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Cognitive Disorders (M Geschwind, Section Editor)

Treatment of Behavioral and Psychological Symptoms of Alzheimer's Disease

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Opinion statement

Behavioral and psychological symptoms of dementia (BPSD) are frequent amongst people with Alzheimer's disease (AD) and other dementias, commonly confer risk to that person and others, and present a significant management challenge for clinicians. There is increasing evidence to support the value of simple psychological interventions and the treatment of pain as a first-line management strategy prior to pharmacotherapy. The most widely prescribed pharmacological treatments—atypical antipsychotics—have a modest but significant beneficial effect in the short-term treatment of aggression (over 6–12 weeks) but limited benefits in longer-term therapy. In addition, there have been increasing concerns regarding the potential for serious adverse outcomes, including stroke and death. The potential pharmacologic alternatives to atypical antipsychotics with the most encouraging preliminary evidence include memantine, carbamazepine, citalopram, and prazosin. Large, prospective, randomized placebo-controlled trials are needed to establish the role of these agents as clinical therapies for the treatment of BPSD.

Introduction

Worldwide, 35 million people suffer from dementia [1], the majority of whom have Alzheimer's disease (AD). It is a devastating illness, which results in a progressive decline in cognitive ability and functional capacity and the emergence of behavioral and psychological symptoms of dementia (BPSD).

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The progressive decline and the BPSD cause immense distress to patients, their carers and families, and have an enormous societal impact.

Over the course of the illness, more than 90% of people with dementia develop at least one BPSD [2]. Aggression occurs in approximately 20% of people with AD in contact with clinical services [3] or living in the community [4] and 40% to 60% in care facilities [5]. The distress, and on occasions the risk, associated with these symptoms makes them a high treatment priority. In most of these individuals, the BPSD have a clinically significant impact [6]. They are often distressing for the patients who experience them [7], lead to stress and depression in those who care for them [8, 9], are associated with a reduced quality of life [10], and are often the trigger for institutional care [11].

A broad clinical assessment is essential before specific therapies are considered. Physical health problems such as infection (including urinary tract, chest, or dental infections), pain, or dehydration are common and often precipitate BPSD, as can visual and auditory impairment, which should be treated when possible [12, 13]. A comprehensive review of pharmacologic treatments may identify therapies exacerbating depression, confusion, or other BPSD.

Pain is difficult to assess in people with dementia and is under-diagnosed, but better pain management does reduce BPSD [14]. A recent cluster randomized trial compared stepped analgesia with usual care over 8 weeks and showed a marked and significant reduction in agitation in the group receiving analgesia, which was correlated with improvement in pain [15•]. This perhaps indicates that treating even minor, low-level pain may confer considerable benefit as part of the management of agitation and other BPSD.

Treatment

Simple psychological interventions

- All best practice guides recommend non-drug approaches as the first-line treatment option for BPSD, except in exceptional circumstances of substantial risk or extreme distress [16].
- BPSD that are sporadic and do not cause distress or risk may be effectively managed without a specific therapy or may respond well to simple psychological therapy approaches. When symptoms are mild to moderate, valuable insights can be gained by working with relatives or care staff to monitor the symptoms and avoid the need for more intensive treatment.
- As an example of a practical approach to implementing nonpharmacologic interventions for BPSD, a range of psychological intervention tools have been developed by Cohen-Mansfield and colleagues [17, 18]. These interventions are based on activities and interactions that can be personalized within the structured framework of a care home setting, such as structured social interaction and personalized music. These approaches were rigorously evaluated in a robust, randomized controlled trial (RCT) with 167 participants, which showed significant benefits in agitation overall. A smaller 6-week study also showed improvement in specific symptoms of agitation such as shouting [17, 18]. Despite these positive outcomes, it can be difficult to implement these individualized interventions in all clinical and care home settings because of the level of skill required of the care staff.

- To address this issue, our group designed a simplified version of the Cohen-Mansfield intervention called the Brief Psychosocial Therapy (BPST). The BPST involves a daily personalized social interaction for 10 to 30 minutes to be delivered by a care assistant under the supervision of a therapist who has attended a 2-day BPST training course [19]. The BPST was evaluated in an open trial of more than 200 participants and showed a significant seven-point improvement on the Cohen-Mansfield Agitation Inventory. It should be noted that the absence of a control treatment means that it is difficult to determine the proportion of the benefit attributable to the intervention. Nevertheless, this study supports best practice guidance for BPSD, providing professionals with options for simple, first-line non-drug interventions, and highlights the finding that most individuals experience improvement without pharmacologic treatment.
- It should also be noted that reminiscence therapy confers modest but significant benefits in BPSD and may be valuable as part of a personalized treatment and care plan.

Intensive psychosocial interventions

- People experiencing more severe or challenging BPSD may benefit from more intense individualized psychological interventions. Evidence from large case series and a couple of small but well-designed clinical trials supports the effectiveness of individualized, comprehensive interventions delivered by a clinical psychologist and designed using "antecedent, behavior, consequence" (ABC) charts. For example, one cluster randomized trial compared a clinical psychology model based on the ABC principles with a traditional old-age psychiatry service in 55 referrals of people with BPSD. Both groups showed favorable responses to the interventions, but the model led by the clinical psychologist resulted in additional reduction of antipsychotic prescriptions and fewer hospital days [20].
- An alternative intensive approach to managing BPSD is through training of care staff. Studies evaluating this approach have reported variable results, with many shorter studies indicating that initial benefits are not sustained beyond the end of the training period. However, more recent RCTs of intensive training packages and practice interventions have conferred substantial benefit for 4–12 months. One 9-month cluster RCT analyzed the effectiveness of a person-centered care training package delivered 2 days a week by a healthcare professional. The study was performed in 12 care homes with 347 residents and led to a significant reduction in antipsychotic prescriptions for people with dementia, without increasing agitation or disruptive behavior [21]. Similar benefits have also been demonstrated in a study that delivered a nursing home liaison service to nine care homes, involving a part-time old-age psychiatrist and a community psychiatric nurse. This study was based on Cognitive Behavioral Therapy as a first-line treatment choice [22]. Further evi-

dence to support training approaches includes an excellent three-arm cluster RCT that demonstrated the additional value of Dementia Care Mapping to person-centered care in 15 care homes with 289 participants with dementia. The Dementia Care Mapping was used as a tool to improve person-centered care planning and substantially reduced agitation by more than 10 points on the Cohen-Mansfield Agitation Inventory compared with treatment as usual (standardized effect size Cohen's $d > .5$ for both treatments) [23•].

Pharmacologic treatment

Antipsychotics

- Antipsychotics have been widely prescribed for BPSD since the 1960s, partly inferring potential efficacy for the treatment of psychotic symptoms because of their benefit in treating psychosis in schizophrenia and bipolar disorder, but also perceiving benefit because of their sedative properties. Although the use of typical antipsychotics has declined, atypical antipsychotic drugs remain the first-line pharmacologic treatment for BPSD. For example, a recent Department of Health report in the UK emphasized that up to 180,000 people with dementia (almost 25% of people with dementia in the UK) are prescribed these treatments [24]. However, increasing safety concerns regarding this class of compound in people with AD and other dementias has resulted in warnings from regulatory authorities internationally, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and agencies in individual European countries. In 2005, the FDA issued a warning regarding the increased risk of mortality associated with atypical antipsychotics in patients with dementia, and this warning was extended in 2008 to include typical antipsychotics [26]. Based upon these safety concerns, there is a clear imperative to review clinical practice in this area.

Typical antipsychotics

In the literature, 11 placebo-controlled trials have evaluated the efficacy of typical antipsychotics for the treatment of BPSD. Most of the trials have involved small sample sizes and have been performed over periods of 4–12 weeks. A good outcome in these studies is defined by convention as a 30% improvement on standardized behavioral rating scales. Typical antipsychotics confer a significant but modest advantage compared with placebo (59% versus 41%), albeit in the context of a very high placebo response [27].

The most comprehensive evidence base for the treatment of agitation and aggression by agents in this drug class pertains to haloperidol, for which four RCTs [27] have been completed. These trials indicate a significant improvement in symptoms of aggression with haloperidol and more modest but significant benefits in the treatment of psychosis, compared with placebo. There is no evidence for substantial improvement in other symptoms such as agitation. Very little clinical trial evi-

dence is available regarding the efficacy of other typical antipsychotics for the treatment of BPSD.

Typical antipsychotics are associated with numerous severe adverse effects in patients with AD. These include parkinsonism [28], dystonia, tardive dyskinesia, acceleration of cognitive decline, and prolongation of the QTc interval on ECG [29], leading to added risk of cardiac arrhythmias. There is also a significant increase in mortality, even greater than the mortality risk associated with atypical antipsychotics [30, 31]. Until 2000, thioridazine, promazine, and haloperidol were all widely used in the clinical setting, but prescribing practice has changed substantially in response to specific concerns related to the cardiac safety of thioridazine and general concerns regarding the side effect profile of typical antipsychotics. The use of haloperidol remains controversial, and it is still recommended and widely prescribed as a treatment for aggression and psychosis in some countries despite higher risks of important side effects, including mortality [27, 30].

Atypical antipsychotics

A more substantial number of trials have focused on atypical antipsychotics for the treatment of BPSD. In total, 18 placebo-controlled RCTs have been conducted [27, 32] examining efficacy in people with AD over 6–12 weeks. The best evidence of efficacy for the treatment of agitation and aggression relates to risperidone. Five trials have indicated a modest but significant improvement in aggression compared with placebo, with a larger effect size conferred by a dose of 2 mg per day. In the Behavioral Pathology in Alzheimer's Disease (BEHAV-AD) rating scale, an effect of −0.84 points (95% CI, −1.28 to −0.40 points) was seen for a dose of 1 mg daily, and −1.50 points (95% CI, −2.05 to −0.95 points) for a dose of 2 mg daily, over 12 weeks of treatment. This equates to a small treatment effect size (Cohen's*d* 0.2 at the optimal dose). However, there is only limited evidence that risperidone confers benefit in the treatment of BPSD other than agitation and aggression [27, 32].

Additional evidence from two trials shows that aripiprazole confers a similar magnitude of benefit to that seen with risperidone [32]. The evidence for olanzapine is more equivocal [27], and there is clear evidence that quetiapine is ineffective [27, 33]. There is limited evidence from published RCTs regarding other atypical antipsychotics [27, 32].
The evidence base pertaining to the treatment of psychosis in AD is more limited. A recent meta-analysis [32] discussed seven trials that reported psychosis as an outcome. Three trials demonstrated a modest but significant improvement with risperidone compared with placebo at a dosage of 1 mg per day but not at other dosages (−0.8 point in BEHAV-AD, standardized effect size Cohen's*d* <0.2), and two trials with olanzapine showed a nonsignificant trend towards benefit.

The only RCT to specifically demonstrate benefit for clinically significant psychosis in people with AD reported that aripiprazole conferred significant benefits for the treatment of clinically significant psychosis in more than 400 people with AD in care settings [34]. The only published placebo-controlled RCT examining quetiapine in people with AD found it to be ineffective in controlling agitation [35].

Evidence for longer-term efficacy (6 months or longer) of antipsychotics for the treatment of BPSD is very limited. The AGIT and DART studies did not demonstrate any advantage for antipsychotics compared with placebo over 6 months [35, 36], and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) described no overall benefit [37]. However, the CATIE did indicate that antipsychotics were less likely than placebo to be discontinued because of perceived ineffectiveness over 9 months [37].

Widely reported adverse effects of atypical antipsychotics include extrapyramidal symptoms, sedation, gait disturbances, and falls. Many agents also lead to anticholinergic side effects including delirium [27, 32]. A meta-analysis also identified a significant increase in respiratory and urinary tract infections and peripheral edema among people treated with risperidone, compared with placebo [27]. These are likely to be class effects for atypical antipsychotics. The limited trial data for other atypical antipsychotics precluded a comprehensive meta-analysis of adverse events.

Over the past few years, the most serious concerns regarding atypical antipsychotics have related to emergent data suggesting an increase of cerebrovascular events and increased mortality in AD patients. Observation of combined data from placebo-controlled trials shows that risperidone has been associated with a threefold increased risk of serious cerebrovascular adverse events when compared with placebo (37/1,175 vs 8/779; OR, 3.64; 95% CI, 1.72–7.69; P=0.0007) [27]. In the trial of aripiprazole by Mintzer et al. [34], cerebrovascular adverse events were reported in four patients who were prescribed aripiprazole (10 mg/day) but in none of the placebo-treated patients. Other sources of information, such as prescription event monitoring, would indicate that this is probably a class effect.

In 2005, the FDA published a warning highlighting a significant increase in mortality risk (OR, 1.7) for people with AD treated with atypical antipsychotics compared with individuals receiving placebo in RCTs [25]. Schneider and colleagues [38] have reviewed the evidence from 15 of these trials and confirmed a significant increase in mortality (OR, 1.54), with no difference between specific agents. The recent DART-AD RCT indicated that this excess mortality risk continues over longer periods of prescribing, with an increasing impact on the absolute number of attributable deaths [39••].

Despite the safety concerns, the best evidence of efficacy for the pharmacologic treatment of aggression relates to atypical antipsychotics, particularly risperidone. Risperidone is also the only antipsychotic specifically licensed for the treatment of aggression, with use according to the license restricted to short-term management (6 weeks) of severe physical aggression causing tangible risk or extreme distress, when non-drug treatments have not been effective. This is consistent with best practice guidelines. Over longer periods of use, antipsychotics confer minimal benefit, the absolute increased mortality risk rises significantly, and the impact on cognitive decline appears to be substantial [35–37, 39••]. As the risks associated with the use of antipsychotics have become increasingly clear, there has been considerable pressure to reduce pre-

scribing them and increase monitoring, review, and discontinuation for people with dementia.

Pharmacogenetics: In a 3-year cohort study, Angelucci et al. [40] reported that the T allele of the 5HT2A T102C polymorphism is significantly associated with poorer response to risperidone treatment than the C allele. More recently, preliminary findings in the only genetic-association RCT study to date [41] to investigate the adverse effects of atypical antipsychotic treatment in dementia indicate that the length polymorphism in the serotonin transporter gene (5-HTTLPR) is associated with a greater number of early side effects and reduced early treatment response in risperidone-treated individuals. Although this finding does require replication, it serves to highlight the importance of close monitoring in some individuals prescribed antipsychotics and shows that genetic data may assist with the initial clinical decision about prescribing.

Other pharmacologic treatments for agitation/aggression and psychosis

Cholinesterase inhibitors

A meta-analysis demonstrated a small but significant overall advantage of cholinesterase inhibitors (ChEIs) over placebo with regard to the treatment of BPSD in AD [42]. Additional support for beneficial effects of ChEIs on BPSD comes from a randomized withdrawal study, in which cessation of donepezil was associated with a significant worsening of the total Neuropsychiatric Inventory (NPI) score within 6 weeks [43]. However, there was no short-term benefit for treatment of clinically significant agitation with donepezil over 12 weeks in a large RCT [44], suggesting that ChEIs do not appear to be useful in the management of acute agitation. ChEIs appear to have their greatest effects on depression and dysphoria, apathy and indifference, and anxiety [45]; they probably are not an effective treatment for clinically significant agitation or aggression in AD, at least over a 3-month period.

Memantine

Individual studies, meta-analyses, and pooled analyses indicate that memantine may confer benefit in the treatment of mild to moderate irritability and lability, agitation or aggression, and psychosis over 3–6 months in patients with AD [46–49]. Although this evidence is very encouraging with respect to memantine as a useful adjunct to treatment for mild BPSD, contributing to the reduced emergence of BPSD [49], there are not yet any published RCTs specifically involving patients with clinically significant agitation or aggression. Data presented at the recent International Conference on Alzheimer's Disease (ICAD) from the recently completed Memantine for Agitation in Dementia (MAGD) placebo-controlled RCT did not indicate significant benefit. It is hoped that ongoing RCTs in Canada and in the UK may clarify the role of memantine in treating agitation and aggression in patients with AD.

Antidepressants for agitation and aggression

In a 17-day trial in psychiatric inpatients with severe BPSD related to AD, Pollock and colleagues [50] reported that citalopram was superior to placebo, with the greatest efficacy for agitation or aggression, an effect not seen with perphenazine. In a later study, citalopram was found to be comparable in efficacy to risperidone, differentiated by its significant effect on agitation symptoms and its superior tolerability in the treatment of moderate to severe BPSD [51]. RCTs of sertraline [52] and trazodone [53] have been less promising.

Anticonvulsants

Two small parallel-group RCTs of carbamazepine for the treatment of agitation and aggression in AD, both conducted over a period of 6 weeks or less, suggested potential benefit [54, 55]. A meta-analysis of the two trials [56] indicates significant improvement on both the Brief Psychiatric Rating Scale (mean difference −5.5; 95% CI, −8.5 to −2.5) and on Clinical Global Improvement (OR, 10.2; 95% CI, 3.1–33.1). Both studies also suggest good tolerability. In contrast, valproate has not shown treatment benefits for BPSD [57].

Other treatments

It will also be important to use our best scientific understanding of the biological basis of specific symptom clusters such as delusions, hallucinations, aggression, and agitation to develop more targeted therapies. One example is the potential use of muscarinic agonists for the treatment of delusions: A number of post mortem studies have indicated an association between altered muscarinic receptor binding and delusions in dementia patients [58], and preliminary data from secondary analyses of RCTs with muscarinic agonists such as xanomeline [59] indicate a potential treatment effect on psychosis.

Another example is the relationship between altered adrenoceptors and agitation or aggression in post mortem studies in people with AD [60]; a preliminary, small RCT of the alpha-adrenoceptor blocker prazosin indicates potential benefit in the treatment of BPSD in AD patients [61•]. Targeted drug development based upon the principles of evidence-based experimental medicine is more likely to lead to the development of effective therapies.

Advice on best practices

- The available evidence indicates that it is important to implement nonpharmacologic treatments before considering pharmacologic therapies for BPSD. We advise at least 4 weeks of ongoing assessment and monitoring, addressing any underlying medical issues, treating pain, reviewing care plans, and implementing simple, nondrug treatment. Many symptoms will spontaneously resolve over this period, particularly with the addition of simple first-line therapies.
- If no improvement is evident, and there is severe distress to the person with dementia or tangible risk to that person or others, then a phar-

macologic treatment approach should be considered (Table 1). Conversely, the potential adverse consequences of pharmacologic intervention should lead to its avoidance unless distress or clear risk are evident.

- Based on the evidence base and current drug licenses, risperidone should probably the preferred treatment if a pharmacologic therapy is needed. The evidence base is more robust than for other atypical

Table 1. Pharmacologic treatment of agitation and aggression in people with dementia: Summary of key evidence for treatments conferring potential benefit

Treatment approach	Trials	Evidence	Major adverse effects	Interpretation
Typical antipsychotics	11 randomized, placebo-controlled trials; mostly small sample sizes and 4–12 weeks in duration (1≤16 weeks)	• Early meta-analysis concluded significant but modest advantage over placebo in treating behavioral symptoms • Recent meta-analysis reports only 1 placebo-controlled trial showed significant benefit of thioridazine • Small thiothixene study suggested efficacy at low doses; symptoms return after discontinuation • Meta-analysis of haloperidol indicates improvement in aggression but not in other symptoms of agitation	Parkinsonism, dystonia, tardive dyskinesia; QTc prolongation; significant increase in mortality risk compared with atypical antipsychotics (≤180 days, RR, 1.37)	Adverse events associated with typical antipsychotics make their use inadvisable in people with AD.
Atypical antipsychotics	18 placebo-controlled trials over 6–12 weeks; only 3 trials of 6–12 months	Significant benefit in the treatment of aggression within 12 weeks. More limited benefit for other symptoms; do not appear to be beneficial over longer periods	Extrapyramidal symptoms, sedation; increased mortality (1.5–1.7-fold); threefold increase in cerebrovascular adverse events	Probably still the best option for short-term (6–12 weeks) treatment of aggression that is severe, persistent, and treatment-resistant. Serious adverse effects are a major caution to long-term therapy.
Other treatments				
Carbamazepine	2 very preliminary placebo controlled trials over 4–6 weeks	Meta-analysis of the 2 studies provides provisional evidence of benefit on global clinical outcome and neuropsychiatric symptoms	Duration too short to assess safety	
Citalopram	1 small placebo-controlled trial over 17 days	Significant benefit in agitation and aggression	Duration too short to assess safety	
Memantine	Several post hoc analyses of placebo-controlled trials of memantine to examine impact on agitation and psychosis	These retrospective analyses indicate potential for modest but significant benefit for mild to moderate agitation	Good tolerability	
Prazosin	1 small placebo-controlled trial (22 patients) over 8 weeks	Significant benefit in neuropsychiatric symptoms and global clinical outcome	Good tolerability; no serious hypotension-related adverse events in this preliminary study	
Xanomeline	Secondary analysis of a placebo-controlled trial	Significant improvement in psychotic symptoms	High prevalence of gastrointestinal adverse events	

antipsychotics, and it is specifically licensed for the treatment of severe aggression in people with AD. The severe potential adverse effects such as stroke and death can probably be reduced by closer monitoring of potential mediating factors such as oversedation, dehydration and early signs of chest infection. A pretreatment ECG to determine the QTc interval may also be helpful. Risperidone or other atypical antipsychotics should not be used for more than 12 weeks, other than in exceptional circumstances.

- The evidence base for other non-antipsychotic psychotropic drugs is limited, so they should not be considered as a first-line treatment for any BPSD symptoms. If an individual has not responded to 12 weeks of risperidone and severe distress and risk persist, possible alternatives may be carbamazepine, citalopram, or memantine, although the evidence base for each is less than ideal.
- These principles have been outlined in a new best-practice tool developed by the Alzheimer's Society and the Department of Health in the UK [62]. This tool builds on the best available evidence and emphasizes the importance of reducing the use of these drugs within the context of improved overall treatment and care. The tool aims to support health and social care professionals in implementing clinical practices to reduce the emergence of BPSD and to provide alternative treatment options when symptoms do occur. This guide also provides a framework for monitoring and reviewing of ongoing prescriptions, with a focus on encouraging the discontinuation of antipsychotics after 12 weeks [36].

Disclosure

Conflicts of Interest: A. Corbett: Consulting fees from Acadia Pharmaceuticals for BPST trial, Speaker's honoraria from Lundbeck Ltd., Bial Pharmaceuticals, and Novartis; J. Smith: none; B. Creese: none; C. Ballard: Consultancy and speaking fees from Lundbeck, Esai, Bristol-Myers Squibb, Janssen, Acadia, and Novartis pharmaceutical companies; Research support to his institution from Lundbeck and Esai pharmaceutical companies.

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