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EXPERT OPINION

Progresses in treating agitation: a major clinical challenge in Alzheimer's disease

Francesco Panza[†], Vincenzo Solfrizzi, Davide Seripa, Bruno P Imbimbo, Andrea Santamato, Madia Lozupone, Camilla Prete, Antonio Greco, Alberto Pilotto & Giancarlo Logroscino

[†]*University of Bari Aldo Moro, Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, Bari, Italy*

Introduction: Treatment of neuropsychiatric symptoms (NPS) represents a major clinical challenge in Alzheimer's disease (AD). Agitation and aggression are frequently seen during institutionalization and increase patient morbidity and mortality and caregiver burden. Off-label use of atypical antipsychotics for treating agitation in AD showed only modest clinical benefits, with high side-effect burden and risk of mortality. Non-pharmacological treatment approaches have become the preferred first-line option. When such treatment fails, pharmacological options are often used. Therefore, there is an urgent need to identify effective and safe pharmacological treatments for efficiently treating agitation and aggression in AD and dementia.

Areas covered: Emerging evidence on the neurobiological substrates of agitation in AD has led to several recent clinical trials of repositioned and novel therapeutics for these NPS in dementia as an alternative to antipsychotics. We operated a comprehensive literature search for published articles evaluating pharmacological interventions for agitation in AD, with a review of recent clinical trials on mibampator, dextromethorphan/quinidine, cannabinoids, and citalopram.

Expert opinion: Notwithstanding the renewed interest for the pharmacological treatment of agitation in AD, progresses have been limited. A small number and, sometimes methodologically questionable, randomized controlled trials (RCTs) have produced disappointing results. However, 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.

Keywords: aggression, agitation, Alzheimer's disease, antidepressants, antipsychotics, brexpiprazole, cannabinoids, citalopram, dementia, dextromethorphan/quinidine, dronabinol, mibampator, neuropsychiatric symptoms, prazosin, risperidone, scyllo-inositol, selective serotonin reuptake inhibitors: treatment

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1. Conceptual framework for the definition of agitation in Alzheimer's disease

Neuropsychiatric symptoms (NPS) in dementia [1], previously denominated as behavioral and psychological symptoms of dementia (BPSD), are often more distressing, impairing, and costly than cognitive symptoms, representing a major health burden for older adults [2]. NPS can manifest early in the course of neurodegenerative diseases and Mild behavioral impairment (MBI) has been proposed as a

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Article highlights.

- Neuropsychiatric symptoms (NPS), particularly agitation, are often more distressing, impairing, and costly than cognitive symptoms in patients with Alzheimer's disease (AD).
- Off-label use of atypical antipsychotics for treating AD-related agitation showed only modest efficacy or no benefits compared with placebo, and often increased risk for cerebrovascular events and mortality.
- Consensus guidelines and working group statements recommended non-pharmacological approaches as first-line treatment.
- There is still an urgent need of effective treatments for agitation/aggression in AD and dementia, when non-pharmacological approaches fail.
- Evidence coming from recently completed randomized controlled trials on novel or repositioned drugs showed interesting 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 agitation in patients with AD and dementia.

This box summarizes key points contained in the article.

diagnostic construct aimed to identify patients with an increased risk of developing dementia, but who may or may not have cognitive symptoms [3]. Very recently, the NPS Professional Interest Area of the International Society to Advance Alzheimer Research and Treatment 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 [4].

Among NPS, agitation is a frequent manifestation of Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and other dementia syndromes [5], 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 [5]. Agitation differs from psychosis and depression of AD in that it may be conceptualized as a single symptom or a symptom complex [6]. 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 nonaggressive types [7].

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 [8]. 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' [7]. However, very recently, the International Psychogeriatric Association (IPA) formed an Agitation Definition Working Group 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, verbal 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 [8].

Finally, given that agitation in dementia may be conceptualized as a single symptom or a symptom complex [6], 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 particular, the Behavioral Subgroup of the European Alzheimer's Disease Consortium (EADC) has performed a factor analysis of the Neuropsychiatric Inventory (NPI) [9] in a homogeneous sample of patients with AD, analyzing the largest AD population ever studied for this purpose [10]. The Behavioral Subgroup of the EADC identified four separate neuropsychiatric syndromes: affective, apathetic, psychotic, and hyperactive [10]. This last neuropsychiatric syndrome included AD patients with agitation, euphoria, disinhibition, irritability, and aberrant motor behavior [10], stressing the importance of thinking about neuropsychiatric syndromes instead of separate NPS in AD patients.

2. Current and alternative pharmacological approaches to the treatment of agitation in AD

In recent years, a number of pharmacological and psychosocial approaches have proven inadequate, and antipsychotics, acetylcholinesterase inhibitors (AChEIs), antidepressants, anticonvulsants, and other classes of drugs have been used for treating agitation in AD [11,12]. Secondary analyses of randomized controlled trials (RCTs) conducted in AD patients with low levels of NPS at baseline provided some limited evidence suggesting that AChEIs might reduce agitation in AD and improve overall NPS, although the advantage over placebo was modest [13]. A randomized withdrawal trial further supported this evidence reporting that study participants who continued on donepezil versus placebo for 12 weeks had a reduction in NPS [14]. However, a secondary analysis of a more recent randomized withdrawal trial found no significant difference in NPS in patients with moderate to severe AD randomly assigned to continuation or discontinuation of donepezil [15]. Furthermore, two RCTs evaluating

rivastigmine and donepezil in patients with clinically significant agitation at baseline showed no treatment benefit compared with placebo [16,17], indicating that AChEIs could not be useful in the management of acute agitation in AD. A systematic review conducted on 14 RCTs of AChEIs for NPS in AD reported that only three studies had found a statistically significant but modest benefit for these drugs compared with placebo, concluding that the evidence to support their use for this indication was limited [18]. Considering the overall NPS spectrum in AD, AChEIs have the best evidence for their effect on depression and dysphoria, apathy, and anxiety [19], but no specific benefit in the treatment of agitation or aggression. Primary and secondary analyses of a 12-week RCT that analyzed the change in agitation comparing galantamine with risperidone, an atypical antipsychotic, showed that the levels of agitation decreased in both treatment groups, but the main analyses suggested that the improvement was significantly larger in the risperidone group [20,21]. The US FDA has not yet approved any medication for treating agitation associated with dementia and AD, while in the European Union and Australia, only risperidone is indicated for the short-term management of persisting and severe aggression in AD patients with unsuccessful non-pharmacological methods. As a result, most agents are used off-label [22]. 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-analytic evidence has not indicated significant benefit for non-aggressive symptoms of agitation [23]. However, in a meta-analysis of 10- to 12-week RCTs (n = 5110) of all-cause dementia, death occurred in 3.5% of dementia subjects treated with atypical antipsychotics and 2.3% of controls [24]. In 11 RCTs of olanzapine and risperidone, 2.2% drug-treated patients experienced cerebrovascular adverse events compared with 0.8% placebo-treated patients [25]. Other observational studies reported increased mortality in older demented patients exposed to either conventional or atypical antipsychotics [26,27], with some notable exceptions [28,29]. 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, 3-year survival doubled in those randomized to cease treatment [30]. On the other hand, in AD patients with psychosis or agitation who had responded to risperidone therapy for 4 – 8 months, discontinuation of risperidone was associated with an increased risk of relapse [31]. However, 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 [32]. When adjusting for relevant covariates, the presence of NPS, including psychosis and agitation, may be 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.

Therefore, at present, no clear pharmacological or non-pharmacological treatment algorithms for agitation in AD and dementia exist [11,12,33], with the challenge of managing these disturbing NPS using drugs that may pose life-threatening adverse effects. A comprehensive review article recently published on Expert Opinion on Pharmacotherapy focused on the status of recent clinical trials for the alternative pharmacological treatment of agitation in AD [34]. 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 [1,5]. Central synaptic or circuit disconnections in frontal-subcortical and corticocortical networks, dysfunction in ascending monoaminergic systems involving serotonin, norepinephrine, or dopamine neurons, glutamate-mediated excitatory neurotoxicity, tau-mediated pathology, and inflammatory mediators may have a role for the development of NPS in AD [1,5,9,35-38]. These CNS dysfunctions may occur concurrently and mediate synergistically NPS onset. The most promising potential pharmacological alternatives include both repositioned and novel drugs such as citalopram, dextromethorphan/quinidine, cannabinoids, scyllo-inositol, brexpiprazole, and prazosin [34]. At present, none of these agents have sufficient clinical evidence in treating agitation in AD to be recommended 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, 30-mg daily dose of the selective serotonin reuptake inhibitor citalopram showed a significant decrease in agitation in 186 patients with AD [39]. However, QTc prolongation and cognitive worsening were observed in the citalopram group [39,40], representing safety concerns for clinicians. Dextromethorphan/quinidine (AVP-923, Avanir Pharmaceuticals), 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: NCT01584440), dextromethorphan/quinidine significantly improved AD-associated agitation, reduced caregiver burden, and was generally well tolerated [41].

Among novel drugs with completed RCTs, mibampator (LY451395, Eli Lilly and Company) 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 [42]. While no evidence of efficacy on cognition was found in this RCT, 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 [43]. In this 12-week double-blind study on 132 outpatients with probable AD and agitation/aggression, no significant benefits were observed for 3 mg of oral mibampator compared to placebo on agitation/aggression symptoms. However, a secondary outcome ecological measure of behaviors associated with prefrontal cortical dysfunction was positively affected by the drug [43]. 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 [4]. Among the reviewed alternative options for the treatment of AD-related agitation in the recent issue of Expert Opinion on Pharmacotherapy [34], the Phase II trial (ELND005-AG201, ClinicalTrials.gov Identifier: NCT01735630) on scyllo-inositol (ELND005, Transition Therapeutics Ireland Limited and Elan Pharmaceuticals), 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. On June 24, 2015, Transition Therapeutics published a press release announcing that the ELND-005 AG201 study failed to meet its primary efficacy endpoint, that is, the change from baseline in the NPI Clinician Rating scale (NPI-C). In the study, both the treatment and placebo groups showed a significant, but similar, reduction in agitation and aggression relative to baseline. There was a greater than expected reduction in agitation and aggression observed in the placebo group as measured in weeks 4, 8, and 12, while the safety and tolerability profile of ELND005 was consistent with previous studies in AD at the 250 mg bid dose. 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 Δ9-tetrahydrocannabinol (THC, ECP002A) (ClinicalTrials.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 3 weeks, though it is well tolerated [44]. 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 [45,46]. The lack of adverse effects may suggest that the dosage was too low requiring further studies with higher dosages of oral THC 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**) [5,34]. One of these drugs is brexpiprazole (OPC-34712 or Lu-AF41156, H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.), 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 enhanced antagonism for 5-HT2A and α1-adrenoreceptors [47]. This drug is currently under review by the US FDA as a monotherapy for schizophrenia [48] 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**) [5,34]. In July 2013, the first Phase III trial (ClinicalTrials.gov Identifier: NCT01862640) started to evaluate the safety, efficacy, and tolerability of 3 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 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, 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: NCT01922258) 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) 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 3 months of treatment in 300 patients with AD-related agitation/aggression symptoms measured by the NPI-C as primary outcome. The estimated study completion date is February 2017.

Table 1. Principal ongoing Phase II and III randomized controlled trials (RCTs) for the treatment of agitation/aggression in Alzheimer's disease (AD).

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)

3. Expert opinion

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 [49-52]. Options include only caregiver education, training in problem solving, and targeted interventions to induce specific behaviors [33]. 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 [53]. 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]. To develop novel drugs targeting NPS and agitation in AD, 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 [1]. 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 also be 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 [54]. Moreover, a significant association was found between the APOE $\varepsilon 4$ allele and an increase in agitation/aggression, hallucinations, delusions, and late-life depression or anxiety in AD [2], 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 [34]. 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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Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Affiliation

Francesco Panza[†1,2,3], Vincenzo Solfrizzi[4], Davide Seripa[3], Bruno P Imbimbo[5], Andrea Santamato[6], Madia Lozupone[1], Camilla Prete[7], Antonio Greco[3], Alberto Pilotto[7] & Giancarlo Logroscino[1,2]
[†]Author for correspondence
[1]University of Bari Aldo Moro, Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, Bari, Italy,
E-mail: geriat.dot@geriatria.uniba.it
[2]University of Bari Aldo Moro, Department of Clinical Research in Neurology, "Pia Fondazione Cardinale G. Panico", Tricase, Lecce, Italy
[3]Geriatric Unit & Laboratory of Gerontology and Geriatrics, Department of Medical Sciences, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy
[4]University of Bari Aldo Moro, Geriatric Medicine-Memory Unit and Rare Disease Centre, Bari, Italy
[5]Research & Development Department, Chiesi Farmaceutici, Parma, Italy
[6]University of Foggia, Physical Medicine and Rehabilitation Section, "OORR" Hospital, Foggia, Italy
[7]Geriatrics Unit, Department of OrthoGeriatrics, Rehabilitation and Stabilization, Frailty Area, Galliera Hospital NR-HS, Genova, Italy