The Modern Role of Antipsychotics for the Treatment of Agitation and Psychosis in Alzheimer's disease

Abstract

Introduction: Antipsychotics have long been the mainstay of treatment for agitation and psychosis in Alzheimer's disease. Despite their current use successive studies have shown that they only confer a modest benefit which must be balanced against their well-established serious side effects (extrapyramidal symptoms, stroke, accelerated cognitive decline and mortality).

Areas covered: This review outlines the current guidance on antipsychotic usage and the evidence of their continued usage against a backdrop of emerging pharmacological treatments and an increasing emphasis on the importance of non-pharmacological interventions.

Expert commentary: We appraise the current justification for antipsychotic use in the context of the changing landscape of prescribing and provide a view on the most promising alternative candidates to this class of drug.

Keywords agitation, Alzheimer's disease, atypical antipsychotics, dementia, psychosis.

1. Introduction

Dementia affects an estimated 47 million people worldwide and is expected to increase to 132 million people by 2050. Alzheimer's disease (AD) is the most common form of dementia accounting for more than 60% of cases. Neuropsychiatric symptoms (NPS, also known as behavioural and psychological symptoms of dementia, BPSD) are a frequent and often debilitating feature of AD, encompassing, among other symptoms, agitation, mood and affective disturbances and psychosis.

The cumulative prevalence of NPS is estimated to be as high as 80% [1]. They are associated with earlier institutionalization, more severe cognitive impairment, lower quality of life, greater caregiver distress and increased mortality [2-4].

Despite the near universal presence of NPS, treatment options are limited. One of the most widely prescribed class of psychotropic medications for many of these symptoms are atypical antipsychotics. Of these agents, only risperidone is licenced for the treatment of aggression in Europe with no FDA-approved medication in the USA.

The mid-2000s represented a step-change in the role of antipsychotics in dementia. The emerging evidence around their safety and long-term prescriptions led to significant public health concerns and various efforts aimed at highlighting their danger and reducing their use, including the FDA black box warning. In the UK, according to NICE and POMH-UK between 2011 and 2016 there was a 19% reduction in the use of antipsychotics (although there is wide variation in prescription rates across the country) and those that were still prescribed were more often for appropriate reasons. This is supported by a large study examining antipsychotic use in over 65s with dementia in the UK and Italy which reported a fall from 11% to 9% in atypical antipsychotic use in the UK between 2009 and 2012. But there were rises in Italy from 11% to 18% over the same period and frequencies in care homes are still reported to be as high as 17% [5]. This is significant given the large body of literature supporting the harmful effects of antipsychotic drugs, namely a 1.5-1.7-fold increased mortality risk, and increased risk of stroke, oedema and pneumonia (box 1) [6].

In Europe only risperidone licensed for the short-term treatment of aggression. Several studies have shown statically significant improvements in aggression over 6-12 weeks - with some benefit to psychosis – but the clinical significance of this benefit in minimal [7,8]. The literature surrounding the use of other atypical antipsychotics in people with dementia is less well developed, but the majority of trials that have been published do not support a strong effect. In spite of this many antipsychotics besides risperidone are used off-license in AD, with

quetiapine being among those most commonly prescribed. Solid evidence from meta-analysis shows that quetiapine has no effect on NPS [7].

Any modest benefits must be seen in the context of the safety of profile of this class of drug but there is some research emerging which may have potentially important implications for the use of antipsychotics in current clinical practice. Patel et al. (2017) et al showed that severe hallucinations during treatment with antipsychotics were associated with a three-fold greater risk of relapse after discontinuation [9]. Research of this nature, which unpicks broader clinical syndromes such as psychosis which are often the target of antipsychotic treatment, has the potential to aid with a more person-centered prescription practice.

Typical antipsychotics are rarely used in current practice. Eleven randomized controlled trials (RCTs) have been published which overall show only a modest benefit which must be considered alongside the body of evidence linking their use to a number of serious side effects. These include worsening of cognitive decline, parkinsonism, prolonged QTc interval, and increased mortality (box 1) [10]. This evidence and the availability of newer agents means that typical antipsychotics are not recommended for use in people with dementia, with haloperidol being the one drug in this class that is still occasionally prescribed.

Box 1: Major adverse events associated with typical and atypical antipsychotic use.

Antipsychotic class	**Major adverse events**
Typical	Cognitive decline, parkinsonism, dystonia, tardive dyskinesia, QTc prolongation, mortality.
Atypical	Cognitive decline, extrapyramidal symptoms, sedation, oedema, pneumonia, stroke, mortality.

Encouragingly, there are a number of new agents in clinical trials for agitation in AD, although this number is much smaller for psychosis. Moreover, we are understanding increasingly more about the underlying biology of these symptoms. Both of these factors will likely lead to some re-evaluation of the role of atypical antipsychotics in the treatment of agitation and psychosis in AD. Here we review the current guidance on antipsychotic usage, alternative strategies and the evidence to support their continued usage against a backdrop of emerging pharmacological treatments, an increasing emphasis on the importance of non-pharmacological interventions and an ever increasing understanding of their etiology. As atypical antipsychotics, even when used off label, are frequently prescribed for the management of agitation and psychosis, and because most new agents in development target these symptoms, we predominately focus on these for the remainder of this review. A summary of the phenomenology of these symptoms is shown in Box 2.

Box 2: Common symptoms of agitation and psychosis in AD

Agitation	**Psychosis**
Repetitive mannerisms, hoarding, screaming, hitting, wandering, verbal aggression, and general restlessness.	Delusions concerning theft, harm and spousal infidelity; visual hallucinations.

2. Treatments for agitation and psychosis in dementia: current options and emerging candidates

2.1 Disease mechanisms

Neurobiological factors associated with agitation and psychosis have been described in detail elsewhere [11,12] but a brief description here of progress and challenges is included to give context to the modern use of antipsychotics and development of novel treatments. Disruptions to the dopaminergic, serotoninergic and cholinergic neurotransmitter systems have been reported in AD-related psychosis and agitation [13-15]. These changes are consistent with

the mechanism of action of many antipsychotic and non-antipsychotic drugs currently in use or in trials, though there is a clear need for the identification of novel treatment targets, particularly for psychosis. A potentially novel angle is highlighted by studies showing that AD-related pathology also appears to play a role, with a higher density of neurofibrillary tangles in the neocortical areas associated with both agitation and psychosis [16-18] (though this has not been universally shown [19]) and increased concentrations of phosphorylated tau in frontal cortex [20,21]. These findings point towards the potential utility of anti-tau agents, particularly for psychosis, of which there are a number in development for AD itself but no investigations are as yet underway for the treatment of NPS.

The broad range of neurobiological alterations point towards a complex etiology with a multitude of potential novel treatment targets. There is an urgent need for more programs of research to evaluate the disease mechanisms underlying these symptoms in order to develop novel treatments. Environmental factors are also key and are widely recognized to be major antecedents of agitation [22] and as such must be considered in clinical decision making (see below).

2.2 Non-pharmacological interventions

Non-pharmacological interventions should play a key role in the clinical use of antipsychotics. The current UK NICE guidelines recommend an early and comprehensive assessment of the person with dementia experiencing non-cognitive symptoms that cause significant distress. This comprehensive assessment should aid in the identification of potential causes of NPS in dementia, and also support a person centred approach to care. While there is now a substantial body of evidence to support the use of non-pharmacological interventions as a first line treatment for agitation and other NPS the evidence for psychosis is limited. In other words, there are no effective treatments – pharmacological or non-pharmacological – for psychosis, underscoring the urgent need for the development of new treatments.

The evaluation of non-pharmacological interventions is beyond the scope of this review but there is evidence from the WHELD programme to support the use of exercise and social interaction alongside person centred care for the management of a range of NPS [23]. An additional key element of the WHELD programme which has important implications for current prescribing practice is formal review of antipsychotics. Here, antipsychotic review led to a 50% reduction in use but these individuals had significantly worse neuropsychiatric outcomes over nine months. However, when combined with the social interaction intervention, antipsychotic review significantly reduced mortality with no overall worsening of NPS. These findings are in line with others which show that meaningful reductions in antipsychotic use can be achieved without worsening of symptoms [24,25]. This highlights the importance of a joined up approach to the management of NPS; there is a clear rationale to ensure appropriate prescription of antipsychotics but this must be considered alongside appropriate non-pharmacological strategies to mitigate any detrimental impact.

The WHELD program was extended into a major RCT of key psychosocial interventions in around 1,000 people in the UK [26]. The principle aim was to distil what works in psychosocial care into a package of care which is deliverable in a care home setting. The study found that while there was only a modest but significant effect of the intervention it was more cost effective than usual care. Other emerging evidence of non-pharmacological interventions include the DCM™-EPIC study [27]. This study aims to evaluate the impact of Dementia Care Mapping™ (an observational tool designed to improve dementia care quality by focusing on person-centred care principles) on enhancing person-centred care and reducing agitation in people with dementia in care homes. Findings are due in 2018 will represent another important empirical evaluation of the long-term sustained benefit of evidence-based psychosocial interventions in the treatment of NPS, the results of which will likely feed into the circumstances in which antipsychotic prescription is considered appropriate.

2.3 Non-antipsychotics

2.3.1 Cholinesterase inhibitors and memantine

The use of cholinesterase inhibitors (ChEIs) for the treatment of NPS has received a high degree of focus. A meta-analysis of 16 studies found only modest benefit, with the greatest effects on affective symptoms [28,29]. ChEIs do not seem to be efficacious in the treatment of agitation or psychosis in AD [30] but there is some evidence that they form represent an appropriate alternative to antipsychotics in dementia with Lewy bodies where there is efficacy of rivastigmine in the treatment of psychosis [31].

Although initial meta-analyses indicated a modest benefit of memantine for the treatment of agitation and psychosis in AD [32,33], two subsequent RCTs – one long-term study and one over 12 weeks in patients with clinically significant agitation – failed to show any impact [34,35].

2.3.2 Muscarinic agonists

The use of muscarinic receptor agonists in the treatment behavioural symptoms in AD show some clinical promise. In an early phase III clinical trial, xanomeline, an M1 and M4 agonist, significantly reduced agitation and psychosis in AD in a dose dependent manner. Despite the encouraging results around efficacy, the tolerability profile was poor with a discontinuation rate of >50% in the high dose arm due to adverse events, with intolerable gastro-intestinal side effects at the main cause [36], More recently, a phase I pilot study in heathy adults assessing only the tolerability of a combination of xanomeline and trospium chloride (a peripheral muscarinic antagonist) showed a 46% reduction in cholinergic side-effects. There are now future plans to initiate a phase II study in schizophrenia [37] and given the previous efficacy data in AD this novel combination may represent an important step towards re-evaluating the role of xanomeline in AD.

2.3.3 Antidepressants

Although there are questions over the efficacy of antidepressants to treat affective symptoms in dementia there is emerging evidence of efficacy of selective serotonin reuptake inhibitors and mirtazapine for agitation. Sertraline was well tolerated in a small trial and while it failed to

meet its primary outcome there was evidence of efficacy in an analysis restricted to patients with at moderate to severe agitation at baseline. This showed about 60% response rate in BPSD symptoms compared with 40% of those in placebo [38]. The CIT-AD study built on previous evidence of efficacy of citalopram [39] showing significant improvements in agitation over 9 weeks [40]. Importantly, this study was the first that was designed to evaluate safety and showed citalopram was associated with QTc prolongation and worsening cognition. A major RCT of mirtazapine, an antidepressant with alpha-2 adrenergic and 5-HT2 and 3 antagonist properties is currently underway. This study is the first to examine the efficacy of mirtazapine for agitation and follows on from promising initial findings in open label studies [41,42] and secondary analysis of a depression RCT [43]. With regard to other antidepressants, two studies have examined the efficacy of trazodone but did not find any evidence to support its efficacy [44,45].

Antidepressants remain a potential alternative to antipsychotics but results from further trials are awaited. At present the best evidence is for citalopram, although there are safety concerns at current therapeutic doses.

2.3.4 Anticonvulsants

Two small RCTs of carbamazepine and one of oxcarbazepine have shown preliminary evidence of efficacy for the treatment of agitation [46-48]. All were of short duration making safety difficult to comprehensively assess but larger, longer studies are now underway. In contrast valproate has shown no benefits, and there are concerns of over its tolerability at therapeutic doses [49]. Data for other anticonvulsants is very scarce, and is mostly based in small number of open label studies.

2.3.5 Analgesia

There is RCT evidence that analgesics significantly improve agitation in care home settings, reflecting the multifactorial nature of this group of symptoms [50]. An analysis of over 900 people in care homes reported higher prescriptions of antipsychotics in those with pain,

possibly highlighting a high degree of mismanagement of pain or the inappropriate treatment of pain-related agitation [51]. These findings underscore the importance of pain as a major antecedent to agitation and more broadly the availability of a safe and effective alternative to antipsychotics for the treatment of agitation.

2.4 Novel treatments

Atypical antipsychotics are all characterized by their antagonism of the 5HT2A receptor. However they act on a wide number of other receptor sites to varying degrees including other serotonergic sites, dopamine, histamine H1, alpha adrenergic and muscarinic. On the basis of post-mortem and imaging studies 5HT2A is likely to be a key receptor target for antipsychotic action. While the mechanisms underlying the harmful effects of antipsychotics are not known it is thought that their sedative properties are key mediators, warranting research into more selectively acting agents [10]. Pimavanserin, a highly selective 5HT2A receptor inverse agonist (i.e. binding to the 5HT2A receptor but eliciting the opposite response to an agonist), represents a refinement of atypical antipsychotic action and is a potential major step forward in the treatment of psychosis in AD. It has been recently approved by the FDA in the US for treatment of psychosis in Parkinson's disease [52] and a phase II RCT of 181 participants with psychosis in AD was recently completed with encouraging top line results. Of those in the treatment arm 55% experienced an improvement in psychosis of 30% or more, when compared to those in the placebo arm at the primary end point of 6 weeks (where 37% improved by 30% or more, p=0.0159) [53]. At 12 weeks, however, there was no benefit to pimavanserin over placebo, suggesting there may not be any sustained benefit. In this study and others pimavanserin has been shown to have a favorable safety profile compared to other antipsychotics but longer term studies should be undertaken in order to evaluate impact on cognition as cognitive outcomes have limited sensitivity to change over 12 weeks, particularly in more advanced patients. Pimavanserin is now entering phase III trials in AD psychosis alongside other planned investigations into its efficacy for agitation and psychosis in other dementias.

The pimavanserin findings are encouraging but should be viewed in the wider context of treatment development for psychosis in AD, where it is only one of a small number of compounds in trials. MP-101 a metabotropic glutamate receptor type 2 (mGluR2) and 3 (mGluR3) agonist is currently in phase II trials. Binding at these receptors is implicated in schizophrenia and the phase II trial of this compound in AD psychosis is representative of a potential shift towards more novel agents but there remains a significant and urgent unmet treatment need for a safe and effective therapy for AD-P

The landscape of emerging treatments for agitation is more encouraging with several ongoing RCTs and several more which have recently completed. Another novel antipsychotic, lumateperone (with both serotonin and dopamine antagonist properties), is currently in phase III trials while a number of adrenergic antagonists are currently under investigation for efficacy in in treating agitation. These include ORM-12741 (alpha-2C) the results of which are awaited, mirtazapine (see above), and prazosin - which is a repurposed antihypertensive. Two initial 8 week studies of prazosin showed a good safety profile and a positive effect on agitation measured by the NPI [54]; larger studies are planned and alongside the evidence for mirtazapine, adrenergic antagonism may emerge as a promising mechanism of action. Other novel compounds include cannabinoids, although the evidence base is at present too limited to draw any firm conclusions. One placebo-controlled trial has reported efficacy of dronabinol for agitation but the study was small [55] and the rest of the evidence base is made up of case reports, retrospective analyses or very small trials [56-59]. Larger RCTs of both dronabinol and nabilone are under way.

Among the emerging non-antipsychotic agents dextromethorphan-quinidine (AVP-786) is a particularly attractive alternative to antipsychotics due to its known safety profile, resulting from its existing license for pseudobulbar affect. A major phase II 10-week RCT has shown evidence of a statistically significant but modest improvement in agitation and aggression among those randomized to treatment (reduction in NPI agitation/aggression from 7.1 to 3.8 compared with 7 to 5.3 in the placebo group). Moreover, at each stage of the study the

response favored the treatment arm [60]. The mechanism of action of dextromethorphan is relevant to agitation in AD, notably inhibition of serotonin and norepinephrine reuptake. It also has analgesic properties which is consistent with the findings described above suggesting analgesia as an effective therapy for agitation [50]. Adverse events included falls, UTI and diarrhea but not cognitive decline, sedation or clinically meaningful QTc prolongation. The increased rate of falls, although not statistically significant, is of concern and it is premature to draw concrete positive conclusions around safety as this was a relatively small study (N=220) and safety is difficult to comprehensively assess over a 10 week period. Longer studies are needed to conclusively demonstrate safety. Phase III trials are now underway in much larger samples over a 12 week period, with completion due in 2019 and importantly, there will also be an extension study examining safety over a period of 56 weeks in 700 people.

3. Conclusion

Atypical antipsychotics should not be a first line treatment for any NPS in dementia. Their use should always follow an assessment of the patient to determine underlying causes, followed by non-pharmacological management such as psychosocial interventions or environmental modifications. If used, the best evidence base remains for risperidone over the short term only (<12 weeks), but there are several emerging antipsychotic treatments which may represent safer more effective alternatives to older atypical agents; pimavanserin is the most promising agent in this class for the treatment of psychosis but there is a need for further evaluations around safety and cognition in longer term studies. For agitation, results from dextromethorphan-quinidine trials show the greatest promise while there remain safety concerns around citalopram, although there is good evidence for efficacy. A summary of RCTs of the most promising agents is shown in Table 1. The enduring use of antipsychotics is likely in part due to the lack of available alternatives; the number of agents in trials for agitation in encouraging but there is still a lack of options in the drug development pipeline for psychosis, which needs to be urgently addressed.

Table 1: Summary of major clinical trials in agitation and psychosis (see text for further discussion of results and around safety).

Drug	Indication	Primary outcome	Results at primary outcome
Citalopram [40]	Agitation	NBRS-A and mADCS-CGIC at 9 weeks	Significant benefit over placebo: mean difference NBRS-A: −0.93 [95% CI: −1.80 to −0.06]; mADCS-CGIC: 40% moderate/marked improvement in treatment arm vs. 26% in placebo arm.
Analgesics [50]	Agitation	CMAI at 8 weeks	Significant benefit over placebo: mean difference −7.0, 95% CI −3.7 to −10.3]
Pimavanserin [53]	Psychosis	NPI psychosis subscale at 6.	Significant benefit over placebo: mean difference -1.84 [95% CI −3·64 to −0·04].
Dextromethorphan-quinidine [59]	Agitation	NPI agitation/aggression subscale	Significant benefit over placebo: mean difference −1.5 [95% CI, −2.3 to −0.7].

NPI: Neuropsychiatric Inventory; NBRS-A: Neurobehavioral Rating Scale, agitation subscale; mADCS-CGIC: modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change.

4. Expert commentary

The reduction in antipsychotic use in dementia over the past decade is a major success but it is of concern that a number of agents which have a very limited evidence base - or where there is solid evidence against efficacy - are still in use in care home settings; these include quetiapine and haloperidol. Part of their enduring use is likely to be in part down to the lack of available alternatives but the number of novel agents in trials for agitation and psychosis is encouraging. It is notable that most agents in trials are refinements of mechanisms of action of existing drugs. While this is a sensible approach the lack of research into disease mechanisms underlying these symptoms is likely impeding efforts to identify novel treatment targets for drug development.

The very nature of these symptoms - complex and occurring in the context of AD - make preclinical modelling in animals particularly difficult. Post-mortem and genetic work, meanwhile, have historically been hampered by the low availability of high quality clinical history data to accompany samples. But this appears to be changing. Initiatives like Brains for Dementia Research in the UK and the NIAGADS resource in the USA are excellent resources for the study of biological etiology in post-mortem tissue the full extent of the rich clinical data that accompanies the tissue has yet to be exploited fully for the purposes of research into neuropsychiatric symptoms. Moreover, research in genetics is taking exciting steps forward; we are seeing increasing numbers of large cohort studies with genetic material and high quality clinical data. The emerging work around the shared genetic risk and similar neural mechanisms between schizophrenia and psychosis in AD [61,62] may lead to clearer rationales for or against the repositioning of treatments across the spectrum of psychiatric disorders. This feeds in to research seeking to target treatments to symptoms better, which is too an under researched area but one with great potential.

Another important avenue is the development of effective non-pharmacological interventions. While there are naturally considerably fewer safety concerns this does not obviate the need for robust research into therapeutic and cost efficacy. The latter has been absent from many evaluations of non-pharmacological approaches in the past and is probably one reason for the

lack of uptake of evidence-based non-pharmacological interventions into clinical practice. Achieving this will be instrumental in reducing antipsychotic use further and changing modern prescribing practices. On the balance on current evidence and experience, it is likely that for an intervention to be well received it will need to be simple and delivered with only limited ongoing specialist support, especially in the care home sector.

5. Five year view

The safety profile of antipsychotics in dementia is poor and along with their only modest effect size, and the high prevalence of agitation and psychosis, this means that the need for new treatments will be sustained well into future. The question is, how likely will is that need to be met over the medium term? Pimavanserin is the closest agent to regulatory approval for psychosis and it is likely that new drugs with similar mechanisms of actions will enter into the development pipeline soon. There are some interesting novel candidate compounds in clinical trials but it is unlikely that any will reach the point of becoming a first line treatment in the next five years. For agitation, dextromethorphan-quinidine shows promise and may well receive regulatory approval over the next five years. Preclinical biomedical research into the disease mechanisms of agitation and psychosis is likely to increase with the availability of large deep phenotyped cohorts; genetic epidemiology is an area that will likely see particularly rapid growth. It is unlikely that new treatments will be in human trials as a result of further biomedical research over the next five years but the ambition should be to create a solid foundation on which to reach this goal.

Finally, the WHELD study results demonstrating efficacy and cost effectiveness of a non-pharmacological intervention - along with a sustained focus on other such interventions – suggest that a new evidence based intervention package will emerge in the coming years such that current atypical antipsychotics become a truly second line treatment option, reflecting current guidance.

Key issues

- Antipsychotics remain commonly prescribed for the treatment of agitation and psychosis in AD, despite a modest effect size and considerable safety concerns.
- Current guidelines advise their use only after first line non-pharmacological interventions and for up to 12 weeks.
- There are a number of promising candidates in trials but still no licensed treatments. These include pimavanserin for psychosis, and dextromethorphan-quinidine and citalopram for agitation.
- There is a need for more concerted research into the disease mechanisms and epidemiology of agitation and psychosis so that novel targets can be identified and optimal strategies can be developed for existing treatments.

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