | Current rate 33% | Current rates: SAD 39%, PD 31%, OCD 16%, GAD 10%, PTSD 3% |
| Goes *et al*[121], 2012 (*n* = 1416) | | Prevalence: PD 23%, SP PHOBIA 10%, SOC PHOBIA 8%, OCD 6% |
| Chang *et al*[122], 2012 (*n* = 325) | Lifetime rates: BP I 27%, BP II 39% | Lifetime rates (BPI/BP II): GAD 10%/29%, PD 5%/9%, SOC PHOBIA 4%/5%, PTSD 3%/2%, OCD 2%/4%, SP PHOBIA 1%/4% |
| Angst *et al*[123], 2013 (*n* = 903) | Mean prevalence: BP I 17%; BP II 27% | Mean prevalence (BP I/BP II): GAD 6%/12%, PD 12%/18%, SOC PHOBIA 5%/8%, OCD 6%/11% |
| Castilla-Puentes *et al*[124], 2013 (*n* = 8129 youth) | Prevalence: Non RCBD 51%; RCBD 65%; BP I 41%-65%; BP II 69%-75%; | Prevalence (RCBD): GAD 55%, SAD 44%, OCD 11%, PTSD 9%, PD 9%, SP PHOBIA 8% |

| Young *et al*[125], 2013 (*n* = 304) | Lifetime rate 22% | PD 40%, SP PHOBIA 24%, OCD 15%, GAD 13%, SAD 10%, AGORA 8% |
| Asaad *et al*[126], 2014 (*n* = 350) | Prevalence 2.3% | |
| Baek *et al*[127], 2014 (*n* = 417) | Lifetime rate 30% | Lifetime rates: PD 13%, SP PHOBIA 13%, OCD 13%, SOC PHOBIA 9% |

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; RCBD: Rapid cycling bipolar disorder; STEP-BD: Systematic Treatment Enhancement Program for Bipolar Disorder.

was much less evident[8,14,16,18,36].

### Other clinical features

Rapid cycling, mixed states or features, and psychotic symptoms are other clinical characteristics frequently associated with anxiety disorder comorbidity in BD[8,9,16,17,22].

### Additional comorbidities

Among all comorbid conditions associated with anxiety disorder comorbidity in BD, the most common was substance use comorbidity. Patients with comorbid anxiety disorders and BD were twice as likely to have an additional diagnosis of SUD[9]. The high prevalence of comorbid SUDs in those with anxiety disorders and BD has been noted by a number of meta-analyses and systematic reviews[8,18,20,22,42]. It has been repeatedly documented by almost all major epidemiological studies[74,87,150,152,153], and by the Systematic Treatment Enhancement Program for Bipolar Disorder and Stanley Foundation studies, as well as other large-scale clinical studies of anxiety disorder comorbidity[14,52,100,114,117]. Conversely, only a few studies have been unable to find this relationship between anxiety disorders and SUDs in BD[9,28,113]. The presence of a combination of anxiety disorders and SUDs in BD not only complicates the diagnosis, but also impairs treatment response and can lead to a more severe course of illness and increased suicidal risk[10,17,27,69,154]. Apart from associated SUD comorbidity, anxiety disorders in BD have also been linked with other comorbid conditions such as attention deficit hyperkinetic disorders, eating disorders, and a range of personality disorders[9,14,18,22,42]. Rates of medical comorbidity were also greater in those with comorbid anxiety disorders and BD[155,156].

### Bipolar subtypes

In contrast to other clinical correlates, findings regarding the association of anxiety disorder comorbidity with bipolar subtypes I and II have been equivocal and contradictory. While one meta-analysis found somewhat greater rates in patients with bipolar subtype II[20], others have either found a higher prevalence of anxiety disorders in bipolar subtype I[30,33], or more commonly, no significant differences between the two subtypes[18,19,32,36]. This inconsistent association between anxiety disorders and bipolar subtypes has also been found in other reviews[8,10,15-17], in epidemiological studies[78,81,82,84,91], and in clinical samples of patients with BD[52,100,120]. On the other hand, more than a few reviews have reported a considerably higher prevalence of bipolar spectrum disorders[7,42,46,66,128], sub-threshold BD, or subsyndromal bipolar symptoms[7,14,66,69,139] among comorbid anxiety and BDs.

## IMPACT OF ANXIETY DISORDER COMORBIDITY IN BD

As is evident from Table 5, existing literature has been fairly consistent in reporting the widespread negative impact of anxiety disorder comorbidity among patients with BD on almost all aspects of the course and outcome of the illness.

### Increased symptom-burden

The presence of anxiety disorders in BD has been linked with a marked increase in symptom-burden including increased psychological distress, increased irritability, greater severity of acute episodes, and greater burden of both manic and depressive symptoms.

### Longer episodes

The greater severity of mood episodes in individuals with comorbid anxiety disorders is also reflected by the longer duration of these episodes, particularly depressive ones, and the higher rates of chronicity in BD with anxiety disorders.

### Poorer remission and recovery

Patients with comorbid bipolar and anxiety disorders have been found to have

**Table 5  Correlates and impact of anxiety disorder comorbidity in bipolar disorder**

| | Principal findings | Ref. |
| --- | --- | --- |
| **Demographic correlates** | | |
| Age | Higher prevalence in younger patients with BD | [8,20,30,32,40,42] |
| | No differences in rates according to age | [9,33,36,70] |
| Gender | Higher prevalence among women | [8-10,14,16-18,24, 40] |
| | No gender differences | [30,32,33,36,42,52,69,70] |
| Marital status | No differences according to marital status | [20,70] |
| Education | Higher levels more comorbidity | [20] |
| | Lower levels greater comorbidity | [8,9,14,66] |
| | No effect of education | [33,36,70] |
| Socioeconomic status | Greater comorbidity among those with lower socioeconomic status | [8,9,14,74] |
| | No effect of socioeconomic status | [33,36] |
| Ethnic and cross-national differences | Differences in comorbidity across nations and ethnicities | [11,16,19,30,69,74,135] |
| **Clinical correlates** | | |
| Age of onset | Lower age of onset is associated with higher levels of comorbidity | [8-10,14,16-18,20,21-24,27,30,31,33,36,40,42,49,52,56,57,60,66,70,136-142] |
| BP I *vs* BP II | Greater comorbidity in BP I | [15,17,30,33,49,60,84] |
| | Greater comorbidity in BP II | [4,9,20,128] |
| | No clear differences in comorbidity between BP I and BP II | [7,8,10,16,18,19,28,32,36,42,50,52,66,69,78-81,93,137] |
| Depression | Anxiety comorbidity is associated with more frequent and severe depressive episodes | [8,10,14-17,26,36,42,49,52,57,66,69,137-139,143] |
| | No clear evidence of predominance of depressive pathology | [19,28,70] |
| Mania | Anxiety comorbidity is associated with more frequent and severe manic episodes | [8,16,19] |
| | No clear evidence of association with mania | [14,18,28,36,40,49,70] |
| Euthymia | Anxiety comorbidity is associated with shorter durations of euthymia | [8,9,14,16,17,21,22,50,52,66,67,69] |
| Rapid cycling and mixed features | Anxiety comorbidity is associated with rapid cycling and mixed states | [8-10,13,15-18,40,49,52,67,69,141,142] |
| | No association with rapid cycling and mixed features | [19,28,66,70,144] |
| Psychotic symptoms | Anxiety comorbidity is associated with psychotic symptoms | [5,8,16,20,22,25,40] |
| | No association with psychotic symptoms | [70] |
| Insight | Anxiety comorbidity is associated with greater insight | [9] |
| Cognitive impairment | Anxiety comorbidity is associated with greater cognitive impairment | [15, 66] |
| Bipolar spectrum | Anxiety comorbidity is associated with bipolar spectrum disorders | [7,8,40,42,45,46,66,128] |
| Subsyndromal symptoms | Anxiety comorbidity is associated with subsyndromal symptoms | [14,66,69,139] |
| Substance-use disorders | Anxiety comorbidity is associated with greater prevalence of substance use and substance use disorders | [5,8-10,12-14,16-18,20,22-25,27,40,42,50,57,60,66,67,69,70,139,141-143] |
| Other comorbidity | Anxiety comorbidity is associated with greater prevalence of ADHD, eating disorders, personality disorders. | [9,12,14,20,22,42,139,145] |
| **Impact** | | |
| Course of illness | Anxiety comorbidity is associated with poorer course and outcome in BD in terms of greater illness severity, frequent episodes, and greater risk of hospitalization | [5,8-10,13-18,20,22,23,26,27,33,36,40,42,49,52,56,57,60,70,128,137-139,141-143,146] |
| Treatment response | Anxiety comorbidity is associated with poorer treatment response in BD | [4-6,8-10,12-14,16-18,22-27,40,49,57,60,66,67,69,137-139,141,142,146,147] |

| Suicide | Anxiety comorbidity is associated with increased risk of suicidality in BD | [4,5,8-10,13,14-18,21-27,33,36,40,42,49,50,52,57,60,66,67,69,128, 136-139,141,142,148,149] |
|---|---|---|
| Functioning | Anxiety comorbidity is associated with impaired functioning in BD | [8-10,14-18,21,22,25,27,33,36,40,42,49,50,66,67,69,128,139] |
| Quality of life | Anxiety comorbidity is associated with impaired quality of life in BD | [8-10,14-17,21,22,25,27,36,39,42,50,66,67,138,139] |
| Outcome of BD | Anxiety comorbidity is associated with incomplete remission and recovery in BD | [5,8,10,14,16,17,21,22,26,36,50,66,69,128,138] |
| Adherence | Anxiety comorbidity is associated with irregular treatment-adherence in BD | [10,16] |
| Delayed diagnosis-costs-service utilization | Anxiety comorbidity is associated with delayed diagnosis increased health-care utilization and costs in BD | [24,27,41,49 69,137] |

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; ADHD: Attention deficit hyperactivity disorder.

significantly longer times to remission, less likelihood of achieving complete remission or recovery, persistence of subsyndromal symptoms, shorter durations of remission, greater risk of developing an early relapse or recurrence, and higher risk for hospitalizations.

### Impaired functioning and quality of life
Patients with comorbid anxiety disorders and BD have greater functional impairment and poorer quality of life than those without this comorbidity.

### Inadequate treatment response
Many reviews and studies on anxiety disorder comorbidity in BD have also reported poorer treatment response, delayed diagnosis and institution of treatment, more severe medication side-effects, non-adherence with treatment, increased health-care utilization, and increased costs of care.

### Elevated suicidal risk
A large meta-analysis of suicidal risk in BD found that comorbid anxiety disorders were strongly associated with suicide attempts with an odds ratio of two derived from eight studies[148]. Another systematic review also found an increased risk of suicidal behaviour among patients with comorbid panic disorders[149]. Similar increases in suicide risk have been reported among other comorbid anxiety disorders including GAD, PTSD, OCD, and social phobia[33,36,42,45,50]. The elevated risk of suicide has been proposed to be the result of increased illness severity, greater depressive symptom-burden, additional SUD comorbidity, the presence of comorbid personality disorders, and several maladaptive traits such as impulsivity or neuroticism[18,26,33,46,148].

## TREATMENT OF ANXIETY DISORDER COMORBIDITY IN BD

In contrast to the substantial data on rates, correlates, and impact of anxiety disorder comorbidity in BD, research on the efficacy of different modalities of treatment for comorbid anxiety disorders in BD has been rather scarce. Table 6 provides a brief summary of this research.

Treatment of anxiety comorbidity in BD is challenging because of inherent difficulties in diagnosing comorbid bipolar and anxiety disorders and the high prevalence of inadequate response to treatment[6,10,17,18,172]. Treatment options include both pharmacotherapy and psychotherapy. Only two randomized-controlled trials of medication treatment have been conducted in comorbid BD and anxiety disorders. One showed some efficacy for olanzapine and lamotrigine in treating anxiety symptoms[173], while the other failed to show similar efficacy for risperidone[174]. Therefore, findings from treatment of bipolar depression have been extrapolated to provide the necessary evidence-base for pharmacotherapy of anxiety comorbidity in BD[10,26,15,17,162]. However, despite the lack of evidence there appeared to be considerable consensus that the primary aim of treatment is mood stabilization, although there was little agreement about the mood stabilizer of choice[6,7,9,10,162]. Following mood stabilization, treatment with other specific medications might be considered. Options include second-generation antipsychotics, specific serotonergic reuptake inhibitors, anticonvulsants, and benzodiazepines, though each medication group appears to have its advantages and disadvantages[6,10,15,17,162]. Although psychotherapy, particularly cognitive behavioural treatment is also recommended as a first-line

**Table 6  Treatment of anxiety disorder comorbidity in bipolar disorder**

| | Findings | Ref. |
| --- | --- | --- |
| Pharmacotherapy | | |
| Evidence base | Few RCTs of treatment of comorbid anxiety disorders in BD | [7-10,15,22,26,49,55,60,141,142,157-162] |
| | RCTs of treatment of BD reporting change in anxiety symptoms as secondary outcomes | [6,10,26,15,16,25,33,49,162] |
| Principles of treatment | Mood stabilization is the first priority | [3,6,7,9,10,12,15,48,49,55,128,157-159,162] |
| Add-on treatments | SGAs *e.g.*, quetiapine and olanzapine first line choices | [6,7,9,10,12,15,17,22,26,33,48,55,128,141,142,158-162] |
| | SSRIs *e.g.*, paroxetine but risk of mood destabilization | [6,7,9,10,12,15-17,22,25,26,33,48,55,128,157-159,162] |
| | Anticonvulsants *e.g.*, valproate, lamotrigine and gabapentin but no strong evidence | [6, 7, 9, 10, 12, 15, 17, 22, 25, 48, 55, 60, 67, 158, 159, 162] |
| | Benzodiazepines only for short-term treatment because of risk of abuse and dependence | [6,7,9,10,15-17,22,33,48,162,163] |
| Psychotherapy | | |
| Evidence base | Psychotherapy such as CBT may be effective in promoting recovery in those with comorbid anxiety and BD but there are only a few RCTs | [10,22,25,26,162,164-171] |
| Principles of treatment | Psychotherapy such as CBT is a first-line add-on treatment option | [6,7,9,12,10,15,17,22,25,26,67,128,157-159,162,164,165] |

BD: Bipolar disorder; RCTs: Randomized controlled trials; SGAs: Second generation antipsychotics; SSRIs: Specific serotonergic reuptake inhibitors; CBT: Cognitive behavioural treatment.

treatment option, the evidence base for cognitive behavioural treatment was meagre until recently[164]. However, lately several new randomized-controlled trials of cognitive behavioural treatment have demonstrated its efficacy in treating anxiety symptoms in BD, making it a legitimate option for concomitant treatment of anxiety disorders in BD[165,168-171].

## AETIOLOGY OF ANXIETY DISORDER COMORBIDITY IN BD

Though there is no clarity regarding the aetiology of anxiety disorder comorbidity in BD, several lines of evidence have suggested that family genetics, neurobiology, trauma, and other psychosocial factors may be involved in the genesis of anxiety disorders in BD[6,20]. Different conceptual models have been proposed to explain the co-occurrence of anxiety disorders and BD[3,6,9,13,16]. The first model suggests that comorbid bipolar and anxiety disorders occur together simply by chance. However, the high rates of anxiety disorders in BD negate the possibility of a chance association. The second model suggests that a pathophysiological link between anxiety disorders and BD explains the high rates of anxiety disorder comorbidity in BD. Two possibilities exist within this conceptual model; either the anxiety disorder predisposes to the development of BD, or BD increases the chance of the anxiety disorder emerging. The first possibility is supported by studies indicating that anxiety disorders serve as prodromal conditions preceding the development of BD[7,11,45,175,176]. The second possibility of BD contributing to emergence of anxiety disorders is indicated by the evidence suggesting that anxiety symptoms are an integral part of BD[6,8,16], by the episodic course of anxiety disorders in a subset of patients with BD and anxiety disorders[177], by familial genetic links between the two disorders[9,10,17,69,178], and by the benefits of mood stabilization as a primary mode of treatment[3,6,9,10]. The third model posits that higher-order pathophysiological mechanisms contribute to the onset of both anxiety disorders and BD. The list of such core pathophysiological processes includes familial genetic, neurobiological, and psychosocial factors. There is reasonable evidence suggesting genetic links between anxiety disorders and BD[69,130,157], particularly for panic disorder[53,57,112,128,179] and OCD[40,42,70,176,178]. Neurotransmitter disturbances, structural and functional brain changes, and alterations of synaptic plasticity could also provide the common link[9,10,20,53,130]. Psychosocial factors such as early childhood adversities, particularly trauma as an aetiological factor for comorbid PTSD, have also been implicated[9,10,17,39,50]. Finally, a fundamental disturbance in affective regulation, suggested by the presence of abnormal temperamental and personality characteristics among those with BD and

comorbid anxiety disorders, is also a likely underlying mechanism[9,33,50,180].

## UNIQUE FEATURES OF ANXIETY DISORDER COMORBIDITY IN BD

In their review of publication trends on the subject, Provencher *et al*[5] concluded that research on anxiety disorder comorbidity in BD, which had been expanding since the 1990s had almost stopped 20 years later. They also noted that the bulk of the publications were non-specific or descriptive in nature, with little research on causal mechanisms or management of this comorbidity. Similar apprehensions have been expressed by a number of other researchers[6,9,18,70,137]. The results of the current review, however, suggested that such concerns might only be partly true. The present review identified more than 100 prior reviews and over 350 studies on the subject. Therefore, the volume of extant research on this comorbidity was by no means inadequate and interest in the topic does not appear to be diminishing. Then again, the findings of the current review also showed that the majority of the research pertains to rates, correlates, and impact of comorbid anxiety disorders in BD, while research on treatment and aetiological processes is relatively limited.

The principal findings of this review were consonant with prior research in profiling the unique features of anxiety comorbidity in BD. The results reiterated the fact that at least half of those with BD are likely to develop an anxiety disorder in their lifetimes and a third of them will manifest an anxiety disorder at any point of time. The markedly elevated rates of anxiety disorders in BD were not only several fold higher than general population rates of anxiety disorders[18-20,23,35], but also higher than those found in unipolar disorders[6,13,15,20,43] and schizophrenia[181,182]. There was also some evidence, particularly from epidemiological studies, to indicate that anxiety disorders may be the most common comorbid conditions in BD and even more prevalent than comorbid SUDs[8,15,20,60,183]. Other notable characteristics included the coexistence of multiple anxiety disorders and additional comorbidities, especially the link with SUDs. The adverse clinical profile of comorbid bipolar and anxiety disorders as well as its association with poorer course and outcome, including the strong association with increased suicidality were additional distinctive features of anxiety disorder comorbidity in BD. Although these aspects of comorbid anxiety and BDs have been documented earlier, by collating findings from a larger and updated database the present review re-emphasized the significance and uniformity of these findings across multiple types of reports. Moreover, being based on more reliable sources of evidence it provided stronger endorsement for these unique attributes of comorbid anxiety disorders in BD.

## LACUNAE IN EXISTING RESEARCH

### *Treatment and aetiological research*
Although concomitant anxiety disorders have important implications for management of BD, evidence on this aspect was scarce. Additionally, the lack of research on aetiology of comorbid bipolar and anxiety disorders was also evident. The expectation that examination of this comorbidity would reveal the etiopathogenetic processes underlying BD has thus not been fully realized.

### *Methodological issues*
Despite the sizeable body of evidence on anxiety disorder comorbidity in BD, meta-analytic reviews have indicated that only 50 studies or less are of sufficient methodological rigor[11,18,19,30,34]. The same meta-analyses have revealed significant heterogeneity in rates of anxiety disorders, while almost all the other reviews have also noted the wide variation in rates. Many potential sources of bias could account for this discrepancy across studies including the method of diagnostic ascertainment, the type of investigators employed, the source and nature of patient samples, study designs, and the type of rates used[11,15,16,26,27]. Notwithstanding these numerous methodological confounders, two meta-analyses have concluded that all these methodological variables did not fully explain the heterogeneity in rates across studies, suggesting that unknown and unexplored factors were possibly the chief sources of the differences found[19,35].

### *Conceptual issues*
Although there is substantial evidence that anxiety disorder comorbidity is commonplace in BD, critics have proposed that some of this apparent comorbidity

could be an artefact of current nosological systems and diagnostic practices[3,13,157,184,185]. In medicine (from where the term comorbidity originates), Feinstein's definition specified that the two co-occurring disorders should be independent and distinct, presumably based on aetiological differences between the disorders[186]. This concept cannot be easily transposed to psychiatry because of the lack of knowledge about the causes of most psychiatric disorders and because of overlap in diagnostic criteria sets in current classifications[26,28,139,184]. Therefore, it remains uncertain whether this comorbidity is a product of two independent disorders, or of additive interactions between two coexisting disorders, or simply a part of the range of symptomatic expression of BD[11,18,22,26]. True comorbidity presupposes that the comorbid conditions will be fully diagnosable axis I or axis II disorders with minimal overlap in the content of their symptoms[1,3]. However, certain studies have moved beyond these precise definitions by including sub-threshold anxiety disorders or anxiety symptoms as a part of the anxiety disorder comorbidity of BD. This often leads to over-diagnosis and over-inflated rates of comorbidity[3,13]. Finally, a series of meta-analyses, systematic reviews, and studies of comorbid OCD in BD have found that spurious comorbidity, in which OCD was confined to the depressive episodes and disappeared during mania or remission, was present in nearly 50% to 75% of patients with BD-OCD comorbidity[30,32,42,68,177]. Truly comorbid OCD, where OC symptoms were not confined exclusively to mood episodes was less common. Unfortunately, there are very few longitudinal studies of BD, which could allow an accurate estimation of the rates of such true anxiety disorder comorbidity in BD.

## LIMITATIONS OF THE PRESENT REVIEW

Though the current review was based on a reasonably comprehensive literature search, some sources especially those not in English may have been missed. Additionally, the present review relied mainly on results of prior meta-analyses and reviews, while it only included selected epidemiological and clinical studies. Thus, some findings from smaller studies might have been ignored. Moreover, it was difficult to know which source to trust when findings from the three sources were in conflict. However, an attempt was always made to present a balanced perspective by considering both the more dependable findings from research as well as the controversial ones.

## CONCLUSIONS

Despite the deficiencies of research and limitations of the present review, it is quite clear that clinicians need to be fully aware of the substantial nature of anxiety disorder comorbidity in BD and its deleterious consequences, especially because it often goes unrecognized in routine clinical practice[9,12,33,46]. Such awareness is necessary for proper identification and accurate diagnosis of both BD and the anxiety disorder[3,6,9,15,19]. Firstly, patients with BD will need to be routinely screened for the presence of anxiety disorders; when detected a comprehensive and systematic assessment of the anxiety disorder comorbidity should be performed. Similarly, clinicians should examine patients presenting with anxiety disorders for the presence of comorbid BD[3,7,8,30,45]. Secondly, while managing anxiety disorder comorbidity in BD precedence is almost always given to adequate mood stabilization as the first step in treatment[3,6,7,9,10]. Following this, clinicians can either adopt a sequential or a hierarchical approach to treatment[3,10]. The hierarchical approach involves determining the primary condition and comprehensively managing it before focusing on the treatment of the secondary condition[3]. In the more commonly used sequential approach, after initial mood stabilization a stepped-care strategy may be employed in which pharmacological and psychosocial interventions can be added sequentially depending on the patient's treatment needs[3,10,164]. In either approach utmost caution must be exercised to prevent the treatment of one condition from adversely affecting the outcome of the other. The final component of management is regular monitoring and on-going treatment to prevent the long-term adverse consequences of this comorbidity[48].

For researchers there are many unresolved questions to answer including the significance of anxiety disorder comorbidity in BD, the nature of its underlying mechanisms, and the best possible ways to effectively manage this comorbidity[5,13,18,20,26]. The current investigative methodology needs to be improved by examining truly representative samples of patients, focusing on individual disorders as well as overall anxiety disorder comorbidity, and by longitudinal and more in-

depth analyses of comorbid anxiety and BDs. However, since added efforts on the part of both clinicians as well as researchers are likely to alleviate the burden of anxiety comorbidity on patients with BD, they are worth pursuing.

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**Observational Study**

# Parenting preschoolers with autism: Socioeconomic influences on wellbeing and sense of competence

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## Abstract

*BACKGROUND*
Previous research suggests that parents raising a child with autism experience higher levels of psychological distress than parents of typically developing children and parents of children with other developmental disorders. Little is known, however, about the intersection between the effects of socioeconomic status (SES) on the wellbeing and sense of parental competency of parents of pre-schoolers with autism and how it relates to child symptom severity.

*AIM*
To examine the relationship between their child's symptom severity, SES, as measured by neighbourhood advantage and occupational status, on the psychological wellbeing and perceived parenting competence among parents of preschoolers with autism.

*METHODS*
Parents of 117 preschool-aged children with a diagnosis of autism spectrum disorder (ASD), 107 mothers and 54 fathers, completed questionnaires about their child's symptoms of ASD and functioning, their own perceptions of their wellbeing and parental competence on entry to an early intervention program in Sydney, Australia. Parents also provided demographic information pertaining to their occupation, level of education attained and address (postcode). All children were also assessed for their severity of symptoms using the Autism Diagnostic Observation Schedule. The Australian Socioeconomic Index of occupational

status as a measure of familial SES and the Index of Relative Socio-economic Advantage and Disadvantage as a measure of neighbourhood advantage were used to examine the impact of SES on parental sense of competence and wellbeing.

*RESULTS*
Compared to normative populations, both mothers and fathers in our sample reported significantly higher levels of parenting sense of efficacy but lower levels of interest in the parenting role. Mothers also displayed higher levels of satisfaction. Both mothers and fathers displayed higher levels of depression than normative populations with mothers also reporting greater levels of stress and anxiety. Child symptom severity was associated with maternal parenting competency with these relationships amplified among mothers with higher familial SES and who lived in areas of greater neighbourhood advantage. Increased adaptive functioning was associated with better maternal wellbeing, particularly among mothers who lived in areas of greater neighbourhood advantage. Contrastingly, paternal parenting competence was generally not influenced by child adaptive functioning or symptom severity, although for those in higher familial SES brackets, children's symptom severity and maladaptive symptoms were negatively related to paternal sense of parenting efficacy. There was a trend towards moderate relationships between lower familial SES and greater depression, stress and anxiety among fathers, but no relationship with their child's ASD symptom severity or functioning.

*CONCLUSION*
SES differentially impacts wellbeing and sense of parenting competence and its relationship to the impact of child symptoms for mothers and fathers of preschoolers with autism.

**Key words:** Wellbeing; Parenting competency; Autism; Autism spectrum disorder; Parent; Mother; Father; Socioeconomic status

**Core tip:** Previous research suggests that parents raising a child with autism experience comparatively higher levels of psychological distress than other parents. Little is known, however, about how socioeconomic status (SES) affects perceived parenting competence and overall wellbeing and how these factors relate to the nature of children's autism. In this study, a cross-sectional analysis of parents of preschoolers with autism found that mothers and fathers were differentially affected by SES and their children's symptom severity. Those working with parents of pre-schoolers with autism need to consider differential effects of factors, such as SES and symptom severity, in contributing to maternal and paternal wellbeing and their experiences of parenting.

# INTRODUCTION

Autism spectrum disorder (ASD) is a life-long neurodevelopmental disorder characterised by deficits in communication and social interaction, and restricted, repetitive patterns of behaviour, activities or interests[1]. The prevalence of ASD appears to be rising worldwide[2] with autism currently estimated to affect around one in every 59 children aged 8 years old[3]. Parenting children with autism can be physically, psychologically, socially and financially demanding[4,5].

Parents of children with autism face multiple challenges such as difficulties associated with the diagnostic process, finding appropriate intervention and

educational programs, managing symptoms and behaviour on a daily basis, stressors further compounded by the financial burden due to the high cost of services[6-8]. Consequently parents of children with autism have been reported to show clinically elevated stress levels, poorer mental and physical health and lower quality of life across a range of studies[9-12]. A meta-analysis of 16 studies found higher levels of psychological distress among parents of children with autism relative to parents of children with other neurodevelopmental disabilities and medical conditions[10]. In addition to the impact on parental wellbeing, high levels of parenting stress have been found to reduce the effectiveness of a range of early interventions[13] and increase the use of ineffective parenting strategies that contribute to a decrease in the child's executive functioning and an increase in behavioural regulation problems[14].

Parenting sense of competence is a construct that has emerged as having a significant impact on parental wellbeing among parents of children with autism. Greater scores on dimensions of parenting competence including parents' satisfaction with the role of parents and perceived self-efficacy is associated with improved parental wellbeing[12,15,16]. The limited research to date suggests no difference in perceived satisfaction with the parenting role and a third dimension, interest and engagement with the parenting role, but increased sense of parenting efficacy in a small sample of mothers of children with autism compared with the normative data of Rogers and Matthews[17,18].

The effect of the severity of a child's overall autism symptoms on parental wellbeing is however not clear. While some studies have found it to be a significant contributor to lower parental wellbeing[19,20], other studies have found limited evidence for a link between parental wellbeing and symptom severity[21-23]. The one study examining the relationship between ASD severity and parenting sense of competency suggested that there is lower sense of satisfaction with the parenting role with increased symptom severity of ASD[15]. Some research has attributed the high level of psychological distress among parents of children with autism to the core traits of social communication deficits[10,24] and restrictive, repetitive behaviours[24-26] in their children. These hallmark deficits often make it difficult for parents to form secure, reciprocal relationships with their children[27,28]. Expressive communication difficulties may also contribute to the high levels of maladaptive, destructive and self-injurious behaviours found among children with autism[29-32]. The severity of a child's maladaptive behaviours, negative behaviours directed towards the self (termed internalising behaviours) and towards others (externalising behaviours), have also been found to be a significant contributor to the wellbeing of mothers of children with autism[33-36]. However, research has not yet been conducted into the impact of children's adaptive and maladaptive functioning on parental sense of competency[15].

Recent analyses suggest that environmental factors, including socioeconomic status (SES) may have a greater impact on parent stress than child-related factors[37]. Key measures of SES include family measures including household income and parental level of education, and measures of community SES including community resources. The inadequate resources available to those from lower SES background have been proposed to exacerbate parenting stress and decrease wellbeing[38]. Additionally, internalising disorders such as depression and anxiety have been found to be directly associated with lower SES within the general population, findings which have been theorised to be a product of the everyday stressors associated with poverty[39]. Living in deprived neighbourhoods is also linked to poorer mental health independent of personal SES[40]. A number of studies have found evidence to suggest that having a child with autism or other disability is associated with reductions in household income, and thus lower SES[41,42]. However, the impact of SES on wellbeing in parents of children with autism is unclear. Among parents with children with autism, while higher family income has been associated with increased maternal wellbeing and self-reported quality of life[37,43,44], greater levels of stress among parents of children with autism and other disabilities have been related to higher levels of education[45-47]. Conversely, other research suggests that higher levels of education but not income improve paternal quality of life in those with children with autism[48]. One study that examined the impact of income of parenting competence found that mothers with greater incomes had increased parenting satisfaction but had lower efficacy relative to mothers with lower incomes[15]. Families with low SES encounter a greater number of structural barriers which impair their capacity to meet their children's needs[49] which in turn may have an adverse impact on parental wellbeing.

With the potential relationship between symptoms of ASD and parental wellbeing, it is important to also consider how SES relates to ASD symptomatology and functioning in children with ASD. The little research that has been conducted suggests an increase in mood and behaviour problems among children with autism from low SES families[50,51], and that living in impoverished neighbourhoods is associated with greater comorbid intellectual disability among children diagnosed

with autism[52,53]. Further, differential access to diagnostic services based on the SES may also contribute to delayed diagnosis within more deprived neighbourhoods, consequently delaying intervention and increasing the severity of a child's ASD symptoms[42,53-57].

The literature relating to the relationship between SES and symptoms of ASD is complicated by the inclusion of a high proportion of participants living below the poverty line[48,58], the use of author-generated measures of economic support[37] and the country in which the research was conducted with different patterns of findings emerging in countries with universal healthcare compared to American studies. The variation in the use of measurements of SES further complicates the conclusions that can be drawn. Further research is therefore required to understand the role of SES using validated measures in the Australian setting.

This study aimed to clarify the relationship between child related factors relating to ASD symptom severity and adaptive and maladaptive behaviours, and parental psychological wellbeing and whether this relationship is moderated by measures of SES. Additionally, we sought to explore whether there are differences between fathers and mothers in terms of these factors. We hypothesised that there would be significantly greater levels of symptoms of depression, anxiety and stress in parents of children with autism as compared to general population. We also hypothesised that there would be an association between greater autism symptom severity and maladaptive behaviours and lower parental psychological wellbeing and sense of parental competence and that this relationship would be moderated by measures of SES.

## MATERIALS AND METHODS

### Participants

Parents of children who started attending an Autism Specific Early Learning and Care Centre (ASELCC) in outer metropolitan Sydney, Australia between July 2010 and January 2015, were invited to participate in the study. The centre is one of six ASELCCs established by the Australian Government providing long day child care for children aged two to six years with a diagnosis of ASD. The centre is staffed by a multidisciplinary team including Child Care Workers, Early Childhood Teachers, Speech Pathologists, Occupational Therapists, and a Family Counsellor. Children enrolled in the program received individual and group-based early intervention using the Early Start Denver Model, an evidence-based intensive behavioural intervention for preschool children with ASD[59-61].

All children received a diagnosis of autistic disorder or pervasive developmental disorder by a community-based physician using the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV), which are encompassed under the diagnosis of ASD under the DSM-5[1]. Exclusion criteria included conditions with a known genetic aetiology (*e.g.*, Fragile X Syndrome) or neurological (*e.g.*, epilepsy) disorders, and significant vision, hearing, motor or physical problems. Additional criteria for entry to the Centre included the ability to meet fee payment through personal and funding bodies including government funding, and for children to be able to physically attend the Centre.

### Procedure and measures

This study was approved by the local institutional Human Research Ethics Committee. After providing informed consent to participate at the time of their child's enrolment in the ASELCC, parents completed a demographic questionnaire as well as standardised questionnaires assessing parental psychological wellbeing and the severity of their child's autism symptoms. An objective assessment of the child's severity of symptoms of autism was also undertaken by researchers at the Centre. All assessment tools used in this study have strong psychometric properties.

### Parental wellbeing

Parental wellbeing was assessed using the Parenting Sense of Competence Scale (PSOC)[62] and the Depression Anxiety Stress Scales (DASS)[63].

The PSOC includes 17 items designed to measure parental self-efficacy, and generates scores on three subscales: Satisfaction, Interest and Efficacy. The PSOC was scored such that higher scores indicated higher levels of self-perceived competency. This involved reverse scoring the Efficacy subscale, on which higher scores indicate lower levels of efficacy. The PSOC has strong psychometric properties including satisfactory internal consistency, rest-retest reliability, convergent validity with measures of child behaviour and high levels of temporal stability[17].

The DASS is a 21-item self-report measure that assesses negative affect, generating separate scores for the subscales of Depression, Anxiety and Stress. Higher scores indicate greater symptomatology. The DASS-21 has excellent psychometric properties with high levels of internal consistency across the Depression, Anxiety and Stress subscales as well as high levels of temporal validity, higher levels of convergent validity than other anxiety and depression scales[63-65].

### Autism severity

The severity of the child's autism symptoms was measured using the Social Communication Questionnaire (SCQ)[66] and the Autism Diagnostic Observation Schedule (ADOS)[67] or the ADOS second edition[68].

The SCQ is a 40-item, parent-report measure of autism-specific symptoms, with higher scores indicating increased autism severity. The SCQ produces a total score, with a score of 15 or greater considered being indicative of autism. The SCQ has three subscales assessing problems in the domain of communication (SCQ Communication subscale), problems in reciprocal social interaction (SCQ Social subscale) and the presence of restricted, repetitive and stereotyped behaviours (SCQ RRSB subscale). A greater score on each subscale indicates a greater level of difficulty. The SCQ has robust psychometric properties including levels of interenal consistency, test-retest reliability and good discriminative validity between preschoolers with autism and non-clinical samples[69-71].

The ADOS and ADOS-2 are semi-structured, standardised play-based assessments to examine key symptoms of autism including communication, social interaction, play and creativity, and other behaviours including restricted and repetitive behaviours[67,68]. The assessment was conducted by researchers trained in the administration and scoring of the ADOS. The ADOS has a cutoff score above which autism is considered and it also provides scores indicating the likely level of severity of autism spectrum symptoms. The ADOS and ADOS-2 have sound psychometric properties, including high levels of internal consistency, interrater reliability, test-retest reliability and diagnostic predictive validity[67,68]

Children's adaptive functioning was assessed using the Vineland Adaptive Behaviour Scales, Second Edition (VABS-II)[72]. The VABS-II assesses parents' perceptions of their child's everyday adaptive functioning across broad domains including communication, daily living skills, socialisation and motor skills. A norm-referenced standardised Adaptive Behaviour Composite is calculated, with higher scores indicating greater levels of adaptive functioning. The maladaptive behaviour domain assesses problem behaviours, with higher scores indicating greater difficulties. The VABS-II has well-established strong psychometric properties in the preschool age group, including high levels of internal consistency, test-retest reliability, interrater reliability and has been found to be a valid measure of the severity of autism symptomology[72].

### Socio-economic status

SES is used in this paper to describe the position of a person within a hierarchical social structure[73]. Two mechanisms were used to assess SES; the first was based on parents' occupation and education levels using the Australian Socioeconomic Index of occupational status (AUSEI06)[74]. The AUSEI06 is a socio-economic index developed in response to the introduction of the Australian and New Zealand Standard Classification of Occupations (ANZSCO) by the Australian Bureau of Statistics[75]. The AUSEI06 is used to convert ANZSCO codes into occupational status scores ranging from 0 to 100, with higher scores indicative of higher SES. Where both parents are employed, the AUSEI06 is calculated by taking the score of the parent with the highest occupational status. When an individual is not in paid employment, the score is assigned using his or her educational level. Where two parents indicated employment - the highest AUSEI06 code was used; where one parent indicated employment, their AUSEI06 code was used; where neither parent was employed, the highest imputed AUSEI06 code was used. The AUSEI06 is based on the International Socioeconomic Index[76] in which occupation is described as the "engine" that converts education into income. The AUSEI06 possesses adequate psychometric properties[75].

The second mechanism of assessing SES was the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) from the Socio-economic Indexes for Areas (SEIFA) 2016 based on the 2016 Census of Population and Housing[77,78]. The definition of relative advantage and disadvantage refers to "people's access to material and social resources, and their ability to participate in society"[79], with the IRSAD providing a summary measure[77,78]. Percentile ranking of postcodes from across Australia can be used to ascertain the SEIFA score. Lower scores indicate relatively greater disadvantage and general lack of advantage, while higher scores indicate generally greater advantage and a relative lack of disadvantage[78].

*Statistical analysis*

Statistical analyses were conducted using SPSS version 25.0. *T*-tests were used to compare participants' scores on the PSOC and DASS to Australian normative data presented by Rogers and Matthews[17] for the PSOC and Crawford *et al*[78] for the DASS. Pearson's *r* correlations were conducted to examine relationships between SES, parental wellbeing and severity of autism symptoms, with hierarchical multiple regression then used to explore possible moderating effects of SES. Correlations were considered as statistically significant for $P \leq 0.01$ to partially control for multiple comparisons, however relationships to $P \leq 0.03$ are reported to examine trends. Cohen's categorisation of correlation coefficients was used in this study with $\geq 0.1$ denoting a small effect size, $\geq 0.3$ a medium effect size and $\geq 0.5$ a large effect size[80].

## RESULTS

Of the 165 children enrolled at the Centre in the study period, data for at least one parent for the PSOC and/or the DASS and at least one measure of socio-economic background was available for 117 children. For the PSOC, data was available for 107 mothers and 54 fathers; for the DASS, data was available for all subscales for 101 mothers and 53 fathers. Demographic information is presented in Table 1. The majority of children were male, with a mean age of 4.1 years at the time of enrolment. More than half were from a culturally and linguistically diverse (CALD) background, and close to half had English as an additional language spoken at home. The most common languages spoken at home were Vietnamese (*n* = 20, 18% of sample) and Arabic (*n* = 11, 9.9% of sample). Mothers were the predominant primary carer. In terms of SES, the majority of families lived in postcode areas in the bottom and middle thirds of IRSAD. However, when considering the AUSEI06 rankings, the majority of the sample fell in the top third.

Means and standard deviations for measures of ASD symptom severity are reported in Table 2. Means and standard deviations for measures of PSOC and DASS are presented in Table 3, with Table 4 providing results comparing our data with the Australian normative data presented by Rogers and Matthews[17] for the PSOC and Crawford *et al*[78] for the DASS.

There were no statistically significant differences on any of the three subscales of the PSOC between mothers and fathers in our sample. When compared with the Australian normative data presented by Rogers and Matthews[17], mothers in our sample had significantly higher levels of parenting sense of efficacy, but lower levels of interest in the parenting role and comparable levels of satisfaction. For fathers in our sample, there were no differences in levels of parenting satisfaction compared with the normative data. However, they had significantly higher levels of parenting efficacy and lower levels of interest in the parenting role than the normative data.

There were also no statistically significant differences in levels of symptoms of depression, anxiety or stress as measured by the DASS between mothers and fathers in our sample. However, mothers in our sample had significantly greater levels of symptoms of depression, anxiety and stress than the Australian normative data presented by Crawford *et al*[78]. Fathers in our sample on the also had significantly greater levels of symptoms of depression than the normative data. However, there were no differences in the levels of symptoms of anxiety or stress between fathers in our sample compared with normative data.

There were no statistically significant differences between scores of parental wellbeing and levels of symptoms of depression, anxiety or stress as measured by the DASS among CALD and non-CALD mothers and fathers. There was also no statistically significant difference in the levels of parenting satisfaction as measured by the PSOC between CALD and non-CALD mothers and fathers.

There were no statistically significant correlations between measures of SES and measures of ASD symptom severity. There was a small but significant positive correlation between SES, measured through the IRSAD and mothers' interest in parenting scores (Table 5). No other correlations between measures of SES and parenting sense of competence or wellbeing met significance.

There were small but significant negative correlations between children's communication skills and mother's parenting satisfaction and small to moderate negative correlations between mothers' sense of parenting efficacy and children's communication skills and restrictive, repetitive and stereotyped behaviours (Table 5). There was also a trend towards a small negative correlation between children's social interaction skills and maternal parenting satisfaction, and a trend towards a small positive correlation between children's adaptive functioning and maternal satisfaction.

| Table 1  Demographic information | |
| --- | --- |
| **Demographic information** | ***n* (%)** |
| Sex of child (male: female, *n* = 117) | 96 (82.1): 21 (17.9) |
| Age of child in years at enrolment at Centre (*n* = 117) | |
| mean (SD) | 4.13 (0.53) |
| Median (range) | 4.15 (2.74-5.79) |
| Country of birth of child (Australia: overseas, *n* = 110) | 106 (96.4): 4 (3.6) |
| Indigenous background (*n* = 88) | 4 (4.5) |
| CALD background (*n* = 107) | 63 (58.9) |
| English as additional language (*n* = 111) | 49 (44.1) |
| Primary carer (*n* = 75) | |
| Mother | 68 (90.7) |
| Father | 5 (6.7) |
| Other extended family | 2 (2.7) |
| IRSAD percentile ranking (*n* = 116) | |
| mean (SD) | 38.8 (25.06) |
| Median (range) | 34 (4-95) |
| IRSAD categories (*n* = 111) | |
| Lowest third | 43 (38.7) |
| Middle third | 49 (44.1) |
| Top third | 19 (17.1) |
| AUSEI06 percentile ranking (*n* = 112) | |
| mean (SD) | 65.56 (20.56) |
| Median (range) | 71.6 (7.9-100) |
| AUSEI06 (*n* = 109) | |
| Lowest third | 7 (6.4) |
| Middle third | 33 (30.3) |
| Top third | 69 (63.3) |

CALD: Culturally and linguistically diverse; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; AUESI06: Australian Socioeconomic Index 2006.

No correlations between fathers' parenting sense of competence and severity of children's ASD symptoms met significance. There were also no significant correlations between mothers' or fathers' sense of wellbeing as measured through the DASS and severity of ASD symptoms.

There were significant correlations between mothers' DASS and PSOC scores, fathers' DASS and PSOC scores and the PSOC and DASS scores of mothers and fathers (results not reported; contact authors for results) (Table 6).

When correlations were conducted splitting the groups into three levels of SES (low - 0-33.3 percentiles, medium - 33.4-66.6 percentiles and high - 66.7 to 100 percentiles for the AUSEI06 and IRSAD separately), there were significant correlations between parenting sense of competence and wellbeing for different levels of SES, particularly for those in the higher SES brackets (Table 5). No results are presented for fathers in the middle SES tertile when using the AUSEI06 as the sample size was less than 10. It is noteworthy that there were no significant correlations for mothers or fathers between symptoms of stress measured through the DASS against child's ASD symptom severity when the sample was split into the three SES groupings.

Moderation analyses revealed no significant interaction between SES (AUSEI06 or IRSAD) and ASD symptom severity as measured by VABS adaptive and maladaptive functioning scores, SCQ scores or ADOS comparison scores for any parent measures of parenting sense of competence or wellbeing.

## DISCUSSION

This study sought to assess the extent to which SES moderates the impact of child-specific factors on the psychological wellbeing and sense of parenting competency in mothers and fathers of preschoolers with autism. We found that, while there was no

| Table 2  Means and standard deviations for measures of autism spectrum disorder symptom severity | |
| --- | --- |
| ASD symptom severity measure | mean (SD, range) |
| SCQ communication (*n* = 109) | 5.66 (2.09, 0-12) |
| SCQ social (*n* = 110) | 7.19 (3.47, 0-14) |
| SCQ RRSB (*n* = 110) | 4.36 (2.32, 0-8) |
| SCQ total (*n* = 110) | 18.36 (6.29, 2-36) |
| VABS adaptive (*n* = 99) | 64.56 (12.48, 42-106) |
| VABS maladaptive (*n* = 106) | 19.26 (1.87, 15-24) |
| ADOS severity score (*n* = 99) | 7.11 (1.76, 1-10) |

SCQ: Social Communication Questionnaire; RRSB: Restricted, repetitive and stereotyped patterns of behaviour; VABS: Vineland Adaptive Behavior Scales; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism spectrum disorder.

effect of SES on levels of parental wellbeing or parenting competence and efficacy overall, distinct factors impacted the wellbeing of mothers and fathers.

While there has been significant research examining the wellbeing of parents of children with autism, the majority of this research has been primarily focused on the experiences of mothers[80]. While there was no statistically significant relationship between SES and paternal wellbeing or competence across our whole sample, there was a moderate trend towards lower levels of family SES being associated with increased levels of stress and anxiety among fathers. This trend is broadly consistent with previous qualitative research that has highlighted fathers of children with autism often take up the role of "breadwinner"[81], consequently lower personal SES may have a greater impact on fathers. Our findinng of a trend in this direction rather than a signifciant finding may reflect the limited sensitivity of the AUSEI06, which estimates SES based on parental occupation or education levels, as an accurate estimate of personal SES. Our findings do however contrast the results of much of the existing literature which has not found an influence of SES on parental wellbeing[25,82,83] or has found that higher personal SES was associated with increased wellbeing among mothers but not fathers[58]. These different findings may be due to differences in the conceptualisation of SES and the homogeneous demographic characteristics of the previous studies. These studies used measures such as household income[58] or composite estimates of SES that incorporated personal disadvantage, occupational status and income[25] or educational status and overall income[82]. The disparity in these findings suggest that further research is needed with more sensitve tools and more specific categorisations of SES to better understand the impact of SES on fathers and mothers of preschoolers with autism.

Importantly, our study revealed further differences in the effect of child-specific factors on the parenting competence and wellbeing of mothers and fathers was affected by both gender and SES. In this regard, parent reports of child ASD symptom severity and adaptive functioning were associated with lower satisfaction and efficacy among mothers but not among fathers. When the relationship between SES and parental efficacy and satisfaction was examined separately across the three SES brackets, this relationship was only found among mothers in the highest family and highest and middle community SES brackets. Among fathers in the highest family SES bracket from advantaged backgrounds, greater levels of maladaptive behaviour and greater symptom severity in children were associated with a lower sense of parenting efficacy.

The finding that low paternal parenting efficacy is associated with greater child maladaptive behaviours is consistent with the findings of earlier studies that have found a similar relationship among fathers of typically developing children[63,83]. However, it is unclear why our finding was specific to fathers from higher SES brackets only. One possible explanation is that parents with a higher SES have higher expectations of their children compared to parents with a lower status[84]. Alternatively, parents in higher SES brackets who are working may have less time to spend with their children and address their behavioural needs. This novel finding warrants replication with a larger sample of fathers to clarify whether differences exist between the effect of community SES and personal SES on paternal wellbeing and to explore the underpinnings of such a differential relationship.

There was also a trend towards maternal depression and lower levels of adaptive skills that was found to be significant among mothers from the highest community

| Table 3 Means and standard deviations for mothers' and fathers' parenting sense of competence and symptoms of depression, anxiety and stress | | |
| --- | --- | --- |
| | Mothers, mean (SD, range) | Fathers, mean (SD, range) |
| PSOC satisfaction | 3.67 (1.04, 1-6), *n* = 107 | 3.74 (0.91, 2.17-5.67), *n* = 54 |
| PSOC efficacy | 4.34 (0.89, 1.43-6), *n* = 107 | 4.31 (0.67, 2.71-5.71), *n* = 54 |
| PSOC interest | 4.88 (1.12, 1-6), *n* = 107 | 4.66 (1.00, 2.50-6), *n* = 54 |
| DASS depression | 3.57 (3.68, 0-13), *n* = 102 | 3.78 (4.32, 0-16), *n* = 54 |
| DASS anxiety | 2.76 (3.03, 0-11), *n* = 101 | 2.45 (3.01, 0-13), *n* = 53 |
| DASS stress | 5.32 (3.92, 0-15), *n* = 101 | 5.04 (4.42, 0-15), *n* = 53 |

PSOC: Parenting Sense of Competence; DASS: Depression Anxiety Stress Scale.

SES bracket. However other relationships emerged between child-related factors and paternal wellbeing. Overall our results suggest that symptom severity may have a greater impact on the wellbeing, efficacy and competence of higher SES parents and contradicts the findings of earlier studies that symptom severity and adaptive functioning affects maternal distress but not paternal distress[20-22]. Notably the experiences of parents of children with autism from different SES brackets have not been examined separately as such these findings contribute to a more nuanced understanding of the influence of SES on parental wellbeing and efficacy. Further investigation is however needed to untangle the differential effects between fathers versus mothers and those from high versus low SES (personal SES) and those from deprived versus advantaged backgrounds (community SES).

Interestingly the differences between mothers and fathers in parenting competence and wellbeing in our sample emerged only in the analysis of parental reports of their child's ASD symptom severity using SCQ but no differences emerged in the analysis of severity as measured by the gold standard ADOS assessments. As a parent report measure, the SCQ score may better reflect parental awareness and perception of symptoms and their severity as opposed to the objective measure of the ADOS.

Consistent with our hypothesis, we found significantly greater levels of symptoms of depression, anxiety and stress among mothers of children with autism compared to the normative Australian data, and higher levels of symptoms of depression in fathers. Our findings of elevated symptoms of depression, anxiety and stress levels in mothers with children with ASD is consistent with previous research[4,10,85,86]. We also found that fathers experienced significantly more symptoms of depression but comparable levels of anxiety and stress levels to the normative sample. This is also in keeping with the existing data where mothers have been found to have lower wellbeing scores and higher stress scores compared to fathers of children with autism[37,87-89]. It is possible that the primary responsibility for caring for a child with autism has traditionally rested with mothers and the adverse psychological impact observed in mothers may be a function of this primary carer responsibility rather than the gender of the parent[21]. While in our sample the primary caregiver role was also predominantly served by the mothers, the intervention program delivered through the Centre encourages the involvement of both parents. This in turn may have resulted in fathers in our sample also being closely involved in parenting and early intervention services and therefore experiencing similar levels of depression, anxiety and stress as the mothers. While previous studies found that the depressive symptoms reported by fathers of children with autism were comparable to those reported by fathers of typically developing children[88], these studies have included parents of school aged children and adolescents who may have different parenting demands. Our study suggests that both mothers and fathers of preschoolers with autism may be at risk of heightened psychological distress.

Both mothers and fathers in our sample displayed greater parental efficacy but lower interest in the parenting role compared with normative samples[17], with mothers also displaying greater satisfaction with their parenting. This extends the findings of previous research carried out at the same early intervention centre[18] in a larger sample and provides information on not only mothers but also fathers. While other studies have found lower parenting efficacy among mothers of children with autism[12,90], our finding of increased parental self-efficacy may be due to the parental involvement and participation in the early intervention program for ASD that is provided at the Centre where the study was conducted. Similar finding of better parenting efficacy has been found following behavioural interventions for ADHD[91,92]. Further research using community-based recruitment methods are necessary to understand the nature and interaction of the relationship between parenting

| Table 4 Comparison of our data with normative data | | |
| --- | --- | --- |
| | **Mothers** | **Fathers** |
| PSOC satisfaction[1] | t(864) = 2.160, P = 0.031[a] | t(351) = -1.572, P = 0.117 |
| PSOC efficacy[1] | t(864) = 13.065, P < 0.001[d] | t(351) = 3.788, P < 0.001[d] |
| PSOC interest[1] | t(125.573) = -2.036, P = 0.044[a] | t(61.599) = -2.972, P = 0.004[b] |
| DASS depression[2] | t(597) = 2.399, P = 0.017[a] | t(549) = 2.158, P = 0.031[a] |
| DASS anxiety[2] | t(596) = 3.318, P = 0.001[b] | t(548) = 1.760, P = 0.079 |
| DASS stress[2] | t(596) = 2.090, P = 0.004[b] | t(548) = 1.703, P = 0.089 |

[a]P < 0.05.
[b]P < 0.01.
[d]P < 0.001.
[1]Compared with normative data presented in Rogers and Matthews[17].
[2]Compared with normative data presented in Crawford *et al*[78].
PSOC: Parenting Sense of Competence; DASS: Depression Anxiety Stress Scale.

preschoolers with autism and parenting efficacy vis-a-vis participation in early intervention programs. The limited associations between child ASD symptom severity, child adaptive and maladaptive behaviours and SES on parental wellbeing and parenting sense of competence suggests that other factors may play an important role. The large relationship between scores on the Parenting Sense of Competency and Depression, Anxiety and Stress Scale in supplementary analyses suggests an interrelationship between these facets, consistent with the previous literature[12,15,16], however the directionality of this relationship needs further exploration. Further, the large relationship between mothers' and fathers' wellbeing and sense of competency suggests the interdependence of parenting competence and wellbeing within a family. These relationships also provide insight into the lack of differences in wellbeing and parenting competence between mothers and fathers. Our finding of no relationship between SES and ASD symptomology is contrary to our hypothesis and deserves further exploration. Given the suggestion that autism in the absence of intellectual disability may be diagnosed later among lower SES families[53,91-93], and the low numbers of families from the lowest AUSEI06 categories who participated in this study, it is possible that our study may not have fully captured the impact of SES on ASD severity.

The current study has the advantage of exploring both maternal and paternal wellbeing and sense of competence in parents of preschoolers with autism whereas much of the previous literature has not included fathers of children with autism. Additionally this study had a high proportion of children from CALD backgrounds and it is of interest that there were no significant differences between the wellbeing and competence of parents from CALD and non CALD backgrounds in our study. However, our study examines this only in those attending an Autism Specific Early Learning and Care Centre (ASELCC) in one specific location in Australia. Whether these findings extend to parents of preschoolers attending other ASELCCs throughout Australia, attending other childcare or preschool settings or not attending any out of home day care needs to be verified through further research.

Our study also had a limited number of families in the lowest family SES category based on AUSEI06, with a particularly restricted limited number of fathers in the lower SES categories. Since it has been suggested that lower SES families may experience delays in diagnosis due to differential access to diagnostic services[53,91-93], it is possible that lower SES families have not had the benefit of early identification and enrolment to early intervention such as the centre from where this study was conducted. Alternatively, it is possible that lower income families were less likely to participate in research due to time constraints.

As with much of the existing literature, the recruitment from a centre which provides specialised services for children with ASD may have resulted in sampling bias, as the parents of these children are already showing parenting interest and efficacy by virtue of the fact that they have sought early intervention support. It is possible that the relationship between the factors we assessed may differ among families with limited access to early intervention, health or social services programs. Future studies which recruit from the community settings may overcome these limitations.

Another potential reason for the limited number of parents categorised to be in the low family SES group in this study may be due to inflation of AUSEI06 scores for families with no parent reported to be working. In such circumstances, the AUSEI06

**Table 5  Means and standard deviations for culturally and linguistically diverse and non-culturally and linguistically diverse parents' parenting sense of competence and symptoms of depression, anxiety and stress**

|  | CALD, mean (SD, range) | Non-CALD, mean (SD, range) |
| --- | --- | --- |
| **Mothers** | | |
| PSOC satisfaction | 3.65 (1.06, 1.2-5.6), *n* = 57 | 3.78 (0.98, 2-6), *n* = 41 |
| PSOC efficacy | 4.32 (0.84, 1.86-6), *n* = 57 | 4.34 (0.99, 1.43-5.71), *n* = 41 |
| PSOC interest | 4.76 (1.3, 1-6), *n* = 57 | 5.01 (0.90, 3-6), *n* = 41 |
| DASS depression | 3.39 (3.56, 0-13), *n* = 51 | 3.49 (3.77, 0-13), *n* = 41 |
| DASS anxiety | 2.66 (2.97, 0-9), *n* = 50 | 2.63 (2.99, 0-11), *n* = 41 |
| DASS stress | 5.60 (3.57, 0-13), *n* = 50 | 4.61 (4.41, 0-15), *n* = 41 |
| **Fathers** | | |
| PSOC satisfaction | 3.90 (0.93, 2.17-5.67), *n* = 29 | 3.55 (0.78, 2.33-5), *n* = 20 |
| PSOC efficacy | 4.35 (0.93, 3-5.71), *n* = 29 | 4.26 (0.80, 2.71-5.57), *n* = 20 |
| PSOC interest | 4.52 (0.95, 2.5-6), *n* = 29 | 4.85 (1.05, 2.5-6), *n* = 20 |
| DASS depression | 2.70 (3.68, 0-15), *n* = 30 | 5.10 (4.99, 0-16), *n* = 20 |
| DASS anxiety | 2.45 (2.71, 0-11), *n* = 29 | 2.35 (3.51, 0-13), *n* = 20 |
| DASS stress | 4.24 (3.77, 0-15), *n* = 29 | 5.85 (5.07, 0-15), *n* = 20 |

CALD: Culturally and linguistically diverse; PSOC: Parenting Sense of Competence; DASS: Depression Anxiety Stress Scale.

score is based on education level, however the current study did not differentiate between TAFE or other vocational educational or post-secondary education and university bachelor level qualifications. Thus, all who indicated tertiary level education received the same higher AUSEI06 score. This use of educational level to impute SES may be particularly problematic in the case of parents of children with autism and other developmental disabilities as previous studies have found that although parents tend to have higher education levels, due to the significant challenges in caring for their children, they may be unemployed or underemployed and may have lower than expected income compared to their full educational potential[42,58,94-98]. Further, the AUSEI06's failure to consider the extent to which a parent participates in the workforce, whether full time or part time, could have also inflated parental SES. The majority of studies examining SES have failed to include personal and environmental measures of SES and the inclusion of a measure of community SES is a significant strength of our study. Further exploration of the relationship between ASD symptom severity and parental wellbeing and sense of parenting competency using alternative measures of SES such as household income is therefore required.

Our study suggests that SES differentially impacts wellbeing and sense of parenting competence and its relationship to the impact of child symptoms for mothers and fathers of preschoolers with autism. Such differences between mothers and fathers need to be further understood to inform targeted parental intervention. Given the integral role of parents in ensuring the success of early intervention programs[13], it is essential that these interventions address the determinants of parental wellbeing as well as child-specific outcomes.

**Table 6 Significant correlations between measures of parenting sense of competence and wellbeing and autism spectrum disorder symptom severity for the whole sample and by levels of socioeconomic status**

| Mothers | | | Fathers | | |
|---|---|---|---|---|---|
| Full sample | Sample by AUSEI06 | Sample by IRSAD | Full sample | Sample by AUSEI06 | Sample by IRSAD |
| **PSOC satisfaction** | | | | | |
| Negative: SCQ communication, r(99) = -0.270, *P* = 0.007 | **Top third of SES:** Negative: SCQ total, r(60) = -0.317, *P* = 0.013 | **Middle third of SES:** Negative: SCQ communication, r(39) = -0.457, *P* = 0.003 | | | |
| Negative: SCQ total, r(100) = -0.264, *P* = 0.008 | Negative: SCQ communication, r(59) = -0.300, *P* = 0.021 | **Top third of SES:** Negative: SCQ communication, r(17) = -0.545, *P* = 0.024 | | | |
| Negative: SCQ social, r(100) =-0.226, = 0.024 | | Negative: SCQ RRBI, r(17) = -0.553, *P* = 0.021 | | | |
| Positive: VABS - adaptive, r(90) = 0.235, *P* = 0.026 | | Negative: SCQ total, r(17) = -0.572, *P* = 0.016 | | | |
| **PSOC efficacy** | | | | | |
| Negative: SCQ social, r(100) = -0.291, *P* = 0.003 | **Top third of SES:** Positive: VABS - adaptive, r(56) = 0.360, *P* = 0.006 | **Top third of SES:** Negative: SCQ communication, r(17) = -0.719, *P* = 0.001 | | **Top third of SES:** Negative: VABS - maladaptive, r(37) = -0.461, *P* = 0.004 | **Bottom third of SES:** Negative: VABS - maladaptive, r(23) = -0.487, *P* = 0.018 |
| Negative: SCQ RRSB, r(100) = -0.307, *P* = 0.002 | Negative: SCQ total, r(60) = -0.374, *P* = 0.003 | Negative: SCQ social, r(17) = -0.609, *P* = 0.010 | | Negative: SCQ total, r(39) = -0.449, *P* = 0.004 | |
| Negative: SCQ total, r(100) = -0.348, *P* < 0.001 | Negative: SCQ Social, r(60) = -0.304, *P* = 0.018 | Negative: SCQ Total, r(17) = -0.660, *P* = 0.004 | | | |
| Positive: VABS - adaptive, r(90) = 0.230, *P* = 0.029 | Negative: SCQ RRBI, r(60) = -0.312, *P* = 0.015 | | | | |
| **PSOC interest** | | | | | |
| Positive: IRSAD, r(106) = 0.278, *P* = 0.004 | | **Middle third of SES:** Negative: SCQ communication, r(39) = -0.364, *P* = 0.023 | | | |
| | | **Top third of SES:** Negative: SCQ communication, r(17) = -0.553, *P* = 0.021 | | | |
| **DASS depression** | | | | | |
| Negative: VABS - adaptive, r(85) = -0.258, *P* = 0.017 | | **Top third of SES:** Negative: VABS - adaptive, r(14) = -0.664, *P* = 0.010 | Negative: AUSEI06, r(52) = -0.323, *P* = 0.020 | | |
| Positive: SCQ total, r(95) = 0.238, *P* = 0.020 | | | | | |
| **DASS anxiety** | | | | | |
| | | **Top third of SES:** Positive: VABS - maladaptive, r(14) = 0.644, *P* = 0.013 | Negative: AUSEI06, r(52) = -0.316, *P* = 0.023 | | |
| **DASS stress** | | | | | |
| | | **Top third of SES:** Positive: ADOS comparison (severity) score, r(14) = 0.635, *P* = 0.015 | Negative: AUSEI06, r(53) = -0.305, *P* = 0.026 | | |

The value in parenthesis after "r" is the sample size for the analysis (*n*). PSOC: Parenting Sense of Competence; DASS: Depression Anxiety Stress Scale; SCQ: Social Communication Questionnaire; VABS: Vineland Adaptive Behavior Scales; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; AUESI06: Australian Socioeconomic Index 2006; SES: Socioeconomic status.

## ARTICLE HIGHLIGHTS

### Research background

There is converging evidence that higher levels of stress and psychological distress is experienced by parents of children with autism compared to typically developing children.

### Research motivation

There is limited research on the role of socioeconomic status (SES) on the wellbeing of parents of preschool children with autism and its impact if any on parental competency and children's autism symptom severity

### Research objectives

The primary objective of this study was to examine the relationship between symptom severity, SES and psychological wellbeing among parents of preschoolers with autism. The findings will have implications for future planning of services to support the parents and also for future research on family and psychosocial predictors of treatment response.

### Research methods

The study assessed parents (mothers and fathers) of preschool-aged children with autism on their own perceptions of parental competence and wellbeing using questionnaires and children were assessed using objective standardised measures of autism severity, cognitive level and parent reports of adaptive functioning.

### Research results

A differential impact was observed for mothers and fathers as to the impact of SES and their child's symptom severity on their parenting competence and sense of wellbeing.

### Research conclusions

The findings from this study suggest that SES differentially impacts the wellbeing and sense of parenting competence in fathers and mothers of preschool children with autism. While both mothers and fathers displayed higher levels of depression than normative populations, mothers also reported greater levels of stress and anxiety. Child symptom severity was associated with maternal parenting competency, and this was exaggerated among mothers with higher familial SES and who lived in areas of greater neighbourhood advantage. However, paternal parenting competence was generally not influenced by child adaptive functioning or symptom severity, albeit for those from higher familial SES background, there was an inverse relationship between children's symptom severity and maladaptive symptoms and paternal sense of parenting efficacy. This has implications for service provision as it highlights the need for comprehensive assessment of the support needs for both fathers and mothers independently.

### Research perspectives

Since this study was done in a specialised early intervention centre, the findings may have been influenced by sampling bias in terms of access to such services. In this regard, families in the lowest SES category were underrepresented and this was particularly the case for father participation in this research project. It is possible that lower SES families may not have had the benefit of early identification and enrolment to early intervention centres such as the one where this project was undertaken. This may have been compounded by the fact that fathers from lower SES background may have less time availability and capacity to participate in research. Future studies would benefit from targeted recruitment of those sections of the autism community who are currently not engaging with routine health services and are also underrepresented in research.

## ACKNOWLEDGEMENTS

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**EDITORIAL**

# Evidence for using pimavanserin for the treatment of Parkinson's disease psychosis

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## Abstract

The aim of this editorial is to evaluate the evidence for using pimavanserin for the treatment of Parkinson's disease psychosis (PDP) from randomized controlled trials (RCTs). We only identified two published trials that evaluated the use of pimavanserin among individuals with PDP. Both studies found that pimavanserin improved psychotic symptoms among individuals with PDP when compared to placebo. Pimavanserin was fairly well tolerated in both studies and did not appear to cause significant sedation or worsen motor symptoms among individuals with PDP. However, given the limited data, additional confirmatory studies are required before pimavanserin can be considered as a first line agent for the treatment of psychotic symptoms among individuals with PD.

**Key words:** Pimavanserin; Parkinson's disease; Parkinson's disease psychosis; Psychosis; Antipsychotic

**Core tip:** Pimavanserin is an atypical antipsychotic that was the first medication to be

approved by the Food and Drug Administration for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). There are only two published trials that have evaluated the use of pimavanserin among individuals with PDP. Both studies are of good quality and found that pimavanserin improves psychotic symptoms among individuals with PDP when compared to placebo. Additionally, pimavanserin was fairly well tolerated in both studies and did not appear to cause significant sedation or worsen motor symptoms among individuals with PDP.

# INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that presents with tremors, bradykinesia, rigidity and postural instability[1]. After Alzheimer's disease (AD), PD is the second-most common neurodegenerative disorder in the United States[2]. Approximately 630000 individuals in the United States have a diagnosis of PD, with the diagnosed prevalence of PD likely to double by 2040. The prevalence for PD increases with age ranging from approximately 41 per 100000 people of 40 to 49 years of age to 1903 per 100000 population in individuals ≥ 80 years of age[3]. The economic burden of PD is reflected by the incurred medical expenses approximating $14 billion in 2010 which was $8.1 billion higher than expected for a similar population without PD[2].

Psychotic symptoms are not uncommon among individuals with PD with a prevalence rate of approximately 25%-30%[4,5]. The National Institute of Neurological Disorders and Stroke and National Institute of Mental Health combined work group used the term "PD psychosis" (PDP) to describe the various psychotic symptoms that present as a continuum of PD progression rather than representing a distinct symptom class[6]. For the diagnosis of PD psychosis to made, the following criteria should be met: (1) The presence of at least one of the following symptoms: illusions, false sense of presence, hallucinations or delusions; (2) A primary diagnosis of PD; (3) Meet the United Kingdom brain bank criteria for PD; (4) The psychotic symptoms occurred after the diagnosis of PD was made; (5) The symptom(s) are recurrent or continuous for 1 mo; (6) The symptoms are not better accounted for by another cause of Parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium; and (7) These symptoms could be associated with or without insight, with or without dementia, and with or without treatment for PD.

Risk factors for PDP include the presence of dementia, older age, reduced vision, longer duration of illness, high severity of illness, presence of depression, sleep disturbance and REM behavior disorder, axial rigidity subtype of PD, and exposure to dopamine agonists (DA)[7,8]. The presence of PDP is associated with greater caregiver stress, poorer quality of life for the individual with PD, higher rates of institutionalization or nursing home placement, and increased mortality[8]. A recent analysis of all health resource utilization (HRU) and total costs found that mean 12-mo HRU per patient was 2.3 times higher and costs were 2.1 times higher in the PDP cases, while falls were 3.4 times higher and fractures 2.3 times higher respectively[9].

The pathogenesis of PDP is yet to be clearly understood but present data indicates significant dysfunction in attention, executive functions, and visuospatial functions in these individuals[10]. Additionally, neuroimaging studies reveal grey matter atrophy in regions of the brain corresponding to dorsal and ventral visual pathways, the hippocampus, and cholinergic structures. Furthermore, functional imaging studies suggest the existence of an aberrant top-to-bottom visual processing system which dominates the normal bottom-to-top system in individuals with PD and visual hallucinations. Nucleotide polymorphisms of several genes have been studied among individuals with PDP, but thus far the 45C>T polymorphisms of the cholecystokinin gene (*CCK*) appears to have had the most potential in elucidating pathological pathways of PDP[10].

PDP may also occur partially due to medications that are used to the treat motor symptoms of PD[11]. Hence, a part of treating PDP also involves the reduction or discontinuation of anticholinergic medications, monoamine oxidase inhibitors, levodopa, or DA which may be worsening or causing symptoms of PDP[12,13]. If medication adjustments are not appropriate or they do not resolve the PDP symptoms, then available data from controlled trials indicate there is some benefits for use of antipsychotic medications, the acetylcholinesterase inhibitor-rivastigmine, and NMDA antagonist-memantine for treating PDP[4]. Uncontrolled trials also indicate some benefit for low-dose apomorphine[4,14-17] and electroconvulsive therapy (ECT)[18-20] for treating PDP. However, none these therapies are approved by the United States Food and Drug Administration (FDA) for the treatment of PDP.

A recent systematic review by Wilby *et al*[21] that assessed the treatment for PDP included data from 16 studies. Eleven of these studies compared active drugs to placebo whereas 5 studies compared clozapine to another active drug. The placebo-controlled trials demonstrated benefit for clozapine and pimavanserin (Nuplazid) for the treatment of PDP with no definitive benefits noted for either quetiapine or olanzapine. The comparative studies demonstrated improvements in PDP symptoms when clozapine or comparator drug were assessed alone. However, the data did not suggest any superiority of one active drug over the other drugs.

Pimavanserin is an atypical antipsychotic medication and is now the first medication to be approved by the FDA for the treatment of hallucinations and delusions associated with PDP[22]. Pimavanserin is a selective 5-HT2A inverse agonist that has low affinity for 5-HT2C and sigma-1 receptors. Additionally, pimavanserin lacks activity at dopaminergic, muscarinic, adrenergic, and histaminergic receptors. Pimavanserin is mainly metabolized in the liver through the cytochrome P450 system (CYP3A4 and CYP3A5) and is excreted primarily through the urine. Approximately 95% of pimavanserin is protein bound. Pimavanserin has a mean peak onset in 6 h with a half-life of 55 to 60 h.

## EVIDENCE FOR USING PIMAVANSERIN FOR THE TREATMENT OF PARKINSON'S DISEASE PSYCHOSIS

We identified and reviewed a total of two randomized controlled trials (RCTs) that evaluated the use of pimavanserin among individuals with PDP[23,24]. Both studies were rated as being of good quality based on the center for evidence-based medicine criteria[25] (Table 1). We discuss both studies in depth below, while a brief summary of both studies is outlined in Table 2.

### Meltzer *et al*[23] study

The study by Meltzer *et al*[23] was a phase 2 multicenter, randomized, placebo-controlled, double-blind trial that compared pimavanserin to placebo among individuals with PDP. The trial was 4 wk in duration with a 4-wk follow-up period. The participants received pimavanserin or placebo in a 1:1 ratio, after completion of screening and baseline evaluations. The dosing of the study drug was 20 mg on day 1 with possible increases to 40 mg a day and 60 mg a day on study days 8 and 15, depending on the participants' response to the medication. The staging of PD was done at baseline using the modified Hoehn and Yahr Unified Parkinson's Disease Rating Scale (UPDRS Part V). The psychotic symptoms were evaluated using the Scale for the Assessment of Positive Symptoms (SAPS), the Parkinson's Psychosis Rating Scale (PPRS) and the Clinical Global Impression-Severity (CGI-S) scale. The effect of treatment on mentation, behavior, mood, complications of therapy and activities of daily living were assessed using the UPDRS Parts I, IV and VI. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale. The motor symptoms were assessed using the UPDRS Parts II (Activities in Daily Living) and III (Motor Examination) respectively. An adverse event check list, vital signs, laboratory tests, physical examinations and electrocardiograms (ECG) were also completed.

The participants were assessed at screening/baseline (up to 14 d prior to study day 1). The study visits were days 1, 8, 15, 28, and 57. Visit day 57 was a safety data evaluation visit. The investigators completed a physical examination, vital signs and laboratory tests at each study visit. From day 1 to 57, the adverse events were noted and assigned severity and relationship to treatment.

The investigators noted improvements in the global rating of hallucination ($P = 0.02$, effect size 0.71), persecutory delusions domain score ($P = 0.009$, effect size 0.69) and in the ideas and delusions of reference domain score ($P = 0.05$, effect size 0.56) in the pimavanserin group when compared to the placebo group. Additionally, improvements were noted in the global rating of delusions ($P = 0.03$, effect size 0.58)

**Table 1  Quality of studies reviewed**

| Name of publication of study | Yr | Random-ization? | Similar groups initially? | Equal treatments? | All participants accounted for? | Analyzed in groups to which they were randomized? | Objective/"bli-nd" treatments? | Overall quality of the study |
|---|---|---|---|---|---|---|---|---|
| Meltzer *et al*[23] | 2010 | Yes | Yes | Yes | Yes | Yes | Yes | Good |
| Cummings *et al*[24] | 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Good |

and the sum of global ratings total (hallucinations and delusions) scores ($P = 0.02$, effect size 0.66) in the pimavanserin group when compared to the placebo group. Furthermore, a trend was noted in improvement in the sum of total (hallucinations and delusions) domain scores ($P = 0.09$, effect size 0.56) in the pimavanserin group when compared to the placebo group. The investigators also noted improvements in the UPDRS Part I total score ($P = 0.05$, effect size 0.43) in the pimavanserin group when compared to the placebo group. Improvements were also noted in the UPDRS IV (complications of therapy) scores ($P = 0.06$, effect size 0.55) in the pimavanserin group when compared to placebo but did not reach statistical significance. However, there were no significant improvements noted in the UPDRS Part II and III ($P = 0.83$, 0.40, 0.74 respectively), the PPRS scores ($P = 0.11$, effect size 0.48), the CGI-S ($P = 0.20$, effect size 0.58) and the UPDRS VI (activities of daily living) scores ($P = 0.22$, effect size 0.41) in the pimavanserin group when compared to placebo group.

The investigators did not identify any significant differences between the pimavanserin and placebo groups on the treatment-emergent adverse events (72.4% *vs* 77.4%). The most common adverse effects noted in the pimavanserin group were somnolence, edema and increase in blood urea nitrogen (all 10.3%). They noted that balance disorder and freezing phenomenon occurred in 6.9% of pimavanserin treated individuals when compared to none of the placebo treated individuals. Additionally, "on and off" phenomenon was noted in 3.4% of pimavanserin treated individuals when compared to none of the placebo treated individuals.

There are multiple weaknesses in in this study to be highlighted. The study had a small sample size; only 44 total subjects (20 in pimavanzserin group and 24 in placebo group) completed the study. There was also noted to be a relatively high attrition rate in the pimavanserin group ($n = 9$ or 31%) compared to placebo group ($n = 7$ or 23%) with the most common reason they dropped out being described as "other reasons". The dropout rate was greater than the estimated 10% dropout rate the authors predicted in their analysis, although they report that ITT and PP analysis results were similar. It is also noteworthy that in the study design utilized relatively rapid dose escalation. Pimavanserin takes 10-14 d to reach steady state. Thus, escalating the dose after 1 wk of treatment may have led to insufficient time to achieve full efficacy. The study also did not assess the time of onset of delusions or hallucinations in relation to the duration of treatment with L-DOPA, which leaves a potential confounding factor. An additional confounding factor to consider is that they also did not assess the efficacy of primavanserin in patients who were not receiving dopaminomimetic drugs. Also since the study is just placebo controlled, there is no comparison of efficacy/tolerability between pimavenserin and other antipsychotics such as cloza-pine.

### Cummings *et al*[24] study

The study by Cummings *et al*[24] study was a randomized, double-blind, parallel group, placebo-controlled trial that enrolled participants with PDP from 52 centers (academic hospitals or neurology research centers) in the United States and two centers in Canada. The eligible participants were randomized to receive either pimavanserin (40 mg daily) or matched placebo in a 1:1 ratio in a double-blind manner. The assessments were completed at baseline and days 15, 29 and 43. The primary outcome was the change in total Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) score from baseline to day 43. The secondary outcomes were the change by day 43 in CGI-S and improvement (CGI-I) scale scores. The other measures were the Zarit 22-item care giver burden scale, scales for outcomes in PD-sleep (parts B and C) assessing night-time sleep quality (SCOPA-NS) and daytime wakefulness (SCOPA-DS) and the UPDRS II and III. Safety was assessed by evaluating the use of concomitant drug use, adverse events, physical examination, clinical laboratory tests, vital signs and ECG.

| Table 2  Summary of studies | | | | | | | |
|---|---|---|---|---|---|---|---|
| Name of study | Yr | Country of origin | Total number of participants | Age | Type of setting | Comparators | Duration |
| Meltzer *et al*[23] | 2010 | United States | 60 | Mean age 70.9 yr | Unclear | Pimavanserin *vs* placebo | 4 wk |
| Cummings *et al*[24] | 2014 | United States and Canada | 199 | Mean age 72.4 yr | Academic hospitals and neurology research centers | Pimavanserin *vs* placebo | 6 wk |

The investigators noted improvements in the total SAPS-PD score ($P = 0.0014$, effect size 0.50), the CGI-I score ($P = 0.0012$, effect size 0.50) and the CGI-S score ($P = 0.0007$, effect size 0.52) in the pimavanserin group when compared to placebo group. Additionally, improvements were noted in the SCOPA-night score ($P = 0.04$, effect size 0.31) and the SCOPA-day wake score ($P = 0.01$, effect size 0.39) in the pimavanserin group when compared to placebo group. Furthermore, improvements were noted in the Zarit Caregiver burden score ($P = 0.0016$, effect size 0.50) in the pimavanserin group when compared to placebo group. The investigators also noted non-significant improvements in both pimavanserin and placebo groups (-1.69 and -1.40) in the motor function (UPRDRS II and III) composite score.

The investigators did not find any treatment related impairment of motor functioning in the pimavanserin or placebo group. 10% of the participants in the pimavanserin group discontinued the study due to adverse events when compared to 2% of the participants in the placebo group. They did not identify any significant difference between the pimavanserin and placebo groups on the occurrence of treatment emergent adverse events. A total of 11% of participants in the pimavanserin group and 4% of the individuals in the placebo group had serious adverse events. There was a 7.3 ms increase in the QTc interval on day 43 in the pimavanserin group when compared to none in the placebo group.

There are some weaknesses to consider with this study. The study does not provide sufficient safety data or evidence about durability of response beyond 6 wk. The duration of the trial also limits the ability to look at long term benefits such as reduced nursing home admission and caregiver burden. A confounding factor to consider is that 99% of subjects in both placebo and pimavanserin group were using dopaminergic medications at baseline and throughout the RCT indicating they were not able to study efficacy of pimavanserin in patients not on dopaminergic drugs. Additionally, as with the Meltzer *et al*[23] study there is no comparison of efficacy/tolerability between pimavenserin and other antipsychotics such as clozapine.

## DISCUSSION

Data available from these two well-designed studies indicates that pimavanserin improves psychotic symptoms (delusions and hallucinations) among individuals with PDP when compared to placebo[23,24]. Additionally, pimavanserin appears to be fairly well tolerated with no worsening of the motor symptoms of PD. Furthermore, no increase in mortality rates was noted among pimavanserin treated individuals in both studies.

A meta-analysis by Yasue *et al*[26] that included data from 4 RCTs that studied the use of pimavanserin for PDP. This meta-analysis included 417 pimavanserin-treated and 263 placebo-treated individuals with PDP. The investigators found that pimavanserin decreased the symptoms of hallucinations and delusions when compared to placebo [weighted mean differences (WMD) = –2.26, $P = 0.005$]. In addition, pimavanserin was found to be superior to placebo when evaluating the reduction in the symptoms of hallucinations (WMD = –2.15, $P = 0.001$) and delusions (WMD = –1.32, $P = 0.010$) independently. The investigators did not find any significant difference between pimavanserin and placebo on the all-cause discontinuation rates for adverse events, death, Parkinson motor symptoms and the incidence of individual adverse events. Pimavanserin was also associated with less orthostatic hypotension when compared to placebo (risk ratio = 0.33, $P = 0.008$, number needed to harm = 17, $P = 0.01$). The investigators concluded that pimavanserin is beneficial for the treatment of symptoms of PDP and is well tolerated.

In addition to the data from the two studies that we found from our literature search, Yasue *et al*[26] included data from two unpublished studies of pimavanserin

among individuals with PDP in their meta-analysis[27,28]. Both the studies were multicenter trials that were of 6 wk in duration. The average age of the participants among the two studies was 69.3 and 72 years respectively. The first study had 295 participants and the second study had 121 participants. The first study compared pimavanserin 10 mg a day and 40 mg a day to placebo, and the second study compared pimavanserin 10 mg a day and 20 mg a day to placebo. Although pimavanserin was well tolerated in these studies, pimavanserin did not appear to significantly improve psychotic symptoms among individuals with PDP when compared to placebo. Pimavanserin appeared to be well tolerated in these studies with no difference noted between pimavanserin and placebo groups in terms of discontinuation rates for any cause, adverse effects, serious adverse effects and deaths.

A summary of the United States FDA's review of the safety and effectiveness for pimavanserin for PDP included a total of 616 individuals who received at least 1 dose of pimavanserin, with a total exposure of 825 patient-years in the PDP population[29]. The FDA found that pimavanserin 34 mg a day was effective in treating hallucinations and delusions among individuals with PDP. Available data indicated that 80.5% of individuals treated with pimavanserin experienced at least some improvement in symptoms when compared to 58.1% of placebo treated individuals. Pimavanserin did not appear to worsen motor functioning among individuals with PDP. The authors concluded that pimavanserin is the only FDA-approved treatment for the hallucinations and delusions among individuals with PDP. Despite pimavanserin's different pharmacologic mechanism when compared to other atypical antipsychotics, the FDA remains concerned about the increased risk of death seen with other antipsychotic use among older adults. Thus Pimavanserin was also given the same boxed warning regarding the risk of death associated with antipsychotic use among older adults with dementia.

Pimavanserin's package insert indicates that the drug prolongs QT interval and its use should be avoided among individuals with known QT prolongation or in combination with other drugs that can prolong the QT interval including antiarrhythmics (quinidine, procainamide, amiodarone), certain anti-psychotic medications (ziprasidone, chlorpromazine, thioridazine) and certain antibiotics (gatifloxacin, moxifloxacin)[30]. Additionally, pimavanserin should be avoided among individuals with a history of cardiac arrhythmias, in situations that may increase the risk of torsades de pointes and/or sudden death including symptomatic bradycardia, hypokalemia or hypomagnesemia, and in the presence of congenital prolongation of the QT interval. However our review of the literature did not find any evidence of clinically significant increase in QTc with the use of pimavanserin among individuals with PDP. This data is consistent with the data from the Yasue *et al*[26] meta-analysis.

A recent 6-wk randomized, placebo-controlled, double-blind study that included 181 participants who lived in nursing homes and had possible or probable AD and psychotic symptoms found that pimavanserin improved psychotic symptoms among these individuals at 6 wk when compared to placebo (Cohen's d = -0.32; $P$ = 0.045)[31]. However, by week 12 the investigators found no significant advantage for pimavanserin when compared to placebo ($P$ = 0.561). Common adverse events noted in the study when comparing pimavanserin *vs* placebo were falls (23% *vs* 23%), urinary tract infections (22% *vs* 28%) and agitation (21% *vs* 14%). Treatment discontinuation due to adverse events was seen in 9% of pimavanserin treated individuals when compared to 12% of the placebo treated individuals. There was no significant difference between the pimavanserin and placebo treated individuals on cognition or motor functioning.

A Pennsylvania-based non-profit organization published reports of post-marketing adverse events include hallucinations, confused states and deaths with the use of pimavanserin[32]. The data published by Institute for Safe Medication Practices in November 2017 indicates that in total there were 2236 adverse events for the 12 mo post-marketing observation period ending in March 2017[33]. The four most frequently reported adverse events were hallucinations 487 (21.8%) drug ineffectiveness 333 (14.9%), confused state 258 (11.5%) and death 244 (10.9%).

The United States FDA completed a review of all post-marketing reports of deaths and serious adverse events reported with the use of pimavanserin[34]. The FDA did not identify any new or unexpected safety findings with pimavanserin or findings that were inconsistent with the established safety profile currently described for the drug. The FDA concluded that the drug's benefits outweigh its risks for patients with hallucinations and delusions of PDP.

## CONCLUSION

Data available from two well-designed studies indicates that pimavanserin improves psychotic symptoms among individuals with PD when compared to placebo. In addition, pimavanserin appears to be fairly well tolerated with no serious adverse effects and it does not appear to worsen the motor symptoms of PD. Additional well controlled studies with positive data for both efficacy and safety are required before pimavanserinin can be designated as the first line agent for use among individuals with PDP.

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**Observational Study**

# Problematic Internet use in drug addicts under treatment in public rehab centers

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## Abstract

*BACKGROUND*
Problematic Internet use (PIU) or Internet addiction has been recognized to be a behavioral addiction characterized by excessive or poorly controlled preoccupations, urges, or behaviors regarding computer use and Internet access that leads to impairment or distress resembling substance abuse.

*AIM*
To investigate the prevalence and characteristics of Internet use and abuse in a group of drug addicts from Southern Italy, by means of a specific questionnaire ["Questionario sull'Utilizzo delle Nuove Tecnologie" (QUNT)].

*METHODS*
All subjects (183) were heavy smokers, almost 50% of them used heroin and/or opioid compounds, 30% alcohol, 10% cannabis, 8% cocaine, and 5% were polydrug users. Almost 10% of the individuals were also suffering from gambling disorder.

*RESULTS*
The time spent online was more than 4 hours a day in the total sample, with a slight prevalence in male subjects. Cocaine and cannabis users spent more than 6 hours online, significantly more than opioid and alcohol abusers. Distribution of the QUNT factors was not different in both sexes. Cocaine users showed higher scores at the "loss of control", "pornography addiction", and "addiction to social networks" factors, for the stimulant effect of this substance. Moreover, 15 out of the total 17 cocaine users were pathological gamblers. Positive and statistically significant relationships were observed between some QUNT factors and body mass index.

*CONCLUSION*

These findings indicate that PIU is less severe in subjects taking sedative substances, such as heroin/opioids and alcohol, than in subjects taking stimulants. Alternatively, it may be used as a "stimulant" trigger in cocaine and cannabis users. Flattening effect of abuse drugs was noted on possible sex-related differences in QUNT items. We observed a sort of "protective" effect of a love relationship and/or living together with a partner, as those engaged subjects showed lower scores on different items than single subjects or those living alone. The relationship between time spent online (and related sedentary lifestyle) and body mass index would suggest that Internet use might be a contributing factor to increasing weight gain and obesity amongst adolescents and young adults worldwide. Our findings also highlighted the specific vulnerability of drug addicts who use stimulants, rather than sedative compounds, to other kinds of behavioral addictions, such as gambling disorder.

**Key words:** Internet; Problematic Internet use; Behavioral addictions; Drug abuse; Rehab centers

**Core tip:** This study investigated the characteristics of Internet use and problematic Internet use (PIU) in drug addicts through a specific questionnaire. The findings indicated that PIU is more common in subjects taking cocaine and cannabis than in subjects taking opioids or alcohol, and that the also affected by pathological gambling disorder. This suggests a favoring role of stimulant drugs towards the development of behavioral addictions. The relationship between time spent online and body mass index indicates that Internet use might be a factor that promotes weight gain and obesity. Addiction prevention should take into consideration PIU, which currently represents a worldwide epidemic.

## INTRODUCTION

New technologies, when used appropriately, undoubtedly constitute a resource that can greatly improve the quality of an individual's life. The Internet is probably one of the biggest revolutions of the last few years because it has transformed the way of communicating, exchanging information, participating in real-time events thousands of kilometers away, and finding easily and rapidly any kind of information[1,2]. In the same way, it should be noted that the mismatched use of the Internet constitutes, especially where predisposing psychopathological factors are present, a real risk for a subject's mental health, as it may become a problem out of his/her control.

In particular, the abuse of the Internet represents the most dangerous and probable threat that may cause serious impairment to the social, psychological, working, and emotional individual adjustments. Over the last 15 years, the number of Internet users has increased by 1000%[3] , as documented by the Internet World Stats, Pigdom, a society that features up to date world Internet usage, population statistics, and other issues[3]. Not surprisingly, as a result, studies on abuse of the Internet have proliferated. This problem is not yet well understood, and research on its etiology is still at its beginning[4].

Problematic Internet use (PIU) or Internet addiction is a behavioral addiction[5] that can be defined as "use of the Internet that creates psychological, social, school, and/or work difficulties in a person's life"[6].

Increasing literature on PIU led the American Psychiatric Association to include Internet Gaming Disorder in section 3 of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5), but the current opinion is that more data are needed before incorporating it in the manual as a condition with a nosological dignity[7-9]. In 2008, Block[7] suggested four diagnostic criteria essential to a possible diagnosis of PIU

as an addictive behavior, as follows: "Excessive Internet use associated with a loss of sense of time; withdrawal, including feelings of anger, depression and tension when Internet is not accessible; tolerance, including the need for better computer equipment, more software, or more hours of use, and adverse consequences, including arguments, lying, poor school/work or vocational achievement, social isolation, and fatigue"[7].

Generally, PIU subjects are not aware that they have a problem[10-12] that may progressively impair family, school, work, or social life[13] or lead to severe social withdrawal[12,14] and even suicide[12,15-17]. Several studies have documented the negative consequences of PIU, but the literature does not reflect a consistent conceptualization of this behavior[18,19]. Specifically, it is unclear whether PIU should be classified as a type of behavioral addiction[19], an impulse control disorder, a subtype of obsessive-compulsive disorder[20-24], or an impaired way of coping with stress[25-27].

The most common symptoms of PIU are similar to those of substance use disorders (SUDs) according to DSM-5[28] including unpredictable behavior and mood[14,15], craving, excessive concerns about Internet activities, and inability to reduce its use[29,30]. Some researchers made some parallelisms with behavioral addictions, including gambling disorder[22,31]. Again, neurobiological studies indicate that PIU shares with SUDs several neurobiological characteristics[15,32-34]. Although PIU has been found frequently comorbid with other psychiatric disorders[35], the literature on the relationship between PIU and SUDs is meager.

The same is true for data on PIU prevalence and characteristics in our country. Therefore, the present study aimed at exploring these phenomena in a peculiar population constituted by individuals following a rehab program for drug addictions in public centers (Servizio Tossicodipendenze, SERT) through a questionnaire called "Questionario sull'Utilizzo delle Nuove Tecnologie" (QUNT) that we had created for this purpose.

## MATERIALS AND METHODS

### Self-assessment questionnaire
A specific interactive platform and website (http://dronet.araneus.it/questionario) on new technologies were created on an external server. The platform allowed access to the self-assessment questionnaire only *via* the Internet.

At the same time, a self-assessment questionnaire referred to the acronym QUNT was developed. The QUNT consists of two sections, one for demographic data and another consisting of 101 items (Appendix 1). Forty-five out of the total 101 items had five possible answers, according to a Likert five-point scale with 1 indicating "completely false" and 5 indicating "completely true"; three items were multiple-choice questions; ten were focused on the use of "instant messaging" (with five possible answers, according to a Likert five-point scale with 1 indicating "completely false" and 5 indicating "completely true"), and 42 items on the use of "social networks" (instant messaging: Whatsapp, Telegram, Skype, and social networks: Facebook, Twitter and Instagram) (with five possible answers, according to a Likert five-point scale with 1 indicating "completely false" and 5 indicating "completely true"). The item #101 was actually a question on the satisfaction/utility or not with the questionnaire. The items considered of greater relevance were put together in order to identify factors built according to *a priori* criteria extrapolated from the data available in the scientific literature[6,26,29]. These factors were "time spent online" (item 2, 3, 4, 5, 6, 7, 25, 33), "social withdrawal" (item 8, 10, 18, 22, 30, 35), "abstraction from reality" (item 11, 13, 24), "loss of control" (item 19, 20, 32, 36), "addiction to pornography" (item 26, 27), "ludopathy" (item 40, 41, 42, 43), and "addiction to social networks" (49, 50, 51, 52, 53, 54, 55, 56, 57). The "addiction to social networks" factor was further divided into the following sub-factors: "Addiction to Facebook" (item 61-75), "addiction to Twitter" (item 76-86), and "addiction to Instagram" (item 86-97). The factor scores were calculated as the sum of the scores obtained in each item divided by the maximum score in percentage. We established the answer 4 (between 4 and 6 hr/d) or 5 (> 6 hr/d) of item 2 "time spent online". As the cut-off points to identify the presence of, respectively, possible or certain/severe PIU, in agreement with current literature, although controversies do exist[8]. In no way it was possible to identify the participants whose anonymity was warranted.

### Data collection procedure
The link for QUNT was communicated to the offices in charge of the territorial outpatient's services for drug-addicted individuals, SERTs, located in the Calabria region, in order to ask their patients to fill it in. A total of 1500 subjects were asked to

fill in the questionnaire on a voluntary basis. The present study was approved by the Ethics Committee at Pisa University.

### Statistical analysis

The independent *t*-test was applied to compare the mean scores of the factors on the basis of these variables: Sex (M/F); single (yes/no living together (yes/no). One-way analysis of variance followed by Bonferroni's test for *post-hoc* was used to assess the comparisons of body mass index (BMI) categories. The $\chi^2$ analysis was used to compare categorical variables. All statistics were carried out by the Statistical Package for Social Sciences (SPSS), version 22 (Armonk, NY, United States)[36].

## RESULTS

### Characteristics of the study population

The returned questionnaires numbered 183, of which 148 (80.87%) were from men and 35 (19.13%) were from women, out of the total 1500 invitations. The majority of the subjects (86, 47%) had completed 8 years of school, 73 (39.9%) the high school, 14 (7.7%) 5 years of primary school, and 10 (5.5%) were graduated. Ninety-two (50.3%) subjects were single, 64 (14.8%) were married, and 27 (14.8%) were involved in a love relationship. The mean length of attendance at the public rehab center was between 1 and 60 mo (mean ± standard deviation (SD): 32 ± 20).

### Types of substance abuse and/or behavioral addiction

The most abused drugs were heroin or opioids (*n* = 88, 48.1%), alcohol (*n* = 55, 30.1%), cannabis (*n* = 20, 9.8%), cocaine (*n* = 17, 7.7%), and amphetamines (*n* = 3, 1.6%). Polydrug abuse (amphetamine, cannabis, cocaine, ecstasy) was present in nine (4.9%) individuals, while gambling disorder was diagnosed in 18 (9.3%). All 183 subjects were heavy smokers (Table 1).

The smartphone was found to be the most common device utilized by all subjects to access the Internet. The time spent online was similar in men and women, 4.12 ± 2.9 h. Interestingly, the time spent online by 30% of cocaine and 25% of cannabis users was significantly higher (> 6 h) than that of the other groups.

### QUNT factors and gender

The distribution of the QUNT factors was not different in the two sexes; however, men using cannabis showed a trend towards higher scores (mean ± SD) at the following factors: "Social withdrawal" (2.44 ± 0.38 *vs* 2.23 ± 0.39, *P* < 0.001) and "abstraction from reality" (3.12 ± 1.74 *vs* 2.24 ± 0.46, *P* < 0.001). Cocaine users showed a higher score than the other subjects at the "loss of control" (3.64 ± 1.12 *vs* 2.51 ± 0.36, *P* < 0.001), "pornography addiction" (3.59 ± 1.44 *vs* 2.54 ± 0.41, *P* < 0.001), and "addiction to social networks" (3.22 ± 0.98 *vs* 2.66 ± 0.76, *P* < 0.001) factors.

### QUNT factors and affective relationship

The analysis of the difference in QUNT factors regarding being single (*n* = 92) or involved in a love relationship (*n* = 91) showed that single subjects had higher scores at the following factors (mean ± SD): "Time spent online" (2.95 ± 0.47 *vs* 2.17 ± 0.44, *P* < 0.001); "social withdrawal" (1.40 ± 0.35 *vs* 1.34 ± 0.32, *P* < 0.001); "abstraction from reality" (1.90 ± 0.40 *vs* 1.56 ± 0.62, *P* < 0.001); "addiction to pornography" (3.12 ± 0.88 *vs* 1.99 ± 0.79, *P* < 0.001); and "addiction to social networks" (2.89 ± 1.08 *vs* 2.06 ± 0.33, *P* < 0.001).

The analysis of the differences between partners living (72) or not living together (17) with the partner showed some significant differences. The following factors showed higher scores in subjects who did not live with the partner *vs* those who lived with the partner: "Time spent online" (3.03 ± 0.53 *vs* 2.16 ± 0.76, *P* < 0.001), "addiction to pornography" (3.15 ± 0.99 *vs* 2.33 ± 0.71, *P* < 0.001), "ludopathy" (3.42 ± 1.08 *vs* 2.96 ± 0.66, *P* < 0.001), and "addiction to social networks" (2.99 ± 0.91 *vs* 2.01 ± 0.44, *P* < 0.001).

### QUNT factors and BMI

The total sample was then subdivided according to the BMI values. Fifteen subjects had a BMI below 18.50 (underweight, UW), 69 between 18.51 and 24.9 (normal weight, NW), 60 between 25 and 30 (overweight, OW), 26 between 30.1 and 34.9 (first degree of obesity, OB1), and 13 greater than 35 (second degree of obesity, OB2). The categories OB1 and OB2 were merged in the category "Obese" (OB). The comparisons of QUNT factor scores in the four BMI categories are reported in Table 2, which shows that the greater the BMI values the greater the scores. Moreover, as shown in Figure 1, as BMI increased the percentage scores of the five factors, "time spent online", "social

| Table 1  Types of substance abuse and/or behavioral addiction | |
| --- | --- |
| | *n* (%) |
| Heroin or opioids | 88 (48.1) |
| Alcohol | 55 (30.1) |
| Cannabis | 20 (9.8) |
| Cocaine | 17 (7.7) |
| Amphetamines | 3 (1.6) |
| Polydrug abuse | 9 (4.9) |
| Gambling disorder | 18 (9.3) |
| Smokers | 183 (100) |

withdrawal", "abstraction from reality", "ludopathy", and "addiction to social network", also trended upward. Finally, fifteen of the total cocaine users were also pathological gamblers (mainly online gamers) and showed a significantly higher score at the "ludopathy" factor (3.20 ± 0.45 *vs* 2.86 ± 0.51, *P* < 0.001).

## DISCUSSION

The present study reports the results of a collaborative survey investigating the prevalence and characteristics of Internet use by new technologies (PCs, smartphones and tablets), as well as of PIU, amongst subjects undergoing a program of rehabilitation in public rehab centers in a region from southern Italy. According to our knowledge, this is the first study carried out in this peculiar adult population, as previously only samples of adolescents were investigated[37].

Several subjects received the invitation from their psychiatrists/psychologists to fill in a questionnaire, the so-called QUNT, which was developed by us for this purpose. The specificity of the QUNT, as compared with those utilized in different studies, is that it is very detailed in order to assess the variety of individual features of both Internet use and PIU. The item 2 "time spent online" was considered crucial to identify the possible presence of PIU when it was between 4 and 6 hr/d (answer 4), or of severe PIU, when it was > 6 hr/d (answer 5).

About 10% of the subjects returned the QUNTs correctly filled in that were valid for statistical analyses. This can be ascribed to the peculiar personality of drug addicts, especially chronic ones that represent the majority of our sample, and it would indicate both a low propensity to collaborative studies and compliance as well as amotivation[38]. The most used device (100% of subjects) to access the Internet was the smartphone. There was a high preponderance of men over women, which reflects the distribution of sexes in public rehab centers in Italy, in agreement with national data showing that the ratio male:female is 4:1[39].

All subjects were heavy smokers, almost 50% of them used heroin and/or opioid compounds, 30% alcohol, 10% cannabis, 8% cocaine, and 5% were polydrug users. Only three subjects were amphetamine users and, therefore, were not included in the statistical analyses. Almost 10% of individuals were also suffering from gambling disorder, while the presence of other psychiatric disorders was set as an exclusion criterion.

The time spent online was quite high, more than 4 hr/d in the total sample, with a slight, albeit not significant prevalence in male subjects. Cocaine and cannabis users spent more than 6 hr/d online, significantly more than opioid and alcohol abusers. Therefore, they were probably affected by a severe PIU, according to the setpoint defined by us (answer 5 of item 2) and literature data[12,40-42]. Taken together, these findings indicate that although PIU is possibly present in all categories of drug addicts, it is less severe in subjects taking sedative substances, such as heroin/opioids and alcohol. Alternatively, it may be used as a "stimulant" trigger in cocaine and cannabis users. This is supported by the high prevalence of gaming disorder amongst cocaine abusers, in agreement with literature data[43-45].

The analysis of the distribution of the QUNT factors showed no sex-related differences and a slight trend towards higher scores at the "social withdrawal" and "abstraction from reality" items in men. This is in contrast with a previous study carried out in healthy subjects that revealed significant differences between men and women. A possible explanation might be the flattening effects of abused drugs that tend to "minimize" sex differences[46]. As compared with the other groups, cocaine
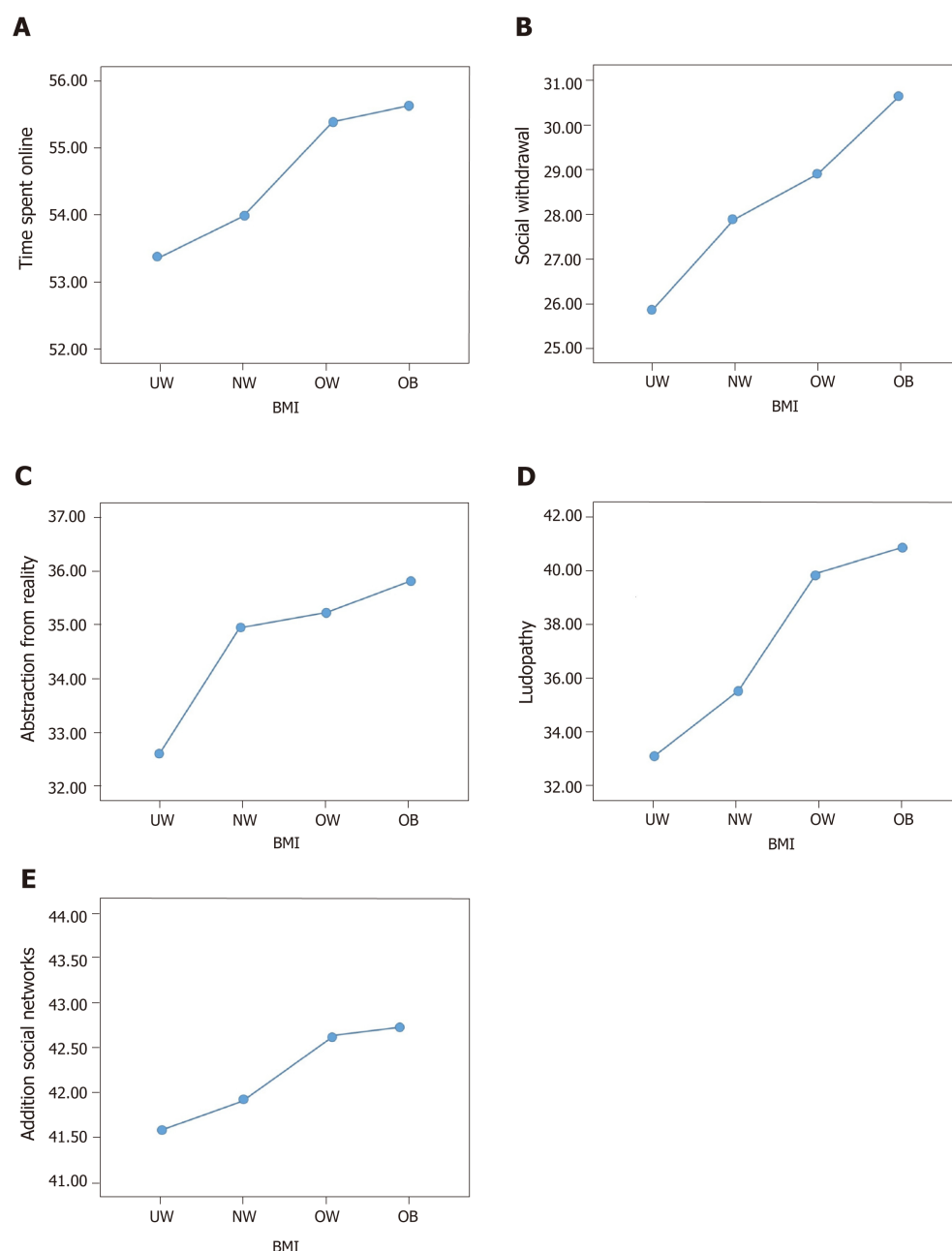
**Figure 1 Trend of the percentage scores of some QUNT factors and body mass index.** A: Time spent online; B: Social withdrawal; C: Abstraction from reality; D: Ludopathy; E: Addiction to social networks. BMI: Body mass index; UW: Underweight; NW: Normal weight; OW: Overweight; OB: Obesity; QUNT: Questionario sull'Utilizzo delle Nuove Tecnologie.

users showed higher scores at the "loss of control", "pornography addiction", and "addiction to social networks" factors. This is not surprising given the stimulant effect of this substance[47].

Our findings confirmed the "protective" effects of a love relationship and/or living together with a partner[48], as single subjects or those living alone with no family support showed higher scores on different items, specifically "time spent online", "social withdrawal", "abstraction from reality", "addiction to pornography", and "addiction to social networks". This clearly indicates that Internet was mainly used for passing time or recreation.

Not surprisingly, those subjects who spent more time online, as shown by the higher score of the "time spent online", "social withdrawal", "abstraction from reality", and "addiction to social network" factors, had a higher BMI. Therefore, the excessive use of the Internet can be considered another factor that increases sedentary behaviors[49], and it may be particularly risky in drug addicts who are already more vulnerable subjects already exposed to different medical diseases[50]. Reduced sleeping time and altered circadian rhythms due to PIU are other factors that may increase the

**Table 2  Comparisons of the QUNT factor scores in the four BMI categories**

| Factors | UW | NW | OW | OB | *F* | *P* value | *Post-hoc* comparison:Significantfor *P* < 0.05 |
|---|---|---|---|---|---|---|---|
| Time spent online | 53.44 ± 13.68 | 53.80 ± 13.12 | 54.91 ± 12.71 | 55.83 ± 14.10 | 3.87 | 0.009 | OW > UW |
| Social withdrawal | 25.39 ± 6.35 | 27.55 ± 7.61 | 28.73 ± 8.94 | 30.81 ± 10.14 | 9.91 | 0.001 | OW > UW; OB > UW; OB > NW |
| Abstraction from reality | 32.33 ± 10.02 | 34.90 ± 10.13 | 35.11 ± 12.98 | 36.11 ± 13.44 | 2.69 | 0.045 | None |
| Loss of control | 28,10 ± 9.11 | 29.79 ± 10.11 | 31.04 ± 12.49 | 31.21 ± 10.87 | 1.95 | 1.98 | None |
| Addiction to pornography | 43.32 ± 12.28 | 41.95 ± 13.70 | 41.34 ± 11.03 | 42.09 ± 13.45 | 1.55 | 0.250 | None |
| Ludopathy | 33.26 ± 13.17 | 36.23 ± 10.85 | 39.88 ± 22.91 | 41.16 ± 22.39 | 4.28 | 0.005 | OW > NW |
| Addiction to instant messaging | 54.05 ± 18.33 | 56.02 ± 16.47 | 56.24 ± 18.36 | 55.60 ± 17.09 | 1.72 | 0.197 | None |
| Addiction to social networks | 41.60 ± 12.61 | 42.13 ± 13.15 | 41.80 ± 12.19 | 44.14 ± 18.90 | 1.81 | 0.187 | None |

QUNT: Questionario sull'Utilizzo delle Nuove Tecnologie; BMI: Body mass Index; UW: Underweight; NW: Normal weight; OW: Overweight; OB: Obesity.

probability of metabolic, medical, and psychiatric disorders[11,16,51] as well as of a disruption of work, family, social, or school performance[52,53].

Finally, the majority (15 out of the total 17) of cocaine users were also pathological gamblers (mainly online gamers), and showed a significantly higher score at the "ludopathy" factor. This would suggest a specific vulnerability of drug addicts to other kinds of addictions, especially if they use stimulants rather than sedative drugs[43]. Our study has some limitations that should be acknowledged. The QUNT questionnaire was not validated, although this is quite common in studies in this field[12,40-42]. The prevalence of PIU was inferred from one item only, but it was a corollary of the main objective of the study exploring primarily the characteristics of Internet use. Similarly, no information was gathered on emotional distress or disturbed behaviors that are currently under investigation.

Taken together, our results suggest that the excessive use of Internet through smartphones is very common in drug addicts, as shown by their time spent online, and that PIU is very common in these individuals, especially in those taking cocaine and cannabis. The relationship between time spent online (and related sedentary lifestyle) and BMI would suggest that Internet use might be a contributing factor for increased weight and obesity amongst adolescents and young adults world-wide[49,54]. Our findings would suggest specific vulnerability of drug addicts, mainly if they use stimulants rather than sedative compounds, not only to other kinds of pharmacological but also to behavioral addictions, such as PIU or pathological gaming. Prevention of addictions should take into consideration the novel, and still poorly explored, domain of behavioral addictions, especially of PIU that today represents a worldwide epidemic[12,54-56].

## ARTICLE HIGHLIGHTS

### Research background
Problematic Internet use (PIU) is a novel behavioral addiction characterized by excessive Internet use that is becoming an increasing problem worldwide. Although no agreement exists on precise diagnostic criteria, PIU is considered a behavioral addiction sharing with substance use disorders (SUDs) and other addictions several features and perhaps neurobiological underpinnings.

### Research motivation
Unfortunately, no information is available on the prevalence of PIU amongst drug-addicted subjects, in spite of the given evidence, that these individuals tend to be affected by polydrug use and also by behavioral addictions, as if the presence of one or more addictions would represent a sort of vulnerability towards a worsening of the clinical picture through the onset of other kinds of these disorders.

### Research objectives
The investigation of the possible existence and prevalence of PIU amongst drug-addicts under treatment in rehab centers would permit the implementation of specific treatments to prevent the onset of other kind of addictions that could worsen the clinical picture and the rehabilitation programs.

### Research methods
A specific questionnaire to be filled online, the so-called Questionario sull'Utilizzo delle Nuove

Tecnologie (QUNT), was developed to explore the prevalence and characteristics of both Internet use and PIU. The QUNT consists of two sections, one for demographic data and another consisting of 101 items grouped in factors built according to *a priori* criteria extrapolated from the data available in scientific literature. All subjects who volunteered to participate in the study (*n* = 183) reported that the QUNT was useful and were satisfied with it. The factor scores were calculated as the sum of the scores obtained in each item divided by the maximum score in percentage. We chose the answer 4 (between 4 and 6 hr/d), and the answer 5 (> 6 hr/d) of item 2 "time spent online". In order to identify the body mass index (points for, respectively, the possible or certain (and severe) presence of PIU.

### Research results

The time spent online was more than 4 hr/d in the total sample, with a slight, although not significant, prevalence amongst male subjects. Cocaine and cannabis users spent more than 6 hours online, significantly more than opioid and alcohol users. The distribution of the QUNT factors was not different in both sexes. Cocaine users showed higher scores at the "loss of control", "pornography addiction", and "addiction to social networks", probably because of the stimulant effect of this substance. Moreover, 15 out of the total 17 cocaine users were also pathological gamblers. Positive and statistically significant relationships were also observed between some QUNT factors and body mass index (BMI). These results, while showing that PIU is common amongst stimulant drug abusers, require to be replicated in larger samples from other countries. Nevertheless, they underline the risk of behavioral addictions in drug addicts, a problem that should be taken into account when planning prevention and intervention strategies.

### Research conclusions

The new findings of this study are represented by the large percentage of PIU amongst drug addicts, especially if they use cocaine or cannabis. This suggests that, although the abuse of Internet is present in all drug addicts, PIU is less common in subjects taking sedative substances, such as heroin/opioids and alcohol, while it may become a sort of "stimulant" trigger in cocaine and cannabis users, as supported by the high prevalence of pathological gaming amongst cocaine abusers. Further, PIU is more frequent in single subjects or subjects living alone, a result stressing the protective effects of loving or social relationships in general against the onset of addictions. Those subjects who spent more time online, as shown by the higher score of the "time spent online", "social withdrawal", "abstraction from reality", and "addiction to social network" factors, had a higher BMI. Therefore, the excessive use of the Internet can be considered as another factor increasing sedentary behaviors that may be particularly risky in drug addicts, subjects already prone to different medical diseases. Reduced sleeping time and disrupted circadian rhythms due to PIU are other factors that may increase the probability of metabolic, medical, and psychiatric disorders as well as the impairment of work, family, social, or school performance.

### Research perspectives

The findings of the present study indicate that behavioral addictions, such as PIU, can broaden polydrug use, especially in subjects taking stimulants or cannabis. In addition, PIU may be considered another factor increasing negative life habits, already impaired in drug addicts, while promoting sedentary behaviors and maladjustments in different individual's domains. Future studies should take into consideration the impact of PIU on drug addicts by means of specific instru-ments to assess it, in order to prevent, not only its detrimental consequences, but also those related to a broadening of addictive behaviors.

## ACKNOWLEDGEMENTS

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# World Journal of
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### ORIGINAL ARTICLE

#### Observational Study

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**Observational Study**

# Medical student depression and its correlates across three international medical schools

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## Abstract

*BACKGROUND*
Medical students have high rates of depression, anxiety, and burnout that have been found to affect their empathy, professional behaviors, and performance as a physician. While studies have examined predictors for burnout and depression in the United States (US), no study, to our knowledge, has compared depression in medical students cross-culturally, or has attempted to examine the effect of factors influencing rates including burnout, exercise, stress, unmet mental health needs, and region.

*AIM*
To examine rates of depression in three international cohorts of medical students, and determine variables that may explain these differences.

*METHODS*
Convenience samples of medical students from three countries (US, China, and a Middle Eastern country whose name remains anonymous per request from the school) were surveyed in this observational study. Using the Patient Health Questionnaire-2 (PHQ-2) and a modified Maslach Burnout Inventory, depression and burnout were examined among medical students from the three cohorts (*n* = 473). Chi-square test and analysis of variance were used to examine differences in demographics, behavioral, and psychological variables across these three schools

to identify potentially confounding descriptive characteristics. Analysis of covariance compared depression and the emotional exhaustion component of burnout identified through Principal Component Analysis across countries. Multiple linear regression was used to analyze the impact of demographic, behavioral, and psychological variables on screening positive for depression.

*RESULTS*
Medical students from the Middle Eastern country had the highest rates of positive depression screens (41.1%), defined as a PHQ-2 score of ≥ 3, followed by China (14.1 %), and then the US (3.8%). More students in the Middle Eastern school had unmet mental health needs (50.8%) than at the medical school in China (34.8%) or the school in the US (32.8%) (Pearson chi-square significance < 0.05). Thus, PHQ-2 scores were adjusted for unmet mental health needs; however, the Middle Eastern country continued to have the highest depression. Adjusting for PHQ-2 score, medical students from the US scored the highest on emotional exhaustion (a measure of burnout). Demographic variables did not significantly predict medical student depression; however, lack of exercise, unmet mental health needs, stress, and emotional exhaustion predicted nearly half of depression in these cohorts. In comparison to the US, coming from the Middle Eastern country and China predicted higher levels of depression.

*CONCLUSION*
Depression rates differ in three international cohorts of medical students. Measured factors contributed to some observed differences. Identifying site-specific prevention and intervention strategies in medical student mental health is warranted.

**Key words:** Medical students; Wellness; Burnout; Depression; International

**Core tip:** Depression among medical students places them at increased risk for suicide, and impacts many aspects of professional performance. Medical students around the world share common stressors, including competitive selection processes, intense coursework, and pressure for high achievement. However, differences in depression rates are influenced, in part, by burnout, exercise, stress, unmet mental health needs, and region.

## INTRODUCTION

Medical students have high rates of depression, anxiety, and burnout, significantly higher than age-matched samples and the general population[1,2]. In fact, a recent meta-analysis found depression or depressive symptoms among medical students to be 27.2%, with a prevalence of suicidal ideation of 11.1%[3]. Burnout and depression affect both the student and their future patients, as they are associated with lowered academic performance[4], decreased empathy[5], increased suicidal ideation[6], unprofessional behaviors, and lack of altruistic goals for their future careers[7]. Despite the risk for suicidality, most depressed and burned out students go untreated: Only 12.9% of depressed students in one study sought treatment[8], and only one-third of students with high burnout seek help[9].

Many studies have examined explanations for high rates of burnout in this population. The overall learning environment[2] seems to be the most cited reason, with higher rates of burnout associated with lack of support from faculty and staff, working with cynical residents[10], lack of supportive resources and time off[11], and being mistreated or bullied[12]. Specific grading schemes have been independently

associated with burnout; students were found to be more likely burned out and with high stress in schools with letter grading as opposed to pass/fail[13]. Other studies have found associations with perfectionism, low academic self-efficacy[14], more advanced year of training, negative personal life events in the last 12 mo[15], alcohol abuse and dependence[16], and decreased social intimacy[17]. Sleep quality[17], pathological sleepiness, and sleeping less than seven hours a night also seem to independently predict burnout, however exercise does not[18].

Depression also correlates with high levels of burnout[18]. Studies on predictors of depression in medical students suggest that mistreatment, poor role modeling[19], low optimism[20], gender (females with higher rates) and year of study[8] seem to correlate with higher rates of depression. Resilience and hope are negatively correlated with depression[21].

Studies looking at depression and burnout among medical students in Asia[22] and the Middle East[23-25] report high rates of burnout and depression. To our knowledge, no study has compared depression in medical students cross-culturally, or has attempted to examine the effect of factors influencing rates including burnout, exercise, stress, unmet mental health needs, and region. The purpose of this study is to examine rates of positive screening for depression in three different groups of medical students, each from an internationally distinct medical school: Yale University School of Medicine in the United States (US), Central South University Xiangya School of Medicine in China, and a School of Medicine in the Middle East whose research collaborators chose to remain anonymous. A secondary aim is to examine whether there are differences in other variables across these sites, including age, gender, sleep, exercise, unmet mental health needs, emotional exhaustion, stress, as well as nationality, that may explain any differences in depression.

## MATERIALS AND METHODS

### Study participants
Convenience samples of medical students from three countries: US, China, and a Middle Eastern country (whose name remains anonymous per request from the school) were surveyed in this exploratory study. The US sample (*n* = 205) was made up of medical students at the Yale School of Medicine, one of the leading medical schools in the US. Students completed surveys in the fall of 2013 *via* anonymous online distribution with electronic consent. The Chinese sample (*n* = 142), surveyed in November and December 2015, consisted of third- to sixth-year students from an 8-year Doctor of Medicine (MD) program at Xiangya School of Medicine, a leading medical school in China whose curriculum closely resembles that of a US medical school; third and fourth years are preclinical years (equivalent to MS1 and MS2 in the US) and fifth and sixth year are clinical years (equivalent to MS3 and MS4 in the US). The Middle Eastern sample (*n* = 126), surveyed in Fall 2014, consisted of fifth year medical students enrolled at a medical school in the Middle East, one of the top five medical schools in the region. These students completed surveys anonymously *via* paper/pencil after a one-time seminar on mental health, self-care, and help-seeking behaviors, and left their responses in a box near the seminar exit.

The Yale and Middle Eastern School's IRBs deemed this study exempt. The Ethics Committee of Xiangya approved the study. All students were assured of both confidentiality and anonymity, and participation was voluntary. Paper questionnaires were preserved, and data were typed into the computer using anonymous identifiers by investigators. No incentives were offered at Xiangya or the Middle Eastern School for participation; a gift card raffle was offered at Yale.

### Survey measures
The survey questionnaire consisted of the following parts: (1) Self-reported questions on demographics, health-seeking behaviors, and personal health behaviors such as sleep and exercise patterns; (2) Patient Health Questionnaire-2 (PHQ-2)[26] screening for depression; (3) A modified version of the Maslach Burnout Inventory (MBI)[27] assessing burnout; (4) Attitudes toward Mental Illness Questionnaire assessing stigma[28]; and (5) Six questions related to comfort with feedback, admitting mistakes, and help-seeking. A detailed description of the survey and its sections can also be found in a previous study[29].

The original survey was translated into both Mandarin and a language native to the Middle Eastern country by contributing authors. The translations were then re-translated back to English by colleagues in the US who were fluent in both languages to assure that the surveys administered to all cohorts of students were comparable. Specific wording was changed in a few questions to more accurately reflect culture

and each country's curriculum of medical education. Ethnicity questions were country-specific to include relevant ethnic groups. No questions about drug or alcohol use were included in the Middle Eastern survey, as consuming alcohol is against Islamic law and religion. The country is officially not at war with another country.

### Analyses

Principal components analysis was used to analyze the six items of the modified MBI. One component explained 44.0% of variance, and the second component explained 20.5%. Analysis of eigenvalues, a scree plot, and subjective content of individual items suggested that two components be retained. The first component, which we will call "emotional exhaustion" (*i.e.*, the "emotional exhaustion" portion of the MBI) had high component loadings (> 0.65) on the four questions about being drained, used up, burned out, and uninterested. The second component had high component loadings (> 0.56) on the two questions about personal accomplishment. Of these two components, emotional exhaustion is most relevant to the current study. We created a scale using the four emotional exhaustion items, and computed scale scores by calculating the mean item score across the four items (as long as at least 66% of the questions were answered by the student). Missing data imputation methods applied to less than 5% of students, suggesting any potential bias would be inconsequential. Cronbach's alpha for the four item emotional exhaustion scale was 0.74.

Chi-square test and analysis of variance were used to examine differences in demographics, behavioral, and psychological variables across these three schools. The purpose of these statistics was to identify potentially confounding descriptive characteristics. Analysis of covariance (ANCOVA) was then used to compare depression among these three countries adjusted for differences in "unmet mental health needs". Unmet mental health need was defined as agreeing to the Likert scale question "there are times I have a mental health need for which I do not seek care", where agree and strongly agree were collapsed into one response. Bonferroni type corrections were applied for multiple comparisons. Adjusting for the total PHQ-2 score, Emotional exhaustion was compared between student populations. For each relevant item on the questionnaire, adjusted means of the answers were examined among regions in pairwise comparisons.

To determine the possible predicative variables for medical student depression, multiple linear regression analysis was performed. The analysis included: Demographic variables (age and gender), behavioral variables (sleep, exercise, unmet mental health needs), and psychological variables (stress, emotional exhaustion). The possibility of multicollinearity was ruled out. All analyses were done using SPSS version 25, and statistical significance was evaluated at the *P* < 0.05 level.

## RESULTS

Response rates differed by cohort. At Yale, 205 out of 519 students (39.5%) responded to the survey. At the Middle Eastern school, 172 out of 203 students (84.7%) and at Xiangya, 142 out of 150 (94.7%) responded to the survey. Responses to specific questions were included in the analyses, even if the survey was not fully completed.

### Descriptive statistics

A positive screen for depression was defined as a PHQ-2 score of ≥ 3. According to that definition, students in the Middle Eastern country were significantly more likely to screen positive for depression (41.1% of students screened positive) than students in China (14.1% screened positive). Both cohorts were more likely to be depressed than the US cohort (3.8% screened positive) (Table 1). Other characteristics were also significantly different between schools. For example, in all three cohorts, students in China slept the least number of hours, and students in the Middle East exercised the least. More students in the Middle Eastern school had unmet mental health needs (50.8%) than in China (34.8%) or the US (32.8%) (Pearson chi-square significance < 0.05).

### ANCOVA analysis

ANCOVA, with adjustment for differences in unmet mental health needs, showed that on scores from question 1 of the PHQ-2 [F (2.435) = 54.60, *P* < 0.001], a measure of anhedonia, students from the Middle Eastern country reported significantly higher scores than those from the other two cohorts. Students from China also had scores that were significantly higher than those reported from the US. Scores from question 2 of PHQ-2 [F (2.434) = 49.79, *P* < 0.001], a measure of depressed mood, followed the same pattern, with students from the Middle Eastern country having the highest scores, followed by China, then the US. On the total score of PHQ-2 [F (2.434) = 71.48,

**Table 1 Chi-square and analysis of variance comparisons of group characteristics**

| Variable | Yale University School of Medicine, *n* = 205 | Middle Eastern Medical School, *n* = 126 | Xiangya School of Medicine, *n* = 142 | Entire population, *n* = 473 | Statistics |
|---|---|---|---|---|---|
| Age, mean (SD[1]) | 25.3 (2.4) | 22.1 (1.0) | 22.0 (1.5) | 23.4 (2.5) | $F = 174.7^a$ |
| Gender | 43.4% Male (M) 56.6% Female (F) | 37.3% M 62.7% F | 43.7% M 56.3% F | 41.8% M 58.2% F | $\chi^2 = 0.5$ |
| Sleep[2] in hr, mean (SD) | 6.6 (1.0) | 6.6 (1.0) | 6.5 (0.9) | 6.5 (1.0) | $F = 5.6^a$ |
| Exercise[3], mean (SD) | 2.5 (1.8) | 1.4 (1.7) | 1.6 (1.8) | 1.9 (1.8) | $F = 18.1^a$ |
| Depression screening by PHQ-2[4] category | Not depressed: 62.8% Mild depression: 33.3% Depressed: 3.8% (*n* = 7) | Not depressed:10.5% Mild depression: 48.8% Depressed: 41.1% (*n* = 51) | Not depressed: 16.2 % Mild depression: 69.7% Depressed: 14.1% (*n* = 20) | Not depressed: 33.6% Mild depression: 49.0% Depressed: 17.4% (*n* = 78) | $\chi^2 = 161.1^a$ |
| Stress[5] | Yes: 58.4% (*n* = 108) | Yes: 75.4% (*n* = 95) | Yes: 82.9% (*n* = 116) | Yes=70.9% (*n* = 319) | $\chi^2 = 25.3^a$ |
| Unmet mental health need[6] | Disagree: 49.5% Neutral: 17.7% Agree: 32.8% | Disagree: 32.5% Neutral: 16.7% Agree: 50.8% | Disagree: 47.1% Neutral: 18.1% Agree: 34.8% | Disagree: 44.1% Neutral: 17.6% Agree: 38.3% | $\chi^2 = 12.1^b$ |

[a]$P < 0.01$;

[b]$P < 0.05$;

[1]SD: Standard deviation;

[2]For the purposes of scale measurement, if a participant answered < 4 h a night, 3.5 was the number coded, 4-5 h a night = 4.5; 6-7 h a night = 6.5, and > 8 h a night was coded as 8.5;

[3]Mean number of days per week spent exercising at least 30 consecutive minutes;

[4]PHQ-2: Patient Health Questionnaire-2; where not depressed = 0, mild depression is 1-2, depressed is ≥ 3;

[5]Response to question "Are you stressed?";

[6]Answer of agreement to Likert scale question "there are times I have a mental health need for which I do not seek care". Agree and Strongly Disagree were collapsed into one category; Agree and Strongly Agree were collapsed into another.

$P < 0.001$], a screen for depression, students from the Middle Eastern country reported significantly higher scores than those from each of the other countries. Again, students from China also had scores that were significantly higher than those from the US (Table 2).

ANCOVA, with adjustment for differences in PHQ-2 total scores, measured differences in burnout (Table 3). On the burnout item "I feel emotionally drained by my studies" [F (2.430) = 33.31, $P < 0.001$], students from the US reported significantly higher scores than those from each of the other regions, followed by China where scores were significantly higher than those reported from the Middle Eastern country. On the item "I feel used up at the end of a day in medical school" [F (2.438) = 13.41, $P < 0.001$], students from the US reported significantly higher scores than those from each of the other countries. However, on this item, the other schools scores were not significantly different from each other.

Examining answers to the item "I feel burned out from my studies" [F (2.445) = 10.06, $P < 0.001$], students from the US and the Middle Eastern country reported significantly higher scores than China, but the scores from the students in the Middle Eastern country and China were not significantly different from one another. On the final item "I have become less interested in my studies since my enrollment in medical school" [F (2.445) = 7.27, $P = 0.001$], students from the US and the Middle Eastern country again reported significantly higher scores than China, but the scores were not significantly different from one another. For the overall emotional exhaustion component measurement [F (2.444) = 19.26, $P < 0.001$], students from the US reported significantly higher scores than those from each of the other countries. The scores from the students in China and the Middle East were not significantly different from each other.

### Multiple linear regression

Results from the multiple linear regression analyses on medical student depression (as measured by total PHQ-2 score) are listed in Table 4. Demographic variables did not significantly predict medical student depression. Among behavioral variables, exercise and unmet mental health needs significantly predicted medical student depression, but amount of sleep did not. Both unmet mental health needs and emotional exhaustion were positively related to medical student depression, while the amount of exercise had a negative impact on depression (*i.e.*, more time exercising, lower depression score). Both psychological variables, stress as well as the emotional exhaustion component of burnout, were predictors of medical student depression. Stress was measured by answering "yes" to the question "are you stressed?".

**Table 2  Comparison of samples of medical students on depression (ANCOVA)[1]**

| Over the past 2 wk, how often have you been bothered by any of the following problems? (PHQ-2[2]) | a United States | b Middle Eastern country | c China | Paired comparison |
|---|---|---|---|---|
| | LS mean (SE) | LS mean (SE) | LS mean (SE) | |
| 1 Little interest or pleasure in doing things | 0.37 (0.05) | 1.18 (0.06) | 0.92 (0.06) | b > a, c; c > a |
| 2 Feeling down, depressed or hopeless | 0.36 (0.05) | 1.07 (0.06) | 0.76 (0.05) | b > a, c; c > a |
| Total Score | 0.73 (0.08) | 2.25 (0.10) | 1.68 (0.09) | b > a, c; c > a |

[1]Adjusted for differences in unmet mental health needs;
[2]PHQ-2: Patient Health Questionnaire-2; where not depressed = 0, mild depression is 1-2, depressed is ≥ 3. LS mean: Least square mean; SE: Standard error.

Admitting stress at the interview was negatively related to depression (*i.e.*, more stress, less depression). In comparison to the US, coming from the Middle Eastern country and China predicted higher levels of depression. The total model explained 47% of the variance of medical student depression (F = 41.621; df = 9,418; *P* < 0.001). The effect size (*i.e.*, Cohen's f² = 0.90) was large.

## DISCUSSION

Medical students are known to be at increased risk of depression, stress, and burnout. While previous studies have examined depression and burnout at individual medical schools in the US and abroad[24-25,29-30], to our knowledge this is the first study to compare depression and its correlates across three very different cohorts of international medical students. A recent meta-analysis[8] reported a global prevalence of depression among medical students of 28%. In comparison, our study revealed significantly lower rates of positive depression screens among medical students attending Yale in the US (3.8%) and Xiangya in China (14.1%), and higher rates of positive depression screens among students attending medical school at the site in the Middle East (41.1%). These rates were significantly different from one another, and even when controlling for the differences in unmet mental health needs between the groups, the school in the Middle East had consistently and significantly higher scores.

The high rate of depression in Middle Eastern students is consistent with data from previous studies[23-25]. Possible hypotheses for this high rate vary in the literature. Assadi *et al*[25] surmised that increased depression in Middle Eastern medical students compared to interns and general practitioners may be due to psychosocial factors such as the state of campus conditions, extensive exams, and limited employment opportunities. They also reported an association between psychiatric distress and high levels of indifference and cynicism, factors like those described in the literature on burnout. Farahangiz *et al*[23] reported an association between satisfaction with the field of study and mental health, with higher satisfaction being associated with better mean scores on the General Health Questionnaire-28. In our study, however, students in the Middle East were not the most emotionally exhausted after adjusting for the influence of depression. Our data instead suggest that unmet mental health needs (which is largest in this cohort) is associated with increased depression. Even though this was assessed only with a single question and therefore does not provide a full picture of what is meant by unmet needs, this may be a potential target for intervention in the future.

Other unmeasured environmental variables may also contribute to high rates of depression among medical students at some locations in the Middle East. Nedjat *et al*[31] reported that choosing medicine as a career in many circumstances is based on societal prestige and pressure from family and friends. Education has been described as a major determinant of class mobility[32] and, as entry into medical school is extremely competitive and significantly based on an entrance exam (with < 1% of applicants ultimately accepted), students often face enormous academic pressure during high school. As perfectionism and imposter syndrome have been linked with distress in health professional students[33], it is possible that students who prepare extensively and perform very well on the entrance exam and then face academic challenges in medical school may be at higher risk for emotional distress. However, it also seems plausible that pressure to do well on a high stakes exam [*i.e.*, the Medical

**Table 3 Comparison of samples of medical students on emotional exhaustion (ANCOVA)[1]**

| Survey items | a United States | b Middle Eastern country | c China | Paired comparison[1] |
|---|---|---|---|---|
| | LS mean (SE) | LS mean (SE) | LS mean (SE) | |
| I feel emotionally drained by my studies. | 2.82 (0.07) | 1.92 (0.08) | 2.31 (0.07) | a > b, c; c > b |
| I feel used up at the end of a day in medical school. | 3.44 (0.08) | 3.05 (0.10) | 2.84 (0.08) | a > b, c |
| I feel burned out from my studies. | 2.83 (0.07) | 2.81 (0.09) | 2.41 (0.08) | a > c, b > c |
| I have become less interested in my studies since my enrollment in medical school. | 2.51 (0.08) | 2.40 (0.10) | 2.07 (0.09) | a > c, b > c |
| Emotional exhaustion component | 2.90 (0.05) | 2.55 (0.07) | 2.42 (0.06) | a > b, c |

[1]Adjusted for differences in Patient Health Questionnaire-2 total score. LS mean: Least square mean; SE: Standard error.

College Admission Test (MCAT)] and subsequent stress in medical school might predict similar rates of psychological distress in the US, which we did not observe among students enrolled in the US site. This may be due, in part, to the fact that admission to medical school in the US is based on a number of factors in addition to the MCAT, and not on the test alone. It might also highlight the fact that personality and societal variables don't quite account for the significant differences observed. In fact, simply the request for anonymity from the Middle-Eastern school suggests that there is difficulty in acknowledging the reality of depression and burnout among students by the authorities of this school. The behavior of the administration itself could be a key difference in the culture of this institution that may help explain its high rates.

Medical students at Xiangya were also more likely to screen positive for depression than medical students at Yale. While two studies of medical student mental health in China report rates of depression as low as 3-5%[34-35], a number much lower than suggested by our study, another multi-site study of depression among Chinese medical students reported a prevalence rate of 66.8%[21]. This was similar to rates of depression among Chinese physicians in general[36]. One hypothesis for high rates in this region is that stigma is preventing access to care[37]. Alternatively, treatment-seeking may be limited logistically and financially by a lack of continuity of care and access to a range of evidence-based treatments in China, such as Cognitive Behavioral Therapy. This lack of access to and stigma towards mental health treatment may explain why unmet mental health needs are higher in China than the US. This difference, in turn, may predict higher depression in this population. Other hypothesized reasons for higher rates of depression as compared to the US cohort include the effects of academic pressure and stress from grading, professional satisfaction, and family environment on students' mental health[35], as well as lack of social support and negative life events[38]. As these factors may also be seen in the US cohort, there are likely other unmeasured environmental stressors unique to Chinese medical students. One example is that a recent increase in reports of serious doctor-patient conflicts in China may lead to concerns about a future in medicine[36], and therefore could contribute to negative mental health among students.

While we found that emotional exhaustion was lowest in this cohort, stress was significantly higher in China than in other groups. While one might hypothesize high stress would lead to higher rates of depression, and thus this data might explain the high rates in the Chinese cohort, this is not what we found in our regression model. Instead, we found higher stress led to lower depression. This may be because stress is more readily and easily admitted to by students than depression. As such, the students that are stressed are less likely to screen positive for depression. However, this inverse relationship could also be a fault of the binary measurement and/or different interpretations of the term "stress".

It is also worth considering what factors may have contributed to Yale's lower rate of screening positive for depression. Unlike the other two countries, the US has a medical education system so structured that students matriculate after having completed four (or more) years of undergraduate study. Yale is not unique among US medical schools in this regard; yet rates of positive depression screening at Yale are lower than rates reported in other US studies, which are as high as 21%[39-40]. Again,

**Table 4 Multiple linear regression on medical student depression measured by patient health questionnaire-2 in response to demographic, behavioral and psychological variables**

| Predictor variables | $R^2$ | Adjusted $R^2$ | F | Significance | B | Std. Error | β | t |
|---|---|---|---|---|---|---|---|---|
| Model | 0.473 | 0.461 | 41.621 | *P* < 0.001 | | | | |
| Age | | | | | 0.025 | 0.027 | 0.043 | 0.906 |
| Male | | | | | -0.089 | 0.101 | -0.032 | -0.881 |
| Sleep | | | | | 0.006 | 0.105 | 0.002 | 0.055 |
| Exercise[a] | | | | | -0.120 | 0.044 | -0.103 | -2.756 |
| Unmet mental health needs[a] | | | | | 0.235 | 0.041 | 0.228 | 5.780 |
| Emotional exhaustion[a] | | | | | 0.496 | 0.072 | 0.271 | 6.903 |
| Stress | | | | | -0.264 | 0.122 | -0.086 | -2.155 |
| Middle Eastern country[a] | | | | | 1.477 | 0.157 | 0.475 | 9.439 |
| China[a] | | | | | 1.005 | 0.155 | 0.338 | 6.492 |

[a]*P* < 0.01. Associated changes in $R^2$ for the following independent variable last added into the model, as its unique contribution to the improvement in the model's goodness-of-fit: Exercise: 0.01; Unmet mental health needs: 0.045; Emotional Exhaustion: 0.061; Stress: 0.006; Middle Eastern country: 0.113; China: 0.054

this might be a function of convenience sampling, however this may also be because Yale does not formally grade medical students during the first two years, unlike many other US medical schools. Studies suggest that pass/fail curricula improve student wellness and overall satisfaction with medical education[13,41]. Additionally, Yale does not rank students. At Xiangya and in the Middle East, more traditional numerical grading systems are utilized, and at Xiangya, students are aware of their ranking on exam scores and grades, which may be a source of increased emotional distress in these populations in comparison. Students at Yale also reported the statistically significantly highest number of hours of exercise and least amount of unmet mental health needs between the groups, which may be due to the fact that mental health providers are readily available and free to students. As more exercise correlated with lower depression, and higher unmet needs correlated with higher depression, these factors may contribute to Yale's overall lower rate of depression. Lastly, it is possible that lower rates of positive depression screening at Yale may be explained by the low response rate (39.5%) and students' concerns about survey confidentiality, which may have influenced their likelihood of participating or endorsing depressive symptoms. Yale's low response rate as compared to the other two schools, in fact, might itself suggest an unmeasured "cultural" difference, *i.e.*, conformity and respect for authority, not seen in the US, but very central to the two non-Western schools.

We were also interested in factors that predicted depression rates in medical students. One such factor that is often seen in studies to be correlated with depression[18] is burnout. Our study confirmed this correlation given that in our regression model, emotional exhaustion predicted depression. Yet, emotional exhaustion alone did not account for the differences in depression. We know this because when controlling for PHQ-2 total scores, the US had much higher emotional exhaustion scores than the other cohorts; the US also had much lower overall depression rates. Stress as well as unmet mental health needs contributed to depression in our model, however gender and age did not. Burnout and depression as consequences of inadequate sleep and exercise had been previously reported in a single site in the US[18]. However, here we are reporting findings from a multi-national study, where lack of exercise but not sleep correlated with depression across study sites in three countries. Additionally, given the vastly different rates of depression between cohorts, we hypothesized that region may be predictive of increased depression. The regression model suggested that the effect of internationally distinct medical school sites on overall depression scores was significant. Given that the total model explained 47% of the variance of medical student depression, it is likely that many unmeasured variables, including environmental, cultural, and region-specific ones, were unmeasured in our model and should be points of study in the future.

Our study has several limitations. The study design only involved three medical schools and may not have been broadly representative of medical students in the three countries, or other medical universities in these countries. Due to our research collaborators' request for anonymity, we cannot report the exact country or school of origin for the data in the Middle East. Response rates were much lower in the US (39.5%) compared with other sites (84.7% in the Middle East and 94.7% in China), which attenuates comparability across groups and could explain some portion of the

differences we observe across sites. It is possible that students who are most distressed may be less likely to complete a survey on mental health, which would create significant sampling bias when response rates are low. Although all students were given assurance of anonymity and confidentiality, some students may have felt reluctant to participate in a survey addressing their personal health and behaviors, particularly in cultures that are less comfortable openly discussing mental illness. The survey at the Middle Eastern school was also given to students immediately following a mental health seminar that may have influenced their willingness to participate and/or may have affected their responses to survey questions. Information bias might have also accounted for the differences in depression. Finally, sampling was also done out of convenience and that may have biased the results.

The survey itself also had limitations. For example, the PHQ-2 was used to measure depression screening rates, and not the PHQ-9. Though the PHQ-2 has been validated and is as effective as longer instruments like the Beck Depression Inventory[42,43] for better understanding of depressive symptoms and a higher positive predictive value, those who screen positive should have been given the PHQ-9. "Stress" and "unmet mental health needs" were also both measured with a single question. As evidenced by our results and variance explained by our model, variables that may account for the differences across sites were not identified in the current study. These could include cultural, political, financial, social support, access to evidence-based treatment, and other factors. While these were not included in the surveys or current study, they warrant further investigation. Differences in educational programs may also contribute to the differences in the results. We surveyed the entire school and included all class years in the same group for the US, whereas we surveyed only one class in the others. It is not clear whether results would have been significantly impacted had we surveyed the entire school in all countries and analyzed class groups separately. Additionally, as this study is cross-sectional in nature, it cannot assess cause and effect relationships. Lastly, our results may also be affected by survey translation. Though we made every effort to ensure accurate translation both linguistically and culturally, it is possible that miscommunication occurred.

Future research might include focus groups to explore site-specific factors associated with depression, stress, and burnout that were not included in our survey. This might allow for a more complete picture of depression and associated factors across internationally-distinct medical school sites. Specifically, future studies might explore the relationship between motivations for entering medicine (*e.g.*, personal desire *vs* family/societal pressures) and emotional distress among medical students. Equally important is to investigate the effectiveness of interventions designed to support student mental health, such as Xiangya's peer psychological support program and Yale's peer advocate program. While a previous study in New Zealand was not able to show a statistically significant change in mental health with the addition of peer support[44], Yale's peer advocate program is known to help lead students towards counseling, as mental health concerns were the most common reason a student reached out to the peer advocate[45]. The Middle Eastern site has recently launched a voluntary faculty mentorship program, wherein students are given the option of having a faculty member assigned to them as a longitudinal mentor for academic and personal support. A similar, though mandatory, program exists at the site in China. As comfort with academic help-seeking and supportive faculty relationships have been found to be possible protective factors in student mental health[29], it would be worthwhile studying the impact of mentoring programs on rates of depression.

In conclusion, this study suggests that mental health concerns affect a significant proportion of medical students worldwide. We compared three internationally distinct groups of medical students which, though individually unique, all share common stressors: The competitive pre-selection into medical school, the academic rigor and significant burden of coursework while in medical school, and pressure for high achievement during and after medical school. Rates of depression using ANCOVA were found to be the highest in the Middle East, then China, then the US. Linear regression suggested that emotional exhaustion, stress, unmet mental health needs, region, and exercise predicted nearly half of depression in these cohorts. Though rates of depression vary among the three groups studied, and response rate differences might have influenced the outcomes, our results suggest that continued efforts toward identifying site-specific prevention and intervention strategies in medical student mental health are warranted, and additional socio-cultural variables should be studied.

## ARTICLE HIGHLIGHTS

### Research background

Medical students have high rates of depression and burnout. These high rates are also seen internationally, including in populations in Asia and the Middle East. While burnout and depression affect the student's academic performance, decrease empathy, and increase unprofessional behaviors, very few students seek mental health treatment when they need it. Some studies have examined explanations for the high rates of burnout and depression. For depression, predictors included mistreatment, poor role models, low optimism, gender, and year of study. The overall learning environment was most often cited as a reason for burnout, with other explanations ranging from specific grading schemes to sleep. To our knowledge, no study has compared depression in medical students from different international populations. Additionally, we are unaware of other studies that have examined whether there are differences in other variables across international sites, including age, gender, sleep, exercise, unmet mental health needs, emotional exhaustion, stress, as well as nationality, which may explain any differences in depression. This study seeks to add to the literature by examining both of these questions and reporting on the data from three different groups of medical students, each from an internationally distinct medical school: Yale University School of Medicine in the United States (US), Central South University Xiangya School of Medicine in China, and a School of Medicine in the Middle East whose research collaborators chose to remain anonymous.

### Research motivation

The motivation behind this research is that depression and burnout in medical students affect patient care outcomes, and also contribute to high suicide rates among medical students and physicians. We have yet to fully understand why medical students have such high rates of depression and burnout, nor do we understand the global scope of the problem. We hope that by looking at these questions, we can better develop interventions to address depression in medical students. Currently, no best-practices exist, so a better understanding of the correlates of depression and need for site-specific interventions is warranted.

### Research objectives

The primary aim of this research was to compare depression rates in medical students across three internationally distinct populations. By doing so, we hoped to examine and better understand the universality of depression in medical students. The secondary aim of this research was to examine whether there are differences in other variables across these sites, including age, gender, sleep, exercise, unmet mental health needs, emotional exhaustion, stress, as well as nationality, which may explain any differences in depression. By doing so, we hoped to better understand the correlates of depression in medical students, as well as develop a better understanding of cross-cultural differences. The importance of looking at both of these aims is to better describe depression and its correlates in medical students, which can then help determine intervention strategies or identify additional variables to be studied in the future.

### Research methods

Convenience samples of medical students from the US, China, and a Middle Eastern country were surveyed in this exploratory study. Incentives were only offered at Yale (a gift card raffle), and participation was confidential, anonymous, and voluntary at all sites. The authors designed the survey utilizing some previously validated questionnaires for more accurate results. The Patient Health Questionnaire-2 measured depression, and a positive screen was defined as a PHQ-2 score of $\geq 3$. A modified version of the Maslach Burnout Inventory (MBI) assessed burnout. Prior to analyzing the survey data, principal components analysis was used to analyze the modified MBI and develop a component called "emotional exhaustion", which had high component loadings on the first four survey items about feeling drained, used up, burned out, or uninterested. Other questions on variables like sleep, exercise, and mental health need were assessed with self-reported multiple-choice questions. The original survey was translated into Mandarin, and by a language native to the Middle Eastern country by contributing authors. The translations were then re-translated back to English by colleagues in the US who were fluent in both languages to assure that the surveys administered to all cohorts of students were comparable. Chi-square test and analysis of variance were used to examine differences in demographics, behavioral, and psychological variables across these three schools. Analysis of covariance (ANCOVA) was then used to compare depression among these three countries adjusted for differences in "unmet mental health needs". Unmet mental health need was defined as rating one's agreement with the Likert scale item "There are times I have a mental health need for which I do not seek care", where agree and strongly agree were collapsed into one response. To determine the possible predictive variables for medical student depression, multiple linear regression analysis was performed. The analysis included: demographic variables (age and gender), behavioral variables (sleep, exercise, unmet mental health needs), and psychological variables (stress, emotional exhaustion). The possibility of multicollinearity was ruled out. All analyses were done using SPSS version 25, and statistical significance was evaluated at the $P < 0.05$ level.

### Research results

Response rates differed by cohort. At Yale, 205 out of 519 students (39.5%) responded to the survey. At the Middle Eastern school, 172 out of 203 students (84.7%) and at Xiangya, 142 out of 150 (94.7%) responded to the survey. Students in the Middle Eastern country were significantly more likely to screen positive for depression (41.1% of students screened positive) than students in China (14.1% screened positive). Both cohorts were more likely to be depressed than the US cohort (3.8% screened positive). Students in China slept the least number of hours, and students

in the Middle East exercised the least. More students in the Middle Eastern school had unmet mental health needs. When ANCOVA was used to adjust for unmet mental health needs, the students from the Middle Eastern country continued to have significantly higher rates of screening positive for depression, followed by China, and then the US. ANCOVA was also used to adjust rates of emotional exhaustion by PHQ-2 scores, and students from the US reported significantly higher scores than those from each of the other countries. The scores from the students in China and the Middle East were not significantly different from each other. Results from the multiple linear regression analysis on medical student depression found that demographic variables did not significantly predict medical student depression. Among behavioral variables, exercise and unmet mental health needs significantly predicted medical student depression, but amount of sleep did not. Both psychological variables, stress, as well as the emotional exhaustion component of burnout, were predictors of medical student depression. Stress was measured by answering "yes" to the question "are you stressed?". Admitting stress was negatively related to depression (*i.e.*, more stress, less depression). In comparison to the US, coming from the Middle Eastern country and China predicted higher levels of depression. The total model explained 47% of the variance of medical student depression (F = 41.621; df = 9,418; *P* < 0.001). The effect size (*i.e.*, Cohen's f$^2$ = 0.90) was large. Our results contribute to the field, as we found statistically significant differences in depre-ssion across our three international cohorts, and differences in other correlates, like emotional exhaustion, sleep, and unmet mental health needs, which had not previously been described. We also found that our model only predicted 47% of depression, with region as the greatest predictor. While this identified some of the potential correlates for depression, including unmet needs that could be better targeted in each program, our results also show that there are inherent differences by region that need to be further assessed. For example, future studies might explore the relationship between motivations for entering medicine (*e.g.*, personal desire *vs* family/societal pressures) and emotional distress among medical students. Equally important is to investigate the effectiveness of interventions designed to support student mental health to better understand ways to improve these high rates internationally.

### Research conclusions

This study found that depression, as measured by the PHQ-2, was highest among students in the Middle East, followed by China, and then the US. Emotional exhaustion was highest, however, in the US. Linear regression suggested emotional exhaustion, stress, unmet mental health need, region, and exercise predicted nearly half of depression in these cohorts. Even though the study design only involved three medical schools and may not have been broadly representative of medical students in the three countries, or other medical universities in these countries, we know that depression is a key problem in medical students internationally, it varies between groups and region, and other site-specific factors are important reasons for these high rates. We also know that unmet mental health needs must be addressed. Although rates of depression vary among the three groups studied, and response rate differences might have influenced the outcomes, our results suggest that continued efforts toward identifying site-specific prevention and intervention strategies in medical student mental health are warranted, and that additional socio-cultural variables should be studied.

### Research perspectives

In carrying out this research, the authors learned that while specific curricula are unique at each individual medical school, medical students in three countries share common experiences and stressors: Competitive entry to medical school, and the pressure and academic rigor of studying to be a physician. For some students, these experiences can lead to depression and burnout. The reasons behind this are complex, and further research is warranted to fully elucidate them. In this study, the authors also learned a great deal about international collaboration. This was a rich experience, yet came with some unplanned challenges. For example, one important lesson learned is that when translating surveys, they should always be translated back into the original language before administration to assure the questions read as originally intended. Additionally, with the request by one collaborating institution for anonymity in publication, we learned that sometimes there is difficulty in acknowledging the reality of depression and burnout among students by the authorities of schools. This can limit research studies in their dissemination. Future research should further explore site-specific factors associated with depression. One way to do this would be to include focus groups that help inform survey design. This might allow for a more complete picture of depression and associated factors across internationally distinct medical school sites.

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# Substance use disorders among older adults: A review of randomized controlled pharmacotherapy trials

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## Abstract

Substance use disorders (SUDs) are a growing problem among older adults. Acamprosate, disulfiram, and naltrexone are United States Food and Drug Administration (referred to as FDA) approved for the treatment of alcohol use disorder, and buprenorphine is approved for the treatment of opiate use disorder among adults. However, the data on the use of these medications for the treatment of SUDs among older adults are unclear from randomized controlled trials (referred to as RCTs). A review of the literature indicates that there are only two RCTs that evaluated the use of pharmacologic agents for SUDs among older adults (≥ 50 years). One trial evaluated the use of naltrexone when compared to placebo for the treatment of alcohol use disorder among individuals, 50-70 years in age. The other trial evaluated the use of naltrexone or placebo as adjuncts with sertraline in the treatment of alcohol use disorder among individuals older than 55 years in age. Both trials indicated that the use of naltrexone reduced the rates of relapse among older adults with alcohol use disorder. However, we did not identify any RCTs that studied the use of buprenorphine, acamprosate, or disulfiram for SUDs among older adults. Based on available evidence, it would be safe to conclude that limited data indicate some efficacy for naltrexone in the treatment of alcohol use disorder among older adults. However, data from controlled trials on the use of other medications that are FDA approved for the

treatment of SUDs among younger adults are nonexistent among older adults with SUDs.

**Key words:** Older adults; Substance use; Naltrexone; Acamprosate; Disulfiram; Buprenorphine

**Core tip:** Substance use disorder is a growing problem among the older adult population. Unfortunately, there is very limited controlled research data on pharmacotherapy to help with this situation. Our review indicates benefits for naltrexone in the treatment of alcohol use disorder, but we were not able to find data regarding pharmacotherapy for any other substance use disorder among older adults. This review is our attempt to draw attention towards the topic of substance use disorder treatment among older adults and to encourage further research in this field.

## INTRODUCTION

The number of adults over the age of 65 years who are expected to need substance use treatment is projected to increase from 1.7 million in 2001 to nearly 4.4 million by 2020[1]. Substance use disorders (SUDs) among older adults are often unidentified and under- or mis-diagnosed[2]. In this population, substance use causes greater harm due to the underlying physiological changes inherently related to aging, the presence of chronic medical illness, and due to drug-medication interactions[2]. Prolonged exposure to illicit substances can also have negative physiological and psychological effects that are especially relevant in older adults[2]. These include delirium, memory loss or cognitive impairment, suicide, falls and consequential fractures, and exacerbation of underlying medical comorbidities[2]. The goals of rehabilitation for SUDs for older adults are comparable to any other age group: to encourage, sustain motivation, and prevent relapse[3].

There are several pharmacologic treatments available for SUDs that have been approved by the FDA for adults[4,5]. The FDA has approved naltrexone, acamprosate, and disulfiram for the treatment of alcohol use disorder, whereas buprenorphine is approved for the treatment of opioid use disorder[4,5]. Naltrexone, an opioid-receptor antagonist, reduces cravings associated with heavy alcohol use and is thought to prevent the rate of relapse in individuals with alcohol use disorder. Acamprosate is a glutamate modulator agonist that acts in the putamen and is thought to decrease the physical and psychological discomfort that is associated with acute withdrawal from alcohol. Disulfiram is an inhibitor of the enzyme acetaldehyde dehydrogenases that is involved in alcohol metabolism and causes unpleasant physical symptoms when it interacts with alcohol[4]. Buprenorphine is a partial agonist at the mu opioid receptor and can be used in the treatment of opioid use disorder[5].

The aim of this editorial is to review the literature on published randomized control trials (RCTs) that evaluated the efficacy and tolerability of the four treatment modalities (acamprosate, disulfiram, naltrexone, and buprenorphine) for the treatment of SUDs among older adults (defined as individuals greater than 50 years in age).

## EVIDENCE FROM RCTs

A review of literature only found two trials that evaluated the use of pharmacologic agents for SUDs among older adults from RCTs (Table 1)[7,8]. Although both the studies used placebo as the comparator to naltrexone for alcohol use disorder among older adults, one study assessed the efficacy of treatment of depression with the

concurrent SUD[8]. Both studies were assessed as being of good quality based on the Centre for Evidence-Based Medicine criteria (Table 2). The details of the two studies are described in Table 3. We did not find any RCTs that investigated the use of acamprosate, disulfiram, or buprenorphine for the treatment of SUDs among individuals ≥ 50 years in age.

## DISCUSSION

Available data from RCTs on the use of pharmacotherapy, *i.e.* buprenorphine, acamprosate, or disulfiram, for SUDs among older adults are currently non-existent. The only two trials that we found in the literature evaluated the efficacy of naltrexone in reducing the rates of alcohol relapse among older adults when compared to placebo.

In the first included study, naltrexone was found to be effective in reducing the rates of relapse among a group of older male veterans[7]. However, it was not effective in reducing craving for alcohol or in reducing reported measures of depression and anxiety. In the second study, naltrexone did not enhance the treatment responsiveness either for depression or for alcohol consumption when combined with sertraline and individualized psychosocial support[8]. There was a significant correlation between alcohol relapse during the trial and poor response to depression treatment, but the study did not distinguish between relapse in alcohol use with no improvement in depression versus worsening of depression. The favorable outcome in drinking behavior was similar to the results of using naltrexone alone from previous studies, and the addition of antidepressants or individualized psychosocial support did not demonstrate additional efficacy.

The major limitation for both studies was the small sample sizes; and in the case of one of the studies, a limitation was that the majority of the participants were men[8]. These aspects limit the ability to extrapolate and apply any resulting conclusions to the general population or even specifically to all older adults. There is a need for further research that overcomes these limitations, assesses concurrent variables like gender, and addresses the need for larger sample sizes and generalized applicability.

In general, very few treatment options have been studied for SUDs in older adults. Among these interventions, naltrexone appears to be the most widely used for the treatment of alcohol use disorder and is the most studied. In contrast, disulfiram is less commonly used due to the risk of cardiovascular side effects, medication interactions, and exacerbation of underlying medical conditions or mood disorders in this population[9]. Of note, studies analyzing other pharmacological treatments such as acamprosate, disulfiram, and buprenorphine are lacking among older adults[10].

Several prior studies have assessed the use of non-pharmacological interventions, such as cognitive-based therapy for substance use in older adults[10]. However, there is limited data on the effectiveness of combining these therapies with pharmacological interventions. This highlights the need for further research on both the efficacy and safety of a variety of pharmacological interventions for SUDs in older adults and on the combination of pharmacotherapy with other skill-based therapies.

## CONCLUSION

This review indicates that there is a scarcity of evidence for the use of pharmacotherapy for the treatment of SUDs among older adults. There are only two controlled studies available in this population, and these studies indicate that naltrexone may show some benefit in the treatment of alcohol use disorder among older adults. However, the studies had a limited number of participants and predominantly included men, which further restricts the generalizability of the results. The need to investigate further the effectiveness of different pharmacotherapeutic modalities for the management of SUDs among older adults is, therefore, essential.

## Table 1 Summary of included studies

| Study | Number of participants | Age in yr | Setting | Comparators | Duration in wk |
|---|---|---|---|---|---|
| Oslin et al[7], 1997 | 44 | 50-70 | Veterans affairs | Naltrexone *vs* placebo | 12 |
| Oslin et al[8], 2005 | 74 | ≥ 55 | Outpatient | Naltrexone + sertraline *vs* placebo + sertraline | 12 |

## Table 2 Quality of included studies

| Study | Randomization | Similar groups initially? | Equal treatment? | Analyzed groups in which they were randomized | Objective/ "blind" treatments? | Overall quality of study |
|---|---|---|---|---|---|---|
| Oslin et al[7] | Yes | Yes | Yes | Yes | Yes | Good |
| Oslin et al[8] | Yes | Yes | Yes | Yes | Yes | Good |

## Table 3 Results summary from included studies

| Name of study | Outcomes | Tolerability | Limitations |
|---|---|---|---|
| Oslin et al[7] | (1) Those who drank alcohol was 1.9% of days for the naltrexone group *vs* 6.5% of days in the placebo group, *P* = 0.275; (2) The relapse rates were 25% in all clinical subjects; 14.3% in the naltrexone group *vs* 34.8% in the placebo group, *P* = 0.117; (3) Those who sampled alcohol and relapsed: 3 of 6 in the naltrexone group *vs* 8 of 8 in the placebo group, *P* = 0.024; (4) There were no differences in the abstinence rates between the two groups, *P* = 0.659; (5) There were no differences in prolonging abstinence between the two groups, *P* = 0.532 | (1) Most common side effects were sleep disturbances and anxiety; (2) For naltrexone, the common side effects were depression, sedation, and constipation; (3) For placebo, the common side effects were memory lapse, asthma attack, "fleeting thoughts", and frequent urination; (4) None of the subjects dropped out of study due to medication effects | (1) There were a small number of subjects; (2) The method of assessment was self-report |
| Oslin et al[8] | (1) Those who relapsed on alcohol use was 35.1% in the naltrexone group *vs* 32.4% in placebo group, OR: 1.25, *P* = 0.690; (2) Those who were abstinent from alcohol use was 43.2% in the naltrexone group *vs* 54.1% in the placebo group, OR: 1.34, *P* = 0.575; (3) Those individuals in whom the depression had remitted was 51.4% in the naltrexone group *vs* 54.1% in the depression group, OR: 1.40, *P* = 0.537; (4) Overall improvement was noted in 40.5% of individuals in the naltrexone group *vs* 43.2% in the depression group, OR: 1.40, *P* = 0.537 | (1) Common adverse events noted during treatment included; 58.1% headache, 51.4% anxiety, 41.9% nausea, 39.2% decreased sexual functioning, 24.3% vomiting; (2) The occurrence of adverse effects was not different between the two groups; (3) The symptoms were not related to the completion of the trial or to the adherence with the medication | (1) There were a small number of veterans and were mainly male; (2) The method of assessment was self-report; (3) The outcomes measured were dually dependent on depression remission and the lack of relapse on alcohol |

OR: Odds ratio.

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# World Journal of
# *Psychiatry*

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## RESPONSIBLE EDITORS FOR THIS ISSUE

# Dissociation and disasters: A systematic review

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## Abstract

*BACKGROUND*
Dissociation, which is defined as the failure to associate consciousness, memory,
identity, emotion, perception, body representation, motor control, and behavior
into an integrated whole, has long been assumed to be generated by trauma. If
dissociation is a product of trauma exposure, then dissociation would be a major
mental health outcome observed in studies of disaster survivors. Although some
studies have examined dissociation in disasters, no systematic literature reviews
have been conducted to date on the topic.

*AIM*
To systematically evaluate the literature on the association between disaster and
dissociation to determine the prevalence and incidence of dissociation after
exposure to disaster and further examine their relationship.

*METHODS*
EMBASE, Medline, and PsychINFO were searched from inception to January 1,
2019 to identify studies examining dissociative disorders or symptoms related to
a disaster in adult or child disaster survivors and disaster responders. Studies of
military conflicts and war, articles not in English, and those with samples of 30 or
more participants were excluded. Search terms used were "disaster*" and
dissociation ("dissociat*," "multiple personality," "fugue," "psychogenic
amnesia," "derealization," and "depersonalization"). Reference lists of identified
articles were scrutinized to identify studies for additional articles.

*RESULTS*
The final number of articles in the review was 53, including 36 articles with
samples of adults aged 18 and above, 5 of children/adolescents under age 18, and
12 of disaster workers. Included articles studied several types of disasters that
occurred between 1989 and 2017, more than one-third (38%) from the United
States. Only two studies had a primary aim to investigate dissociation in relation

to disaster and none reported data on dissociative disorders. All of the studies used self-report symptom scales; none used structured interviews providing full diagnostic assessment of dissociative disorders or other psychopathology. Several studies mixed exposed and unexposed samples or did not differentiate outcomes between exposure groups. Studies examining associations between dissociation and disaster exposure have been inconclusive. The majority (75%) of the studies compared dissociation with posttraumatic stress, with inconsistent findings. Dissociation was found to be associated with a wide range of other psychiatric disorders, symptoms, and negative emotional, cognitive, and functional states.

*CONCLUSION*
The studies reviewed had serious methodological limitations including problems with measurement of psychopathology, sampling, and generation of unwarranted conclusions, precluding conclusions that dissociation is an established outcome of disaster.

**Key words:** Dissociation; Dissociative disorders; Disaster; Systematic review; Methodology; Diagnostic validity; Psychopathology; Normative response; Posttraumatic stress; Association *vs* causation

**Core tip:** Almost all existing studies of dissociation in relation to disaster have not focused specifically on this purpose but rather on the relationship of dissociation to other disaster outcomes. Instead of dissociative disorders, broadly defined dissociative phenomena have been examined in disaster survivors. The literature uniformly contains unsurmountable methodological limitations such as reliance on nondiagnostic dissociation measures, lack of temporal specificity to postdisaster time frames, and problems with disaster exposure issues pertaining to sampling, measurement, and analysis. It cannot be concluded from the research that dissociation is an established outcome of disasters.

# INTRODUCTION

The current Diagnostic and Statistical Manual of Mental Disorders (5th edition) (*DSM-5*)[1] defines dissociation as "a disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior" (p. 291). Dissociative disorders listed and defined in *DSM-5* are Dissociative Identity Disorder, Dissociative Amnesia, and Depersonalization/Derealization Disorder, as well as Other Specified Dissociative Disorder and Unspecified Dissociative Disorder. The concept of dissociation was first introduced in the field of medicine in the 1800s by the French physician Pierre Janet who described it as a breakdown of the integration, or the compartmentalization, of the mental processes required for a unified experience of consciousness and of self[2,3]. A variant of dissociation also introduced by Janet was described as "narrowing of the field of consciousness," reflecting reduced capacity to assimilate elements of sensation into complex personal perceptions, a process that has subsequently been linked to hysteria[4,5]. Current concepts of dissociation encompass a wide range of phenomena including highly pathological disturbances of memory such as in states of amnesia, disturbance of consciousness such as in fugue states, and identity disturbance as well as common and benign experiences involving attention such as absorption, daydreaming, and fantasy[6-8].

Dissociation has long been assumed to develop as a mechanism for coping with severe trauma[3,9]. Extensive literature has documented a relationship between trauma and dissociation and elaborated presumptive psychological mechanisms in a "trauma model of dissociation"[10]. It follows logically that if dissociation is a product of trauma

exposure, then dissociation would be a major mental health outcome observed in studies of disaster survivors. Despite the publication of some studies of dissociation in disaster survivors, no major systematic reviews of this literature have been conducted. Therefore, the lack of reviews of research on dissociation and disasters in the context of widespread assumptions that trauma generates dissociative psychopathology, the purpose of this article is to provide a systematic review of published studies on dissociation and disaster to determine the prevalence and incidence of dissociation after exposure to disaster and further examine their relationship.

## MATERIALS AND METHODS

A systematic literature search was undertaken to locate studies examining dissociative disorders or symptoms related to a disaster in adult or child disaster survivors and rescue/recovery workers. Only studies with samples of ≥ 30 were included, because of known problems with non-normal sampling distributions in smaller studies[11]. Articles not in English and studies of military conflicts and war were excluded.

EMBASE, Medline, and PsychINFO were used to identify articles before January 1, 2019. Search terms used were "disaster*" and dissociation ("dissociat*," "multiple personality," "fugue," "psychogenic amnesia," "derealization," and "depersonalization"). Reference lists of identified articles were inspected for additional articles. Figure 1 provides a flow chart of this article selection process. The manuscript was prepared and revised according to the PRISMA 2009 Checklist[12]. The search strategy and list of excluded articles with the reason of exclusion are presented in Supplementary table 1.

### Quality appraisal

The quality of the included studies was measured using a modified version of a tool generated for assessing the quality of prevalence studies[13,14]. The features assessed included description of target population, inclusion/exclusion criteria, sampling method, demographic characteristics, information on nonresponders, use of validated and professional-administered diagnostic instruments, and report of prevalence estimates. This instrument has 10-items and allows for the calculation of a total quality score (range = 0-10), with higher summed scores indicating higher study quality.

### Assessment of risk of bias

The Hoy Risk of Bias Tool (RoBT)[15] was used to assess methodological bias. The RoBT consists of 10 items evaluating external (4 items) and internal (6 items) validity. Studies were classified as having a low risk of bias when 8 or more of the 10 items were answered as "yes (low risk)," a moderate risk of bias when 6 to 7 of the questions were answered as "yes (low risk)," and a high risk of bias when 5 or fewer questions were answered as "yes (low risk)"[16].

### Statistical analysis

Simple chi-square analyses were conducted to compare proportions of two different comparison groups with positive findings, substituting Fisher's exact tests for expected cell sizes of < 5.

## RESULTS

### Included studies

The final number of articles in the review was 53, including 36 articles with adult (aged ≥ 18) samples (Table 1), 5 of children/adolescents (< age 18) (Table 2), and 12 of disaster workers (Table 3). These articles, published between 1993 and 2019, included 51 original articles, 1 letter to the editor, and 1 doctoral dissertation. The disasters occurred between 1989 and 2017, and 60% were from countries: United States (*n* = 20), Netherlands (*n* = 4), Italy (*n* = 4), and Turkey (*n* = 4). The types of disasters included earthquakes (*n* = 17), explosive accidents (*n* = 11), terrorist attacks (*n* = 8), hurricanes/typhoons (*n* = 7), ferry sinkings (*n* = 3), firestorms (*n* = 2), floods (*n* = 2), tsunamis (*n* = 2), fires (*n* = 1), plane crashes (*n* = 1), train crashes (*n* = 1), and mass shootings (*n* = 1). Multiple disasters were examined in five of the articles. Specific population subgroups, namely women, older adults (aged ≥ 60), and pet owners were the focus in three adult survivor studies represented in four articles. More than one-third (36%) of the articles involved longitudinal prospective studies and the
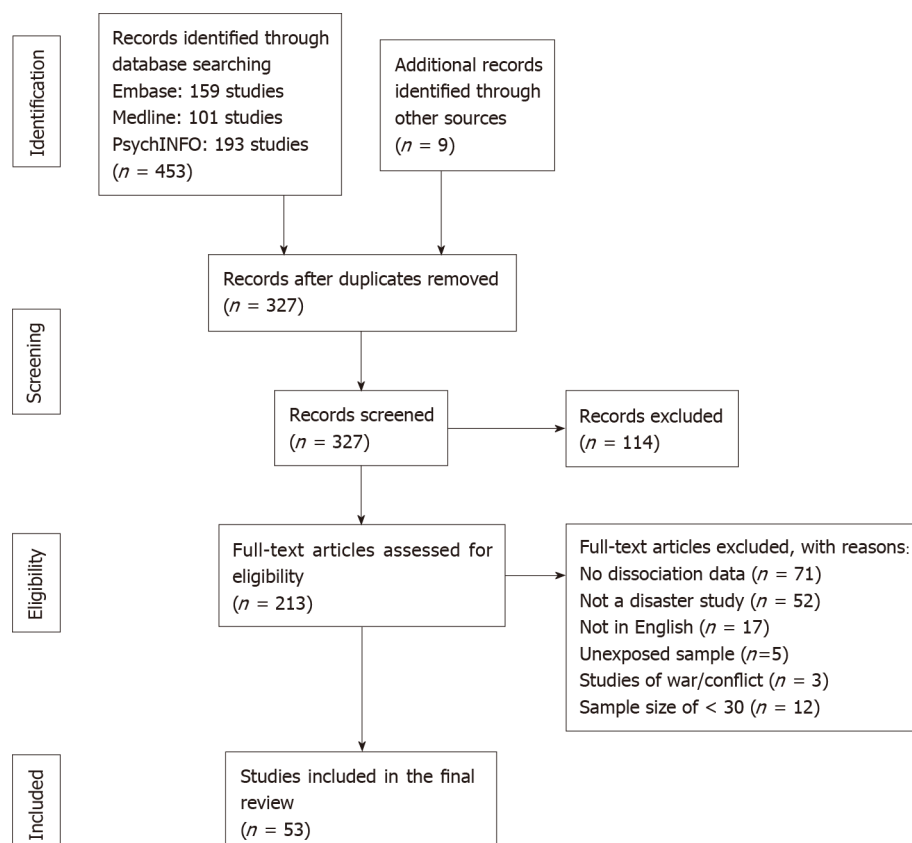
**Figure 1 Flow chart of selection process for articles in the review.**

remainder described cross-sectional studies.

### Quality and risk of bias
The total quality score of the studies ranged from 1 to 5 (out of a maximum possible of 10), indicating that none of the studies included had good quality (Supplementary table 2). According to the RoBT, the majority of studies had a high risk of bias with only three having a moderate risk (Supplementary table 3).

### Focus of the studies
Only two of the studies in the review focused solely on dissociation without including other disaster mental health outcomes such as posttraumatic stress[17,18]. The majority of studies (*n* = 40) had a primary focus on posttraumatic stress, including dissociation only as a secondary topic, typically examining it in relation to posttraumatic stress. The remaining few studies (*n* = 10) had a joint focus on posttraumatic stress and dissociation, investigating the relationship between these two entities.

### Dissociation measures
All of the studies used self-report symptom scales; none used structured diagnostic interviews for dissociative disorders. The Peritraumatic Dissociative Experiences Scale (PDEQ)[19] was used in 49% of the studies and the Dissociative Experiences Scale (DES)[20,21] was used in 13%. The Maslach Burnout Inventory–Human Services Survey (MBI-HSS)[22] was used to measure depersonalization in four studies. Dissociative symptoms embedded in Criterion B of acute stress disorder were assessed by three studies; two others approximated dissociation respectively with one panic disorder symptom and a single traumatic event-related amnesia item.

### Dissociation levels and associations with demographic and psychopathological variables
Several studies in this review (for example[23-27]) reported dissociation levels in mixed samples of exposed and unexposed survivors without differentiating results between exposure groups. In some studies, references to disaster exposures did not differentiate between disaster trauma exposure specifically, and the experiences of other stressors in the disaster such as property damage or loss of possessions. The presentation of dissociation data was limited to univariate results in two

## Table 1 Studies of dissociation in adult disaster survivors

| Disaster | Sample | Measures | Results |
| --- | --- | --- | --- |
| Ferry sinking (Baltic Sea 1994)[93,94] | 42 survivors | 3 ASD dissoc. items | 3-mo dissoc. associated with 3-mo and 1-yr but not 14-yr posttraumatic stress |
| Earthquake (Haiti 2010)[28] | 167 exposed volunteers | PDEQ | Mean 27-mo PDEQ score = 25. Dissoc. predicted posttraumatic stress symptoms and depression |
| Explosion (France 2001)[95-97] | 430 survivors from local EDs | PDEQ | 6-mo dissoc. posttraumatic stress at 6 and 15 mo but not 5 yr |
| Train crash (Israel 2005)[50] | 53 survivors | DES, PDEQ | Scores higher in survivors with *vs* without fibromyalgia (9 *vs* 2; 20 *vs* 9) |
| Earthquake (San Francisco, CA 1993)[17] | 100 exposed volunteer college students | SASRQ | All 5 dissoc. subscale scores higher at 1 wk than 4 mo |
| Explosion (Denmark 2004)[29,42] | 169 evacuees | 4 TSC dissociation items | Mean dissoc. Score = 6 (of 12). 3-mo dissoc. predicted 1-yr posttraumatic stress in women only and not 1-yr somatization |
| Floods/ mudslides (Italy 2009)[48] | 287 exposed residents | DES, PDEQ | DES, difficulty identifying feelings, and externally oriented thinking predicted 27-mo PDEQ. PDEQ explained 44% of IES-R |
| Explosion (Belgium 2004)[98] | 1027 exposed residents | PDEQ | 5-mo dissociation predicted 5-mo (not 14-mo) posttraumatic stress |
| 9/11, WTC (NYC 2001)[23] | 1009 Manhattan residents, workers | 1 DTS dissoc. item (event amnesia) | Event amnesia was least endorsed item (2%) |
| Earthquake (NZ, 2011)[40] | 101 exposed treatment seekers | PDEQ (4 items) | Dissoc. predicted posttraumatic stress symptoms, anxiety at 2-8 wk |
| 9/11 Pentagon (Washington, DC 2001)[44] | 77 exposed military, civilian staff | PDEQ | Dissoc. associated with posttraumatic stress (18 *vs* 5) and alcohol use and negatively with perceived safety |
| 3 technological accidents (Netherland)[99] | 49 affected individuals | PDEQ, SDQ-P | 20-d dissoc. did not predict 6-mo posttraumatic stress symptoms |
| Hurricane Katrina (New Orleans, LA 2005)[100] | 65 exposed pet owners | PDEQ | Dissoc. associated with having to abandon pet (mean PDEQ = 30 *vs* 23), depression, acute stress, and posttraumatic stress symptoms. |
| Hurricane Katrina (New Orleans, LA 2005)[32] | 117 people in mandatory evacuation zones | PDEQ | Mean PDEQ score = 12 (unknown timing). Dissoc. associated with property damage |
| Earthquakes; floods (Australia/NZ 2010-2011)[101] | 662 exposed residents | PDEQ | Dissoc. associated with posttraumatic stress symptoms and negative beliefs about memory |
| Firestorm (Oakland/Berkeley 1991)[18,102] | 94 referral center help seekers, 93 local students | SASRQ | 1-mo dissoc. associated with 7-9-mo posttraumatic stress symptoms but not intrusions |
| 9/11 WTC (NYC 2001)[24] | 2001 NYC residents | 2 DIS dissoc. panic attack items | 4-5 mo dissoc. associated with posttraumatic stress symptoms, older age, female sex, non-white race, and fear of death or injury |
| Earthquake (Haiti 2010); tsunami (Japan, 2011)[103] | 140 Haiti/12 Japan disaster exposed; 80 other trauma exposed | DES | Dissoc. scores (unknown timing) not different between trauma groups |
| Mass shooting (DeKalb, IL 2008)[25] | 583 female university students | 4 PDEQ items | 2-wk dissoc. predicted 2-wk to 3-mo and 8-mo probable posttraumatic stress |
| Earthquake (Iran 2017)[80] | 230 exposed volunteers from 2 cities | DES, PDEQ | 3-4 mo dissoc. associated with posttraumatic stress |
| Earthquake (Turkey 2011)[26] | 583 randomly sampled residents | DES (with Taxon) | 2-yr DES Taxon membership = 25%. Dissoc. predicted posttraumatic stress symptoms, re-experiencing, avoidance, and hyperarousal but not functional impairment |
| Earthquake (Turkey 2011)[27] | 317 volunteer college students | DES (with Taxon) | High (21%) DES Taxon membership (unknown timing). DES predicted posttraumatic stress symptoms. Pathological dissoc. mediated between posttraumatic stress symptoms and ADHD symptoms |

| | | | |
|---|---|---|---|
| Earthquake (Italy 2009)[35] | 84 university student volunteers | 14 TSI dissoc. items | 7-yr dissoc. scores in exposed than unexposed. Dissoc. not associated with exposure |
| Hurricane Ike (Texas coast, 2008)[66,104] | 75 older residents | PDEQ | Mean PDEQ = 11. Dissoc. associated with 3-mo posttraumatic stress but not 3-mo depression. Dissoc. not associated with posttraumatic stress trajectories |
| Tsunami (Indonesia 2004)[30] | 660 evacuated Danish tourists | 4 ERDTS dissoc. items | 10-mo dissoc. predicted posttraumatic stress symptoms, depression |
| 9/11 WTC (NYC 2001)[36,105] | 75 exposed NYC residents | PDEQ, DES, CDS, CADDS | Mean PDEQ = 35, DES = 17. 3-mo dissoc. not associated 1-yr posttraumatic stress symptoms. Dissoc. not associated with exposure |
| Explosion (Taiwan 2015)[47] | 116 burn survivors | SDQ | 25-mo dissoc. associated with posttraumatic stress but not depression |
| Fire (Nether-lands, 2000)[31] | 662 residents | PDEQ | Mean PDEQ = 24. 2-3 wk dissoc. not associated with 18-mo or 4-yr posttraumatic stress symptom severity |
| Fire and explosion (Netherlands 2001, 2004)[106] | 94 disaster, 111 non-disaster burn survivors | 3 ADS dissoc. items | 1-wk dissoc. Disaster > others. Disaster: 1-wk dissoc. not associated with 12-mo posttraumatic stress |

ADS[107]: Anxiety and Dissociation Scale; ASD: Acute stress disorder measure; CDS[105]: Cambridge Depersonalization Scale; CADDS[108]: Clinician Administered Dissociative States Scale; DES[20,21]: Dissoc.: Dissociation; Dissociative Experiences Scale; DIS[109]: Diagnostic Interview Schedule; DTS[110]: Davidson Trauma Scale; ERDTS[30]: Emotional Reactions During Trauma Scale; NYC: New York City; NZ: New Zealand; PDEQ[19]: Peritraumatic Dissociative Experiences Scale; SASRQ[111]: Stanford Acute Stress Reaction Questionnaire; SDQ[112]: State Dissociation Questionnaire; SDQ-P[113]: Somatoform Dissociation Questionnaire-Peritraumatic; TSC[114]: Trauma Symptom Checklist; TSI[115]: Trauma Symptom Inventory; WTC: World Trade Center.

studies, one[17] documenting a decline in dissociation from 1 wk to 6 mo and the other[23] reporting event amnesia in only 2% of the sample. Demographic factors reported to be associated with dissociation in bivariate comparisons included advanced age[24,28], female sex[24,28-31], African American or Hispanic race[24], and limited education[31].

The findings of associations between dissociation and disaster exposure in the studies reviewed are inconclusive. Dissociation was found to be significantly associated with disaster exposure in three studies. Non-traumatic stressor exposures by themselves or included in a mixed list of traumatic and other stressful disaster exposures were associated with dissociation in a firestorm study[18] and a hurricane study[32], and specific trauma exposures were associated with higher dissociation scores among children in a severe earthquake[33]. Several studies did not identify associations between dissociation and disaster exposures. Dissociation was not found to be associated with disaster trauma exposures or exposure proxies such as physical proximity to the World Trade Center towers in the 9/11 attacks[24], losing significant others or possessions in the disaster[24,34], or being trapped under earthquake rubble[34,35]. A study of survivors of the 9/11 attacks found that levels of dissociation were not associated with immediate life threat in the disaster, indirect exposure *via* threat to loved ones, or participation in rescue efforts[36]. Depersonalization in disaster workers responding to a typhoon was not found to be associated with contact with disaster survivors or witnessed disaster trauma exposures[37].

Three-fourths (75%) of the studies (40 articles) compared dissociation with posttraumatic stress. These articles used self-report posttraumatic stress measures such as the Impact of Event Scale-Revised, Posttraumatic Stress Disorder (PTSD) Checklist, PTSD Symptom Scale, and Child Posttraumatic Stress Disorder-Reaction Index. As for dissociation, none of the studies of posttraumatic stress used structured diagnostic assessment interviews. Of the 25 studies reporting results of bivariate comparisons, 100% reported significant associations between dissociation and posttraumatic stress. Of the 30 studies reporting results of multivariate models, only 60% found significant associations between dissociation and posttraumatic stress, a significantly lower proportion ($\chi^2$ = 12.79, *df* = 1, *P* < 0.001). Of the 16 longitudinal multivariate studies, only one-fourth (25%) found that dissociation measured shortly after a disaster was associated with long-term posttraumatic stress, significantly less often than in cross-sectional multivariate studies ($\chi^2$ = 5.12, *df* = 1, *P* = 0.024).

Of the seven studies conducting bivariate comparisons of dissociation with depressive pathology, all reported significant associations (for example[26,28,34,38,39]).

**Table 2 Studies of dissociation in child and adolescent disaster survivors**

| Disaster | Sample | Measures | Results |
|---|---|---|---|
| Hurricane Katrina (New Orleans, LA 2005)[41] | 112 exposed students with ≥ 1 other trauma exposure | 9 TSCC dissoc. items | 4-mo to 7-yr dissoc. associated with posttraumatic stress symptoms, anger, anxiety, depression |
| Earthquake (Turkey 2011)[34] | 738 exposed high school students | A-DES | 6-mo dissoc. associated with posttraumatic stress, anxiety, prior mental health problems, metacognitions, but not with age, sex, disaster exposure, prior exposure to trauma |
| Earthquake (Turkey 1999)[33] | 202 exposed, 101 unexposed children | 11 TDGS dissoc. items | Exposed children had higher 4-5 mo perceptual distortions (1.3 *vs* 1.2), body-self distortions (1.1 *vs* 1.1) (range = 1-3 for both subscales) |
| Ferry disaster (South Korea 2014)[65] | 57 child and adolescent survivors | 3 PDEQ items | 20-mo dissoc. associated with posttraumatic symptoms |
| Earthquake (China 2010)[116] | 753 exposed middle school students | 1 UPRI dissoc. item (derealization) | Majority (77%) positive for derealization. 6-mo derealization predicted PTSD |

A-DES[117]: Adolescent Dissociative Experiences Scale; dissoc.: Dissociation; TDGS[33]: Traumatic Dissociation and Grief Scale; TSCC[118]: Trauma Symptom Checklist for Children; UPRI[119]: The University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index.

Only two of five studies comparing dissociation with depressive pathology in multivariate models reported significant associations[28,30], a significant difference from the bivariate analysis findings (Fisher's exact test, $P = 0.021$). Other problems found to be positively associated with dissociation in sporadic studies included anxiety[34,40,41], somatization[42], adult attention-deficit/hyperactivity disorder[27], general mental health problems[43], increased postdisaster use of alcohol[44] or tobacco[38], suicidality[26], hopelessness[26], anger[41], hostility[45], feeling unsafe[44,46], fear during the disaster[24,47], alexithymia[48], trauma memory disorganization[47], trauma-related rumination[47], maladaptive coping strategies[49], lower academic achievement[27], greater injury-related functional impairment[47], lower health-related quality of life[26], and fibromyalgia syndrome[50]. Dissociation was also associated with early traumatic experience[51] and religiosity[28]. In the above studies, none were found in which dissociation was not associated with any of these outcomes.

## DISCUSSION

Although there are a number of reviews[52-55], meta-analyses[56,57], and a bibliometric analysis[58] examining the studies on mental health outcomes of disasters, no prior reviews have been published specifically on dissociation associated with disasters even though a few reviews of PTSD and dissociation included very small numbers of disaster studies without specific comment on them[59-62]. The current review found 53 published articles on this topic among adult and child survivors of disasters as well as disaster workers. Only 2 of the 53 studies reviewed was designed for the main purpose of examining the prevalence of dissociation following a disaster. The main purpose of the remaining 51 studies was to examine the occurrence of other outcomes (posttraumatic stress in the majority) after disaster, and dissociation was included only as a secondary outcome in relation to the primary outcome of interest. The quality of the studies reviewed was exceedingly limited by methodological problems inherent in them. Problems with measurement of psychopathology, sampling issues, assessment time frames, and generation of conclusions unwarranted from the data represented serious methodological weaknesses in this literature.

### Dissociation measures

Problems in the instruments of assessment were fundamental limitations in all of the studies reviewed. None used diagnostic instruments assessing accepted standards such as *DSM-5* criteria for dissociative disorders; dissociative identity disorder, dissociative amnesia, and depersonalization/derealization disorder were not mentioned in any of these studies' findings. All depended on symptom measures to assess dissociation, with 72% using the PDEQ, DES, or MBI-HSS. These self-report questionnaires inquire about many kinds of experiences not generally corresponding to the established symptoms of *DSM-5* dissociative disorders; these items are then

**Table 3 Studies of dissociation in exposed disaster workers**

| Disaster | Sample | Measures | Results |
|---|---|---|---|
| 9/11, WTC (NYC 2001)[38] | 90 disaster workers | PDEQ | Number of 2-3 wk dissoc. symptoms associated with probable ASD |
| Typhoon Haiyan (Philippines 2013)[37] | 61 religiously, spiritually oriented humanitarian aid workers | MBI-HSS (5 depersonalization items) | Mean 8-mo depersonalization score = 1.1 (of 30). Depersonalization associated with negative religious coping but not with indirect exposure, direct exposure, or positive religious coping |
| Earthquake (Japan 2011)[43] | 34 healthcare providers | MBI-HSS (5 depersonal-ization items) | Mean 2-yr depersonalization score = 0.6 (of 30). Depersonalization not associated with general mental health |
| Plane crash (Sioux City, IA 1989)[39] | 207 exposed, 421 unexposed disaster workers | 3 ASD dissoc. items | Number of 2-mo dissoc. symptoms associated with 13-mo posttraumatic stress but not depression. Any 2-mo dissoc. symptoms not associated with 13-mo posttraumatic stress or depression |
| 9/11 WTC (NYC 2001)[46] | 89 disaster responders | PDEQ | 2-wk dissoc. negatively associated with perceived safety |
| Hurricane Katrina (New Orleans, LA 2005)[51] | 441 rescue personnel | PDEQ | 2-yr dissoc. associated with being single, exposure severity, physical victimization |
| Earthquake (Loma Prieta, CA 1989)[67,68] | 198 exposed, 251 unexposed rescue personnel | PDEQ | 1.5-yr dissoc. associated with 3.5-yr posttraumatic stress symptoms, intrusion, avoidance, hyperarousal |
| Earthquake (Italy 2009)[49,120] | 285 healthcare workers at one hospital | MBI-HSS (5 depersonal-ization items) | Mean 6-yr depersonalization score = 1.1 (of 30) Depersonalization associated negatively associated with planning and positively with behavioral disengagement and self-distraction |
| Terror attacks (Norway 2011)[121] | 238 rescue personnel | 5-item scale developed by authors | 8-11 mo dissoc. predicted posttraumatic stress |
| Fire (Netherlands 2000)[45] | 66 ambulance personnel | PDEQ | 2-3 wk dissoc. predicted 18-mo hostility, but not posttraumatic stress symptoms or depression |

ASD: Acute stress disorder; dissoc.: Dissociation; MBI-HSS[22]: Maslach Burnout Inventory–Human Services Survey; NYC: New York City; NZ: New Zealand; PDEQ[19]: Peritraumatic Dissociative Experiences Scale; WTC: World Trade Center.

tabulated and summarized into indistinct "dissociation" scores of unclear meaning or significance. The PDEQ, which was used in about half of the studies, collects information about lack of awareness that is not reflected in diagnostic criteria for any dissociative disorder, and its other items do not provide data on symptoms of dissociative identity disorder, dissociative amnesia, or depersonalization/ derealization disorder[63,64]. Numerous studies using the PDEQ have not been faithful to the full instrument (for example[25,40,44,65,66]) or its scoring algorithms[50,51,67,68], creating further threats to its validity in these studies. DES scores have been demonstrated to correlate with dissociative disorder diagnoses, but its subscales are not only not specific to dissociation but they also correlate with other psychopathology more broadly[69,70]. The MBI-HHS depersonalization subscale does not measure diagnostic constructs incorporated into depersonalization/derealization disorder.

A major problem with these dissociation measures is the potential for conflation of nonpathological experiences with the pathological components of dissociative disorders. Conceptually, many DES items elicit experiences that are common in general populations and reflect benign or everyday processes such as not remembering parts of conversations or complete absorption of attention in a television program or a movie, especially the items contained in the "imaginative absorption" subgroup comprising about half of its items[7]. For example, "missing part of a conversation" was endorsed by 83% of the general population in one study, and even "feeling as though one were two different people" was endorsed by nearly half[7]. Because the imaginative absorption subscale of the DES has been demonstrated to reflect nonpathological processes[7,71,72], the total dissociation score from this instrument includes a substantive amount of nonpathological material contributed by this subscale. To address this problem, a specifically pathological dissociative taxon

was constructed from the DES items considered to be most pathological (and specifically not including any of the imaginative absorption subscale items)[73]. The DES taxon has been superior to the entire DES in correlating with dissociative diagnoses[72,74,75], but it has not been demonstrated to have the ability to classify or even identify dissociative disorders with reasonable accuracy[72,74]. No other dissociation scales have been systematically examined for their ability to differentiate diagnosable psychopathology from benign or nonpathological experiences.

Another problem with many dissociation measures (especially DES and MBI-HSS) is the lifetime collection of dissociative experiences that is far broader than the time frame of interest, *i.e.* the postdisaster period. Thus, much of the data collected with these instruments may pertain to predisaster periods only, which thus cannot reflect effects of the disaster ostensibly examined in these studies. In contrast, the PDEQ does focus on the acute postdisaster time frame and thus its data does have the potential to provide information relevant to effects of the disaster. However, the collection of PDEQ data months and even years after the disaster in many of these studies introduced potential recall bias through the fading of memory with time elapsed since the event.

### Trauma exposures

Correct measurement of exposure is critical to the ability to determine if an outcome is related to the disaster. Disaster research requires special attention to trauma exposures, because of the conditional nature of the diagnostic construct of PTSD requiring a qualifying exposure to trauma to consider symptoms or a diagnosis to be disaster-related, and because psychosocial outcomes are highly linked to trauma exposures[76]. Trauma exposure data are also needed in studies of dissociation to determine associations with disaster to support assumptions of a causal role of disaster trauma in the development of dissociation. If it is unknown whether the sample was even exposed, it cannot be stated whether exposure to disaster leads to dissociation. Many of the reviewed studies enrolled samples without disaster trauma exposure or mixed trauma-unexposed and trauma-exposed survivors resulting in problems of sample heterogeneity. Many studies either did not specify disaster trauma exposure or mixed exposure groups without controlling for them in the analyses. Some studies did not differentiate exposure to disaster trauma from other disaster-related stressors. Many of the studies reviewed did not even compare exposures with outcomes.

### Prevalence of dissociation in different populations

Notwithstanding the many identified methodological problems in the studies of dissociation reviewed here, comparison of levels of dissociation in disaster-affected populations with dissociation in other populations provides a broader view of the occurrence of dissociation in different settings. A number of studies have used the DES to measure dissociation prevalence in general populations, disaster-affected populations, and treatment populations, allowing comparison of these populations using a consistent measure. General population studies using the DES have identified average dissociation scores of 7-11 (out of a possible 100)[7,77-79]. Studies of disaster survivors using the DES have found somewhat higher scores, 11-26[36,48,50,80]. Studies of patients with dissociative disorders using the DES have found even higher scores, 24-60 (for example[81-85]). Thus, disaster survivors in these studies seem to have observably greater dissociation than in general populations, but it does not rise to the far higher levels of dissociation patient populations.

The higher prevalence of dissociative findings in disaster survivor populations than in general populations could possibly relate to two possibilities: (1) that actual dissociative psychopathology generated by disaster exposure; or (2) that benign or nonpathological experiences generated by the extreme circumstances of disaster exposure generating detectable scores on dissociation measures. Considering the first possibility, if exposure to disaster trauma precipitates the development of dissociative disorders, then it is possible that the somewhat higher dissociative scores in these groups could reflect modest numbers of individuals with dissociative disorders. However, because none of the dissociative measures in the studies reviewed assessed the diagnostic criteria for dissociative disorders, it is impossible to know if new dissociative disorders follow disaster exposure. Considering the second possibility, the somewhat higher dissociative scores in disaster survivor populations than in general populations require careful interpretation. They could at least partially represent normative responses to disaster exposure that may not reflect pathological states. Again, because none of the dissociative measures in the studies reviewed assessed the diagnostic criteria for dissociative disorders, assumptions that the dissociation measured represents dissociative pathology may constitute a conflation of nonpathological responses with psychopathology.

The conflation of normative responses to disaster trauma with psychopathology may naturally arise from the extreme and unusual disaster circumstances promoting a sense of bizarreness and unreality akin to a dream, fantasy, or movie, because it is unlike other kinds of experience occurring in real waking life. Additionally, the focus of attention in disasters may be narrowed to the most important parts of the experience, preventing memories of some parts of the experience whose absence might be inadvertently interpreted as pathological amnesia rather than a natural consequence of constricted attention. All of these disaster experiences may be considered to be examples of the cognitive processes of the dissociative absorption and imagination factor, which Ross *et al*[7] and Merckelbach *et al*[86] have interpreted as nonpathological in modest amounts, such as in these studies of general populations and disaster survivors. To the extent that general populations register small but detectable scores of dissociation measures, they may have endemic levels of benign dissociative phenomena, and the higher scores in disaster survivors may reflect generation of more of these phenomena through extreme trauma exposure.

The still higher prevalence of reported dissociation in patients with dissociative disorders than in disaster survivors may relate to presence of the dissociative psychopathology that defines dissociative patient populations as well as to patient reporting styles[87]. In part, because all patients with dissociative disorders have dissociative disorders, their scores on dissociative measures would be expected to be higher than in other populations not selected for psychiatric illness, such as disaster-exposed groups. Again, however, because the dissociative measures in the disaster studies reviewed do not diagnose dissociative disorders, there is no information about the incidence of dissociative disorders following disaster exposure. Dissociative disorders are not listed among the classical responses to disasters[88], and even case reports of dissociative disorders in disaster survivors are very rare[89]. Thus, the association of new dissociative disorders with disaster exposure has not been demonstrated, much less causation of dissociative disorders by disaster exposure. Because a well-established characteristic of patients with dissociative disorders is a strong tendency to over-endorse symptoms[87], it is difficult to know to what degree the very high levels of dissociation in this population are an artifact of their symptom endorsement styles and how much of it truly reflects dissociative disorders.

### Dissociation and PTSD

Most of the disaster studies reviewed here compared dissociation with posttraumatic stress. Like the measures for dissociation, the posttraumatic stress measures used in these studies did not assess diagnostic criteria for PTSD, did not link symptoms to PTSD-qualifying trauma exposures, included individuals not exposed to disaster trauma, did not differentiate psychopathology from normative reactions, and did not necessarily capture material from the acute postdisaster time frame. Most of the studies comparing dissociation with posttraumatic stress reported significant associations between them. Because of the many serious limitations of both sets of measures and the presence of other methodological issues, the interpretation of this association may be tenuous[59], and even significant associations in bivariate analyses did not hold up in multivariate analyses and longitudinal assessment. The presence of an association between dissociation and posttraumatic stress might reflect well-known patterns of vulnerabilities to psychopathology broadly, as well as consistent effects of endorsement styles on both dissociative and posttraumatic stress measures. Even reviews[61,62] and meta-analyses[59,60,90] examining studies of associations of dissociation with PTSD more broadly do not find consistent associations between these two entities.

### Dissociation and other psychopathology

In the studies reviewed, dissociation was associated not only with posttraumatic stress, but with a wide range of other psychiatric disorders, symptoms, and negative emotional, cognitive, and functional states. There could be a number of reasons for such broad relationships and nonspecificity of associations with dissociation. This could represent measurement problems related to the known problems of nonspecificity of certain dissociation instruments as discussed above. It is possible that the phenomenon known as publication bias[91] or file drawer bias[92], in which studies with significant or positive findings have a much greater likelihood of being published, might have contributed to such broad associations with dissociation. Again, the apparent relationships of various disorders and negative states might occur as artifacts of consistent reporting biases within individuals across different measurements.

### Conclusions

In summary, the body of literature on studies of dissociation in relation to disaster has

emerged almost completely from studies not focused specifically on this purpose but rather to investigate the relationship of dissociation to other disaster outcomes. These studies uniformly contain unsurmountable methodological limitations such as reliance on nondiagnostic dissociation measures with threats to validity including conflation of nonpathological experiences with psychopathology, lack of temporal specificity to postdisaster time frames, and problems with disaster exposure issues pertaining to sampling, measurement, and analysis. Given this collection of methodological limitations in these studies, it cannot be concluded from this literature that dissociation is an established outcome of disaster. Of particular interest is the observation that no published articles, to the best of our knowledge, have presented dissociative disorders as identified outcomes of any disaster studied. If there is a relation of dissociative phenomena more broadly and the experience of disaster, it is unclear from the research conducted what these experiences represent in terms of negative mental health outcomes.

Methodologically rigorous research is needed to determine the prevalence of dissociative phenomena after disasters and their relationship to trauma exposure. Studies are needed that provide systematic diagnostic assessment of dissociative disorders such as structured interviews to formally establish the prevalence and incidence of established dissociative disorders after disasters. Nosological research is needed to further clarify the distinctions between benign or normative and pathological dissociative responses to disaster trauma exposure, such as by examining associations between observed dissociative phenomena and established indictors of psychopathology such as clinically significant distress, functional impairment, seeking treatment, and associations with other established psychopathology. Additionally, a long list of serious methodological limitations identified in the studies reviewed will need to be addressed in future research on dissociation and disaster trauma can move forward to provide data of sufficient quality to render empirically based conclusions.

### Lessons learned

The literature on dissociation in relation to disaster contains unsurmountable methodological limitations such as reliance on nondiagnostic dissociation measures, lack of temporal specificity to postdisaster time frames, and problems with disaster exposure issues pertaining to sampling, measurement, and analysis. It cannot be concluded from the research that dissociation is an established outcome of disasters.

## ARTICLE HIGHLIGHTS

### Research background

Trauma has long been assumed to be causally associated with the development of dissociation. If trauma causes dissociation, then dissociation would be expected to emerge in disaster-exposed populations.

### Research motivation

Although some studies have investigated dissociation in disaster survivors, no prior reviews have been published specifically on dissociation associated with disasters.

### Research objectives

This review aimed to systematically evaluate existing studies on dissociation in disaster-exposed populations and to examine the relationship between dissociation and exposure to disaster.

### Research methods

A systematic search was performed using Embase, Medline, and PsychINFO databases to identify studies reporting on dissociative disorders or symptoms after disasters in adult or child disaster survivors and rescue/recovery workers. The search used the following key terms: "disaster*," "dissociat*," "multiple personality," "fugue," "psychogenic amnesia," "derealization," and "depersonalization". Only studies in English and those with a sample size of 30 or more were considered. Studies of military conflicts and war were excluded.

### Research results

The final review contained 53 articles, more than two-thirds (68%) reporting dissociation in adults, about one-tenth (9%) in children or adolescents, and about one-fourth (23%) in rescue/recovery workers, involving many different types of disasters. None of the included studies assessed or provided data on dissociative disorders; all used self-report symptom scales. Only two studies focused primarily on dissociation as a disaster outcome. Many of the samples had no disaster trauma exposures or only some members with exposures, and some studies did not differentiate exposure to disaster trauma from other disaster-related stressors. Most of the disaster studies compared dissociation with posttraumatic stress and did not find consistent associations between these two entities. A wide range of other psychiatric disorders, symptoms,

and negative emotional, cognitive, and functional states were found to be associated with dissociation in disaster-exposed populations.

### Research conclusions

The existing body of research on dissociation as an outcome of disaster is fraught with serious methodological limitations in sampling, assessment of dissociation and other psychopathology, and unwarranted causal assumptions. The magnitude of these limitations precludes definitive conclusions regarding whether dissociation is an established outcome of disaster.

### Research perspectives

Methodologically rigorous research that provide systematic diagnostic assessment of dissociative disorders such as structured interviews is needed to determine the prevalence of dissociative phenomena after disasters and their relationship to trauma exposure. Further nosological research is needed to adequately differentiate between benign/normative and pathological dissociative responses to disaster trauma exposure. Also, important methodological limitations identified in the studies reviewed should be addressed in future research on the relationship of dissociation and disasters.

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**Observational Study**

# Outcomes of administrative involuntary hospitalization: A national retrospective cohort study in Japan

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## Abstract

*BACKGROUND*
Treatment for offenders with mental disorders is a key concern in public mental health. Provision of adequate psychiatric treatment is important for the offender and their community. An approach used in Japan to address this issue is administrative involuntary hospitalization. Under this scheme, a person at risk for harming themselves or others because of a mental disorder can be involuntarily hospitalized in a designated psychiatric hospital. However, this scheme does not include tracking of these patients after discharge. Although some data for administrative involuntary hospitalizations are available, it remains unclear what happens to these patients after discharge.

*AIM*
To evaluate follow-up of patients under administrative involuntary hospitalization after discharge and obtain data for later comparisons with outcomes.

*METHODS*
We used a retrospective design and conducted a national survey of administrative involuntary hospitalizations. Questionnaires were distributed to 939 facilities across Japan. The questionnaire collected data for selected involuntary hospitalization cases in the hospital on June 30, 2010 (census date), and the prognoses of each patient on a specified date in 2011 and 2012. We also asked about the treatment provided to each patient. We stratified patients by prognosis (good or poor), and used logistic regression analysis to examine the

relationship between treatment and prognosis.

*RESULTS*
We received completed questionnaires from 292 facilities (response rate 31.1%); 105 facilities had no relevant patients. Our analysis included data for 394 patients with valid data. Official statistics indicated 1503 patients were under administrative involuntary hospitalization as at June 30, 2012, meaning the capture rate was 27.2%. Approximately a fourth (104/394) at 1 year, and a third (137/294) at 2 years after the census had unknown prognosis. Treatment content included multi-disciplinary team meetings (78.2% of patients), counseling by public workers (59.9%), and discussion with external specialists (32.5%). Overall, 116 patients were categorized as having a good prognosis at 1 year, and 168 had a poor prognosis. At the 2-year point, 102 patients had a good prognosis and 150 had a poor prognosis. "Discussion with external specialists" was positively associated with a good prognosis at both 1 year ($P = 0.016$) and 2 years ($P = 0.036$).

*CONCLUSION*
We found that facilities in Japan currently have limited ability to track the prognoses of patients who were hospitalized involuntarily. Discussion with external specialists is associated with a good prognosis.

**Key words:** Involuntary hospitalization; Japan; Mental disorders; Offenders; Discharge; Outcomes; Follow-up

**Core tip:** In Japan, involuntary hospitalization by the prefectural governor's order is applied to psychiatric patients with risks for harming themselves or others. A certain amount of them cannot be followed up the practitioners. Good prognosis can be associated with discussion with external specialist before discharge.

## INTRODUCTION

How offenders with mental disorders should be treated is a concern for the general public and for forensic mental health specialists[1,2]. In the case of offenses directly driven by psychiatric symptoms, it is doubtful if legally punishing the offender effectively prevents recidivism. Rather, proper psychiatric treatment should be provided for the offender and the community in which they will be reintegrated[3].

Japan has two different schemes that address this issue. First, an administrative involuntary hospitalization scheme was established in 1950. This scheme has been succeeded by the Mental Health and Welfare Act (amended in 2013), without any major alteration. Under this scheme, if a person is recognized to be at risk for harming themselves or others because of a mental disorder, the police and prosecutor report the case to the prefectural governor. The governor can then order the person to be hospitalized in a designated psychiatric hospital, based on an assessment by two designated psychiatrists that involuntary hospitalization is necessary. On the other hand, there are scarce legislation regarding the content of treatment under the involuntary hospitalization by the prefectural governor's order. According to a local survey we conducted before, considerable proportion of psychiatrists believe that qualified treatment, such as electro convulsive therapy, long acting injection of antipsychotic drugs, use of clozapine, confrontation of the offense, and home nursing before discharge, are beneficial for many patients. In reality, however, clozapine is rarely used to such patients mainly because of the issue of informed consent[4].

Second, when a person has committed a serious crime (*e.g.*, murder or arson) and is

deemed to be in a state of insanity or diminished responsibility at the time of the offense, the prosecutor makes an allegation to the court. If the court panel (comprising a judge and a psychiatrist) agree, the person is sent to a special hospital according to the Medical Treatment and Supervision Act. This legislation was enacted 14 years ago[5], and has frequently been discussed by forensic mental health researchers and policy makers. Confrontation to their offense and prevention of recidivism are included in standard care program in this scheme. As well, the process about gaining the consent to treatment from inpatient is described in the guidelines. Hundreds of patients are subject to this scheme, many of whom can be discharged into society without reoffending[5]. People subject to the Medical Treatment and Supervision Act are under supervision by the probation office, and their prognoses are statistically clarified. According to an official government report, of the 2247 patients who were permitted to be discharged by the court panel up to 2017, only 1.8% committed further serious crimes[6].

In contrast, the administrative involuntary hospitalization scheme has not been modified since the Medical Treatment and Supervision Act came into force. Therefore, the main people subject to the administrative involuntary hospitalization scheme are those who have committed relatively non-serious crimes under the dominant influence of mental disorders. The court is not involved in decision-making regarding their admission or discharge. In addition, there is no way to track the prognosis of patients discharged from a designated hospital. According to a government report, 753 patients were hospitalized by order of the prefectural governor in June 2015 nationwide; of these, 45 patients remained under administrative involuntary hospitalization after 1 year[7]. However, it was unclear where discharged patients went.

Many practitioners are concerned about the incomplete follow-up of patients who were hospitalized by prefectural government order. To date, some researchers have reported statistical data regarding administrative involuntary hospitalization. For example, the corresponding author conducted a local survey in 2011 to clarify the clinical prognosis of patients who had been hospitalized under this scheme[4]. The results showed that many cases could not be followed up after discharge. Some practitioners suggested a new tracking system to follow patients was needed, similar to that used for the Medical Treatment and Supervision Act, especially because these patients tend to withdraw from medical treatment[8].

On July 26, 2016, an ex-employee intruded a residence for people with disabilities and killed 19 residents; this act was motivated by his prejudiced ideology[9]. This incident was considered the worst massacre committed by an offender in Japan since World War II. Public attention about the forensic mental health system was ignited after it was revealed that this person had been ordered to be involuntarily hospitalized by the prefectural governor a few months before the case occurred, as well as the fact that he was cannabis abuser.

The government submitted a bill for amendment of the Mental Health and Welfare Act following the publication of a report by the special team that examined the incident[10]. The amended bill contained a new scheme covering official follow-up of ex-inpatients who had been under administrative involuntary hospitalization. However, this bill was criticized by politicians and lawyers who were concerned about the risk for unnecessary censoring of patients. As the Prime Minister dissolved the Diet (Lower House) in 2017 because of political conflict not relevant to this issue, the bill remained unapproved[11]. Instead, the Japan Ministry of Health, Labour and Welfare published guidelines based on a similar scheme to strengthen support for patients with mental disorders after discharge. The corresponding author was involved in developing these guidelines[12,13].

Reform of administrative involuntary hospitalization is expected to improve the quality of medical treatment for offenders with mental disorders. A key indicator of functional execution of this scheme will be the follow-up rate of patients, because many criminal acts are committed by psychiatric patients who have quit or received insufficient psychiatric treatment[4]. Therefore, we conducted a national survey to evaluate the current quality of administrative involuntary hospitalization, with the intention of providing data for later comparison with outcomes.

This study aimed to examine the extent to which mental health service providers could track the prognoses of ex-inpatients who had been hospitalized under order of the prefectural governor, and examine the content of the medical treatment they actually received. The data collected in this study are expected to be compared with data gathered in a further study.

## MATERIALS AND METHODS

### Subjects

The target population for this study was all psychiatric hospitals that accepted patients who were hospitalized by order of the prefectural governor. They included public psychiatric hospitals and designated psychiatric hospitals administered by the private sector. We listed these hospitals based on official reports, and included the 939 facilities that accept administrative involuntary hospitalization as the study sample.

### Methods

We sent a questionnaire to the administrators of each hospital, and asked them to complete and return the form by mail. We gathered data for patients staying in the hospital on June 30, 2010 (census date) by order of the prefectural governor. If there were over five eligible patients, we collected data for only five patients to avoid placing too much burden on the hospital administrators. Questionnaire items included the prognoses of each patient on a specific day (June 30) in 2011 and 2012. We also asked about the content of treatment provided to each patient. Detail of the questionnaire is shown in the Supplementary document.

### Statistical analysis

To investigate the association between the content of services provided to each patient and their medical prognosis, we first stratified the data for prognoses. We classified patients who had regularly visited an outpatient unit (at either the hospital of admission or another hospital) as a "good" prognosis because withdrawal from regulatory visiting hospital is known as a major risk factor of relapse for many psychiatric patients. Patients who had stayed at any hospital or who were deceased were deemed as having a "poor" prognosis. Other patients, including those with an unknown prognosis were excluded from further analyses. Specific answers describing the patient's prognosis were classified as either good (*e.g.*, staying at a health center for older adults, occasional telephone consultation with a hospital, or treatment completion) or poor (*e.g.*, escaped from hospital, accidental withdrawal from outpatient treatment, arrested, detained, or incarcerated).

Next, we used logistic regression analysis to examine the impact of the treatment provided to patients during hospitalization on their prognosis, as an exploratory analysis. We set the binary value "prognosis" (as defined above) as the dependent variable. Independent variables were: "multi-disciplinary team meeting while admitted," "counseling by public workers while admitted," "discussion with persons other than the psychiatrist in charge before dismissal of the prefectural governor's order," and "discussion with specialists external to the hospital before dismissal of the prefectural governor's order." We used stepwise logistic regression analysis with increasing variables. Statistical analyses were performed using SPSS for Windows, Version 24 (IBM Corp., Armonk, NY, United States). The level of significance was set at $P < 0.05$.

### Ethical issues

Because this study did not include any intervention with patients, there was no possible harm to patients. All data gathered in this study were those previously obtained by the participating psychiatric hospitals. In addition, we did not gather any personal information pertaining to patients. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine at Chiba University on June 6, 2016 (no. 237). We registered this study with the Clinical Trials Registry of the University Hospital Medical Information Network (UMIN, Tokyo, Japan), with the unique trial number UMIN000027318.

## RESULTS

### Response rate

We sent questionnaire forms to 939 facilities; 292 facilities returned a completed form, giving a response rate of 31.1%. Of these, 105 facilities had no applicable patients. One patient was reported in 187 facilities, two in 95 facilities, three in 57 facilities, four in 40 facilities, and five or more in 30 facilities. Therefore, we gathered data for 409 patients. An official report indicated that 1503 patients were hospitalized under order of a prefectural governor as at June 30, 2012[6], meaning the capture rate was 27.2%.

### Prognosis

Fifteen of the 409 patients had invalid information. Of the remaining 394 patients, 151

(38.3%) had stayed at the hospital of admission, 92 (23.4%) had regularly visited an outpatient unit at the hospital of admission, five (1.3%) had stayed at another hospital, 22 (5.6%) had regularly visited an outpatient unit at another hospital, and 11 (2.8%) were deceased. In addition, 104 (26.4%) had an unknown prognosis, and nine (2.3%) had a prognosis other than those listed above at 1 year after the census.

We also examined the 2-year prognosis. Of the 294 patients, 127 (32.3%) had stayed at the hospital of admission, 83 (21.1%) had regularly visited an outpatient unit at the hospital of admission, four (1.0%) had stayed at another hospital, 17 (4.3%) had regularly visited an outpatient unit at another hospital, and 17 (4.3%) were deceased. The 2-year prognosis was unknown for 137 (34.9%) patients, and eight (2.0%) had a prognosis other than those listed above; of these, two were recorded as having been arrested or incarcerated. A summary of patients' prognosis at 1 and 2 years after the starting point is shown in Figure 1.

### Social status
Regarding living conditions after discharge, 147 (36.0%) patients were living with family members, 77 (18.9%) were single, and 51 (12.5%) were in a facility. In addition, 95 (23.3%) were still in a hospital and 31 (7.6%) had moved hospitals. We requested information about a key person at discharge for all sampled patients. A family member was suggested as the key person for 293 (72.0%) patients. For nine (2.2%) patients, a person other than a family member was deemed the most suitable key person. In 32 (7.9%) cases, professionals took the role of key person for the patient. Forty-one patients had no particular key persons identified.

### Provided treatment and services
The responses from the participating hospitals indicated that multi-disciplinary team meetings were conducted for 319 (78.2%) patients. Counseling delivered by public workers was conducted for 243 (59.9%) patients. In 222 (56.3%) cases, discussions with persons other than the psychiatrist in charge were held before dismissal of the prefectural governor's order. However, discussion with specialists external to the hospital was only conducted in 127 (32.5%) cases.

After discharge, 58 (16.9%) patients received a nurse visit service. Day- or night-care after discharge was implemented for 35 (10.2%) patients. Outpatient care services for daily life in the community were reported for 44 (12.9%) patients, and residential care services were implemented for 30 (8.8%) patients.

Regarding collaboration with other facilities/agencies, 249 (63.7%) cases had some collaboration with the prefectural government after discharge. In 102 (26.1%) cases, other hospitals were involved in the patients' care after discharge. Public nursing centers were involved in 42 (10.8%) cases. Police concern after discharge was reported in 54 (13.8%) cases, but only two (0.5%) cases had contact with drug control offices after discharge. Involvement of other service providers was reported for 71 (18.2%) patients.

### Association between prognosis and treatment provided
According to the criteria defined in the Methods section, 116 patients (29.4%) were categorized as having a good prognosis at 1 year, and the remaining 168 (42.6%) had a poor prognosis. In addition, 102 patients (25.9%) had a good 2-year prognosis and 150 (38.1%) had a poor prognosis.

The logistic regression analysis suggested that only "discussion with specialists external to the hospital before dismissal of the prefectural governor's order" was positively associated with a good prognosis at both 1 year [B = 0.020, standard error (SE) = 0.008, Wald = 5.766, *df* = 1, *P* = 0.016, Exp(B) = 1.020] and 2 years (B = 0.015, SE = 0.007, Wald = 4.387, *df* = 1, *P* = 0.036, Exp(B) = 1.015) after the census.

## DISCUSSION

In this national survey, we examined whether psychiatric facilities accepting administrative involuntary hospitalizations could track the prognosis of patients after discharge. We also examined the services that were provided to support patients' mental health in the community. The results clarified that facilities did not know the prognoses of approximately one-fourth of these patients within 1 year, and one-third within 2 years. The overall results were consistent with those of a local survey previously conducted by the corresponding author[4]. The response rate of this study was 31.1%. Considering that implementation of this survey relied on voluntary cooperation of each hospital, this response rate is acceptable.

This result should be cautiously interpreted because "unknown" prognoses do not necessarily mean undesirable treatment outcomes. For example, some facilities mainly
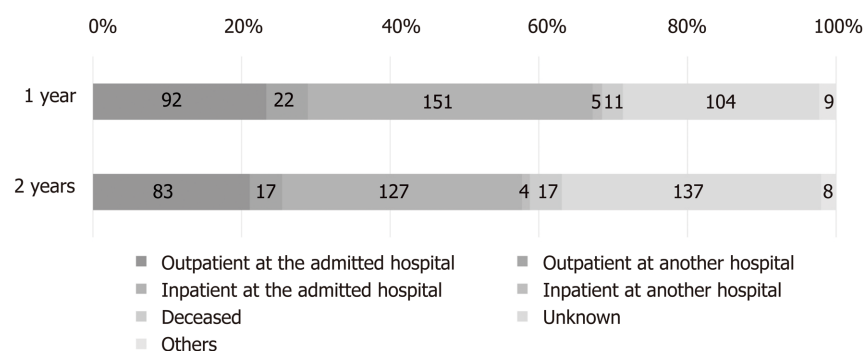
**Figure 1 Prognoses of patients admitted by the prefectural governor's order.**

providing psychiatric emergency care transfer patients in the early stage of inpatient treatment to another hospital that is located near to each patient's hometown. In these cases, the facility accepting the patient may not initially know the patients' prognosis. Therefore, hospitals providing qualified psychiatric emergency services rarely track each patient's prognosis. It is therefore possible that many patients whose prognosis is not clarified lived without trouble in the community independently from the hospital in which they received inpatient care.

We excluded patients with an unknown prognosis from further analysis to examine the association between treatment and prognosis. Because these patients were involuntarily hospitalized to receive treatment for mental disorders, continuous treatment should be important to maintain their mental health, even after dismissal of the order. We considered patients who had regularly visited an outpatient clinic as having a good prognosis. In contrast, longitudinal hospitalization or death was considered proof of a poor prognosis. In addition, unexpected withdrawal from outpatient treatment may predict the relapse of psychiatric illness.

The logistic regression analysis suggested that discussion with specialists who were external to the hospital in which the patient was admitted was associated with a good prognosis 1 and 2 years after the census point. In Japan, there is no official scheme of collaborative discussion with external specialists in psychiatric treatment. Some medical practitioners are willing to consult with external specialists spontaneously. The concrete content of discussion with specialists was not clarified in this survey. In general, consultation with specialists outside the hospital is time consuming and costly. Thus, in cases where such consultation was performed, the patient and practitioners surely discussed deeply whether the patient could adapt to life in the community. In some cases, discharge plan might be rearranged after the discussion. We believe delicate and sincere consideration for community treatment among supporters may have a positive impact of the outcome of discharged patients. In the future, it may be beneficial that collaborative discussion with external specialists is conducted more frequently especially in complicated cases.

The present study suggested that 4.3% of patients admitted under administrative involuntary hospitalization were deceased within 2 years. Even considering the poor mortality rate among patients with mental disorders[14], this percentage seems to be high, especially as the crude death rate of forensic patients was estimated as 0.325% per year in a meta-analytical review of international datasets[15]. When a person commits suicide, the police usually contact hospitals that might have been connected with that person. Therefore, psychiatric hospitals are usually aware when an ex-patient is deceased by suicide. In this study, it is unlikely that cases of suicide were included among those with unknown prognosis. Psychiatric patients also have higher risk for physical illnesses than healthy controls[16]. We did not ask the reason for death in each deceased case. Further investigation is needed to draw any conclusions regarding this point.

Overall, it was difficult to evaluate the effectiveness of the current system of administrative involuntary hospitalization by order of the prefectural governor. There are several outcome measures in forensic mental health, none of which have been decisively approved[17]. For example, Edwards *et al*[18] investigated the outcomes of patients admitted to a medium secure unit in England; the mean duration of admission was 26 mo, and approximately 10% of the patients were convicted of another offence within 2 years. Compared with this result, the outcomes in the present study appear to be better, with few patients reported to have been arrested and at least one-fourth of the patients had regularly visited an outpatient clinic over 2 years. However, the characteristics of the patients in this study may differ from those

of other studies because administrative involuntary hospitalization orders in Japan do not cover patients who have committed serious crimes. Therefore, the present study could not definitively evaluate the quality of care in the current situation in Japan. However, we will be able to examine whether the quality of care improves by comparing the present result with data gathered in the next few years.

The present study is a retrospective survey using the existing data in each participating hospital. Therefore, there are limitations to derive some conclusions from the results. Each patient's past medical history was not included into analysis. Sampling biases could not be avoided. A prospective cohort with larger and non-biased sampling is necessary to confirm the finding of this study.

In conclusion, we investigated the prognoses of patients under administrative involuntary hospitalization. At 2 years after the census, one-third of the patients had stayed at the ordered psychiatric hospital, one-fourth had regularly visited an outpatient clinic, and one-third had an uncertain prognosis. Discussion with specialists external to the admitting hospital was associated with a good prognosis. These results should be considered as a standard when the system of hospitalization by the prefectural governor's order is amended.

## ARTICLE HIGHLIGHTS

### Research background
In Japan, patients with mental disorder having a risk for harming self or others are hospitalized by the prefectural governor's order.

### Research motivation
We have to know the outcome of patients who were hospitalized involuntarily.

### Research objective
To clarify the performance and outcome of the scheme of involuntary hospitalization by the prefectural governor's order.

### Research methods
Retrospective cohort by examining medical record of hospitals accepting involuntary hospitalization.

### Research results
A total of 394 subjects were examined. Approximately a fourth at 1 year, and a third at 2 years after the census had unknown prognosis. Approximately a third was identified as good prognosis. Discussion with external specialists before discharge were associated with good prognosis.

### Research conclusions
Psychiatric hospitals in Japan have limited ability to track the prognoses of patients who were hospitalized involuntarily by the prefectural governor's order.

### Research perspectives
Constructive discussion with external specialists before discharge is possible to improve the outcome of the patients with mental disorder. To confirm this hypothesis, a prospective cohort study is necessary.

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# Do adjunctive art therapies reduce symptomatology in schizophrenia? A meta-analysis

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**Author contributions:** Laws KR designed the study, checked all searches and re-ran all analyses; Conway W conducted initial searches and analyses; Laws KR and Conway W wrote the paper.

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## Abstract

**BACKGROUND**
Art therapies are advocated by national bodies, such as the United Kingdom's National Institute for Health and Care Excellence, to alleviate the negative symptoms associated with schizophrenia. The last decade has however, seen several new larger well-controlled trials published suggesting an update is timely.

**AIM**
To asses randomised controlled trials (RCT) of art therapies for reducing the symptoms of schizophrenia – particularly negative symptoms.

**METHODS**
Searches of PubMed and Scopus were conducted until May 2019 for RCTs examining the impact of art therapies on psychosis (positive, negative and total) symptoms in people diagnosed with schizophrenia. Study quality was assessed using the Cochrane risk of bias tool. Random effects meta-analyses were used to derive overall effect sizes. Moderator analyses were conducted using both meta-regression and categorical comparisons.

**RESULTS**
We identified 133 articles, of which 9 RCTs involving 948 participants (475 assigned to art therapies and 473 controls) met our inclusion criteria. Using random effects models, we calculated pooled effect sizes (Hedges $g$) for end-of-trial symptomatic outcomes. Effect sizes both for total symptoms [$g$ = -0.27, 95% confidence interval (CI) -0.60 to 0.05, $k$ = 6] and for positive symptoms ($g$ = -0.10, 95%CI -0.35 to 0.15, $k$ = 6) were non-significant; however, we did find significant reduction of negative symptoms ($g$ = -0.42, 95%CI -0.70 to -0.14, $k$ = 9). Meta-regression revealed that negative symptom reduction was larger in trials with a greater proportion of women and in trials with younger patients. Crucially, the negative symptom reduction following art therapies was limited to lower quality trials and did not emerge in trials that used blind assessment of outcomes.

*CONCLUSION*
This review presents a comprehensive meta-analysis of art therapies in schizophrenia in terms of both studies included and participant numbers. We found that art therapies did not significantly reduce total or positive symptoms. A "small" therapeutic effect was found for negative symptoms, but we show that the effect is not present in blind trials and may be subject to publication bias.

**Key words:** Schizophrenia; Symptoms; Art therapy; Meta-analysis; Bias

**Core tip:** This meta-analysis examines data from randomised controlled trials looking at whether art therapies reduce the symptoms of schizophrenia-particularly negative symptoms. Our study indicates that art therapies do not significantly reduce total symptoms or positive symptoms. While we found a "small" therapeutic effect on negative symptoms, the effect appears to reflect two forms of bias-first, no effect emerges when trials use blind outcome assessment; second, the trials also point to the possibility of publication bias.

# INTRODUCTION

Over the past 60 years art therapies have been promoted as a medium in which individuals may engage with psychotherapy in a non-judgemental, creative space and has been applied to numerous conditions and situations. Encompassing a variety of non-verbal, creative interventions, arts therapies typically combine the use of art materials and psychotherapeutic techniques with the aim of achieving psychological change, *e.g.*, promoting insight and general well-being. Such interventions include not only traditional art therapy, but also dance therapy, music therapy and body-oriented psychotherapy (a form of therapy that involves an explicit theory of body–mind functioning designed to improve emotional, cognitive, physical and social integration)[1-5].

Adding adjunctive psychological interventions to pharmacotherapy has become more common in efforts to help improve the mental state and functioning of those living with schizophrenia. While much research and debate has centred on the efficacy of Cognitive Behavioural Therapy (CBTp) for psychosis[6-8], much less attention has been paid to the role of art therapies as an adjunctive to medication.

Art therapies may have some potential advantages over more traditional talk-based psychological interventions for those diagnosed with schizophrenia. For example, individuals experiencing the negative symptoms of schizophrenia (*e.g.*, impoverished speech) may find it difficult to verbally communicate their thoughts and emotions to a conventional therapist. Art therapies therefore are unique in their potential to circumvent this obstacle, with a nuanced relationship between the service-user, the therapist and the artwork itself[6].

The first systematic review undertaken by the Cohrane Collaboration[9] was limited to two small underpowered traditional art therapy trials and they concluded that "There is no evidence to support the use of art therapy as part of policy" (p. 12). The Cochrane review was updated two years later[10] although it failed to locate any further studies. Later meta-analyses by the National Institute of Clinical Excellence (NICE, 2009)[11] refer more broadly to art therapies (including art therapy or art psychotherapy, dance movement therapy, body psychotherapy, drama therapy and music therapy) and featured 5 randomised controlled trials (RCTs). While NICE reported that art therapies did not significantly reduce total symptoms [-0.49 (-0.98 to 0.01), *k* = 4] or positive symptoms [0.06 (-0.67 to 0.79), *k* = 2] at end-of-trial, they reported a significant benefit in reducing negative symptoms [-0.59 (-0.83 to -0.36), *k* = 5]. Nonetheless, the findings were somewhat limited– based on five trials involving only 148 receiving art therapies and 146 controls in total. Despite this, the NICE

recommendation 1.4.4.3 asserts that "…clinicians should offer art therapies to all people with schizophrenia, particularly for the alleviation of negative symptoms". As currently practised in the United Kingdom, arts therapies comprise: Art therapy or art psychotherapy, dance movement therapy, body psychotherapy, drama therapy and music therapy.

By contrast, however, the latest treatment guideline published by the Scottish Intercollegiate Guidelines network (2013)[12], came to a quite different conclusion that "There is insufficient high-quality evidence on which to base any recommendation for arts therapies in general" (p. 25). In a similar vein, and more recently, the Royal Australian and New Zealand College of Psychiatry[13] concluded that the evidence from RCTs "is inconclusive" and that more research and assessment is required before art therapy could be recommended. In the most recent systematic review covering studies published from 2007 onwards, Attard and Larkin (2016)[14] concluded that while "High quality *quantitative* articles provided inconclusive evidence for the effectiveness of art therapy in adults with psychosis…high-quality *qualitative* articles indicated that therapists and clients considered art therapy to be a beneficial, meaningful and acceptable intervention, although this conclusion was based on a small number of studies" (our italics).

A central suggestion for future research proposed by NICE in their 2009 CG178 guideline was that "an adequately powered RCT should be conducted to investigate the clinical and cost-effectiveness of arts therapies as compared to an active control in people with schizophrenia" (p. 200). Since this recommendation, the two largest-ever clinical trials have been conducted. Both trials unequivocally reported no significant alleviation of negative symptoms for those receiving art therapies *vs* their respective control group. Crawford *et al*[15] note that while "many service users greatly value using art materials and taking part in other creative activities, the widespread referral of people with established schizophrenia to group art therapy as delivered in this study did not lead to measurable improvements in patient outcomes or provide a cost effective use of resources" (p. 41). Slightly more positively perhaps, Priebe *et al*[16] concluded that their study "…does not support group body psychotherapy as a treatment for negative symptoms of schizophrenia. Reviewing the effectiveness of different arts therapy modalities separately may be informative to determine whether existing guidelines should be more cautious in recommending art and body psychotherapy specifically, or whether this extends to arts therapies as a whole" (p. 7).

Conflicting conclusions concerning the efficacy of art therapies for individuals diagnosed with schizophrenia may reflect several factors including that: Meta-analytic data are now a decade-old, the initial body of clinical research was modest and earlier RCTs may not have been as well-controlled as more recent trials. With several larger, appropriately powered and better-controlled trials published since the NICE guidance in 2009, it seems timely to re-assess whether art therapies aid in alleviating the symptoms of schizophrenia, particularly negative symptoms. This review will also conduct separate analyses assessing any impact on both positive and total symptoms. Finally, we examine whether blinding of the outcome assessment has a mediating effect on results (something that has not been examined in previous meta-analyses, including NICE guidance).

## MATERIALS AND METHODS

A literature review was conducted in accordance with Preferred Reporting for Systematic Reviews and Meta-analysis guidelines[17] (for checklist, see appendices). The search strategy involved identifying peer-reviewed articles published in English since the NICE review[9] and so included the period of 2008 to May 2019 (earlier trials were retrieved from the NICE review).

We searched the electronic databases PubMed and Scopus according to the PICO strategy (Patients: Diagnosed with schizophrenia; Intervention: Arts therapies; Comparator: Any control group; and Outcome: Symptom measures). The search terms were comparable to those originally used by NICE and included: (1) "schizophrenia" OR "psychosis" OR "schizo*" paired with the descriptors; (2) "art therapy" OR "arts psychotherapy" OR "creative arts therapy" using all possible combinations. The comparator was a control group of any description and the outcome was negative (positive or total) symptom measures (see below). The electronic search was supplemented by "hand-searching" of obtained article reference lists for any trials not identified by the online searches.

Our inclusion criteria closely mirrored those used by NICE, with studies included (Figure 1) if after the initial screening of title, abstract and keywords, they featured: (1)

A formal diagnosis of schizophrenia, in accordance with standardised diagnostic criteria *e.g.*, DSM-V; (2) A randomised control trial with ≥ 10 participants per arm; (3) A parallel control group of any type as a comparator, *i.e.*, an active control, waitlist or treatment as usual; (4) An intervention of art therapy, both individual or group, which could also include variations, *i.e.*, dance therapy, music therapy; (5) Reporting means, standard deviation and sample size for a measure of negative symptoms; and (6) The full-text was available in English.

### Data extraction and procedure
Effect sizes were derived from the post-intervention symptom rating scores using Hedges *g* (*i.e.*, the standardized mean difference using group means divided by the pooled standard deviation, corrected for the tendency towards overestimation in small studies). The scales used included: the positive and negative symptom subscales of the PANSS, the Schedule for the Assessment of Positive Symptoms, the Schedule for the Assessment of Negative Symptoms; and the Brief Psychiatric Rating Scale. All analyses used random effects models were conducted using Comprehensive Meta-Analysis (Version 2). We examined studies for possible follow-up assessments (ranging from 12 weeks to 2-years after initial post-data measurements); however, the limited number of studies with relevant data meant that no analyses were feasible for follow-up. If data were unavailable in a paper, authors were contacted. Effect sizes are described using Cohen's convention: an effect size of 0.20 was considered small, 0.50 moderate, and 0.80 large.

Heterogeneity was examined by calculating $I^2$. Following Higgins *et al*[18] (2011), we interpreted $I^2$ values of 0-40% as suggesting that heterogeneity may not be important, 30%-60% representing moderate heterogeneity, 50%-90% substantial heterogeneity, and 75%-100% as potentially representing considerable heterogeneity. Potential publication bias was examined using Duval *et al*[19]'s (2000) trim and fill method.

Data pertaining to participants age (mean age range 35.4 to 41, *k* = 9), gender (proportion of males: 0.43 to 0.73, *k* = 9), duration of illness (years: 8.9 to 12.8, *k* = 5), and the number of therapy sessions (8 to 72, *k* = 9) were also extracted, for potential moderator analyses using meta-regression. Despite no definitive minimum number of studies being required to complete a meta-regression, a general recommendation proposed by Cochrane is at least 6 to 10 studies for a continuous variable[14]. On this criterion, moderator variables which failed to meet this minimum requirement were not selected for further analysis and as such, meta-regressions were only conducted on gender (percentage of participants that were male) and the total number of therapy sessions in each study; the latter of which was proposed as a topic of future research by NICE[9]. Data relating to blinding the assessment of outcome was extracted to examine any effects on the primary outcome variable *i.e.*, negative symptoms.

Risk of bias was using the Cochrane risk of bias tool (RoB2)[20] covering the following areas of potential bias: Sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective reporting, researcher allegiance.

## RESULTS
Following our search a total of 9 articles were included for the final review[15,16,21-27] (Table 1 and Figure 1), providing a sample of 948 participants: 475 randomly assigned to art therapies including conventional art therapy (*k* = 3), music therapy (*k* = 3), body-oriented psychotherapy (*k* = 2) and dance therapy (*k* = 1); and 473 were assigned to control conditions.

### Risk of bias
Risk of bias was assessed using the RoB2[16]. The RoB tool assess five areas of potential bias in trials: (1) Bias arising from the randomisation process (randomisation and allocation concealment); (2) Bias due to deviations from intended interventions (blinding of participants and personnel); (3) Bias due to missing data (incomplete outcome data); (4) Bias in measurement of the outcome (blinding of outcome assessment); and (5) bias in selection of the reported result (selective reporting).

Using these criteria, 3 trials were overall at high risk of bias[17,20,23]; the remaining 6 showed "some concern" (Figure 2), largely reflecting the inability of participants to be blind to whether they received the psychological intervention or control.

### Effect sizes
The pooled effects size for the 6 studies of total symptoms was nonsignificant [*g* = -0.27, 95% confidence interval (CI) -0.60 to 0.05, *P* = 0.10]. These studies were also heterogeneous (Q = 24.5, *P* < 0.001) with an $I^2$ value of 79.6. For forest plot see Figure 3

**Figure 1 PRISMA flow diagram.**

(negative sign favours art therapies). The pooled effect size for the 6 studies of positive symptoms was non-significant ($g$ = -0.10, 95%CI -0.34 to 0.15, $P$ = 0.44). The studies were again heterogeneous (Q = 11.2, $P$ = 0.05) with an $I^2$ value of 55.4 (Figure 4). The pooled effect size was for negative symptoms in 9 trials was significant ($g$ = -0.42, 95%CI -0.70 to -0.14, $P$ = 0.004). The studies were heterogeneous (Q = 31.3, $P$ < 0.001), with an $I^2$ value of 74.4 (Figure 5).

Examination of publication bias was assessed using Duval and Tweedie's trim and fill[19], indicated 5 potentially missing studies–adjusting for these studies reduced the effect size to -0.01 (95%CI -0.13 to 0.10), which became nonsignificant (Figure 6). We also analysed possible bias using Egger's[28] regression intercept and this confirmed significant funnel plot asymmetry ($P$ < 0.01; 2 tailed).

### *Moderator analyses*

Meta-regressions were run on samples with a minimum of 6 trials[18], which included the influence of gender (the proportion of male participants) and the number of therapy sessions. Table 2 provides a summary of the meta-regressions completed in this review (see below).

Trials with a greater proportion of female participants and with younger participants reported significantly larger effect sizes for the alleviation of negative symptoms (Figure 7). The number of therapy sessions offered to participants throughout each trial, ranging from 8 forty-five-minute sessions to 72 two-hour sessions, was not a significant predictor of the effect size for negative symptoms.

Turning to categorical variables, trials with high risk of bias had significantly larger effect sizes than those at lower risk of bias [($g$ = -0.82, -1.14 to -0.50, $k$ = 3) *vs* ($g$ = -0.15, -0.37 to 0.10, $k$ = 6), Q = 11.59, $df$ = 1, $P$ < 0.001]. We assessed the specific impact blinding of outcome assessment as a categorical moderator for negative symptoms. The pooled effect size for 6 blind studies was nonsignificant ($g$ = -0.15, 95%CI -0.37 to 0.06, $P$ = 0.17), whereas that in 3 non-blind studies was highly significant ($g$ = -0.82, 95%CI -1.14 to -0.50, $P$ < 0.001). The effect size for blind trials was significantly smaller than that for nonblind trials (Q = 11.55, $df$=1, $P$ < 0.001, Figure 8). Heterogeneity was non-significant for both blind and nonblind trials (Q = 8.78, $df$ = 5, $P$ = 0.12, $I^2$ = 43.16; Q = 2.39 $df$ = 2, $P$ = 0.30, $I^2$ = 16.26, respectively).

## DISCUSSION

A key aim of the current paper was to analyse evidence from RCTs regarding the

| | Art (*n*) | Control (*n*) | Blind assess | Sessions | Control | Art therapy type |
|---|---|---|---|---|---|---|
| Yang *et al*[21], 1998 | 40 | 30 | No | 6 per week × 3 mo | TAU | Music |
| Röhricht *et al*[22], 2006 | 24 | 121 | Yes | 20 over 20 wk | Supp couns | Body-oriented psychotherapy |
| Ulrich *et al*[23], 2007 | 21 | 16 | Yes | Mean = 7.5 | TAU | Music |
| Richardson *et al*[24], 2007 | 43 | 47 | No | 12 | TAU | Art |
| Talwar *et al*[25], 2008 | 33 | 48 | Yes | Median = 8 | TAU | Music |
| Crawford *et al*[15], 2010 | 140 | 137 | Yes | Weekly for 12 mo | Activity | Group art therapy |
| Montag *et al*[26], 2014 | 16 | 19 | Yes | 12 over 6 wk | TAU | Psychodynamic art therapy |
| Lee *et al*[27], 2015 | 18 | 20 | No | 1 per week × 12 wk | TAU | Dance/movement |
| Priebe *et al*[16], 2016 | 140 | 135 | Yes | 20 | Pilates | Body psychotherapy |

efficacy of art therapies to reduce the symptoms of schizophrenia, especially negative symptoms. Like previous meta-analyses[9-11], we found no significant benefit of art therapies in reducing total symptoms or positive symptoms. On the key claim regarding negative symptoms, we did find a significant reduction, thus replicating the earlier finding reported by NICE[9]. Crucially, however, this interpretation must be qualified – as any symptom reduction was subject to potential biases.

Although overall bias - as assessed by the RoB2[20] - was not high in most trials, trials at high-risk did produce significantly larger effect sizes for negative symptoms. An issue of central concern is that effect sizes were exaggerated considerably by non-blind assessment of outcomes. The pooled effect size for 3 non-blind trials was more than five-times larger than that for 6 blind trials (-0.82 *vs* -0.15). This accords with observations at the level of individual RCTs, where each of the 3 non-blind trials produced moderate-large significant effect sizes, while 5 out of 6 blinded trials produced nonsignificant outcomes. The failure to use blind assessment clearly inflates the apparent efficacy of art therapies and crucially, this source of bias was not assessed in previous meta-analyses. Such effect size inflation in unblinded trials is well-documented in medicine[29-32], but the impact is exacerbated in trials that use more subjective measures such as clinician rating scales to assess symptomatic outcomes[26]. The same bias has been reported in trials of CBT for schizophrenia, where effect sizes are inflated between 4 and 7 times by non-blind compared to blind outcome assessment for various symptom ratings[6]. This inflation is in the same range as that documented here for art therapies where unblinded assessment of negative symptoms produced an effect size more than 5 times that for blind assessment. To put the latter into perspective, the difference between blind and nonblind effect sizes is larger than the mean effect size reported by NICE to underpin their recommendation of art therapies for negative symptoms.

Evidence of possible publication bias also emerged for negative symptoms from the trim and fill analysis (and Egger's test) - with 5 imputed missing trials reducing the effect size for negative symptoms effectively to zero (regardless of blinding). Of course, such tests do not provide *direct* evidence of publication bias and are estimates based upon various assumptions. The influence of unblinded assessment and the evidence of publication bias both undermine findings regarding the efficacy of art therapies to reduce negative symptoms.

One advantage of the current study is that it almost doubles the number of trials and more than triples the number of participants that were assessed by NICE (475 art therapies and 473 control participants vs 148 art therapies and 146 controls analysed by NICE). In their critique of NICE guidance (CG178), Taylor *et al*[33] (2015, p. 358) allude to the issue of statistical power questioning the fact that NICE "…concludes that there is sufficient evidence only for art therapies to be offered to service users with psychosis and schizophrenia (recommendation 9.3.8.1) based on a limited review of six RCTs. These RCTs had small sample sizes (*n* = 24-90)". The current analysis includes newer larger trials and in contrast to previous meta-analyses, was sufficiently powered (0.8) with 9 trials to detect the mean effect size (-0.42) we report[34]. By contrast, the NICE analysis of art therapies was severely underpowered – having a mean power of just 0.37 to detect the overall effect size for negative symptoms reported here.

The recent additions of the MATISSE[15] and Priebe *et al*[16] trials provide – to date - the largest RCTs assessing art therapies. These two studies are the only published trials that are sufficiently powered (at 0.83 and 0.82 respectively) to detect the modest effect size reported in this meta-analysis; and both reported zero effect sizes - 0.03 and

**Figure 2  Risk of bias in each trial according to the Cochrane RoB2 tool.**

0.06 respectively. Indeed, each of these two trials alone contained almost as many participants as all 5 trials combined in the NICE[11] meta-analysis for negative symptoms. Crucially both trials were also pre-registered and did not deviate from what was proposed in terms of approach, recruitment and analyses. Nonetheless, meta-analyses are only as reliable as the individual studies that are assessed. While the MATISSE trial is the largest assessment of art therapy and exceptionally well-controlled, it is not without its critics[35,36]. Holttum *et al*[35] raised a series of methodological and procedural issues relating to the trial, which they believe may have influenced the null findings. For example, although actual trial drop-out was reasonable, attendance at sessions was often quite low. On another point, Wood[36] has argued that the MATISSE trial failed to actually test art therapy as currently practised in the UK. The MATISSE authors have responded to many of these points[37]. The other large well conducted trial by Priebe *et al*[16] has also received some critical commentary. Crawford *et al*[38] raise important questions concerning why so many phase III trials, especially of complex psychological interventions such as the body-oriented psychotherapy trial by Priebe *et al*[16] fail to build on earlier promising exploratory studies. Psychological interventions are clearly complex and Crawford *et al*[38] note that they "are often relational in nature and rely even more on a clinician's ability to navigate interpersonal relationships and actively engage people in treatment" – this therefore makes them less predictable than, for example, a drug trial. While art therapies may not lend themselves as readily to randomised control designs, current treatment guideline such as those of NICE rely heavily upon RCTs as their gold standard evidence.

A further recommendation that NICE[11] proposed for future research was to assess the optimal number of sessions that should be offered to people with schizophrenia. The number of trial sessions included in the current meta-analysis varied considerably - the least offered was 8[25], while the most was 72[15]. Our meta-regression analysis revealed that number of intended sessions was not a predictor of the efficacy of art therapies on negative symptomatology.

While we found no evidence for symptom reduction, it may be that art therapies produce other benefits or are beneficial for some individuals and not others. Maujean *et al*[4] in their systematic review concluded that "It is possible that limited exposure to art therapy is insufficient to bring about change in such a significant illness as schizophrenia and …may not be expected to reduce global symptoms or enhance overall quality of life, but could be reasonably expected to improve emotional states" (p. 42). Related concerns have arisen regarding the "quasi-neuroleptic" focus on symptom reduction in art therapies as well as other psychological interventions *e.g.*, CBT for psychosis[39]. Psychological interventions in general and art therapies in particular might be better placed to focus on non-symptomatic outcomes such as reducing distress (associated with symptoms), depression or anxiety or improving
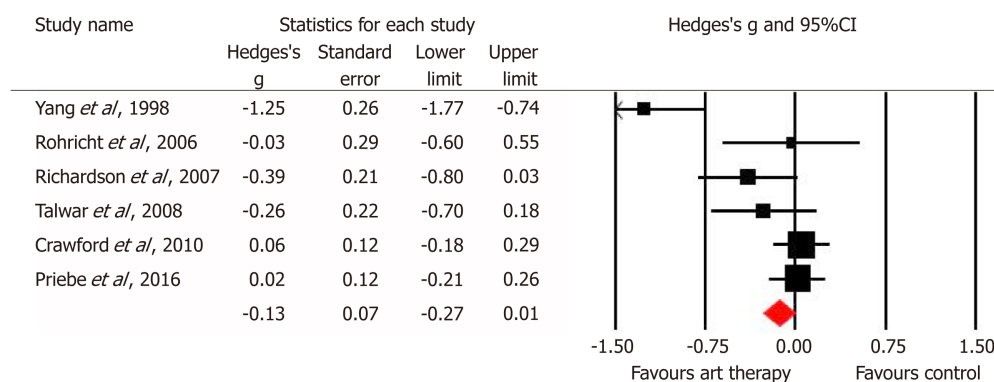
| Study name | Statistics for each study | | | | Hedges's g and 95%CI |
|---|---|---|---|---|---|
| | Hedges's g | Standard error | Lower limit | Upper limit | |
| Yang *et al*, 1998 | -1.25 | 0.26 | -1.77 | -0.74 | |
| Rohricht *et al*, 2006 | -0.03 | 0.29 | -0.60 | 0.55 | |
| Richardson *et al*, 2007 | -0.39 | 0.21 | -0.80 | 0.03 | |
| Talwar *et al*, 2008 | -0.26 | 0.22 | -0.70 | 0.18 | |
| Crawford *et al*, 2010 | 0.06 | 0.12 | -0.18 | 0.29 | |
| Priebe *et al*, 2016 | 0.02 | 0.12 | -0.21 | 0.26 | |
| | -0.13 | 0.07 | -0.27 | 0.01 | |



**Figure 3 Forest plot of the studies in the meta-analysis for total symptoms.**

functioning and quality of life; and for future trials of art therapies to consider moving away from a symptom reduction focus[8].

As already noted, art therapy is an umbrella term that encompasses a diverse range of approaches (including dance therapy, music therapy and body-oriented psychotherapy) and this might account for some effect size heterogeneity. While we included the same broad forms of art therapies indicated by NICE, the number of trials limit assessing whether any specific approach might be more successful pursued than others. Nonetheless, Crawford *et al*[15] used a more conventional art therapy, while Preibe *et al*[16] used group body psychotherapy and neither found a significant effect.

Turning to the question of "individuality", some may benefit more from art therapies than others. In this context, our moderator analyses revealed a significantly greater negative symptom reduction in trials with more female patients and those who are younger. The role of patient gender requires further investigation – especially since better outcomes for women in art therapy have been reported in other patient groups[40]. Moreover, since art therapists are also more likely to be women - the American Art Therapy Association suggest a ratio of 10 to 1 female: Male[41], the relationship role itself might further be examined. Turning to age, the range was limited and any future trials might investigate whether the benefits are greater for those who are younger and/or have a shorter duration of illness.

Certain limitations of the current meta-analysis should be considered. The number of randomised control trials published to date is low. Although the current analysis did have sufficient power, the small number of trials allied to missing data did mean that some planned moderator analyses were not feasible *e.g.* length of illness. Similarly, it was not possible to examine any impact of art therapies at follow-up because it was so rarely assessed.

In summary, the current meta-analysis found no evidence that art therapies alleviate positive or total symptoms in schizophrenia. Like previous meta-analyses, we found some evidence that they may alleviate the negative symptoms of schizophrenia, but this finding did not emerge in trials using blind outcome assessment and may also be prone to publication bias. In this context, national guidelines, such as that by NICE[11] suggesting that art therapy reduces negative symptoms require reconsideration.

**Table 2 Meta-regressions findings for moderator variables**

| Moderator variable | *k* | Q-statistic |
|---|---|---|
| Age | 9 | Q = 4.66, *df* = 1, *P* = 0.02 |
| Percentage of female participants (%) | 9 | Q = 5.10, *df* = 1, *P* = 0.02 |
| Number of therapy sessions | 9 | Q = 0.07, *df* = 1, *P* = 0.78 |

| Study name | Statistics for each study | | | | Hedges's g and 95%CI |
|---|---|---|---|---|---|
| | Hedges's g | Standard error | Lower limit | Upper limit | |
| Rohricht *et al*, 2006 | 0.47 | 0.30 | -0.11 | 1.05 | |
| Talwar *et al*, 2008 | -0.28 | 0.23 | -0.72 | 0.16 | |
| Crawford *et al*, 2010 | 0.09 | 0.12 | -0.15 | 0.32 | |
| Montag *et al*, 2014 | -0.81 | 0.35 | -1.49 | -0.13 | |
| Lee *et al*, 2015 | -0.37 | 0.32 | -1.00 | 0.26 | |
| Priebe *et al*, 2016 | -0.04 | 0.12 | -0.28 | 0.19 | |
| | -0.10 | 0.13 | -0.34 | 0.15 | |

Favours art therapy — Favours control

**Figure 4 Forest plot of the studies in the meta-analysis for positive symptoms.**

| Study name | Statistics for each study | | | | Hedges's g and 95%CI |
|---|---|---|---|---|---|
| | Hedges's g | Standard error | Lower limit | Upper limit | |
| Yang *et al*, 1998 | -0.97 | 0.25 | -1.47 | -0.48 | |
| Rohricht *et al*, 2006 | -0.73 | 0.30 | -1.32 | -0.13 | |
| Richardson *et al*, 2007 | -0.58 | 0.21 | -1.00 | -0.16 | |
| Ulrich *et al*, 2007 | -0.41 | 0.33 | -1.05 | 0.23 | |
| Talwar *et al*, 2008 | -0.30 | 0.23 | -0.74 | 0.15 | |
| Crawford *et al*, 2010 | 0.03 | 0.12 | -0.21 | 0.26 | |
| Montag *et al*, 2014 | -0.23 | 0.33 | -0.89 | 0.42 | |
| Lee *et al*, 2014 | -1.11 | 0.34 | -1.78 | -0.44 | |
| Priebe *et al*, 2016 | 0.06 | 0.12 | -0.18 | 0.29 | |
| | -0.42 | 0.14 | -0.70 | -0.14 | |

Favours art therapy — Favours control

**Figure 5 Forest plot of the studies in the meta-analysis for negative symptoms.**
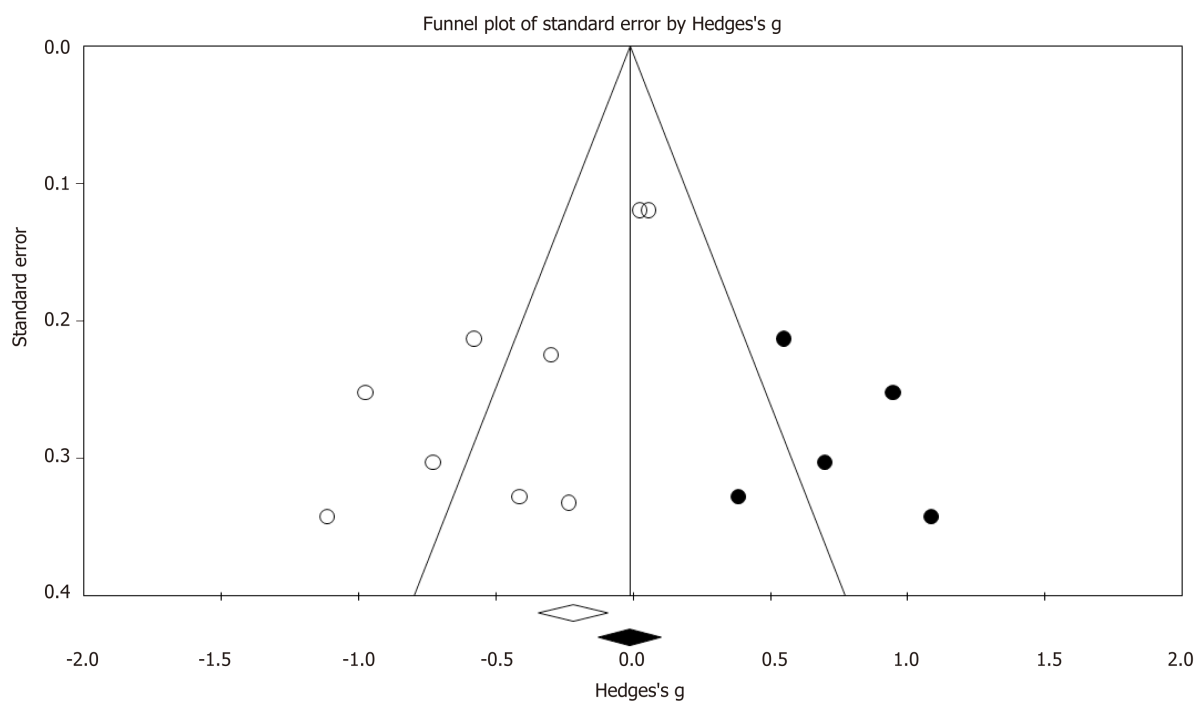
**Figure 6  Funnell plot outlining trim and fill estimates for imputed missing trials (dark circles) for negative symptoms.**
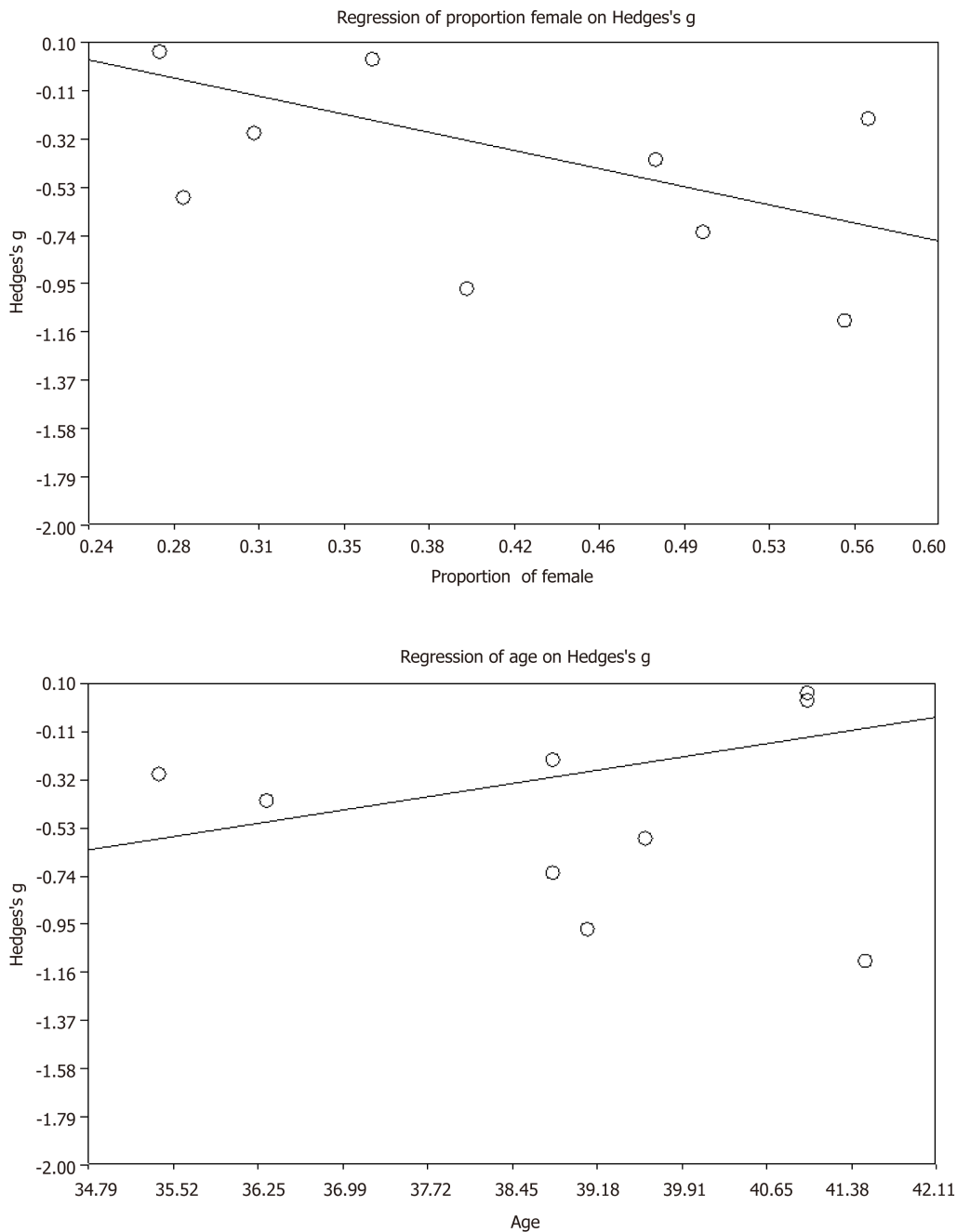
Figure 7 **Regression plots showing effect size for negative symptoms against proportion of female patients per trial (top) and mean age (bottom).**
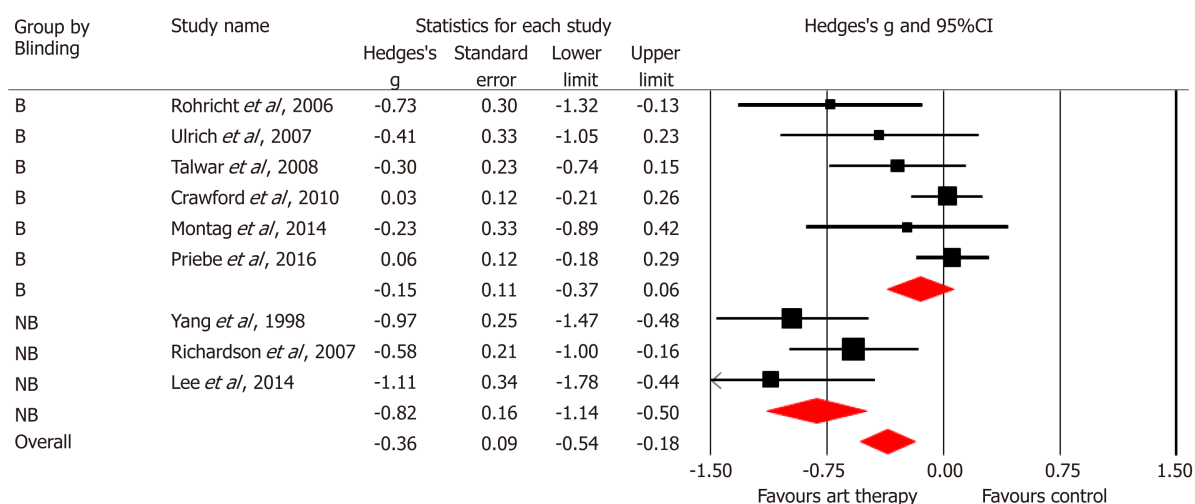
| Group by Blinding | Study name | Statistics for each study | | | | Hedges's g and 95%CI |
|---|---|---|---|---|---|---|
| | | Hedges's g | Standard error | Lower limit | Upper limit | |
| B | Rohricht *et al*, 2006 | -0.73 | 0.30 | -1.32 | -0.13 | |
| B | Ulrich *et al*, 2007 | -0.41 | 0.33 | -1.05 | 0.23 | |
| B | Talwar *et al*, 2008 | -0.30 | 0.23 | -0.74 | 0.15 | |
| B | Crawford *et al*, 2010 | 0.03 | 0.12 | -0.21 | 0.26 | |
| B | Montag *et al*, 2014 | -0.23 | 0.33 | -0.89 | 0.42 | |
| B | Priebe *et al*, 2016 | 0.06 | 0.12 | -0.18 | 0.29 | |
| B | | -0.15 | 0.11 | -0.37 | 0.06 | |
| NB | Yang *et al*, 1998 | -0.97 | 0.25 | -1.47 | -0.48 | |
| NB | Richardson *et al*, 2007 | -0.58 | 0.21 | -1.00 | -0.16 | |
| NB | Lee *et al*, 2014 | -1.11 | 0.34 | -1.78 | -0.44 | |
| NB | | -0.82 | 0.16 | -1.14 | -0.50 | |
| Overall | | -0.36 | 0.09 | -0.54 | -0.18 | |



**Figure 8  Forest plot comparing blind *vs* non-blinded outcome assessment.** B: Blind; NB: Non-blinded.

## ARTICLE HIGHLIGHTS

### Research background

Art therapies are advocated by national bodies, such as the United Kingdom's National Institute for Health and Care Excellence, particularly to alleviate the negative symptoms associated with schizophrenia. The last meta-analysis is now a decade old and several new larger well-controlled trials have been recently published. A meta-analytic update is timely.

### Research motivation

The present study aimed to assess randomised controlled trials (RCT) of art therapies for reducing the symptoms of schizophrenia – particularly negative symptoms.

### Research objectives

A key objective is to evaluate and update evidence for future guidelines concerning treatment suggestions.

### Research methods

A search of PubMed and Scopus was conducted until May 2019 for RCTs assessing symptomatic outcomes following art therapy. Study quality was assessed using the Cochrane risk of bias tool. Random effects meta-analyses were conducted using Comprehensive Meta-Analysis (version 2). Moderator analyses were conducted using both meta-regression and categorical comparisons.

### Research results

We identified 133 articles, of which 9 RCTs involving 948 participants (475 assigned to art therapy and 473 controls) met our inclusion criteria. Using random effects models, we calculated pooled effect sizes (Hedges $g$) for end-of-trial symptomatic outcomes. Effect sizes were non-significant for total symptoms [$g$ = -0.27, 95% confidence interval (CI) -0.60 to 0.05, $k$ = 6] and positive symptoms ($g$ = -0.10, 95%CI -0.35 to 0.15, $k$ = 6); however, we did find significant negative symptom reduction ($g$ = -0.42, 95%CI -0.70 to -0.14, $k$ = 9). Meta-regression revealed that negative symptom reduction was larger in trials with a greater proportion of women and in trials with younger patients. Crucially, the negative symptom reduction following art therapies did not, however, emerge in trials that used blind assessment of outcomes.

### Research conclusions

This review presents a comprehensive meta-analysis of art therapies in schizophrenia in terms of both studies included and participant numbers. We found that art therapies did not significantly reduce total or positive symptoms. A "small" therapeutic effect was found for negative symptoms, but we show that the effect is not present in blind trials and may be subject to publication bias. The findings have implications for clinical practice and future treatment guidelines (*e.g.*, National Institute of Clinical Excellence) that have previously recommended using art therapies to alleviate negative symptoms in people with schizophrenia.

### Research perspectives

The current meta-analysis suggests that RCTs of art therapies do not provide evidence of any reduction in total, positive or indeed, negative symptoms. The latter is important as this has been viewed as a key aspect of art therapies in schizophrenia – being recommended in influential national guidelines such as that by National Institute of Clinical Excellence. Future trials might investigate whether one particular form of art therapy offers more benefit than others. They might also look at whether younger individuals and women do benefit more than men.

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