

Editors: **Michael Woodward**, Director, Aged and Residential Care Services, **Stephen Campbell**, Consultant Geriatrician, **Rohan Elliott**, Clinical Pharmacist, **Graeme Vernon**, Drug Information Pharmacist, **Francine Tanner**, Clinical Pharmacist, Austin Health; **Robyn Saunders**, Consultant Pharmacist, Victoria.

Psychotropic Medication Use in Older People

Malcolm J Hopwood

ABSTRACT

Older people have high rates of mental health disorders such as mood and anxiety disorders, bipolar affective disorder, psychotic disorders, and dementia. All of these disorders are associated with significant morbidity and mortality and have been historically under-recognised and under-treated. Recent advances in psychopharmacology have brought great benefit to many young patients with these conditions where they are supported by a clear evidence base. To date, this evidence base has been incompletely developed for older people leaving the prescriber with many difficult decisions. There is moderate and growing evidence supporting the use of antidepressants in this population. The use of mood stabilisers and antipsychotics for indications other than the behavioural and psychological symptoms of dementia currently occurs in the absence of effective evidence. *J Pharm Pract Res* 2007; 37: 153-6.

INTRODUCTION

Mental health disorders are a leading cause of disability in older people in our population. They also contribute to increased mortality, either directly via suicide or indirectly by contributing to poor control of comorbid physical health conditions.

Management of mental health disorders in older people continues to be initially dependent upon the individual presenting to a health professional and that professional making an accurate diagnosis. The professional requires the ability to elicit symptoms and signs of mental health disorder and then use this information to make an appropriate hierarchical diagnosis. The reliability of mental health diagnosis has improved considerably over recent decades with the introduction of standardised diagnostic systems such as the American Psychiatric Association's DSM-IV. Clinicians need to be aware of these diagnostic systems as most of the available evidence relating to the use of mental health interventions is based on samples defined using these standard diagnostic criteria. It is also important to acknowledge the clinical axiom that mental health disorders are more likely to be comorbid with another mental health condition. For example, diagnostic evaluation of any elderly patient presenting with depression should involve careful searching for common comorbid diagnoses such as dementia, anxiety, substance abuse or the possibility that this episode is part of a bipolar disorder.

Together with psychological, social and environmental interventions, psychotropic drugs continue to form an important part of the treatment of mental health disorders in the elderly. Available evidence suggests that the rates of use of psychotropic drugs in older people are high, particularly for those in residential care settings.¹ The evidence also suggests that there are examples where the targeting and review of this treatment is of unclear quality. This is of concern given the well documented increased potential for adverse effects with most psychotropic

drugs when used in older people. Age-related changes in adiposity, renal clearance, hepatic mass and blood flow, all have the capacity to influence pharmacokinetics significantly, leading to potential toxicity-related adverse effects of psychotropic drugs.² In their examination of changes in hepatic cytochrome P450 subsystems (primary site of initial metabolism of the majority of psychotropic drugs) in older people, Pollock et al. described how the range of enzymatic activity increased with age, likely broadening the effective dose range for any given drug. However, if this variation is not clinically predictable, the risk of inappropriate dosing is heightened.³ The important issue of drug-drug interactions adds to the complexity. The elderly are often on many medications for a range of conditions.

These issues strongly support the need for a clear, evidence-based approach to psychopharmacology in older people. This evidence base would enable informed choice of drug for any set of individual symptoms and comorbidities. In this review the focus will be on available data on the use of psychotropic drugs specifically in older populations. The primary focus will be on data relating to the use of the major groups of psychotropic drugs—antidepressants, mood stabilisers and antipsychotics in the treatment of the major psychiatric conditions—depression, behavioural and psychological symptoms of dementia (BPSD), anxiety disorders, bipolar disorder and schizophrenia in the elderly.

ANTIDEPRESSANTS

Antidepressants remain the treatment of choice for mood disorders in older people including major depression, dysthymia or minor depression, and depression secondary to medical conditions such as stroke or idiopathic Parkinson disease.⁴⁻⁶ Antidepressants may also be used to treat depression in association with psychoses such as schizophrenia, prolonged or severe depressive phases of bipolar affective disorder, and mood symptoms seen with dementias such as Alzheimer's disease. Of growing relevance is the recognition of the role of antidepressants in the treatment of anxiety disorders.

The cross-sectional prevalence of major depression in those over 60 years has been estimated at 2 to 5%, with the rate increasing considerably in those with comorbid physical illness.⁷⁻⁹ Major depression in older people is clearly associated with increased health care use and burden, in addition to the increased morbidity and mortality mentioned above.¹⁰ Minor depression may be a more common disorder, with lesser but significant levels of associated morbidity and burden.^{11,12}

A wide range of antidepressants are available in Australia. All drugs registered for the indication of major depression are implicitly registered for the treatment of major depression in older people, seemingly independent of whether specific efficacy data are available for that drug in older people. It is hoped that this gap will be diminished by the recent policy of the European regulatory authorities to encourage pre-registration trials of new drugs in older people by facilitating early consideration of applications that include such data in a general application. This complements the policy of the US Food and Drug Administration to similarly support applications containing paediatric data.

Malcolm J Hopwood, MD, FRANZCP, Director, Veterans' Psychiatry Unit, Director, Brain Disorders Program, Austin Health, Heidelberg West, Victoria
Address for correspondence: Associate Professor Malcolm Hopwood, Veterans Psychiatry Unit, Austin Health, Heidelberg West Vic. 3081, Australia
 E-mail: malcolm.hopwood@austin.org.au

A meta-analysis of all available placebo-controlled trials on the treatment of major depression in older people suggests an overall response rate of 60 to 70%, with placebo response rates of 30%.¹³ This rate is comparable to that seen in young adults with major depression. Similar response rates have also been observed in trials examining the response of older people with minor depression to antidepressants.⁶ There is a trend in this evidence to suggest that time to response may be longer in older patients.^{14,15} It should be noted that this observation could be artefactual, resulting from trial design in older people involving low starting doses and slow rates of dose escalation.

Active comparator trials offer the opportunity to examine differences between antidepressants in terms of efficacy and adverse effect profile. The number of trials available of this nature is limited, with the largest number relating to comparisons between tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). In a recent meta-analysis no difference was found between TCAs, SSRIs and other drugs for which comparator data were available (predominantly the monoamine oxidase inhibitors, venlafaxine, mirtazapine) in overall efficacy.¹⁶ However, there were significant differences between the groups in overall dropout rates during trials with dropouts significantly more likely in those receiving TCAs (OR vs SSRIs RR 1.24, 95% CI 1.05–1.46). This meta-analysis revealed a predictable pattern of side effects, with anticholinergic adverse effects most common with the TCAs, and gastrointestinal adverse effects most common with the SSRIs. It should be noted that the relatively small size of the data set would not show up uncommon side effects that may be specific to or more common in older people. It would also not show up the issue of potential lethality in overdose, which is clearly a more significant issue with the TCAs. Of some concern is evidence suggesting an association of both the TCAs and SSRIs with an increased risk of falls in older people.¹⁷ A range of issues may contribute to this association, including the risk associated with the mental health problem under treatment.

The clinical implications of these findings can be summarised as supporting the role of antidepressants as efficacious treatment for major and, probably minor, depression in older people. Given the relative vulnerability of older patients to adverse effects, the favourable adverse effect profile of newer drugs such as the SSRIs means that they should probably be seen as the treatment of initial choice.⁷

Another area for clinical consideration is the role of antidepressants in the treatment of anxiety disorders in older people. Along with the development of specific psychotherapies such as cognitive behavioural therapy, the use of antidepressants in the treatment of anxiety disorders such as generalised anxiety disorder, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder and social anxiety disorder in adults is now associated with a large evidence base and a major reduction in the suffering of many individuals. Sadly, the level of investigation of the epidemiology of anxiety disorders in older people is significantly less than in younger adults. There is a clinical suspicion that they are significantly under-diagnosed in older people. The limited available pharmacotherapeutic treatment data suggest that the antidepressants are also effective for treatment of anxiety disorders in older people.^{18,19} Further, this body of evidence tends to support the conclusion that the newer drugs, particularly the SSRIs are the treatment of choice for most anxiety disorders in older people.²⁰ This area is hopefully one of significant future evaluation through rigorous trials.

Of equal significance to the emergence of the use of antidepressants for anxiety disorders is the corresponding reduction in the use of anxiolytics such as the benzodiazepines

for this set of indications. This change has been of such significance that there is no new data on the use of anxiolytics in older people available in the last decade. This may not yet be reflected in decreased overall prescription rates for benzodiazepines given the widespread use of these drugs in older people for other indications, such as sleep difficulties.

MOOD STABILISERS

Mood stabilisers currently in use in Australia include lithium, and the antiepileptics valproate and carbamazepine. Lamotrigine, another antiepileptic is associated with a considerable body of evidence suggesting efficacy in bipolar affective disorder but is not registered for this indication in Australia. A number of other drugs are currently under investigation. Recently, a number of the atypical antipsychotics have also gained the indication for treatment of acute episodes of bipolar disorder and in the case of olanzapine maintenance treatment of bipolar disorder. Controversy persists over the role of antidepressants in the treatment of depressive phases of bipolar affective disorder; recent data mainly obtained from adult populations showed no benefit in their addition to standard mood stabiliser treatment.²¹

Mood stabilisers are used primarily in the treatment of bipolar disorder but are also used frequently in the treatment of refractory unipolar major depression, schizoaffective disorder and in the management of impulsivity associated with conditions such as acquired brain injury.

Bipolar disorder has a prevalence rate of 1 to 2%, but it is reported that 10% of all patients develop it after the age of 50 years. Further, bipolar disorder accounts for 5 to 19% of all mood disorder presentations in older people and an estimated 5% of inpatient psychiatric admissions for older patients.^{22,23} Bipolar disorder in younger populations is associated with high levels of disability and is frequently quoted as the psychiatric disorder associated with the highest rate of suicide, with most estimates of the lifetime risk between 12 and 20%.

Given the above it is extremely disappointing that there are essentially no well designed trials that specifically examine efficacy and tolerability of the mood stabilisers in older people with bipolar disorder. Data extrapolated from those studies involving mixed-aged subjects, case reports and clinical experience suggest that these drugs may have equivalent efficacy in the older group to that seen in younger patients, but that conclusion can only be viewed as presumptive. In young patients, lithium is considered the gold standard for efficacy in the treatment of bipolar disorder. Lithium's narrow therapeutic index along with the influence of age-related deterioration in renal excretion of lithium, make the drug more complex to use in older patients. This may be successfully managed with the use of dosages lower (and serum levels) than in younger patients, together with more frequent monitoring of serum levels. Patients and their carers also require very clear and repeated information about the common drug-drug interactions associated with lithium. The most important of these interactions are with drugs that increase the renal excretion of lithium and thus can produce toxicity. Such interactions can occur with diuretics (especially the thiazides), non-steroidal anti-inflammatory drugs, ACE inhibitors and metronidazole.

Sodium valproate would now be the other most widely used mood stabiliser for bipolar disorder in some adult services, but there is little specific evidence about its use in elderly patients at this time. While serum level monitoring may be of less value in determining efficacy than is the case for lithium, it remains a useful guide in relation to toxicity and compliance.

ANTIPSYCHOTICS

Antipsychotics available in Australia are broadly divided into older typical antipsychotics and atypical antipsychotics. The definition of atypicality is hotly debated but the essential characteristic is the reduced risk of acute and chronic movement disorders in comparison with the typical antipsychotics.²⁴ This difference is thought to relate to the centrality of the D2 receptor blockade to the action of the typical antipsychotics.²⁵ Because of their relatively favourable adverse effect profile, atypical antipsychotics have rapidly become the treatment of choice in most situations, but recent evidence of possible specific adverse effects in older people have thrown this into some doubt. Antipsychotics are used for the treatment of psychotic disorders such as schizophrenia, schizoaffective disorder, and severe bipolar affective disorder. Of great relevance, they are also used at times for the management of BPSD.

Recent interest in the use of antipsychotics in the elderly has focused on their use in individuals with dementia.²⁶ Five per cent of people over the age of 65 years and 20% of those over the age of 80 years have dementia, with more than 50% of those diagnosed as suffering from BPSD. BPSD are clearly distressing for the patient, their carers and are often significantly predictive for the need for nursing home placement.²⁷⁻²⁹

Several studies have highlighted the efficacy of oral atypical antipsychotics, risperidone and olanzapine in the treatment of BPSD.³⁰⁻³⁵ Risperidone is currently the only drug listed and funded for this indication in Australia. A recent meta-analysis has addressed the issue of a possible increase in mortality associated with the use of these drugs in the elderly with dementia, mainly related to possible stroke-like events.³⁶ A recent Cochrane review concluded that while there was evidence of efficacy, particularly for risperidone, the risks were significant.³⁷ At a clinical level this would suggest that the use of atypical antipsychotics is best reserved for patients with more severe BPSD, particularly those with clear psychotic symptoms, severe agitation or impulsive aggression resulting in a clear risk to the safety of the patient or others. This complex area is reviewed in detail in several of the articles.³⁸

By contrast, the level of investigation into the use of antipsychotics in the treatment of schizophrenia in older people is limited.³⁷ Schizophrenia is a relatively common mental health disorder with a lifetime incidence of approximately 1%. It is estimated that the prevalence in individuals aged over 65 is 1 to 10 per 1000, with up to 12% of all nursing home residents suffering from schizophrenia. The severe disability and mortality associated with schizophrenia is well acknowledged. However, a recent meta-analysis of studies examining the efficacy and tolerability of atypical antipsychotics in older people with schizophrenia revealed only three small short-term trials.³⁹ The authors noted that no significant conclusions could be drawn and that further studies were urgently needed. This clearly leaves the clinician treating the older patient with schizophrenia in a difficult position, armed with information suggesting efficacy of the atypical psychotics with a favourable adverse effect profile in young patients with schizophrenia, but at the same time awareness of the information from patients with BPSD suggesting significant risk. Clinically, there remains little doubt that elderly patients with schizophrenia require ongoing antipsychotic treatment, as the risk of relapse remains high. It also appears true clinically that overall the adverse effect profile of the atypical psychotics is better than that of the older drugs in this situation, but there is essentially no current evidence to clearly back up this conclusion. It is also clinically noticeable that while the recommendation from the manufacturers of most atypical antipsychotics is that lower doses are often required in

the elderly, in the treatment of schizophrenia specifically in the elderly, doses required for optimal efficacy may be in the same range as those used in younger adults.

CONCLUSION

While it is indisputably true that mental health disorders remain a major cause of disability and mortality throughout the life cycle, evidence on the use of psychopharmacological interventions in the elderly with mental health issues remains patchy at best. The clinician is frequently required to interpret data from studies involving subjects of younger age and assume that the conclusions are valid in older people. Clear theoretical reasons exist to believe this may not be true, and in the case of atypical antipsychotics, some reasons to be particularly concerned that the situation may be very different. Further research is desperately needed, particularly in the use of mood stabilisers and antipsychotics for issues other than BPSD in the elderly. Only when this research is available will the clinician be in an adequate position to provide effective, evidence-based care.

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