



The Use of Antipsychotics in the Management of Delirium in Palliative Care

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Summary

- In the management of delirium, non-pharmacological measures and environmental support are recommended first line.
- An initial delirium screen is recommended to identify treatable underlying precipitating factors (e.g. pain, infection, constipation, dehydration, hypercalcaemia, medication).
- Drug toxicity accounts for approximately 30% of all cases of delirium. A review of medication is an important initial step in the management of delirium.
- There is very limited research on the use of antipsychotics in the management of delirium.
- The use of antipsychotics in the management of delirium should be assessed on an individual patient basis. In the palliative care setting, the degree of patient and family distress, as well as the goals of care, may justify the use of antipsychotics.
- Haloperidol is the most studied antipsychotic used in the management of delirium.
- There is a lack of evidence to support other treatment options. Benzodiazepines have a limited role in the treatment of delirium. They are primarily indicated in cases of sedative and/or alcohol withdrawal or when antipsychotics are contraindicated.

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Background

Delirium is a complex neurological condition which is characterised by a disturbance of awareness and cognition developing suddenly over a short period of time¹. Prevalence in patients with end of life palliative care needs is reported to be between 50-80%, but can be as high as 90%^{1,2}. Persistent delirium is associated with poorer patient outcomes, increased risk of mortality and decline in cognitive state³, with delirium doubling patient mortality rates¹.

In the management of delirium, non-pharmacological measures and environmental support are recommended first line^{4,5,6}. It is well documented that the most important approach in the management of patients with delirium is the early identification and treatment of underlying contributing factors. An initial delirium screen is recommended to identify treatable underlying precipitating factors (e.g. pain, infection, constipation, dehydration, hypercalcaemia, medication).

Where pharmacological therapy has been recommended, it is generally reserved for patients who experience severe agitation and are at risk to either themselves or those around them^{1,4,5,6,7}.

Haloperidol is the most studied antipsychotic used in the management of delirium, as such certain guidelines indicate that is the first line choice of antipsychotic^{4,8}. Although there have been numerous studies on the use of antipsychotics in the management of delirium, the number of randomised placebo controlled trials are limited.

Summary of Available Evidence

A 2016 systematic review of antipsychotics for the prevention and treatment of delirium concluded that there is insufficient evidence to support the use of antipsychotics routinely in practice, in both the prevention and treatment of delirium⁹. Similarly, a Cochrane Review of drug therapy for delirium in terminally ill adults, performed in 2012, recognised that there is limited evidence on the use of antipsychotics in the management of delirium in patients at the end of life and therefore could not make recommendations on their use².

The Palliative Care Formulary emphasises the importance of treating any possible underlying causes of delirium prior to the use of pharmacological treatment¹⁰. It suggests that pharmacological therapy with antipsychotics should be considered alongside non-pharmacological measures¹⁰. This recommendation is based on the results of three randomised placebo controlled trials¹⁰. These three trials, however, have been recognised as having methodological flaws and potential risk for bias^{11,12}. All three studies were inadequately powered and the severity of delirium observed is difficult to establish owing to differing measures of symptom severity^{2,8}. Of note, these studies were not performed in the palliative care setting. These three studies are outlined below:

- Tahir et al¹³:

A double blind randomised placebo controlled trial was carried out to assess the effectiveness of quetiapine in the treatment of delirium. This trial was carried out over a period of 10 days with follow up at day 30. The DRSR-98 scale was used to assess severity of delirium (inclusion of value greater than 15). Although the study reported that quetiapine showed a faster response to reduce symptom severity the trial was prematurely discontinued on request of FDA due to concerns of risks associated with antipsychotic use in elderly patients.

- Devlin et al¹⁴:

A double blind randomised placebo controlled study was carried out comparing quetiapine added to as needed intravenous haloperidol in the treatment of delirium in ICU patients. The trial was continued until the subject was deemed to no longer have delirium, 10 days had elapsed, the patient had been discharged from ICU or an adverse event related to the study drug had occurred. The Intensive Care Delirium Screening Checklist was used to assess for delirium (inclusion of value greater than 4). Quetiapine was shown to shorten the time to decreased symptom severity, reduce the duration of delirium and increase the likelihood of hospital discharge compared to placebo.

- Hu et al¹⁵:

A randomised placebo controlled study was carried out on patients with senile delirium, assessing the effect of olanzapine and haloperidol. Patients were observed for one week and assessment was made based on clinical global

impression scale-severity of illness. Scores were significantly lower from baseline in patients treated with olanzapine, haloperidol and control. In the two treatment groups the marked effects were significantly different from that in the control group ($p < 0.01$). Both antipsychotics were reported to have similar effects in treating senile delirium.

Of note, two adequately powered placebo controlled studies of antipsychotics in critically ill adults, in the ICU setting, found no difference in the prevalence or duration of delirium when compared to placebo^{16,17}.

In a study published in 2017 Agar et al¹² identified the need for an adequately powered comparison to evaluate antipsychotics in the management of delirium in the palliative care setting. They designed a trial that specifically aimed to assess control of symptoms of delirium associated with distress in the palliative care population. It was a double blind randomised placebo controlled trial which was conducted in inpatient hospice or hospital palliative care services. Patients were randomly assigned to receive haloperidol, risperidone or placebo. This study reported that patients treated with risperidone or haloperidol had significantly greater delirium symptom scores than the placebo group at study end. The use of midazolam as rescue therapy was significantly lower in those in the placebo group. It was reported that patients receiving antipsychotics were approximately 1.5 times more likely to die when compared to those receiving placebo. They concluded that antipsychotics should not be added to manage specific symptoms of delirium that are known to be associated with distress in patients with mild to moderate delirium.

Choice of Antipsychotics to Manage Delirium

The following recommendations are made for the use of antipsychotics in delirium:

- Use only one antipsychotic at any time⁴
- Use small doses at regular intervals⁴
- Titrate according to clinical response⁴
- Tailor doses according to patient age, body size and clinical presentation⁴
- Review the continued need for antipsychotics every 24 hours⁴
- Discontinue antipsychotics 7-10 days after symptom resolution⁴

Haloperidol is the most commonly used antipsychotic in the management of delirium¹⁸. Although new evidence suggests second generation antipsychotics present less risk of extrapyramidal side effects and QT prolongation haloperidol is continually recommended as the first line choice in guidelines, including NICE and Scottish Palliative Care Guidelines. It is considered first line as it has a high potency and is the most studied pharmacological treatment in the management of delirium⁸. Haloperidol is also available in oral and parenteral formulations which can allow multiple methods of administration. It has no active metabolites, has few cardiovascular adverse effects and has very few anticholinergic side effects⁸. The efficacy and tolerability of olanzapine, haloperidol and quetiapine have been shown to be comparable¹⁰. A study has shown that low dose haloperidol, olanzapine, risperidone and quetiapine were all equally efficacious and safe in the treatment of delirium however the treatment response rate for olanzapine was significantly lower in patients over 75 years old²⁴.

Table 1: Choice of antipsychotic therapy and relevant information*

Drug	Dose	Time to peak plasma concentration	Adverse effects
Haloperidol (1st generation antipsychotic)⁴	PO: 0.5-1mg twice daily, additional doses may be given every 4 hours if necessary. IM: 0.5-1mg, repeat after 30-60 minutes if needed ⁴	PO: 2-6 hours ¹⁰ IM: 20-40 minutes ⁴	<ul style="list-style-type: none"> • Prolonged QT interval⁴ • Increase risk of stroke in those with dementia⁴ • Extrapyramidal side effects may present an issue at doses >3mg.⁴
Olanzapine (2nd generation antipsychotic)⁴	2.5-5mg once daily PO to a maximum of 20mg/day ⁴	5-8 hours ¹⁰	<ul style="list-style-type: none"> • Sedation⁴ • Increased risk of stroke in those with dementia⁴
Risperidone (2nd generation antipsychotic)⁴	0.5mg twice daily PO- additional doses may be given every 4 hours if necessary. Usual maximum 4mg/day ⁴	1-2 hours ⁴	<ul style="list-style-type: none"> • Hypotension⁴ • Extrapyramidal side effects⁴ • Increased risk of stroke in those with dementia⁴
Quetiapine (2nd generation antipsychotic)⁴	12.5-50mg twice daily PO. This dose may be increased every 12 hours to 200mg daily if tolerated. ⁴	1.5 hours ⁴	<ul style="list-style-type: none"> • Sedation⁴ • Postural hypotension⁴ • Increased risk of stroke in those with dementia⁴

*Adapted from The Maudsley Prescribing Guidelines in Psychiatry⁴.

It is important to recognise antipsychotics are not currently licenced for the management of delirium^{20,21,22,23}. Antipsychotics should be used at very low doses and titrated gradually according to clinical response¹⁸. A risk-benefit analysis should always be

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considered before prescribing antipsychotics for elderly patients due to the associated increased risk of mortality, stroke and transient ischaemic attack¹⁹.

Medication Review

Drug toxicity accounts for approximately 30% of all cases of delirium²⁵. Thus, the most important initial step is a medication review²⁵. Delirium can occur even with "therapeutic" levels of such agents as digoxin or lithium, particularly in at risk patients⁶. The withdrawal of alcohol and/or sedatives has been commonly noted in prospective studies of delirium⁶. Clinicians should be careful not to neglect over-the-counter agents, medication prescribed by other physicians, or medication belonging to other household members.

Table 2: Medication believed to cause or prolong delirium or confusional states*

Class	Examples
Analgesics	NSAIDs and opioids (especially pethidine)
Antibiotics and Antivirals	Aciclovir, aminoglycosides, antimalarials, cephalosporins, fluoroquinolones, isoniazid, linezolid, macrolides, metronidazole, penicillins, rifampin and sulfonamides.
Anticholinergics	Atropine, hyoscine and glycopyrronium
Anticonvulsants	Carbamazepine, levetiracetam, phenytoin and valproate.
Antidepressants	Mirtazapine, Selective Serotonin Reuptake Inhibitors (SSRIs) and tricyclic antidepressants
Cardiovascular and Hypertension Agents	Antiarrhythmics, beta blockers, clonidine, digoxin, diuretics and methyldopa
Corticosteroids	Prednisolone and dexamethasone
Dopamine agonists	Amantadine, bromocriptine, levodopa, pergolide, pramipexole and ropinirole.
Gastrointestinal Agents	Antiemetics, antispasmodics, histamine receptor blockers and loperamide.
Herbal Preparations	Mandrake, St John's Wort and Valerian
Hypoglycaemics	Gliclazide
Hypnotics and sedatives	Barbiturates and benzodiazepines
Muscle Relaxants	Baclofen
Other CNS-active agents	Donepezil and lithium

*Adapted from UpToDate. This list is not exhaustive.

Other Treatment Options

- Benzodiazepines

Benzodiazepines have a limited role in the treatment of delirium⁶. They are primarily indicated in cases of sedative and/or alcohol withdrawal or when antipsychotics are contraindicated^{4,6}. Benzodiazepines (e.g. lorazepam 0.5 to 1.0 mg) have a more rapid

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onset of action (five minutes after parenteral administration) than the antipsychotics, but they can worsen confusion and sedation⁶. Lorazepam has been associated with prolongation and worsening of symptoms of delirium^{4,6}.

- Acetylcholinesterase inhibitors

Very limited evidence suggests that acetylcholinesterase inhibitors do not have a role in the treatment or symptom management of delirium^{4,6}.

- Trazodone

There is very limited evidence to support the use of trazodone in patients with delirium therefore its use is not recommended⁴.

Conclusion:

There is very limited evidence on the role of antipsychotics in the management of delirium in the palliative care setting, therefore careful consideration should be given to their use. The use of antipsychotics in the management of delirium should be assessed on an individual patient basis. In the palliative care setting, the degree of patient and family distress, as well as the goals of care, may justify the use of antipsychotics²⁷.

Treatment of the underlying cause is of utmost importance. For distressing symptoms of delirium, non-pharmacological or environmental support strategies should be instituted wherever possible⁴. Furthermore, consideration should be given to the risks associated with the use of antipsychotics including QTc prolongation, extrapyramidal side effects, metabolic disturbances, increased risk of mortality⁷. Further randomised placebo controlled clinical trials are needed to assist clinical decision making, nonetheless caution is advised.

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