Review of antidepressants in the treatment of behavioral and psychiatric symptoms in dementia (BPSD)

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ABSTRACT

Behavioral disturbances are commonplace among patients with dementia. Management of these symptoms has proved difficult.[1,2] Currently, there are no FDA approved pharmacologic treatments for the treatment of BPSD.[3] Traditionally, atypical antipsychotics have been used to treat behavioral disturbances despite modest efficacy and undesirable adverse effects.[3,4,5] Because of the increase in mortality, there is a continued push to reduce antipsychotic utilization in this population.[9,10] Thus, many clinicians are using alternative agents such as antidepressants and mood stabilizers to help treat BPSD, while avoiding using antipsychotics. The goal of this review is to review, analyze, and discuss the current literature available on the use of antidepressants to treat BPSD.

KEYWORDS

BPSD, antidepressants

INTRODUCTION

Management of behavioral and psychiatric symptoms in persons with dementia (BPSD) have proved difficult.[1,2] These behavioral symptoms are described in this edition of the Mental Health Clinician by Borovicka reviewing mood stabilizers in the treatment of BPSD. Non-pharmacologic interventions that promote cognition, activities of daily living and social functioning are recommended primarily for the management of BPSD.

Pharmacologic interventions may be necessary to manage persistent behavioral issues that can put the patient and/or others at risk for danger.[3] Currently, there are no FDA approved pharmacologic treatments for the treatment of BPSD.[3] Traditionally, atypical antipsychotics have been used to treat short term behavioral disturbances despite modest efficacy and undesirable adverse effects.[3,4,5] However, due to recent research, the use of antipsychotics in this patient population is no longer recommended due to increased risk of mortality.[6,7,8]

As a result of the increased risk associated with the use of antipsychotics to treat BPSD, there is warranted exploration of the efficacy of other possible pharmacologic agents to treat certain neuropsychiatric symptoms in this patient population.[9,10] Conventionally, antidepressants have been used to treat depression related to dementia. The goal of this review is to explore, analyze, and discuss the current literature available on the use of the various antidepressants to treat BPSD. We will then use knowledge gained from our review to discuss the importance of antidepressant use in this patient population and the results of the "Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms" (DESEP) trial.[11]

Although there are several case reports of antidepressants being used to treat BPSD, the purpose of this article is to review data from mostly randomized controlled trials. Other antidepressants discussed in this review consist of certain selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other antidepressants.

We initially searched PUBMED using search terms "BPSD and Antidepressants," "Antidepressants and agitation in dementia," "BPSD and Dementia," "Antipsychotics and Dementia," "Antipsychotics and BPSD," " SSRIs and BPSD," "Citalopram and BPSD," "Sertraline and BPSD," "Fluvoxamine and BPSD," "Fluoxetine and BPSD," "TCAs and BPSD," "MAOIs and BPSD," "Buspirone and BPSD," "Trazodone and BPSD," "SNRIs and BPSD," "Mirtazapine and BPSD," and "Bupropion and BPSD." We also searched "Antidepressants and Neuropsychiatric Symptoms." The most studied antidepressants in BPSD are the SSRIs which will be summarized below.

SSRIS

Citalopram

The first prospective study investigating citalopram in treating BPSD was a 4 week, randomized, placebo-controlled trial comparing citalopram to placebo in 98 dementia patients with emotional disturbance. Citalopram was started at 20 mg and titrated up to 30 mg on the third week if no clinical benefit was noted. Primary outcome in this study was the change on the Clinical Global Impression (CGI) scale. When compared to placebo, the results from this study showed citalopram improved the CGI score and tolerability between the two treatment groups was similar. [12]

The second trial investigating citalopram's efficacy in BPSD was a randomized trial comparing citalopram to perphenazine and placebo. A total of 85 patients with dementia were randomized to receive citalopram 20 mg, perphenazine 0.1 mg/kg/day, or placebo for 17 days. The primary measure of efficacy was change on the Neurobehavioral Rating Scale (NBRS). The study population consisted of demented inpatients with significant agitation and psychosis related to dementia. Specific dementia diagnosis varied, including Alzheimer's, Vascular, Mixed, and Dementia with Lewy-Bodies. Citalopram was found to be more effective than placebo in reducing the total score of the NBRS, along with reducing agitation and liability subscales ($p \leq 0.0001$). Citalopram also showed improvement in cognition and retardation factors. Interestingly, the perphenazine treatment group was shown not to be more effective than placebo ($p = 0.14$). Tolerability with citalopram and perphenazine was similar to placebo. Utilization of rescue lorazepam for greater than 5 days was not significantly different for the three treatment groups. It should be noted that 54% of the patients did not complete the 17 day trial, with the majority of the patients dropping out of the study secondary to lack of efficacy (n=23 patients).[13]

A third prospective trial investigated the use of citalopram versus risperidone in the treatment of BPSD in dementia. The 12 week trial enrolled 103 patients with various types of dementia. The primary outcome measure in this trial was change on the NBRS scale; however, several secondary scales were measured in this trial, which included the Neuropsychiatric Inventory (NPI), Cornell Scale for Depression in Dementia (CDSS), Mini Mental Status Exam (MMSE) and the Severe Impairment Battery (SIB). Citalopram dose was titrated up to a maximum dose of 40 mg and risperidone maximum dose was titrated up 2 mg/day. Changes in the NBRS did not differ between citalopram and the risperidone groups, however, both groups responded compared to baseline ($p<0.001$). There was a significant decrease in agitation and psychosis scores with citalopram, whereas risperidone improved only the psychosis score and not the agitation score on the NBRS. Adverse events were more common with risperidone, with somnolence being the most commonly reported adverse event. Extrapyramidal Symptoms (EPS) rates did not differ between the two treatment groups. Similar to the perphenazine/citalopram study, dropout rates were high (56.3%). Dropouts were similar between the two treatment groups and causation of dropping out did not differ. Most common reasons for patients dropped from the study were due to intercurrent medical problems, adverse events, and psychiatric worsening.[14]

Sertraline

The first study evaluating sertraline's efficacy in the treatment of BPSD was a randomized, double-blind, placebo controlled, crossover trial involving 22 patients with severe dementia. Patients were randomized to receive either 100 mg of sertraline or placebo for 4 weeks. After the 4 weeks, patients underwent a one week washout and then switched to the other treatment group for 4 weeks. NPI and Cohen-Mansfield Agitation Inventory (CMAI) were the primary measure of efficacy. Altogether, 38% of the patients responded to sertraline therapy (NPI change score greater than 4) but overall change was not statistically significant (p=.08). Predictors of response appeared to favor low levels of baseline agitation, female gender, and serotonergic function (measured by a fenfluramine challenge). Adverse event rates were similar to placebo.[15]

A second study evaluating sertraline's efficacy was a double blind, controlled, parallel group study that determined the safety and efficacy of sertraline 25-200 mg per day in those with dementia with BPSD. In this trial, all subjects were given donepezil 5 to 10 mg daily for the 8 weeks of the trial. If the patients continued to have significant behavioral symptoms, then they were randomized to add either sertraline or placebo to their current medication regimen for an additional 12 weeks. Patients were enrolled in the trial if they had a total NPI score of greater than 5 or a severity score of greater than 2 on any domain. A total of 276 patients enrolled in the trial, with 81% of the patients completing the trial. The primary outcome measures in this trial were the change in the NPI score, Clinical Global Impression-Improvement (CGI-I), and Clinical Global Improvement in Severity (CGI-S). This study concluded that there was no significant change with augmentation of donepezil with sertraline

versus placebo on the NPI score (p=0.29), CGI-I endpoint scores (p= 0.20), or the CGI-S (p= 0.24). Sertraline therapy was considered to be well tolerated with diarrhea occurring more often than compared to placebo (p<0.05). All other adverse events were similar when compared to placebo, including changes in the ECG and basic metabolic panel.[16]

The only randomized, double-blind, comparison study investigated the efficacy of sertraline versus haloperidol in patients with agitation in dementia over 10 weeks. Twenty-two patients were randomized to either 25 or 50 mg of sertraline or 1 to 2 mg of haloperidol per day. Primary outcome of agitation reduction was assessed using the (CMAI) at baseline and study endpoint. No significant changes in the CMAI were noted between the sertraline and haloperidol group (p value not reported). The authors did not discuss the overall tolerability or adverse events in the treatment groups.[17]

Fluvoxamine

Two studies have been conducted in evaluating the efficacy of fluvoxamine in the treatment of BPSD. The first study was a double-blind, placebo controlled study with 46 subjects receiving either 50 to 150 mg of fluvoxamine or placebo daily. Total length of the clinical trial was 6 weeks. Main measure of efficacy was the Gottfried, Brane, and Steen Scale (GBS). There were no differences in the change of agitation, behavior, or cognition between the two treatment groups. There is no mention of adverse events in the trial. The authors concluded that the data does not support the use of fluvoxamine in BPSD.[18]

The second study was a randomized, placebo-controlled, crossover trial of 20 outpatients with dementia with psychotic features. The patients were randomized to two groups, perphenazine plus fluvoxamine or perphenazine plus placebo. The first week of drug therapy consisted only of 12 mg/day of perphenazine, and then starting week two, 50 mg of fluvoxamine was introduced. At week 4, patients were crossed over to the other treatment group. Primary outcomes measures were the Brief Psychiatric Rating Scale (BPRS) and CGI. The results demonstrated that fluvoxamine and perphenazine reduced the scores on the BPRS and CGI significantly more than perphenazine and placebo (p=.004). There were no reported adverse events in this trial and there were no changes in the AIMS score between the two groups. Authors concluded that fluvoxamine was effective at reducing psychotic symptoms associated with dementia. However, cytochrome P450 interactions may have caused an increase in perphenazine levels, thus providing a greater effect by increasing the blood level of antipsychotic versus pure pharmacologic effect from fluvoxamine.[19]

Fluoxetine

Only one prospective trial investigating the use of fluoxetine in BPSD has been published. The trial was a 6 week, pilot study comparing haloperidol, fluoxetine, and placebo in 15 community dwelling patients with probable dementia with significant agitation and aggression (≥25 on the CMAI).[9] The primary measure of efficacy was change in the CMAI. Patients were randomized to receive either placebo, 3 mg/day of haloperidol, or 20 mg/day of fluoxetine. The results of the study showed no significant improvement in agitation and aggression among the three treatment groups (p=0.82). Placebo was found to be better tolerated when compared to the treatment groups (p=0.05). The most common adverse reactions in the haloperidol treated group were EPS, depression, and anxiety. Fluoxetine's most common adverse events reported were anxiety, worsening of confusion, and tremor.[20]

No published articles were identified with the use of vilazodone, escitalopram, or paroxetine in the treatment of BPSD. In summary, out of the SSRI's studied, citalopram consistently showed efficacy in the three clinical trials. Fluvoxamine had one trial showing efficacy when added to perphenazine, however, had another failed trial when compared to placebo. Sertraline and fluoxetine failed to show benefit when compared to placebo or active in comparator in all four clinical trials studying efficacy in BPSD. Limitations of the studies which could have impacted the results will be discussed further in this paper.

TRICYCLIC ANTIDEPRESSANTS (TCA'S) AND MONOAMINE OXIDASE INHIBITORS (MAOI)

Tricyclic antidepressants (TCA's) and monoamine oxidase inhibitors (MAOIs) have been on the market the longest within the antidepressant class. However, there are limited studies of these medication classes with dementia, in particular the TCA's. Because of the adverse events and drug interactions within the TCA's and MAOI's, these agents are not recommended in the elderly and should only be used in treatment refractory cases. That being said, the only agent prospectively studied was selegiline. Selegiline was initially studied with optimism due to its potential neuroprotective properties in Parkinson's disease.[21] In 2002, a Cochran Review of 17 studies, analyzed the short and long term use of selegiline in Alzheimer's disease. There was no evidence in clinical

improvement within any aspect of dementia, including psychosis and agitation. As a result, selegiline cannot be recommended in treating BPSD.[21]

BUSPIRONE

Buspirone, a $5HT_{1A}$ receptor agonist, used as an anxiolytic agent, has sporadic case reports and no published, randomized, controlled trialsof BPSD in the literature. Buspirone is not recommended, first- or second-line in behavioral disturbances in dementia due to lacking evidence from randomized controlled trials.[22, 23]

TRAZODONE

Despite the lack of data with buspirone, TCA's, and MAOI's, trazodone, a serotonergic antidepressant, has two prospective studies comparing trazodone to haloperidol in BPSD. Sultzer and colleagues studied the use of trazodone versus haloperidol in 28 patients with BPSD in a 9 week trial. The average doses of trazodone and haloperidol were 200 ± 75 mg per day and 1.8 ± 1 mg per day, respectively. Overall, trazodone showed an improvement in the CMAI scores similar to that of haloperidol. Both groups significantly reduced the CMAI score (P<0.001). Trazodone had two patients develop sedation and gait abnormalities. Seven patients (50%) had an adverse reaction to haloperidol, with EPS being the most commonly reported adverse event.[24]

The second study, conducted by Teri and colleagues, investigated the use of trazodone, placebo, haloperidol, and behavioral management techniques in the treatment of BPSD. In this 16 week, parallel, randomized, placebo controlled trial, 148 patients were randomized to one of the 4 treatment groups. Patients could receive a maximum of 3 mg of haloperidol, 300 mg of trazodone, placebo, or 11 weeks of classes on behavioral management techniques. Average daily doses of haloperidol and trazodone were 1.8 mg and 200 mg, respectively. Primary efficacy was measured using the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIS). Secondary analysis was conducted using the CMAI, Agitated Behavioral Inventory for Dementia (ABID), MMSE, and caregiver burden. Primary outcome on the ADAS-CGIS showed 34% of subjects improved across all treatment arms. However, this improvement was similar to placebo across all treatment groups (p=0.80). Thus, active treatments or placebo were equally effective regarding change on the ADAS-CGIS. It should be noted that 46% of patients worsened in all treatment groups on the primary outcome over the course of 16 weeks. Regarding adverse events, haloperidol was more likely to have Parkinsonism and bradykinesia than any other treatment group.[25]

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI'S)

Research of SNRIs in the management of behavioral and psychological symptoms in dementia is limited. Venlafaxine has been shown to be safe and effective for depression in elderly patients; however, there are no randomized controlled trials specifically addressing BPSD.[26]

MIRTAZAPINE

Research using mirtazapine in the management of behavioral and psychological symptoms in dementia has been limited. Mirtazapine has shown limited significance in alleviating the adverse events of dementia.[27] Mirtazapine was noted to show some significance in the treatment of psychotic symptoms associated with Parkinson's disease patients. In a limited number of reported cases, mirtazapine has been shown to improve persistent psychotic symptoms, including visual hallucinations, without exacerbating motor symptoms.[28]

A 12-week open-label prospective study investigated the efficacy of mirtazapine in agitated patients with dementia. Sixteen patients were enrolled with 13 patients completing the study. The study used the CMAI-Short Form (CMAI-SF), the CGI--Severity (CGI-S) scale, the Geriatric Depression Scale, and the MMSE to assess changes in behavioral symptoms. Among those that completed the study, 11 patients were much or very much improved. Statistically significant improvements between baseline and the 12th week of treatment were noted in both CGI-S and CMAI-SF scores (p<0.001). Three patients dropped out of the study due to mirtazapine's sedative effects. The authors hypothesized that agitation could be related to sleep disorders, further stating, if sleep disorders are solved, then perhaps daytime agitation can be decreased.[29] No other studies using mirtazapine for the treatment of aggression or agitation in dementia were reported.

BUPROPION

There are currently no prospective studies investigating the use of bupropion in the treatment of BPSD.

DISCUSSION/CONCLUSION

While current data show elderly patients with dementia are at an increased risk of adverse events with atypical antipsychotics, these medications seem to have the best documentation regarding efficacy in treating BPSD. Secondary to the black box warning of the use of

antipsychotics in dementia, many clinicians are utilizing the antidepressants to treat BPSD. However, this review of published clinical trials utilizing antidepressants to treat BPSD demonstrates that, overall, data are very much lacking to support the use of antidepressants for this indication, despite the widespread use in clinical practice. Of all the trials discussed in this review, only three antidepressants showed promise in the management of BPSD (i.e., citalopram, trazodone, and mirtazapine).

Citalopram consistently showed improvement in the treatment of BPSD. However, in two of the three trials, doses above 20 mg were utilized. With the FDA warning limiting the use of citalopram to less than 20 mg in persons >60 years of age, secondary to increase in the QTc interval, even citalopram's efficacy may be limited at this point in time. Yet, based upon this review, if an antidepressant is warranted for the treatment of BPSD, citalopram would be the drug of choice. Currently, the "Citalopram for agitation in Alzheimer's disease" (CitAD) trial is underway and will help further delineate the efficacy and safety of citalopram in the treatment of BPSD.[30] While escitalopram is an enantiomer of citalopram, no studies have been conducted to investigate whether or not it has benefit in alleviating behavioral symptoms in dementia. As a result, the efficacy of escitalopram is unknown in this patient population.

Trazodone appears to have mixed results regarding efficacy. The Sultzer et al study showed trazodone to be equally efficacious as haloperidol in BPSD. However, the Teri et al study showed trazodone, placebo, and haloperidol to be all equally efficacious when compared to each other. Utilizing the Cochrane Collaboration's tool for assessing risk of bias, there is low risk of bias when comparing the internal validity of the trazodone trials.[31] As a result, it is unclear if trazodone is better than placebo in the treatment of BPSD. Mirtazapine also showed efficacy in treatment of BPSD, however, the trial was an open-label pilot study with no active comparator.

All these clinical trials reviewed in this paper are severely limited by the internal validity of the trial design. Most of the clinical trials suffered from low enrollment with several treatment arms (increased probability of making a Type II error), high drop-out rates, high rates of adverse events, and/oruse of non-standardized rating scales; thus significantly decreasing the utility of these agents in clinical practice. It should also be noted that most of the trials conducted a wash out period before the initiation of the trial, resulting in the possibility of rebound agitation prior to study initiation. Finally, several trials compared various active treatments to each other rather than employ the use of a placebo-controlled arm. Placebo response in this literature appeared to have a similar efficacy when compared to active treatment (approximately 30% reduction on primary efficacy measure). Clinical trial design, such as in the literature reviewed, can lead to the possibility of overstating the clinical effectiveness of active treatments in the trials without a placebo arm. Utilizing the Cochrane Collaboration's tool for assessing risk of bias, the trials reviewed were determined to have an unclear risk of bias.[31]

Although prospective studies have not found data to show a robust response regarding efficacy of antidepressants in management of BPSD, the DESEP trial demonstrates that patients may have rebound agitation and aggression once the antidepressant is discontinued. The DESEP study was a 25-week, double-blind, parallel group, randomized, placebo-controlled trial comparing continuation versus discontinuation of four SSRIs (i.e., escitalopram, citalopram, sertraline, paroxetine) in patients with dementia. Patient scores on the Cornell scale for depression and dementia along with the neuropsychiatric inventory were the primary endpoints of the study. Secondary endpoints, consisting of dementia, cognitive impairment, and extra pyramidal side effects, were assessed at baseline and after 25 weeks using the clinical dementia rating scale, severe impairment battery, unified Parkinson disease rating scale, and Lawton and Brody's physical self- maintenance scale. Subgroup analysis of the individual SSRIs was not done. Results of the primary endpoints concluded patients in the discontinuation arm had a significant increase in depressive symptoms than the continuation arm ($p=0.045$). Neuropsychiatric symptoms increased shortly after antidepressant discontinuation; however, there was no difference in agitation scores at 25 weeks ($p=0.068$). There were no significant differences in secondary endpoints between the two groups.[11]

Overall, there is a lack of conclusive evidence that antidepressants are clinically effective in this area, thus the need for more well-designed clinical trials in the treatment of BPSD, such as the CitAD trial.[30] The only agent that consistently showed improvement in the clinical trials was citalopram. All other antidepressant agents either failed to separate from placebo or clinical trial design was not rigorous enough to make definitive conclusions.

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