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Contents

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Contents

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Editorial Board Member of *World Journal of Psychiatry*, Laura Orsolini, MD, MSc, PhD, Academic Research, Doctor, Senior Research Fellow, Psychopharmacology Drug Misuse and Novel Psychoactive Substances Research Unit, University of Hertfordshire, Hatfield AL109AB, Herts, United Kingdom

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EDITORIAL

Evidence for using dextromethorphan-quinidine for the treatment of agitation in dementia

Rajesh R Tampi, Pallavi Joshi, Padmapriya Marpuri, Deena J Tampi

ORCID number: Rajesh R Tampi (0000-0001-6754-6567); Pallavi Joshi (0000-0002-9622-4580); Padmapriya Marpuri (0000-0001-7407-4625); Deena J Tampi (0000-0002-4349-7622).

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Rajesh R Tampi, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44106, United States

Rajesh R Tampi, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH 44195, United States

Pallavi Joshi, Department of Psychiatry and Behavioral Sciences, Northwell Health-Staten Island University Hospital, Staten Island, NY 10306, United States

Padmapriya Marpuri, Department of Psychiatry, Einstein Medical Center, Philadelphia, PA 19141, United States

Deena J Tampi, Diamond Healthcare, Richmond, VA 23219, United States

Corresponding author: Rajesh R Tampi, MD, Chairman, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44106, United States. rajesh.tampi@yale.edu

Abstract

Behavioral and psychological symptoms including agitation are common in dementia, and are associated with decreased quality of life, increased risk of institutionalization, and greater patient and caregiver distress. Pharmacological agents used for management of behavioral and psychological symptoms of dementia are limited by their tolerability, prompting a need for identifying efficacious and safe pharmacological treatments for managing agitation in dementia. The combination of dextromethorphan and quinidine sulfate is approved for pseudobulbar affect, and may be effective in managing agitation in dementia. A review of literature found only one randomized controlled trial that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia when compared to placebo. Data from this trial demonstrated that dextromethorphan-quinidine decreased agitation in dementia, and was well tolerated. Although promising, further research is needed before dextromethorphan-quinidine combination can be accepted as a standard treatment for agitation in dementia.

Key words: Dextromethorphan; Quinidine; Agitation; Dementia; Behavioral and psychological symptoms of dementia

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Core tip: Dextromethorphan-quinidine is approved for the treatment of pseudobulbar affect and may be effective in managing agitation in dementia. There is only one published trial that has evaluated the use dextromethorphan-quinidine for agitation in dementia. The study was of good quality and found that dextromethorphan-quinidine decreases severity of agitation when compared to placebo. Additionally, dextromethorphan-quinidine was fairly well tolerated and did not appear to cause significant sedation or worsen cognitive symptoms among individuals with dementia.

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INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms and behaviors including agitation and aggression that are unsafe, disruptive, and impair the care of the individual in a given environment[1]. BPSD is seen in one-third of individuals with dementia who live in the community and in up to 80% of individuals with dementia who live in skilled nursing facilities[2]. The prevalence of agitation in dementia can be up to 46%, and is associated with decreased quality of life and increased risk of institutionalization for these individuals, in addition to greater caregiver burden and higher social and economic burden of caring for these individuals[3,4].

Non-pharmacological interventions are recommended as first-line for management of agitation in dementia. Pharmacotherapy including antipsychotics, antidepressants, anticonvulsants and cognitive enhancers are used when non-pharmacological interventions are ineffective[5]. Unfortunately, these medications are burdened with a significant side effect profile including QTc interval prolongation, weight gain, anticholinergic effects and cardiovascular adverse effects that carry substantial risks for the geriatric population[5]. Therefore, there is a great need for identifying efficacious and safe pharmacological treatments that are suitable for managing agitation in dementia.

Dextromethorphan is a low-affinity, uncompetitive N-methyl-D-aspartate receptor antagonist, σ1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist[6]. Dextromethorphan has low and variable bioavailability when administered alone because of its rapid first-pass metabolism and subsequent elimination. The addition of quinidine, a potent inhibitor of the cytochrome P450 (CYP) liver enzyme CYP2D6, inhibits dextromethorphan metabolism and yields greater bioavailability[6]. The combination of dextromethorphan and quinidine sulfate is approved for the treatment of pseudobulbar affect in the United States and European Union. Evidence suggesting a potential effect of dextromethorphan-quinidine for agitation in dementia comes from controlled clinical trial data in non-demented patients with pseudobulbar affect[7].

The aim of this editorial is to review the literature on published randomized control trials (RCTs) that evaluated the efficacy and tolerability of dextromethorphan-quinidine for the management of agitation in dementia.

EVIDENCE FOR USIGN DEXTROMETHORPHAN-QUINIDINE FOR AGITATION IN DEMENTIA

A review of literature found only 1 RCT that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia (Table 1)[8]. The study was assessed as being of good quality based on JADAD criteria (Table 2). The details of the study are described in Table 3.

DISCUSSION

Available data from RCTs on the use of dextromethorphan-quinidine for the

Table 1 Summary of included studies

Ref.	Country of origin	Number of participants	Age (yr)	Setting	Comparators	Duration
Cummings *et al*[8], 2015	United States	220	50-90	Outpatient clinics, assisted living and nursing facilities	Dextromethorphan-quinidine *vs* placebo	10 wk

management of BPSD is extremely limited. The only trial that we found in our literature review evaluated the efficacy of dextromethorphan-quinidine in reducing severity of agitation among individuals with Alzheimer's disease when compared to placebo. This is the first dementia-related trial to use a sequential parallel comparison design[8]. In studies using this design, the first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo non-responders from stage 1 are rerandomized and are included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences and reduces the required sample size[8].

In this trial, treatment with dextromethorphan-quinidine demonstrated statistically significant decrease in agitation and aggression when compared to placebo. The reduction in agitation was considered clinically significant as measured by clinician rated scales. While the Alzheimer disease–related agitation characteristics of patients in this study were generally consistent with the International Psychogeriatric Association definition of agitation[8], patient emotional distress in patients was not directly measured.

Dextromethorphan-quinidine was generally well tolerated in this elderly population and was not associated with cognitive impairment. Most adverse events, including dizziness and diarrhea, were consistent with those observed in dextromethorphan-quinidine trials for pseudobulbar affect[8]. Falls were more common among patients receiving dextromethorphan-quinidine when compared to placebo. This may be explained by greater duration of exposure to dextromethorphan-quinidine and the lack of randomization to groups based on fall risk.

The strengths of the study include the use of the sequential parallel comparison design; inclusion of stable concomitant medications, including psychotropic medications, high retention rate, blinding of study sites to all aspects of the study, use of prespecified sensitivity analyses to corroborate the primary efficacy end point, and consistent results among multiple secondary outcomes and primary end point. Limitations of this trial include a short duration (10 wk), and a dose-escalation schedule that limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine, tricyclic antidepressants, monoamine oxidase inhibitors, or phenothiazines, as well as cardiac parameters limit the generalizability of study findings. Finally, the patient population was predominantly outpatient, with only 5.5% of study participants domiciled in nursing homes. The treatment response may not be generalizable to patients in nursing homes and should be further explored.

In the study reviewed, the combination of dextromethorphan-quinidine was clinically efficacious for agitation and was generally well tolerated. However, evidence-based trials are limited, as is the generalizability of the results to wider clinical and nursing home populations. This highlights the need for further research on both the efficacy and safety of dextromethorphan-quinidine and other pharmacological interventions for agitation in dementia.

CONCLUSION

This review indicates that there is a scarcity of evidence for the use of dextromethorphan-quinidine for the management of agitation in dementia. There is only one available trial, which demonstrated a decrease in agitation and aggression compared with placebo. However, the trial had a limited number of participants and low representation of patients in nursing home, which further restricts the generalizability of the results. The need to further investigate the effectiveness of different pharmacotherapeutic modalities for the management of agitation in dementia is, therefore, essential.

Table 2 Quality of included studies

Ref.	Randomization	Similar groups initially?	Equal treatment?	Analyzed groups in which they were randomized	Objective/ "blind" treatments?	Overall quality of study
Cummings *et al*[8], 2015	Yes	Yes	Yes	Yes	Yes	Good

Table 3 Results summary from included studies

Ref.	Outcomes	Tolerability	Limitations
Cummings *et al*[8], 2015	In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo, $P < 0.001$. In stage 2, mean NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo, $P = 0.02$. The prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine *vs* only placebo for the entire 10 weeks of the trial also favored dextromethorphan-quinidine over placebo, $P = 0.003$. Response to dextromethorphan-quinidine compared with placebo did not appear to differ by disease stage. The additional prespecified analysis that included both placebo responders and non-responders who were rerandomized in stage 2 did not alter the significance or magnitude of effect of the primary analysis. Sequential parallel comparison design analysis of prespecified secondary outcomes showed significant improvement favoring dextromethorphan-quinidine on global rating scores. Results for changes in the quality of life–Alzheimer disease score, ADCS activities of daily living Inventory, MMSE, and ADAS-Cog were not significant *vs* placebo. Post hoc analyses showed similar improvement in NPI Agitation/Aggression scores with dextromethorphan-quinidine in patients taking concomitant acetylcholinesterase inhibitors, memantine, antidepressants, or antipsychotics n when compared with those not receiving these agents. Lorazepam rescue medication was used by 6.6% of patients in the dextromethorphan-quinidine group during treatment and by 10.4% during treatment with placebo	Treatment-emergent adverse events were reported by 61.2% of patients in the dextromethorphan -quinidine group and 43.3% with placebo group. The most commonly occurring treatment-emergent adverse events were falls (8.6% *vs* 3.9%), diarrhea (5.9% *vs* 3.1%), urinary tract infection (5.3% *vs* 3.9%), and dizziness (4.6% *vs* 2.4%). Serious adverse events occurred in 7.9% patients receiving dextromethorphan-quinidine and in 4.7% of patients receiving placebo. Serious adverse events in patients receiving dextromethorphan-quinidine included chest pain ($n = 2$), anemia, acute myocardial infarction, bradycardia, kidney infection, femur fracture, dehydration, colon cancer, cerebrovascular accident, aggression, and hematuria. Serious adverse events in patients receiving placebo included idiopathic thrombocytopenic purpura, vertigo, pneumonia, gastroenteritis, contusion, transient ischemic attack, and agitation. Eight patients (5.3%) receiving dextromethorphan-quinidine and 4 (3.1%) receiving placebo discontinued treatment owing to adverse events. No deaths occurred during the study. No clinically meaningful between-group differences in electrocardiographic findings were observed	The duration was limited to 10 wk. The dose-escalation schedule limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine and specific electrocardiographic/cardiac parameters that restricted patient enrollment, may limit the generalizability of study findings. Treatment at experienced trial sites by specialized clinicians under a clinical protocol prescribing frequent assessments may not reflect general practice. The patient sample consisted predominantly of outpatients; agitation in nursing home residents was underrepresented

NPI: Neuropsychiatric inventory; ADCS: Alzheimer's disease cooperative study; MMSE: Mini mental state examination; ADAS-Cog: Alzheimer disease assessment scale–cognitive subscale.

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REVIEW

Moderators and mediators of antipsychotic response in delusional disorder: Further steps are needed

Alexandre González-Rodríguez, Armand Guàrdia, Diego José Palao, Javier Labad, Mary V Seeman

ORCID number: Alexandre González-Rodríguez (0000-0003-1855-8566); Armand Guàrdia (0000-0002-3908-0875); Diego José Palao (0000-0002-3323-6568); Javier Labad (0000-0003-2214-1886); Mary V Seeman (0000-0001-6797-3382).

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Alexandre González-Rodríguez, Armand Guàrdia, Diego José Palao, Javier Labad, Department of Mental Health, Parc Taulí University Hospital, Autonomous University of Barcelona, Sabadell 08280, Spain

Mary V Seeman, Department of Psychiatry, University of Toronto, Toronto, ON M5P 3L6, Canada

Corresponding author: Mary V Seeman, DSc, FRCP (C), MD, Emeritus Professor, Department of Psychiatry, University of Toronto, 260 Heath Street West, Suite #605, Toronto, ON M5P 3L6, Canada. mary.seeman@utoronto.ca

Abstract

Delusional disorder (DD) has been traditionally considered a relatively rare and treatment-resistant psychotic disorder. In the last decade, increasing attention has focused on therapeutic outcomes of individuals affected by this disorder. The aim of this paper is to provide a synthesis of the literature addressing two very important questions arising from DD research: (1) For which patients with DD do antipsychotic medications work best (the moderators of response); and (2) What variables best explain the relationship between such treatments and their effectiveness (the mediators of response). We searched PubMed and Google Scholar databases for English, German, French and Spanish language papers published since 2000. We also included a few classic earlier papers addressing this topic. Variables potentially moderating antipsychotic response in DD are gender, reproductive status, age, duration of illness, the presence of comorbidity (especially psychiatric comorbidity) and its treatment, brain structure, and genetics of neurochemical receptors and drug metabolizing enzymes. Antipsychotic and hormonal blood levels during treatment, as well as functional brain changes, are potential mediating variables. Some, but not all, patients with DD benefit from antipsychotic treatment. Understanding the circumstances under which treatment works best can serve to guide optimal management.

Key words: Delusional disorder; Psychosis; Moderators; Mediators; Antipsychotic response

Core tip: Although patients with delusional disorder have traditionally been viewed as treatment-resistant, many do experience benefits from antipsychotic medications, but not all respond similarly. The identification of mediators and moderators of treatment

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response is clinically useful in that understanding under what circumstances treatment works best provides a reliable guide to effective management.

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INTRODUCTION

Delusional disorder (DD) is defined in DSM-5 as a psychotic disorder characterized by the persistence, for at least one month, of one or more delusions that do not markedly impair personal, social or occupational function and that are present independently of schizophrenia, affective disorder or substance abuse disorder[1]. The disorder is characterized by a high prevalence of psychiatric morbidity. Delusional beliefs in this condition are encapsulated and usually monothematic; they lack the bizarreness of delusions found in schizophrenia[2]. The various commonly seen delusional themes designate subtypes of DD - *e.g.*, erotomania, grandiosity, delusional jealousy, paranoia, and somatization[3]. DD has been widely considered a relatively rare disorder with a cited lifetime prevalence of 0.02%[1,4]. It is a disorder that starts relatively late in life; the mean onset age is 40, but this ranges from 18 to the nineties. The disorder is somewhat more common in women than in men[5,6]. The individual's ethnic and religious background is an important consideration when making a diagnosis; it determines whether a strongly held irrational belief is a delusion or a traditional mindset.

DD has been described by Kendler[7] as an inherently treatment-resistant disorder but others have challenged this view, attributing most of the failure to respond to treatment to widespread non-adherence. Individuals with this disorder characteristically do not see themselves as ill, and, therefore, often do not take prescribed drugs[8-10].

As in other diseases, there has been a growing interest in the field of DD studies to enable the monitoring of both adherence and response to therapeutic drugs[11]. However, to the best of our knowledge, to date, no clinical trials have been conducted on the effectiveness of currently used medications, which renders specific treatment recommendations impossible to make at this time[10]. Only one randomized controlled trial of treatment effectiveness exists in DD and this has evaluated a psychotherapeutic approach rather than a pharmacological one. The trial evaluated group cognitive-behavioral therapy *vs* supportive group therapy conducted over a 24-wk period[12]. Cognitive-behavioral therapy proved to be more effective than the control measure on 3 of 7 dimensions of the Maudsley Assessment of Delusion Schedule, but the participant sample was very small (12 participants per group).

One problem in investigating treatment outcomes in DD is the lack of consensus on the definition of antipsychotic response as it applies to this disorder[13]. Different investigators use different definitions of response and many base their judgement solely on a clinical evaluation, which is, by its nature, necessarily subjective. Cut-off points on assessment scales are sometimes used, but the scales differ[14]. Adding to the problem is the difficulty of accurately assessing issues of adherence[11,15].

Despite difficulties in evaluating treatment outcomes, most reports agree that response is variable and heavily dependent on patient factors, such as adherence to the prescribed regimen[16].

Patient pre-existing characteristics that influence response are referred to as moderators. Several have been suggested in the context of DD. Identifying a moderator helps to determine when and under what conditions treatment is most effective, and for whom[17-19]. In contrast, a mediator, or intervening variable, is one that can alter the relationship between the independent and dependent variables, in this case, antipsychotic treatment and outcome[18,19]. Moderators are in place before treatment begins. Mediators mediate the process during treatment. Moderators of treatment efficacy are inherent in the patient or the patient's environment. Mediators of treatment efficacy are measurable changes in the patient that occur during the course of treatment[20] (Figure 1).

Moderators and mediators of an intervention are important to identify. They have

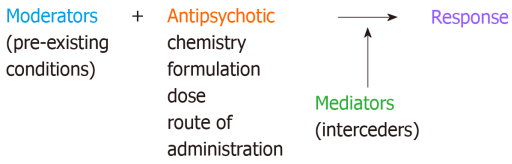

Figure 1 Moderators and mediators.

never been reported for DD but have been specifically addressed in other psychiatric domains, for instance, in affective disorders and substance abuse[21-23].

Specifying moderator and mediator factors in DD clarifies such questions as: For whom do available treatments work, how do they work, and when do they work.

LITERATURE SEARCH

We searched PubMed and Google Scholar databases for English, German, French and Spanish language papers published since 2000 that pertained to the role of moderators and mediators of antipsychotic response in DD. Several thousand abstracts were initially screened. Most were excluded because, although they addressed predictors, mediators, and moderators of antipsychotic response, they did so for schizophrenia only. In the end, by consensus, 40 primary articles were selected as relevant to our goals. These included a few classic earlier papers on the topic that we considered to be still relevant. For purposes of comparison, additional papers addressing moderators/mediators in psychoses other than DD were also included. After the screening and selection process, the collected information was divided into the following sections: (1) Moderators of treatment response in DD; and (2) Mediators of treatment response in DD.

MODERATORS OF TREATMENT RESPONSE

In other psychotic disorders, moderating variables, or pre-treatment characteristics of patients that predict response to drugs, have included gender, reproductive status, age at treatment, duration of illness, psychiatric comorbidity, abnormalities of brain structure or function, aberrant biochemistry, and gene variants, especially those coding for neurochemical receptors and drug metabolizing enzymes (Table 1). In DD, consideration of moderating variables involved in antipsychotic response has not been previously attempted.

Gender and hormonal status

There is a literature on gender differences in DD. As part of the Halle Delusional Syndromes Study, Wustmann *et al*[24] investigated gender-related features of DD in a carefully diagnosed sample of 43 inpatients (22 men and 21 women) consecutively admitted to one hospital over a long period of years. Thirty-three patients were re-interviewed from 3 to 24 years after the onset of their symptoms. Gender distribution in this sample was almost equal; age of onset was significantly later in women; the diagnosis persisted in women whereas, in a third of the men, it was changed to schizophrenia over time. Women were more compliant with treatment and, thus, received medication more often than men. Paradoxically, while over 80% of the women remained unremitted at follow up, this was true for only half of the men. The authors concluded that DD in women is more severe and more persistent than in men, but this study does not directly address the effect of gender on treatment response[24].

Román Avezuela *et al*[25] investigated gender differences in DD in a sample of 50 first admission inpatients. All were diagnosed according to DSM-IV criteria and were retrospectively evaluated by review of medical records, the OPCRIT 4.0, and a symptom inventory specially designed for the study. The proportion of women to men was 1.27:1. As in the Wustmann *et al*[24] study, the age of first admission was higher in women. Men misused substances more than women and women suffered depression more often than men. Men were more likely to present with grandiose, jealous or persecutory delusions whereas women more frequently had erotomaniac delusions. No gender differences in the course of illness were observed but, again, treatment response was not directly examined[25].

These two studies yielded some similar and some contradictory results, which is to be expected because sample sizes were small and methodologies differed. Even with

Table 1 Potential moderators and mediators of antipsychotic response in delusional disorder

Moderators	Mediators
Gender	Antipsychotic plasma concentrations
Reproductive status	Blood flow to brain
Age	Brain glucose metabolism
Comorbidity	Dopamine receptor occupancy
Brain lesions	Estrogen levels
Genetic factors	
D2 receptor genes	
Metabolizing enzyme genes	

identical methodology, results of gender studies can easily diverge because a variety of potential moderating variables differ by gender, comorbid substance use and treatment adherence for instance, and this can skew group gender response in opposing directions depending on the composition of the sample[5].

In patients with psychoses other than DD, women have been observed to respond more robustly to antipsychotics than men, but only during their reproductive years[26,27]. This has been attributed to estrogens potentiating treatment response[28-30], a potentiation that has been shown to end at menopause[31]. DD begins relatively later in life than schizophrenia so that most women with this disorder cannot count on circulating estrogens to assist with antipsychotic response. In fact, the drop of estrogen at menopause may be what determines the higher prevalence of DD in women than in men[6].

When studies that control for potentially confounding factors are conducted in DD, it seems likely that gender will prove to be a moderator of antipsychotic response, as it is in other psychoses.

Age

Age is known to moderate antipsychotic response in many psychotic illnesses. Both age at treatment and also age at onset of illness, often a proxy for illness duration, can impact therapeutic outcomes in psychosis.

Mangoni *et al*[32] have highlighted a person's age at treatment as a moderator of medication response. Age changes the bioavailability, distribution, metabolism and elimination of drugs. As people age, there is a gradual reduction in renal and hepatic clearance, as well as a relative increase in the volume of drug distribution[33]. The net effect for lipophilic drugs such as antipsychotics is a tendency for drug accumulation in lipid stores[34], which can lead to drug toxicity. Toxic drug levels impair subsequent adherence, thereby undermining treatment effectiveness. To date, no studies have specifically investigated the impact of age at treatment on therapeutic outcomes in DD. Conclusions can only be inferred from studies in schizophrenia populations and from other pharmacological research in aging populations.

Age at onset of illness has been considered a moderator of antipsychotic response in schizophrenia[35]. Usually, the younger the onset, the more severe the illness, which equates with poor response to treatment[35]. With respect to DD, the severity of symptoms has not generally been seen as varying with onset age although the results of the Wustmann *et al*[24]'s study do suggest that later onset correlates with symptom severity. DD almost always starts relatively late in adult life when the physiological and psychological process of aging and age-related co-morbidities make recovery from any illness increasingly challenging. This undoubtedly contributes to the generally poor antipsychotic response in DD. It is possible that larger samples will, nevertheless, find that, here too, younger onset correlates with illness severity. Young onset age usually means longer duration of illness at the time of ascertainment. In most illnesses, long untreated duration makes recovery less likely[36], but the relevant studies in DD have not been done. Interestingly, DD subtypes seem to differ with respect to age at onset. Out of 51 outpatients diagnosed with DD at one psychiatric clinic, the persecutory subtype showed the oldest onset age while the youngest onset age was associated with the somatic subtype[37].

In general, age, whether at the time of treatment or at the time of onset of symptoms, is a powerful moderator of treatment outcome in psychosis[38] and may prove to be so in DD as well.

Comorbid psychiatric disorders

It is known that patients with DD suffer from many psychiatric comorbidities,

especially depressive disorders[39]. Mood disorders are reportedly seen in one half of patients with DD[40].

Maina *et al*[39] investigated the occurrence and clinical correlations of comorbid psychiatric diagnoses in 64 patients with DD. Patients with one comorbid psychiatric disorder (as compared to those with no co-morbidity) showed an earlier age of DD symptom onset, came to psychiatric attention at an earlier age, and were, as a group, younger. Antipsychotic response was, however, not evaluated[39]. Other research groups have confirmed the extent of comorbidity in DD. In a study of 86 outpatients with DSM-IV DD, and using the Mini International Neuropsychiatry Interview as a diagnostic tool, de Portugal *et al*[40] found that 46.5% of study participants suffered from at least one additional lifetime psychiatric diagnosis, depressive disorder being the most common one. This is in agreement with Marino *et al*[41] who reported that, in 42% of 67 patients with DD (44 women and 23 men), a mood disorder had preceded the onset of DD.

Substance abuse may also precede DD. Román Avezuela *et al*[25], in the study referred to earlier, showed that men frequently suffered from alcohol or cannabis dependence at least one month prior to the diagnosis of DD. Depression and substance abuse comorbidity are both associated with a worse prognosis in DD[25,41], especially if the comorbid condition precedes the onset of DD symptoms.

In psychotic illness in general, substance abuse is a frequently seen secondary condition[42,43], a way, some have speculated, of coping with disturbing thoughts or with medication side effects. In one study from India, 11 out of 13 first episode, drug-naive DD patients from a tertiary care center were found to suffer from at least one psychoactive substance use disorder[43]. Since these patients were unmedicated, the substances were probably used to drown out disturbing thoughts, although it is also possible that the effect of early onset substance use may have contributed to the induction of DD.

The connection between comorbid psychiatric diagnoses and antipsychotic treatment response has not been sufficiently investigated in DD. When it is, it may prove to significantly moderate antipsychotic response, as it does in related illnesses.

Brain changes on neuroimaging

Structural and functional brain changes have been reported in neuroimaging case studies of patients with DD[44], giving rise to the possibility that such changes may moderate treatment response.

In 1989, Miller and co-workers carried out a prospective study on a sample of patients with late-life onset psychosis. Five patients (3 diagnosed with DD, 1 with schizophrenia, and 1 with bipolar disorder) underwent either magnetic resonance imaging or computed tomography. The investigators found that multiple lacunar infarcts were associated with poor neuropsychological performance and non-response to treatment. They suggested that the presence of brain structural lesions could predict treatment response[45]. A similar correlation between brain lesion and treatment failure has been seen in schizophrenia[46,47]. Freudenmann *et al*[48] have reported fronto-striato-thalamo-parietal network lesions that correlated with antipsychotic response in one patient with delusional parasitosis.

Other neuroimaging studies in DD, however, have been unable to show a correlation between brain structure and therapeutic response[49,50]. Howard and collaborators, for instance, found that lateral ventricle volumes in DD were greater than in schizophrenia, but they could not show an association between this finding and response to antipsychotic medications[50].

As of now, it is unclear what brain lesion, if any, predicts antipsychotic response in DD patients.

Biological factors: Biochemistry and genetics of receptors and enzymes

Hyperdopaminergic states have been implicated in many psychoses[51], buttressed by the fact that all antipsychotic drugs currently in use block D2 dopamine receptors, as elucidated by the pioneering work of Philip Seeman[52] and reconfirmed many times over the years[53,54]. Since one-third of patients with schizophrenia show poor response to available antipsychotics, the implication is that the dysregulation of other neurochemical pathways (serotonergic, cholinergic, glutaminergic) may also, to varying degrees, lead to psychosis[55-58].

Morimoto *et al*[59] investigated the relationship between antipsychotic response, plasma homovanillic acid (pHVA), dopamine receptor (DR) genes and tyrosine hydroxylase (TH) in 57 patients with DD, 48 patients with schizophrenia, and 48 healthy controls. DD patients homozygous for the Ser9Ser dopamine D3 receptor (DRD3) genetic variant showed higher pretreatment levels of pHVA, -*i.e.* higher dopamine function, than heterozygous (Ser9Gly) patients. The pHVA level fell (by nearly 30 pmol/mL) after 8 weeks of treatment with the antipsychotic, haloperidol,

suggesting that polymorphisms in the DRD3 gene can moderate response to antipsychotics.

It has been reported that genetic variants of cytochrome P450 enzymes responsible for antipsychotic drug metabolism either raise or lower antipsychotic plasma levels of specific drugs, and can thus contribute to treatment response[60]. Recent work has investigated the benefits of pharmacogenetics in maximizing antipsychotic treatment effectiveness in psychosis. The study sample included 58 patients with DD. When dose adjustments were made to antipsychotic drugs according to the presence of relevant polymorphisms in CYP1A2, CYP2C19, CYP2D6 and CYP3A5 enzymes, an improved symptom response was expected. Unfortunately, this was not found[60]. Genetic variants of CYP2D6 enzymes have been able, however, to predict which doses of which drugs result in side effects[61].

Subtherapeutic plasma levels of antipsychotics, attributable to activity differences in CYP enzymes (among other factors that occur during the course of treatment), are held to be a major cause of treatment resistance in most psychoses[62]. The investigation of genetic variants of genes encoding for cytochrome P450 enzymes has revealed that some patients are fast or ultra-fast metabolizers, while others metabolize drugs much more slowly. Speed of metabolism affects serum concentration and subsequent entry into the brain.

Therapeutic drug monitoring is a promising new area in DD. As early as 1998, Silva and co-workers explored the effect of giving pimozide at increasing doses to 7 patients with DD over a 6-wk period. Pimozide levels and psychopathology scores as per the Brief Psychiatric Rating Scale (BPRS) were assessed every week[63]. Had some patients improved, this study could have yielded a plasma concentration/therapeutic response index. Unfortunately, pimozide had no effect on any dimension of the BPRS, although pimozide levels confirmed that patients were taking their medication.

Therapeutic effectiveness can, as mentioned earlier, be defined in a variety of ways. Herbel and Stelmach conducted a study where they defined effectiveness as the restoration of decisional competence in previously incompetent patients with DD[64]. This outcome was determined in their study by retrospective chart review. Where the plasma level of haloperidol was done (only one case), a low level (2.9 ng/mL) was associated with failure to achieve competence.

More recently, antipsychotic plasma concentrations obtained by high-performance liquid chromatography in 27 patients with DD and 27 patients with schizophrenia were used to examine treatment both adherence and response[65]. The association between antipsychotic response and plasma levels of antipsychotics could not be determined, however, due to the naturalistic design, the several antipsychotics with which patients were treated, and the relatively small sample size[65].

The serum concentration of a drug is affected, of course, by more than genetic variants of metabolizing enzymes. Given strict adherence to a prescribed regimen, it is primarily determined by drug dose, but also by route of administration, by liver and kidney health, volume of distribution, and by interaction with concomitant drugs, tobacco, and the ingestion of specific foods[66]. Some of these factors are moderators of response; some are mediators.

Available evidence from patients with other psychoses[62,67,68] suggests that the determination of plasma drug concentrations, especially when the antipsychotic in question is clozapine, is very useful in predicting treatment outcome. If, in the future, antipsychotic plasma concentration are linked to response in DD, then genetic variants of cytochrome P450 enzymes that help to determine antipsychotic blood levels will be categorized as moderators of response, as they are in other psychoses.

MEDIATORS OF TREATMENT RESPONSE IN DD

Several mediators of response (factors that emerge from the interaction of patient and antipsychotic treatment) have been identified in patients with DD: Antipsychotic drug levels, functional changes in the brain, and hormonal levels (see Table 1).

Plasma level of the drug

As mentioned, and as is well known, the blood level of an antipsychotic drug predicts how much of it will enter the brain and, thus, how effective it will be at its target site. Blood level is determined by many factors, some of which are moderators (genetics of metabolizing enzymes, genetics of drug receptors, genetics of body mass, genetics of liver and kidney health) because they characterize the person prior to treatment, and some of which are mediators because they occur during treatment (drug dose, route of administration, smoking status, concomitant drugs, ingestion of certain foods such as grapefruit, which can raise the blood level of some drugs and lower the level of

others).

As described earlier, plasma levels of antipsychotics have been examined in DD but it has not yet been possible to correlate them with treatment response.

Functional brain changes during treatment

In schizophrenia, many investigations have been conducted into the relationship between changes in regional blood glucose metabolism (measured by single-photon emission tomography - SPECT) and clinical response to antipsychotic treatment. Cerebral blood flow (CBF) to different regions of the brain has also been studied in a variety of patients undergoing treatments with antidepressants, antipsychotics, and electroconvulsive therapy[69-73].

In DD, specifically in delusional parasitosis, cerebral blood flow changes before and after successful treatment with antipsychotics have also been reported. Narumoto and colleagues described the case of an 82 year old man who had had symptoms of delusional parasitosis for 5 years beginning one month after he suffered a stroke in the right temperoparietal region of the brain[74]. Cerebral blood flow in the patient was assessed at baseline by SPECT and again after 6 weeks of risperidone therapy, by which time the patient had fully recovered from his delusional symptoms. At baseline, there was a global decrease of CBF, which the investigators attributed to the influence of the prior stroke. Post-treatment SPECT, however, showed a marked increase in regional cerebral blood flow (rCBF) in bilateral frontal and left temperoparietal regions. The decreased rCBF in the right temperoparietal region remained unchanged. Increased blood flow to large brain regions other than the lesion area seems to have mediated the improvement of clinical symptoms[74].

Freudenmann *et al*[48] described another case of a 27 year old woman with delusional parasitosis who was treated with aripiprazole. She achieved full remission when dopamine 2 receptor occupancy reached 63%-78% occupancy, as measured by photon emission tomography[48]. Using SPECT, cerebral glucose metabolism was also investigated in this patient. Before treatment, glucose metabolism in the thalamus and putamen was left dominant. This remained unchanged after treatment.

Although only individual case reports exist at this time, functional neuroimaging changes may prove, in the future, to be quantifiable mediators of antipsychotic response in DD (Table 2).

Changes in hormonal levels

In other psychoses, various hormonal levels have been investigated as potential mediators of treatment response. Many preclinical, clinical and epidemiological studies have concluded that elevated estrogen levels are neuroprotective in psychosis[75-78], which would partly explain why schizophrenia in women, until the age of menopause, is, on the whole, a less severe disease than it is in men[26,79]. Hypothetically, normal fluctuations of estrogen levels influence the response of psychotic symptoms to antipsychotic treatment either by action at the dopamine 2 receptor or by modification of the activity of drug metabolizing agents.

During the reproductive years, the level of estrogen in women fluctuates with menstrual phase and also with pregnancy stage[78,79]. This is reflected in clinical measures of the severity of symptoms; the higher the level of estrogen, the more attenuated the symptoms[80].

Because DD is a disorder of older age, fluctuating estrogen levels may not be as relevant as they are in schizophrenia[81,82] but, by checking hormone levels, one would be able to determine whether exogenous estrogens (and perhaps other hormones) can boost antipsychotic response in DD.

CONCLUSION

Although many patients with DD experience benefits from treatment with antipsychotics, this is not true for all patients. Understanding for whom and under what circumstances treatment works best can guide management strategies for DD patients. Based on the literature on DD and other psychoses, moderators of antipsychotic response probably include gender, reproductive status, age, comorbid psychiatric disorders, baseline brain abnormalities, biochemistry, and genes coding, for instance, for brain receptors and drug metabolizing enzymes. Suggested mediating variables include measurable functional brain alterations during treatment, such as changes in neuronal receptor occupancies, blood flow to the brain, brain glucose metabolism, and blood hormone levels.

Understanding moderators has substantial clinical relevance. For instance, knowing that comorbid psychiatric illness such as mood disorders and substance abuse disorders often precede DD opens an avenue to early intervention. Understanding

Table 2 Therapeutic implications of brain lesions in delusional disorder

Ref.	Study design	Imaging method	Age	Contrast group	DD type	Main findings
Moderators of treatment response (structural brain findings)						
Miller *et al*[45], 1989	Prospect	CT, MRI	Case 1: 86 Case 2: 72 Case 3: 62	Schizophr (n = 1) Bipolar disorder (n = 1)	Persecutory	Structural brain disease in all 3 cases contributed to treatment resistance
Mediators of treatment response (changes in functional brain findings)						
Wada *et al*[69], 1999	Case report	SPECT	Age = 78	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes improved at remission
Ota *et al*[70], 2003	Case report	SPECT	Age = 72	-	Somatic	Decreased perfusion in the left temporal and parietal lobes improved after treatment
Hayashi *et al*[71], 2004	Case report	SPECT	Age = 77	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes improved after treatment
Narumoto *et al*[74], 2006	Case report	SPECT	Age = 82	-	Somatic	Global decrease in rCBF Reversed in all non-stroke areas after remission
Hayashi *et al*[72], 2010	Case report	SPECT	Age = 42	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes normalized after treatment
Freudenmann *et al*[48], 2010	Prospect.	PET SPECT	Age = 27	Organic DD (n = 1)	Somatic	*SPECT*: D2R occupancy predicted remission *PET*: Glucose metabolism in putamen and thalamus did not normalize with remission
Uezato *et al*[73], 2012	Case report	SPECT	Age = 53	-	Somatic	Hyperperfusion in the right temporal lobe normalized after electroconvulsive therapy

DD: Delusional disorder; CT: Computerized tomography; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; rCBF: Regional cerebral blood flow; PET: Positron emission tomography. DaT: Striatal dopamine transporter; D2R: D2 receptor.

mediating factors in DD patients who are adherent to medication but nevertheless not responding helps clinicians by suggesting different ways (other than raising the dose) by which plasma levels can be increased, for instance via smoking cessation, changes in diet or drug regimes, or by the addition of adjunctive hormones.

DDs have been traditionally difficult to treat. Awareness of the moderators and mediators of treatment response can help to make recovery possible.

FUTURE DIRECTIONS

The identification of moderators and mediators of response in delusional disorders, which traditionally do not respond well to standard antipsychotic treatment, facilitates the development of personalized treatments. A better understanding of

these factors will help clinicians decide which form of treatment works best for which patient[60].

Several moderators of antipsychotic response in delusional disorder have been suggested: Gender, reproductive status, age and comorbid medical disorders, comorbid psychiatric disorders, baseline brain abnormalities, biochemical factors, genetics of both liver enzymes and neurochemical receptors in the brain[39,44,59]. In the future, randomized controlled trials will need to ascertain whether these or other factors do, indeed, moderate response in DD.

Future studies will also need to investigate potential mediating variables of antipsychotic response in DD, such as functional brain changes, antipsychotic plasma levels and estrogen and other hormone levels.

Delusional disorder may respond better to psychotherapeutic interventions than to medications. Moderators and mediators of cognitive behavioral therapies, for instance, will need to be investigated in the future.

All subcategories of DD may not respond in the same way to treatment. Currently, most studies have only researched the somatic subtype[48,49]. It is possible that patients with erotomania or delusional jealousy respond differently than those with delusional parasitosis – this question needs to be thoroughly examined.

The future will undoubtedly be able to overcome the problem of research sample availability of relatively rare conditions such as delusional disorders. Large international collaborations will almost certainly be part of the solution.

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ORIGINAL ARTICLE

Basic Study

Comparison of novel tools with traditional cognitive tests in detecting delirium in elderly medical patients

David J Meagher, Henry O'Connell, Maeve Leonard, Olugbenga Williams, Fahad Awan, Chris Exton, Michael Tenorio, Margaret O'Connor, Colum P Dunne, Walter Cullen, John McFarland, Dimitrios Adamis

ORCID number: David J Meagher (0000-0001-8324-8017).

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David J Meagher, Henry O'Connell, Maeve Leonard, Olugbenga Williams, Fahad Awan, Margaret O'Connor, Colum P Dunne, Walter Cullen, John McFarland, Dimitrios Adamis, Cognitive Impairment Research Group, Graduate Entry Medical School, University of Limerick, Limerick V94 YVHO, Ireland

Chris Exton, Michael Tenorio, Department of Computer Sciences, University of Limerick, Limerick V94 YVHO, Ireland

Walter Cullen, School of Medicine, University College Dublin, Dublin 4 D04 V1W8, Ireland

Dimitrios Adamis, Sligo Mental Health Services, Ballytivan, Sligo F91 CD34, Ireland

Corresponding author: David J Meagher, MD, PhD, Chairman, Professor, Head, Department of Psychiatry, Graduate Entry Medical School, University of Limerick, Limerick V94 YVHO, Ireland. david.meagher@ul.ie

Abstract

BACKGROUND

Efficient detection of delirium and comorbid delirium-dementia is a key diagnostic challenge. Development of new, efficient delirium-focused methods of cognitive assessment is a key challenge for improved detection of neurocognitive disorders in everyday clinical practice.

AIM

To compare the accuracy of two novel bedside tests of attention, vigilance and visuospatial function with conventional bedside cognitive tests in identifying delirium in older hospitalized patients.

METHODS

180 consecutive elderly medical inpatients (mean age 79.6 ± 7.2; 51% female) referred to a psychiatry for later life consultation-liaison service with delirium, dementia, comorbid delirium–dementia and cognitively intact controls. Participants were assessed cross-sectionally with conventional bedside cognitive tests [WORLD, Months Backward test (MBT), Spatial span, Vigilance A and B, Clock Drawing test and Interlocking Pentagons test] and two novel cognitive tests [Lighthouse test, Letter and Shape Drawing test (LSD)-4].

RESULTS

Neurocognitive diagnoses were delirium (n = 44), dementia (n = 30), comorbid delirium-dementia (n = 60) and no neurocognitive disorder (n = 46). All

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conventional tests had sensitivity of > 70% for delirium, with best overall accuracy for the Vigilance-B (78.3%), Vigilance-A (77.8%) and MBT (76.7%) tests. The sustained attention component of the Lighthouse test was the most distinguishing of delirium (sensitivity 84.6%; overall accuracy 75.6%). The LSD-4 had sensitivity of 74.0% and overall accuracy 74.4% for delirium identification. Combining tests allowed for enhanced sensitivity (> 90%) and overall accuracy (≥ 75%) with the highest overall accuracy for the combination of MBT-Vigilance A and the combined Vigilance A and B tests (both 78.3%). When analyses were repeated for those with dementia, there were similar findings with the MBT-Vigilance A the most accurate overall combination (80.0%). Combining the Lighthouse-SA with the LSD-4, a fail in either test had sensitivity for delirium of 91.4 with overall accuracy of 74.4%.

CONCLUSION
Bedside tests of attention, vigilance and visuospatial ability can help to distinguish neurocognitive disorders, including delirium, from other presentations. The Lighthouse test and the LSD-4 are novel tests with high accuracy for detecting delirium.

Key words: Visuospatial function; Attention; Vigilance; Letter and Shape Drawing test; Lighthouse test; Delirium; Dementia; Phenomenology; Assessment

Core tip: This study examines the accuracy of a range of conventional and novel bedside cognitive tests in identifying delirium amongst older medical patients within a general hospital setting. The novel tests (Letter and Shape Drawing test, and Lighthouse test) compare favourably with conventional tests and may be particularly useful by virtue of their capacity to provide highly consistent testing in real world practice.

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INTRODUCTION

Major neurocognitive disorders are linked to a variety of adverse outcomes in hospitalized elderly[1,2]. However, these disorders are under-detected in everyday practice, leading to avoidable morbidity and mortality, rendering more accurate and timely recognition a key healthcare target[3,4]. A major obstacle to improved management of neurocognitive difficulties is the lack of clarity regarding optimal approaches to bedside cognitive assessment[5].

Recent studies exploring the phenomenological profile of major neurocognitive disorders suggest that tests of attention, vigilance and visuospatial abilities have particular utility in distinguishing neurocognitive disorders because these domains are disproportionately affected in delirium[6-10]. The results of such studies have the potential to lead to identification of a "cognitive vital sign" for routine and systematic assessment of cognition at the bedside in everyday practice.

Traditional or conventional bedside tests of cognition can assist in identifying delirium-relevant cognitive disturbances. However, these tests were developed in the last century and predate the modern concept of delirium that has been widely accepted since Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980[11]. Among their limitations for assessing for delirium are that they are subject to "bottoming-out" effects because they are too difficult for many patients, who cannot meaningfully engage with testing procedures[12]. Moreover, although these tests are widely used, there is major disparity in how they are administered and interpreted. For example, Meagher *et al*[13] found marked inconsistency in use of the Months Backward test (MBT) with almost no evidence of similar scoring of test performance

across 22 clinical studies. Similarly, a review of 16 studies of the Clock Drawing Test (CDT) in delirium identified 11 different scoring methods[14]. As such, more systematized and reliable methods of cognitive testing are needed, either based upon existing tests or by developing novel approaches to testing that draw upon modern (*e.g.*, computer-assisted/smartphone) technologies.

To this end, the Cognitive Impairment Research Group at the University of Limerick developed two novel tests specifically for the purpose of detecting cognitive difficulties that characterize delirium: The Lighthouse test, which focuses on attention/vigilance and the Letter and Shape Drawing test (LSD-4), which focuses upon visuospatial abilities[15-17]. This study the accuracy of a series of commonly used conventional tests as well as these novel tests in the detection of delirium in a real world sample of older hospital medical patients. Specifically, the aims were to (1) compare performance on these different tests in identifying delirium in elderly inpatients with varying neurocognitive disorder profiles as well as those with normal cognition; (2) examine how they compare (both individually and in combination) in terms of their specificity, sensitivity, positive and negative predictive value in detecting delirium and comorbid delirium-dementia in older medical inpatients; and (3) explore how accuracy is impacted upon by comorbid dementia.

MATERIALS AND METHODS

Subjects and design

A cross-sectional study of cognitive performance was conducted in referrals to a consultation-liaison psychiatry service of patients with delirium, dementia, comorbid delirium-dementia, as well as comparison subjects with no neurocognitive diagnosis (NNCD). Consecutive cases with altered mental state were identified on daily rounds by the medical team and referred for assessment and diagnosis by the research team.

Assessments were conducted by raters (Leonard M, Awan F, O'Connell H, Williams O, Meagher DJ) specifically trained in the use of the tests included herein (see below) and to further enhance inter-rater reliability, ratings associated with any uncertainty were discussed and agreed by consensus between raters.

Patients were assessed during the usual working day and in the majority of cases the process of receiving referrals and responding meant that this occurred in the early afternoon when the anchors of the day are thought to be optimally active. The assessments were conducted at the bedside to mimic real world practice.

Delirium was diagnosed according to a cut-off score of ≥ 15 on the severity scale of the Delirium Rating Scale-Revised-98 (DRS-R98)[18] and/or presence of DSM IV criteria[19] based upon a full clinical assessment. This approach was used because it allows for high diagnostic specificity in populations that include substantial numbers of patients with comorbid dementia. Dementia was defined as a clear history of documented DSM-IV[19] dementia (based on all available information at the time of assessment including clinical case notes and collateral history from family and/or carers) *or* a short Informant Questionnaire on Cognitive Decline in the elderly (IQCODE) score of ≥ 3.5[20]. Comorbid delirium-dementia was defined as the presence of both disorders.

Each subject was assessed with a battery of nine conventional (Rater A) and 2 novel (Rater B) tests (see below). Standard cut off performances were used to apply a binary (pass/fail) for each test where a fail corresponded with evidence of clinically significant impairment. Assessors were not aware of the patients' formal neurocognitive diagnoses. The cognitive tests were conducted in a fixed sequence as described below.

Informed consent

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry into the study it was presumed that many might not be capable of giving informed written consent. Because of the non-invasive nature of the study, University Hospital Limerick Regional Ethics Committee approved (REC 100/12) an approach to establishing consent by virtue of augmenting patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical Research involving human subjects[21].

Assessments

Demographic data and medication at the time of the assessment were recorded. All available information from medical records and collateral history was used. Nursing staff were interviewed to assist rating of symptoms over the previous 24 h.

The DRS-R98[18] is designed for broad phenomenological assessment of delirium. It is a 16-item scale with 13 severity and 3 diagnostic items with high interrater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations. Each item is rated 0 (absent/normal) to 3 (severe impairment) with descriptions anchoring each severity level. Severity scale scores range from 0-39 with higher scores indicating more severe delirium. Delirium typically involves scores above 15 points (Severity scale) or 18 points (Total scale) when dementia is in the differential diagnosis.

The IQCODE-SF is a validated screening tool for detecting cognitive impairment. The short version of the IQCODE includes 16 items that rate cognitive change over time, each of which are rated by an informant on a 5 point Likert scale. The total score divided by the number of questions provides a mean item score where ratings ≥ 3.5 are considered indicative of longstanding cognitive difficulties and dementia[20].

Cognitive testing

WORLD backwards: The WORLD backwards test was applied according to the Mini–Mental State Examination[22]. Each participant was asked to spell WORLD backwards. Patients who self-corrected their own mistakes without prompting when spelling WORLD backwards were not penalized. Failure to correctly recite all five letters is considered to equate with clinically significant inattention (and thus a failed test).

MBT: In this test, the participant was asked to recite the months of the year in reverse order starting from December. Test duration was a maximum of 90 seconds at which point the subject's best performance was noted. Scoring in subjects over age 60 is that failure to reach July without more than one error of omission equates with clinically significant inattention (and thus a failed test)[13].

Spatial span forwards: This was conducted according to the description in the Cognitive test for delirium (CTD)[23]. The Spatial span forwards is a visual form of the digit span forwards. The subject is asked to copy the examiner in touching squares on a card (A5 size with 8 cm × 1 cm red squares). Each square represents a number and the test on each occasion requires that the squares corresponding to the digit span code are tapped at one second intervals. Two trials are conducted and the best performance is used. Failure to correctly complete a sequence of 5 or more numbers is considered to equate with clinically significant inattention (and thus a failed test).

Spatial span backwards: Similarly, the Spatial span backwards uses squares (blue) that are repeated in reverse order to that indicated by the assessor. Two trials are conducted and the best performance is used. Failure to correctly complete a sequence of three or more numbers is considered to equate with clinically significant inattention (and thus a failed test).This was also conducted according to the description in the original description of the CTD[23].

Vigilance A test: The vigilance "A" test was also derived from the CTD scale[23]. A list of 29 letters with the letter "A" included on 11 occasions was presented to the patient and they were asked to indicate each time the letter "A" was mentioned. Scores are calculated by subtracting commissions from correct responses (scored double) and rated as unable to engage with the test (0), score 1-9 (1), score 10-18 (2), score 19-26 (3), score > 27 (4). For the purposes of a binary (pass/fail) cutoff, we used failure to score > 27 to equate with significantly impaired vigilant (or sustained) attention.

Vigilance B test: This is similar to the vigilance A test except that there are two required letters ("C" and "E"). Scores are calculated by subtracting commissions from correct responses (scored double) and rated as unable to engage with the test (0), score 1-9 (1), score 10-18 (2), score 19-26 (3), score > 27 (4). For the purposes of a binary (pass/fail) cutoff, we used failure to score ≥ 19 to equate with significantly impaired vigilant (or sustained) attention[23].

Global assessment of visuospatial abilities: Visuospatial ability was rated according to a four point scale based upon DRS-R98 item 13[24] using both patient and collateral sources regarding ability to perceive differences in shape and distance as well as practical abilities such as navigating the ward environment and response to specific probes of describing how to get somewhere (*e.g*., bathroom), recognising shapes ("*what shape is the window*?") and differences in distances ("*which is closer the window or the hallway*?"). Patients with moderate or greater impairment in terms of responses to probes and/or reported need for redirection to keep from getting lost in the environment or difficulty locating familiar objects in immediate environment were considered to have pathological impairment of visuospatial abilities (failed test).

Intersecting Pentagons test: This geometric copying test is derived from the original Bender Gestalt test[25].The subject is presented with a copy of two intersecting pentagons drawn at angles to one another producing a diamond shape where they overlap. The subject is requested to copy the design on the blank half of the page. For scoring, we applied the six-point hierarchical scoring scale where 6 represents a perfect reproduction and 1 represents the poorest effort with scores < 4 equated with a failed performance[26].

CDT: The CDT examines visuospatial abilities as well as receptive language, numerical knowledge, working memory, and executive functions. It is widely used in geriatric practice as a cognitive scan. In this study, subjects were provided with a pre-drawn circle onto which the participant was requested to place all the numbers and the large and small hands on the clock face to show the time "ten past eleven". We used the scoring method of Sunderland *et al*[27] (1989) rating performance from 0 to 10 according to spatial representation of the numbers and hands of the clock. A score of < 6 equates with a failed performance.

LSD: The LSD is a novel test designed to emphasize visuospatial abilities[15]. It consists of a series of 4 designs that link 1cm spheres arranged in increasingly complex grids that the subject copies to an adjacent blank grid. The complexity ranges from very simple (copying an "X" on a 3 by 3 grid which is thought to assess awareness and basic understanding of the test procedures as well as physical ability to engage with testing) to increasingly more complex figures (*e.g*., on a 6 by 6 grid) designed to challenge those with higher levels of cognitive ability (Figure 1). A correct performance requires that all relevant spheres are connected to complete the required shape. Omissions (but not commissions) are rated as errors. Subjects are permitted a single trial of each of the 4 items. Each item is scored 0 or 1 depending on whether all target zones on the grid are completed, allowing for a total score ranging from 0-4. Scores less than 3 are considered to reflect clinically significant impairment of performance and equate with a failed performance[17].The test typically takes 1-2 min to complete. The test can be presented either as pen and paper or digitalised formats. The latter can allow for delivery of a more versatile test (that can be readily adapted to individual characteristics such as impaired visual or motor skills)[16]. The LSD thus provides a brief and easily interpreted bedside test of visuospatial function.

The Lighthouse test: The Lighthouse test was developed by the Cognitive Impairment Research Group as an objective assessment of awareness, focused and sustained attention. It is administered using an Android smartphone and involves presentation of an image of a flashing lighthouse on a standard screen (3" × 5")(Figure 2). The test has 3 main sections; (1) assessing whether the subject recognizes the lighthouse as such; (2) assessing the subject's capacity to focus attention to describe the number of times the lighthouse flashes (×3 sequences; 4, 3, 5). Subjects are requested to identify the number of flashes; and (3) testing the capacity to sustain attention to count sequences of flashes (×3) (*i.e*. 4-3-2, 3-2-5, 2-4-3) that last 12-15 seconds in duration. Again, subjects are requested to identify the total number of flashes.

Statistical analyses

Statistical analysis was conducted using SPSS-19[28]. Continuous data are presenting as means plus standard deviation. Categorical data are presented as counts and percentages. When multiple comparisons were conducted (ANOVA) the Bonferroni correction for multiple comparisons was used. The accuracy of tests of cognition (and their combinations), sensitivity and specificity as well as positive and negative likelihood ratio, Positive Predictive Value, and Negative Predictive Value were calculated, with confidence intervals testing significance at 95%. Post hoc power calculation for the main research question (the ability of LSD-4 to detect delirium against no delirium) was performed by using the G*Power v3.1.2. software. With a = 0.05, effect size = 0.5 and df = 3, a sample size of 180 indicated power of almost 1 (0.99).

RESULTS

A total of 180 patients were assessed [mean age 79.6 ± 7.2; 91 (51%) female]. The frequencies of neurocognitive diagnoses were; delirium (n = 44), dementia (n = 30), comorbid delirium-dementia (n = 60) and NNCD (n = 46). Demographic, medication and general clinical data for these four groups are shown in Table 1. There were no significant differences between the four groups in respect of age, gender distribution

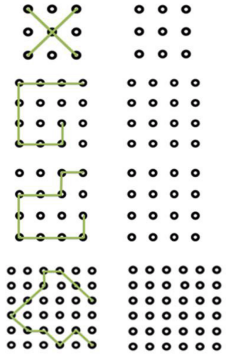

Figure 1 The Letter and Shape Drawing test.

or number of medications received, while psychotropic medication use was higher in those with any neurocognitive diagnosis.

Table 1 compares mean scores for the four groups for the DRS-R98 and IQ-CODE. Both delirium groups were more impaired than the dementia and NNCD groups on total scores for the DRS-R98. For the short IQCODE mean scores both dementia groups scored well above the suggested cut-off score and higher than the delirium-only and NNCD groups.

Table 2 and Table 3 show the performance on the conventional cognitive tests for the four neurocognitive groups, including accuracy for delirium diagnosis in the overall group as well as within the group with diagnosed dementia (n = 90) (Figure 3). Of note, all tests of attention and vigilance had a sensitivity for delirium of > 70% but, in terms of overall accuracy, the Vigilance A and B and MBT were the best performing tests. The tests of visuospatial ability were less sensitive to delirium, with the global assessment of visuospatial abilities (GVS) performing slightly better than the CDT and Intersecting Pentagons test (IPT).

Tables 4 and 5 show the performance on the three components of the Lighthouse test and the LSD-4. Overall, only one third of patients were able to identify the lighthouse correctly, with one third unable to describe it while the other third described it in a variety of ways including as "a lampost", "a traffic light", "a chimney" and "the Eiffel tower". The identification and focused attention components of the Lighthouse had substantially lower sensitivity and overall accuracy compared to the sustained attention (LH-SA) element and when combined with the LH-SA did not substantially add to its accuracy. The LH-SA alone compared favourably with the conventional tests of attention. Similarly, the LSD-4 compared favourably with the conventional tests of visuospatial abilities in terms of sensitivity and overall accuracy for detecting delirium, especially in those patients with dementia.

We examined the accuracy of various combinations of the conventional tests and the LH-SA/LSD in detecting delirium in the overall group and in the dementia group. The better performing combinations (*i.e*. those with sensitivity > 90% and overall accuracy ≥ 75%) are shown in Table 6. For the overall group, the MBT-GVS and the combined Vigilance A and B tests were the most sensitive combination (93.3%), while the MBT-Vigilance A and the combined Vigilance A and B tests had the highest overall accuracy (78.3%), with the LH-SA/LSD combination demonstrating similar levels of accuracy. When these analyses were repeated for the population with DSM-IV defined dementia, there were similar findings with the MBT-Vigilance A the most accurate overall combination (80.0%), followed by the LH-SA/LSD and combined Vigilance A and B tests (both 77.8%).

DISCUSSION

Performance on bedside tests of attention and visuospatial ability was compared in elderly medical inpatients with a variety of neurocognitive diagnoses and also with normal cognition. Participants were carefully diagnosed using a full neuropsychiatric assessment with well-validated instruments. Patients with active delirium (both with and without comorbid dementia) were distinguished from patients with dementia-alone in respect of performance on simple bedside tests. Moreover, combining tests of attention with visuospatial ability allowed for greater accuracy of delirium detection. Two novel cognitive tests, the LSD test both compare favourably with conventional tests and may offer advantages for use in everyday practice.

Figure 2 The Lighthouse test.

One important implication of this study is that formal testing using any conventional test can assist delirium detection – all tests were quite sensitive to the presence of delirium but the Vigilance A and B and the MBT were the best individual tests in terms of overall accuracy. This is in keeping with previous studies that have included direct comparisons of cognitive tests in the identification of delirium in elderly general hospital inpatients and which have consistently found that bedside tests of attention (including sustained or vigilant attention) are sensitive to the presence of delirium, with the Months Backward Test emerging as the most versatile individual test[10,29-33].

The Lighthouse is a novel test that includes three components designed to assess awareness/comprehension, focused attention and sustained attention. Somewhat surprisingly, only one third of subjects could correctly identify the Lighthouse thus, raising the possibility that the visual graphics are suboptimal. Although the ID and FA components did not individually add to the accuracy of the Lighthouse test for delirium, the testing procedures involved engaging with the stimulus and simple testing and may thus have optimised arousal and attention for the sustained attention component.

The LSD performed well in terms of delirium detection, demonstrating greater accuracy than the conventional visuospatial bedside tests (CDT and IPT), especially in those patients with dementia. Previous work has emphasised visuospatial function as a cognitive function that, along with attention, is particularly affected in delirium[6-10]. However, other work suggests that conventional tests such as the CDT lack specificity for delirium compared to dementia[14,32,34]. In contrast, the LSD which has been designed with the aim of optimising delirium-relevance, evidenced better specificity for delirium.

Efforts to identify optimal bedside cognitive testing for delirium monitoring should recognise that combining two tests that focus upon different aspects of cognition that are impaired in delirium can enhance accuracy of testing as well as inform delirium diagnosis which requires evidence of generalised disturbance to brain function. This should include impaired attention with deficits in at least one other cognitive domain[35] - visuospatial functioning offers a suitable second domain. In terms of accuracy, this work suggests that combining two tests can achieve > 90% sensitivity with high overall test accuracy. Combining the MBT with the Vigilance-A test is a particularly useful approach using conventional tests, while the combination of the LSD-4 with the sustained attention component of the Lighthouse test offers a novel approach that has similar accuracy. The latter has the advantage of being delivered by smartphone/tablet technology which can allow for enhanced consistency and reliability in test administration and interpretation. Moreover, digital technology offers the prospect of developing testing procedures that can be readily adapted according to individual patient characteristics such as visual acuity, frailty and motor dexterity – for example by altering the dimensions of presented material and/or the size of target zones on the LSD-4.

The LSD-4 and the Lighthouse are designed to emphasize consistency of administration and ease of interpretation. The methods applied in this study allowed for highly consistent administration procedures and detailed scoring systems that are not typically applied in everyday practice when using conventional bedside tests. Recent reviews[13,14] emphasize that conventional tools such as the MBT and the CDT are subject to considerable variability in use, with a lack of consensus as to optimal methods of administration and interpretation. As such, the accuracy of the conventional tests is likely to be lower in real world use. In contrast, the Lighthouse

Table 1 Demographic and clinical data for the total group and four neurocognitive groups (mean + SD)

	Total group (*n* = 180)	Delirium (*n* = 44)	Comorbid delirium-dementia (*n* = 60)	Dementia (*n* = 30)	No neurocognitive disorder (*n* = 46)
Female (%)	51%	53%	56%	37%	48%
Age	79.6 ± 7.2	77.7 ± 8.4	80.1 ± 7.0	81.8 ± 4.6	79.3 ± 7.5
Total number of medications	10.1 ± 4.7	10.0 ± 4.2	10.3 ± 5.0	9.7 ± 4.4	10.3 ± 5.1
Number of psychotropics[2]	1.7 ± 1.6	1.9 ± 1.6	2.2 ± 1.7	1.7 ± 1.6	0.8 ± 1.1
DRS-R98 total[12]	17.0 ± 9.2	22.9 ± 5.7	24.0 ± 6.0	10.9 ± 4.4	6.5 ± 3.3
Short IQCODE[3]	3.7 ± 0.7	3.1 ± 0.1	4.4 ± 0.5	4.0 ± 0.5	3.1 ± 0.1

[1]Delirium and comorbid delirium-dementia > dementia at $P < 0.001$.
[2]Delirium-only, dementia-only and comorbid delirium-dementia groups > no neurocognitive diagnosis (NNCD) at $P < 0.001$.
[3]Dementia and comorbid delirium-dementia groups > delirium and NNCD groups at $P < 0.001$. DRS-R98: Delirium Rating Scale-Revised-98; IQCODE: Informant Questionnaire on Cognitive Decline in the elderly.

test and the LSD-4 are more likely to maintain the accuracy evident herein due to their presentation in computerized format which enhances consistency of delivery and scoring and which may be associated with relatively less reduction in accuracy when used in everyday practice. In addition, we expect that the Lighthouse and LSD will be less subject to language-related inaccuracies than many other tests because they do not emphasize verbal skills. Future work can examine these issues, including the relative accuracy of computerized forms.

The combination of simple tests can allow for rapid and efficient assessment of delirium-relevant cognitive domains and achieved a sensitivity of almost 90% for delirium presence with these cross-sectional assessment methods. Serial monitoring of performance on these tests as a "cognitive vital sign" could allow for highly consistent detection of delirium in real world practice. Moreover, presentation in computerized formats could make for highly systematized assessment procedures that, given the modest specificity of 55%, would ideally be enhanced by a second phase of assessment for patients who identify as positive. This two-step approach to delirium detection is increasingly advocated as an effective means of improving detection rates in everyday clinical practice[5,36]. It is important to note that although identifying cognitive impairment is central to delirium diagnosis, actual diagnosis requires that the timing (relatively acute onset) and context (a deterioration from usual baseline, not better explained by another neuropsychiatric condition and due to a physical etiology) also be determined. Tools such as the confusion assessment method[37] and DRS-R98[18] incorporate these additional considerations to allow for formal diagnosis. Ultimately, systematized cognitive testing is key to delirium screening efforts and can also be used to support the cognitive assessment that is inherent to formal diagnosis. Psychometric data to guide the choice of test in particular settings is relatively lacking but ultimately the choice of cognitive testing tool is determined by a variety of factors that relate to patient, tester and other resource issues that are particular to the healthcare environment. Further work exploring the impact of these factors on the efficiency of providing cognitive-friendly healthcare is needed to guide choice of testing methods across settings.

Study limitations

This work has some notable shortcomings which include (1) We studied consecutive referrals to a consultation-liaison service for assessment of neuropsychiatric status. As such, these patients are likely to have a heightened symptom burden and are not representative of elderly inpatients in general; (2) We applied binary cut off ratings for each of the tests based upon best convention but for many tests a clear and consistently agreed pass/fail distinction is lacking; (3) We used a fixed order for presentation of the tests which may have influenced performance due to changing levels of arousal during the testing process and with the competing effects of practice versus fatigue[38]; and (4) We did not specify the stage or primary cause of dementia or take account of clinical subtypes of delirium (*i.e*. hypoactive, hyperactive and mixed motor subtype) although evidence indicates that neurocognitive disturbance varies across dementia types and severity[39].

Implications

Improved identification of major neurocognitive disorders is a key healthcare

Table 2 Performance on the Conventional bedside cognitive tests for the overall population and for each of the neurocognitive diagnostic groups (number completing correctly and %)

	Overall group (*n* = 180)	Delirium (*n* = 44)	Comorbid delirium-dementia (*n* = 60)	Dementia (*n* = 30)	NNCD (*n* = 46)
World backwards test	42 (23)	6 (14)	5 (8)	6 (20)	25 (54)
Months backwards test	74 (41)	12 (28)	8 (13)	20 (66)	34 (74)
Spatial span forwards	68 (38)	14 (32)	12 (20)	13 (43)	29 (63)
Spatial span backwards	67 (37)	15 (34)	8 (13)	15 (50)	29 (63)
Vigilance A test	88 (49)	16 (36)	10 (17)	23 (77)	39 (85)
Vigilance B test	49 (27)	3 (7)	3 (5)	13 (43)	30 (65)
Global visuospatial test	72 (40)	9 (20)	15 (25)	12 (40)	37 (80)
Clock drawing test	78 (43)	16 (36)	13 (22)	14 (47)	35 (76)
Interlocking pentagons test	87 (48)	17 (39)	14 (23)	18 (60)	38 (83)

NNCD: No neurocognitive diagnosis.

challenge. In particular, accurate and consistent detection of delirium is a priority because evidence indicates that more than half of cases are missed or detected late in everyday practice, with implications for morbidity, length of stay in hospital and mortality. A fundamental factor in enhancing recognition rates is to identify simple and brief methods for establishing the presence of clinically significant cognitive impairment at the bedside. Although both delirium and dementia involve generalised disturbance of cognitive function, delirium can be distinguished by virtue of the disproportionate impairment of attention and visuospatial ability. These cognitive domains can be readily assessed in everyday clinical practice using simple bedside tests. Both the Lighthouse and the LSD-4 provide accurate and delirium-oriented means of assessing cognitive function in delirium and in combination achieve a sensitivity of over 90% for delirium detection. Their impact upon delirium detection in everyday practice warrants further study as we seek to develop more efficient delirium monitoring in everyday practice.

Table 3 Accuracy of conventional bedside tests of cognition for delirium diagnosis in the overall population (*n* = 180) and for those with dementia (*n* = 90)

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Overall accuracy (95%CI)
Overall population (*n* = 180)					
WORLD	89.4% (81.9–94.6)	40.8% (29.7–52.7)	67.4% (62.9-71.6)	73.8% (60.2-84.0)	68.9% (61.6-75.6)
MBT	80.8% (71.9-87.4)	71.1% (59.5-80.9)	79.3% (72.6-84.6)	73.0% (64.0-80.4)	76.7% (69.8-82.6)
SSF	75.0% (65.6-83.0)	55.3% (43.4-67.0)	69.6% (64.0-75.1)	61.8% (52.3-70.5)	66.7% (59.3-73.5)
SSB	77.9% (68.7-85.4)	57.9% (46.0-69.1)	71.7% (65.6-77.1)	65.7% (56.0-74.2)	69.4% (62.2-76.1)
Vigilance A	75.0% (65.6-83.0)	81.6% (71.0-89.6)	84.8% (77.4-90.1)	70.5% (62.7-77.2)	77.8% (71.0-83.6)
Vigilance B	94.2% (87.9-97.9)	56.6% (44.7-67.9)	74.8% (69.6-79.4)	87.8% (76.3-94.1)	78.3% (71.6-84.1)
GVS	76.9% (67.6-84.6)	63.2% (51.3-73.9)	74.1% (67.6-79.6)	66.7% (57.5-74.7)	71.1% (63.9-77.6)
CDT	72.1% (62.5-80.5)	64.5% (52.7-75.1)	73.5% (66.7-79.4)	62.8% (54.3-70.6)	68.9% (61.6-75.6)
IPT	70.2% (60.4-78.8)	73.7% (62.3-83.1)	78.5% (71.1-84.4)	64.4% (56.6-71.4)	71.7% (64.5-78.1)
Dementia population (*n* = 90)					
WORLD	91.7% (81.6-97.2)	20.0% (7.7-38.6)	69.6% (65.4-73.6)	54.6% (28.5-78.3)	67.8% (57.1-77.3)
MBT	86.7% (75.4-94.1)	66.7% (47.2-82.7)	83.9% (75.6-89.7)	71.4% (55.6-83.3)	80.0% (70.3-87.7)
SSF	80.0% (67.7-89.2)	43.3% (25.5-62.6)	73.9% (66.8-79.8)	52.0% (36.1-67.5)	67.8% (57.1-77.3)
SSB	86.7% (75.4-94.1)	50.0% (31.3-68.7)	77.6% (70.5-83.4)	65.2% (47.3-79.7)	74.4% (64.2-83.1)
Vigilance A	83.3% (71.5-91.7)	76.7% (57.7-90.1)	87.7% (78.1-93.2)	69.7% (55.8-80.7)	81.1% (71.5-88.6)
Vigilance B	95.0% (86.1-99.0)	43.3% (25.5-62.6)	77.0% (70.9-82.2)	81.3% (57.2-93.4)	77.8% (67.8-85.9)
GVS	75.0% (62.1-85.3)	40.0% (22.7-59.4)	71.4% (64.3-77.6)	44.4% (30.1-59.8)	63.3% (52.5-73.3)
CDT	78.3% (65.8-87.9)	46.7% (28.3 -65.7)	74.6% (67.2-80.8)	51.9% (36.8-66.6)	67.8% (57.1-77.3)
IPT	76.7% (64.0-86.6)	60.0% (40.6-77.3)	79.3% (70.8-85.9)	56.3% (42.7-68.9)	71.1% (60.6-80.2)

MBT: Months Backward test; SSF: Spatial span forwards; SSB: Spatial span backwards; GVS: Global assessment of visuospatial abilities; CDT: Clock Drawing test; IPT: Intersecting Pentagons test.

Table 4 Performance on Letter and Shape Drawing test and Lighthouse components (number completing correctly and %)

	Overall group (*n* = 180)	Delirium (*n* = 44)	Comorbid delirium-dementia (*n* = 60)	Dementia (*n* = 30)	NNCD (*n* = 46)
LH-identification	60 (33)	16 (36)	11 (18)	10 (33)	24 (52)
LH-FA	83 (46)	18 (41)	14 (23)	20 (66)	31 (67)
LH-SA	64 (36)	9 (21)	7 (12)	18 (60)	30 (65)
LSD	84 (48)	17 (39)	10 (17)	19 (63)	38 (83)

NNCD: No neurocognitive diagnosis; LSD: Letter and Shape Drawing test; LH: Lighthouse.

Table 5 Accuracy of Lighthouse components and Letter and Shape Drawing test for delirium diagnosis in the overall population (*n* = 180) and in those with dementia (*n* = 90)

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Overall accuracy (95%CI)
Overall population (*n* = 180)					
LH-ID	74.0% (64.5-82.1)	44.7% (33.3-6.6)	64.7% (59.2-69.8)	55.7% (45.5- 65.5)	61.7% (54.1-68.8)
LH-FA	69.2% (59.4-77.9)	67.1% (55.4-77.5)	74.2% (67.1-80.3)	61.5% (53.4- 68.9)	68.3% (61.0-75.1)
LH-SA	84.6% (76.2-90.9)	63.2% (51.3-73.9)	75.9% (69.8-81.0)	75.0% (64.9-82.9)	75.6% (68.6-81.6)
LSD	74.0% (64.5-82.1)	75.0% (63.7-84.2)	80.2% (73.0-85.9)	67.9% (59.8-75.0)	74.4% (67.4-80.6)
Dementia population (*n* = 90)					
LH-ID	81.7% (69.6-90.5)	33.3% (17.3-52.8)	71.0% (64.9-76.4)	47.6% (30.3-65.5)	65.6% (54.8-75.3)

LH-FA	76.7% (64.0-86.6)	66.7% (47.2-82.7)	82.1% (73.1-88.6)	58.8% (45.8-70.7)	73.3% (63.0-82.1)
LH-SA	88.3% (77.4-95.2)	60.0% (40.6-77.3)	81.5% (73.8-87.4)	72.0% (54.7-84.6)	78.9% (69.0-86.8)
LSD	83.3% (71.5-91.7)	63.3 % (43.9-80.1)	82.0% (73.7-88.1)	65.5% (50.4- 78.1)	76.7% (66.6- 84.9)

LSD: Letter and Shape Drawing test; LH: Lighthouse.

Table 6 Most accurate combinations of conventional bedside tests and the combined sustained attention of Lighthouse/Letter and Shape Drawing Test

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Overall accuracy (95%CI)
Overall population (*n* = 180)					
MBT plus GVS	93.3% (86.6-97.3)	48.7% (37.0-60.4)	71.3% (66.5-75.7)	84.1% (71.4-91.8)	74.4% (67.4-80.6)
Vig A plus GVS	92.3% (85.4-96.6)	57.9% (46.0-69.1)	75.0% (69.6-79.7)	84.6% (73.3-91.7)	77.8% (71.0-83.6)
Vig A plus Vig B	93.3% (86.6-97.3)	57.9% (46.0-69.1)	75.2% (69.9-79.9)	86.3% (75.0-93.0)	78.3% (71.6-84.1)
MBT plus Vig A	90.4% (83.0-95.3)	61.8 % (50.0-72.8)	76.4% (70.7-81.3)	82.5% (71.8- 89.7)	78.3% (71.6- 84.1)
LSD-4 plus Lighthouse-SA	91.4% (84.2-96.0)	51.3 % (39.6-63.0)	72.0 % (66.9-76.5)	81.3% (69.1-89.4)	74.4% (67.4-80.6)
Dementia population (*n* = 90)					
MBT plus GVS	93.3% (83.8-98.1)	30.0% (14.7-49.4)	72.7% (67.6-77.3)	69.2% 43.0-87.0)	72.2% (61.8-81.2)
Vig A plus GVS	95.0% (86.1-98.9)	33.3% (17.3- 52.8)	74.0% (68.7- 78.7)	76.9% (49.8-91.8)	74.4% (64.2- 83.1)
Vig A plus Vig B	95.0% (86.1-98.9)	43.3% (25.5-62.6)	77.0% (70.9-82.2)	81.3 (57.2-93.4)	77.8% (67.8-85.9)
MBT plus Vig A	95.0% (86.1-98.9)	50.0% (31.3-68.7)	79.2% (72.6-84.5)	83.3% (61.1-94.1)	80.0% (70.3-87.7)
LSD-4 plus LH-SA	95.0% (86.1-99.0)	43.3% (25.5-62.6)	77.0% (70.9-82.2)	81.3% (57.2-93.4)	77.8% (67.8-85.9)

MBT: Months Backward test; GVS: Global assessment of visuospatial abilities; CDT: Clock Drawing test; IPT: Intersecting Pentagons test; LH: Lighthouse; LSD: Letter and Shape Drawing test.

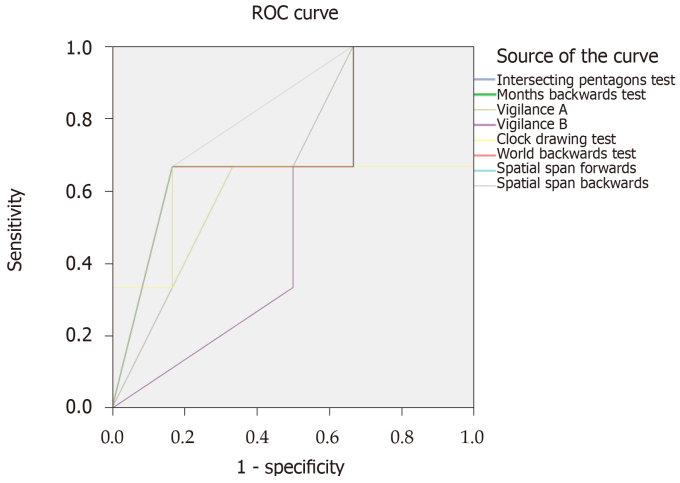

Figure 3 Receiver operating characteristic analyses depicting the accuracy of conventional bedside tests of cognition for delirium diagnosis in the overall population (*n* = 180). ROC: Receiver operating characteristic analyses.

ARTICLE HIGHLIGHTS

Research background

Efficient detection of delirium and comorbid delirium-dementia is a key diagnostic challenge. It's a key challenge of developing of new, efficient delirium-focused methods of cognitive assessment for improved detection of neurocognitive disorders in everyday clinical practice.

Research motivation

This study the accuracy of a series of commonly used conventional tests as well as these novel

tests in the detection of delirium in a real world sample of older hospital medical patients.

Research objectives
The authors aimed to compare the accuracy of two novel bedside tests of attention, vigilance and visuospatial function with conventional bedside cognitive tests in identifying delirium in older hospitalized patients.

Research methods
This cognitive performance study was conducted in referrals to a consultation-liaison psychiatry service of patients with delirium, dementia, comorbid delirium-dementia, as well as comparison subjects with no neurocognitive diagnosis. Altered mental state consecutive cases were identified on daily rounds.

Research results
All conventional tests had sensitivity of > 70% for delirium, with best overall accuracy for the Vigilance-B, Vigilance-A and Months Backward tests. The sustained attention component of the Lighthouse Test was the most distinguishing of delirium.

Research conclusions
Vigilance and visuospatial ability can help to distinguish neurocognitive disorders, including delirium, from other presentations. The Lighthouse test, Letter and Shape Drawing test are novel tests with high accuracy for detecting delirium.

Research perspectives
Lighthouse test, Letter and Shape Drawing tests' impact upon delirium detection in everyday practice warrants further study.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for depression in patients with chronic obstructive pulmonary disease

Hui-Ming Yao, Ren-Sen Xiao, Ping-Liang Cao, Xiao-Lei Wang, Wei Zuo, Wei Zhang

ORCID number: Hui-Ming Yao (0000-0003-0067-2379); Ren-Sen Xiao (0000-0003-1358-2217); Ping-Liang Cao (0000-0002-1429-7752); Xiao-Lei Wang (0000-0002-9079-235X); Wei Zuo (0000-0003-2391-1678); Wei Zhang (0000-0002-6459-7614).

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Hui-Ming Yao, Ren-Sen Xiao, Wei Zuo, Wei Zhang, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

Ping-Liang Cao, Xiao-Lei Wang, Second Department of Cardiovascular Medicine, Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Nanchang 330006, Jiangxi Province, China

Corresponding author: Wei Zhang, MD, PhD, Professor, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanchang University, No. 17 Yongwaizheng Street, Donghu District, Nanchang 330006, Jiangxi Province, China. weizhang1963@163.com

Abstract

BACKGROUND

The prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) ranges from 10% to 42%, but the diagnosis of depression in patients with COPD is often unrecognized and untreated. Unrecognized depression has major implications for compliance with medical treatment, prolonged lengths of stay, increased frequency of hospital admissions, and increased consultations with primary care physicians. Many studies have attempted to identify risk factors for progression, prognosis and response to therapy in patients with depression. However, few studies have examined the risk factors for depression in patients with COPD, and some results remain controversial.

AIM

To identify the potential risk factors to define patients with COPD who are at "high risk" of depression.

METHODS

The clinical data of 293 patients with COPD were reviewed from January 2017 to December 2018. The correlations between demographics, clinical characteristics and depression were analyzed. The risk factors for depression in patients with COPD were identified by multivariate logistic regression analysis. The cutoff value, sensitivity and specificity of the independent correlation factors were calculated with a receiver operating characteristic curve.

RESULTS

Of the 293 patients included, 65 (22.18%) individuals were identified to have

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depression. Significant differences were detected between patients with and without depression in terms of body mass index (BMI), forced expiratory volume in 1 s (FEV1), and COPD assessment test (CAT) score (all $P < 0.05$). Low BMI, low FEV1, and high CAT were independent risk factors for depression in patients with COPD and the cutoff values of BMI, FEV1, and CAT scores were 21.373 kg/m^2, 0.855 L and 12.5, respectively.

CONCLUSION
Low BMI, low FEV1, and high CAT score were identified as independent risk factors for depression in patients with COPD.

Key words: Depression; Chronic obstructive pulmonary disease; Body mass index; Forced expiratory volume in 1 second; Chronic obstructive pulmonary disease assessment test scores; Risk factors

Core tip: The prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) ranges from 10% to 42%. However, the risk factors for depression in patients with COPD have been examined in few studies, and some results remain controversial. The purpose of the current study is to investigate the correlation between clinical parameters and the symptoms of depression, and to identify independent risk factors to define patients with COPD who are at "high risk" of depression. Low body mass index, low forced expiratory volume in 1 s and high chronic obstructive pulmonary disease assessment test score were identified as independent risk factors for depression in patients with COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity with an economic and social burden that is both substantial and increasing[1,2]. COPD is currently the fourth-leading cause of death and is expected to surpass stroke within the next decade to become the third leading cause of death[3]. Because medical treatments have made limited inroads, patients with COPD experience recurring acute exacerbations, frequent hospital admissions, poor survival, and impaired physical functioning and quality of life[4-6]. The reported prevalence of depression in patients with COPD ranges from 10% to 42%, a proportion much higher than that in the general population[7,8]. Although evidence suggests that certain interventions such as antidepressants, pulmonary rehabilitation, and counseling may improve health outcomes, the diagnosis of depression in patients with COPD is often unrecognized and untreated in primary and specialty care[9,10]. Unrecognized depression has major implications for compliance with medical treatment, prolonged lengths of stay, increased frequency of hospital admissions, and increased consultations with primary care physicians, all of which could decrease quality of life in patients[11,12]. The Hospital Anxiety and Depression Rating Scale (HADS) is one of the most commonly used instruments for depression in the literature[13]. The HADS is subjective and is intended for anxiety and depression screening of patients in general hospitals. It is a 14-item self-report questionnaire comprising two subscales: HADS-anxiety subscale (HADS-A) and HADS-depression subscale (HADS-D), which are scored from 0 to 21 to detect the presence of symptoms of anxiety and depression. The scale is designed for use in patients with physical illness; therefore, none of the items include somatic symptoms of depression or anxiety. Although the screening tool is widely available, it cannot provide enough information for early diagnosis.

Many studies have attempted to identify risk factors for progression, prognosis and response to therapy in patients with depression[10,14]. However, few studies have

examined the risk factors for depression in patients with COPD, and some results remain controversial[14]. Thus, further research is needed to detect depression in patients with COPD for early diagnosis and treatment. The purpose of the current study is to investigate the correlation between clinical parameters and the symptoms of depression, and to identify independent risk factors to define patients with COPD at "high risk" of depression.

MATERIALS AND METHODS

Patients

This was a retrospective study with no involvement in clinical or animal research. The requirement for ethical permission was waived according to the statements regarding the application of ethical permission by the Ethical Committee of the First Affiliated Hospital of Nanchang University. A retrospective study was conducted and a series of consecutive patients newly diagnosed with COPD between January 2017 and December 2018 were included in this study. COPD diagnosis was made according to the Global Initiative for Chronic Obstructive Lung Disease[15]. We studied the files of the patients carefully to ensure that all factors that might affect the outcome of the assessment were considered when the patients were included in this study. Standard treatment was given to each patient. The diagnosis of depression mainly relied on the HADS-D, and the HADS scale was carried out by an experienced psychiatrist when the patients were stable. A review and meta-analysis of studies reported that a cutoff of 8 or more on the HADS-D produced a sensitivity of 0.82 (95%CI: 0.73–80) and a specificity of 0.74 (95%CI: 0.60–0.84) for depressive disorders[16]. Therefore, we used a cutoff of 8 or more on the HADS-D to dichotomize the HADS-D scores for the purposes of the regression analyses. All the patients were inpatients and were recruited from medical hospital wards.

Patients presenting with confounders of comorbidity or other conditions that could potentially affect the evaluation of risk factors, such as dependent care living situations, life expectancy of less than six months, trouble with eye-sight, and diagnosis of dementia or Alzheimer's disease, were excluded from this study. For patients already diagnosed with depressive disorder or history of such disorder, only those with depression associated with COPD were included in this study and the judgments were made by an experienced psychiatrist. Patients receiving antidepressants, anxiolytics or other psychiatric medication were excluded in order to avoid introducing bias as treatment options might have a potential impact on HADS scores.

Data collection

The demographics and clinical characteristics of the patients in this retrospective study included age, gender, marital status, household income, smoking status, duration of respiratory symptoms, number of acute exacerbations in the previous year, body mass index (BMI, kg/m^2), forced expiratory volume in 1 s (FEV1, L), and Modified British Medical Research Council Questionnaire (mMRC) and Chronic Obstructive Pulmonary Disease assessment test (CAT) scores at the time of the primary diagnosis of COPD. The correlation between clinical parameters and depression was analyzed, and the risk factors for depression in patients with COPD were identified.

Statistical analysis

All analyses were performed using IBM SPSS Version 22 (SPSS Inc. Chicago IL, USA). Qualitative variables were expressed as numbers and percentages, and were assessed by the χ^2 test or Fisher's exact test. Continuous variables were reported as the mean ± SD and were compared with independent samples *t*-tests or univariate analysis. Independent risk factors related to depression were analyzed using a multivariate logistic regression analysis model. A receiver operating characteristic (ROC) curve was used to assess the predictive value of risk factors in patients with depression. Statistical significance was set as a *P* value less than 0.05.

RESULTS

Patient demographics

A total of 293 patients with COPD were included in this study (Figure 1). Patients' demographics are shown in Table 1. Of the 293 patients who were eligible for inclusion, 65 individuals were identified to have depression. The overall incidence of

depression in this study was 22.18% (65/293). Most of the patients were male (240 patients, 81.91%), with an average age of 65.62 ± 7.31 years. Among these patients, 38.91% were past smokers, and 33.79% were current smokers. The household income type of most patients was low income (149 patients, 50.85%) or medium income (105 patients, 35.84%).

The correlation between diverse clinical factors and depression

The differences between clinical parameters and depression were investigated and the results are presented in Table 2. The results revealed that depression in patients with COPD was associated with the duration of respiratory symptoms, the number of exacerbations per year, BMI, FEV1, and the mMRC dyspnea scale and CAT scores as significant differences were found between patients with and without depression for these factors (all $P < 0.05$). These results indicated that the duration of respiratory symptoms, the number of exacerbations per year, BMI, FEV1, and the mMRC dyspnea scale and CAT scores were potentially related to depression in patients with COPD. No statistically significant differences in age, gender, marital status, household income and smoking history were observed between the 2 groups ($P > 0.05$).

Risk factors for depression in patients with COPD

Multivariate logistic regression analysis was carried out to identify the potential risk factors for depression in patients with COPD. Low BMI (OR = 0.893, $P < 0.05$), low FEV1 (OR = 0.325, $P < 0.05$), and high CAT score (OR = 1.111, $P < 0.05$) were independent risk factors for depression. No significant differences were found for the duration of respiratory symptoms or the number of exacerbations per year between COPD patients with and without depression ($P > 0.05$) (Table 3).

The cutoff value, sensitivity, and specificity of BMI, FEV1, and CAT score for diagnosing depression

Figure 2, Figure 3 and Figure 4 show the ROC curves of BMI, FEV1, and CAT score for predicting the risk of depression; these factors had comparable accuracy in predicting depression in COPD patients (the AUC of these factors were 0.705, 0.702 and 0.694, respectively). The cutoff values of these factors were 21.375 kg/m^2, 0.855 L and 12.5, respectively. BMI had the highest diagnostic accuracy for predicting the risk of depression (AUC = 0.705, $P < 0.05$), with a sensitivity and specificity of 49.6% and 83.1%, respectively. Additionally, combined BMI and FEV1 with CAT score had a higher AUC (BMI + FEV1: 74.5%; BMI + CAT: 73.5%; FEV1 + CAT: 73.0%; BMI + FEV1 + CAT: 76.6%) than that of one single factor (Table 4).

DISCUSSION

COPD is a major respiratory noncommunicable disease and is currently the third leading cause of death worldwide[17]. Depression occurs in up to 42% of persons with COPD[11], almost twice as often as in those without COPD[18]. In line with previous studies, the incidence of depression in our study was 22.18%, based on a population of 293 patients. Depression in patients with COPD is associated with physical impairment[19], readmission[20], increased dyspnea[21,22], and mortality[23]. Due to the considerable overlap between the physical symptoms of depression and the symptoms of COPD, patients with COPD may not be able to recognize this mental illness, and diagnosis is easily missed by doctors compared with that in patients with other comorbidities or depression alone[24]. Due to these factors, depression may reduce patient compliance with COPD treatment, thus leading to deterioration related to COPD. Therefore, identifying valuable predictive factors that are readily available could meaningfully benefit timely intervention to cure depression. In this retrospective study, we evaluated the association between clinical factors and depression in patients with COPD. Previous studies reported that depression in patients with COPD was associated with multiple factors, including age, gender, marital status, smoking history and social performance[25-27]. However, in this study, a correlation between the above-mentioned factors and depression was not found. The reason for this result may be that these studies were performed primarily in patients with severe COPD, and few of them focused on risk factors in patients with mild COPD.

BMI had been widely used to measure obesity, and there is growing evidence that BMI is an independent predictor of mental disorders[28]. A previous study reported that the average depression score in an obesity group was higher than that in a normal BMI group[28]. Zhao *et al*[29] revealed that obese individuals (≥ 25.0 kg/m^2) were 38% more likely to experience depression, and were 40% more likely to have lifetime depression after fully adjusting for several factors, such as obesity-related

Table 1 Baseline characteristics of patients, *n* = 293 (%)

Patient characteristics	Number of patients
Age at diagnosis (mean ± SD, yr)	65.62 ± 7.31
Gender	
Female	53 (18.09)
Male	240 (81.91)
Smoking history	
Never smoker	80 (27.30)
Past smoker	114 (38.91)
Current smoker	99 (33.79)
Household income	
Low income	149 (50.85)
Medium income	105 (35.84)
High income	39 (13.31)
Patients with depression	65 (22.18)
HADS-D score	5.09 ± 2.73

HADS-D: Hospital anxiety and depression scale-depression.

comorbidities, demographics, and psychosocial factors. Lee *et al*[30] indicated that adjusted odds ratios for depression formed a U-shaped relationship with BMI categories (underweight group: 1.31, overweight group: 0.94, obese group: 1.01, severely obese group: 1.28). The BMI level with the lowest likelihood of depression was 18.5-25 kg/m^2 in women and 23-25 kg/m^2 in men[30]. However, few studies have analyzed the relationship between BMI and depression in patients with COPD. In the current study, we identified BMI as an independent risk factor correlated with depression. The cutoff value was 21.375 kg/m^2. This finding suggested that BMI levels < 21.375 kg/m^2 could help to distinguish populations of patients with COPD at a higher risk of depression.

Previous data highlighted the association between FEV1 and depression. A study reported that among 100 dairy farmers with COPD, as defined by a postbronchodilator FEV1/forced vital capacity ratio < 0.7, depression in patients was associated with lower FEV1, as well as with certain COPD-related characteristics (current smoking, dyspnea severity, and poorer quality of life)[31]. Von Siemens *et al*[32] demonstrated that FEV1 was significantly (P < 0.05) related to the Patient Health Questionnaire 9 score, which is one of the screening tools for depression. Significant differences were found for FEV1 levels, reflecting COPD severity, between patients with and without depression[33]. This result could help patients with depression avoid being untreated or undertreated[34]. Consistent with previous studies, our study indicated that FEV1 was an independent risk factor for depression in patients with COPD. The cut-off value was 0.855 L, and the sensitivity and specificity were 71.5% and 63.1%, respectively.

The CAT score was developed in 2009 as a patient-administered, short questionnaire to test health-related quality of life in patients with COPD[35]. Lower scores indicated less severe symptoms. There was a significant difference in CAT scores between patients with depression and without depression[35]. The analyses by von Siemens *et al*[32] revealed, with a cut-off CAT score of 20, an AUC of 0.81. Based on the close relationship between the tests, the CAT score and depression were also omitted from further analysis. Interestingly, this value was similar to the critical value of 18, which had been proposed to be better than the conventional threshold of 10 in terms of the classification of COPD severity. Lee *et al*[36] indicated that the CAT score and symptoms were correlated with the formation of depression in patients with COPD. In line with previous studies, the results of our study showed significant differences in CAT scores between patients with and without depression, and we identified that the CAT score was an independent risk factor correlated with depression. The cutoff value was 12.5. This finding indicated that a CAT score > 12.5 was a risk factor for depression in patients with COPD.

To identify the predictive accuracy of combined risk factors for predicting depression in patients with COPD, we analyzed the combined risk factors for depression in the present study. Compared to BMI, FEV1 or CAT score alone, we found that combining FEV1 and CAT score with BMI had higher predictive value for predicting depression in patients with COPD. This finding indicated that the

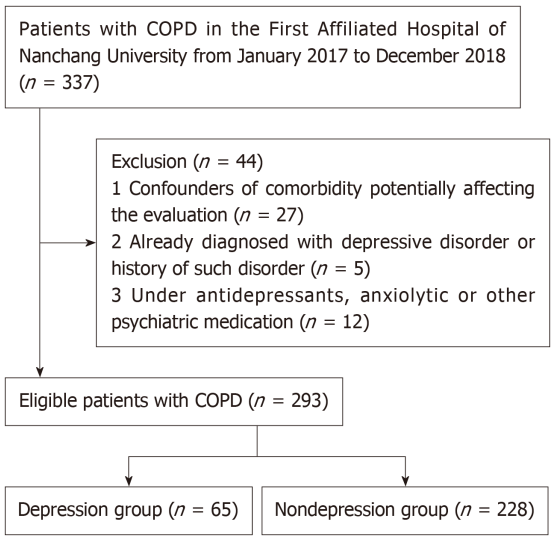

Figure 1 Selection of the study participants. COPD: Chronic obstructive pulmonary disease.

combination of risk factors appeared to be more useful for predicting depression.

To our knowledge, we have been successful in identifying low BMI, low FEV1 and high CAT score as independent depression associated risk factors in patients with COPD. Although the results are interesting, limitations to our study still exist. First, this was a retrospective study with a relatively small sample, which may have resulted in bias during analysis of the results. Second, we only collected variables from patients with COPD at the time of diagnosis, and some variables, such as the time to depression and follow up, were not reported. Third, patient variables were from a single medical institution and the results of our study for predicting depression were not satisfactory. Thus, a multicenter study with more patients is needed to verify our results. Fourth, some studies indicated that the HADS was saturated by the presence of a common distressing factor, in part because it was intended to focus on lack of pleasure and autonomous arousal, leading to the difficulty in distinguishing depression from anxiety. This explained the result that the HADS anxiety scale and depression scale served the same purpose as a screening tool for depression[37]. For research purposes, the use of a summed HADS total score was recommended and appeared to provide an adequate estimate. In clinical practice, HADS is not recommended when it is necessary to distinguish between anxiety and depression. Due to its poor trait coverage and narrow focus, short tools covering broad anxiety and depression symptoms may be more appropriate[38,39]. COPD patients have greater disease burden than other populations. In addition to the widespread symptoms of depression, our results also identified several risk factors for depression including low BMI, low FEV1, and high CAT score. However, barriers to recognition exist at the provider and system levels. At the provider level, lack of ambitions and stereotypes can be obstacles. At the system level, poor integration of mental health services with primary health care is another obstacle.

In conclusion, based on this analysis, we established that approximately one-fifth of patients with COPD developed depression. Additionally, we identified low BMI, low FEV1, and high CAT score as risk factors for depression in COPD patients. Combining these factors predicted the highest risk of developing depression. However, a prospective study with a large sample size and multicenter analysis is needed to prove the conclusions of our study.

Table 2 Correlation between diverse clinical factors and depression

Factors	Depression	No depression	*P* value
Age at diagnosis (mean ± SD, yr)	65.12 ± 7.62	65.76 ± 7.23	NS
Gender	65	228	NS
Female	9	44	
Male	56	184	
Marital status	65	228	NS
Married or partner	52	194	
Single, divorced, separated or widowed	13	34	
Household income	65	228	NS
High income	12	27	
Medium income	20	82	
Low income	33	119	
Smoking history	65	228	NS
Never smoker	15	49	
Past smoker	24	96	
Current smoker	26	83	
Duration of respiratory symptoms (mo)	111.28 ± 41.92	79.51 ± 112.47	0.026
Exacerbation rate (prior yr)	2.09 ± 1.28	1.58 ± 0.94	0.004
BMI (kg/m^2)	18.51 ± 3.34	20.75 ± 4.09	0.000
FEV1 (L)	0.82 ± 0.30	1.11 ± 0.44	0.000
mMRC dyspnea scale	1.86 ± 0.75	1.67 ± 0.69	NS
CAT score	13.08 ± 3.71	10.30 ± 4.20	0.002
HADS score	9.18 ± 1.27	3.93 ± 1.72	0.000

BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; mMRC: Modified medical research council; CAT: Chronic obstructive pulmonary disease assessment test; HADS: Hospital Anxiety and Depression Rating Scale; NS: Not significant.

Table 3 Multivariate logistic regression analysis of risk factors

Factors	β	OR	95%CI	*P* value
Duration of respiratory symptoms	0.002	1.002	0.999-1.004	NS
Exacerbation rate (prior yr)	0.13	1.139	0.854-1.518	NS
BMI (kg/m^2)	-0.113	0.893	0.830-0.962	0.003
FEV1 (L)	-1.124	0.325	0.132-0.803	0.002
CAT score	0.105	1.111	1.021-1.209	0.004

β: Coefficient regression; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; CAT: Chronic obstructive pulmonary disease assessment test; NS: Not significant.

Table 4 Cutoff value, sensitivity, and specificity of body mass index, forced expiratory volume in 1 s, and chronic obstructive pulmonary disease assessment test score for diagnosing depression

Factors	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95%CI	*P* value
BMI (kg/m^2)	21.375	49.6	83.1	0.705	0.633-0.776	0.001
FEV1 (L)	0.855	71.5	63.1	0.702	0.634-0.770	0.003
CAT score	12.5	63.1	70.6	0.694	0.624-0.765	0.001
BMI+FEV1		76.9	66.7	0.745	0.684-0.807	0.000
BMI+CAT		72.3	67.1	0.735	0.669-0.802	0.000
FEV1+CAT		76.9	60.5	0.730	0.667-0.794	0.000
BMI+FEV1+CAT		72.3	75.0	0.766	0.705-0.827	0.000

BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; CAT: Chronic obstructive pulmonary disease assessment test; AUC: Area under curve; CI: Confidence interval.

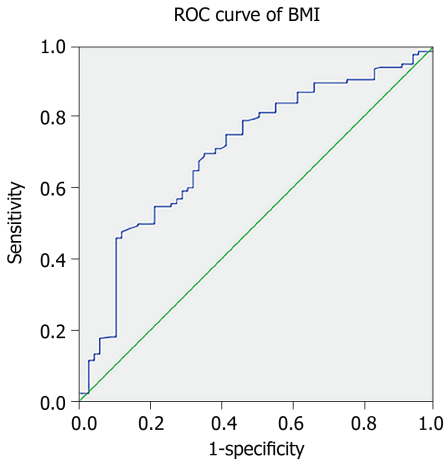

Figure 2 Receiver operating characteristic curve of body mass index. The receiver operating characteristic curve demonstrated the sensitivities and specificities of body mass index for predicting the risk of depression in patients with chronic obstructive pulmonary disease. ROC curve: Receiver operating characteristic curve; BMI: Body mass index.

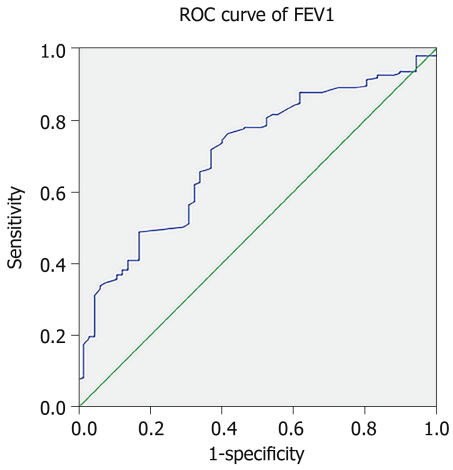

Figure 3 Receiver operating characteristic curve of forced expiratory volume in 1 s. The receiver operating characteristic curve demonstrated the sensitivities and specificities of forced expiratory volume in 1 s for predicting the risk of depression in patients with chronic obstructive pulmonary disease. ROC curve: Receiver operating characteristic curve; FEV1: Forced expiratory volume in 1 s.

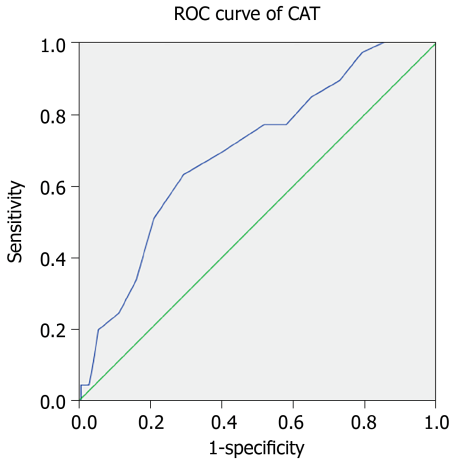

Figure 4 Receiver operating characteristic curve of chronic obstructive pulmonary disease assessment test score. The receiver operating characteristic curve demonstrated the sensitivities and specificities of the chronic obstructive pulmonary disease assessment test score for predicting the risk of depression in patients with chronic obstructive pulmonary disease. ROC curve: Receiver operating characteristic curve; CAT: Chronic obstructive pulmonary disease assessment test.

ARTICLE HIGHLIGHTS

Research background

The reported prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) ranges from 10% to 42%, a proportion much higher than that in the general population. Certain interventions such as antidepressants, pulmonary rehabilitation, and counseling may improve health outcomes, but the diagnosis of depression in patients with COPD is often unrecognized and untreated in primary and specialty care. Unrecognized depression has major implications for compliance with medical treatment, prolonged lengths of stay, increased frequency of hospital admissions, and increased consultations with primary care physicians, all of which could decrease quality of life in patients.

Research motivation

Many studies have attempted to identify risk factors for progression, prognosis and response to therapy in patients with depression. However, few studies have examined the risk factors for depression in patients with COPD, and some results remain controversial.

Research objectives

The main objective of the current study is to investigate the correlation between clinical parameters and the symptoms of depression, and to identify independent risk factors to define patients with COPD at "high risk" of depression.

Research methods

The Hospital Anxiety and Depression Rating Scale (HADS) is one of the most commonly used instruments for depression in the literature. A series of consecutive patients newly diagnosed with COPD were included in this study. The diagnosis of depression mainly relied on the HADS, and the HADS scale was carried out by an experienced psychiatrist when the patients were stable. We used a cutoff of 8 or more on the HADS to dichotomize the HADS scores for the purposes of the regression analyses. The correlation between clinical parameters and depression was analyzed, and the risk factors for depression in patients with COPD were identified.

Research results

Multivariate logistic regression analysis was carried out to identify the potential risk factors for depression in patients with COPD. Low body mass index (BMI), low forced expiratory volume in 1 s (FEV1), and high COPD assessment test (CAT) score were independent risk factors for depression. BMI had the highest diagnostic accuracy for predicting the risk of depression. Additionally, combined BMI and FEV1 with CAT score had a higher area under curve than that of one single factor.

Research conclusions

Approximately one-fifth of patients with COPD developed depression. Additionally, we identified low BMI, low FEV1, and high CAT score as risk factors for depression in COPD patients. Combining these factors predicted the highest risk of developing depression.

Research perspectives

Some variables, such as the time to depression and follow up, were not reported, which may have resulted in bias during analysis of the results. A prospective study with a large sample size and multicenter analysis is needed to prove the conclusions of our study.

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META-ANALYSIS

Diagnostic accuracy and clinical utility of non-English versions of Edinburgh Post-Natal Depression Scale for screening post-natal depression in India: A meta-analysis

Paul Swamidhas Sudhakar Russell, Swetha Madhuri Chikkala, Richa Earnest, Shonima Aynipully Viswanathan, Sushila Russell, Priya Mary Mammen

ORCID number: Paul Swamidhas Sudhakar Russell (0000-0001-6463-2750); Swetha Madhuri Chikkala (0000-0002-1462-1751); Richa Earnest (0000-0002-1701-8392); Shonima Aynipully Viswanathan (0000-0002-3792-0009); Sushila Russell (0000-0003-0055-1542); Priya Mary Mammen (0000-0001-7182-6959).

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Paul Swamidhas Sudhakar Russell, Swetha Madhuri Chikkala, Richa Earnest, Shonima Aynipully Viswanathan, Sushila Russell, Priya Mary Mammen, Child and Adolescent Psychiatry Unit, Department of Psychiatry, Christian Medical College, Vellore 632 002, India

Corresponding author: Paul Swamidhas Sudhakar Russell, MBBS, MD, Professor, Child and Adolescent Psychiatry Unit, Department of Psychiatry, Christian Medical College, Bagayam, Vellore 632 002, India. russell@cmcvellore.ac.in

Abstract

BACKGROUND

The prevalence of post-natal depression (PND) is high in India, as it is in many other low to middle income countries. There is an urgent need to identify PND and treat the mother as early as possible. Among the many paper and pencil tests available to identify PND, the Edinburgh Postnatal Depression Scale (EPDS) is a widely used and validated measure in India. However, the summary diagnostic accuracy and clinical utility data are not available for this measure.

AIM

To establish summary data for the global diagnostic accuracy parameter as well as the clinical utility of the non-English versions of the EPDS in India.

METHODS

Two researchers independently searched the PubMed, EMBASE, MEDKNOW and IndMED databases for published papers, governmental publications, conference proceedings and grey literature from 2000-2018. Seven studies that evaluated the diagnostic accuracy of EPDS in five Indian languages against DSM/ICD were included in the final analysis. Two other investigators extracted the Participants' details, Index measures, Comparative reference measures, and Outcomes of diagnostic accuracy data, and appraised the study quality using QUADS-2. Deek's plots were used to evaluate publication bias. We used the area under the curve of the hierarchical summary area under the receiver operating characteristic curve, with the random effect model, to summarize the global diagnostic accuracy of EPDS. Using the 2 × 2 table, we calculated positive and negative likelihood ratios. From the likelihood ratios, the Fagan's nomogram was built for evaluating clinical utility using the Bayesian approach. We calculated the 95% confidence interval (95%CI) whenever indicated. STATA (version 15) with MIDAS and METANDI modules were used.

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RESULTS

There was no publication bias. The area under the curve for EPDS was 0.97 (95%CI: 0.95-0.98). The pre-test probability for the nomogram was 22%. For a positive likelihood ratio of 9, the positive post-test probability was 72% (95%CI: 68%, 76%) and for a negative LR of 0.08, the negative post-test probability was 2% (95%CI: 1%, 3%).

CONCLUSION

In this meta-analysis, we established the summary global diagnostic parameter and clinical utility of the non-English versions of the EPDS in India. This work demonstrates that these non-English versions are accurate in their diagnosis of PND and can help clinicians in their diagnostic reasoning.

Key words: Clinical-utility; Diagnostic-accuracy; Edinburgh Postnatal Depression Scale; Meta-analysis; India; Validation

Core tip: Post-natal depression (PND) affects both the mother and baby. Currently, although one of the most common psychiatric disorders among women, early identification and treatment is underprovided in low and middle-income countries. Paper-and-pencil tests remain the primary mode of identifying PND, and the Edinburgh Postnatal Depression Scale is widely used and validated in many languages in India. This meta-analysis documents that the diagnostic parameters are good for Edinburgh Postnatal Depression Scale in India, and that its use can significantly help to scale up the services for PND.

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INTRODUCTION

India is a low-middle income country with a birth rate of 20/1000 population, and the summary prevalence of Post-natal Depression (PND) was 22% in the country in 2017[1-3]. There is compelling evidence that PND is associated with morbidity and mortality in the mother-infant dyad[4,5]. Therefore, scaling-up identification and early, effective management of the identified mother-infant dyad is very much needed in India.

The Edinburgh Postnatal Depression Scale (EPDS) is an accurate screening measure[6,7] and improves the follow-up care of PND and maternal mental health[8]. In India, it is the most commonly used screening measure for PND. A recent meta-analysis demonstrates that 29 of the 38 prevalence studies on PND have used EPDS in India[3]. This measure has been translated and validated in the eight regional languages of India: Assamese, Bengali, Gujarati, Kannada, Konkani, Marathi, Punjabi and Tamil, and has been validated in both clinical and community settings in India against a variety of reference standards. The total EPDS threshold score for diagnosing PND has ranged from 6/7 to 12.5/13. Reflecting the possible effect of the varying prevalence of PND, the setting of the study, the threshold-score of EPDS, and the reference standard used or other methodological differences, the sensitivity and specificity have varied from 71%-100% and 77%-98%, respectively (further details are given in Table 1). Furthermore, good diagnostic accuracy does not always translate into good clinical utility among measures. The clinical utility of EPDS has not previously been studied in India. Therefore, because of the wide variation in diagnostic accuracy parameters, there is a need to generate summary diagnostic accuracy parameters from pooled studies for use across India, and its clinical utility needs to be demonstrated.

Using this meta-analysis, we aim to fill in the lacunae in the existing literature,

Table 1 Summary of the included and excluded studies with their individual Quality Assessment of Diagnostic-Accuracy Studies-2 details

PICO details								QUADAS-2						
								Risk of bias				Applicability concerns		
Ref.	Sample, *n*	Setting, Age, PN	EPDS language	EPDS threshold	Interview schedule, Reference standard	Sn	Sp	PS	IT	RS	F&T	PS	IT	RS
Patel *et al*[13], 2002	270	Clinic, 18-40 yr, 6-8 wk PN	Konkani	11/12	CIS-R, ICD-10	92	85	UC	L	L	UC	UC	UC	UC
Benjamin *et al*[14], 2005	121	Clinic, 17-35 yr, NA-PN	Tamil	8/9	CIS-R, ICD-10	94.1	90.2	UC	L	UC	UC	L	L	L
Werrett and Clifford[15], 2006	25	Clinic, 23-40 yr; 5-8 wk, 10-14 wk PN	Punjabi	12.5/13	CIDI, ICD-10	71.4	93.7	L	L	L	L	L	L	L
Fernandes *et al*[16], 2011	194	Clinic, 3rd trimester	Kannada	12/13	MINI-Plus, DSM-IV	100	84.9	UC	L	L	UC	L	L	L
Desai *et al*[17], 2011	200	Clinic, 18-35, up to 6 mo PN	Gujarati	10.5/11	SSI, DSM-IV	100	98	UC	L	UC	UC	L	L	L
Savarimuthu *et al*[18], 2012	137	Community 21-30 yr, 4-6 wk PN	Tamil	6/7	CI, ICD-10	85.3	77.7	UC	L	UC	L	L	L	L
Kalita *et al*[19], 2015	200	Clinic, 18-42 yr, 6 wk PN	Assamese	13	CI, ICD-10	88.9	85.3	UC	L	UC	H	L	L	L
Maity *et al*[20], 2015	105	Clinic, NA, NA	Bengali	13	NA	84	91	H	UC	H	H	H	H	H
Khapre *et al*[21], 2017	280	Community, 25 yr median, 2 wk PN	Marathi	12/13	SSI, ICD-10	93.8	94.9	UC	L	UC	UC	L	L	L

Patient selection (PS): Describe methods of patient selection; Index text (IT): Describe the index test and how it was conducted and interpreted; Reference standard (RS): Describe the reference standard and how it was conducted and interpreted; Flow and timing (F&T): Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2×2 table, and describe the interval and any interventions between index tests and the reference standard; H: High bias (if any signalling question was answered "no,"); L: Low bias (if the answers to all signalling questions for a domain were "yes,"); UC: Unclear (if insufficient data were reported to permit our judgment). PICO: Participants, Index measure, Comparative reference measure and Outcome of diagnostic accuracy; CIS-R: Clinical Interview Schedule (Revised); CI: Clinical Interview; CIDI: Composite international diagnostic interview; ICD-10: International Classification of Diseases, Edition 10; DSM-IV: Diagnostic and Statistical Manual, IVth Edition; MINIPlus: Mini International Neuropsychiatric Interview Plus; SSI: Semi-structured Interview; PN: Post-natal period; NA: Not available; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2.

namely the absence of a summary global diagnostic accuracy and clinical utility parameter for use in India for non-English EPDS. Hence we: (1) Establish the summary global diagnostic accuracy of the non-English EPDS versions in India; and (2) Evaluate the clinical utility of the measure for post-natal Depression.

MATERIALS AND METHODS

Literature search

Two researchers (SMC and ER) independently electronically searched for relevant published studies in the PubMed, EMBASE (international database), MEDKNOW and IndMED (regional database) databases as well as hand-searched to augment the search with cross-references, published conference abstracts, Government of India publications, and grey literature from January 2000 to February 2018. We combined the search terms as follows: "diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields]) AND accuracy[All Fields] AND ("psychiatric status rating scales"[MeSH Terms] OR ("psychiatric"[All Fields] AND "status"[All Fields] AND "rating"[All Fields] AND "scales"[All Fields]) OR "psychiatric status rating scales"[All Fields] OR ("Edinburgh"[All Fields] AND "postnatal"[All Fields] AND "depression"[All Fields] AND "scale"[All Fields]) OR "Edinburgh postnatal depression scale"[All Fields]) AND ("India"[MeSH Terms] OR "india"[All Fields].

Study selection and data extraction

Two other researchers (SR and SAV) extracted the required details independently, resolved any differences in extraction by consultation with another researcher (PSSR), and entered the information as electronic data. They extracted the participants, index measure, comparative reference measure and outcome of diagnostic accuracy details of each study. For a study to be included in the final analysis, it should have been conducted in India or among Indian populations, and must have compared the diagnostic accuracy of EPDS against either the Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) for PND as the reference standard. Finally, each study had to report sufficient data to construct 2 × 2 tables for calculating the true positive, false positive, false negative and true negative values of EPDS against the reference standard.

Quality appraisal and risk of bias

Two researchers (SAV and PMM) also appraised the quality of the studies with Quality Assessment of Diagnostic-Accuracy Studies, version 2 (QUADAS-2)[9]. We calculated the Deek's plot for publication bias[10].

Statistical analysis

We used the Area Under the Characteristic Curve of the Hierarchical Summary Receiver Operating Curve (HSAUROC), with random effects model, to establish the global diagnostic accuracy of EPDS[11]. This was the first outcome of this meta-analysis. Using the 2 × 2 table, we calculated the positive and negative likelihood ratios (+LR and –LR, respectively). From these likelihood ratios, we evaluated the post-test probabilities of EPDS using the Fagan's nomogram (Bayesian approach); these post-test probabilities indicating the clinical utility was the second outcome of our study[12]. We calculated the 95% confidence interval (95%CI) whenever indicated. All analyses were done at the study level and not at the participant level. The analyses were done with STATA (version 15) using the MIDAS and METANDI modules.

RESULTS

Study characteristics

The search strategies provided 2108 titles and the diagnostic accuracy of EPDS was documented in nine studies in seven of the official languages of India[13-21]. One study in Kannada was excluded, as it included participants during their third trimester of pregnancy and not the post-natal period[16]. Another study in Bengali was excluded due to the poor quality of the study[20]. Figure 1 captures the PRISMA details, and Table 1 summarises the participants, index measure, comparative reference measure and outcome of diagnostic accuracy details and QUADAS -2 appraisal of each of the studies that were included or excluded in the final analysis (n = 1227). The QUADAS-2 appraisal demonstrated that in the risk of bias criteria, one study was rated as "at low risk of bias" across all domains. A rating of an unclear risk of bias was the most common rating across the appraisal domains. The Deek's plot for publication bias is presented in Figure 2. In terms of applicability criteria, all seven studies were rated as applicable on all domains (Figure 3 for QUADAS-2 details). All studies had a cross-sectional design.

Diagnostic accuracy and clinical utility

The global diagnostic accuracy of EPDS as ascertained by HSAUROC was 0.97

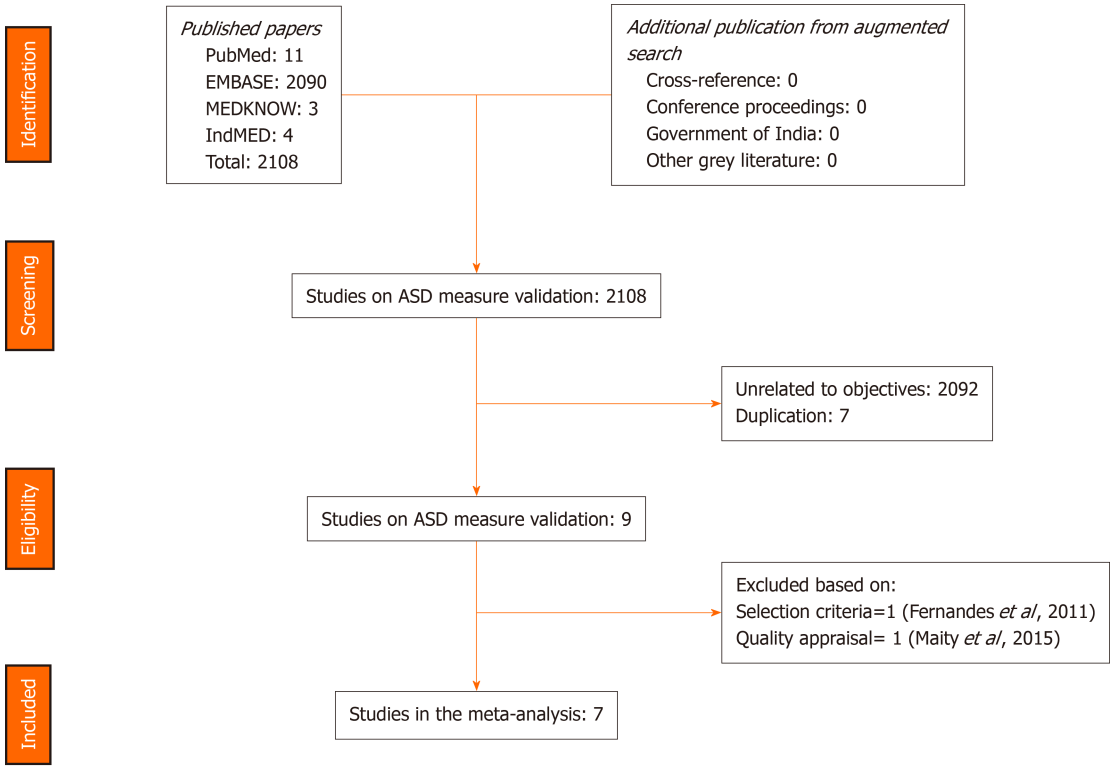

Figure 1 Overview of PRISMA selection process of studies.

(95%CI: 0.95-0.98) (Figure 4). The pre-test probability for the nomogram was 22%. For a +LR of 9, the positive post-test probability was 72% (95%CI: 68%, 76%) and for a -LR of 0.08, the negative post-test probability was 2% (95%CI: 1%, 3%) (Figure 5).

DISCUSSION

Firstly, the global diagnostic accuracy of EPDS was excellent for the five different non-English versions in India. This HSAUROC value of 0.97 when converted to a more comprehensible clinical effect size of Cohen's *d* or correlation coefficient *r* was 2.66 or 0.79, respectively[22]. This was a large effect size in the context of the diagnostic accuracy of EPDS when used as a screening measure for PND. Secondly, for the pre-test probability of 22%, the positive increment in diagnostic utility was 51% and the negative decrement was 20% for the post-test probability of EPDS. Given that the prevalence of PND in India is 22%[3], our incremental changes in post-test probability values have added considerable certainty to the diagnosis of PND when EPDS is used[12]. Thus, if a postnatal mother tests positive for EPDS, the chance she has PND increases from 22% to 72%; the clinician might therefore decide to actively engage in treatment. Conversely, if the patient tests negative, the chance of having PND decreases from 22% to 2%, and the clinician might decide not to actively treat the PND but engage instead in watchful waiting. Our finding about the diagnostic accuracy of EPDS versions is comparable with the values reviewed for the English versions in native English-speaking countries[6,7]. In comparison to some of the other selected non-English EPDS versions among African languages, the Chichewa version in Malawi, the Shona version in Zimbabwe, and the Nigerian version have relatively lower diagnostic accuracies than the summary value that is reported in this meta-analysis[23,24]. The translated version of EPDS in Afrikaans, Zulu, Tswana, Sotha, and Xhosa has demonstrated higher diagnostic accuracy for EPDS in South Africa[25]. Among European languages, the Danish version of EPDS has an Area Under the Curve of 0.96 and is comparable to our summary data[26], the Spanish version had an overall accuracy of 87.4%[27], and the French versions of EPDS has a sensitivity and specificity of 80% and 92%, and thus had lower diagnostic accuracy[28]. The other Asian language where EPDS has been validated includes Arabic[29], Chinese[30], and Japanese[31]; they have been found to have lower or similar diagnostic accuracies as in our meta-analysis.

The strengths of this study from a methodological perspective are that we followed

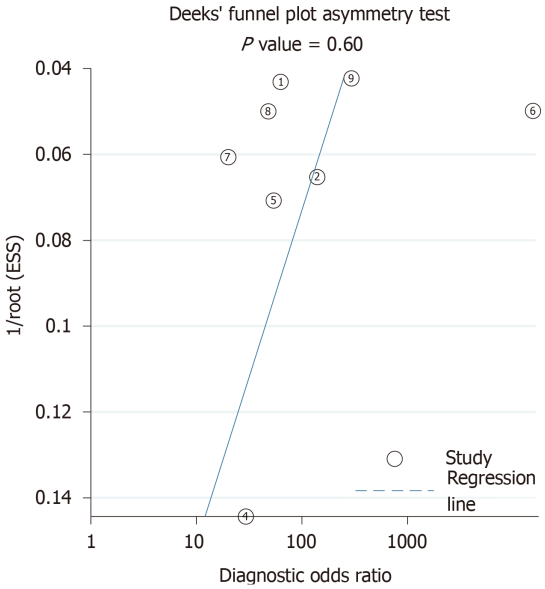

Figure 2 The Deek's plot for publication bias.

the guidelines recommended by the Cochrane Diagnostic Test Accuracy Protocol. To present the summary of the global diagnostic accuracy of the EPDS, we used a summary line (HSROC) then summary point, as studies with various EPDS threshold values and two reference standards were analysed together. Furthermore, we anticipated the sensitivity as well as specificity of EPDS to differ widely between studies from the literature, and used the random effects model over the fixed effects model for analysis[6,7]. There was no publication or small study bias in our meta-analysis. Finally, from the policy implication standpoint, in about 69069 births expected per day in India[32], the need to identify the 22% of mothers with PND and deliver the integrated management of mother-baby dyad is a huge task. However, this can be achieved if PND is identified and EPDS is used as a valuable measure[33]. The National Mental Health Program should routinely incorporate the use of EPDS as the screening measure for PND in India through its District Mental Health approach.

In light of these findings, we conclude that the EPDS, with its many language versions and its brevity, is eminently suited for the screening of PND in India, where mental health resources are low but burden is high.

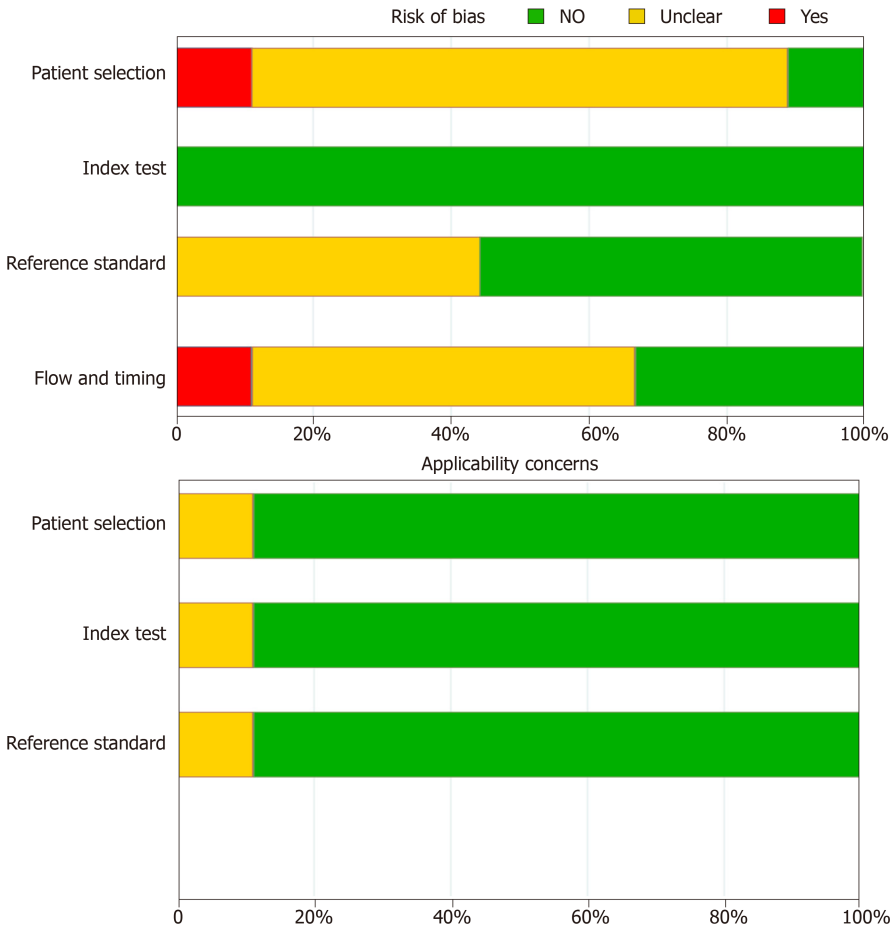

Figure 3 The average Quality Assessment of Diagnostic-Accuracy Studies, version 2 appraisal for all included studies.

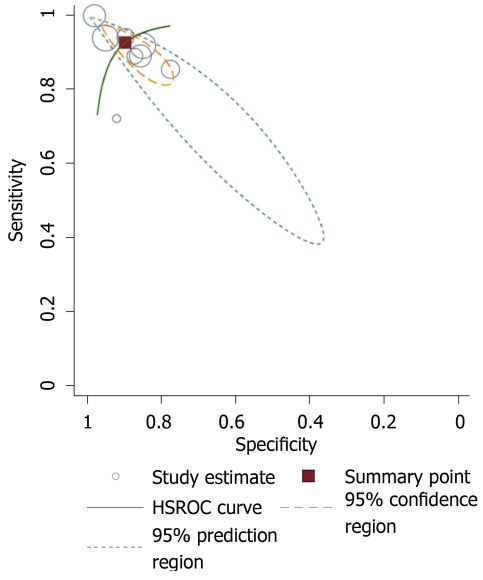

Figure 4 The Hierarchical Summary Receiver Operating Characteristic Curve of Edinburgh Postnatal Depression Scale with its confidence and prediction contours. HSROC: Hierarchical Summary Receiver Operating Curve.

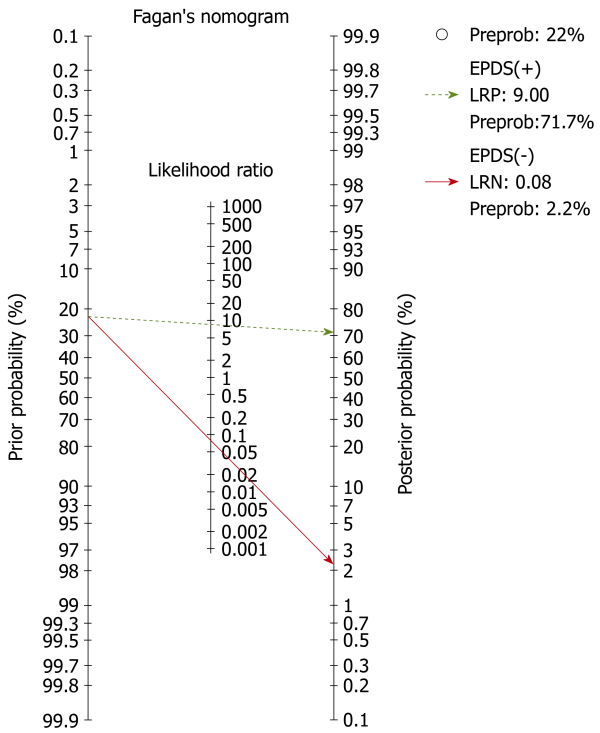

Figure 5 The post-test probability of Edinburgh Postnatal Depression Scale calculated with Fagan's nomogram.

ARTICLE HIGHLIGHTS

Research background

Various language versions of Edinburgh Postnatal Depression (EPDS) have been validated in India. The summary global diagnostic accuracy and clinical utility of these versions was established.

Research motivation

The diagnosis of postnatal depression (PND) is often missed or misdiagnosed. This affects both the mother and the baby, with significant morbidity. The widely used EPDS in India has to be proven for the early identification of PND.

Research objectives

The aim of this meta-analysis was to document the summary diagnostic accuracy and clinical utility of the various language versions of EPDS in India.

Research methods

Seven studies were included in the analysis following the PRISMA guidelines. We used Area Under the Characteristic Curve of the Hierarchical Summary Receiver Operating Curve, with random effect model, to summarize the diagnostic accuracy of EPDS; Fagan's nomogram was used for calculating clinical utility.

Research results

The global diagnostic accuracy of EPDS, as ascertained by Area Under the Characteristic Curve of the Hierarchical Summary Receiver Operating Curve, was 0.97 (95%CI: 0.95-0.98). For a PND prevalence of 22%, the positive post-test probability was 72% (95%CI: 68%, 76%) and the negative post-test probability was 2% (95%CI: 1%, 3%).

Research conclusions

We established the summary global diagnostic accuracy and clinical utility of the various versions of EPDS. The EPDS is effective in the early identification of PND.

Research perspectives

The EPDS in its various versions in India could be used for the scaling-up of PND treatment. The specific diagnostic parameters need to be further studied.

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