Alternative pharmacological treatment options for agitation in Alzheimer's disease

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Abstract

In patients with dementia and Alzheimer's disease (AD), treatment of neuropsychiatric symptoms (NPS) is a major concern in the management of these devastating diseases. Among NPS in AD, agitation and aggression are common with earlier institutionalization, increased morbidity and mortality, and greater caregiver burden. Pharmacological treatments for AD-related agitation, specifically off-label use of atypical antipsychotics, showed only modest improvements, with increased side-effect burden and risk of mortality. Non-pharmacological treatment approaches have become the preferred first-line option. However, when such treatments fail, pharmacological options are often used. Therefore, there is an urgent need to identify effective and safe pharmacological treatments for agitation/aggression in AD and dementia. Unfortunately, progresses have been slow, with a small number of methodologically heterogeneous randomized controlled trials (RCTs), with disappointing results. However, evidence coming from recently completed RCTs on novel or repositioned drugs (mibampator, dextromethorphan/quinidine, cannabinoids, and citalopram) showed some promise in treating agitation in AD, but still with safety concerns. Further evidence will come from ongoing Phase II and III trials on promising novel drugs for treating these distressing symptoms in patients with AD and dementia.

Introduction

Neuropsychiatric symptoms (NPS) in dementia,[1,2] previously denominated as behavioral and psychological symptoms of dementia, are often more distressing, impairing, and costly than cognitive symptoms, representing a major health burden for older adults.[3] NPS varied according to dementia subtype and severity and induced marked disability in functional status, increasing, prevalently, the distress of the caregivers of patients with dementia. NPS in Alzheimer's disease (AD) are thought to reflect one or more types of central nervous system (CNS) dysfunction. Among these CNS alterations, central synaptic or circuit disconnections in frontal-subcortical and corticocortical networks, dysfunction in ascending monoaminergic systems involving serotonin, norepinephrine, or dopamine neurons, and glutamate-mediated excitatory neurotoxicity may have a role on NPS in AD.[2,4,5] These CNS dysfunctions may occur concurrently and mediate synergistically NPS onset.

A better knowledge of neuropsychiatric pattern of the different forms of dementia could affect significantly treatment approaches.[6] Furthermore, NPS can manifest early in the course of neurodegenerative diseases and mild behavioral impairment (MBI) has been proposed as a diagnostic construct aimed to identify patients with an increased risk of developing dementia, but who may or may not have cognitive symptoms.[7] Very recently, the NPS Professional Interest Area of the International Society to Advance Alzheimer Research and Treatment (ISTAART) proposed research diagnostic criteria for MBI, as an extension of the preexisting MBI construct to include, but not mandate cognitive impairment, including mild cognitive impairment (MCI) in the MBI framework.[8]

Among NPS, agitation is a frequent manifestation of AD, vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and other dementia syndromes,[9-11] appearing to be a clinically important behavioral complication of dementia that warrants further study. The prevalence of agitation in dementia ranges from 20 to 60%, depending on diagnostic definitions used and the population studied.[12,13] Agitation differs from psychosis and depression of AD in that it may be conceptualized as a single symptom or a symptom complex.[14] Agitation refers to emotional distress, excessive psychomotor activity, disruptive irritability, and disinhibition, and while it may include aggressive behaviors, agitation can occur without aggression (*i.e.*, repetitious mannerisms, rocking, or pacing). In fact, some subtypes of agitation that may have important clinical differences were also characterized, including physical *versus* verbal and aggressive *versus* non-aggressive types.[15] Agitation in dementia often co-occurs with psychosis and depression. There is substantial evidence that verbal agitation is associated with depression, and there may be some relationship to delusions.[14,16] Psychosis, particularly delusions, and depression occur with increased frequency in aggressive patients and may be a causative factor of agitation/aggression.[17] Agitation and aggression have frequently been termed *dysexecutive* symptoms because of their relationship to *executive* or higher-order loss of behavioral control.[18,19]

At present, there is no consensus on a commonly accepted definition of agitation, with no widespread agreement on what elements should be included in the syndrome.[20] Historically, a formalized definition of agitation was proposed as *inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual*.[15] However, very recently, the International Psychogeriatric Association (IPA) formed an Agitation Definition Working Group (ADWG) with a group of experts to develop a provisional consensus definition of agitation in patients with cognitive disorders broadly defined as: i) occurring in patients with a cognitive impairment or dementia syndrome (*e.g.*, AD, FTD, DLB, VaD, other dementias, or a predementia cognitive impairment syndrome such as MCI or other cognitive disorders); ii) exhibiting behavior consistent with emotional distress; iii) manifesting excessive motor activity, ver-

bal aggression, or physical aggression; and iv) evidencing behaviors severe enough to cause excess disability and not solely attributable to another disorder (psychiatric, medical, or substance-related) or a suboptimal care condition.[20] This provisional definition has been developed to advance interventional and non-interventional research of agitation in patients with cognitive impairment.

Finally, given that agitation in dementia may be conceptualized as a single symptom or a symptom complex,[14] emerging diagnostic constructs for neuropsychiatric syndromes in dementia are drawn from and have theoretical congruence with nondementia diagnoses in psychiatry (*e.g.*, psychotic disorders, or affective disorders). In a large sample of community-dwelling individuals and those residing in nursing homes with late-onset AD, a principal components analysis of the neuropsychiatric inventory (NPI)[21] identified four interpretable neuropsychiatric endophenotypes: behavioral dyscontrol (euphoria, disinhibition, aberrant motor behavior, and sleep and appetite disturbances), psychosis (delusions and hallucinations), mood (depression, anxiety, and apathy), and agitation (aggression and irritability), with scores on the four components associated with severity of cognitive impairment.[22] Higher behavioral dysfunction, agitation, and mood component scores were associated with lower age at onset.[22] More recently, the Behavioural Subgroup of the European Alzheimer's Disease Consortium (EADC) has performed a factor analysis of the NPI in a homogeneous sample of patients with AD, analyzing the largest AD population ever studied for this purpose.[23] The Behavioural Subgroup of the EADC identified four separate neuropsychiatric syndromes: affective, apathetic, psychotic, and hyperactive,[23] providing also evidence of the relative consistency of neuropsychiatric syndromes across dementia subtypes, age and gender.[24] In particular, the hyperactive syndrome included AD patients with agitation, euphoria, disinhibition, irritability, and aberrant motor behavior,[23] stressing the importance of thinking about neuropsychiatric syndromes instead of separate NPS in AD patients.

Current pharmacological approaches to the treatment of agitation in Alzheimer's disease

With both the approaches, single symptom or neuropsychiatric syndrome, agitation is common, persistent, and very difficult to treat.[25-28] In recent years, a number of pharmacological and psychosocial approaches have proven inadequate, and antipsychotics, antide-

pressants, acetylcholinesterase inhibitors, anticonvulsants, and other classes of drugs have been used for treating agitation in AD.[27,28] The US Food and Drug Administration (FDA) has not yet approved any medication for treating agitation associated with dementia and AD, while in the European Union, only risperidone, an atypical antipsychotic, is indicated for the short-term management of persisting and severe aggression in AD patients. In Australia, the regulatory authority, the Pharmaceutical Benefits Advisory Committee (PBAC), indicates risperidone for the treatment of psychotic symptoms and aggression with unsuccessful non-pharmacological methods.
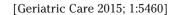
As a result, most agents are used off-label.[29] In particular, both conventional and atypical antipsychotics are used to treat NPS and agitation associated with AD and dementia, and off-label use of atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) has significantly increased over the past two decades. Atypical antipsychotics, mainly risperidone, have the best evidence for short-term efficacy (6-12 weeks), although meta-analyses have not indicated significant benefit for non-aggressive symptoms of agitation.[30,31] However, in a meta-analysis of 10-12 week randomized controlled trials (RCTs) (N=5110) of all-cause dementia, death occurred in 3.5% of dementia subjects treated with atypical antipsychotics and 2.3% of controls, resulting in a number needed to harm of 100 (range 53-1000) and a number needed to treat of 4-12.[32] In 11 RCTs of olanzapine and risperidone, 2.2% drug-treated patients experienced cerebrovascular adverse events compared with 0.8% placebo-treated patients.[33] Other observational studies reported increased mortality in older demented patients exposed to either conventional or atypical antipsychotics,[34,35] with some notable exceptions.[36,37] Consequently, in April 2005, the US FDA issued a *black-box* warning for atypical antipsychotics in the treatment of NPS in older patients with dementia because of a 1.6- to 1.7-fold higher death rate in those taking such drugs compared with those taking placebo. In a pivotal RCT of demented patients already on conventional or atypical antipsychotics, three-year survival doubled in those randomized to cease treatment.[38] On the other hand, in AD patients with psychosis or agitation that had responded to risperidone therapy for 4 to 8 months, discontinuation of risperidone was associated with an increased risk of relapse.[39] The large clinical antipsychotic trials of intervention effectiveness Alzheimer's disease (CATIE-AD) RCT showed non-significant treatment effects of three antipsychotics (olanzapine, quetiapine, and risperidone) when compared with placebo. Moreover, time to discontinuation due to intolerable side effects was higher for those taking the antipsychotics *versus* placebo.[40,41]

However, findings from a recent observational study challenged these findings by showing that after controlling for important risk factors such as cardiovascular risk and severity of psychosis, antipsychotic use was not associated with premature death or increased institutionalization.[42] These results suggested that, when adjusting for relevant covariates, the presence of NPS, including psychosis and agitation, was linked to poor outcomes rather than the medications themselves. Taken together, these results as well as the limited efficacy of these medications point to significant gaps in our knowledge of the specific neurobiology of these symptoms in AD. Thus, at present, no clear treatment algorithms for agitation in AD and dementia exist, with the challenge of managing these disturbing NPS using drugs that may pose life-threatening adverse effects.

Alternative pharmacological approaches to the treatment of agitation in Alzheimer's disease

Therefore, pharmacological and non-pharmacological treatment of agitation is an unmet need in the care of patients with dementia.[27,28,43] A recent comprehensive review article focused on the status of recent clinical trials for the alternative pharmacological treatment of agitation in AD.[44] Emerging evidence on the neurobiological substrates of agitation in AD has led to investigation of repositioned and novel therapeutics for these NPS in dementia as an alternative to antipsychotics.[2,4,5] The most promising potential pharmacological alternatives include both repositioned and novel drugs such as citalopram, dextromethorphan/quinidine, cannabinoids, scyllo-inositol, brexpiprazole, dronabinol, and prazosin.[44] At the present time, none of these agents have sufficient clinical evidence in treating agitation in AD to be recommend using in routine clinical practice. However, two of these drugs showed phase II and III evidence of efficacy for the treatment of agitation/aggression in AD. In a phase III trial, the citalopram for agitation in Alzheimer's disease study (CitAD), 30-mg daily dose of the selective serotonin reuptake inhibitor citalopram showed a significant decrease in agitation in 186 patients with AD.[45] However, QTc prolongation and cognitive worsening were observed in the citalopram group,[45,46] representing safety concerns for clinicians. Furthermore, data from the CitAD database were used to assess potential genetic influences on citalopram treatment efficacy for agitation in AD and treatment outcomes in CitAD showed modest, although statistically significant, influence of genetic variation at serotonin receptor 2A (HTR2A-T102C) and sero-

tonin receptor 2C (HTR2C-Cys23Ser) loci.[47] Dextromethorphan/ quinidine (AVP-923; Avanir Pharmaceuticals, Inc., Aliso Viejo, CA, USA), a combination drug containing dextromethorphan, a N-methyl-D-aspartate receptor antagonist and high affinity sigma-1 receptor agonist, and the class I antiarrhythmic agent quinidine, is the first FDA-approved drug for the treatment of pseudobulbar affect. Very recently, in a phase II trial on 220 AD patients with clinically meaningful agitation (ClinicalTrials.gov Identifier: NCT0158 4440), dextromethorphan/ quinidine significantly improved AD-associated agitation, reduced caregiver burden, and was generally well tolerated.[48]

Among novel drugs with completed RCTs, mibampator (LY451395; Eli Lilly S.p.a., Sesto Fiorentino (FI), Italy) is a biarylpropylsulfonamide amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor potentiator previously assessed in a phase II trial for its effects on cognition in 181 patients with mild-to-moderate AD.[49] While no evidence of efficacy on cognition was found in AD trials, a significant improvement on the NPS secondary measure was evident, fueling another Phase II trial to further assess the efficacy and safety of mibampator in patients with AD and clinically significant agitation/aggression symptoms.[50] In this double-blind study, 132 outpatients with probable AD and agitation/aggression, were randomized to receive for 12 weeks 3 mg of oral mibampator or placebo. No significant benefits were observed for mibampator compared to placebo on agitation/aggression symptoms.

However, a secondary outcome ecological measure of behaviors associated with prefrontal cortical dysfunction was positive affected by the drug.[50] One possible reason for lack of efficacy could be ascribed to the extensive neurodegenerative damage of the frontolimbic networks at the time of study entry, It is likely that drugs may need to be initiated much sooner in the disease process and the field is indeed moving toward earlier diagnosis of dementia-related NPS at or before MCI stage as in the proposed diagnostic construct of MBI.[6] Among alternative treatment options for the treatment of AD-related agitation,[44] the phase II trial (ClinicalTrials.gov Identifier: NCT01735630) on scyllo-inositol (ELND005; Transition Therapeutics Inc., Toronto, ON, Canada; Elan Pharmaceuticals, Dublin, Ireland), an inositol stereoisomer that is thought to neutralize toxic β-amyloid oligomers and prevent them from aggregating, for the treatment of agitation and aggression in 350 patients with moderate to severe AD has ended on May 2015, but results are presently not available. Furthermore, the phase II trial (ClinicalTrials.gov Identifier: NCT01126099) on the α1-adrenoreceptor antagonist prazosin to compare a 12-week course of 8 mg/day of prazosin to placebo followed by 12 weeks of prazosin offered open-label to treat disruptive agitation in AD patients has ended on March 2014 instead of July 2015 and such as early termination leaded to small numbers of participants analyzed (20 instead of the planned 120) and technical problems with measurement leading to unreliable or uninterpretable data. On the other hand, one of the two recently completed phase II studies on delta-9-tetrahydrocannabinol (THC, ECP002A) (Clinical Trials.gov Identifiers: NCT01302340 and NCT01608217) provided evidence that for patients with dementia-related NPS, low-dose THC (4.5 mg daily) did not significantly reduce NPS after three weeks, though it is well-tolerated.[51] This RCT tested a very similar molecule to dronabinol, synthetic THC, indicated for the treatment of chemotherapy-induced nausea and vomiting, or for anorexia with weight loss in patients with acquired immunodeficiency syndrome. This was the largest RCT on THC for treating NPS in dementia and unfortunately was negative. Previous studies with THC (2.5-7 mg daily) all reported positive effects on NPS in dementia.[52,53] The lack of adverse effects may suggest that the dosage was too low. Further studies with higher dosages of oral THC may be required to properly test its potential in the treatment of dementia-related NPS. Ongoing phase II and III trials with novel and repositioned promising drugs may provide alternatives for treating agitation in AD (Table 1).[5,44] One of these drugs is brexpiprazole (OPC-34712 or Lu-AF41156; H. Lundbeck A/S, Valby, Denmark; Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA), a novel molecular compound chemically and structurally similar to aripiprazole and with broad activity across multiple monoamine systems with reduced partial agonism for D2, 5HT1A receptors, and

Table 1. Principal ongoing phase II and III randomized controlled trials for the treatment of agitation/aggression in Alzheimer's disease.

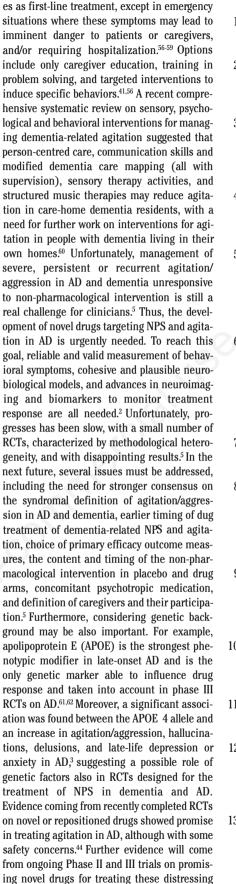| Compound (Company) ClinicalTrials.gov identifier	Mechanism of action	Estimated enrollment	Characteristics	Status
Brexpiprazole (OPC-34712) (H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.) NCT01862640	Dopamine D2 receptor partial agonist	420 patients with probable AD and associated agitation (2013-2017)	1 or 2 mg of brexpiprazole administered orally once daily for 12 weeks	Phase III trial (currently recruiting)
Brexpiprazole (OPC-34712) (H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.) NCT01862640	Dopamine D2 receptor partial agonist	230 patients with probable AD and associated agitation (2013-2017)	A flexible dose of brexpiprazole titrated between 0.5 to 2 mg administered orally once daily for 12 weeks	Phase III trial (currently recruiting)
Brexpiprazole (OPC-34712) (H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.) NCT01862640	Dopamine D2 receptor partial agonist	360 patients with probable AD and associated agitation (2014-2017)	0.5, 1 or 2 mg of brexpiprazole administered orally once daily for 8 weeks	Phase III trial (currently recruiting)
ORM-12741 (Orion Corporation, Orion Pharma, Finland and Janssen Pharmaceuticals) NCT02471196	α-2c adrenergic receptor antagonist	300 patients with probable AD and associated agitation (2015-2017)	Low or high dose of ORM-12741 administered orally twice daily for 12 weeks	Phase II trial (currently recruiting)

AD, Alzheimer's disease.

enhanced antagonism for 5-HT2A, and α1-adrenoreceptors.[54] This drug is currently under review by the US FDA as a monotherapy for schizophrenia[55] and an adjunct to antidepressant medication for major depressive disorder (ClinicalTrials.gov Identifier: NCT01838681). At present, two phase III trials with brexpiprazole are underway for agitation associated with AD (Table 1).[5,44] In July 2013, the first phase III trial (ClinicalTrials.gov Identifier: NCT01862640) started to evaluate the safety, efficacy, and tolerability of three months of treatment with 1 and 2 mg of brexpiprazole or placebo given as a fixed dose once daily for the treatment of agitation in 420 patients with probable AD living in an institutionalized setting (*e.g.*, dementia unit, nursing home, assisted living facility, or other residential care facility) or in a non-institutionalized setting where the subject is not living alone. The primary endpoint is change from baseline in the Cohen-Mansfield agitation inventory (CMAI), but the trial will also measure changes in aggression, global clinical status, and quality of life. In September 2013, the second phase III trial (ClinicalTrials.gov Identifier: NCT01922 258) started enrolling a total of 230 patients and exploring brexpiprazole using a flexible dose titrated between 0.5 to 2 mg/day depending on efficacy and tolerability in a given patient. Furthermore, a 2-month, observational, rollover trial (ClinicalTrials.gov Identifier: NCT02192554) started in June 2014 to enroll 360 patients with AD-related agitation previously who previously participated in one of the two phase II trials. Finally, ORM-12741 (Orion Corporation, Orion Pharma, Finland and Janssen Pharmaceuticals, Espoo, Finland) is an orally available α-2c adrenergic receptor antagonist shown to modulate brain activity during stress. ORM-12741 was originally synthesized as part of a schizophrenia drug discovery program, but after some early clinical studies in Europe it was abandoned for this indication. After seven phase I trials in more than 200 healthy volunteers in Finland, France, and the Netherlands, in June 2015, a phase II trial (ClinicalTrials.gov Identifier: NCT02471196) was started to evaluate the efficacy of three months of treatment in 300 patients with AD-related agitation/aggression symptoms measured by the NPI clinician rating scale as primary outcome. The estimated study completion date is February 2017.

Conclusions

Off-label use of atypical antipsychotics for treating dementia-related NPS and agitation showed only modest improvements or no benefits compared to placebo, with evidence of increased risk for cerebrovascular events and mortality.[2,5] Consensus guidelines from medical organizations and working group statements recommended non-pharmacological approaches as first-line treatment, except in emergency situations where these symptoms may lead to imminent danger to patients or caregivers, and/or requiring hospitalization.[56-59] Options include only caregiver education, training in problem solving, and targeted interventions to induce specific behaviors.[41,56] A recent comprehensive systematic review on sensory, psychological and behavioral interventions for managing dementia-related agitation suggested that person-centred care, communication skills and modified dementia care mapping (all with supervision), sensory therapy activities, and structured music therapies may reduce agitation in care-home dementia residents, with a need for further work on interventions for agitation in people with dementia living in their own homes.[60] Unfortunately, management of severe, persistent or recurrent agitation/aggression in AD and dementia unresponsive to non-pharmacological intervention is still a real challenge for clinicians.[5] Thus, the development of novel drugs targeting NPS and agitation in AD is urgently needed. To reach this goal, reliable and valid measurement of behavioral symptoms, cohesive and plausible neurobiological models, and advances in neuroimaging and biomarkers to monitor treatment response are all needed.[2] Unfortunately, progresses has been slow, with a small number of RCTs, characterized by methodological heterogeneity, and with disappointing results.[5] In the next future, several issues must be addressed, including the need for stronger consensus on the syndromal definition of agitation/aggression in AD and dementia, earlier timing of dug treatment of dementia-related NPS and agitation, choice of primary efficacy outcome measures, the content and timing of the non-pharmacological intervention in placebo and drug arms, concomitant psychotropic medication, and definition of caregivers and their participation.[5] Furthermore, considering genetic background may be also important. For example, apolipoprotein E (APOE) is the strongest phenotypic modifier in late-onset AD and is the only genetic marker able to influence drug response and taken into account in phase III RCTs on AD.[61,62] Moreover, a significant association was found between the APOE 4 allele and an increase in agitation/aggression, hallucinations, delusions, and late-life depression or anxiety in AD,[3] suggesting a possible role of genetic factors also in RCTs designed for the treatment of NPS in dementia and AD. Evidence coming from recently completed RCTs on novel or repositioned drugs showed promise in treating agitation in AD, although with some safety concerns.[44] Further evidence will come from ongoing Phase II and III trials on promising novel drugs for treating these distressing symptoms in patients with dementia.

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