Treatment of Delusions in Alzheimer's Disease – Response to Pharmacotherapy

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Key Words

Delusions · Alzheimer's disease · Psychosis · Dementia · Antipsychotics

Abstract

Delusions are commonly encountered symptoms in patients with Alzheimer's disease and may lead to significant morbidity. The purpose of this article is to review all clinical trials to date focusing on the management of delusions in patients with Alzheimer's disease to determine the level of evidence for treatment. To achieve this objective, Medline was searched using the key words delusions, dementia, Alzheimer's disease and psychosis. Three main categories of treatment were identified: atypical antipsychotics, cholinesterase inhibitors, and other miscellaneous treatments. It was concluded that all forms of treatment were effective although the greatest burden of evidence existed for risperidone and donepezil. Side effects were noted in all forms of treatment and included somnolence and extrapyramidal effects for antipsychotic medications, whereas gastrointestinal effects were more prevalent in studies involving cholinesterase inhibitors. Further large scale, double-blind, randomized, controlled studies are required before a definitive conclusion can be reached. To our knowledge this is the only systematic review of this area.

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Introduction

Delusions are commonly encountered symptoms in Alzheimer's disease (AD) [1–4] and may result in significant morbidity [5–8]. Successful treatment of these symptoms is therefore imperative. Delusions may also occur in a number of other psychiatric syndromes such as schizophrenia where there is substantial evidence of response to antipsychotic medications [9, 10].

There has been considerable debate as to whether delusions in patients with AD differ etiologically from delusions in other psychiatric illnesses, in other words, whether they arise from damage to key areas of the brain that have been linked to the presence of psychosis. This has lead to speculation that these symptoms may respond better to symptomatic drugs such as cholinesterase inhibitors. Unfortunately there have been few clinical trials in the past that have examined the response rate of delusions in patients with AD. This paper will look at the existing evidence for the use of various pharmacologic treatments in the management of Alzheimer patients with delusions as well as their tolerability, clarifying which drug treatments may have the greatest efficacy and be least associated with adverse effects.

Methods

A Medline search was conducted looking at citations from 1966 to March 2005. Key words used in the search included: dementia, AD, delusions, psychosis, treatment, antipsychotics (neu-

roleptics), and cholinesterase inhibitors. Studies were included in the review if they were prospective, looked at pharmacologic treatment of delusions in AD, and used monotherapy. Studies that examined psychosis exclusively and did not isolate delusions as a separate outcome were excluded. No restrictions were placed on study methodology or type of drug treatment.

Results

The present Medline search yielded a total of 18 citations which met the inclusion criteria (table 1). Many of the early studies were excluded because they included patients with a variety of dementia diagnoses and did not isolate delusions from hallucinations when considering psychosis as an outcome. Other studies were excluded on the basis of a retrospective design, use of multiple drug therapies and dementia diagnoses other than AD. Most of the studies looked at cholinesterase inhibitors and atypical antipsychotics while some considered novel treatments such as buspirone.

Antipsychotics – Atypical

All three atypical antipsychotics (olanzapine, risperidone, quetiapene) have been studied with respect to delusions in patients with AD. The greatest burden of evidence exists for risperidone while fewer studies have been done looking at quetiapene and olanzapine.

There were four studies looking at the use of risperidone in delusional patients with AD [11–14]. Three have used an open label design [11, 12, 14], while one study was double-blind, placebo-controlled, randomized and multi-centered [13]. All studies showed a beneficial effect with dosages ranging from 0.5 to 2 mg once daily. Adverse effects were noted in three of the four studies and included dose-dependent somnolence and extrapyramidal effects.

There were four studies examining olanzapine in patients with AD and delusions using dosages ranging from 5 to 15 mg [15–18]. Three of these studies employed a double-blind, multi-centered, placebo-controlled design [16–18], while one was open label [15]. One of the three double-blind studies showed no response [17] while the other two showed responses only at specified doses, 5 mg in one case [16] and 7.5 mg in the other [18]. The one negative study [17] is hard to interpret as the emergence of delusions was low in both the placebo and treatment groups – this may have resulted from the short duration of the study and the fact the study looked at delayed emergence as opposed to remission. The open label study [15] showed a significant reduction in delusional intensity over an 18-week period compared to baseline ($p = 0.024$),

although medication dosages varied considerably. Adverse effects noted included somnolence, dose-dependent weight gain and abnormal gait. One study showed no adverse effects compared with placebo [18].

There are two open label trials that have examined the use of quetiapene in delusions among patients with AD [19, 20]. Both studies used small numbers and employed an open label design. Both studies showed effectiveness over a 2- to 3-month period with drug dosages ranging from 25 to 200 mg o.d. Drowsiness was noted in one study [19] while in the other no adverse effects were specified [20].

Cholinesterase Inhibitors

Cholinesterase inhibitors have emerged as an effective therapy for patients with AD [21]. Recent studies have focused more on behavioral outcomes, including delusions.

Donepezil was used in three Alzheimer studies which looked at delusions as a separate outcome [22–24]. Two of these studies were open label in design [23, 24], and one used a double-blind, multi-centered, randomized, placebo-controlled design [22]. The double-blind study was 24 weeks in duration and showed a significant improvement in delusional intensity compared to baseline. The two open label studies, which used significantly smaller numbers, also showed significance. Adverse events were noted in the smaller studies and consisted mainly of mild GI effects.

Rivastigmine's impact on delusional thinking was examined in one open label study [25]. The study was an open label extension (104 weeks in duration) and no response was noted compared to baseline, although behavior overall was improved. Ten of 34 patients who entered the trial did not complete due to adverse events, mainly gastrointestinal in nature. The small sample size, study design and significant number of dropouts makes it difficult to draw any definitive conclusions. Galantamine was looked at in a 21-week, multi-centered, double-blind, placebo-controlled design [26]. While behavior overall was significantly improved at the end of the study, delusions specifically showed no improvement. This may have been a function of the low prevalence of delusions at baseline. It was also noted that patients on galantamine compared to placebo had more agitation overall.

Novel Agents

Two novel drug therapies have been used to treat delusions in AD: xanomeline and buspirone. Xanomeline was used in a 6-month, double-blind, randomized, placebo-controlled design with dosages ranging from 25 to 75 mg

Table 1. Clinical drug trials

Medication and study design	Reference	Participants	Outcome measures	ADR	Conclusion
<i>Galantamine</i>					
21 weeks, multi-centered, parallel group, double-blind, placebo-controlled trial. Patients randomized to placebo, 8, 16, and 24 mg	Cummings et al. [26], 2004	978 patients with mild to moderate AD (Asymptomatic and symptomatic at the baseline) MMSE 10–22	No change in the delusional subscale of the NPI but significant improvement in the overall rating	Minimally greater emergence of agitation in patients assigned to Galantamine therapy	Galantamine, while associated with significant behavioral improvement overall, did not selectively improve delusions in patients with AD
<i>Rivastigmine</i>					
104 weeks, open label extension (dosage range 6–12 mg)	Rosler et al. [25], 1999	34 patients with AD	No change from baseline in the delusional domain of the CIBIC-plus	10 patients did not complete the study due to adverse events	No obvious beneficial effects over the long term
<i>Donepezil</i>					
24 weeks, open label trial (5mg o.d. × 4 weeks, titrated up to 10 mg o.d. × 20 weeks)	Barak et al. [24], 2001	10 patients with AD on a psychogeriatric ward	Significant reduction in presence and intensity of delusions as measured by the NPI ($p < 0.05$)	No major side effects requiring treatment discontinuation – mild gastrointestinal symptoms in 3	Donepezil may be helpful as monotherapy in treating Alzheimer patients with delusions in this small sample
24 weeks, double-blind, multi-centered, randomized, placebo-controlled, withdrawal study (Donepezil 10 mg o.d.)	Holmes et al. [22], 2004	134 patients with AD MMSE 10–27	Significant improvement in the NPI delusional subscale compared to baseline ($p < 0.05$)	No significant adverse events noted	Donepezil has a significant impact on delusional intensity in patients with AD
6 months, open-label trial (5 mg o.d. × 1 month followed by 10 mg o.d. × 5 months)	Paleacu et al. [23], 2002	28 patients with AD MMSE <24	Donepezil significantly reduced the presence of delusions as measured by the NPI ($p = 0.05$)	Three patients had minor adverse events	Donepezil improves delusional intensity over a 6-month period
<i>Risperidone</i>					
8 weeks, open label, flexible dosing study (0.5–2 mg)	Rainer et al. [11], 2001	34 patients with AD, vascular and mixed dementia plus behavioral symptoms MMSE 8–26	Delusions improved from baseline at week 4 and week 8 ($p = 0.0002$) as measured by the NPI	No adverse events attributable to risperidone	Risperidone is effective in terms of reducing delusional intensity in a small sample of patients with Alzheimer and related dementias
1 year, open label extension study, flexible dose design (dose range 0.5–2 mg o.d.)	Jeste et al. [12], 2000	330 patients with AD, vascular or mixed dementia MMSE score n/a	Patients with dementia receiving risperidone in optimal range (0.75–1.5 mg/day) had a significant reduction in delusional intensity compared to baseline ($p = 0.03$) on the BPDRS	Parkinsonism ratings increased through the course of the open label phase compared to baseline; changes in dyskinesia ratings had no relation to risperidone dose	Risperidone at doses above 0.75 has a significant impact on delusional intensity in patients with AD and related dementias, little impact on dyskinesia intensity and a positive impact on rates of parkinsonism
12 weeks, randomized, double-blind, placebo-controlled trial, (patients randomly assigned to 0.5, 1, 2 mg o.d.)	Katz et al. [13], 1999	625 patients with a diagnosis of AD, vascular and mixed dementia plus behavioral symptoms MMSE <23	Patients randomized to risperidone 1 ($p = 0.01$) or 2 ($p = 0.05$) mg doses experienced a significant improvement in delusions at week 12 as measured by the BEHAVE-AD	Dose-dependent increases in somnolence and extrapyramidal effects	Risperidone has a significant impact on delusional intensity in patients with Alzheimer and related dementias at doses of 1–2 mg
Open label cohort design with flexible dosing (0.5–2 mg range)	Shigenobu et al. [14], 2002	16 patients with AD and delusions of theft MMSE not specified (average MMSE 20)	Intensity of delusions as measured by the NPI delusional subscale decreased significantly from baseline ($p < 0.05$)	All patients experienced elimination or reduction of delusions	Risperidone at doses ranging from 0.5 to 2 mg is effective in treating delusions of theft among patients with AD in a small sample over a 12-week period
<i>Olanzapine</i>					
Multi-centered two phase study Phase 1: 6 weeks, double-blind, fixed dose (5, 10, 15 mg/day) Phase 2: 18 weeks, open label, flexible dose treatment	Street et al. [15], 2001	105 Nursing home patients with probable AD MMSE <25	Over the course of the open label extension period the delusional sub-score of the NPI decreased significantly ($p = 0.024$)	Dose-dependent increases in weight gain and somnolence were observed; no significant changes in EPS or other motor symptoms	Olanzapine is effective over a long-term period in reducing the incidence of delusions among patients with AD and is relatively well tolerated over time

Table 1 (continued)

Medication and study design	Reference	Participants	Outcome measures	ADR	Conclusion
6 weeks, multi-centered, placebo-controlled trial with patients randomized to placebo, 5, 10 or 15 mg dose	Street et al. [16], 2000	206 patients with AD MMSE <25	Olanzapine at a dose of 5mg o.d. caused significant improvement in the delusional subscale of the NPI over the 6-week period; 10 and 15 mg doses produced no significant change	No significant changes in EPS or anticholinergic effects compared to placebo; significantly higher prevalence of somnolence and abnormal gait	Olanzapine at doses of 5 mg is significant in reducing delusional intensity among patients with AD compared to placebo; side effects are most notable for somnolence and abnormal gait
6 weeks, multi-centered, double-blind, placebo-controlled trial of patients assigned to placebo or fixed dose olanzapine (5, 10, 15 mg)	Clark et al. [17], 2001	165 patients with AD MMSE <25	No significant difference in the emergence of delusions when compared to placebo as measured by the NPI, although the emergence of delusions across all subgroups was low	Higher prevalence of stooped gait in the 5 and 15 mg treatment arms, higher somnolence rates at the 10 and 15 mg doses	Hard to draw a definitive conclusion as rates of emergence of delusions across subgroups were low
10 weeks, multi-centered, double-blind, placebo-controlled trial in which patients were randomized to placebo, 1, 2.5, 5 and 7.5 mg daily	De Deyn et al. [18], 2004	652 patients with AD and delusions or hallucinations MMSE >5	Significant change in delusional intensity as measured by the delusional sub-scale of the NPI only at the 7.5 mg dose ($p = 0.002$)	No significant changes when compared to placebo	Olanzapine at doses of 7.5 mg o.d. may be beneficial in improving delusions among patients with AD over a 10-week period
<i>Quetiapine</i>					
12 weeks, open label, pilot trial in which patients were randomized to doses ranging from 50 to 150 mg o.d.	Scharre and Chang [19], 2002	10 patients with probable AD and psychosis or aggressive behaviors MMSE – 10–26	Quetiapine, at doses ranging from 50 to 150 mg daily, significantly reduces delusional intensity as measured by the NPI sub-score at 6 weeks ($p = 0.04$) and 12 weeks ($p = 0.02$)	Well tolerated – no effects on EPS, orthostatic hypotension; slight drowsiness	Quetiapine is effective in treating delusion in a small sample of patients with AD; low sample size makes it hard to draw a definitive conclusion
8 weeks, open label trial with patients randomized to varying doses (25–200 mg daily)	Fujikawa et al. [20], 2004	16 patients with AD HDS-R <20	Significant improvement in the delusions subscale of the BEHAVE-AD ($p = 0.0033$)	No change in drug-induced extrapyramidal effects	Quetiapine at varying doses is effective in treating delusions among patients with AD in a small sample
<i>Xanomeline</i>					
6 months, double-blind, placebo-controlled, parallel group trial followed by a 1-month, single-blind, placebo washout (patients randomized to placebo, 25, 50 and 75 mg doses)	Bodick et al. [27], 1997	343 patients with probable AD aged 60–90 years MMSE 14–24	Xanomeline during the double-blind phase prevented the emergence of delusions ($p = 0.001$) and caused them to remit when present ($p = 0.02$)	Dropouts in the treatment arm ranged from 19 to 59% depending on the dosage; most patients discontinued treatment because of gastrointestinal effects	Xanomeline is effective in treating delusional symptoms in patients with AD but is associated with adverse gastrointestinal effects, especially at high doses
<i>Buspirone</i>					
Open label study involving a 1-week placebo lead in and 2 weeks at varying doses	Levy et al. [28], 1996	20 patients with AD and disruptive behavior	Significant improvement in delusional intensity as measured by the delusional subscale of the BEHAVE-AD at the 30 mg dose ($p = 0.014$)	Mild side effects with no patients discontinuing treatment as a result	Buspirone is effective in treating delusions in patients with Alzheimer's disease at a dose of 30 mg
AD = Alzheimer's disease; NPI = neuropsychiatric inventory; CIBIC-plus = caregiver impression of change; BEHAVE-AD = behavioral assessment in Alzheimer's disease scale; EPS = extrapyramidal symptoms; HDS-R = Hasegawa dementia scale-revised.					

[27]. The medication was proven effective both in causing delusions to remit and in delaying their emergence; however, significant gastrointestinal side effects were noted. Buspirone was tried in an open label study involving 20 patients [28]; the study was only 2 weeks in duration but a significant response was noted at the 30-mg dose compared to baseline.

Discussion

Delusions are clinically important symptoms that often develop in the context of AD [1–4]. They are significant for many reasons in that they may be associated with accelerated cognitive decline [28–30], premature institutionalization [31–34], and significant caregiver stress [33].

In spite of the prevalence of these symptoms and their morbidity, the existing literature on the treatment of these symptoms is sparse. There have been few well-designed, large scale, multi-centered studies that have looked exclusively at response rates in patients with AD. Previous trials have had many limitations, including: small sample sizes, retrospective designs, poor outcome measures, and lack of disease specificity. Perhaps the largest limitation of previous studies was that few of them looked at delusions in isolation, choosing to consider delusions along with other psychotic symptoms such as hallucinations. This approach may be somewhat questionable as delusions and hallucinations in AD have been shown to differ significantly in their time of onset, suggesting they may result from different neuroanatomical changes in the brain [35]. Unfortunately, it is not yet clear as to how they differ. In addition, delusions are often considered with other behavioral symptoms in dementia and many studies do not differentiate one behavioral symptom from another. This approach may make some sense, given that the outcome of interest may be an improvement in behavior, although it is not clear from these studies which symptoms improve and which symptoms get worse. Furthermore, delusions may be hard to detect particularly among patients with advanced dementia, leading to skewed studies confined to patients with more mild cognitive changes. Finally, the majority of previous studies have been conducted in patients with different dementia diagnoses. This has been problematic as it is now well understood that the prevalence of delusional thinking may vary from one illness to another (AD versus Lewy body disease for example).

One of the key questions that emerges with respect to treatment effectiveness is the neuropathogenesis of delusions in AD and how this differs from delusions in other psychiatric illnesses such as schizophrenia. Psychotic symptoms, including delusions, in these more traditional psychiatric illnesses have been linked to the presence of excess dopamine [36]. Antipsychotic medications work by decreasing levels of dopamine in the brain thereby improving psychotic symptoms. Alternatively, the greatest burden of evidence exists for the theory that delusions in patients with AD arise from selective damage to the frontal lobe. Studies have demonstrated that when compared to patients with AD who do not have delusions, delusional patients have impaired frontal lobe metabolism, a higher density of senile plaques in the frontal cortex and significantly more deficits in fronto-subcortical circuits [37]. Neuroimaging studies, including SPECT, have supported this as well [38, 39]. Neither antipsychotic medica-

tions nor cholinesterase inhibitors have been shown to have specific effects on frontal lobe function, however, that would explain their effectiveness. Other investigators have suggested that delusions may arise as independent non-cognitive manifestations of AD [40], an argument that would perhaps explain why conventional antipsychotic medications are useful in treating these symptoms. Studies looking at receptors have demonstrated an association with reduced levels of serotonin [41] and abnormalities in the dopamine system [42], postulating a possible mechanism. Still others argue that delusions in patients with AD may arise from the disease process itself [43, 44]. Much of the evidence for this has arisen from postmortem brain biopsies comparing the degree of neuropathology in the brains of AD delusional patients versus patients with AD who do not have delusions. Although some studies have shown no difference [45], others have demonstrated significantly more neuropathology in delusional AD patients when compared to non-delusional AD patients [46]. This may serve as a theoretical argument as to why cholinesterase inhibitors may be effective in treating delusional symptoms.

Apart from effectiveness, an important consideration in determining which drug to administer relates to the presence of side effects. Most of the studies identified drug side effect rates that were higher than placebo. Specifically, antipsychotic medications had more somnolence and extrapyramidal effects associated with them while cholinesterase inhibitors were found to have more of an effect on the gastrointestinal system. An important additional consideration that must be taken into account when prescribing antipsychotic medications to older patients with dementia is recent evidence that such medications may be associated with an increased risk of cerebrovascular disease and premature death [47]. While these medications clearly still have a role to play given their effectiveness and rapidity of onset compared to other treatments, physicians could conceivably come under more pressure to justify the use of these medications.

Even though all of the studies included in this review met predetermined inclusion and exclusion criteria, there were many factors that could have accounted for the variation in results. Not all of the studies were double-blind or placebo-controlled. The sample sizes varied considerably, as did the study duration. Furthermore, different populations were examined (community, nursing home) and the severity of illness varied. Most of the studies alluded to in this literature review excluded patients with high MMSE scores. In the vast majority of cases, the mean MMSE score for most studies ranged from low to

high teens. However, in a few of the studies [12, 13, 15] that were done exclusively in nursing home populations, the mean MMSE score was much lower, often in the single digits. As the baseline rate of delusions may have been higher in these patients, the positive results obtained may be somewhat skewed compared to studies done using patients with higher MMSE scores. Finally, very few studies commented on response rates or the number needed to treat. Specifically, only two studies predefined response as the elimination of the delusion [14, 25]. Only one study predefined response as a 50% reduction in delusional intensity as measured by the NPI [19], and only one study actually gave responder rates compared to placebo [13].

With respect to specific treatments, it was observed that risperidone had more positive studies than olanzapine and seroquel. As all three drugs have similar although not identical mechanisms of action, it is hard to know how to explain the difference in efficacy in favor of risperidone. One theory is that risperidone may be better at targeting the receptor sites specific to delusions in AD. An alternative explanation is that the variation in results reflects methodologic differences in study design (number of study participants, open label versus randomized design). Similarly, with respect to the cholinesterase inhibitors, donepezil was the only drug to consistently show positive results while the other two medications evaluated (rivastigmine, galantamine) were largely negative. Again, it is hard to know whether this variation in the results reflects subtle

differences in favor of donepezil or whether this variation could be explained by methodologic differences between the studies (small numbers, number of open label studies, etc.). Clearly, more head-to-head studies done using large sample sizes with proper methodology are required before these questions can be answered.

Conclusion

In summary, while delusions are common symptoms in AD [1–4] and account for a significant amount of caregiver burden [33], there is limited evidence about effective therapies. Based on a review of the existing treatments, both atypical antipsychotics and cholinesterase inhibitors have a role to play. The greatest burden of evidence appears to exist for risperidone and donepezil, although further randomized controlled studies are required. Adverse effects restricted to the gastrointestinal system seem to be most common among users of cholinesterase inhibitors, while somnolence and extrapyramidal effects tend to be more common among atypical antipsychotics. There are only limited data available on novel therapies and only one study dealing with a specific delusional subtype. While the studies thus far have been encouraging, further studies are required before a definitive conclusion can be reached about individual treatments.

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