Management of agitation and aggression associated with Alzheimer disease

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Abstract | Agitation and aggression are frequently occurring and distressing behavioral and psychological symptoms of dementia (BPSD). These symptoms are disturbing for individuals with Alzheimer disease, commonly confer risk to the patient and others, and present a major management challenge for clinicians. The most widely prescribed pharmacological treatments for these symptoms—atypical antipsychotics—have a modest but significant beneficial effect in the short-term treatment (over 6–12 weeks) of aggression but limited benefits in longer term therapy. Benefits are less well established for other symptoms of agitation. In addition, concerns are growing over the potential for serious adverse outcomes with these treatments, including stroke and death. A detailed consideration of other pharmacological and nonpharmacological approaches to agitation and aggression in patients with Alzheimer disease is, therefore, imperative. This article reviews the increasing evidence in support of psychological interventions or alternative therapies (such as aromatherapy) as a first-line management strategy for agitation, as well as the potential pharmacological alternatives to atypical antipsychotics—preliminary evidence for memantine, carbamazepine, and citalopram is encouraging.

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Introduction

Worldwide, almost 25 million people have dementia, 50–75% of whom have Alzheimer disease (AD).[1] AD is a devastating illness that results in a progressive decline in cognitive ability and functional capacity, causes immense distress to patients, their carers, and their families, and has an enormous effect on society. Numerous issues surround this disease in terms of research priorities and the clinical treatments used; such issues include the development of disease-modifying treatments, the discovery of diagnostic biomarkers, and the identification of effective disease-prevention strategies. Although these are crucial long-term goals, the most frequent issue for people with AD who present to clinical services remains the management of behavioral and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms. Over a 5-year period, more than 90% of people with dementia develop at least one BPSD,[2] with around 85% of cases having serious clinical implications.[3] These symptoms are frequently distressing for the patient,[4] and problematic for the carer,[5] in whom they can result in clinical depression.[6] In addition, BPSD are often the precipitant for transfer of the patient to institutional care.[7]

BPSD present as three main syndromes—agitation, psychosis, and mood disorders[8]—and these syndromes frequently co-exist. Almost all BPSD increase in frequency and severity over time.[2] In the common scenario of a patient who presents with simultaneous and multiple symptoms, clinicians should not group together disparate symptom clusters that could have different biological and psychosocial triggers. For example, apathy and depression are very different from aggression and paranoid delusions, and an appreciation of such complexity is vital to determine the appropriate treatment for BPSD syndromes. This Review focuses on treatment strategies for agitation and aggression. These symptoms become increasingly evident as AD progresses (Figure 1), are the most likely symptoms to require pharmacological intervention, and often present considerable treatment dilemmas for clinicians. Common symptoms of aggression in people with AD include verbal insults and shouting, as well as physical aggression such as hitting and biting others, and throwing objects. These symptoms most commonly manifest when people with AD are being assisted with personal care. Common symptoms of agitation include restlessness and pacing, excessive

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Key points

- Agitation and aggression are frequent and distressing symptoms that present major management problems in people with Alzheimer disease (AD)
- Atypical antipsychotics are widely used in the pharmacological treatment of agitation and aggression, but their benefit is primarily limited to short-term management of aggression
- Serious adverse events are associated with atypical antipsychotics in AD, including increased risk of stroke and death
- An evidence base is emerging to support a variety of practical and easy-to-implement nonpharmacological treatments for the first-line treatment of agitation and aggression in AD
- Further clinical trials of pharmacotherapy for agitation and aggression in AD are urgently needed, but preliminary data indicate that memantine, citalopram and carbamazepine could be promising alternatives to atypical antipsychotics

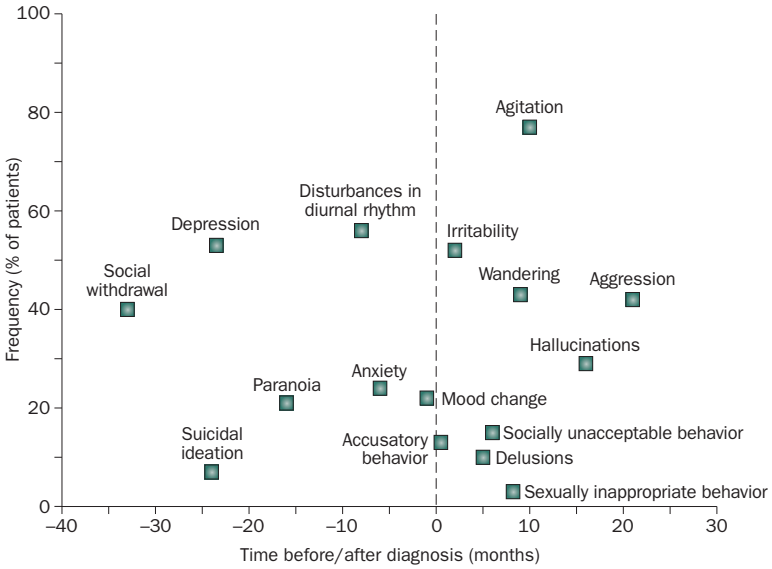

Figure 1 | Peak frequency of behavioral symptoms as Alzheimer disease progresses. Permission obtained from Blackwell Publishing © Jost, B. C. & Grossberg, G. T. *J. Am. Geriatr. Soc.* **44**, 1078–1081 (1996).

fidgeting, motor activities associated with anxiety (such as hand wringing and following a carer around the house), and abnormal vocalizations.

Given the limited evidence base to guide treatment decisions, the management of agitation and aggression is often based on clinical judgment. Such management is becoming a progressively more challenging and controversial area of clinical practice because of increasing evidence that, in people with dementia, the use of antipsychotic drugs—which have traditionally been used as a first-line management approach for these symptoms—is associated with serious adverse effects. In this Review, we present a summary of the evidence for benefit and harm related to the use of antipsychotic drugs for the treatment of agitation and aggression in patients with AD, followed by a review of the evidence for alternative nonpharmacological and pharmacological approaches for the management of agitation and aggression in this group of patients. When specific data are not available on the treatment of agitation and aggression, data on the overall treatment of BPSD will be presented if thought to be of particular importance. We will also briefly discuss emerging biological findings that should inform further development of pharmacological treatments for agitation and aggression. Where the evidence is incomplete, this Review provides the consensus opinion of the authors to help guide clinical decision-making.

Antipsychotics

Antipsychotic drugs (usually now referred to as 'typical antipsychotics') were introduced as a treatment for schizophrenia in the 1950s and 1960s, and by the 1970s these drugs were in frequent clinical use as an 'off-licence' treatment for agitation, aggression, and other BPSD. In the early 1990s, atypical antipsychotics such as risperidone, olanzapine, and quetiapine were introduced for the treatment of schizophrenia. The adverse-effect profiles of atypical agents are generally favorable in comparison to those of typical agents, and consequently atypical antipsychotics became the preferred option for the treatment of agitation and aggression (and other BPSD) in patients with AD by the mid-1990s. However, several important issues relate to the use of these agents in patients with AD, which we outline in the following sections.

Typical antipsychotics

11 randomized, placebo-controlled trials have been carried out of typical antipsychotics for the treatment of BPSD, which mostly involved small sample sizes and were performed over periods of between 4 and 12 weeks (see Table 1).[9–12] With a good outcome defined as a 30% improvement on standardized behavioral rating scales, as per convention, a significant but modest advantage of typical antipsychotics over placebo (59% versus 41%) has been reported, albeit in the context of a high placebo response.[9] The most comprehensive evidence within this drug class on treatment of agitation and aggression pertains to haloperidol, in which four randomized controlled trials (RCTs) have been completed. These trials indicated a significant improvement in symptoms of aggression with haloperidol compared with placebo, but showed no substantial improvement with the drug in other symptoms of agitation.[13] Very little clinical trial evidence is available on other typical antipsychotics in the treatment of agitation or aggression.

Typical antipsychotics are, however, associated with several severe adverse effects in patients with AD. These effects include parkinsonism,[13] dystonia, tardive dyskinesia,[14] and QTc-interval prolongation.[15] The last of these effects has been demonstrated with several previously widely prescribed typical antipsychotics, including thioridazine and droperidol;[15] both have now either been withdrawn or are prescribed infrequently to people with dementia. Furthermore, a significant increase in mortality associated with typical antipsychotics compared with atypical antipsychotics has been identified in people

Table 1 | Pharmacological treatment of agitation and aggression in people with dementia

Trials conducted	Evidence	Major adverse effects	Interpretation
Typical antipsychotics[9,10,12,13,15,16,18]			
11 randomized, placebo-controlled trials, mostly small sample sizes and of 4–12 weeks' duration; one up to 16 weeks' duration	Significant but modest advantage over placebo for behavioral symptoms in early meta-analysis Thioridazine: only one placebo-controlled trial showed significant benefit in recent meta-analysis Thiothixine: a small study suggested efficacy at low doses but that symptoms return after discontinuation Haloperidol: meta-analysis indicated improvement in aggression but not in other symptoms of agitation	Parkinsonism, dystonia, tardive dyskinesias; QTc-interval prolongation; significant increase in mortality compared with atypical antipsychotics (administered for ≤180 days, relative risk 1.37)	Adverse events associated with typical antipsychotics make their use inadvisable in people with Alzheimer disease
Atypical antipsychotics[18,19,22,25]			
18 placebo-controlled trials over 6–12 weeks; only three trials of 6–12 months	Significant benefit in the treatment of aggression over 12 weeks Limited benefit for other symptoms and lack of benefit over treatment periods longer than 12 weeks	Parkinsonism; sedation; increased mortality (1.5–1.7-fold); increased cerebrovascular adverse events (threefold)	Probably still the best option for short-term (6–12 weeks) treatment of aggression that is severe, persistent, and treatment resistant, but serious adverse events are a major contraindication to long-term therapy
Cholinesterase inhibitors[23,49–51,79–81]			
More than 30 RCTs over 6–12 months, but only three specifically in people with clinically relevant agitation	No benefit in agitation over 12–24 weeks in two of the three trials that focused on patients with clinically relevant agitation	Generally well tolerated; gastrointestinal symptoms, including nausea and vomiting, are the most frequent adverse effects	Evidence from the total pool of trials suggests an overall effect on neuropsychiatric symptoms over 6 months, but the main benefits are probably for anxiety and apathy rather than agitation and aggression
Memantine[52–56]			
Six RCTs over 3–6 months, none specifically in patients with clinically important agitation or aggression	Benefit in irritability, lability, agitation, aggression and psychosis over 3–6 months in individual studies, meta-analysis and pooled analyses Significant benefit in a pooled analysis of patients with at least one symptom of aggression, agitation or psychosis	Very well tolerated; low risk of hypertension	Promising treatment, but a prospective study in patients with clinically significant agitation is required
Antidepressants[12,59–62,82]			
One comparative trial and one parallel-group RCT of trazodone; one small placebo-controlled RCT and one active-comparator RCT of citalopram; one RCT of sertaline	Trazodone: meta-analysis concluded insufficient evidence of efficacy Citalopram: equivalence to other active treatments in active-comparator trials, with efficacy over placebo in one small placebo-controlled trial Sertaline: significant benefits for agitation in a post hoc analysis in placebo-controlled RCT	Generally well tolerated	Evidence base for SSRIs is encouraging but preliminary; large placebo-controlled trials of long duration are urgently needed; further work is needed to establish whether a differential response is shown by genotype or in patients with affective and/or psychotic symptoms
Anticonvulsants[64–67,83,84]			
Two small, short, placebo-controlled RCTs of carbamazepine; mainly open trials or case series with other anticonvulsants such as sodium valproate and gabapentin	Carbamazepine: significant improvement in behavioral symptoms in one of the two RCTs, with overall benefit confirmed in a meta-analysis of the two trials Sodium valproate: Cochrane review concluded cannot be tolerated in clinically effective doses Gabapentin: evidence very preliminary	Carbamazepine demonstrated good tolerability over short term in the RCTs, but drug–drug interactions are a potential concern; have the potential to impair balance and increase risk of falls; mortality does not seem to be increased	Promising treatment option; a larger and longer clinical trial is needed; long-term safety also needs to be established; further work is needed to determine whether a preferential response is shown in agitated patients with concurrent affective symptoms

Abbreviations: RCT, randomized controlled trial; SSRIs, selective serotonin reuptake inhibitors.

with dementia (relative risk 1.37 over ≤180 days).[16] Consequently, despite the modest benefits of short-term therapy with typical antipsychotics, serious concerns have arisen over the use of these agents in the treatment of people with dementia. Until 2000, thioridazine, promazine and haloperidol were all widely used in the clinical setting; however, prescription practice has changed substantially following specific concerns related to the cardiac safety of thioridazine, and general concerns regarding the side-effect profile of typical antipsychotics. Atypical antipsychotics

are now more widely prescribed than typical agents, and thioridazine is prescribed very infrequently—although a 2007 study that investigated antipsychotic prescriptions in care homes revealed that of patients with dementia who were receiving an antipsychotic, 28% were prescribed a typical agent.[17]

Atypical antipsychotics

Since 1995, 18 placebo-controlled trials have examined the efficacy of atypical antipsychotics in patients with AD, mainly over treatment periods of 6–12 weeks (see Table 1). Only nine of these studies are in the public domain—four compared risperidone with placebo, one compared risperidone and olanzapine with placebo, one compared olanzapine with placebo, one compared quetiapine with placebo, and two compared aripiprazole with placebo. These studies are reviewed in full by Ballard and Howard[18] and Schneider *et al.*[19]

One key study of olanzapine and several key studies of quetiapine are not in the public domain, which has made meta-analysis of these agents' effects impossible. On the basis of published evidence, neither agent has a significant beneficial effect on agitation overall.[18] Meta-analyses have, however, been conducted of risperidone and aripiprazole, as all trials of these agents are fully in the public domain. These meta-analyses highlight the efficacy of these agents in the short-term management (6–12 weeks) of aggression.[18,19] The magnitude of benefit is similar for both agents, although these findings are based on a substantially larger evidence base for risperidone, for which the effect size compared with placebo on the BEHAV-AD (Behavioral Pathology in Alzheimer Disease) rating scale is −0.84 points (95% CI −1.28 to −0.40 points) 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.[18] No trials that have investigated the use in AD of other widely used atypical antipsychotics (such as amisulpride, sertindole, clozapine, or zotepine) have been reported.

Adverse effects such as extrapyramidal symptoms, drowsiness, and peripheral edema are commonly associated with all atypical antipsychotics. These effects have been best quantified with regard to risperidone because of rigorous adverse-event reporting and a large number of trials with this agent. Meta-analyses of the trials that have compared risperidone against placebo in AD demonstrate a significant increase in extrapyramidal symptoms (1 mg odds ratio [OR] 1.78, 95% CI 1.00–3.17; 2 mg OR 3.39, 95% CI 1.69–6.80), drowsiness (1 mg OR 2.38, 95% CI 1.76–3.20; 2 mg OR 4.46, 95% CI 2.30–8.64), and peripheral edema (1 mg OR 2.75, 95% CI 1.51–5.03; 2 mg OR 3.80, 95% CI 1.74–8.29) over 12 weeks of treatment.[18] A more serious potential concern pertains to cerebrovascular events. Pooled data from the placebo-controlled trials of risperidone in AD showed that risperidone was associated with a threefold increased risk of serious cerebrovascular adverse events compared with placebo (OR 3.43, 95% CI 1.60–7.32; $P = 0.001$).[19] Although extremely worrying, these data are difficult to interpret in a clinical context because the category of 'serious cerebrovascular events' in these trials was broad and was not operationally defined. However, summary data suggest that the increase in the incidence of cerebrovascular adverse events with risperidone was similar to that seen in placebo-controlled trials of olanzapine in AD (1.3% for olanzapine at all doses versus 0.4% for placebo),[20] and the general consensus seems to be that this association is probably a class effect for atypical antipsychotics. Evidence is insufficient to determine whether the increased risk also applies to typical antipsychotics.

Two other key issues have emerged from meta-analyses that have combined the results of trials with all atypical antipsychotics. Firstly, Schneider's meta-analysis highlights a significant acceleration in the rate of cognitive decline in people who received atypical antipsychotics compared with those treated with placebo over 12 weeks; cognitive decline as measured by the Mini-Mental State Examination (MMSE) was 0.73 points greater in the drug group (all atypical antipsychotic trials at all doses: 95% CI 0.38–1.09; $P < 0.0001$).[19] This measured decline was approximately double that expected. Secondly, and of even greater importance, several meta-analyses indicate a significant increase in mortality associated with antipsychotic prescription. The FDA conducted an analysis based on data from 17 of the placebo-controlled trials of atypical antipsychotics, which identified a 1.6–1.7-fold increase in mortality for people taking atypical antipsychotics compared with those taking placebo over the 12 weeks of the trials.[21] On the basis of these findings, the FDA published a warning notice of the significant increase in mortality risk for people with AD treated with atypical antipsychotics. Schneider reviewed the evidence from 15 of these trials, confirming the significant increase in mortality (OR 1.54, 95% CI 1.06–2.23; $P = 0.02$), but he found no difference between specific atypical antipsychotic drugs.[22]

Evidence for the medium-term to long-term efficacy of any of the atypical antipsychotics in AD is very limited; the RCTs that were conducted over periods of 6–12 months either found that atypical antipsychotics conferred no significant benefit in the treatment of aggression and agitation, or found that any advantages were offset by adverse effects.[23–25] In addition, none of the studies that focused on randomized withdrawal of antipsychotic drugs in patients in nursing homes or with dementia (who had been receiving medium-term to long-term treatment with these agents) indicated a significant exacerbation of agitation and aggression, or other BPSD, after antipsychotics were stopped.[26–28] Further to these findings, it seems that the effect of some severe adverse events, such as accelerated cognitive decline and mortality, could be exacerbated with prolonged treatment.[23,29] For example, in the Dementia Antipsychotic Withdrawal Trial (DART-AD), survival at 24 months was 46% in patients randomly assigned to continue antipsychotics, compared with 71% in patients assigned to placebo.[29]

Despite the safety concerns over atypical antipsychotics, these agents do have the best documented evidence for

short-term efficacy in the treatment of aggression, although the meta-analyses conducted to date have not indicated significant benefit for the treatment of non-aggressive symptoms of agitation.[18,19] Use of these drugs should probably be restricted to short-term management (up to 12 weeks) of severe physical aggression. Detailed clinical recommendations are provided later in this Review.

The alternatives to antipsychotics

The treatment of agitation and aggression associated with AD is discussed here in the context of increasing concerns over the widespread use of antipsychotics in people with AD. Firstly, we outline general principles for assessment and treatment of BPSD, with the aim of highlighting the means by which premature or unnecessary administration of treatments for agitation and aggression can be avoided. Secondly, we consider the role of nonpharmacological and alternative therapies for agitation and aggression. Finally, we discuss the most promising pharmacological alternatives to antipsychotics for the treatment of agitation and aggression in AD.

General management principles

Before any specific treatments are considered for patients with AD who present with agitation and aggression, or other BPSD, a broad and detailed clinical assessment is essential. Physical health problems such as infection, pain or dehydration are common in patients with AD and can often precipitate agitation and aggression. Pain can be difficult to assess in people with dementia and is often under-diagnosed. Urinary tract infections and chest infections are frequent triggers for agitation and aggression, but dental infections are also common and are often not recognized. Treatment of concurrent physical health problems will frequently result in the resolution of agitation and aggression, and other BPSD, without recourse to any therapies aimed specifically at targeting the BPSD. Visual and auditory impairment can also precipitate BPSD, which should be assessed for, and treated if possible. Treatment may be as simple as changing the patient's spectacles or hearing aid, or encouraging regular use of such equipment. The degree of environmental stimulation can also be an important trigger for certain BPSD syndromes, including agitation. For example, low lighting and extreme noise levels (high or very low) can be important precipitants of agitation and are often modifiable. These principles are outlined in detail by Lyketsos and colleagues.[30]

Consideration of the severity and consequences of any behavioral or psychiatric symptoms is also important. For example, symptoms might occur very intermittently, might arise only in specific situations, or might not result in distress or risk to the individual or others. Symptoms that are infrequent or do not result in distress or risk might not require any specific therapy, or might be preferentially treated with a nonpharmacological approach, such as a psychological therapy (see next section). Agitation and aggression, and other BPSD, fluctuate greatly in severity and often resolve or improve spontaneously over 4–6 weeks. For mild to moderate symptoms, therefore, a period of monitoring wherein relatives or care staff keep a diary of symptoms can often provide valuable insights and can help to avoid premature and unnecessary treatment for symptoms that might resolve spontaneously. Sometimes, however, additional treatment will be required.

Nonpharmacological treatments

Psychological interventions

Emerging evidence confirms that a variety of psychological or psychosocial interventions confer benefit in the treatment of agitation and aggression and other BPSD (see Table 2). We suggest that these alternative therapies should be considered before pharmacological therapies are prescribed. A systematic review, conducted by Livingston and colleagues, identified 162 studies of specific psychological interventions that satisfied the authors' inclusion criteria; selected trials analyzed "quantitative outcome measures that were either direct or proxy measures of neuropsychiatric symptoms".[31] The majority of studies were small and the evidence base for each specific intervention was modest. Therapeutic approaches used in the trials that met the review criteria included six trials of reality orientation, two trials of validation therapy, four trials of reminiscence therapy, two trials of Snoezelen therapy or multisensory stimulation, six trials of simulated-presence therapy, six trials of structured activity, six trials of music therapy, and three trials of environmental manipulation. For many of these interventions the benefits were unclear or were limited to the period during the intervention.[31] In addition, several of these therapies follow a very structured intervention format and might, therefore, be difficult to implement in routine practice without the local availability of specifically trained practitioners. Of the therapies identified in the Livingston review, we highlight validation therapy as a practical therapy with at least some evidence of efficacy. This therapy is a pragmatic intervention based on principles of providing empathy for the patient and respecting the individual's reality. This therapy is usually delivered in a group format, with involvement of elements such as communication, reminiscence, and activities that involve music and movement.[32] A specific systematic review identified three trials of validation therapy,[32] each of which employed very different methods and comparison groups, which precludes formal meta-analysis. The only study identified that compared validation therapy with usual care indicated a significant benefit for validation therapy on BPSD at 6 weeks. Validation therapy seemed to have similar efficacy to social interaction.[32]

Cohen-Mansfield and colleagues developed a 'tool box' of simple and practical psychological interventions, such as structured social interaction and meaningful activities, which can be individualized to the needs of a particular individual. A recent trial demonstrated a significant decrease in agitation in patients with dementia with this method, in comparison with usual care augmented by

Table 2 | Non-pharmacological treatment of agitation and aggression in people with dementia

Trials conducted	Evidence	Major adverse effects	Interpretation
Psychological therapies[31–33,36,37]			
Two RCTs examined whether staff training can reduce antipsychotic use Two RCTs of individualized psychological intervention, one RCT and one open trial of 'tool box' psychological intervention Three RCTs of validation therapy, several trials of other specific therapies such as reminiscence	Robust evidence from two large RCTs indicates that staff training in nursing homes can reduce use of atypical antipsychotics without worsening patients' behavior The RCTs of individualized psychological intervention and 'tool box' intervention suggest significant benefit In small preliminary RCTs, validation therapy seems to be better than treatment as usual but comparable to social interaction	None—well tolerated and popular therapeutic approaches	Emerging evidence indicates that several methods of training and psychological interventions work well, but these approaches are only effective if implemented systematically by appropriately trained staff—which could limit potential availability Probably the preferred first-line treatment option when no high level of risk or extreme distress is present
Aromatherapy or herbal remedies[38,40,43,85]			
Three short (all ≤4 weeks) placebo-controlled RCTs, two with lavender oil, one with melissa oil	All three trials demonstrated significant benefits, but only the trial with melissa oil was included in the Cochrane meta-analysis because of methodological issues One additional trial that used oral melissa also indicated benefit	None—extremely well tolerated	Safe and popular treatment approach with encouraging emerging evidence

Abbreviation: RCT, randomized controlled trial.

education. Although this was a well-conducted and compelling study, treatment assignment could not be fully randomized, and some caution must, therefore, be exercised in the interpretation of the results.[33] Nevertheless, this study probably provides the best evidence available for a relatively simple and straightforward psychosocial treatment. In addition, an open trial has been conducted of brief psychosocial therapy,[34] a simplified version of the Cohen-Mansfield approach that focuses on structured social interaction between the person with AD and a care assistant for 10–15 min. The initial results were promising, but an RCT is needed.[34]

RCTs have provided evidence that comprehensive and individualized interventions delivered by mental health nurses, clinical psychologists or nursing home staff are also effective; such interventions can be based on assessment methods such as 'antecedent behavior consequence' charts, or the 'tool box' approach.[35,36] RCTs also indicate that intensive 6–12-month programs to educate staff in person-centered care can reduce the use of psychotropic medication in nursing homes, without a negative influence on levels of agitated or disruptive behavior.[36,37]

Other nonpharmacological interventions

A variety of other nonpharmacological treatments have been investigated, including multisensory interventions (such as those reviewed by Livingston *et al.*[31]), herbal remedies,[38] bright light therapy[39] and aromatherapy.[40] While some evidence shows that bright light therapy and related treatments such as melatonin might improve or stabilize sleep and rest–activity rhythms,[41] evidence that such therapy specifically influences symptoms of agitation is limited. The best evidence for alternative treatment approaches to agitation in AD (other than psychological interventions) is, in the view of the authors, for aromatherapy.

Evidence is accumulating that aromatherapy with lavender oil, and therapy with *Melissa officinalis* (lemon balm; as oil used for aromatherapy or extract used as a herbal remedy) are efficacious at reducing agitation in dementia.[38,40,42] The few RCTs that have been conducted in this area are summarized in Table 2; all studies were small and were conducted over periods of 4 weeks or fewer.[43] The largest study, which focused on melissa oil aromatherapy, randomly assigned 72 patients with severe dementia to melissa oil or placebo.[40] The oil was mixed into a base cream that was applied to participants' hands and arms twice daily. The treatment resulted in a highly significant improvement in agitation, without any increase in adverse events, compared with placebo.[40] The trials of lavender oil used an aroma-stream or similar approach to deliver the therapy.[42,43] Both of the described methods are straightforward and can easily be implemented in clinical practice. Larger, longer-duration studies are needed, but the preliminary evidence does indicate some efficacy for lavender or melissa oil aromatherapy in the treatment of agitation. Aromatherapy with these agents has not been widely adopted in clinical practice, but we believe this approach should be seriously considered as an alternative to pharmacological therapy in situations in which no immediate high level of risk is present for the individual or others.

Recommended approach

For agitation and aggression and other BPSD of sufficient severity to require a specific therapy, the majority of best-practice guidelines suggest that psychological interventions should be the first-line approach for most individuals with AD, a recommendation that seems reasonable on the basis

of the available evidence. Validation therapy and structured social interaction are simple, practical treatments that are straightforward to administer. Reasonable evidence is also available to support the value of other nonpharmacological treatments, including aromatherapy. For persistent or severe symptoms, a more comprehensive intervention by a clinical psychologist might be a valuable alternative to pharmacological treatments.

In situations in which the risk to the individual or others is high, or when the patient is extremely distressed, initial treatment with an atypical antipsychotic might still be the best approach. However, in such circumstances, we strongly advise that antipsychotic treatment should not continue for longer than 12 weeks. The introduction of nonpharmacological treatments could also enable the withdrawal of antipsychotic drugs.

Pharmacological treatments

The serious adverse events associated with the use of antipsychotic drugs in people with dementia have produced a strong imperative to develop improved, safer pharmacological treatments for these patients. In current clinical practice, the key questions are whether other available licensed compounds can provide useful pharmacological alternatives to atypical antipsychotics, and when the use of these drugs should be considered. This section reviews the evidence for the best candidate compounds and suggests some recommendations for the use of these treatments in the clinical setting (see also Table 1).

Cholinesterase inhibitors

RCTs have provided evidence for the use of donepezil in AD,[44,45] rivastigmine in dementia with Lewy bodies,[46] and galantamine in vascular dementia and in AD with concomitant cerebrovascular disease,[47] but the behavioral effects of cholinesterase inhibitors (ChEIs) have been little recognized. Consideration of such effects could have positively contributed to the debate about the usefulness of this class of drugs in the management of AD.[48] A meta-analysis demonstrated a small but significant overall advantage of ChEIs over placebo with regard to the treatment of BPSD.[49] Additional support for the benefits of ChEIs in the treatment of 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.[50] However, no short-term benefit was found for treatment of clinically important agitation with donepezil over 12 weeks in a large RCT,[51] which suggests that ChEIs do not seem to be useful in the management of acute agitation. In the treatment of BPSD syndromes, ChEIs seem to be most effective against depression, dysphoria, apathy (or indifference), and anxiety,[44] and these agents are probably not effective for clinically relevant agitation or aggression, at least when used for a 3-month period. In a study that investigated the treatment of agitation over 6 months in patients with dementia, a mean numerical advantage (as measured by the Cohen-Mansfield Agitation Inventory) of 2.2 points was shown for rivastigmine compared with placebo in the treatment of agitation.[23] This difference was not statistically significant, but it perhaps indicates the need for further studies with a focus on the long-term treatment of agitation with ChEIs.

Memantine

Individual studies, meta-analyses and pooled analyses indicate that memantine confers benefit in the treatment of agitation and aggression over 3–6 months in patients with AD.[52–56] The best evidence probably comes from a retrospective analysis of all patients with at least one symptom of aggression, agitation or psychosis, from pooled data of three placebo-controlled trials of memantine in moderate to severe AD (total 593 patients).[56] In the patients on memantine, agitation and aggression improved in 55.3% of patients by week 12, and in 61.0% by week 24. By comparison, the proportions of patients who improved on placebo were 43.1% at week 12, and 45.0% at week 24. A significant difference in favor of memantine was seen at both time points, with an effect size at 12 weeks that was very similar to that seen in placebo-controlled trials of atypical antipsychotics for the treatment of aggression in AD. Memantine was well tolerated, and, compared with individuals who received placebo, significantly fewer memantine-treated patients withdrew from the study (22.9% versus 32.3%; $P<0.01$), or withdrew due to adverse events (10.3% versus 17.3%; $P<0.05$). Rates of treatment-emergent adverse events were similar in the two groups (82.6% versus 79.9%). Benefits in cognition and function were also evident in memantine-treated patients compared with those who received placebo.[56] The positive interpretation of this pooled analysis is that it provides preliminary evidence for a beneficial influence of memantine on agitation and aggression over 12 and 24 weeks of treatment. The results do, however, need to be interpreted with great care as the data were analyzed retrospectively and the severity of agitation and aggression was generally mild. The potential beneficial effects of memantine in the treatment of agitation and aggression in AD are, however, supported by several other preliminary pieces of evidence. In an observational discontinuation study, withdrawal of memantine was associated with increased use of psychotropic drugs,[57] and a further 2008 observational study suggested that treatment with memantine was associated with decreased use of psychotropic medication.[58] Whilst this evidence is very encouraging with respect to memantine, no RCTs have been performed specifically to assess this agent in patients with AD who have clinically relevant agitation or aggression. Prospective RCTs in patients with AD who have clinically significant agitation are needed to support the findings. Ongoing RCTs in Canada and in the UK will hopefully clarify the role of memantine in the treatment of agitation and aggression in AD.

Antidepressants

The use of antidepressants to treat BPSD dates back to the 1980s. Despite this fact, the literature remains limited

Box 1 | Principles to guide pharmacological interventions

If aggression is causing extreme distress or high risk to the patient and/or others: short-term treatment (≤12 weeks) with an atypical antipsychotic is preferred; the best evidence to date favors risperidone. The evidence base for benefit with extended-duration atypical antipsychotic therapy is limited and the risk of serious adverse events considerable, so treatment beyond 12 weeks should be considered only in extreme circumstances. The 12-week treatment period should be used to ensure optimum clinical management and to institute nonpharmacological interventions as appropriate. If a subsequent relapse in aggression occurs and causes extreme distress and risk, we recommend that an alternative pharmacological therapy (citalopram, carbamazepine or memantine) is used.

In patients with moderate-to-severe AD with agitation causing distress but not high levels of risk, in whom memantine is indicated for dementia: memantine is probably the preferred treatment for agitation (and has the advantage of an excellent safety profile).

In patients with distressing, nonaggressive agitation, or aggression in the absence of marked risk, in whom memantine is not indicated for dementia: use citalopram or carbamazepine.

In patients with AD who have distressing agitation or aggression that has not responded to other interventions, who have experienced a relapse of agitation or aggression after discontinuation of an atypical antipsychotic, or in whom another pharmacological agent is felt necessary to enable withdrawal of atypical antipsychotics: memantine, citalopram, or carbamazepine are appropriate. In ongoing treatment, assess the quality of clinical management and consider employment of concurrent nonpharmacological interventions.

No evidence is available to guide long-term prescription of pharmacological treatments other than atypical antipsychotics in patients with AD, and information on long-term safety is limited. We recommend review of pharmacological treatments every 3 months and that discontinuation of the therapy is attempted after a minimum of 6 months, unless the therapy is prescribed for another indication (for example, memantine for cognition, citalopram for depression, or carbamazepine for epilepsy).

and few clear inferences can be drawn. The RCTs that have been conducted examined the efficacy of sertraline, citalopram, and trazodone in the treatment of agitation in AD. In one of the RCTs, sertraline was generally well tolerated.[59] A subgroup analysis within the same study that focused on patients with moderate to severe BPSD identified a significant benefit for sertraline compared with placebo—a 50% improvement was experienced by 60% of patients on sertraline compared with 40% of patients on placebo.[59] In a second, smaller, 17-day trial of patients with dementia who had at least one moderate to severe BPSD conducted in 2002, Pollock and colleagues reported that citalopram was superior to placebo for the treatment of agitation and aggression. Patients in the citalopram group improved by a mean of one point on the agitation subscale of the Neurobehavioral Rating Scale (NBRS), whereas patients in the placebo group improved by a mean of 0.4 points ($P<0.05$).[60] In a later study, citalopram was found to have comparable efficacy to the atypical antipsychotic risperidone over 12 weeks of treatment.[61] Improvement on the agitation subscale of the NBRS was 1.26 points (SD 4.58) for citalopram and 0.73 points (SD 4.91) for risperidone.[61] The results of a double-blind comparison of trazodone and haloperidol for the treatment of agitation in dementia were encouraging with respect to trazodone,[62] but a subsequent parallel-group RCT indicated no benefit of this agent compared with placebo.[12] A large, multicenter trial, with a focus on the treatment of depression in patients with AD, is underway.[63]

Anticonvulsants

With regard to anticonvulsants, some encouraging results have been reported for carbamazepine in the treatment of agitation and aggression related to AD. A number of case series and small crossover trials provide preliminary evidence of possible efficacy for this agent (reviewed by Tariot *et al.*[64] and Konovalov *et al.*[65]). Only two, small, parallel-group RCTs have been conducted of carbamazepine, both over a 6-week period.[66,67] A meta-analysis of the two trials performed as part of the current review indicates significant benefit with this agent both on the Brief Psychiatric Rating Scale (mean difference –5.5 points, 95% CI –8.5 to –2.5 points) and on the Clinical Global Impression scale (OR 10.2, 95% CI 3.1–33.1) in comparison with placebo. Both studies also suggest that this agent is well tolerated, and a subsequent case-register study of individuals aged 65 years or older suggested that carbamazepine confers less mortality risk than antipsychotic drugs do.[68] Studies of sodium valproate have not shown benefits for this agent in the treatment of agitation and aggression, and its tolerability at therapeutic doses might not be acceptable.[65,69,70] Data for other anticonvulsants—such as gabapentin—are preliminary and are largely based on small case series of patients who received open-label treatment.

Recommended approach

In the absence of a robust, or even adequate, evidence base, recommendations for pharmacological treatment rely heavily on our personal interpretation. Pharmacological options should be considered alongside nonpharmacological approaches (see earlier text for recommended approach for nonpharmacological therapies). In our view, pharmacological interventions should generally be reserved for patients who have distressing symptoms of agitation and aggression that cause risk to themselves or others. Except in such situations, where risk could be extremely high, our opinion is that pharmacological treatments should usually only be considered after a trial of a nonpharmacological intervention.

The best evidence for efficacy in the short-term pharmacological treatment of aggression in AD remains in favor of the atypical antipsychotic drugs. However, in view of the potential adverse effects of these agents, alternative pharmacological treatments are needed. On the basis of this emerging evidence, our view is that the best pharmacological alternatives to antipsychotics for the treatment of aggression are memantine, carbamazepine, and citalopram, all of which are currently available, licensed drugs. These agents possess a better evidence base than that for atypical antipsychotic drugs in the treatment of nonaggressive agitation. Other pharmacological interventions, such as ChEIs, might be beneficial for other BPSD symptoms such as apathy, mood disorders, and visual hallucinations;

however, on the basis of currently published evidence, such alternatives do not seem to be the preferred treatment for agitation and aggression.

We suggest a set of principles to be used when making treatment decisions with regard to pharmacological interventions (see Box 1).

Neurobiological correlates

An American College of Neuropsychopharmacology White Paper published in 2008 drew attention to the need for further research to clarify the neurobiological basis of BPSD, and to the search for biomarkers that might enable individual risk:benefit prediction.[71] Association of agitation and aggression with the related symptom of psychosis has been reported with polymorphisms in serotonin receptors types 2A and 2C and in the serotonin transporter,[72–74] and with polymorphisms in dopamine receptor types D_1 andD_3.[75] The best available evidence supports the association between dopamine receptors and serotonin transporter polymorphisms—all three studies that examined dopamine receptor D_1 and D_3 polymorphisms, and four of the seven studies that examined serotonin transporter polymorphisms, identified a significant association of these polymorphisms with agitation (see Table 3). Postmortem studies suggest that certain patterns of neuronal loss,[76] and altered adrenergic function,[77] may also be important factors associated with agitation and aggression in AD. The consistent finding between studies of a probable association between agitation in AD and serotonin transporter polymorphisms further emphasizes selective serotonin reuptake inhibitors as a promising therapeutic approach. Biological studies also highlight the noradrenergic system as a potential treatment target. These studies also raise the possibility that pharmacogenetics could be an attractive approach to refine the selection of optimum pharmacological treatments for individual patients with agitation and aggression in the future.

Interpreting the evidence

Several factors are important to take into account when the published evidence base for agitation and aggression in AD is considered. Firstly, a large proportion of the RCTs, particularly those that have investigated the use of atypical antipsychotics, remains unpublished—the tendency is towards publication of more-positive trials. Secondly, experience has shown that most patients with AD enrolled in RCTs tend to have relatively low levels of behavioral symptoms at baseline. This factor facilitates enrollment of patients into studies and encourages their retention, but it renders the results of trials difficult to generalize with respect to clinical populations and might lead to an underestimation of the potential benefit of therapy. Thirdly, agitation and aggression often co-exist with mood disorders or psychosis,[78] but whether or not such comorbidity influences response to treatment is unknown. Fourthly, whether genetic polymorphisms that are associated with altered risk of agitation and aggression also have an effect on response to treatment is unknown. Finally, evidence is limited with regard to the influence of vascular or other comorbid pathologies on response to treatment. Future RCTs will need to address these key issues.

Table 3 | Reported genetic associations of agitation and related symptoms[86,a]

Gene	Symptom		
	Depression	Psychosis	Agitation and/or aggression
APOE4	1 of 12	0	1 of 11
COMT	0	3 of 3	0
DRD1	0	2 of 2	2 of 2
DRD3	0	1 of 2	1 of 1
HTR2A (5-HT2A)	1 of 5	2 of 5	1 of 3
HTR2C (5-HT2C)	1 of 2	1 of 5	0 of 1
5-HTTLPR	0 of 3	4 of 6	3 of 5
SLC6A4 (5-HTT) VNTR	0 of 2	1 of 2	1 of 2
TPH1	0	0	0 of 1

[a]The table shows the proportion of studies that have reported a significant genetic association. Abbreviations: *APOE4*, variant of apolipoprotein E (*APOE*) gene; *COMT*, catechol-*O*-methyltransferase; *DRD1*, dopamine receptor D_1; *DRD3*, dopamine receptor D_3; *HTR2A* (*5-HT2A*), 5-hydroxytryptamine (serotonin) receptor 2A; *HTR2C* (*5-HT2C*), 5-hydroxytryptamine (serotonin) receptor 2C; *5-HTTLPR*, serotonin-transporter-linked polymorphic region in solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (*SLC6A4*, or *5-HTT*); *SLC6A4* (*5-HTT*) *VNTR*, serotonin transporter gene variable number tandem repeat polymorphism; *TPH1*, tryptophan hydroxylase 1.

Conclusions

Limitations are evident in our understanding of the biological basis of agitation and aggression (as well as other behavioral features) associated with AD, and the efficacy and tolerability of available drug treatments is a matter of debate. Nevertheless, clinicians are required to treat patients on a case-by-case basis, and to make use of their best judgment. Careful identification of target symptoms and their consequences, initial trials of nonpharmacological approaches, and use of the least harmful medication for the shortest period of time, should be the guiding principles in the current management of agitation and aggression in AD. Large, prospective, randomized, placebo-controlled trials are needed to establish the role of the pharmacological alternatives to atypical antipsychotics as clinical therapies for agitation and aggression in AD.

Review criteria

We performed a search of the PubMed and Cochrane databases for articles on the treatment of agitation in Alzheimer disease. We used combinations of the following search terms: “Alzheimer’s disease”, “dementia”, “agitation”, “aggression”, “neuropsychiatric”, “BPSD”, “treatment”, “aromatherapy”, and the names of individual pharmacological and nonpharmacological treatments listed in Tables 1 and 2. We selected 47 randomized, controlled trials for further discussion, supplemented with a more general review of the background literature.

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