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Clinical effectiveness of atypical antipsychotics in elderly patients with psychosis

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Abstract

The elderly represent a unique patient group in the sense that they have a high prevalence of psychotic symptoms that are a manifestation of a variety of psychiatric, neurological and organic disorders. Treatment is complicated by several factors including comorbid diagnoses (psychiatric and medical), polypharmacy, age-related changes in pharmacokinetics and pharmacodynamics and high susceptibility to adverse events. Elderly patients require pharmacological interventions that are effective in reducing symptoms but also are well tolerated, improve everyday functioning, subjective well-being and treatment adherence and reduce family/carer burden. The ability of an antipsychotic to fulfil these requirements determines its clinical effectiveness. To date, few studies have investigated the clinical effectiveness of atypical antipsychotics in elderly patients. However, clear differences exist between the available agents, particularly with regard to tolerability profiles, which have a major impact on the clinical outcome of patients. Clinicians should select an agent that is not only effective in reducing psychotic symptoms but, more importantly, one that has a low incidence of adverse events, such as extrapyramidal symptoms (EPS) and neurocognitive problems, which are of concern in the elderly.

Keywords: Elderly; Psychosis; Antipsychotics; Clinical effectiveness

1. Introduction

The elderly represent one of the fastest growing segments of the population. Indeed, it is estimated that the proportion of the population aged ≥80 years old will almost double in many countries by the year 2020 (World Health Organization, 1998). As a consequence, more elderly patients will be diagnosed with psychoses, increasing the burden on clinicians, carers and society.

Age has a major impact on treatment selections, and the elderly present a number of challenges to the clinician when determining the best possible treatment option. A problem for the clinician is the lack of data that exist for elderly patients with psychosis, particularly with respect to some of the outcome domains of clinical effectiveness, such as subjective well-being, cognitive functioning, carer burden and treatment adherence.

This review will highlight the various issues that impact on the clinical effectiveness of atypical antipsychotics in the elderly. Where available, the data for atypical antipsychotics in each outcome domain will be presented.

2. Diagnostic categories in the elderly

Psychiatric symptoms in the elderly are usually manifested in a variety of disorders such as schizophrenia, major depression, delirium and dementia; neurological conditions such as brain tumours and Parkinson's disease; and medical illnesses and drug-induced psychoses (Table 1). Most new cases of schizophrenia occur in young adults, although 10% of cases occur in patients aged >45 years old. Elderly patients with schizophrenia may be at a greater risk for dementia (Lacro and Jeste, 1997; Targum and Abbott, 1999).

Dementia has a high prevalence in the elderly (being reported in 30% of those aged >85 years old) and can be

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Table 1
Diagnostic categories associated with psychosis in the elderly

Psychiatric disorders	Schizophrenia
	Delirium
	Delusional disorder
	Mood disorder
	Dementia
	Substance abuse (alcohol)
Neurological conditions	Brain tumours
	Parkinson's disease
	Metabolic encephalopathies
Medical illnesses	
Drug-induced psychosis	

attributed to Alzheimer's disease, vascular causes or Lewy body disease (the presence of inclusion bodies in the brain; Targum and Abbott, 1999). The development of Alzheimer's disease may be related to distinct physiological changes that the aging brain undergoes, as shown by neuroimaging studies. For example, reduced volumes of specific areas of the brain have been found in patients with Alzheimer's disease and the rate of atrophy was found to increase with age and was most marked in those aged >70 years old (Scahill et al., 2003). The behavioural signs and symptoms of dementia, such as agitation and aggression, are a particular problem for patients as they are frequently the precipitating reason for psychiatric consultation and can contribute to institutionalisation (Lanctôt et al., 1998; Targum and Abbott, 1999). Some studies have reported rates of behavioural disturbance in up to 70% of patients with Alzheimer's disease (Targum and Abbott, 1999).

Parkinson's disease also has a high prevalence in elderly patients, with up to 40% of patients with the condition experiencing a related psychosis (mostly drug-induced), the incidence of which increases with age (Lacro and Jeste, 1997; Targum and Abbott, 1999). Psychotic symptoms may be a consequence of the medications prescribed for the disorder or emerging dementia. For example, conventional antipsychotics can exacerbate neuromuscular dysfunction and worsen the patient's psychomotor retardation (Targum and Abbott, 1999).

The increased incidence of psychotic symptoms in the elderly, in relation to the general adult population, may be due to factors such as comorbid illnesses, polypharmacy, substance abuse and cognitive changes (Targum and Abbott, 1999). These not only add to the vulnerability for psychosis but also complicate the treatment of symptoms.

3. Issues impacting on clinical effectiveness in the elderly

The studies that aim to determine the efficacy and tolerability of an antipsychotic include carefully selected patient populations that must comply with strict inclusion and exclusion criteria. However, such studies exclude elderly patients who present with comorbid psychiatric or medical disorders and who are taking concurrent medications, i.e., the type of patients seen in clinical practice (Targum and Abbott, 1999). As a result, there is a lack of data on the clinical effectiveness of antipsychotics in the elderly.

Another important consideration is the presence of comorbid illnesses which can mask the primary psychiatric disorder. Symptoms from medical disorders that include delusions and/or hallucinations may meet criteria for delirium (American Psychiatric Association, 1994). Some symptoms (e.g., somatic and visual hallucinations) are more common in the elderly and may have an organic basis which must be excluded. For example, visual hallucinations may be due to poor vision, while auditory hallucinations must be distinguished from tinnitus. Delusions may also be a result of misperceptions due to sensory deficits or cognitive impairment (Targum and Abbott, 1999).

Psychiatric comorbidity is also common in patients with dementia. A retrospective study of 864 patients with a diagnosis of dementia identified two-thirds with a comorbid psychiatric disorder. Patients with dementia and a psychiatric comorbidity have increased medical and psychiatric inpatient days and more psychiatric outpatient visits compared to those without an additional psychiatric diagnosis (Kunik et al., 2003). Studies have also shown that patients with dementia have a higher incidence of comorbid organic illnesses such as diabetes and cardiovascular disease (Leibson et al., 1997; Sanderson et al., 2002).

The presence of a comorbid diagnosis has further implications. Treatment of the comorbid condition means that elderly patients are often on concomitant medications (Masand, 2000). One consequence of polypharmacy is that some drugs (either as a result of drug–drug interactions or dose-related adverse events) can produce psychotic symptoms or disorders such as delirium (Targum and Abbott, 1999). Conversely, agents that are used to treat the primary illness may worsen aspects of a comorbid condition. For example, in Parkinson's disease, dopaminergic agents frequently cause psychotic symptoms, whereas agents that block dopamine worsen mobility and tremor (Masand, 2000).

Thus, the clinician should prescribe an antipsychotic that results in few (if any) drug–drug interactions and avoid those that could further exacerbate psychotic symptoms. Table 2 shows the clinically important drug interactions of some of the atypical antipsychotics. Quetiapine results in few drug–drug interactions, having little interaction with drugs metabolised by the hepatic cytochrome enzymes (DeVane and Nemeroff, 2001). Similarly, there are no problems with the coadministration of quetiapine and psychotropic drugs such as lorazepam (a benzodiazepine), lithium (Potkin et al., 2002c), fluoxetine and imipramine (antidepressants; Potkin et al., 2002b) and haloperidol and risperidone (antipsychotics; Potkin et al., 2002a). Care should be taken when olanzapine or risperidone are coadministered with certain antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) or anti-

Table 2
Principal drug interactions with antipsychotics (Bridler and Umbricht, 2003; Neil et al., 2003)

Antipsychotics	Drug interactions
Quetiapine	Reduced plasma levels with carbamazepine, phenytoin, thioridazine Increased plasma levels with erythromycin, ketoconazole, grapefruit juice, cimetidine, itraconazole, fluconazole Caution is advised with drugs which might increase QT interval Quetiapine may enhance the effects of antihypertensive drugs Quetiapine may antagonise the effects of levodopa and dopamine agonists
Olanzapine	Increased clearance with carbamazepine Bioavailability decreased with activated charcoal Increased plasma levels with ciprofloxacin, fluvoxamine; small increase with fluoxetine Increased risk of seizures with clomipramine Olanzapine may enhance the effects of antihypertensive drugs Olanzapine may antagonise the effects of levodopa and dopamine agonists Coadministration of diazepam or ethanol with olanzapine potentiates orthostatic hypotension observed with olanzapine
Risperidone	Severe EPS with donepezil or phenytoin Reduced plasma levels with carbamazepine; possibility of reduced plasma levels with known enzyme inducers (e.g., rifampin and phenobarbital) Increased plasma levels with quinidine, fluoxetine, paroxetine, perphenazine, thioridazine, levomepromazine Concomitant administration of risperidone and valproate increases peak plasma concentrations of valproate by 20% Risperidone may enhance the effects of antihypertensive drugs Risperidone may antagonise the effects of levodopa and dopamine agonists

biotics, as the increased plasma levels of the antipsychotic can lead to dose-related adverse events such as extrapyramidal symptoms (EPS). On the other hand, in risperidone-treated patients, withdrawal of carbamazepine (associated with reduced risperidone plasma levels) has been shown to result in parkinsonian symptoms (Bridler and Umbricht, 2003), possibly as a result of an increase in plasma levels of the antipsychotic.

In addition to the problems of comorbid illness and polypharmacy, elderly patients are particularly susceptible to the adverse event profiles of antipsychotics, and this should be taken into consideration when selecting the treatment. For example, cardiovascular adverse events of antipsychotic agents include postural hypotension, tachycardia, conduction disturbances and arrhythmias (Maixner et al., 1999). Furthermore, data from large retrospective cohort studies, cross-sectional studies of patients taking different antipsychotics and switch studies of patients changed from one medication to another have consistently shown an increased risk for diabetes in patients treated with clozapine or olanzapine compared with conventional and other atypical antipsychotics (American Diabetes Association, 2004). In addition, the elderly are highly susceptible to EPS including akathisia, tardive dyskinesia and pseudoparkinsonism (Maixner et al., 1999; Masand, 2000). EPS and tardive dyskinesia can contribute to non-adherence, falls, incoherent speech and respiratory stress, as well as psychosocial stigma (Maixner et al., 1999). Furthermore, the rate of tardive dyskinesia in patients aged >50 years old is three to five times greater than among younger adults (Masand, 2000). The conventional antipsychotics (e.g, haloperidol), in particular, are associated with significant EPS and tardive dyskinesia, with EPS occurring in up to 21% of patients with dementia (Lanctôt et al., 1998; Maixner et al., 1999; Neil et al., 2003). The lack of proven treatment for tardive dyskinesia means that it is best to minimise the patient's exposure to antipsychotics that induce these adverse events.

4. Clinical experience with atypical antipsychotics

Antipsychotics are used for treating a variety of psychotic disorders and are increasingly being used for treating the behavioural symptoms of dementia including agitation and aggression (Maixner et al., 1999). The atypical antipsychotics should be considered as first-line treatment for elderly patients with psychosis as they have an improved tolerability profile in comparison with conventional antipsychotics such as haloperidol. Furthermore, reports suggest that several of the atypical antipsychotics may help reduce behavioural symptoms. Most data on the use of atypical agents in the elderly come from studies reporting the drugs' efficacy and tolerability. A small number of studies are beginning to address issues such as the subject's functioning, well-being and treatment adherence. Despite the lack of studies, clear differences exist between the atypical agents, particularly with regard to their tolerability profiles—an important factor for clinical effectiveness in the elderly.

4.1. Symptoms of psychosis

4.1.1. Dementia

There are few studies investigating the atypical antipsychotics in elderly patients with psychosis and fewer studies comparing the atypical and conventional antipsychotics in treating the symptoms of dementia including behavioural disturbances. Those comparative studies that have been conducted have compared an atypical agent with haloperidol and have produced contrasting results.

In a 12-week placebo-controlled study, risperidone resulted in significantly greater reductions in Cohen Mansfield Agitation Inventory (CMAI) total aggression and total nonaggression scores, Behavioural Pathology in Alzheim-

er's Disease (BEHAVE-AD) total and psychotic symptom scores and Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C) scores (Brodaty et al., 2003). These results compare with a 13-week study of risperidone, haloperidol and placebo in 344 nursing home residents with Alzheimer's disease and/or vascular dementia with psychosis (De Deyn et al., 1999). Compared with placebo, risperidone resulted in significant reductions in CGI-S scores, BEHAVE-AD total and aggression cluster scores and CMAI aggression cluster scores at endpoint and week 12. However, there were no significant differences in response rates (30% decrease in the BEHAVE-AD score) between risperidone (54%; mean dose 1.1 mg/day), haloperidol (63%) and placebo (47%; De Deyn et al., 1999). This contrasts with a placebo-controlled study in which risperidone (1 or 2 mg/day) showed a significant response (≥50% decrease in BEHAVE-AD score) compared to placebo (Katz et al., 1999).

Quetiapine has also been compared with haloperidol and placebo and has shown a benefit on some measures of efficacy. A recent 10-week placebo-controlled study in patients with Alzheimer's dementia and psychosis demonstrated that both antipsychotics were superior to placebo in improving Brief Psychiatric Rating Scale (BPRS) total scores and significantly superior to placebo in improving the BPRS agitation factor, while quetiapine was significantly superior to both haloperidol and placebo in improving the BPRS anergia factor (Tariot, P., et al., personal communication). The improvements in efficacy assessments observed with quetiapine in this study are supported by the findings from previous open-label studies in elderly patients. For example, in a long-term (52 weeks) open-label study of 184 patients, psychotic symptoms improved progressively over time with quetiapine treatment, with significant improvements from baseline seen at the first assessment (week 2) and maintained throughout the study (Fig. 1; Tariot et al., 2000). Significant improvements were also observed in the positive and negative symptom clusters

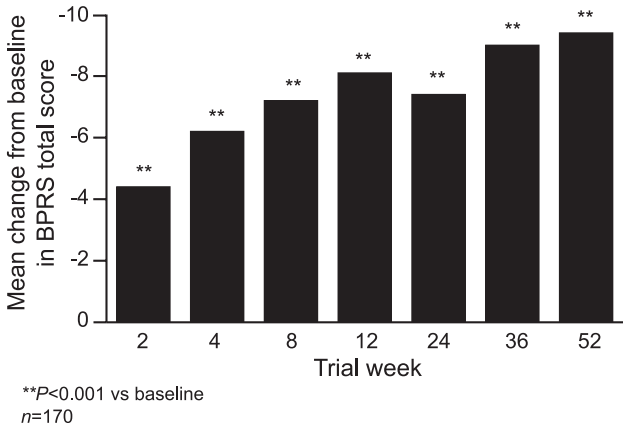

Fig. 1. Mean changes in BPRS total scores at each assessment point in an open-label trial of quetiapine in elderly patients with psychotic disorders (reprinted from Tariot et al. (2000), Copyright 2000, with permission from Excerpta Medica).

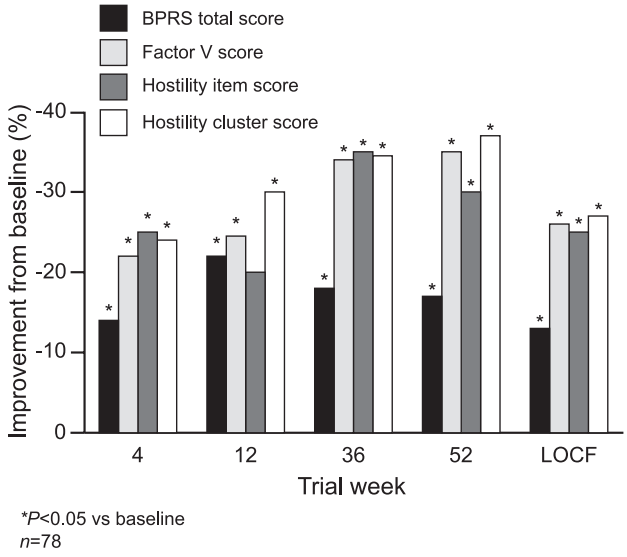

Fig. 2. Mean changes in BPRS total and subscale scores following a 52-week open-label, multicentre trial of quetiapine in elderly patients with Alzheimer's disease and psychosis. Reproduced with kind permission from Schneider et al. (1999).

(Tariot et al., 2000). In addition, in a subset of 78 patients with Alzheimer's disease from this study, quetiapine had a beneficial effect on hostile behaviour (Schneider et al., 1999), assessed using the BPRS factor *V* score (mean of hostility, suspiciousness, uncooperativeness), the BPRS hostility item and a BPRS hostility cluster score (mean of anxiety, tension, hostility, suspiciousness, uncooperativeness). Significant improvements in all assessments were observed from week 4 onwards in patients with Alzheimer's disease (Fig. 2) and those patients who were mildly hostile at baseline (*n*=45; Schneider et al., 1999).

Olanzapine and aripiprazole have also been evaluated in placebo-controlled studies in elderly patients. In these studies, the NeuroPsychiatric Inventory (NPI) was the main assessment scale used in addition to the BPRS. The NPI is based on a structured interview with a carer familiar with the patient's behaviour and evaluates 10 behavioural disturbance domains including delusions, hallucinations, agitation/aggression and irritability (Cummings et al., 1994). In elderly nursing home residents with Alzheimer's disease exhibiting psychosis and/or aggression, patients receiving 5 and 10 mg/day olanzapine had significantly greater improvements on the agitation/aggression, hallucinations and delusions items (core total) of the NPI-Nursing Home (NPI-NH) scale compared to placebo. On the secondary efficacy measures, significant improvements were also recorded in the BPRS total (5 mg/day) and anxiety/depression subscale (5 and 10 mg/day) relative to placebo (Street et al., 2000). These results are in contrast to a previous study involving 238 patients in which low-dose olanzapine (1–8 mg/day) did not differ significantly from placebo relative to efficacy (Satterlee et al., 1995).

Results from a recent placebo-controlled study of aripiprazole in outpatients with Alzheimer's disease were

inconclusive. From baseline to week 6 of the 10-week study, there was little improvement in psychotic symptoms; at week 10, there were no significant differences between the two treatments on the primary outcome, the NPI-psychosis subscale, whereas there was a significant improvement on the BPRS psychosis scale compared to placebo (De Deyn, P.P., et al., personal communication).

Several of the studies described above were conducted in residential care settings. The importance of cognitive functioning in the elderly should not be underestimated, as maintaining a minimal level of cognitive functioning may preclude the need for full-time residential care. Several studies in adult patients have shown that atypical antipsychotics improve cognitive functioning (Meltzer and McGurk, 1999; Sharma, 1999; Velligan et al., 2003), although there are few studies in elderly patients. In a study of elderly patients with schizophrenia or schizoaffective disorder, low doses of risperidone and olanzapine improved cognitive functioning (Harvey et al., 2003). The cognitive effects of quetiapine have been assessed in a 12-week open-label study of elderly outpatients (63–82 years old) with mild or moderate Alzheimer's disease and symptoms of psychosis or aggression (Scharre and Chang, 2002). There were no significant changes in the Alzheimer's Disease Assessment Scale cognitive subscale scores, suggesting that quetiapine does not worsen cognition in the elderly (Scharre and Chang, 2002). Similarly, in a recent open-label study of elderly patients with Parkinson's disease who had failed treatment with clozapine, risperidone or olanzapine, treatment with quetiapine for 24 weeks resulted in significant improvements in recall scores on cognitive measures (Juncos et al., 2004).

4.1.2. Drug-induced psychosis

In addition to the studies in dementia, a number of open-label studies have investigated the use of the atypical antipsychotics risperidone, olanzapine and quetiapine in patients with Parkinson's disease who have drug-induced psychosis (Friedman and Factor, 2000). The results of these studies are summarised in Fig. 3, presented as the percentage of patients whose psychotic symptoms improved or whose motor symptoms worsened following antipsychotic treatment. The atypical antipsychotics were broadly similar, although for quetiapine there was a slight benefit in the improvement of psychosis and a clear benefit in preventing a worsening of Parkinson's disease symptoms (Friedman and Factor, 2000). In addition to these findings, guidelines for the management of Parkinson's disease state that quetiapine should be a first-choice antipsychotic along with clozapine in the treatment of psychosis due to Parkinson's disease (Olanow et al., 2001).

4.2. Tolerability

Elderly patients often receive antipsychotics for the treatment of psychoses with an organic cause so they do not remain on medication for long periods of time, compared to younger patients. Consequently, an antipsychotic that produces minimal adverse events would be the most appropriate treatment.

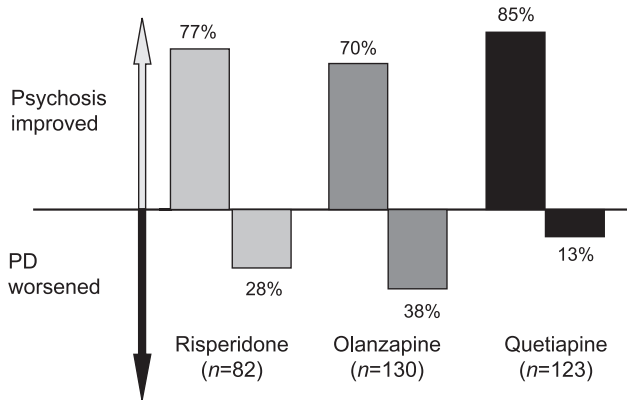

Fig. 3. Percentage of patients with Parkinson's disease and drug-induced psychosis showing improvement in psychosis or worsening of motor symptoms following treatment with risperidone, olanzapine or quetiapine (Friedman and Factor, 2000).

As previously discussed, the elderly are highly susceptible to EPS and related movement disorders. Indeed, early expression of EPS increases the likelihood of developing tardive dyskinesia (Maixner et al., 1999). Both EPS and tardive dyskinesia add to the stigma associated with psychotic disorders, are disfiguring and may hasten the patient's decline in social functioning. Such adverse events are particularly associated with conventional antipsychotics. Indeed, one of the main characteristics that distinguishes the atypical from the conventional antipsychotics is the significantly lower propensity of the atypical agents to cause EPS and tardive dyskinesia (Maixner et al., 1999; Masand, 2000). However, the atypical antipsychotics themselves vary in their ability to cause EPS, and this should be taken into account when selecting the most appropriate treatment.

For example, in a fixed-dose study of risperidone (0.5, 1 and 2 mg/day) in the elderly, dose-dependent increases in EPS were observed. The severity of parkinsonism and hypokinesia (EPS Rating Scale scores) did not differ significantly between patients receiving 0.5 or 1 mg/day risperidone and placebo. However, there was a significant difference between 2 mg/day risperidone compared with placebo ($P<0.001$; Katz et al., 1999). In addition, the incidence and severity of risperidone-induced EPS adverse events, such as acute dystonic reactions, parkinsonism and akathisia, suggest that this agent should not be used in patients with Parkinson's disease (Masand, 2000).

Studies with olanzapine and quetiapine have shown an improved tolerability profile with regard to EPS. A placebo-controlled study of olanzapine has shown that the incidence of spontaneously reported EPS was low, and that such events (including tremor, akathisia and tardive dyskinesia) were not significantly different from placebo (Street et al., 2000). However, caution is warranted with olanzapine, as

some patients with Parkinson's disease do experience a worsening of motor symptoms (Friedman and Factor, 2000), and at least one study with olanzapine has been stopped due to significant worsening of motor symptoms in patients with Parkinson's disease. In contrast, long-term use of quetiapine in elderly patients with psychosis may have a positive effect. In an open-label study of quetiapine administered for 52 weeks in elderly patients with psychosis, EPS, as assessed by mean scores on the Simpson–Angus Scale and Abnormal Involuntary Movement Scale, remained unchanged or improved from baseline during the study (Tariot et al., 2000). Quetiapine is also well tolerated in antipsychotic-naive patients and does not worsen motor symptoms in patients with Parkinson's disease (Friedman and Factor, 2000).

In addition to EPS, all conventional antipsychotics cause an increase in prolactin levels, a problem that is also associated with the atypical agent risperidone. This can potentially lead to a decrease in bone mineral density (BMD) and osteoporosis if associated with oestrogen deficiency, increasing the risk for fractures—a serious cause for concern in the elderly due to the high occurrence of falls in this population (Maixner et al., 1999). Although there are no studies of the effect of atypical antipsychotics on BMD in elderly patients, risperidone treatment results in hyperprolactinaemia and clinically relevant decreases in BMD in premenopausal women when accompanied by amenorrhoea (oestrogen deficiency; Becker et al., 2003).

An adverse event of concern in the elderly is sedation. Some studies of risperidone, particularly at higher doses, have reported sedation and somnolence as a transient adverse event, while clozapine and olanzapine are associated with high rates of sedation (Masand, 2000). A long-term study with quetiapine found that sedation occurred early during treatment but was transient (Tariot et al., 2000).

The risk of falls in elderly patients is significantly increased by some adverse events of atypical antipsychotics, including disturbance of gait, confusion, EPS and orthostatic hypotension, as well as sedation (Masand, 2003). Studies have shown that risperidone was not significantly different from placebo in the rate of falls. Furthermore, risperidone was associated with a significantly lower risk of falls than olanzapine, which is consistent with the higher rate of sedation and gait disturbance with olanzapine (Masand, 2003).

The incidence of cerebrovascular adverse events with risperidone 2 mg/day in a recent study of nursing home residents led to a reanalysis of results from four placebo-controlled trials of risperidone in dementia (Masand, 2003). Patients treated with risperidone reported twice as many cerebrovascular adverse events as those treated with placebo (4% vs. 2%), resulting in an update of the safety information warning for risperidone of a possible higher incidence of stroke in the elderly with dementia (Masand, 2003), although the death rates were no higher than those seen in the olanzapine trials. One caveat was that the trials with risperidone included patients with Alzheimer's dementia, vascular dementia and mixed dementia with preexisting risk factors for cerebrovascular adverse events, while the studies of other atypical antipsychotics have only included patients with Alzheimer's dementia (Masand, 2003).

In addition, cerebrovascular adverse events, including fatalities, have been reported in trials of olanzapine in elderly patients with dementia-related psychosis. In five double-blind, placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events and deaths in patients treated with olanzapine (1.3%) compared to those receiving placebo (0.4%; Wooltorton, 2004). Only two of the five studies have been published in full (De Deyn et al., 2004; Street et al., 2000).

4.3. Everyday functioning and subjective well-being

There are few studies in elderly patients investigating how antipsychotic intervention can impact on patient functioning and subjective well-being. A possible reason for this may be the assumption that elderly patients are not expected to experience a high level of functioning and a good quality of life. However, improving the neuropsychiatric and behavioural symptoms of patients is likely to improve their quality of life. Another factor affecting the evaluation of quality of life is that the measurement scales used have generally only been validated in younger adults.

Some investigators have assessed daily and social functioning in middle-aged and elderly patients with schizophrenia or schizoaffective disorder compared to control subjects (Patterson et al., 1998; Patterson et al., 2001). Using the Direct Assessment Functional Status, patients with schizophrenia had significantly greater disability than control subjects on time orientation, communication, finance and shopping measures. Greater severity of EPS and cognitive deficit were related to lower functioning scores (Patterson et al., 1998). In a separate study that used the Social Skills Performance Assessment, patients with schizophrenia were significantly more disabled in all areas of social functioning, and this was related to the severity of negative symptoms and cognitive deficit (Patterson et al., 2001).

Results from one study suggested that certain antipsychotics may have a detrimental impact on the quality of life of patients with dementia (Ballard et al., 2001). This observational evaluation of quality of life indicated that 20% of those taking conventional antipsychotics, 10% of those taking risperidone but only 5% of those not taking antipsychotics had a poor quality of life. The investigators concluded that this finding may be a consequence of the impact of adverse events on quality of life (Ballard et al., 2001).

A separate study assessed the effect of switching elderly patients with schizophrenia from conventional antipsychotics to olanzapine or risperidone. Olanzapine was statistically significantly superior to risperidone on improvements to the physical, psychological and health satisfaction

domains of the World Health Organization Quality of Life (brief) scale (Ritchie et al., 2003).

4.4. Family/carer burden

The burden experienced by the carers of patients with Alzheimer's disease and Parkinson's disease reduces their health-related quality of life, which, in turn, reduces the ability of the patients to manage their disease and worsens their outcome (Bell et al., 2001). A number of patient-related factors contribute to the burden experienced by carers, including functional impairment, cognitive impairment, depression, agitation, aberrant motor behaviour and delusions (Aarsland et al., 1999), in addition to the carer-related factors such as closer kinship to the patient and the presence of depressive symptoms (Annerstedt et al., 2000).

The relationship between reduction of psychotic symptoms in patients and level of carer burden has not been studied with the atypical antipsychotics. However, the ability of the atypical antipsychotics, such as quetiapine, to reduce psychotic symptoms, as well as being well tolerated, suggests that this agent may also help to relieve carer burden.

4.5. Treatment adherence

Studies have shown that treatment with atypical antipsychotics resulted in improved adherence in adult patients with schizophrenia or bipolar disorder; however, there are few studies in elderly patients. Two recent evaluations in middle-aged and older patients with schizophrenia or schizoaffective disorder have used the Medication Management Ability Assessment, a performance-based measure of medication management, to assess treatment adherence (Jeste et al., 2003; Patterson et al., 2002). Significantly more patients were classified as non-adherent compared to control subjects, which was related to the extent of cognitive deficit, particularly conceptualisation and memory (Jeste et al., 2003; Patterson et al., 2002).

5. Dosing to maximise the clinical effectiveness of atypical antipsychotics

The availability of atypical antipsychotics provides the clinician with a means to control symptoms of psychoses in elderly patients, so selecting the most appropriate dose is essential to achieve the optimal outcome. However, there are several factors that impact on the dose that should be administered.

Age-related changes to pharmacokinetics and pharmacodynamics should be taken into account when prescribing any medication to the elderly. For example, the elderly often exhibit reduced renal clearance and reduced hepatic metabolism which can adversely influence the efficacy of treatment (Gareri et al., 2003; Gregory and McKenna, 1994; Masand, 2000). In addition, changes in pharmacodynamics may lead to adverse events with doses that are therapeutic in younger adults. Increases in total body fat mean that fat-soluble drugs, including antipsychotics, distribute more widely and may take longer to clear (Gareri et al., 2003; Maixner et al., 1999). Age-related changes in body composition also occur, such as decreased lean muscle mass, total body matter, liver mass, hepatic blood flow, serum albumin levels and renal blood flow, and these will affect the dose that should be used (Gareri et al., 2003; Maixner et al., 1999).

These factors mean that elderly patients often have higher plasma concentrations of the drug and its metabolites. Consequently, the general rule when administering antipsychotics in the elderly is to "start low and go slow." Starting with a low dose followed by gradual increases will allow the most effective plasma concentration to be reached while minimising the occurrence of adverse events due to accumulation of the agent (Gareri et al., 2003). Indeed, the oral clearance of one of the atypical antipsychotics, quetiapine, is reduced by 30–50% in the elderly (Wong et al., 1997), suggesting that the clinically effective dose for elderly patients may be 50% lower than that for younger patients. Similarly, the clearance of the atypical agents olanzapine and risperidone is reduced, suggesting that reduced doses should be administered to elderly patients.

Consequently, patients must be treated and the doses administered on an individual basis. It is important to note that for elderly patients with dementia, the dosing of antipsychotics is generally lower than for other psychotic disorders. This is particularly true for olanzapine and risperidone as lower doses are necessary to reduce the risk of EPS (Lalonde, 2003). Quetiapine can be administered at doses of 100–300 mg/day; higher doses have been tolerated in some patients with psychosis or behavioural symptoms related to Alzheimer's dementia, while Lewy body dementia usually requires a low dose. Patients with Parkinson's disease require lower doses of antipsychotics, particularly as some patients experience a worsening of symptoms with some agents (Friedman and Factor, 2000). Quetiapine can be administered at doses of 50–75 mg/day in these patients. By being aware of the issues that impact on the dosing of antipsychotics, clinicians will be able to optimise patient outcome without producing harmful adverse events, thus ensuring that clinical effectiveness is achieved.

6. Conclusions

Although data are accumulating to demonstrate the improved efficacy and tolerability of various antipsychotics, including atypical agents, in elderly patients with psychosis, there is a clear need for further studies investigating the various domains of clinical effectiveness in this unique patient population. There is also a necessity for quality of life measures more applicable to the elderly and for such

measures to be verified in the clinical setting. Additional studies should focus on patient satisfaction with treatment and the impact of treatment on social and interpersonal functioning. Although research frequently focuses on the needs of the patient, studies often overlook the needs of carers. Carers play an important role in patient outcome and experience considerable burden which impacts on their ability to help patients. Thus, effective management of patient symptoms not only improves outcomes for the patient but also has the potential to reduce the burden of the carer. Studies investigating the impact of atypical antipsychotics in this regard are warranted.

Elderly patients are more vulnerable to adverse events of medication than younger adults. Choosing an agent that is well tolerated, with little potential to cause debilitating adverse events, is of equal, if not greater, importance than the efficacy of the agent in reducing symptoms. The atypical agent quetiapine has demonstrated efficacy in the treatment of psychosis and, more importantly, has a low incidence of EPS and other potentially debilitating adverse events, suggesting that this agent is a first-line atypical antipsychotic for use in elderly patients. Optimal dosing of the chosen agent on an individual basis will ensure that the clinical effectiveness of the drug is maximised and improve the outcome for patients.

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