Practice Debate

Practice debate is an occasional series when we pick up an area of therapeutic controversy and invite questions and feedback. It is often an area which would benefit from the development of national consensus and practice guidance.
In general these articles are short and to the point but references and further readings are provided in the bibliography.

Comments and questions are invited from GPs, specialists and pharmacists and these will be collated and followed up in a future edition of best practice journal. We are particularly interested in your practical recommendations and experience.

Send your response to ***editor@bpac.org.nz***

What is the role of antipsychotics in the treatment of behavioural and psychological symptoms of dementia?

What are the safety concerns?

Background

Conventional antipsychotics (e.g. haloperidol) and atypical antipsychotics (e.g. risperidone) are widely used to treat some of the non-cognitive symptoms of dementia.
Over the last four years regulatory authorities in several countries have raised concerns about an apparent increased rate of cerebrovascular events and death associated with atypical antipsychotics (risperidone and olanzapine) in dementia trials. In the UK and USA this has led to advice against using these for the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD) but in New Zealand risperidone remains approved for this indication. Although safety concerns surround the use of the atypicals there is no clear evidence that conventional agents are safer. All antipsychotics are associated with significant risks of adverse effects in this population.

What is the role of antipsychotics in the treatment of BPSD?

In general antipsychotics are only indicated for symptoms that are associated with psychotic type features or aggression and potential for harm. They are not generally recommended or effective for treating wandering, restlessness, fidgeting, poor self care, anxiety, insomnia and agitation that is not a danger to self and others.

Expert Review: Dr Ian Hosford, Consultant Psychogeriatrician - Hawkes Bay DHB and Marilyn Tucker, Clinical Pharmacist - Wellington IPA and Karori PHO.

Haloperidol (recommended starting dose 0.25 mg daily) is the most widely assessed conventional antipsychotic drug and it appears particularly useful in the control of aggression. Adverse effects such as extrapyramidal symptoms (EPS), sedation and increased confusion can be problematic. Conventional antipsychotics in particular may give rise to tardive dyskinesia with prolonged use and this population is especially prone to this effect.

The atypical antipsychotics risperidone and olanzapine are useful in the management of aggression and psychoses associated with dementia and usually cause fewer EPS than conventional agents. Olanzapine is associated with abnormal gait and all antipsychotics may increase the risk of falls.

Do antipsychotic drugs increase the risk of cerebrovascular adverse events in people with dementia?

Pooled results of a number of published and unpublished randomised placebo controlled trials in dementia patients have indicated an increased risk of cerebrovascular adverse events (CVAE) with risperidone and olanzapine.[1] With risperidone a sub-analysis found no increase in serious events (defined as death from stroke or hospitalisations) and the pooled results of the olanzapine studies showed the overall risk of CVAE was not significantly different compared to placebo. Some publications have combined the results of the olanzapine and risperidone trials but this is flawed as the patient populations were significantly different. Other methodological problems cast some doubt on the validity of the conclusions, not least that these trials were not initially designed to look for CVAE. Patients may also have been at high baseline risk of CVAE; for example in the risperidone studies there was an over representation of subjects with vascular dementia who would be more at risk for CVAE. Furthermore recent observational studies have not confirmed the findings of the randomised controlled trials (RCTs).

Finally, there is no clear evidence that atypical antipsychotics pose a higher risk of CVAE than conventional agents, in patients with dementia.

In New Zealand the Medicines Adverse Reaction Committee (MARC) has assessed the evidence so far and supports the continued availability of risperidone for use in patients with dementia. Olanzapine and Quetiapine are not approved for the treatment of BPSD in New Zealand but appear to be used in practice.

Do antipsychotics increase the risk of all cause mortality in patients with dementia?

An analysis by the U.S. Food and Drug Administration (FDA) of 17 placebo controlled trials of atypical antipsychotics showed a mortality rate of 4.5% which was almost twice that of placebo treated patients. Death was mainly due to cardiovascular problems and infections such as pneumonia.[2] The authors of a more recent meta-analysis of RCTs estimated a number needed to harm (NNH) of 100 – that is one extra death for every 100 patients treated with a atypical antipsychotics for 10 – 12 weeks.[3]

In contrast to RCT data, four observational studies have shown no increase in the risk of death associated with atypical antipsychotic treatment and the results also suggest that they may be associated with a lower death rate than conventional drugs. There are no head-to-head RCT comparisons between atypical and conventional antipsychotics.

In summary, although not supported by observational studies, the results of the RCTs cannot be discounted and warnings of a possible increased mortality risk are mentioned in the New Zealand product information for risperidone and olanzapine. The FDA report indicated a class effect so this warning should also apply to quetiapine which appears to be widely used for BPSD although not approved (as per drug data sheet) for this indication.

Practical conclusions: antipsychotics in the treatment of BPSD

Both conventional and atypical agents may be effective in patients with BPSD who have psychotic type features, aggression or potential for harm. There is no clear evidence that atypical antipsychotics are more likely to cause CVAE than conventional antipsychotics. The increased death rate from RCTs with atypical agents is of concern but there is no evidence that conventional drugs are any less likely to cause events. It seems likely that all antipsychotics are associated with an increase in CVAE and possible mortality in patients with dementia. This is perhaps not surprising due to their range of adverse effects, including effects on the cardiovascular system, and the underlying fragility and comorbidities of the target population. The choice of agent is largely determined by the respective adverse reaction profiles of each drug class and clinical experience of response.

- Before considering drug therapy try non-pharmacological measures first. These include environmental modification, diversion techniques, caregiver education and therapeutic activity programmes.
- Avoid any antipsychotic for mild to moderate non-cognitive symptoms associated with dementia.
- Avoid antipsychotics in patients with DLB (Dementia with Lewy bodies) because of the risk of severe adverse reactions.
- In severe BPSD only prescribe antipsychotics if there is a clear indication and if non-drug options have been tried first. Where possible avoid antipsychotics in patients with a history of CVAE or at high risk of CVAE.
- Use the lowest possible dose and if possible down titrate after initial control of symptoms.
- Regularly review the need for ongoing treatment with an antipsychotic.
- Antipsychotics may cause excessive sedation and confusion which may cause morbidity such as falls.
- Antipsychotics have many potential drug interactions which may also increase the risk of adverse events.
- If symptoms worsen after starting one of these agents consider the medicine as a potential cause.

References and Bibliography

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