Atypical antipsychotics to treat the neuropsychiatric symptoms of dementia

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Abstract: Neuropsychiatric symptoms are common in older adults with dementia and can be associated with a rapid decline in cognitive and functional status. This article reviews the current literature supporting the use of atypical antipsychotic medications in this population. Among the currently available atypical antipsychotics, risperidone and olanzapine have been the most widely studied in double-blind, randomized, placebo-controlled clinical trials. Despite the common use of other atypical antipsychotic medications, their efficacy and safety in older adults with dementia has not been as extensively studied. Some controversy surrounds the use of atypical antipsychotic agents in older adults with the suggestion that they may increase the incidence of stroke or even death. Despite the potential for increased risk of harm from the use of these medications, atypical antipsychotics are often effective in treating troublesome neuropsychiatric symptoms refractory to other treatments. Whenever possible, these atypical antipsychotic drug treatments should be combined with non-pharmacological treatments to limit the need and dose of antipsychotic drugs and constant monitoring for potential harms should be maintained. The choice of which atypical antipsychotic agent can be guided by the nature and severity of the target symptom and the medication least likely to cause harm to the patient.

Keywords: atypical antipsychotics, dementia, risperidone, olanzapine

Introduction

Neuropsychiatric symptoms associated with dementia are common, and occur in the majority of patients at some point during the course of their illness. Of those who experience behavioral changes, many will experience multiple symptoms concurrently (Sink et al 2004; Steinberg et al 2004). Some patients may experience changes in sleep patterns, mood disturbance, or wandering, while others may develop agitation, aggression or psychosis. In general, the severity of behavioral and psychological symptoms of dementia (BPSD) seems to be positively correlated with the stage of dementia; however, neuropsychiatric symptoms have been shown to be prevalent in patients with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) (Hwang et al 2004). The severity of these symptoms can vary considerably from one person to another. This variation in presentation may be related, in part, to the different underlying types of dementia. For example, patients suffering from dementia with Lewy bodies may be more prone to present with visual hallucinations, while patients with frontotemporal dementia may be more likely to experience changes in personality early on during the course of their illnesses. Nevertheless, even within a group of patients with the same clinical diagnosis, considerable variability of symptom presentation exists. In the later stages of dementia, all forms of neuropsychiatric symptoms can be present regardless of underlying diagnosis.

The presence of neuropsychiatric symptoms of dementia is associated with an increased level of caregiver burden and distress (Rinaldi et al 2005). A faster functional decline is predicted by the presence of psychotic symptoms such as paranoid ideation

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and hallucinations (Mortimer et al 1992). Even the presence of milder neuropsychiatric disturbance may predict a poorer outcome in patients with dementia. The presence of one or more difficult behaviors has been associated with an increased likelihood of institutionalization (Steele et al 1990;Yaffe et al 2002). Many prior studies of the treatment of neuropsychiatric symptoms in older adults with dementia have not included measures of quality of life (Ballard and Margallo-Lana 2004), yet reduction of troubling symptoms would likely also lead to an improvement in quality of life and improve outcomes.

Atypical antipsychotics are among the most commonly prescribed medications used to treat mood and behavioral disturbance associated with dementia. Despite their frequent use, there is some controversy regarding the safety and efficacy of atypical antipsychotics in this population. This article reviews the currently available atypical antipsychotic agents that have been studied in older adults with dementia, and summarizes the evidence supporting their efficacy and the potential concerns that have been raised about their safety.

Treatment of neuropsychiatric symptoms

The management of BPSD has not been well standardized. The heterogeneity of neuropsychiatric symptoms experienced by patients with dementia may contribute to the lack of consensus regarding the best way to treat these symptoms. Clinicians often make the choice of treatment guided by the underlying diagnosis of the type of dementia, the nature of the target behavior being treated, and the tolerability of the treatment being offered. Both non-pharmacological and pharmacological treatments have been explored. Non-pharmacological therapy can be cognitive, behavioral, or environmental. Several non-pharmacological interventions have all been shown to have a positive effect on neuropsychiatric symptoms (Livingston et al 2005). Behavior management therapies, specific types of caregiver and residential care staff education, and possibly cognitive stimulation appears to have lasting effectiveness. Treatments centering on sensory stimulation have been shown to be effective in reducing agitation and behavioral problems, but the long-term effects are not clear. Most of these interventions have not been studied in large randomized clinical trials. Furthermore, the time commitment and training required to administer non-pharmacological treatments can limit their usefulness in certain situations; however, given that they are generally safe and well tolerated, non-pharmacologic interventions are largely considered to be first line therapy, or at least adjunctive treatment, in all patients with BPSD.

Despite the use of non-pharmacological measures, use of medications is often required for acute situations or refractory symptoms. There are many medication options that have been used for the treatment of BPSD. Among the medication options available, antipsychotic therapy has been the most studied (Sink et al 2005) and these medications are commonly prescribed for the treatment of patients with dementia. Antipsychotic medications are commonly divided into two groups, the typical antipsychotics (sometime referred to as conventional antipsychotics), and the newer atypical antipsychotics (second-generation antipsychotics).

For many years, typical antipsychotic drugs were the most commonly prescribed for the treatment of BPSD. Examples of conventional antipsychotics include haloperidol, perphenazine, chlorpromazine, and thioridazine. These medications exert their primary mechanism of action by blocking D_2 receptors in the mesolimbic pathway of the brain. Although there has been extensive experience with their use, typical antipsychotics appear to be only modestly effective and have potentially serious adverse effects that limit their usefulness in older adults (Schneider et al 1990; Lanctot et al 1998). Sedation, extrapyramidal symptoms (EPS) and falls have been associated with the use of conventional antipsychotics. Low potency typical antipsychotics (eg, chlorpromazine) may be less appropriate for older adults with dementia because of anticholinergic properties. A Cochrane review showed that there is no evidence to support the use of the low potency antipsychotic, thioridazine, in older patients with dementia and that its use may expose patients to excess side-effects (Kirchner et al 2000). Between 1964 and 2001, the UK Committee on Safety of Medicines received 42 reports of suspected heart rate and rhythm disorders associated with thioridazine (Committee on Safety of Medicines/Medicines Control Agency 2001). Thioridazine has recently been removed from the Canadian market because of concerns regarding its potential to induce cardiac arrhythmias (Health Canada 2005b).

Concerns about overuse of these medications led to the Omnibus Budget Reconciliation Act (OMBRA) of 1987 (National Coalition for Nursing Home Reform, 1987) which was US legislation that attempted to reduce psychotropic medication prescriptions among residents of nursing homes. Due to the potentially deleterious effects of these medications on older adults, OBRA 87 recommended their use only as a last resort for the management of behavioral problems, and

further required physicians to periodically reassess the need for their use to prevent inappropriate long-term exposure to these drugs. This legislation initially had a significant impact on reducing the use of antipsychotic drugs in nursing homes (Shorr et al 1994; Llorente et al 1998). The presumed benefit of the legislation led others to explore how similar policies might be adapted to other countries such as the United Kingdom (Hughes et al 1999). There is a growing trend towards moving away from legislated restrictions that focus on poor prescribing practices and instead focusing on improving quality of care for residents of nursing homes (Hughes and Lapane 2005). Despite the call for improved education, multidisciplinary collaboration, and attention to the needs of nursing home residents, antipsychotic use is increasing. One study from Canada (where no such legislation exists) demonstrated that up to 24% of new residents in a nursing home were started on an antipsychotic medication within one year (Bronskill et al 2004). Despite the initial reduction in use of these medications after introduction of OBRA 87, a recent study demonstrated that the use of antipsychotic medications among nursing home residents is increasing once again, though the majority of nursing home residents are now being prescribed atypical antipsychotics as opposed to conventional agents (Briesacher et al 2005).

Atypical antipsychotics

Newer antipsychotic medications such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole have been collectively referred to as the atypical antipsychotics. Like typical antipsychotics, atypicals block D_2 receptors along with other dopaminergic pathways, but they also antagonize serotonergic receptors such as 5-HT_2 (Meltzer 1989; Meltzer 1992). It is possible that serotonin antagonism interacts to increase cortical dopamine release, thus explaining their effect on the treatment of the negative symptoms associated with diseases like schizophrenia (Ichikawa et al 2001). The characteristics of how atypical antipsychotics actually bind to the dopamine receptors may also differentiate them from conventional agents (Kapur and Seeman 2001; Strange 2001). Depending on the type of atypical agent, there may be affects on muscarinic, alpha-adrenergic or histaminic receptors. The actions of atypical antipsychotics on these other receptors contribute to the differences in side effect profile between agents. These medications are referred to as a class due to the perception that they all share a lower risk of EPS than older conventional antipsychotics like haloperidol.

Clozapine

Clozapine (Clozaril®) is a dibenzodiazepine derivative that acts on dopamine binding to D1, D2, D3 and D5 receptors, and it has a high affinity for D4 receptors. It also acts as an antagonist against adrenergic, muscarinic, histaminergic and serotonergic receptors. In contrast to conventional antipsychotics, clozapine produces minimal to no elevation in prolactin levels.

Introduced commercially in the United States in 1989, clozapine was observed to cause fewer extrapyramidal symptoms compared to conventional antipsychotic agents like haloperidol. Although clozapine is considered to be effective in treating refractory psychosis and suicidal behavior in younger patients with schizophrenia, there is a lack of information regarding its efficacy in treating older adults with dementia. Much of the evidence to support the use of clozapine in older patients has been gained from studies that looked at the treatment of primary psychotic disorders (Sajatovic et al 1997) or schizophrenia (Howanitz et al 1999). Patients with Parkinson's disease and psychosis have also been shown to benefit from treatment with clozapine (Ellis et al 2000; Klein et al 2003; Pollak et al 2004). There are no randomized controlled trials (RCT) assessing the use of clozapine in dementia.

The potential for clozapine to induce neutropenia and the emergence of alternative atypical antipsychotics has led to limited use of this medication. Due to the risk of agranulocytosis, clozapine users are required to perform frequent monitoring of their white blood cell count weekly for the first 6 months and then every other week for as long as the patient takes this medication. Monitoring of the white blood cell count is recommended to continue for 4 weeks after discontinuation of therapy. Other adverse effects such as sedation, hypersalivation, hypotension, cardiovascular effects such as myocarditis, percarditis, and pericardial effusion, and seizures limit its use even further.

Risperidone

Risperidone (Risperdal®) is a benzisoxazole derivative with high affinity for 5-HT_2 receptors, D_2 receptors, and α_1-adrenergic receptors, and a lower affinity for other 5-HT receptors, α_2-receptors and histaminergic receptors. It is thought to have little affinity for D_1 receptors and no affinity for muscarinic receptors.

Risperidone has been shown to benefit older adults with primary psychotic disorder or schizophrenia (Sajatovic et al

1999; Davidson et al 2000), and of all the atypical antipsychotic agents, risperidone has the most RCT evidence to support its use in older adults with dementia (Lee et al 2004; Sink et al 2005). DeDeyn et al (1999) performed a 12-week trial in nursing home residents with dementia using flexible doses of 0.5–4 mg/day of risperidone (mean dose 1.1 mg/day) versus placebo. The primary outcome was the proportion of subjects achieving a greater than 30% reduction from baseline to endpoint in Behavioral Pathology in Alzheimer's Disease Rating Scale (Reisberg et al 1987) (BEHAVE-AD) total scores. For this outcome, risperidone was not found to be superior to haloperidol or placebo. The study reported a statistically significant difference between risperidone and placebo on several of their secondary endpoints. Katz et al (1999) performed a 12-week trial using fixed doses (0.5, 1, 2 mg/day) of risperidone versus placebo in nursing home residents with dementia. Subjects who received 1 or 2 mg/day of risperidone showed significant improvements compared to the placebo group on the BEHAVE-AD as well as several secondary outcome measures. Brodaty et al (2003) used flexible doses of risperidone (mean 0.95 mg/day) versus placebo in another study of nursing home residents with dementia. The primary outcome measure, the mean adjusted Cohen-Mansfield Agitation Inventory (Cohen-Mansfield 1986; Cohen-Mansfield et al 1989) (CMAI) total aggression scores, were significantly better with risperidone as compared to placebo. BEHAVE-AD total scores as well as several subscales of BEHAVE-AD and CMAI also improved with risperidone.

The trials by De Deyn et al (1999) and Brodaty et al (2003) (mean doses of approximately 1 mg/day of risperidone) did not document significant differences in treatment-emergent EPS compared to placebo, although EPS was more common with haloperidol than risperidone. The Katz trial (Katz et al 1999) did find a dose-dependent increase in EPS with risperidone that was significant for subjects receiving 2 mg/day. Other adverse events were frequently documented in the trials, but were similar with treatment and placebo. Somnolence was more common with risperidone than placebo in the trial by De Deyn et al (1999).

Risperidone can cause dose-dependent side-effects, so minimizing the use of excessive doses is desirable. The more common side-effects associated with risperidone use in elderly patients are postural hypotension, sedation, and EPS. These side effects (especially EPS) are dose-related, suggesting a need for caution in increasing the dose (Rochon et al 2005).

Olanzapine

Olanzapine (Zyprexa®) is a thienobenzodiazepine derivative with selective monoaminergic antagonism with high affinity for 5-$HT_{2A/2C}$, dopamine receptors D_{1-4}, M_{1-5} muscarinic receptors, H_1 histaminergic receptors and α-1 receptors. It binds with lesser affinity to $GABA_A$, receptors and β receptors. Olanzapine has been studied in the treatment of older adults with schizophrenia or primary psychotic disorders (Madhusoodanan et al 2000). In older adults with dementia, Street et al (2000) studied olanzapine in fixed doses (5, 10, 15 mg per day) versus placebo. The primary endpoint of this study was the Neuropsychiatric Inventory-Nursing Home (Cummings et al 1994) (NPI-NH) Core Total score, which was used to classify patients as responders (greater than 50% reduction from baseline) versus non-responders. On this measure, olanzapine 5 and 10 mg per day were superior to placebo. The subjects receiving 15 mg/day of olanzapine had worse outcomes compared to the subjects receiving 5 mg per day. It is probably advisable to use caution when prescribing doses of olanzapine higher than 10 mg per day in older adults with dementia. Another study performed by De Deyn et al (2004) assessed fixed doses of olanzapine (1, 2.5, 5, and 7.5mg/day) versus placebo in the elderly with dementia. No significant differences were seen between the treatment groups on their primary measures of efficacy, the NPI-NH Psychosis Total (delusions and hallucinations) subscale or the Clinicians' Global Impression of Change (National Institute of Mental Health 1976) (CGI-C). There were some positive benefits noted on certain secondary measures for the 7.5 mg per day dose group compared to placebo.

Street et al (2000) documented more somnolence and abnormal gait among subjects receiving olanzapine versus those on placebo. The trial by De Deyn et al (2004) did not demonstrate any worsening of motor function or significant anticholinergic effects on treatment with olanzapine. Although increased weight, anorexia, urinary incontinence were noted to be significantly different among the treatment groups, they were not significant compared to the placebo group. The placebo group had a statistically higher incidence of abnormal behavior compared to the group receiving 7.5 mg of olanzapine per day (3.9% versus 0.0%, $p = 0.028$).

Quetiapine

Quetiapine (Seroquel®) is a dibenzothiazepine derivative that has affinity for 5-$HT_{1A/2}$ and dopamine D_{1-2} receptors. It also has high affinity for histamine H1 receptors and α-1

receptors, and a lesser affinity for α-2 receptors. Quetiapine has reportedly no appreciable effect on muscarinic or benzodiazepine receptors. Quetiapine's lack of muscarinic receptor affinity and its lack of tendency to cause slowing on encephalographic monitoring was thought to make it less likely to cause cognitive impairment in older adults with dementia (Byerly et al 2001); however, an RCT by Ballard et al (2005) compared quetiapine (25–50 mg twice daily) to rivastigmine (3–6 mg twice daily) or placebo. The group on treatment with quetiapine did not show a significant improvement on behavioral problems measured by the CMAI compared to the other groups, and in fact demonstrated a worsening in cognition as measured by the Severe Impairment Battery (Saxton and Swihart 1989) (SIB). Other than the trial by Ballard et al, there is very limited published RCT evidence to support the use of quetiapine in older adults. It has been best studied in patients with Parkinson's disease (Fernandez et al 1999).

Aripiprazole

Aripiprazole (Abilify®) exhibits high affinity for dopamine $D_{2\text{-}3}$, 5-$HT_{1A/2A}$, moderate affinity for D_4, 5-$HT_{2C/7}$, α-1 adrenergic and H1 receptors and muscarinic receptors. Although approved for use in the United States and United Kingdom, it is not available in Canada. Aripiprazole has been reported to be minimally successful in treating patients with probable Parkinson's disease and drug-induced psychosis (Fernandez et al 2004) In a population that included subjects who were previously treated with other atypical antipsychotics, only 2 out of 8 had resolution of their psychosis, while 6 out of the 8 discontinued therapy. In a 10-week, double-blind, placebo-controlled randomized trial in older adults with Alzheimer's disease, 208 community-dwelling patients were randomized to treatment with either aripiprazole (up to 15 mg per day) or placebo (De Deyn et al 2005). Those subjects on treatment with aripiprazole (mean 10 mg per day) showed no difference compared to placebo on the NPI-psychosis subscale, but statistically significant improvement from baseline on the Brief Psychiatric Rating Scale psychosis and core subscales. Somnolence appeared more frequently in patients on treatment with aripiprazole, but overall adverse events appeared to be similar between treatment and placebo groups.

Ziprasidone

Ziprasidone (Geodon®) exhibits high affinity for the $D_{2\text{-}3}$, serotonin 5-$HT_{1A/1D/2A/2C}$ and α-1 adrenergic receptors, moderate affinity for histamine H1 receptors. Ziprasidone is not approved for prescription in Canada or the United Kingdom. There is very limited evidence to support the use of ziprasidone in the elderly. The cardiac safety of intramuscular ziprasidone in agitated elderly patients with dementia was studied in a retrospective chart review (Greco et al 2005). In small open label study, four patients with dementia and agitation or psychosis showed improvement while receiving oral doses of ziprasidone (20–160 mg per day) without any evidence of problematic side-effects (Cole et al 2005). Ziprasidone has been associated with prolongation of the QT interval. Due to the risk of potentially fatal arrhythmias such as torsade de pointes, it should not be used in patients with QT prolongation or cardiac arrhythmias.

Other atypical antipsychotics

Sertindole, amisulpride, and zotepine are atypical antipsychotic agents that have not been approved for use in Canada or United States. Sertindole (Serdolect®) is a phenylindole derivative. Its activity appears to be specific to D_2, 5-HT_2 and α-1 adrenergic receptors and largely confined to the limbic dopamine system of the brain. The availability of sertindole was voluntarily suspended by the manufacturers following reports of cardiac arrhythmias and sudden death associated with the use of this medication. It was remarketed to the United Kingdom in 2002, but its use is fairly restricted. Amisulpride (Solian®) is a substituted benzamide that binds selectively with a high affinity for dopaminergic D_2 and D_3 receptors and lacks affinity for D_1, D_4 and D_5 receptor subtypes. It has reportedly no affinity for serotonergic alpha-adrenergic, H_1 histaminergic or cholinergic receptors. Zotepine (Zoleptil®) has a high affinity for $D_{1\text{-}2}$ recepetors and it also affects on 5-$HT_{2A/2C/6/7}$ receptors. Due to the extremely limited experience with the use of these medications and the potential for life-threatening side-effects, the use of sertindole, amisulpride and zotepine is not recommended in older adults with dementia.

Safety of atypical antipsychotics

Atypical antipsychotic agents are thought to cause less striatal dopaminergic receptor antagonism compared to typical antipsychotic medications (Ichikawa and Meltzer 1999). Traditionally, use of atypical antipsychotics is thought to have less risk of extrapyramidal symptoms (EPS) such as Parkinsonism and tardive dyskinesia in older adults compared to conventional antipsychotics (Jeste et al 1999, 2000). Based on large retrospective cohort studies using administrative

databases, there is some suggestion that the incidence of Parkinsonism and tardive dyskinesia may be higher than initially expected among users of atypical antipsychotics compared to typical antipsychotics (Lee et al 2005; Rochon et al 2005).

Patients with dementia with Lewy bodies or Parkinson's disease can be sensitive to treatment with antipsychotic medications. Even though generally viewed to be safer in these patients than conventional antipsychotics, patients with dementia with Lewy Bodies or Parkinson's disease can be very sensitive to atypical antipsychotics as well (Ellis et al 2000; Morikawa Kishimoto 2002; Sadek and Rockwood 2003; Aarsland et al 2005). Among the atypical antipsychotic agents, it is thought that quetiapine (Fernandez et al 2003), and possibly clozapine are the most well tolerated in terms of neuroleptic sensitivity in patients with either of these disorders (Baskys 2004).

There is considerable concern about the potential metabolic effects of antipsychotic medications including atypical agents. Some evidence suggests that different atypical antipsychotics have variable effects on weight gain, insulin sensitivity and lipids. For instance, in younger patients with schizophrenia, olanzapine was shown to be associated with increased weight gain, and increases in glucose and lipid metabolism (Lieberman et al 2005). In a study of patients with a diagnosis of psychosis, olanzapine and clozapine appeared to increase the risk of acquiring or exacerbating type 2 diabetes mellitus while use of risperidone did not (Gianfrancesco et al 2002). In 2003, the US Food and Drug Administration (FDA) required all manufacturers of atypical antipsychotics to include a warning about the risks of hyperglycemia and diabetes. The use of olanzapine and clozapine, but not risperidone, has been found to be associated with hyperlipidemia in patients with schizophrenia (Koro et al 2002). A recent review of the atypical antipsychotics quetiapine, olanzapine and clozapine, for patients with schizophrenia suggested that they are associated with higher risk of hyperlipidemia (Koro and Meyer 2005). While schizophrenia itself may be associated with a metabolic syndrome, there are a number of other factors including the use of antipsychotic medications that can contribute (Thakore 2005). The effect of these medications in older adults with dementia has not been as well studied. The few RCTs performed assessing the use of atypical antipsychotics in the elderly have been of short duration. This may not have allowed sufficient time for potential metabolic effects of the medications to develop. Yet, in a retrospective cohort study performed specifically in older adults, there was no association demonstrated between the new use of risperidone, olanzapine or quetiapine and the development of diabetes mellitus (Etminan et al 2003).

The potential association between atypical antipsychotics, cerebrovascular events and deaths was first reported among subjects receiving risperidone in a trial evaluating the use of this drug in older adults with dementia published by Brodaty et al (2003). In the risperidone group, 6 cerebrovascular adverse events (CVAEs) were noted while none occurred in the placebo group. All subjects who experienced a cerebrovascular event had other risk factors for stroke including atrial fibrillation, hypertension, prior transient ischemic attacks or strokes. Health Canada and Janssen-Ortho released a statement regarding the possible link between risperidone use and CVAEs based on a meta-analysis of risperidone trials for treatment of older adults with dementia. The FDA issued a similar warning as well. More recently, pooled data from clinical trials evaluating olanzapine have suggested that it may also be associated with an increased risk of CVAEs in patients with BPSD. The UK Committee on Safety of Medicines (CSM) issued a warning advising that risperidone and olanzapine should not be initiated to manage BPSD (Duff & Committee on Safety of Medications 2004). The European Agency for the Evaluation of Medicinal Products (EMEA) has issued warnings about the use of olanzapine in elderly patients with dementia related psychosis or behavioral disturbance (European Agency for the Evaluation of Medicinal Products 2004). Despite the potential link with an increased risk of CVAE in older adults with dementia compared to placebo, a large retrospective cohort study showed similar rates of CVAEs between users of atypical antipsychotics compared to conventional antipsychotics (Gill et al 2005).

Health Canada and the FDA issued public warnings based on their own analysis of data from published and unpublished RCTs showing increased mortality in older adults with dementia receiving atypical antipsychotics (Health Canada 2005a; United States Food and Drug Administration 2005). In their review of 17 RCTs involving risperidone, olanzapine, quetiapine, and aripiprazole, the mortality rate was approximately 1.7 times higher than placebo. The warnings extend to all currently available atypical antipsychotics. A meta-analysis of clinical trials assessing atypical antipsychotics, also showed an increased risk of death in older adults with dementia who were on treatment with an atypical antipsychotic medication compared to placebo (Schneider et al 2005b).

Unfortunately, many of the RCTs evaluating these drugs have not been published. In a meta-analysis by Schneider et al (2005a) 9 of the 15 RCTs included in the meta-analyses had not been published. The odds ratio by meta-analysis in this study was 1.54 (95% CI 1.06–2.23, p = 0.02).

Antipsychotic medications including atypical antipsychotics have the potential to cause fatal reactions like neuroleptic malignant syndrome (NMS). Clinically, NMS manifests as fever, rigidity, confusion, autonomic instability, rhabdomyolysis and renal failure. Prompt recognition, supportive treatment and close monitoring are essential for patients with NMS (Caroff et al 1998; Bhanushali and Tuite 2004).

Summary

Despite the controversy that surrounds the use of atypical antipsychotic agents in older adults with dementia, these medications are frequently being prescribed for the treatment of neuropsychiatric disturbances. If initiation of therapy with antipsychotic medication is considered, it should be only after the potential benefits and risks are assessed. Given the serious concerns about the safety of the use of atypical antipsychotic medications in elderly patients with dementia, the use of non-pharmacological approaches and/or alternative drug treatments which might have a more favorable adverse effect profile should be considered first. While atypical antipsychotic medications may share common pharmacokinetic characteristics, there are enough differences between them to result in different efficacy and tolerability profiles. The final choice of atypical antipsychotic agent should be guided by the nature and severity of the target symptom being treated, and the medication least likely to cause harm to the patient. Whenever possible, these atypical antipsychotic drug treatments should be combined with non-pharmacological treatments to limit the need and dose of antipsychotic drugs. After starting therapy with an atypical antipsychotic, constant monitoring for potential harms should be maintained. Finally, after the target symptoms have stabilized, a trial of tapering and discontinuing the medication should be attempted if possible.

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