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ATYPICAL ANTIPSYCHOTIC USE IN PATIENTS WITH DEMENTIA: MANAGING SAFETY CONCERNS

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Introduction

In the elderly population, the largest number of prescriptions for atypical antipsychotics is written for the neuropsychiatric symptoms (NPS) of dementia (1). NPS (e.g., delusions, depression, agitation) affect up to 97% of people with dementia over the course of their illness (2). No atypical antipsychotic is FDA-approved for the treatment of any NPS in dementia.

The decision to initiate an atypical antipsychotic in the elderly with dementia is not one to be taken lightly. Large scale meta-analyses of clinical trials have consistently demonstrated a 1.5–1.7 times increased risk of mortality with their use in dementia (3,4). All atypical antipsychotics carry a black box warning from the FDA about this risk (5), and a similar warning applies to conventional antipsychotics. Atypical antipsychotics are also linked to a 2–3 fold higher risk of cerebrovascular events (CVAE) (absolute risk of approximately 1%) (6). The 2012 American Geriatric Society (AGS) Beers consensus criteria for safe medication use in the elderly (7) recommend avoiding antipsychotics to treat NPS of dementia due to the increased mortality and CVAE risk “unless nonpharmacological options have failed and patient is threat to self or others”. Additional adverse effects include cardiovascular and metabolic effects, extrapyramidal symptoms, cognitive worsening, infections and falls. In one study of patients in long-term care facilities (8), those taking atypical or conventional antipsychotics were at increased risk for preventable adverse events (adjusted OR= 3.4), and these events occurred most often at the ordering or monitoring stages. Rochon et al (9) found that among community-dwelling adults with dementia, those prescribed an atypical antipsychotic were 3.2 times more likely to be hospitalized or die during the 30 days of follow-up. A similar but less pronounced pattern was noted among those living in a nursing home.

Efficacy data for all atypical antipsychotics show at best modest benefit for NPS in dementia (10,11,12). The CATIE-AD study (13) demonstrated no significant difference between risperidone, olanzapine, quetiapine, or placebo in time to discontinuation for any reason, although risperidone and olanzapine had an advantage over placebo when time to

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discontinuation for lack of efficacy was considered. Analyses of individual symptoms indicated that certain symptoms, such as anger, aggression, and paranoid ideas were more likely to improve (14).

Despite these concerns about safety and limited efficacy, no current evidence exists to confidently recommend alternative psychotropic classes (e.g., antidepressants, anticonvulsants, benzodiazepines) as being either more effective or safer options (15,16), although several expert recommendations are available (for example, Ballard et al. (17)) to treat these symptoms. Notably, evidence for the benefits of psychosocial and behavioral interventions as alternatives is inconclusive (1). When symptoms such as delusions or aggression are severe, they cause significant distress and can place the patient or others at significant safety risk. Use of an atypical antipsychotic is indicated when symptoms are severe and alternative strategies are either not sufficiently beneficial or not indicated (1,7). Safety concerns are reviewed below, followed by recommendations about proper medication selection and close monitoring to minimize the occurrence of adverse outcomes.

Mortality

A community-based cohort study found that both atypical and conventional antipsychotics were associated with higher rates of mortality than most other psychotropic classes with the exception of anticonvulsants (18). This increased mortality risk has been shown to persist over at least 6–12 months (18,19). In one study (20), participants receiving antipsychotic treatment for 12 months had reduced survival rates even at 24-month and 36-month follow-up. Conventional antipsychotics appear to be associated with an as great (18,21), if not greater (22, 23), mortality risk in dementia.

Although use of an atypical antipsychotic in dementia patients increases risk of mortality, the absolute increased risk to a given individual, at least with short term treatment, is likely small (approximately 1–2%) (1,3,4). The precise mechanisms of death remain uncertain. The majority of deaths in clinical trials were due to cardiovascular or infectious diseases. The differential mortality risk among individual atypical antipsychotics remains uncertain. One meta-analysis of 15 placebo-controlled trials of 10–12 week duration (3) found similar mortality rates among participants who received risperidone, olanzapine, quetiapine, or aripiprazole. A more recent retrospective cohort study (16), however, found that among the atypicals risperidone was associated with the highest mortality risk and quetiapine with the lowest, and these differences in mortality risk were strongest in the first 120 days of treatment. Haloperidol was associated with the highest mortality risk of all medications studied, while that for valproic acid was lower than with olanzapine, but higher than with quetiapine.

Cerebrovascular events

In 2003, the FDA warned of an association between risperidone and cerebrovascular events (CVAE), including stroke, in elderly patients with dementia (24). Additional clinical trials of risperidone, olanzapine, and aripiprazole show similar risks (1), and the FDA warning now applies to all atypical neuroleptics. The risk for CVAE appears to be highest during the initial weeks of treatment and may revert to background level after 3 months (25). Atypical and conventional antipsychotics are associated with a similarly increased risk for CVAE (4). Potential mechanisms underlying increased CVAE risk include orthostatic hypotension, thromboembolic effects, dehydration, caused by excessive sedation, hyperprolactinemia, impairing endothelial function, and venous stasis due to sedation and/or extrapyramidal symptoms (1,4,26). Increased CVAE risk may be associated with baseline diabetes, hypertension, and atrial fibrillation, especially when poorly controlled (26), as well as with a diagnosis of vascular dementia or a history of prior cerebrovascular accident (1,27).

Metabolic effects

While atypical antipsychotic use in the general adult population has been linked to metabolic abnormalities (28), the extent to which these abnormalities occur in the elderly population, with or without dementia, is less known. A recent retrospective chart review of elderly nursing home residents found no association between short term use of an atypical antipsychotic and either weight gain or diabetes mellitus (29), and similar outcomes have been demonstrated in nursing home residents with Alzheimer's disease (30). In the CATIE-AD trial (31), however, clinically significant weight gain, increasing over 36 weeks, occurred in participants treated with olanzapine and quetiapine, but not risperidone. The weight gain was clinically significant in women but not men. No atypical antipsychotic appeared to affect blood pressure, glucose or triglycerides.

Extrapyramidal symptoms

Among the atypical antipsychotics, risperidone is associated with the highest incidence of extrapyramidal symptoms (EPS), and quetiapine and clozapine with the lowest (32,33). The Beers Criteria (7) list all antipsychotics except for quetiapine and clozapine as potentially inappropriate to use in the elderly with Parkinson's disease. For this case study patient, who had mild Parkinsonism at baseline, a switch to risperidone resulted in worsening leading to prompt discontinuation. As noted by Trifiro et al., (4) most studies of EPS with atypical antipsychotics have focused on patients with diagnoses other than dementia. In one retrospective cohort study of elderly adults prescribed antipsychotics (34), the risk of Parkinsonism with use of high dose atypical antipsychotics was similar to the risk with use of conventional. A review by Jeste (35) found that atypical antipsychotic use in the elderly is associated with lower risks of tardive dyskinesia, particularly when used in lower doses. However, this lower risk may not extend to patients with dementia. In a retrospective population-based cohort study by Lee (36), the rate of 5.19 cases of tardive dyskinesia or other movement disorders over 100 person-years in patients with dementia was similar to the rate observed for conventional antipsychotics.

Falls

While use of psychotropics in the elderly is associated with increased fall risk, (37), uncertainty remains regarding the relative risk posed by antipsychotics, as opposed to other agents. The Beers Criteria (7) list antipsychotics along with benzodiazepines, anticonvulsants, tricyclic antidepressants and serotonin-specific reuptake blockers (SSRIs) as potentially inappropriate to use in the elderly with prior falls or fractures. A study of fractures in patients over the age of 50 (38) actually found highest risk in patients treated with SSRIs, while the relationship with antipsychotics was not significant. Another study (39), however, found both typical and atypical antipsychotics increased the risk of femur fracture, with highest risks found for risperidone and haloperidol. In a self-controlled case-series comparing periods of antipsychotic exposure to unexposed periods within the same individual (40), the risk of hip fracture with atypical antipsychotics in the elderly was highest in the first week of treatment and then declined, albeit still significantly increased, with longer (>12 week) continuous exposure. With conventional antipsychotic use, the risk was increased one week after beginning treatment and persisted with longer continuous use. The association between antipsychotic use and falls in the dementia population has not been well-studied. One nested case control study (41) did find a small increased risk (OR= 1.26) of hip fracture with antipsychotic use in dementia, with atypical antipsychotics conferring a slightly lower risk than conventional agents. Pre-existing Parkinsonism, as in this case study, may increase fall risk (42). In a recent nested case-control study (42), the use of atypical

antipsychotics in patients with Parkinsonism was associated with an increased fracture rate by as much as 130% compared to risk-set sampling defined controls.

Cognitive worsening

Atypical antipsychotics may worsen cognition in dementia. Although one retrospective chart review comparing outpatients who received atypical antipsychotics for six months or longer to those who did not (43) found no significant difference in rate of cognitive decline, the CATIE-AD study (44), found treatment with an atypical antipsychotic to be associated with cognitive decline over 36 weeks consistent with one year's deterioration compared to placebo. In another randomized, placebo-controlled 26-week trial (45), quetiapine was associated with greater cognitive decline than placebo.

Cardiovascular effects

Due to increased risk of orthostatic hypotension, the Beers Criteria (7) list olanzapine use in the elderly as potentially inappropriate in the setting of syncope. Elderly patients with dementia who receive atypical antipsychotics may also be at increased risk for cardiac arrhythmias. Prolonged QTc intervals can place patients at risk for potentially fatal arrhythmias such as torsades des pointes. Adverse cardiac events do appear to be less common with atypical than conventional antipsychotics (4). Among the atypical agents, QTc prolongation appears to be most common with ziprasidone, followed by quetiapine, risperidone and olanzapine (4). Data regarding risk specifically to the elderly is sparse. One case-control study of nursing home residents (46) found that while use of conventional antipsychotics was associated with increased risk of hospitalization for ventricular arrhythmias and cardiac arrest, no such risk occurred with atypical antipsychotic use.

Pneumonia

The FDA black box warning links atypical antipsychotic use in the elderly with dementia to increased risk of death due to pneumonia. One case-controlled study (47) found a three-fold increased risk of pneumonia with atypical antipsychotic use in the elderly, with highest risk during the first week of treatment. A self-controlled case-series in the elderly (40) found a 70–80% increased risk of pneumonia with >12 week treatment with either atypical or conventional antipsychotics. Potential mechanisms include aspiration, which can be caused by either extrapyramidal side effects or sedation, and dry mouth with subsequent impaired bolus transport (4).

Evidence-based Clinical Management of Neuropsychiatric Symptoms in Dementia

The first step in safe prescribing of an atypical antipsychotic in an elderly patient with dementia is careful consideration as to whether the drug is indeed indicated. This includes a thorough assessment for medical conditions that may be causing or exacerbating the NPS. Pain and infection (especially urinary tract infection) are common causes. Delirium due to polypharmacy, especially psychotropic polypharmacy, is a frequent hazard in the elderly, and a thorough review of the need for and deliriogenic potential of each of the patient's medications is important. Careful physical examination is necessary in most cases to rule out evidence of signs such as abdominal pain, new neurological signs, or acute MMSE decline indicative of a medical cause. Standard laboratory evaluation includes complete blood count, comprehensive metabolic profile, and urinalysis and culture. Suspicion for medical co-morbidity may also prompt referral to the primary care physician for a thorough physical evaluation. The clinician also needs to determine whether factors related to the environment

or caregiver interaction are contributing to the behavior. Inquiry should be made about what non-pharmacological strategies (e.g., reassurance, redirection, increased structure and activities) were attempted. Non-pharmacological interventions are reviewed in detail in Teri and Logsdon (2000) (48) and Cohen-Mansfield (2001) (49).

As outlined by Rabins and Lyketsos (50), the circumstances in which antipsychotic treatment is warranted in dementia are when identifiable risk of harm to the patient or others is present, symptoms are causing significant distress, and non-pharmacological interventions have been unsuccessful. In this case study, all three criteria were met. Expert consultation (e.g., by a psychiatrist or neurologist specializing in dementia) can be helpful in determining whether a trial of an alternative psychotropic class (e.g., antidepressant) may be advisable prior to starting an antipsychotic. Informed consent entails an open discussion with the patient and surrogate decision-maker about the risks and anticipated benefits of treatment. Stroke and mortality risks should be discussed specifically with an opportunity given to answer questions. Alternatives to immediate initiation of an atypical antipsychotic should be reviewed. Available evidence does not support atypical antipsychotics as “mandatory” fist line treatment for most NPS in dementia (1), and a patient’s and surrogate’s choice for no psychotropic intervention or use of a drug from an alternative but potentially safer class, despite even less evidence for efficacy, should be respected.

Conventional antipsychotics may pose an even greater safety risk and should therefore not be offered as potentially “safer” options. The clinician’s choice should be guided by which of the available agents has the least unfavorable adverse effects profile for a given patient. Thus, for a patient with obesity and/or diabetes, olanzapine and quetiapine may be less appropriate choices than risperidone, while the reverse would be true for quetiapine in a patient with parkinsonism. Often, however, patients present with complex medical comorbidity, and a decision needs to be made about which is the “lesser of the two evils.” The Beers Criteria (7) acknowledge the importance of clinician judgment in making prescribing decisions. In this case study, the clinician chose quetiapine for a patient who had multiple metabolic risk factors, but also Parkinsonism. When switching to aripiprazole, and then risperidone, caused intolerable side extrapyramidal symptoms, the decision was made to return to quetiapine, despite only modest efficacy.

Although the association between the dose of an atypical antipsychotic and risk of mortality or stroke remains uncertain, other effects such as sedation and parkinsonism can typically be minimized by starting at the lowest possible doses and titrating slowly when needed. Common target dose ranges in dementia are 0.25–1 mg of risperidone, 2.5–7.5 mg of olanzapine, 12.5–150 mg of quetiapine, and 5–10 mg of aripiprazole.

Given the potential metabolic effects of atypical antipsychotics, baseline chemistry profile, lipid profile, fasting blood glucose, and weight should be assessed. Research suggests that while weight gain occurs with at least some atypical antipsychotics in the elderly population, hyperglycemia and triglyceride elevation are less common. Nevertheless, prudent monitoring of all metabolic parameters is advisable. One expert consensus statement (4) suggests laboratory testing at baseline, 3 months, 6 months, and every six months thereafter. Given the potential for most atypical antipsychotics to increase QTc, obtaining a baseline ECG should be considered, and extra caution should be used in patients with prior cardiovascular history or a baseline borderline or prolonged QTc.

The first follow-up after beginning an antipsychotic should typically take place within one month, and within one week if symptoms are severe or the patient is judged to be at high risk for adverse events. An expert consensus (4) suggests that follow-up visits should occur

at minimum every 3 months. If the patient is not improving within 2–4 weeks, consideration should be given to slow titration of dose or switching to an alternative agent (4).

Research suggests that many patients have only partial remission of the target symptoms. Thus decisions about increasing a dose or switching to an alternative agent should be made based on the degree of distress the symptom is currently causing. The case study illustrates a common scenario in which improvement is only partial, but because symptoms were significantly more manageable and attempts to increase the dose or switch agents resulted in adverse effects, a decision was made to continue with the most tolerated quetiapine dose as partial remission was judged to be an acceptable outcome.

NPS of dementia typically wax and wane (51). In the DART-AD trial (52), among participants with AD who were treated with an antipsychotic for at least 3 months, no significant difference in NPS was found between those who continued treatment and the placebo group. This finding, coupled with the evidence of reduced survival in AD patients treated with neuroleptic for 12 months (18) highlights the need for frequent evaluation of continued need for treatment. In patients who remain relatively asymptomatic on an atypical antipsychotic for 3–6 months, a discontinuation trial should be seriously considered.

Conclusions

Treatment of behavioral symptoms in dementia is especially challenging because, while the symptoms often cause significant distress, no effective alternative medication treatments are available. Efficacy seems best, albeit modest, for atypical antipsychotics, but these must be used with great caution due to risk of adverse events including stroke and death. Before an antipsychotic is started, comprehensive assessment must be performed to rule out a medical etiology, as well as environmental and caregiving factors that could be provoking the targeted behavior. An antipsychotic trial is warranted when non-pharmacological intervention is unsuccessful and behaviors cause significant distress and/or pose a safety risk. Low doses should be used, with slow titration as needed. Patients and surrogate decision-makers should be educated about side effects to observe for, such as fall, Parkinsonism, and sedation. Metabolic parameters should be regularly monitored, although metabolic adverse effects may be of less concern in the elderly. Face-to-face visits are essential to monitor response, tolerance, and the need for continued treatment, and a discontinuation trial should be strongly considered in patients with a 3–6 month history of behavioral stability. Until better treatment options become available, atypical antipsychotics continue to have an important, albeit limited, role in dementia care. Safety risks can be minimized through careful selection of appropriate patients for treatment, education of patients and surrogate decision-makers, and close monitoring, with the understanding that for many patients, short term treatment is sufficient.

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Table 1

Mrs. J is a 78 year-old widowed female with moderate Alzheimer's disease (Mini-Mental State Exam (MMSE) (53)= 13/30), diabetes and hypertension. Over the past six months, she has also developed mild bradykinesia and an asymmetrical bilateral upper extremity tremor, which have been assessed by a neurologist as possibly reflecting early Parkinson's disease. She lives with her daughter, who is also her durable medical power of attorney. The daughter brings her to the psychiatrist because of paranoia and delusions, which have been increasing in intensity over the past month. Most evenings, she believes intruders are trying to enter the house. She repeatedly checks the locks on doors and is awake much of the night pacing. On three occasions, she summoned the police. Her daughter's attempts to reassure and distract her have not been successful. One evening the week prior, when a nephew came to visit, she believed he was an intruder and struck him. No fluctuations in sensorium have been noted, and her MMSE is at recent baseline. Evaluation by her geriatrician (e.g., physical examination, complete blood count, chemistry profile, urinalysis and culture,) for a possible medical etiology of her behavioral change has been unremarkable.

Table 2

Through examination of the patient and discussion with her daughter, the psychiatrist determines that the psychosis is causing the patient severe distress and presents a significant management difficulty at home. The non-pharmacological interventions attempted by her daughter were unsuccessful. The psychiatrist determines that an antipsychotic trial is warranted. After counseling her daughter about the benefits and risks, including metabolic effects, potential to cause and exacerbate Parkinsonism and the FDA warnings regarding use of neuroleptics in the elderly with dementia, a trial of quetiapine at 12.5 mg hs is initiated. The dose is titrated upward over the course of several weeks, and at 50 mg hs, the delusions and sleep are moderately improved. Titration to 100 mg hs, however, results in no further improvement, and the patient's gait becomes unsteady. A switch is made to aripiprazole, titrated up to 7.5 mg hs, but the patient develops increased restlessness, assessed as likely neuroleptic-induced akathisia. With a switch to risperidone, at a dose of 0.25 mg hs, rigidity develops, and the medication is stopped after one day following a fall with no injury. Mrs. J's psychiatrist reviewed the options of either a clozapine trial or resuming quetiapine at the dose that was tolerated, but only moderately beneficial. Her daughter chooses the latter option and at follow-up reports that on this dose and with the addition of a hired caregiver several evenings a week, the psychosis has become more manageable. Metabolic parameters (e.g., weight, fasting glucose, blood pressure), which were assessed at baseline, are monitored, and they remain stable over the ensuing months. Eight months after quetiapine was begun, the delusions persist, but are mild in severity and occur only intermittently. Quetiapine is successfully tapered and discontinued over the course of one month, with no increase in psychosis noted.