REVIEW

Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design

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ABSTRACT

Background: The management of disruptive neuropsychiatric symptom (NPS) such as agitation and aggression (A/A) is a major priority in caring for people with Alzheimer's disease (AD). Few effective pharmacological or non-pharmacological options are available. Results of randomized clinical trials (RCTs) of drugs for A/A have been disappointing. This may result from the absence of biological efficacy for medications tested in treating A/A. It may also be related to methodological issues such as the choice of outcomes. The aim of this review was to highlight key methodological issues pertaining to RCTs of current and emerging medications for the treatment of A/A in AD.

Methods: We searched PubMed/Medline, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for RCTs comparing medications with either placebo or other drugs in the treatment of A/A in AD, between January 2008 and December 2013.

Results: We identified a total of 18 RCTs; of these, 11 were completed and 7 ongoing. Of the ongoing RCTs, only one is in Phase III. Seven of 10 completed RCTs with reported results did not report greater benefit from drug than placebo. Each of the completed RCTs used a different definition of "clinically significant A/A." There was considerable heterogeneity in study design. The primary endpoints were largely proxy-based but a variety of scales were used. The definition of caregiver and scales used to assess caregiver outcomes were similarly heterogeneous. Placebo response was notable in all trials.

Conclusions: This review highlights a great heterogeneity in RCTs design of drugs for A/A in AD and some key methodological issues such as definition of A/A, choice of outcome measures and caregiver participation that could be addressed by an expert consensus to optimize future trials design.

Key words: behavior, agitation, aggression, Alzheimer's, measurement, therapeutics, clinical trial

Introduction

The number of people living with dementia worldwide is estimated at 35.6 million and expected to increase to 115.4 million by 2050 (Prince *et al.*, 2013). Seventy percent of dementia is due to Alzheimer's disease (AD); 98% of people with AD (PwAD) develop at least one neuropsychiatric symptom (NPS) over the course of the disease (Steinberg *et al.*, 2008; Gonfrier *et al.*, 2012). At least 20% of outpatients (Lyketsos *et al.*, 2000) and 40% of long-term care residents (Selbæk *et al.*, 2013) exhibit disrupted NPS such as agitation and aggression (A/A) encompassing a range of affective, verbal, and motor disturbances such as restlessness, cursing, aggression, hyperactivity, combativeness, wandering, repetitive calling out, irritability, and disinhibition (Cohen-Mansfield *et al.*, 1995). A/A

tends to co-occur with sleep disorders, delusions, hallucinations, anxiety or dysphoria (Canevelli *et al.*, 2013). A/A is associated with greater caregiver burden (Okura and Langa, 2011), earlier institutionalization and death (Okura *et al.*, 2011), poorer functioning (Okura *et al.*, 2010), greater cost of care (Murman *et al.*, 2002), and more acute hospitalizations (Soto *et al.*, 2012). Thus, the management of A/A is a major priority in caring for PwAD.

Consensus guidelines and expert opinion statements recommend non-pharmacological approaches to be first line (Benoit *et al.*, 2006; Lyketsos *et al.*, 2006; Rabins *et al.*, 2007; Gauthier *et al.*, 2010; Kales *et al.*, 2014) but there are limited options. Examples include caregiver education, training in problem solving, and targeted interventions to causes for specific behaviors (Gitlin *et al.*, 2012). Patients in both community dwelling (CD) (Brodaty *et al.*, 2012) and nursing home (NH) settings benefit (Deudon *et al.*, 2009; Husebo *et al.*, 2011; Ritcher *et al.*, 2012).

Pharmacological treatment for A/A is recommended when non-pharmacological interventions fail or when A/A is linked to dangerousness to others or marked distress. The most studied medication class is antipsychotics (APs), both conventional and atypical. Between 1999 and 2008, several RCTs assessed APs for treating A/A in PwAD. Eleven RCTs used conventional APs, which mostly involved small sample sizes and with durations of 4 and 12 weeks (Schneider *et al.*, 1990; De Deyn *et al.*, 1999; Teri *et al.*, 2000; Lonergan *et al.*, 2002; Ballard *et al.*, 2009). Outcome was defined as a 30% improvement on standardized behavioral rating scales, as per convention. A high placebo response was found in these RCTs. Since 1995, 18 RCTs have examined the efficacy of atypical APs in patients with AD, mainly with durations of 6–12 weeks (only three trials of 6–12 months) (Ballard and Howard, 2006; Schneider *et al.*, 2006). Small scale trials of treatment with drugs other than APs (antidepressants and anti-convulsants mood stabilizers) have produced equivocal results (Ballard *et al.*, 2009). The available data are limited by small numbers of subjects or shortcomings in study design such as the (non-random) statistical distribution of behavior test scores and lack of consideration of effect size.

In a general description all the previous studies since 1990 were placebo-controlled and were parallel-group, fixed-dose range, or adjustable/titrated-dose trials, in the majority involving nursing home patients with a mean age over 80 years of age. Among subjects studied, there was a wide degree of variation in type and severity of symptomatology. The clinical trials endpoints were based on behavior rating scales, including the Brief Psychiatric Rating Scale (BPRS), the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Neuropsychiatric Inventory (NPI), the Cohen-Mansfield Agitation Inventory (CMAI) and subscales (proxy-based more common than direct observation), and global assessments (Salzman *et al.*, 2008). A non-pharmacologic intervention before enrolling a patient in a clinical trial and a placebo run-in period were not common. Repeated measurement analyses were not performed in most trials.

Atypicals APs, 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 (Ballard and Howard, 2006; Schneider *et al.*, 2006). Efficacy is modest and AP use is associated with serious adverse effects including cerebrovascular accidents and mortality (Schneider *et al.*, 2006; Kales *et al.*, 2012; Langballe *et al.*, 2013). In the European Union, risperidone is indicated for the short-term treatment of severe aggression. 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. The Food and Drug Administration (FDA) has published a black box warning for the use of atypical APs in PwAD. In North America there are no approved drugs for treatment of NPS in AD. As a result, most agents are used off-label (Maher *et al.*, 2011). Thus, management of severe, persistent or recurrent A/A unresponsive to non-pharmacologic intervention is a real challenge for clinicians.

Emerging neurobiological research about pathogenesis has led to investigation of repositioned and novel therapeutics for A/A in PwAD, as an alternative to APs. However, the limited benefits reported so far may result from limited understanding of pathogenesis but also from key methodological issues. We hypothesized that a great heterogeneity in the design of recent RCTs of drugs for A/A in AD would be found and that specific key methodological issues could be identified. Thus, the objective on this paper was to review methodological aspects from recent RCTs of drugs for A/A in AD since 2008; the date of the most recent consensus statement on clinical trials methodology of treatments for A/A in dementia (Salzman *et al.*, 2008).

Methods

Reports of RCTs of medications for the treatment of A/A in AD published in the English language were

identified by searching PubMed between January 2008 and December 2013, using terms ("Dementia"[Mesh] OR "Alzheimer"[Mesh]) AND ("Clinical Trial"[Mesh] OR "therapeutics"[MeSH Terms]) AND ("Agitation"[Mesh] OR "Aggression"[Mesh]) OR "Behavioral symptoms"[Mesh]). Free text was used to identify articles on "neuropsychiatric symptoms," "treatment for neuropsychiatric behaviors," and "behavioral and psychological symptoms of dementia." This search was supplemented by hand searching of reference lists of selected articles, meta-analyses, and review articles. Google Scholar was searched for additional articles, especially of ongoing RCTs and new drugs.

In addition, we searched the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov between January 2008 and December 2013. We included reports (1) whose publication appeared between 2008 and 2013 and (2) registered in a clinical trial registry (including RCTs with no publications or posted results). We included studies where A/A was the primary or co-primary outcome. Studies, where A/A was a secondary outcome, were not included. Studies focused only on psychosis, depression or apathy in PwAD were excluded. Only randomized, parallel-group, controlled trials comparing medication to placebo or to another medication were included.

Results

We identified 18 RCTs evaluating efficacy of medications for treatment of A/A in AD. Of these, 11 were completed RCTs and seven ongoing. These trials were characterized by a great deal of methodological heterogeneity.

The therapeutic agents divide into: (1) repurposed drugs marketed for other indications (e.g., citalopram, dextromethorphan, delta-9-tetrahydrocannabinol (THC) or prazosin) or (2) new chemical entities not approved for any indication (e.g., mibampator or scyllo-inositol). Of these drugs only two were APs.

Table 1 lists RCTs completed between 2008 and 2013. Nine compared drug to placebo; two used an active drug comparator (risperidone vs. escitalopram or risperidone vs. topiramate). Five RCTs had < 50 subjects.

Table 2 lists seven ongoing RCTs, three assessing new chemical entities, and four repurposing drugs marketed for other indications. Only brexpiprazole is in phase III. Most are U.S. trials with some in Europe, Canada, and other regions. The mix of outcomes and industry sponsorship is similar to completed trials.

Completed RCTs do not report superiority of any drug over placebo, or over active comparator, but rather improvement in both groups (Table 1), with three exceptions. The prazosin pilot study (Wang *et al.*, 2009) reported superiority of drug to placebo; the drug is being further studied in an ongoing RCT. Improvements over placebo were reported in a trial of intramuscular aripiprazole (Rappaport *et al.*, 2009). In the very recent CitAD trial, citalopram showed significant improvement compared to placebo on both primary outcome measures (Porsteinsson *et al.*, 2014).

Two trials report no effect on primary outcomes but improvement in secondary outcomes. Mibampator (Trzepacz *et al.*, 2013a) led to better outcomes on the Frontal Systems Behaviors Scale, and memantine-NH on NPI total score (Fox *et al.*, 2012).

The next section highlights key methodological aspects of the completed and on-going RCTs.

Population studied

AGE
Most trials included patients aged between 50 and 90 years; with the youngest of 40 in THC and the oldest of 95 in topiramate versus risperidone trial. There was no age limit in both prazosin RCTs.

DEMENTIA DIAGNOSIS
Diagnosis of AD was based on DSM IV and/or NINDS-ADRDA criteria (McKhann *et al.*, 1984). The ongoing scyllo-inositol trial used recent AD criteria of the National Institute of Aging-AD Association (McKhann *et al.*, 2011). The ongoing THC trial includes patients with vascular or mixed dementia.

DEMENTIA SEVERITY
Dementia severity was assessed on Mini-Mental State Examination (MMSE) (Folstein, 1975) or Clinical Dementia Rating scale (CDR) (Rosen, 1984). The divalproex trial included patients with moderate to severe dementia, while memantine and oxcarbazepine trials studied severe dementia. Citalopram, mibampator, and aripiprazole trials included a wide range of severity. Among ongoing trials, Scyllo-inositol include moderate to moderately-severe AD (MMSE 10–20), while the THC, dextromethorphan-quinidine, and brexpiprazole trials include patients at all severities.

SETTING
Of the 11 completed RCTs, 5 were NH studies, 3 CD studies, while 1 (risperidone vs. escitalopram) assessed hospitalized patients (see Table 1). Only two RCTs (CitAD and prazosin) included patients

Table 1. Completed randomized controlled trials (RCTs) of drugs for agitation and aggression in Alzheimer's disease*

MOLECULE	MECHANISM OF ACTION	REFERENCE	DESIGN TT PERIOD	PRIMARY AIM DEFINITION	INCLUSION CRITERIA	EXCLUSION CRITERIA	OUTCOME PRIMARY MEASURES	DEFINITION OF PRIMARY COMPARISON & ANALYSIS	DESIRED CLINICAL DIFFERENCE	SECONDARY OUTCOMES	STUDY LOCATION & SITES	START DATE	END DATE	N[a]	RESULTS
Citalopram	Selective serotonin reuptake inhibitor (SSRI)	Portsteinsson *et al.*, 2014	Ph 3 9 wk fixed doses	Agitation NPI A/A ≥4 with s≥2	CD & NH NINCDS-ADRDA MMSE 5–28	Major depression	NBRS modified-ADCS-CGIC	ITT LME model of NBRS	NBRS:3–5 p CGIC: 20%	NPI, CMAI, ADCS-ADL, MMSE, NPI-distress, cumulative lorazepam dose	USA 8	July 2009	Jan 2013	186 ↓ 169	Positive for NBRS & mADCS-CGIC
Mibampator	AMPA (glutamate receptor) potentiator	Trzepacz *et al.*, 2013a	Ph 2 12 wk fixed doses	Agitation Aggression NPI≥10 NPI-4-A/A≥4 on 1 domain	CD ≥60 NINCDS-ADRDA DSM MMSE 6–26 NPI-10 ≥10	Delirium Vascular dementia	NPI-4 domain -A/A[b] (max score 48)	ITT. Likehliood-based, MMRM	Effect size of 0.41 in mean change from baseline to end point	CMAI, NPI-10, Cornell, FrSBe, Adas-cog, CGI-S-A/A, NPI-distress	USA 16	Feb 2009	June 2011	150 ↓ 132	Null, positive only or FrSBe
Aripiprazole	Dopamine D2 partial agonist	Rappaport *et al.*, 2009	2 IM fixed doses 24 hours	Acute agitation PANNS-EC > 14 & < 31	NH AD, vascular and mixed		PANNS-EC			ACES, CGI-S, CGI-I	USA 16			129	Positive for all outcomes
Memantine-NH	NMDA agonist	Fox *et al.*, 2012	Ph 4 12 wk fixed doses	Agitation CMAI≥45	NH & Acute psy wards ≥45 y MMSE< 19	Previous memantine usage	CMAI at 6 wk	ITT LME model of CMAI	Difference of 6 p from baseline to 6 wk	CMAI at 12wk, NPI, CGI-C, MMSE, SIB	UK	Sept 2007	Jan 2010	153	Null, positive for total NPI
Memantine-CD[c]	NMDA agonist	Herrmann *et al.*, 2013	Ph 3 24 wk fixed doses	Agitation NPI ≥1 for agitation	CD ≥50 y MMSE 5–15 NINDS-ADRDA & DSM-IV NPI ≥13	Hachinski > 4	Total NPI SIB	ANCOVA analyses of the changes from baseline to Week 24 in NPI and SIB total scores	Effect size of 0.31 in mean change from baseline to end point	CMAI, CIBIC plus, ADCS-ADL	Canada 23	Dec 2003	Sept 2010	450 ↓ 369	Null for all outcomes
Escitalopram vs. Risperidone	SSRI vs. atypical an-tipsychotic	None	Ph 4 6 wk	NPS: A/A, D/H, AMB NPI f> 2, s> 1 on 1 domain	Hospitalized 55–95 y DSM-IV MMSE 5–16	Delirium	Total NPI		Not reported	Time to discontinu-ation drug	Israel 1	April 2008	May 2010	40	None
Topiramate vs. Risperidone	AMPA/GABA modulator vs. atypical anti-psychotic	Mowla *et al.*, 2010	8 wk fixed doses	NPS: A/A, D, H, Irritability NPI> 1 on 1 domain	CD 55–95 y DSM-IV MMSE10–15		Total NPI CMAI CGI	Wilcoxon signed ranks test	Not reported	MMSE	Iran 1	Jan 2008	Mar 2009	48	Null

Table 1. Continued.

MOLECULE	MECHANISM OF ACTION	REFERENCE	DESIGN TT PERIOD	PRIMARY AIM DEFINITION	INCLUSION CRITERIA	EXCLUSION CRITERIA	OUTCOME PRIMARY MEASURES	DEFINITION OF PRIMARY COMPARISON & ANALYSIS	DESIRED CLINICAL DIFFERENCE	SECONDARY OUTCOMES	STUDY LOCATION & SITES	START DATE	END DATE	N[a]	RESULTS
Valproate	Enhanced GABAergic function	Tariot et al., 2011	24 month fixed doses	Agitation & psychosis ≥ 3 on 1 or more NPI items A/A, D, H for 2 wks	CD, ≥54 y MMSE10–20 NINDS-ADRDA NPI < 1 in A/A, D, H since AD onset		Time to ≥ 3 on 1 or more NPI items A/A, D, H for 2 wks	Time to endpoint Cox proportional hazard ratio.	33% difference in incidence rate	Total NPI Total CMAI ADCS-CGIC Qol-AD MMSE ADAS-cog ADCS-ADL CDR	USA 46	Nov 2005	Mar 2009	313	Null for all outcomes, significant adverse events
Prazosin	α 1-adreno receptor antagonist	Wang et al., 2009	Pilot 8 wk flexible doses	Agitation & Aggression 2≥/wk BPRS≥4 in at least 1 item	CD & NH No age limit NINDS-ADRDA	hypotension	Total NPI CGIC	LME model (NPI,BPRS) Mann-Whitney test (CGIC)		BPRS SE Blood pressure	USA 1	Jan 2005	Sep 2007	22	Positive for all outcomes
Melatonin	Melatonin receptor agonist	Gerrman et al., 2009	10 days fixed doses	Agitation & Sleep	NH ≥60 y NINDS-ADRDA Severe AD		Sleep: actigraphy Agitation: CMAI & ABRS	Total sleep time. Analysis of variances	Not reported		USA 1			43	Null for all outcomes
Oxcarbazepine	GABA receptor potentiator	Sommer et al., 2009	Ph 3 8 wk fixed doses	Agitation & Aggression NPI A/A≥6	NH ≥55 y Vascular or AD; ICD-10 MMSE 5–16	Changes in Psycho-tropic drugs	NPI-NH A/A	repeated-measures model with an autoregressive covariance structure	difference between treatments of 1.2 p	BARS, NPI-caregiver distress,	Norway 35	Sept 2005	Oct 2006	103	Null for all outcomes

[*]Completed RCT registered in a clinical trial registry between 2008 and 2013 and/or published between 2008 and 2013.
[a]Randomized, completed.
[b]The NPI-4 A/A is a 4-domain subscale chosen which combines from the NPI-10 four domains: agitation/aggression; aberrant motor behavior; irritability/emotional lability; and disinhibition.
[c]This study was prematurely terminated due to recruitment problems.
Abbreviations: Ph = phase; TT = Treatment; y = years; wk = week; NPS = neuropsychiatric symptoms; A/A = agitation/aggression; D/H = delusions/hallucinations; AMB = Aberrant Motor Behavior; s = severity; f = frequency; AAN = American Academy of Neurology; CD = community-dwelling; NH = nursing home; ITT = intention to treat; NINDS-ADRDA = National Institute Of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, DSM = Diagnostic and Statistical Manual of Mental Disorders; NPI = Neuropsychiatric Inventory; CMAI = Cohen-Mansfield Agitation Inventory; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ADCS-CGIG = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; FrSBe = Frontal Systems Behaviors Scale; CGI-C = Clinical Global Impression of Change; CGI-I = Clinical Global Impression Improvement Score; CGI-S = Clinical Global Impression Severity of Illness Score; PANSS-EC = Positive and Negative Syndrome Scale – Excited Component; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; SIB = Severe impairment Battery; CIBIC-plus = Clinician's Interview-Based Impression of Change-plus version; ABRS = Agitation Behavior Rating Scale; NIA = National Institute of Aging; QoL-AD = Quality of Life-AD; p = points; IN = intramuscular; LME model = linear mixed effects model; ANCOVA = analysis of covariance; MMRM = mixed-effects model repeated measures analysis.

Table 2. Ongoing randomized controlled trials (RCT) of drugs for agitation and aggression in Alzheimer's disease

MOLECULE	MECHANISM OF ACTION	DESIGN	TT PERIOD	PRIMARY AIM A/A DEFINITION	INCLUSION CRITERIA	EXCLUSION CRITERIA	OUTCOME PRIMARY MEASURES	SECONDARY OUTCOMES	STUDY LOCATION & SITES	START DATE	END DATE	N (TARGET)
Scyllo-inositol (ELND005)	Myo-inositol metabolism & phosphoinositol signaling Anti-amyloid	Ph 2	12 wk fixed doses	Agitation & Aggression NPI A/A≥4 (s≥2 & f≥2)	CD 50–88 y NIA-AA MMSE 10–21	Major depression Psychosis	NPI-C combined A/A scores	ADCS-CGIC, NPI, NPI-C domains, CMAI, ADCS-ADL, MMSE	USA Canada Europe 100	Nov 2012	Dec 2013	400
Prazosin	α 1-adrenoreceptor antagonist	Ph 2	12 wk fixed doses 12 wk open label	Disrupted agitated behavior at least twice/wk	CD No age limit	Hypotension	ADCS-CGIC & total NPI	Number of days completed BPRS Total BPRS	USA 1	March 2010	July 2015	120
Brexpiprazole (OPC-34712)	Dopamine D2 receptor partial agonist	Ph3	12 wk 3 fixed Doses 30 days follow-up	Agitation NPI-A/A ≥4	NH 55–90 y NINDS-ADRDA MMSE 5–22	Axis I (DSM 4) Axis II	Total CMAI	CGI-S, total NPI NH, CMAI subscales, NPI individual items, NPI-D/H, caregiver distress, CGI-I, CGI-E, QoL-AD	USA, Canada, Europe	July 2013	June 2017	560
Brexpiprazole (OPC-34712)	Dopamine D2 receptor partial agonist	Ph3	12 wk flexible Doses 30 days follow-up	Agitation CGI-S ≥4	NH 55–90 y NINDS-ADRDA MMSE 5–22	Axis I (DSM 4) Axis II	Total CMAI	CGI-S, total NPI NH, CMAI subscales, NPI individual items, NPI-D/H, caregiver distress, CGI-I, CGI-E, QoL-AD	USA, Canada, Europe	Sept 2013	May 2016	230
Delta-9-tetra hydrocannabinol	CB-1 receptor agonist	Pilot Ph2	2 wk fixed dose	NPS NPI ≥10 and at least 1 domain A/A or AMB ≥1	CD VaD, AD or AD/VaD ≥18 y CDR 1–3 Persistent pain	Major psychiatric disorder	Total NPI	CMAI, Zarit.	Netherlands 2	Sept 2011	Dec[a] 2013	22
Delta-9-tetra hydrocannabinol	CB-1 receptor agonist	Ph2	3 wk fixed[b] dose	NPS NPI ≥10 and at least 1 domain A/A or AMB ≥1	CD VaD, AD or AD/VaD ≥40 y CDR 1–3 Persistent pain	Major psychiatric disorder	Total NPI	CMAI, PACSLAC-D, Caregiver-CGIC, Qol-AD, Barthel	Netherlands 2	June 2012	Feb 2014	150

Table 2. Continued.

MOLECULE	MECHANISM OF ACTION	DESIGN	TT PERIOD	PRIMARY AIM A/A DEFINITION	OUTCOME PRIMARY MEASURES	SECONDARY OUTCOMES	EXCLUSION CRITERIA	INCLUSION CRITERIA	STUDY LOCATION & SITES	START DATE	END DATE	N (TARGET)
Dextromethorphan/ Quinidine (AVP-923)	NMDA receptor antagonist and sigma-1 receptor agonist	Ph2	10 wk fixed dose	Agitation CGI-S ≥4	Total NPI	ADCS-CGIC, Qol-AD, ADCS-ADL, CSI	Myasthenia gravis	NH & CD 50–90 y DSM IV MMSE 6–24	USA 25	June 2012	March 2014	200

[a]Active trial but with a closed recruitment with a 6-month open label safety extension until March 2014.
[b]Three arms = placebo, delta-9-tetra hydrocannabinol and acetaminophen.

Abbreviations: AD = Alzheimer's disease; VaD = Vascular Dementia; Ph = phase; TT = Treatment; y = years; wk = week; NPS = neuropsychiatric symptoms; N = enrollment; A/A = agitation/aggression; AMB = Aberrant Motor Behavior; y = years old; S = severity; F = frequency; D/H = delusions/hallucinations; CD = community-dwelling; NH = nursing home; NIA-AA = National Institute of Aging-AD; NINDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DSM = Diagnostic and Statistical Manual of Mental Disorders; CDR = Clinical Dementia Rating; NPI = Neuropsychiatric Inventory; CMAI = Cohen-Mansfield Agitation Inventory; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; ADCS-CGIG = Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; CGI-C = Clinical Global Impression of Change; CGI-I = Clinical Global Impression Improvement Score; CGI-S = Clinical Global Impression Severity of Illness Score; CSI = Caregiver Strain Index; NIA = National Institute of Aging; SE = side effects; QoL-AD = quality of life-AD; PACSLAC-D = pain assessment checklist for seniors with limited ability to communicate Dutch version.

from both NH and CD. Regarding ongoing RCTs, four are only CD, two NH only (brexpiprazole), and one (dextromethorphan) CD and NH.

DIAGNOSIS OF CLINICALLY SIGNIFICANT A/A

There is not a "gold standard" definition of A/A in AD (Salzman *et al.*, 2008). In its absence two approaches have been used: (1) judgment by experienced clinicians that medication is appropriate and/or (2) severity rating above a scale cut-off indicative of at least moderate A/A. CitAD and dextromethorphan-quinidine trials combined both. A/A encompass a range of recognizable features (such as hitting, pacing, or disinhibition) but these are shared with other behavioral disturbances of AD. It is not surprising that inclusion criteria vary between RCTs. Several trials have used cutoffs on total NPI (mibamptor, and THC). The THC trials additionally require high scores on two domains of the NPI: A/A or motor disturbance.

Although NPI is widely used to define A/A across RCTs, the specific definitions have varied (Tables 1 and 2). Some trials (CitAD, brexpiprazole, and scyllo-inositol) used the NPI A/A domain, while the mibampator trial required the presence of at least one of four NPI domains.

Thresholds for agitation severity similarly vary: in memantine-NH trial agitation was high (CMAI > 45) (Fox *et al.*, 2012), while in the memantine CD trial it was low (NPI A/A ≥ 1) (Herrmann *et al.*, 2013). Recent RCTs (CitAD and mibampator), and the ongoing scyllo-inositol and brexpiprazole trials use a threshold of ≥4 on NPI A/A; CiTAD adds the requirement that A/A occur at least several times/week ("frequently") to improve relevance and applicability to real-life situations.

Moreover, the CitAD, brexpiprazole, and scyllo-inositol trials require a history of poor response to non-pharmacological interventions for inclusion.

The FDA appears to be increasingly accepting A/A as a target indication, examples being the ongoing dextromethorphan and scyllo-inositol trials.

CAREGIVER PARTICIPATION

Most trials require a reliable caregiver as informant for patient symptoms and caregiver burden. In CitAD the requirement was for a primary caregiver who spends at least several hours a week with the patient, supervises his/her care and attends clinic visits with the patient. Mibampator required "frequent or daily contact with the patient." Dextromethorphan requires a caregiver who is with the patient a minimum of three times per week on three separate days, THC requires a caregiver who

is in touch with patient at least twice weekly, while the ongoing prazosin trial requires a caregiver who spends 10 hours per week with the patient.

CONCOMITANT PSYCHOTROPIC MEDICATION

All trials allow AD specific medications (cholinesterase inhibitors and memantine) with doses stable for at least one month prior to enrollment. Criteria for concomitant psychotropics vary considerably. Mibamptor and CiTAD excluded most concomitant psychotropics (except for "rescue" medications). Both memantine trials allowed psychotropic medications at baseline (including antidepressants, antipsychotics, or anxiolytics), while the ongoing prazosin trial allows such medication if the patient is a partial responder. The ongoing THC trial allows psychotropic medications except tricyclics, fluoxetine or carbamazepine.

Study design

RANDOMIZATION

Stratification of randomization varies with some trials stratifying by clinical site and others adding presence of antidepressant treatment (scyllo-inositol), or severity (scyllo-inositol, mibamptor).

PHARMACOLOGICAL INTERVENTION

These are fixed-dose or adjustable/titrated-dose trials. All studies used oral formulations except one trial of intramuscular aripiprazole (Rappaport *et al.*, 2009). In completed RCTs, the duration of treatment was 8–12 weeks except for melatonin (ten days), memantine (24 weeks), or divalproex (24 months). Among ongoing RCTs, the duration of treatment is 12 weeks except for dextromethorphan (10 weeks), and 3 weeks for THC.

ALLOWED RESCUE MEDICATION

All RCTs allowing "rescue" medication for severe A/A used lorazepam with doses ranging from 0.5 mg to 4 mg daily. Trazodone was used at low doses (50 mg per day) for sleep disorders (CitAD) and at higher doses (50–150 mg per day) for severe A/A in the memantine trial (Fox *et al.*, 2012). Haloperidol was used in the oxcarbazepine trial.

NON-PHARMACOLOGICAL INTERVENTION

In CitAD, mibampator and divalproex trials, different interventions, at inclusion and regularly over treatment period, have been used but vary in concept, content, and intensity. In CitAD the psychosocial intervention during the study was more intense than mibampator, for example. The goal of the CiTAD intervention is to systematize education and support in RCTs (Rosenberg *et al.*,

2010) by providing "enhanced usual care" to patients and caregivers regardless of treatment assignment (Drye *et al.*, 2012).

Outcome measures

NPS measures may be narrow spectrum, (assessing depression or agitation, for example), or broad spectrum (Steinberg and Lyketsos, 2008), including the NPI. The NPI originally included 10 domains (Cummings *et al.*, 1994) but expanded to 12 by the addition of sleep and appetite domains (Cummings *et al.*, 1997). Domains of NPI are commonly used in studies with varied degrees of validation. Dennehy *et al.* (Dennehy *et al.*, 2012) evaluated a cluster of items from the NPI in the hope of validating A/A assessment. Based on epidemiology and consultation with clinicians, they selected the individual NPI-10 domains of agitation, irritability, disinhibition, and aberrant motor behavior as a four-item measure of agitation and aggression (NPI-4-A/A). The 4-A/A subscale of NPI-Q was validated in the Alzheimer's Disease Neuroimaging Initiative and National Alzheimer's Coordinating Center cohorts (Trzepacz *et al.*, 2013b).

One limitation of NPI is that assessment relies solely on subjective caregiver input with resultant bias. Recently, the Neuropsychiatric Inventory Clinician Rating (NPI-C) was developed in part to address this issue (de Medeiros *et al.*, 2010). Aberrant vocalization was added as a new domain, whereas the A/A domain of the NPI was split to arrive at a total of 14 domains. Unlike NPI, each domain and each item within a domain can be rated on the NPI-C. Trained clinicians use input from caregiver and patient to rate frequency, severity, and distress of each item. NPI-C was field tested in an international validation study and compared with focused scales to determine convergent validity (de Medeiros *et al.*, 2010). It was found to have greater reliability than the conventional NPI.

The CMAI (Cohen-Mansfield, 1996) is widely used particularly in more advanced dementia and NH settings. Items are rated on a seven-point scale assessing the frequency of agitated behaviors (ranging from "never" to "several times an hour"). Items are presented in four subscales: aggressive behavior; physical non-aggressive behavior; verbally agitated behavior; hiding and hoarding. There are versions for both settings, NH (29 items) and a non-validated CD (36 items). CMAI provides the richest description of A/A but has the limitations of a relatively long administration time and assessments based solely on subjective caregiver input.

The Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) is a clinician-rated judgment of change

from baseline (Schneider *et al.*, 1997) and is based on the Clinical Global Impression of Change (CGI-C) (Guy, 1976). The modified ADCS-CGIC (mADCS-CGIC) version targets global functioning in specific NPS domains is particularly suited to blinded assessments in RCTs. The CitAD and scyllo-inositol trials have chosen a modified version of the ADCS-CGIC assessing specific A/A related domains.

The divalproex trial (Tariot *et al.*, 2011) uniquely measured incident A/A as the primary outcome. Of 18 RCTs, NPI was the primary outcome in ten trials and a secondary outcome in eight. The subscale NPI-4-A/A domain was primary outcome in the mibampator trial (Trzepacz *et al.*, 2013a). The ongoing scyllo-inositol trial has chosen as primary outcome the NPI-C (combined scores on agitation + aggression domains) and other NPI-C domains as secondary outcomes. Three completed and two ongoing trials, such as the brexpiprazole trials, used and are using CMAI as primary outcome. In eight RCTs CMAI was a secondary outcome. All RCTs used a global impression of change measure as secondary outcome except for both prazosin trials and the ongoing CitAD where they were co-primary outcomes.

Other outcomes include: Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) (Galasko *et al.*, 1997) in five RCTs and seven quality of life (Qol-AD, Logsdon *et al.*, 2002) in five RCTs. MMSE is the most widely used cognitive (secondary) outcome. Caregiver burden was assessed in four completed and three ongoing trials, using the NPI-caregiver distress item (total or specific items); one THC trial uses the Zarit Burden Inventory (Zarit *et al.*, 1980).

SAFETY OUTCOMES
Most RCTs of A/A include a typical safety evaluation: adverse events (AE), serious adverse events (SAV), and AEs leading to withdrawal. Specific safety outcomes related to psychotropic medication effects have included cognition (based on MMSE), falls, sedation, weight change, and QT prolongation. After the FDA issued an advisory regarding dose-dependent risk of QT prolongation with citalopram, CiTAD increased surveillance of QT intervals and reported notable QT prolongation with citalopram at 30 mg. Balance, gait, and mobility are targets of assessments for CitAD, brexpiprazole, and THC. Brexpiprazole also assesses specific AEs related to AP use such as extra-pyramidal symptoms (Simpson-Angus Scale), tardive dyskinesia (Abnormal Involuntary Movement Scale), and akathisia (Barnes Akathisia Rating Scale).

Most of trials reported AE and SAV based on caregivers and physicians. AE could be recorded as spontaneous but also a checklist could be used like in CitAD and mibampator trials.

Analytic strategies

All statistical analysis plans for these RCTs were intention-to-treat (ITT). Primary comparisons were made using: (1) Analysis of covariance (ANCOVA) with "last observation carried forward" (LOCF) to estimate change from baseline to endpoint in the memantine CD trial, or (2) mixed models (CitAD, mibampator, memantine in NH, and prazosin). Recently, the general superiority of mixed models over LOCF was established (Siddiqui *et al.*, 2009), especially for RCTs with longer treatment periods.

Among mixed models, linear mixed models or mixed models of repeated measures (MMRM) are options. The latter treat time as a continuous or categorical variable, estimating mean change from baseline, adjusting for baseline performance. MMRMs are attractive because they make no assumption about the shape of the outcome's trajectory over time. A recent paper compared MMRM to linear models using data from several trials (Donohue and Aisen, 2012). Neither approach was more robust to missing data, an important issue in AD trials. CitAD and prazosin used linear effects models with random intercept and slope in the primary comparison, while mibampator used MMRM.

Choice of drug

NPS in AD are thought to reflect one or more types of CNS dysfunction: (1) synaptic or circuit disconnections in specific neuronal networks, (i.e., frontal-subcortical and cortico-cortical networks); (2) dysfunction in ascending monoaminergic systems involving serotonin, norepinephrine, or dopamine neurons primarily located in the brain stem and diffusely projecting via long axons to virtually all parts of the brain; and (3) glutamate-mediated excitatory neurotoxicity. These CNS alterations are not mutually exclusive and likely synergize to mediate NPS.

Scyllo-inositol appears to improve synaptic activity in networks underlying NPS via a dual mechanism of action: (1) regulation of brain myo-inositol metabolism and phosphoinositol signaling, and (2) protection from oligomer-induced toxicity due to amyloid anti-aggregation effects (Townsend *et al.*, 2006). Loss of serotonin in the inferior frontal cortex was reported to be limited to AD patients with prominent aggressive behavior

(Lai *et al.*, 2003). Citalopram, a selective serotonin reuptake inhibitor, improves functional serotonorgic neurotransmission. Aggressive behavior has been associated with up regulation of α1-adrenoceptors in AD prefrontal cortex and excessive noradrenergic reactivity is associated with anxiety and agitation in dementia (Szot *et al.*, 2007). Prazosin antagonizes norepinephrine at postsynaptic α1-adrenoreceptors.

Brexpiprazole is chemically similar to aripiprazole and has broad activity across multiple monoamine systems with reduced partial agonism for D2, 5HT1A receptors, and enhanced antagonism for 5-HT2A, and α1-adrenoreceptors. There is growing interest in modulators of glutamate neurotransmission, implicated in many neuropsychiatric diseases including schizophrenia and AD (Blanchard *et al.*, 2004). Dextromethorphan hydrobromide (DM) (the active main molecule) modulates glutamate signaling in two ways: (1) pre-synaptic inhibition of glutamate release (by sigma-1 receptor agonism), and (2) post-synaptic glutamate response modulation (by weak blockage of NMDA receptor and modulation of NMDA response to glutamate by the sigma-1 receptor). In the compound, quinidine sulfate increases the bioavailability of DM. DM-quinidine is FDA-approved for treatment of pseudo-bulbar affect whose symptoms overlap partially with A/A in AD. Mibampator is an AMPA glutamatergic receptor potentiator (O'Neill, 2004). Activation of AMPA receptors strengthens synapses and changes in glutamatergic synaptic transmission that contributes to neural plasticity in the central nervous system (Yamada, 2000). Memantine's mechanism of action is related to glutamatergic synaptic transmission.

Delta-9- tetrahydrocannabinol (THC) is the most biologically active isomer of THC, a psychoactive compound extracted from the resin of *Cannabis sativa* (marijuana). The ongoing THC trial is testing a very similar molecule to dronabinol, synthetic delta-9-THC, indicated for severe nausea and vomiting caused by chemotherapy, or for anorexia with weight loss in patients with acquired immunodeficiency syndrome. THC activates cannabinoid receptors (mainly type 1), repressing neurotransmitter release in the brain. The rational for its use in NPS is based on its psychoactive effects and association with reduced pain sensation. Although earlier retrospective data reported benefits of dronabinol for A/A in severely demented patients (Woodward *et al.*, 2014), the exact mechanism of action is not known. This could be explained by preventing aggregation of amyloid-beta with consequent microglial activation (Ramirez *et al.*, 2005).

Discussion

We reviewed recent 11 completed and 7 ongoing RCTs of current and emerging medications for the treatment of A/A in AD. The major result of this review is the great heterogeneity found in the design of these RCTs. Only three (pilot prazosin, intramuscular aripiprazole, and CitAD) report results favoring drug treatment of A/A, emphasizing the lack of current evidence for a definitive treatment strategy. Most trials report improvement on placebo likely due to intangible benefits of being in RCTs, variability in outcomes, and variability in the course of A/A (Garre-Olmo *et al.*, 2010), with spontaneous remissions or improvement without treatment. This high rate of response on placebo decreases the statistical power of trials to detect drug effects. Additional challenges include: (1) disentangling treatment effects from competing effects on the outcome in the presence of psychosocial interventions; (2) varied approaches to use of rescue and concomitant psychotropic medications; (3) heterogeneity of target symptoms and overlap of NPS (Lyketsos *et al.*, 2011); (4) variable inclusion criteria; and (5) the use of global AD measures rather than measures specific to A/A or individual A/A symptoms (Drye *et al.*, 2012).

The field does not yet have a tight consensus on primary outcome measures, on what constitutes a clinically significant effect size (Mohlar *et al.*, 2009), or how to translate effect size between different A/A scales. There are two overall approaches to assess treatment response both of which should be used: (1) outcomes based on the judgment of experienced clinicians (such as the mADCS-CGIC) and/or (2) outcomes measuring the severity of A/A symptoms.

The heterogeneous approach toward defining caregiver role and assessing caregiver outcomes is another issue in RCTs of A/A. The field needs consensus on who is a caregiver (family, formal/professional caregiver, time spent with the patient, etc.). Caregiver opinion is clearly necessary in the evaluation of A/A symptoms, which by their nature vary over time, and need to be assessed by history-taking rather than merely observation in the clinic. But caregiver opinion is by its nature subjective and, therefore, vulnerable to reporting bias; there is a role for training the caregiver in the assessment in order to obtain more standardized reports. One important innovation is the NPI-C that provides anchors for experienced clinician judgments that can overcome caregiver biases and allows for input from all available information including the clinical record, caregiver input, and direct observation.

Table 3. Recommendations for future RCTs targeting A/A in patients with AD

METHODOLOGICAL ASPECT	RECOMMENDATIONS
Population studied	
Age	• No limit
Dementia severity	• Mild to severe based on CDR rating of 1–3; stratification
Settings	• Different RCTs for NH or CD preferred; or stratification
Clinically significant A/A	• A/A needs consensus criteria
	• "Clinically significant" = medication is needed based on judgment of experienced clinician combined with severity rating above a cut-off on a A/A scale
Concomitant medications	• "AD treatments" allowed on stable doses for 30–60 days
	• APs not allowed; or allowed stable doses for 30–60 days
	• Antidepressants, mood stabilizers, anticonvulsants: allowed on stable doses for 30–60 days
Caregiver participation	• Caregiver needs a consensus definition
	• Standardized training in recognizing NPS and in rating behavior scales
	• Use of a caregiver diary for real time observations
Study design	
Pharmacological intervention	• Run-in-period before randomization (2–4 weeks)
	• 8–12-week treatment period
	• Consolidation response: to assess time to relapse within responders in each group during a 6–12-month period
Non-pharmacological intervention	• Psychosocial intervention during the run-in and the treatment periods in both groups.
	• Etiologic, non-pharmacologic, person-centered approach during run-in and treatment periods in both groups
Allowed rescue medication	• Defined allowable dosing, monitored use
Outcome measures	
Primary	• Global measure of A/A as primary
	• Validated scales assessing A/A, co-primary or secondary
	• Rated by clinicians with patient and caregiver input
Secondary	• Consider actigraphy
	• Agitation symptoms
	• Aggression symptoms
	• Other NPS: irritability, anxiety, depression, psychosis
	• Cognition, functional ability, quality of life
	• Caregiver distress, other caregiver measures
	• Allowed rescue medication cumulative dose
Analytic strategies	
	• Intention to treat analysis
	• Mixed models: LMM or MMRM

Abbreviations: AD = Alzheimer's disease; NPS = neuropsychiatric symptoms; A/A = agitation/aggression; CD = community dwelling; NH = nursing home; CDR = clinical dementia rating; MMRM: mixed model of repeated measures; linear mixed models.

Methodological enhancements of recent RCTs: suggestions for improvement

We propose in Table 3 methodological considerations for future trials for A/A in PwAD.

Population studied

DISEASE SEVERITY

The THC trial is the first trial to use the CDR to measure dementia severity for inclusion. The MMSE's major limitation is that the estimate of disease severity is based solely on cognitive performance, and does not capture, as CDR does, cognitive and physical impairments which are key features of AD. Therefore, disease severity should be based on CDR.

In recent trials there is a tendency to include patients at all levels of disease severity and, thus, patients at milder stages. This is important, given that the pathological processes leading to AD begins decades before a clinical diagnosis, and drugs targeting NPS may need to be assessed earlier in the disease process.

SETTING

The majority of trials have included patients from CD or from NH settings and only two (CitAD and dextromethorphan trials) have patients from

both. It is important for generalizability to include participants from both settings, either in separate trials or in a single trial; the latter strategy might be best implemented by stratifying randomization by care setting (as is being done in CiTAD, for example). Additionally, it is important to validate methods of caregiver data collection since most caregivers in CD are family members and most in NH are paid staff who may have different agendas and different reporting bias. It is important not to exclude NH participants since the majority of A/A in advanced dementia is in the NH setting.

Concomitant psychotropic medications

Most patients with A/A will already be taking psychotropic medications, and the approach toward these needs to find a middle ground between maximal rigor (no concomitant medications) and maximal generalizality (allow concomitant medications and assess intervention as an "add-on" therapy). Many RCTs have chosen the former approach to assess efficacy of an intervention as monotherapy, with the trade offs of rendering recruitment more challenging, possibly inadvertently excluding the most severe A/A, and limiting generalizability. The alternative approach could be proposed for these reasons. The ongoing prazosin trial follows this approach, allowing all stable concomitant psychotropic medications at inclusion, if the patient is a partial responder. However, doses of concomitant psychotropic should remain stable over the treatment period. Regarding APs medication, since they are the only one having proved efficacy, even modest, their concomitant use it is questionable and should be address by an expert panel (see Table 3).

Study design

Placebo run-in

One design feature to diminish the effect of placebo response is to have a placebo run-in period, which is becoming the norm in other fields of psychopharmacology (Iovieno and Papakostas, 2012), accounting for the benefit of non-pharmacologic interventions, and improving statistical power (Frost *et al.*, 2008). None of these trials included a placebo run-in period before randomization. Two trials in related fields used two to four week placebo run-ins and reported relatively low on-placebo response rates in the randomized treatment period (Howard *et al.*, 2007, Cummings *et al.*, 2013). We suggest that for RCTs of A/A the period be kept to two weeks because this is a reasonable period of time for relying solely on non-pharmacologic interventions, the duration needs

to be short due to the acuity of symptoms (see Table 3).

Pharmacological intervention

Most completed and current RCTs administer drug treatment for 9 to 12 weeks, adequate for assessing acute response, but not stability of response over longer periods of time. Some design strategies partly address this issue. The prazosin trial has included a 12-week open label observation period after the strict RCT period. There is an ongoing safety extension RCT to evaluate persistence of the effects of scyllo-inositol on A/A, beyond the treatment period covered by the trial. All patients will receive scyllo-inositol, but masking from the first trial will be maintained. Another strategy could be a two-week washout after the RCT period to assess if there is a rebound in symptoms.

Open-label observation under treatment drug it could be interesting if the period was long enough to assess "consolidation" of response, preferably 6 to 12 months for maximizing clinical generalizability. However, having no comparator, such a methodology will not inform efficacy. In order to address consolidation efficacy the observation period should be long enough (six6 months to one year) and the analysis should measure time. It will also be interesting to assess time to remission or relapse, as is done in evaluation of anticonvulsants, for example.

Non-pharmacologic intervention

The citalopram and mibampator trials include a psychosocial intervention for all participants regardless of treatment assignment, and this design feature is important to provide ethically "enhanced usual care" to all participants, to improve recruitment and retention, (Drye *et al.*, 2012) and, to reduce variance in outcome reporting by caregivers via education about the features of the disease (Tariot *et al.*, 2011).

Allowed rescue medication

A/A can truly be a crisis for family or institutional caregivers, and rescue medication is often needed to have viable retention. The CiTAD trial is a model, monitoring the use and dose of rescue medication by treatment group (Drye *et al.*, 2012).

Outcome measures

The choice of the optimal primary outcome is probably the most important decision in study design in this field. As this review shows, the choices have been very heterogeneous in completed and ongoing RCTs due to the lack of a gold standard outcome measure. However, the field appears to be

reaching a consensus in using *both* agitation-specific quantitative measures (e.g., relevant domains of NPI-C or CMAI) plus a global rating of change for agitation outcomes (mADCS-CGIC). This combined approach has been successfully used in the CitAD trial. Although the pimavanserin trial is not included in this review (targeting psychosis in Parkinsons' disease) the assessment process is worth noting: central raters assessed the primary outcome, site-based raters assessed CGI, and caregivers assessed the Zarit burden scale (Cummings *et al.*, 2013). Assessing different outcomes with different raters may provide robust support for convergent clinical benefits. Actigraphy offers the possibility of objective measurement of activity associated with agitation and has reasonable validation versus NPI in two studies (Mahlberg *et al.*, 2007; Kirste *et al.*, 2014).

Analytical strategies

An issue to take into account in statistical analyses is measurement variance that may be exaggerated in some trials especially multinational studies where translations and cultural interpretations are required. In most recent RCTs (citalopram, mibampator, memantine (Fox *et al.*, 2012) trials) mixed models have been estimated. Currently, mixed models seem to be more appropriated than ANCOVA and LOCF in RCTs of drugs in AD. However, up to date there is no available data to better propose MMRM or linear mixed models as statistical strategy in RCTs of drugs for A/A in AD.

There are several important methodologic obstacles to drug development in this area that might be best amenable to expert consensus on the: (1) definition of A/A for inclusion; (2) choice of primary outcome; (3) role of adaptive designs to minimize exposure to a drug or placebo that is "not working" (Mugno *et al.*, 2004; Kairalla *et al.*, 2012); (4) standardization of non-pharmacological person-centered interventions (Gitlin *et al.*, 2012) in both arms; and (5) placebo run-in-period prior to randomization. Once eligibility is confirmed at baseline, only patients with persisting A/A or at higher levels of A/A severity would participate in the treatment period. This etiologic non-pharmacological centered person approach, in addition to the psychosocial intervention, should be prolonged over the treatment period. This approach will reflect real-life clinical practice, reduce placebo response rate, and address the real-life issue which is whether a drug can demonstrate superior efficacy to placebo in the presence of non-pharmacological intervention for all participants.

Our review has limitations. First, even all studies were randomized and controlled trials and thus with a high quality, differences in the methodological quality were not deeply analyzed. Second, comparisons between RCTs' reports inter-rater reliability were not available. Third, only publications in English were included.

Finally, in comparison to pre-2008 RCTs, it is notable that other potential pharmacological alternatives to atypical APs, have been and are being tested in recent RCTs. However, despite considerable efforts in crafting appropriate designs for RCTs of promising therapeutics agents for A/A, it is urgent to gain more clarity regarding the underlying neural regions and circuitry involved in NPS, to thereby shed light on symptom pathogenesis. However, so far, there has been very little developmental work based on this better understanding that could offer an opportunity to develop more new targeted drug treatments (Ballard *et al.*, 2013; Geda *et al.*, 2013).

Conclusion

Despite the urgent need to identify effective pharmacological treatments for A/A in PwAD, progress has been slow. In the past six years a small number of RCTs of drugs for treatment of A/A in AD have been conducted with disappointing results. These trials are characterized by methodological heterogeneity. Several issues have been encountered: the need for stronger consensus on the syndromal definition of A/A as a target, choice of primary efficacy outcome measure, the content and timing of the non-pharmacological intervention in placebo and drug arms before and/or during the trial, concomitant psychotropic medication, definition of caregivers and their participation. Consensus is necessary to enhance the design of future trials. The fact that placebo effects are substantial and consistently observed suggests that non-pharmacological approaches are currently the standard of care that we are still waiting for clear and consistent evidence on drug efficacy.

Conflict of interest

Description of authors' roles

M. Soto, B. Vellas, C. Lyketsos, and P. Rosenberg designed the manuscript. M. Soto wrote the manuscript. C. Lyketsos and P. Rosenberg assisted with writing the article. B. Vellas, C. Ballard, S. Andrieu, F. Nourhashemi, P. Robert, and PJ Ousset revised and corrected the manuscript.

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