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Short Communication

Treatment Options for Psychotic Depression in Older People: Focused Literature review by New Zealand Psychogeriatric Team

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Abstract

Background: Psychotic major depressive disorder (PMDD) is complex with poor prognosis, reported in 15% to 25% of episodes with higher rates amongst older inpatients. There is little data on effective pharmacological treatment of PMDD.

Method: A critical review from a focused literature search was conducted. A literature search of controlled trials from: EMBASE (1970-), MEDLINE (1950-) and PsycINFO (1960-) was undertaken. Two authors (SP and YB) independently extracted the data.

Results: Of 386 studies 13 RCTs encompassing1, 359 participants fulfilled inclusion criteria. Of these 556 (41%) were participants in mifepristone trials that proved negative. Only 2 RCT included older patients. Findings suggest combining antidepressant and antipsychotic medications is advantageous in PMDD. This is supported by case series and uncontrolled studies. The practice of antidepressant monotherapy cannot be supported in older adults.

Conclusions: Further studies of pharmacological treatment of PMDD in older people are sorely needed.

INTRODUCTION

Psychotic major depressive disorder (PMDD) is a severe form of MDD linked to adverse outcomes such as suicide, longer inpatient stay, disability, low probability of placebo response, longer duration of depression and recurrence of psychotic features in subsequent episodes and overall worse prognosis than other forms of MDD [1,2]. PMDD is defined as a depressive episode with psychotic features (delusions and/or hallucinations) in the context of a unipolar major depressive disorder. As shorter time to severe relapse was demonstrated in a large European survey wherein patients with depression were treated with an antipsychotic medication, the authors concluded that simultaneous antipsychotic medication use may be a proxy marker for treatment resistant and psychotic depression [3].

Psychotic depression is not infrequent. The rates of PMDD are reported to be in the range of 14% -25% [4]. In the US Epidemiologic Catchment Area Study [5], 14% of participants suffering from MDD had previous episodes with psychotic features. Furthermore, In a US study of hospitalized in patients suffering from depression, 25% met the criteria for PMDD [6]. In a European broad population study, 18.5% of respondents suffering from MDD reported psychotic features with a prevalence of PMDD of 0.4% being one-fifth that of MDD [7].

Patients suffering from PMDD can be an exceptional challenge to treating clinicians as their needs are quite different from those of MDD patients due to substantial physical comorbidity and dissimilarities in response to therapy. PMDD is diverse and its etiology is complex. Treatment of PMDD is currently only loosely based on guidelines. Lamentably, there is a considerable scarcity of literature involving evidence-based clinical practice guidelines and randomized controlled trials in individuals suffering from PMDD. To date meager research was published focusing on the use of second generation antipsychotics for PMDD patients [8]. Treatment guidelines for PMDD are lacking and the evidence is limited regarding the most effective pharmacological treatment. The commonly employed treatment regimens are: combination of an antidepressant plus an antipsychotic, monotherapy with an antidepressant and monotherapy with an antipsychotic. The 2015 Cochrane review concluded that PMDD is profoundly understudied, limiting confidence in the conclusions drawn. Some evidence indicates that combination therapy with an antidepressant plus an antipsychotic is more effective than either treatment alone or placebo. However the authors emphasized

that evidence is limited for mono therapy with an antidepressant or with an antipsychotic [9].

There are only a small number of treatment studies in older PMDD patients. The rates of PMDD are higher in older people and they respond poorly to treatment with medication [10].

The 2015 Cochrane review analyzed only 2 studies from the last decade and the majority of studies analyzed used a first generation antipsychotic. For the second generation antipsychotics the authors analyzed only for 3 olanzapine and 1 quetiapine studies. The present brief review aims to emphasize recent studies focusing on the pharmacological treatment of PMDD in older people.

METHODS

Approach to the reviewing process

This was based in part on the approach recently advocated by Catts and O'Toole [11]. Briefly, the clinical issue reviewed was selected because the authors considered it decidedly relevant to the clinical practice of psychiatrists treating PMDD and likely to impact on health outcomes and its contentious nature is reflected in divergences across guidelines.

This critical review results from a of focused literature search. Although a systematic review would have been desirable, a critical review approach was the feasible way to integrate the literature. Selection of material was strongly weighted by relevance [11].

The following bibliographic databases: EMBASE (1970-), MEDLINE (1950-) and PsycINFO (1960-) were searched. Bibliography of all studies and relevant reviews were screened. Two review authors (SP and YB) independently extracted the data.

Inclusion criteria: For studies to be analyzed in the present review were: (1) randomized controlled trials (RCTs), (2) PMDD diagnosis in all or a subgroup of patients, (3) use of rating scales to quantify depression and/or psychosis, (4) sample size > 20 and (5) publication in the last 10 years.

Exclusion criteria: (1) Dementia of any kind (2) age younger than 18 years.

Efficacy assessments included change from baseline after treatment with psychotropic medication. We used intent-to-treat data and assessed remission rates as the major outcome.

Response and remission criteria are in agreement with those used in other published studies [12], and are considered to be clinically meaningful by clinicians.

It is important to note that studies with the novel agent Mifepristone were also analyzed.

RESULTS

Our search identified 386 abstracts, but only 13 RCTs with a total of 1,359 participants are included in the present review in accordance with inclusion criteria.

Due to clinical heterogeneity, few direct comparisons were possible. The main outcome in the published studies was reduction of severity depression or achieving remission (HAM-D < 7) of depression, not of psychosis. It is important to note that risk of bias is substantial: there were differences between studies with respect to diagnosis, differences in treatment interventions (a variety of antidepressants and antipsychotics) and different outcome criteria.

The highest remission rates were reported in the 2 antipsychotic monotherapy trials: Olanzapine - 63% and Risperidone - 55%

Antidepressant monotherapy

Only two studies were reported. In the first, the authors administered Sertraline 50-200 mgs/daily for 8 weeks. There were 25 participants. Remission was achieved by only 32% of patients. The second study compared the efficacy of imipramine and high-dose venlafaxine in depressed inpatients. There were no significant differences in the primary outcome measures. However, when analyzing a subpopulation of patients without psychotic features a significant difference was found: 5 of 34 (14.7%) patients on imipramine were remitters compared to 12 of 31 (38.7%) patients on venlafaxine [13].

Antipsychotic monotherapy

In the only one study reported Risperidone 0.5-1.8 mgs/daily was administered for 4 weeks. There were 20 participants. Remission was achieved by 55% of patients.

An important indirect contribution comes from the Bergen Psychosis Project (BPP). The hypothesis underlying the BPP is that most effectiveness studies indicated positive effect on mood of some second generation antipsychotics (SGAs). The BPP is a 24-month, pragmatic, randomized, head-to-head comparison of olanzapine, quetiapine, risperidone and ziprasidone in patients acutely admitted with psychosis. It is important to note that the BPP is not funded by any industry stakeholder. The aim of the study was to investigate whether distinct anti-depressive effects exist amongst SGAs. A total of 226 patients were included. A significant time-effect showed a steady decay in depressive symptoms in all medication groups. There was no substantial difference in anti-depressive effectiveness among olanzapine, quetiapine, risperidone or ziprasidone in this clinically relevant sample of patients acutely admitted to hospital for symptoms of psychosis. The drawback to generalizing these conclusions to PMDD patients is that there were only 23 PMDD patients in the sample while the overwhelming majority were patients suffering from schizophrenia spectrum disorders [14].

Antipsychotic + Antidepressant

This was the largest group of studies despite limited evidence for the efficacy of combination pharmacotherapy and no positive trials in older PMDD patients. Five studies employed the following combinations: Haloperidol + Venlafaxine, Quetiapine + Venlafaxine, 2 studies focusing on Olanzapine + Fluoxetine and one study focusing on Olanzapine + sertraline.

There were 630 participants in total treated for 7-14 weeks. Remission was not statistically different in the Haloperidol + Venlafaxine study nor in one of the two Olanzapine + Fluoxetine studies. However, Olanzapine was superior to Olanzapine +

Fluoxetine in one study with a 66% remission rate and Quetiapine + Venlafaxine was superior to Venlafaxine monotherapy.

In the largest study to date focusing on remission rates of PMDD and comparing those treated with a combination of atypical antipsychotic medication plus an SSRI with those treated with antipsychotic monotherapy 259 participants were enrolled. Of these 142 were older participants. After 12 weeks of treatment olanzapine + sertraline combination was associated with higher remission rates than olanzapine and placebo. In the whole sample 42% of subjects who underwent combination therapy achieved remission compared with 24% of subjects treated with monotherapy. This held true for the older subgroup [15].

Mifepristone monotherapy

Four studies of the "Antiglucocorticoid" [type II glucocorticoid receptor antagonist (GR-II)] compound were published. In the three studies wherein treatment duration was 8 weeks there were a total of 103 participants. Remission was not achieved in 2 studies and in the smaller (N=20) study, 55% of patients achieved remission. In the fourth study mifepristone was administered for brief 7 days duration only in comparison to placebo. The sample size was the largest to date with 433patients meeting the criteria for PMDD. The fraction of responders randomized to mifepristone did not statistically differ from placebo [16].

It is of interest to note that although not specifying psychotic features the latest metyrapone study (blocks cortisol synthesis by reversibly inhibiting steroid 11β-hydroxylase) has demonstrated that augmentation of antidepressant therapy with a drug that targets the HPA axis appears to be ineffective in improving response to treatment. The authors thus concluded that metyrapone augmentation of antidepressants is not effectual in a broadly representative population of patients with treatment-resistant depression and currently is not an option for patients with treatment-resistant depression in routine clinical practice [17].

DISCUSSION

Individuals with depression or anxiety disorder reported twice the prevalence of psychotic experiences than in people without these disorders. The presence of psychosis in individuals with depression is commonly associated with a poorer prognosis and, therefore, early treatment requires attention and may be advantageous for the course of psychosis expression [18]. It is unfortunate that little "real-world" data is available to guide treatment decisions for patients suffering from PMDD.

In 2008 a case series of older patients with PMDD was published [19]. Combination treatment for 5 weeks with amisulpride and antidepressants demonstrated resolution of psychotic symptoms in all the patients involved. In the only 2 randomized, controlled trials of acute treatment of older patients with PMDD combination therapy of a second generation antipsychotic and an antidepressant showed superiority over placebo. An earlier study by Mulsant and colleagues in 2001 [20] included an older patients sample with a mean age of 72 years. The researchers completed a randomized study comparing the efficacy of an antidepressant alone versus an antidepressant plus a neuroleptic in the treatment of late-life PMDD. Thirty patients received nortriptyline for at least 4 weeks combined with either perphenazine (N = 14) or placebo (N = 16).Rates of resolution of both depression and psychosis were higher in the combination group but did not reach statistical significance. In the largest published twelve-week, double-blind, randomized, controlled trial of 259 subjects with PMDD treatment with olanzapine and sertraline was associated with higher remission rates during the trial than olanzapine and placebo. Combination therapy was equally superior in both younger (OR, 1.25; 95% CI, 1.05-1.50; P = .02) and older adults (OR, 1.34; 95% CI, 1.09-1.66; P = .01) [14]. Finally, the BPP [13], included only 23 PMDD patients in the sample of which only 14 were older and thus generalization of antipsychotic monotherapy for PMDD from this project is ill advised.

We may cautiously make the following statements; monotherapy strategies for PMDD have mixed reports in the literature with little evidence of success. Early studies demonstrated that TCAs or conventional antipsychotics were inadequate mono therapies. The present analysis does not follow the PRISMA's parameters for systematic review & meta-analysis http://www.prisma-statement.org/. For that reason recommendations should be cautiously interpreted. The present review focused on studies published in the last decade and thus SGAs and SSRIs or SNRIs are mostly analyzed. There is a "signal" that antidepressant monotherapy is ineffective. The novel strategy of antagonizing the GR-II receptor has also failed to show convincing effects. Combination of an antipsychotic and an antidepressant demonstrate better outcome in older people but studies' limitations are pronounced.

An attempt to better understand the clinically important broader dimensions of clinical characteristics of PMDD, through multivariate analysis, in a pure sample of elderly unipolar delusional depressives as well as to test their external validity against a set of demographic, anamnestic and psychopathological validators was published in 2009 [21]. Principal Component Analysis resulted in the extraction of five factors, jointly accounting for 69.7% of the total variance. The five factors were interpreted as representing the dimensions of delusional strength, acute upsetting, delusional organization, incomprehensibility and incitation to actions. Overall, the findings contribute to the further elucidation of major clinical dimensions of delusions in PMDD in the elderly and the testing of their external validity [20]. Studies focusing on treatment response of the various psychotic factors in PMDD to antipsychotic medications will inform us further of the best pharmacological options.

The evidence base for the ideal clinical practice regarding PMDD is inadequate. The degree of consensus among international treatment guidelines on PMDD were recently reviewed [22]. The nine international treatment guidelines considered in the review have opposing opinions on the optimal treatment for PMDD: 6 of 9 suggest antidepressant plus antipsychotic combination therapy, 3 of 9 recommend antidepressant monotherapy and 5 of 9 find electroconvulsive therapy suitable as first line treatment. These results indicate that treatment algorithms regarding PMDD are highly heterogeneous. This finding emphasizes the need for further studies on the treatment of PMDD [22].

In conclusion, large randomized trials are called for to inform

clinicians on the best treatment for older patients suffering from PMDD. In the meanwhile we tentatively suggest combination treatment be the first line in managing this severe condition.

KEY POINTS

1. Psychotic major depressive disorder (PMDD) is a severe form of MDD often associated with adverse outcomes reported in up to 25% of episodes with higher rates recorded for older inpatients.
2. There is little data on the most effective pharmacological treatment of PMDD in older people.
3. Of 386 studies published in the last decade 13 RCTs with a total of 1,359 participants were identified and of these only 2 included older patients.
4. The available evidence suggests that a combination of an antidepressant and an antipsychotic may be advantageous in treating PMDD in older people.

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