EXPERT OPINION

Antipsychotic treatments for the elderly: efficacy and safety of aripiprazole

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Abstract: Delusions, hallucinations and other psychotic symptoms can accompany a number of conditions in late life. As such, elderly patients are commonly prescribed antipsychotic medications for the treatment of psychosis in both acute and chronic conditions. Those conditions include schizophrenia, bipolar disorder, depression and dementia. Elderly patients are at an increased risk of adverse events from antipsychotic medications because of age-related pharmacodynamic and pharmacokinetic changes as well as polypharmacy. Drug selection should be individualized to the patient's previous history of antipsychotic use, current medical conditions, potential drug interactions, and potential side effects of the antipsychotic. Specifically, metabolic side effects should be closely monitored in this population. This paper provides a review of aripiprazole, a newer second generation antipsychotic agent, for its use in a variety of psychiatric disorders in the elderly including schizophrenia, bipolar disorder, dementia, Parkinson's disease and depression. We will review the pharmacokinetics and pharmacodynamics of aripiprazole as well as dosing, diagnostic indications, efficacy studies, and tolerability including its metabolic profile. We will also detail patient focused perspectives including quality of life, patient satisfaction and adherence.

Keywords: aripiprazole, antipsychotics, elderly, adverse drug reaction

Introduction

Antipsychotic medications are commonly prescribed for older adults for the acute management of psychosis in brief psychotic disorders or in psychosis due to a general medical condition or from substance use. Chronic antipsychotic therapy is commonly used in patients with psychosis, schizophrenia, dementia related psychosis, bipolar disorder, and psychosis related to Parkinson's disease.

Elderly patients are at increased risk of adverse drug events because of age-related pharmacodynamic and pharmacokinetic changes. Additionally, as older adults are often prescribed multiple medications, they are at increased risk for drug–drug interactions. Common side effects in the elderly from antipsychotics include orthostatic hypotension, sedation, anticholinergic side effects, extrapyramidal symptoms (tremor and rigidity), and tardive dyskinesia (lip smacking).

This paper provides a review of aripiprazole, a newer atypical antipsychotic agent. We will review the indications and adverse drug reactions of this drug in the elderly. Specifically, we will review pharmacokinetics and pharmacodynamics of aripiprazole as well as dosing, diagnostic indications, efficacy studies, and tolerability. We will also detail patient focused perspectives including quality of life, patient satisfaction and adherence.

Psychosis in the elderly

Delusions, hallucinations and other psychotic symptoms can accompany a number of conditions in late life. A recent Swedish investigation found that the prevalence of any psychotic symptom in a population sample of 85-year-old individuals without dementia was 10.1%.[1] Some conditions that cause psychotic symptoms, such as delirium and substance-induced psychosis are acute and tend to resolve when the underlying condition is treated.[2] Psychotic symptoms in elderly individuals may also arise secondarily to Alzheimer's disease (AD) or other dementias. AD is the most common form of dementia in the elderly population, accounting for 65% to 70% of dementia cases. Approximately 35% to 50% of AD patients manifest psychotic symptoms.[3] Psychosis associated with AD often presents with paranoid and nonbizarre delusions.[4] Misidentification of care givers is common in patients with AD, while schneiderian first rank symptoms are rare.[5]

Schizophrenia in the elderly

Schizophrenia, a chronic, mental illness affects about ~1% of the US population and is characterized by both positive and negative symptoms, cognitive dysfunction and a decline in psychosocial functioning.[6] The etiology of schizophrenia is unknown, but it is believed that monoamine neurotransmitter systems, particularly dopaminergic neurons, are involved.[7] Most individuals with schizophrenia develop the disease in the second or third decade of life. Many patients with schizophrenia now live into older adulthood. Thus, about 80% of older adults with schizophrenia have had an early onset of the disease and have a chronic course spanning several decades.[8] There is another smaller subset of patients who develop psychotic symptoms after age 60 and are diagnosed with very late onset schizophrenia-like psychosis.[9] Factors distinguishing patients with very late onset schizophrenia from early onset schizophrenia patients include a lower genetic load, less evidence of a thought disorder, and evidence of a neurodegenerative component.[10] The prevalence of schizophrenia among individuals aged 45 to 64 is approximately 0.6% and prevalence estimates for elderly individuals range from 0.1% to 0.5%.[11,12]

Longitudinal follow-up of patients with schizophrenia indicates a wide range of outcomes. About 20% of patients experience remission of all symptoms.[13] Another 20% experience worsening of their symptoms and the remaining 60% remain largely unchanged.[14] Factors associated with poorer prognosis include chronicity, insidious onset, premorbid functional deficits, and prominent

negative symptoms.[15] In one large sample of chronically institutionalized patients with schizophrenia, older age was associated with lower levels of positive symptoms and higher levels of negative symptoms.[16] Cognitive performance tends to be stable, although it is worse in patients with schizophrenia than in healthy adults.[17] The degree of functional impairment varies among older adults with schizophrenia. However, one study showed that 30% of a group of older schizophrenic patients was employed at least part-time since the onset of psychosis and that 73% of them were living independently.[18]

Psychosis in Alzheimer's dementia in the elderly

Alzheimer's disease (AD) affects 5% to 15% of the population over age 65 and about 20% of individuals over age 80.[19] There is a high prevalence of psychotic symptoms and behavioral disturbance in AD. A review of studies showed a median prevalence rate of psychosis in AD of 41.1% (range, 12.2% to 74.1%).[20,21] Psychotic symptoms have been linked to increased cognitive and functional decline and increased risk of institutionalization in patients with AD.[22]

Antipsychotic medications are disproportionately used among elderly persons and are prescribed for more than a quarter of Medicare beneficiaries in nursing homes.[23] Such medications are often used for dementia, delirium, psychosis, agitation, and affective disorders.[24] Even though there is no psychotropic medication that is approved by the US Food and Drug Administration (FDA) for the treatment of psychosis in AD, a number of consensus statements prior to 2004 recommend the use of atypical antipsychotic agents as a first line pharmacologic approach to treatment.[25]

Analyses of safety data from several studies have raised concerns about an increased risk of cerebrovascular adverse events such as stroke in the use of certain atypical antipsychotics compared with placebo in elderly patients with dementia.[26,27] This has led the FDA to issue warnings on the use of atypical antipsychotics in the treatment of behavioral symptoms in elderly patients with dementia.[19] In a Public Health Advisory issued in April 2005, the FDA warned that the use of atypical antipsychotic medications nearly doubled the risk of death, as compared with the risk with placebo, in 17 short-term, randomized, controlled trials involving elderly persons with dementia.[28] The FDA has issued a separate warning regarding the increased mortality risk in elderly patients with dementia who are treated with atypical antipsychotics including aripiprazole.[29]

Bipolar disorder in the elderly

Bipolar disorder in older adult populations has gained increasing attention due to the growing proportion of elderly in the United States and worldwide.[30] One study reported the prevalence of bipolar disorder at 0.5% among individuals age 65 and older as bipolar illness persists into later life.[31] A continuing unmet need is the identification of agents that are generally well tolerated and effective in later-life bipolar disorder. Medications that are first-line treatments in younger patients, such as lithium, may be poorly tolerated in older patients due to side effects and renal dysfunction. Additional strategies for bipolar disorder in late-life are needed. There are few evidence-based studies on which to base treatment decisions in geriatric patients with bipolar disorder.[32]

Psychosis in Parkinson's disease

Psychosis affects at least 5% to 8% of medication-treated patients with idiopathic Parkinson's disease (PD).[33] Treatment options include reducing medications used for the treatment of PD-related motor symptoms or introducing an atypical antipsychotic drug. Only clozapine has been demonstrated to be efficacious and tolerated in double-blind controlled trials.[34]

Major depressive disorder in the elderly

Major depressive disorder (MDD) is common in older adults, with estimates of prevalence of 6% to 10% in primary care population.[35] Approximately 50% of older patient with MDD do not respond completely to initial treatment with antidepressant pharmacotherapy.[36] Recently, the use of atypical antipsychotic agents has been studied as adjunctive or augmentation pharmacotherapy for incomplete response in young to middle-aged adults with major depression.[37] The addition of aripiprazole to standard antidepressant pharamacotherapy has been examined in young and mid-life patients with MDD.[38]

Pharmacology and pharmacokinetics/dynamics of aripiprazole

Aripiprazole is a second-generation (atypical) antipsychotic that is approved for schizophrenia, manic or mixed episodes associated with biploar I disorder, and as an adjunctive treatment of major depressive disorder. It exhibits high affinity for D2, D3, 2-HT1a and 5-HT2a receptors, moderate affinity for D4, 5-HT2c, 5-HT7, alpha 1 adrenergic and H1 receptors, and no affinity for muscarinic receptors. It has moderate affinity for the serotonin reuptake transporter.[39] The proposed mechanism of action for its efficacy is a combination of partial agonistic activity at D2 and 5-HT1A receptors and antagonistic activity at 5-HT2A receptors.[40] It is available in several dosage forms: intramuscular injection solution, oral solution, tablets, and orally disintegrating tablets.[41]

Table 1 compares the pharmacokinetic parameters of second-generation antipsychotics. Aripriprazole has an active

Table 1 Pharmacokinetic parameters of selected antipsychotics[101]

Drug	Bioavailability (%)	Half-life (h)	Major metabolic pathway	Active metabolites	Dosage forms
Aripiprazole	87	48–68 Dehydroaripiprazole: 75–46	CYP3A4, CYP2D6	Y	T, O, L
Clozapine	12–81	11–105	CYP1A2, CYP3A4, CYP2C19	Y	T, O
Olanzapine	80	20–70	CYP1A2, CYP3A4, FMO3	Y	T, I, O
Paliperidone ER	28	23	Renal unchanged (59%) Multiple pathway	N	ER
Quetiapine	5–13	7	CYP3A4	Y	T
Risperidone	68	3–24	CYP2D6	Y	T, O, L
Risperidone Consta®		3–6 days	CYP2D6	Y	LAI
Ziprasidone	59	4–10	Aldehyde oxidase, CYP3A4	N	C, I

Abbreviations: C, capsules; ER, extended release; I, injection; L, liquid solution, elixir or suspension; LAI, long-acting injectable; O, orally disintegrating tablets; T, tablet.

metabolite (dehydroaripiprazole) that has affinities for D2 receptors and an elimination half-life of 94 hours. The drug reaches the peak plasma concentration (T_{max}) between 3 to 5 hours, and achieves a steady-state concentration within 14 days. It can be taken with or without food, but high-fat meal delays T_{max} by 3 hours. Aripiprazole has a high volume of distribution (4.9 L/kg) and is highly bound to albumin (>99%). Due to its long half-life, high volume of distribution and high protein binding, the elderly patients may experience drug accumulation and drug interactions. It is particularly true in patients who have low albumin levels, which may end up with higher free aripriprazole drug concentration. Excessive drug effect in this population may justify dose reduction or extended dosing interval. In addition, aripriprazole is metabolized primarily by dehydrogenation and hydroxylation (CYP3A4 and CYP2D6), as well as N-dealkylation (CYP3A4). Due to CYP450 enzyme polymorphism, its elimination half-life may be prolonged to up to 150 hours in poor metabolizers which represents approximately 8% of Caucasians. Approximately 25% of the drug is excreted in the urine (<1% as unchanged drug) and 55% in the feces (18% as unchanged drug). Intramuscular doses have a bioavailability of 100%, and a T_{max} of 1 to 3 hours. Compared to oral doses, intramuscular doses achieve a 19% higher peak plasma concentration, as well as a 90% higher drug exposure within 2 hours of dosing.[41,42]

Aripiprazole interacts with drugs that are inducers or inhibitors of CYP3A4 and CYP2D6 enzymes.[43] The dose should be doubled when coadministered with CYP3A4 inducers, such as carbamazepine. The dose should be reduced to half of the usual dose if coadministered with CYP3A4 inhibitors (ketoconazole) or CYP 2D6 inhibitors (fluoxetine, paroxetine).[44] Appropriate measures should be done when the interacting drugs are discontinued. No dosage adjustment is required in patients with renal or hepatic impairment.[45] Intramuscular injections should be administered slowly into deep muscle mass. Oral doses may be administered with or without food. Tablet and oral solution may be interchanged on a mg-per-mg basis, up to 25 mg. Doses using 30 mg tablets should be exchanged for 25 mg oral solution.[41] Orally disintegrating tablets are bioequivalent to the immediate release tablets, and should be placed in mouth immediately upon removal from foil blister. They dissolve rapidly in saliva and may be swallowed without liquid.

Table 2 shows the relative side effect incidence of selected antipsychotics in all age groups. However, use of antipsychotics in the elderly is linked with many unique concerns. Firstly, anticholinergic effects can be detrimental to those who may already have urinary symptoms, cognitive impairment, dry mouth, blurred vision and cardiac abnormalities. Secondly, orthostatic hypotension and sedation may contribute to falls in patients who have trouble with balance and gait. Thirdly, extrapyramidal symptoms can be associated with long term antipsychotic therapy. Patients with the comorbidity of PD are especially at risk for tremor and muscle rigidity. Aripriprazole has lower incidence of these troublesome adverse effects when compared to other available antipsychotics. A retrospective study evaluated the use of aripriprazole for schizophrenia/schizoaffective disorder, bipolar disorder and major depressive disorder in elderly patients. The study suggested that agitation/activation is the most commonly reported side effect.[46]

Aripiprazole efficacy studies
Schizophrenia
The recommended dosage for schizophrenia is 10 to 15 mg once daily, titrate no more frequently than every 2 weeks, to maximum of 30 mg daily. Aripiprazole demonstrated its efficacy in four short-term placebo controlled trials that enrolled acutely relapsed inpatients with schizophrenia. Three of these studies also included an active control group treated with either risperidone (one trial) or haloperidol (two trials).

Table 2 Relative side effect incidence of selected antipsychotics in the general population[101]

Drug	Sedation	EPS	Anticholinergic	Orthostasis	Weight gain	Hyperprolactinemia
Aripiprazole	+	+	+	+	+	+
Clozapine	++++	+	++++	++++	++++	+
Haloperidol	+	++++	+	+	+	++++
Olanzapine	++	++	++	++	++++	+
Quetiapine	++	+	+	++	++	+
Risperidone	+	++	+	++	++	++++
Ziprasidone	++	++	+	+	+	+

Notes: + = low degree of symptoms, ++ = medium degree of symptoms, ++++ = high degree of symptoms.

The primary measures were the Positive and Negative Syndrome Scale (PANSS)[47] and the Clinical Global Impression (CGI)[48] assessment. PANSS measures positive symptoms (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility) and negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). The CGI assessment reflects the impression of a skilled observer about the overall clinical state of the patient.[48]

Overall, aripiprazole (10 to 30 mg daily) is more efficacious than placebo in all measure outcomes after 4 to 6 week of therapy.[49–51] In a 6-week trial (n = 367), aripiprazole 10 mg daily is superior to placebo in PANSS total score, but the lower dose groups did not demonstrate superiority to placebo.[52] In another 4-week placebo controlled trial (n = 103) comparing the dose range of 5 mg daily to 30 mg daily. Aripiprazole demonstrated efficacy only in a responder analysis based on the CGI-severity score. Overall, higher dose of aripiprazole offered no advantage over the lowest doses. A longer-term trial (n = 310) that enrolled patients who were symptomatically stable on other antipsychotic medications for at least 3 months. These patients were discontinued from their antipsychotic medications and randomized to aripiprazole 15 mg daily or placebo for up to 26 weeks of observation for relapse. Patients receiving aripiprazole experienced a significantly longer time to relapse, defined as CGI Improvement score of ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥20% increase in the PANSS total score.[53] These clinical trials did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.

Clinical trials of aripiprazole included few elderly patients and more data are needed on the effects of aripiprazole in this population, especially those with comorbid medical illnesses.[54] In one study, aripiprazole was used to treat 10 elderly hospitalized patients between 62 and 85 years of age who manifested signs of psychosis related to schizophrenia or schizoaffective disorder. All patients had been treated previously with atypical and classic antipsychotics. Response was assessed by clinical observation of patients' behavior and Clinical Global Impression Scale assigned retrospectively. Seven patients responded to treatment, two did not respond, and one had a partial response. The mean Clinical Global Impression Scale scores improved from 6 (severely ill) at baseline to 2.3 (much improved) at

discharge. Treatment was discontinued in the two patients who did not respond. Of the 7 patients who responded, 4 presented with positive symptoms and showed significant improvement while 3 presented with positive and negative symptoms and both symptoms improved significantly. Four patients had preexisting EPS and these symptoms decreased in three patients. In addition, two patients were able to discontinue antiparkinson medications. The reduction of both positive and negative symptoms of schizophrenia and the lack of significant EPS, tardive dyskinesia, sedation, weight gain, anticholinergic effects, and QTc prolongation gives preliminary indication that aripiprazole may be a safe and effective medication for elderly patients with schizophrenia or schizoaffective disorder.[55]

Psychosis in Alzheimer's dementia in the elderly

There have been three 10-week, placebo-controlled studies that have evaluated the efficacy and tolerability of aripiprazole for the treatment of psychosis related to AD.[19] In the De Deyn et al study, there were 208 outpatients who were given flexible dosing of aripiprazole (doses of 2 to 15 mg/day). There was no statistical difference between aripiprazole and placebo in the primary outcome measure of the caregiver-assessment NPI psychosis subscale. However, the aripiprazole-treated patients showed significantly greater improvement on the Brief Psychiatric Rating Scale (BPRS) Psychosis and BPRS Core subscale scores at end point when compared to placebo. There was no statistical significant difference in the BPRS total score.[56]

In the Streim et al study, there were 256 inpatients with AD-related psychosis who were given flexible dosing of aripiprazole (doses of 2 to 15 mg/day) with a mean aripiprazole dose at end point of 8.6 mg/day. There was also no statistical difference between aripiprazole and placebo in the primary outcome measure of the caregiver-assessment NPI psychosis subscale. There were decreases in the Clinical Global Impression-Severity of Illness (CGI-S), but those were only clinically significant in week 8. There was also statistically significant improvement in the Cohen-Mansfield Agitation Inventory (CMAI).[57]

In the Mintzer et al study, 487 institutionalized nursing home patients were randomized to fixed doses of either 2 mg/day, 5 mg/day, or 10 mg/day. On the 10 mg/d dose, there was a statistically significant difference between aripiprazole and placebo on the Neuropsychiatric Inventory-Nursing Home (NPI-NH) Psychosis subscale score at week 10.[58] It is important to note that the incidence of EPS-related AEs in these

studies was low across all treatment groups.[19] There was no significant difference between placebo and aripiprazole in all the three studies for weight change.[19]

Psychosis in Parkinson's disease

One study evaluated the effect of aripiprazole on psychosis in PD in an open-label pilot study. Fourteen patients meeting entry criteria were started on aripiprazole 1 mg/day and titrated up to a maximum dose of 5 mg as needed. Subjects were evaluated on the Unified Parkinson's Disease Rating Scale (UPDRS) part III for motor function, the Neuropsychiatric Inventory (NPI), and the Brief Psychiatric Rating Scale (BPRS) for psychiatric response. Statistically significant improvement in mean BPRS and positive BPRS subscales occurred with open-label aripiprazole, but 8 subjects discontinued the study due to worsened Parkinsonism (3), worsened psychosis (2), worsening of both (2), and lack of efficacy (1). While some patients had a favorable response, aripiprazole was associated with an exacerbation of motor symptoms. In that small study on psychosis in PD, aripiprazole did not appear promising.[59]

Bipolar disorder

Aripiprazole is approved by the FDA for the treatment of bipolar mania and for the long-term treatment of bipolar disorder. To stabilize the acute manic or mixed episodes, aripiprazole should be initiated at 15 mg once daily as monotherapy or adjunctive to lithium or valproic acid; may increase to 30 mg once daily if clinically indicated. The effective stabilization dose should be continued for up to 6 weeks. Aripiprazole demonstrated its efficacy in four 3-week, placebo-controlled trials in hospitalized patients with bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features, and 2 studies also included patients with or without a rapid-cycling course. The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale that assesses the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight). The secondary instrument included the Clinical Global Impression – Bipolar (CGI-BP) Scale.[60–62]

As a maintenance therapy, aripiprazole is superior to placebo on time to the number of combined affective relapses (manic plus depressive), but it is unclear if it delays the time to occurrence of depression in these patients. In addition,

these clinical trials did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.

One study looking at the use of aripiprazole in elderly patients is an open-label, prospective trial of aripiprazole therapy in 20 older adult patients with bipolar disorder.[30] Older adults with bipolar I disorder (confirmed by the Mini-International Neuropsychiatric Interview) who were currently suboptimally responsive to their prescribed medication treatments received 12 weeks of open-label aripiprazole added on to existing mood stabilizer medication treatment. Aripiprazole was initiated at 5 mg daily and increased as tolerated. Efficacy outcomes included psychopathology measures (the Young Mania Rating Scale [YMRS][63] and the Hamilton Rating Scale for Depression [HAM-D]),[64] extrapyramidal symptoms, and a level of functioning measure (the Global Assessment Scale [GAS]). Twenty older adults (mean age = 59.6 years, range 50 to 83 years) received aripiprazole therapy. Compared to baseline, individuals had significant reductions in mean depression scores (HAM-D baseline = 13.8, HAM-D end point = 6.1, $P < 0.001$), as well as mania scores (YMRS baseline = 8.6, YMRS end point = 3.9, $P < 0.03$). There were also significant improvements in functional status as measured by the GAS ($P < 0.001$). The mean ± SD daily dose of aripiprazole was 10.26 ± 4.9 mg/day. Overall, aripiprazole was adequately tolerated in this older adult population. Aripiprazole therapy may reduce symptoms in bipolar older adults, and it appears to be reasonably tolerated. However, larger, controlled trials are needed to confirm these preliminary findings.[30]

Agitation associated with schizophrenia or bipolar mania

The recommended dosage is 9.75 mg (range 5.25 to 15 mg) as a single intramuscular dose, repeat at no more frequently than every 2 hours to a maximum of 30 mg daily; transit to oral therapy as soon as possible if ongoing therapy is indicated. The efficacy of aripiprazole for the treatment of agitation was established in 3 short-term (24-hour), placebo-controlled trials in agitated inpatients with schizophrenia or bipolar I disorder (manic or mixed episodes, with or without psychotic features). Each trial included an active controlled arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar Mania study). The efficacy measures were the change from baseline in the PANSS Excited Component at 2 hours post-injection and the Clinical Global Impression of Improvement (CGI-I) Scale.[65,66] Again, these studies did not include sufficient numbers of subjects aged

65 and over to determine whether they respond differently from younger patients.

Major depressive disorder

The use of aripiprazole for MDD in older patients has been looked at only in a limited fashion. One open trial of aripiprazole augmentation in 20 older adults with MDD that had not remitted after 6 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI) was associated with improvement in 50% of the patients.[67] Another 12-week, open-label pilot study of 24 patients diagnosed with MDD who responded partially (17-item Hamilton Rating Scale for Depression [HAM-D-17] score of 11 to 15) or not at all (HAM-D score >15) to a 16-week trial of escitalopram (up to 20 mg/day), followed by either duloxetine (up to 120 mg/day) or venlafaxine (up to 225 mg/day) for 12 weeks. Subjects received 2.5 to 15 mg per day of adjunctive aripiprazole (mean dose, 9.0 mg/day) for 12 weeks. The criterion for remission during treatment with aripiprazole was a HAM-D score ≤10 for 2 consecutive weeks. Of 24 subjects in the intent-to-treat study group, 19 completed 12 weeks of augmentation with aripiprazole, 12 of 24 (50%) met criteria for remission, and 2 of 24 discontinued due to side effects (sedation, akathisia). The mean (SD) HAM-D score decreased significantly by 6.4 (5.8) points (paired t test for means, $P < 0.01$, df = 16). There were no relapses among the 12 subjects who participated in continuation treatment over a median period of 27.6 weeks.[68] No known randomized controlled trials have looked at this phenomenon.

Aripiprazole: safety and tolerability

Second-generation antipsychotics (SGAs) are used to treat psychiatric conditions in elderly patients, including schizophrenia, mood disorders, and dementia with agitation and delusions.[25] Aripiprazole is a SGA with partial agonist activity at the D2, D3, and 5HT1A receptors and antagonist activity at the 5-HT2A receptors.[39]

Data from Phase II and III trials

In Phase II and III trials, aripiprazole exhibited a favorable safety and tolerability profile. It showed a low propensity to cause significant adverse effects, such as extrapyramidal side effects (EPS), weight gain, cardiovascular abnormalities, hyperprolactinemia, hypercholesterolemia, or glucose dysregulation.[49,69–70] In a meta-analysis assessing safety and tolerability data from the Phase II and Phase III trials, 1539 patients receiving aripiprazole (n = 926), haloperidol (n = 200), or placebo (n = 413) were assessed. The reported

incidence of common adverse effects with aripiprazole was comparable to that of placebo.[71] The most common side effects reported with aripiprazole (>10% incidence) were headache, insomnia, agitation, and anxiety. Other common side effects were dyspepsia, nausea and vomiting, lightneadedness, somnolence, constipation and akathisia. Discontinuation due to adverse events occurred at an incidence rate of 7% with aripiprazole compared to 8% with haloperidol and 10% with placebo.[71] The most frequent adverse events leading to discontinuation of aripiprazole included psychosis (3.6%), agitation (0.6%) and akathisia (0.6%). The incidence rate of EPS-related adverse events had no significant difference in between the placebo and aripiprazole treatment groups. Tardive dyskinesia was only reported by 2 of the aripiprazole-treated patients (0.2%).[71] At endpoint, patients showed minimal mean increase in body weight from baseline (<1 kg) on aripiprazole. In all, 8.1% of patients on aripiprazole experienced clinically significant weight gain (>7% increase from baseline).[71] Aripiprazole was associated with decreased in serum prolactin levels. There was no dose-response relationship between aripiprazole and changes in the QTc interval.[71] The median increase in fasting total cholesterol from baseline observed with aripiprazole treatment was low and did not differ significantly from placebo. Only 5.5% of patients on aripiprazole had abnormally elevated fasting glucose levels and only 1.4% of the patients on aripiprazole had random levels of glucose above 200 mg/dL.[71] There were no clinically important differences in the adverse event profile when stratified by age, gender or race in patients receiving aripiprazole.[71]

Metabolic profile

Metabolic syndrome is age dependent and more prevalent in older adults across cultures.[72] Additional studies, have validated that aripiprazole has a favorable metabolic safety profile.[40,73] One study of 31 patients with schizophrenia showed that there was a significant decrease in body weight, body mass index, and weight circumference after 3 months of treatment with aripiprazole. There was also a significant reduction in fasting glucose, fasting insulin, insulin resistance index and serum lipid levels.[74] In addition, aripiprazole did not induce hyperprolactinemia at end point compared with baseline in a meta-analysis.[60] In one trial, as compared to olanazpine, aripiprazole was associated with weight loss and lesser changes in total cholesterol.[75]

One retrospective chart review of 52 inpatient geriatric patients who received aripiprazole described side effects attributed to aripiprazole in the charts of 9 (17.3%)

of the patients. Of these 9 patients, 7 had not received aripiprazole until the current hospitalization. Side effects were reported in a higher percentage of male than female patients (25% versus 15%); however, this did not reach statistical significance. The most commonly reported side effect was agitation/activation, which was documented in the charts of 4 patients (8%). Extrapyramidal symptoms were reported in 2 patients, and single cases of confusion, fatigue, and lightheadedness were also reported. The mean dose at which side effects were reported was 11.4 mg/day. Side effects were the reported reason for aripiprazole discontinuation in 12% or 6 of the patients.[46]

Patient-focused perspectives
Quality of life

Quality of life is important for all individuals, especially for people with schizophrenia on chronic medications. However, quality of life can be difficult to define and quantify as it relies on individual perception and self-assessment. Definitions vary from "whatever the individual defines it to be" to those that emphasize fulfillment of personal goals.[76] Quality of life in the geriatric population can be even harder to define as it may depend less on sexual dysfunction and more on functions of activities of daily living (eg, bathing, dressing, food preparation). Additionally, studies on quality of life and patient adherence with aripiprazole (the STAR study) have excluded patients over 65 years of age.[77,78]

Data on the impact of aripiprazole therapy on the quality of life of schizophrenic patients are scarce and characterized by conflicting results.[79–81] The only double-blind study which compared changes in quality of life among patients on aripiprazole versus perphenazine treatment failed to demonstrate statistically significant differences between the groups.[81] A Cochrane systemic review revealed no conclusive evidence of a clinically important improvement in quality of life as assessed by the Quality of Life Scale among 154 patients receiving aripaprazole.[82]

Patients with schizophrenia often have cognitive deficits such as decreases in attention, executive function and motor skills which impede their quality of life.[83] Typical antipsychotics can contribute to such cognitive impairments through parkinsonism motor impairment or anticholinergic side effects. As an atypical antipsychotic, aripiprazole has shown a modest improvement in cognitive function, however such studies are few in number.[84] On open label study revealed no improvement in neurocognitive function in patients on aripiprazole as compared to olanzapine.[85]

Patient satisfaction/acceptability

Patients over age 65 are at greater risk of metabolic side effects of antipsychotics because of their age and presence of comorbidities. Data on aripiprazole's impact on metabolic measures specifically in the geriatric population are not available. Studies have suggested that aripiprazole has a lower risk for weight gain than other atypical antipsychotics.[86] A randomized trial of 173 overweight patients of all ages with schizophrenia or schizoaffective disorder comparing aripiprazole with olanzapine found aripiprazole was associated with weight loss and less effect in total cholesterol at 16 weeks.[75] Some findings suggest that older patients actually gain less weight than their younger counterparts from second-generation antipsychotics (SGA).[87] Furthermore, patients with Alzheimer's disease receiving SGAs may exhibit less weight gain than younger patients without dementia.[88]

Regular physical activity is associated with reduced incidence of metabolic syndrome from SGA. This is true for older adults too. Park et al demonstrated that yearlong exercise of at least 20 minutes daily at 3 or more metabolic equivalents was associated with reduced incidence of metabolic risk factors.[89] Reductions in body mass index were strongly associated with favorable changes in risk factors for metabolic syndrome.[90] While all patients on SGA should be advised on exercise and diet to minimize the potential effects of the metabolic syndrome, older patients may have poor compliance due to physical or financial limitations. Difficulty obtaining healthier food choices because of cost or availability and inability to exercise due to physical functional restrictions can make it harder for geriatric patients to comply with lifestyle changes.

Adherence

Nonadherence with prescribed medication regimens can result in increased morbidity, mortality, and resource utilization.[91,92] Schizophrenic patients with poor adherence with antipsychotic medications have greater symptom levels,[93] sustained functional impairment,[94] poor community adjustment,[95] higher risk of relapse,[96] and more rehospitalization and emergency room use.[97,98] A 2007 meta-analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia measured the impact of nonadherence in terms of direct healthcare costs or inpatient days. The study found poor adherence to antipsychotic medications was consistently associated with higher hospitalization costs with a higher risk of relapse and rehospitalization. However, the studies this article reviewed

did not include the newer atypical antipsychotics including aripirazole, ziprasidone or paliperidone.[99]

Discussion

A variety of psychiatric conditions in the elderly can be treated with antipsychotic medications. Poor adherence to typical antipsychotics due to adverse reactions led to the newer atypical antipsychotics. However, the metabolic side effects of the second generation antipsychotics led to the development of a newer atypical antipsychotic, aripiprazole.

Older patients often require complex decision-making for medication management of psychiatric illness because they frequently have co-morbidity with medical conditions and are prescribed many other medications. They are at greater risk of metabolic and other side effects of antipsychotics because of their age and presence of comorbidities.

In particular, since the FDA black box warning that use of atypical antipsychotic medications in elderly patients with dementia nearly doubled the risk of death, clinicians, patients and caregivers are left with unclear choices for treating people with dementia with psychosis and/or severe agitation. Such behaviors are common and can cause considerable caregiver stress. The alternatives for treatment include no treatment, use of other psychotropic drugs, and psychotherapeutic and psychosocial interventions. No treatment may only be viable in mild cases or if symptoms are not disturbing to the patient or impairing function. There are limited studies on use of antidepressants, cholinesterase inhibitors and memantine for dementia related psychosis which generally were of limited utility (details are beyond the scope of this paper). There are limited randomized-control trials on the role of psychosocial and behavioral treatments for this population; however an individualized approach to such treatments may be appropriate for some patients.[100] Even though there is no psychotropic medication that is approved by the FDA for the treatment of psychosis in AD, a number of consensus statements prior to 2004 recommend the use of atypical antipsychotic agents as a first-line pharmacologic approach to treatment.[25] Careful discussion of risks, benefits and alternative treatments should be conducted by clinicians with patients' caregivers when using antipsychotic medications for patients with dementia-related psychosis. Higher symptom burden will likely contribute to greater acceptance of using antipsychotic in hopes of improving quality of life.

In addition to its use in dementia, aripiprazole may be effective for the treatment of a variety of psychiatric conditions in the elderly including psychosis due to schizophrenia, bipolar disoder, depression, and PD. Although the data on aripiprazole's efficacy in the treatment of psychosis in the geriatric population are very limited, it may have an important role to play in those conditions. As discussed in detail above, aripiprazole has a favorable metabolic profile compared to other second-generation agents in terms of glycemic control, lipid profiles, prolactin levels and weight gain. When appropriate, clinicians should weigh the limited evidence of efficacy in the geriatric population with the potential benefits of less metabolic complications as its metabolic risk profile makes aripiprazole an attractive agent in this population. Additional studies on efficacy of aripiprazole use in the elderly population are needed, although early studies show some promise.

Disclosures

The authors have no conflicts of interest to report.

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