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REVIEW ARTICLE

Role of aripiprazole in the management of behavioural and psychological symptoms of dementia: a narrative review

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Abstract

Behavioural and psychological symptoms of dementia affect in a great way quality of life of both patients and their caregivers, which increases the risk of patient institutionalisation when such symptoms are poorly controlled. One of the drugs that are used for controlling behavioural and psychological symptoms of dementia (BPSD) is aripiprazole. This narrative review aims to solve three basic questions. Is aripiprazole useful for the management of these symptoms? Does aripiprazole play a substantial role regarding safety and efficacy, compared with the other pharmacological options available for the same purpose? Has aripiprazole gained importance in treatment regimens of these symptoms, in current clinical practice? We conclude that aripiprazole is effective to manage BPSD. Moreover, it has shown a good safety profile compared with other antipsychotics in advanced disease and frail patients. Thus, aripiprazole has gained importance in current management algorithms for dementia patients mainly due to its efficacy regarding rapid control of agitation and aggressiveness.

INTRODUCTION

The development of the first dopamine D2 receptor agonist antipsychotic drug provided a new perspective for new drugs for schizophrenia. Until the appearance of aripiprazole (ARP), the existing antipsychotics presented a dopamine D2 antagonist action, which causes extrapyramidal symptoms that vary in severity depending on the receptor blockade level. The antagonist effect is higher in first generation antipsychotic drugs like haloperidol and lower in second generation ones like clozapine or quetiapine. The action of ARP is characterised by an agonist effect on dopamine D2 and D3 and serotonin 5-HT1A receptors, and by an antagonist effect on 5-HT2A receptors, which permits controlling positive, negative, and behavioural symptoms of schizophrenia with few extrapyramidal and metabolic effects.[1] Although the partial agonist effect on presynaptic D2 receptors can improve psychosis symptoms, it may also exacerbate them if it does not have an antagonist effect on postsynaptic D2 receptors.[2] This, together with the effect on the 5-HT1A and 5-HT2A receptors, provides the drug with a stabiliser role of the dopamine-serotonin system.[3] ARP also shows a moderate affinity for alfa1, alfa2, and histamine H1 receptors, as well as a marginal affinity for muscarinic receptors.[4]

ARP reaches its maximum plasma concentration between 3–5 h after being orally administered, and between 1–3 h if the route is intravenous, with this latter administration option providing 100% of bioavailability.[5] This drug has high distribution and binding to proteins; thus, in elderly patients it can produce accumulation and drug-drug interactions, especially in subjects with low albumin levels. In

these cases, the dose should be adjusted to the lowest recommended dosage. Regarding its route of elimination, 25% of a given dose will be eliminated in urine and 55% in the faeces.[5] ARP contains an active metabolite (dehydroaripiprazole) that shows affinity for D2 receptors and that has a half-life of 94 h. Food intake does not interfere with oral administration. Moreover, it is not required to adjust dosage in patients with kidney or liver failure. Importantly, dosage should be increased in cases of co-administration of CYP3A4 inducers (such as carbamazepine) and reduced in co-administration of CYP3A4 (like ketoconazole) or CYP2D6 (as fluoxetine or paroxetine) inhibitors.[5]

The behavioural and psychological symptoms of dementia (BPSD) affect directly the quality of life of patients and their caregivers, being the main cause for patient institutionalisation.[6,7] The aim of this review is to assess if ARP presents advantages compared with other available pharmacological options for the management of BPSD.

EFFICACY AND SAFETY OF ARIPIPRAZOLE IN DEMENTIA PATIENTS

The first experimental studies about ARP in murine models were published in 1995 and the first publication that can be found in PubMed regarding the use of this drug to treat dementia dates back to 2003.[8] In 2004, an expert consensus on the use of antipsychotics in the elderly was published, in which ARP was recommended as a second line drug for the treatment of elderly patients with schizophrenia.[9] At the time, the evidence on the use of this drug for BPSD was virtually non-existent. The available data were only extrapolations from the effects of ARP on schizophrenia, generally in young adults. Now, there are four randomised, double-blind, case-control clinical trials[10–13] (Table 1) and some meta-analyses[14–17] that have evaluated the efficacy and safety of ARP for treating these symptoms.As usual in studies about BPSD, most trials were performed on institutionalised patients.[11–13] For obvious reasons, such studies are difficult to perform in patients at home. These studies are mostly carried out in nursing homes, professional settings that permit monitoring and caring for the patient, as well as including more severe patients with BPSD.[18] Nevertheless, this may hamper the translation of results to the treatment of non-institutionalised patients.[19] In three of these studies, the ARP administration route was oral, prescribed in flexible doses between 2–15 mg/day[10,12] or in fixed doses between 2.5–10 mg/day.[11] All these three trials analysed the effect of ARP, compared with placebo, for the management of psychotic symptoms (delirium and hallucinations) during 10 weeks. In a fourth study, ARP was administered intramuscularly in fixed doses of 5, 10, and 15 mg, in two 2-h-apart injections followed by a follow-up of 24 h. This study is the only one assessing the effect of ARP on agitation in patients with different types of dementia[13] (Table 1). According to the results of these trials, ARP flexible doses, as considered by the treating doctor, did not produce significant changes in the Neuropsychiatric Inventory (NPI) psychosis rating scale compared with placebo;[10,12] all patients experienced a general improvement after 10 weeks, regardless of the group in which they were included (placebo or ARP). Nevertheless, the effects on total NPI, Brief Psychiatric Rating Scale (BPRS), Cohen Mansfield Agitation Inventory (CMAI), and (more severe cases) in Clinical Global Impression–Severity of Illness (CGI-S) were significantly better in the ARP-treated group. The improvement in total NPI was due to a decrease in the score of agitation, aggressiveness, anxiety, and depression. In the study using low fixed doses, the differences between ARP and placebo regarding the effect on NPI psychosis scale did reach significance. This was observed for the 5 mg and, especially, 10 mg doses.[11] In the study by Streim *et al*.[12] a significant improvement in the Cornell Scale for Depression in Dementia (CSDD) in patients treated with ARP was observed, compared with placebo. Moreover, in a study by Rappaport *et al*.,[13] the ARP-treated group improved compared with the placebo group, as assessed through the Positive Negative Syndrome Scale-Excited Component (PEC) and the Agitation-Calmness Evaluation Scale (ACES), as well as through the CGI-S. The effects of a 10 mg dose (5 mg in a first dose and other 5 mg 2 h later, intramuscularly) were similar to the ones provided by 15 mg, but with a lower risk of adverse effects. The results of the meta-analyses that evaluate the effect of different antipsychotic drugs on these patients with dementia, and include ARP for comparison, are similar. The overall control of BPSD with ARP is statistically better than with placebo.[14–17]

Regarding the analysis of adverse effects, somnolence was the most frequently experienced one by patients treated with ARP, although it was mild–

Table 1 Randomised clinical trials of ARP versus placebo in patients with dementia and behavioural and psychological symptoms

	Type of study	Dementia	*N*	Setting	Intervention and duration	Endpoint 1°	Endpoint 2°	Results
De Deyn 2005[10]	RCT	AD + psychotic symptoms	208	Outpatients	ARP vs. placebo: flexible doses 2–15 mg Mean doses: 10 mg Duration:10 weeks	NPI psychosis	BPRS, CGI-S CGI-I	NPI psy, CGI-S and CGI-I: ARP vs. placebo NS. BPRS global and BPRS psy* **Adverse effects:** Somnolence: ARP vs. placebo* (ARP worse) EP symptoms and QTc alteration: ARP vs. placebo NS
Mintzer 2007[11]	RCT	AD + psychotic symptoms	487	Nursing homes	ARP vs. placebo: Fixed doses 2, 5, 10 mg vs. placebo. Duration: 10 weeks	NPI-NH psy	NPI-NH total CGI-S, BPRS, CMAI, MMSE	Doses 10 mg vs. placebo: NPI-NH psy, BPRS psy and global; CMAI y CGI-S* ARP better Doses 5 mg vs. placebo to BPRS and CMAI*. ARP better **Adverse effects:** most common symptom: asthenia, death, cerebrovascular events, QTc, alteration, EPS: NS
Streim 2008[12]	RCT	AD + psychotic symptoms	256	Nursing homes	ARP vs. placebo: flexible doses 2–15 mg. Mean doses: 9 mg Duration:10 weeks	NPI-NH Psy CGI-S	NPI-NH total, BPRS, CMAI, Cornell Depression Scale	NPI-NH psy and CGI-S: NS CGI-S in the most serious patients (5–7 points)* NPI-NH total, (agitation, aggression, anxiety, depression). * BPRS total and CMAI.* **Adverse effects:** mild to moderate somnolence No EPS. Death and CVE: NS
Rappaport 2009[13]	RCT	AD, VD, MD with agitation	129	Healthcare facilities	ARP vs. placebo Doses 5, 10, 15 mg IM half the dose in 2 h. Duration 24 h	Adverse effects Preliminary analysis: effectiveness in Positive and Negative Syndrome Scale—Excited Component (PEC) scores and Agitation-Calmness Evaluation Scale (ACES).	CGI-S	Preliminary analysis: PEC, ACES: ARP better than placebo in all 3 doses. CGI-S: ARP better than placebo in all 3. Doses 10 mg efficacy similar to 15 mg. Global adverse effects: Placebo: 8 (32%); 5 mg: 6 (50%); 10 mg: 41 (54%); 15 mg: 9 (60%) Serious adverse effects: placebo: 2 (8%); 5 mg: 3 (25%); 10 mg: 7 (7′9%), 15 mg: 1 (6′7%)

*$P < 0.05$. AD, Alzheimer's dementia; ARP, aripiprazole; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression–Severity of illness; CMAI, Cohen Mansfield Agitation Inventory; CVE, cerebrovascular events; EPS, extrapyramidal symptoms; IM, intramuscular; MD, mixed dementia; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatry Inventory-Nursing Home; NPI-NH psy, NPI-NH psychosis subscale score; NS, not significant; RCT, randomised clinical trial; VD, vascular dementia.

Table 2 NMA: Network Meta-analysis that compares the efficacy and safety of ARP with one of the other drugs for the treatment of patients with different types of dementia and BPS

	Type of study	Type of dementia	Treatments analysed	*N*	Endpoint 1°	Endpoint 2°	Results	AEs
Yunusa 2019[20]	NMA 17 studies RCT	(AD, MD, VD, DLB) + BPRS	Antipsychotics: RCT antipsychotic trials with each other or vs. placebo	5373	NPI	BPRS, CAMI AEs: CVE, deaths, EPS, somnolence, falls, infections	SUCRA: ARP may be the safest and most effective antipsychotic. ARP: effective vs. placebo in NPI, BPRS and CMAI QUETIAPINA; better in BPRS. Risperidone NA; better in CMAI. No differences between psychotics in effectiveness, deaths, or stroke	Analysing effectiveness with respect to NPI and deaths, NPI and CVEs; ARP behaves as the most efficient and secure
Jin 2019[21]	NMA 146 studies: 133 drug therapy studies and 13 non-pharmacological therapy studies	(AD, MD, VD, PDD; DLB) + BPRS	Antipsychotics, antidepressants, cognitive enhancers, benzodiazepines, anticonvulsants, and non-pharmacological therapies	44 873	NPI, CMAI	AEs	NPI: ARP and escitalopram the most effective. Donepezil, galantamine, memantine, and risperidone were superior to placebo. CMAI: ARP and risperidone were superior to placebo. Pharmacological therapies are superior to non-pharmacological	AEs: Donepezil, galantamine, risperidone and rivastigmine had more AEs compared to placebo

AD, Alzheimer's disease; AEs, adverse events; ARP, aripiprazole; BPRS, Brief Psychiatric Rating Scale; CMAI, Cohen Mansfield Agitation Inventory; CVE, cerebrovascular events; LBD, Lewy body dementia; EPS, extrapyramidal symptoms; MD, mixed dementia; NPI, Neuropsychiatric Inventory; PDD, parkinson disease with dementia; RCT, randomised controlled clinical trials; SUCRA, Surface Under the Cumulative Ranking Curve; VD, vascular dementia.

moderate in severity, was not associated with falls, and led to study withdrawal in only two patients.[10,12,13] There were no significant differences regarding mortality, cerebrovascular events,[11,13] extrapyramidal symptoms[10–13] or prolonged corrected QT interval.[10–12] ARP has shown to be safe and well tolerated in elderly patients, which has been further supported by different meta-analyses.[14–16]

Thus, it can be concluded that ARP is an effective treatment option for severe psychotic symptoms and other disruptive symptoms in dementia. Furthermore, ARP has a good safety profile, which is relevant in cases of elderly and frail patients with dementia.

NETWORK META-ANALYSES TO COMPARE THE EFFECTS OF THE DIFFERENT TREATMENTS FOR BPSD

There are only two network meta-analyses that compare the efficacy and safety of ARP with one of the other drugs for the treatment of patients with different types of dementia (Alzheimer disease, vascular dementia, mixed dementia, Lewy body dementia).[20,21] The meta-analysis by Jin and Liu[21] also includes other non-pharmacological treatments (Table 2).

Yunusa *et al*.[20] included in the meta-analysis 17 randomised studies and a total of 5373 patients. The primary objective was to analyse the effect of treatment on NPI, being the rating scales BPRS and CMAI also considered for the secondary objectives. The following adverse effects were evaluated: mortality, cerebrovascular events, extrapyramidal symptoms, somnolence, falls, and infections. The analysis showed that ARP was more effective than placebo, according to the results obtained in the three rating scales (NPI, BPRS, and CMAI), whereas quetiapine obtained better results in BPRS and risperidone in CMAI. Through treatment ranking ascertainment using the surface under the cumulative ranking curve (SUCRA), ARP was demonstrated to be the most effective and safe drug.

The meta-analysis by Jin and Liu[21] included a population sample of 44 873 patients with diverse types of dementia recruited from 146 different studies: 133 studies on pharmacological treatments that analysed the effects of antipsychotics, antidepressants, acetylcholinesterase inhibitors, memantine, benzodiazepines, and anticonvulsants; and 13 on non-pharmacological treatments. Their efficacy was evaluated using the rating scales NPI and CMAI. In the case of NPI, escitalopram and ARP were the most effective drugs, and donepezil, galantamine, memantine, and risperidone showed better results than placebo. In CMAI results, ARP and risperidone showed to be more effective than placebo. Of note, pharmacological treatments showed better results than non-pharmacological ones, the reason why authors emphasise in their conclusions that pharmacological options should have priority over non-pharmacological treatments, which is contrary to the current recommendations.[22,23] With respect to the adverse effects, galantamine, donepezil, risperidone, and rivastigmine presented a significantly higher rate of adverse effects than placebo.

ARIPIPRAZOLE POSITION IN MANAGEMENT ALGORITHMS FOR BPSD

Davies *et al*.[24] published in 2018 an algorithm for controlling agitation and aggressiveness in Alzheimer, vascular, and mixed dementia in which they propose a sequence of drugs for treatment. In this algorithm, there are six steps of monotherapy considering the frailty of the patient. There are also indications on previous drug elimination and therapies that can be discretionally used. Risperidone is proposed as a first step therapeutic option, being quetiapine and ARP possible alternatives. In case of poor control, the recommended sequency of drugs in monotherapy would be carbamazepine, citalopram, gabapentin, and prazosin. If monotherapy fails, it is recommended to use a combination of the drugs that had shown a partial response, electroconvulsive therapy being the last alternative. In case there are still episodes of agitation and aggressiveness, on-demand trazodone could be indicated; lorazepam would stay as an option limited only to cases of severe agitation and aggressiveness when other treatments have failed to be effective, or to cases of stressful situations that could provoke agitation, like diagnostic tests or dental procedures.[24] These authors[24] claim that ARP is safe, effective, and well tolerated, but the lack of studies comparing it with other antipsychotic agents hampers concluding if it has an added value to the use of the atypical antipsychotic options proposed in the first place. It has to be borne in mind that when this algorithm was published, the

meta-analyses by Yunusa and Jin had not yet been carried out.[20,21]

The algorithm by Chen *et al*.[25] proposes three scenarios with different action guidelines. There is a first scenario called Emergent Situation that requires a rapid action, in which the use of oral medication is limited. The second scenario, called Urgent Situation, is characterised by disruptive symptoms the control achievement of which can be delayed some days or weeks; and the third scenario, Non-Emergent Situation, is defined by a mild or moderate disruption, which permits using more slow-acting but safer drugs. In Emergent Situations in which symptoms are so severe that oral medication is not an option, the first line drug is olanzapine. Nonetheless, authors state that their first option would be ARP if it were available in a parenteral formulation in the Unites States, as it happens in Europe. The second line drug in these situations is haloperidol. If symptom severity persists, these authors recommend 0.5 mg of lorazepam intramuscularly every 4 h, 2 mg being the maximum daily dosage.[25] In countries in which lorazepam is not available in parenteral formulation, 3.5 mg of midazolam every 4 h would be an adequate option.

In the Urgent Situation algorithm, the first drug option is 2.5 mg/day of ARP, with the possibility of increasing this daily dose 2.5–5 mg every two weeks, until a maximum daily dosage of 15 mg. If ARP is not effective, it would be recommended to administer an initial dose of 0.25 mg of risperidone at night, increasing such dose 0.25 mg every day until a maximum daily dosage of 15 mg. Risperidone should be avoided in patients with Lewy body dementia and Parkinson disease, due to its antagonist effect on dopamine receptors. The third option, in case of the two previous drugs not providing the expected results, would be prazosin, at a dose of 1 mg at night and increasing it by 1–2 mg/day for 3–7 days until reaching a maximum daily dose of 2 mg in the morning and 4 mg at night. The last alternative would be electroconvulsive therapy.[25] In a Non-Emergent Situation, the first step would be decreasing acetylcholinesterase inhibitors and adjusting treatment of pain; the second step would be trazodone to optimise sleep. Then, as a third step, the addition of donepezil and memantine would be indicated; the fourth step includes the use of escitalopram and, if all the previous drugs do not work, antipsychotics would be indicated, starting with ARP.[25]

THE IMPORTANCE OF A SYSTEMATIC APPROACH TO BPSD

Due to the important impact that BPSD has on patients and their caregivers, an adequate approach is necessary to allow an early treatment intervention. The DICE approach, which stands for 'describe, investigate, create, and evaluate',[26,27] suggests four steps. (i) Describe thoroughly the symptoms, the context in which they occur, and the impact that they have on the patient and their caregivers. (ii) Investigate the underlying and modifying causes, with a special focus on pain and constipation treatment, which have a high prevalence in elderly dementia patients.[22] (iii) Create a work plan to deal with the underlying causes, disruptive symptoms, caregiver training, and improvement of caregiver-patient communication. (iv) Evaluate if the developed programme is effective or if it should be modified. In the cases in which a pharmacological treatment has been prescribed, mainly with antipsychotics, it is mandatory to periodically follow-up the patient in order to adjust the dosage to the minimum effective dose or to consider drug withdrawal.[26]

FINAL CONSIDERATIONS

Achieving a good control of BPSD is essential for the quality of life of both patients and their caregivers.[6,7] In view of the available evidence, it can be concluded that ARP is efficient for BPSD treatment[10–13,20,21] and that it has a good safety profile, compared with other antipsychotic drugs used for the management of elderly and frail patients with dementia.[20,21] This review highlights the effectiveness and safety profile of an antipsychotic drug that offers pharmacological features useful to treat patients with dementia. The effect of ARP on psychotic symptoms, evaluated through the NPI psychosis subscale and mainly in flexible dose studies, was not significant. The study using 5 mg and, especially, 10 mg fixed doses of ARP did show statistically significant differences regarding the effect on NPI psychosis scale, compared with placebo.[11] It is remarkable that, when psychotic symptoms are evaluated through BPRS, the effect of ARP is clearly significant. This may be

explained by the fact that BPRS is ranked by professionals and NPI psychosis subscale by caregivers.[10,11] In all the trials, the effectiveness of ARP was more significant for severe disruptive symptoms in dementia, such as aggressiveness, agitation, anxiety, and psychotic symptoms. ARP adverse effects are minimal, with no significant differences compared with placebo regarding extrapyramidal symptoms, cerebrovascular events, prolonged corrected QT interval, or mortality.[20] Indeed, ARP was found to be the most effective and safe drug to manage behavioural symptoms.[20]

The main adverse effect of ARP is mild–moderate somnolence, which did not increase the risk of falls or gait disorders and led to study withdrawal only in two patients.[10,12,13] Thus, ARP has gained a relevant position in current management algorithms for dementia patients, mainly due to its efficacy regarding rapid control of agitation and aggressiveness.[24,25] All this helps to establish the patient profile that would benefit the most from ARP treatment: patients with very severe behavioural and disruptive symptoms and anxiety. Moreover, ARP can be a more effective alternative than quetiapine in patients with Parkinson disease signs.

One of the most controversial aspects of this review is whether the pharmacological treatment against the non-pharmacological one is a priority, which needs further research. In the context of behavioural symptoms of dementia, the scenario when the patient arrives to the consulting room is frequently catastrophic, with their caregiver about to give up due to the presence of one or multiple behavioural symptoms in the patient. The importance of the symptoms is neither objective nor steady, as it depends mainly on the distress on both patients and their caregivers. In this way, the same symptom may not require treatment in one patient and be extremely urgent to control in another one. The decision of prioritising pharmacological treatment over a non-pharmacological approach will depend mainly on the level of disruption that the symptom is causing on the patient and their caregiver. Thus, the most realistic and adjusted to clinical practice proposal would be considering different scenarios. Notwithstanding, a non-pharmacological treatment can be started even before the appearance of any behavioural symptom. A correct training of caregivers regarding the management of patients with dementia is substantial for non-pharmacological treatments and has to be dealt with during every visit. Likewise, music therapy, exercise, and other non-pharmacological interventions can be implemented along the disease process, regardless of the presence of behavioural symptoms.

Further research is needed to elucidate the role of ARP in patients with different types of dementia. In the same way, more long-term studies analysing the effects of ARP on both the patients and their caregivers as well as on institutionalisation risk are needed.

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