Delirium is a complex and morbid condition of elderly people that lies at the interface of mental and physical health. It is an acute state with prominent cognitive and behavioural abnormalities triggered by underlying organic causes; therefore, the appropriate and timely management of the condition demands the shared expertise of mental and physical health-care professionals. Occurring in up to 50% of elderly people during admission to hospital, delirium is often missed and is associated with poor outcomes, including prolonged length of stay, sustained functional decline, dementia, institutionalisation, death, and high health-care costs that have been estimated at US $164 billion per year in the USA and €182 billion per year in 18 European countries combined.1

Delirium can be associated with behavioural manifestations such as agitation, inappropriate behaviours, delusions, and hallucinations, which can be distressing to patients and to their families. Moreover, these symptoms can make patients difficult to provide care for and are a source of burden and stress for both health-care workers and informal carers. Largely to address these behavioural symptoms, the field of delirium prevention and treatment has come to focus on clinical trials of antipsychotic drugs.2,3 A search of the PubMed database shows that the annual number of studies of antipsychotic drugs for prevention or treatment of delirium has grown substantially in the past 20 years, from two studies published in 1990 to more than 40 in 2013. This necessitates an urgent call for caution in the use of antipsychotic drugs for the management of patients with delirium. The use of antipsychotics might be regarded as counterintuitive because these drugs can all cause confusion or delirium as side-effects. However, powerful incentives in our health-care systems promote prescription of antipsychotics for patients with delirium, and have led to the frequent use of these drugs. Antipsychotics may have appeal as a potential quick fix compared with non-pharmacological approaches, but clinicians might not fully realise that their attempt to make patients more manageable and less distressed can result in worsened clinical outcomes. In essence, these drugs can be regarded to be a form of chemical restraint, and concern exists that the use of drugs such as haloperidol and atypical antipsychotics for treatment of delirium might often be serving the interests of the providers rather than the patients. The marketing and promotion by the pharmaceutical industry of off-label use of antipsychotics for treatment of agitation in cognitively impaired patients might have also contributed to this surge in use.

Treatment with antipsychotics can be warranted for severe agitation endangering patient safety or for psychotic symptoms causing severe distress, such as hallucinations and delusions. Even in these situations, antipsychotics should be prescribed at the lowest effective dose for the shortest possible duration, generally less than 1–2 days. The continued use of antipsychotic therapy should always be re-evaluated regularly, particularly at any transition of care. In some settings—such as surgery, recovery, and intensive care—sedating drugs might be required to assure patient safety and avoid interruption of essential medical therapies such as mechanical ventilation and central venous or arterial catheters; therefore, the bar must be set differently in these situations. However, the use of these drugs for delirium is common even outside of these settings.

Recommendation of any treatment is contingent on evidence that the benefits of therapy outweigh the potential harms. The putative justification for antipsychotics involves dopaminergic blockade to counteract the postulated dopamine excess and acetylcholine deficiency in delirium.1 Although some evidence from animal models supports this pathophysiology, as do case reports of delirium after anticholinergic drug poisoning and dopaminergic drug excess, whether this mechanism explains most cases of delirium is unclear. Antipsychotics have also been postulated to have central anti-inflammatory effects that might provide benefit in delirium, but direct evidence for this effect is lacking. The authors of several high-quality systematic reviews6–8 have concluded that the evidence to justify the use of antipsychotics for prevention or treatment of delirium is insufficient. Many of the studies reviewed were restricted by small sample sizes and a high risk of bias (ie, they were non-randomised, not masked, or had inadequate control groups). Furthermore, wide variation in pharmacological properties between antipsychotic agents might have influenced the results of previous clinical trials in terms of both efficacy and safety.

In a comprehensive systematic literature review of antipsychotics for treatment of delirium,19 seven high-quality studies were identified; of these, four reported reduced delirium rates, and the other three reported no differences (table). No difference in any other measured clinical outcome was found in five studies, and worse clinical outcomes were found in one. Although a modest effect on delirium symptoms was shown in four of the seven studies, no consistent benefit was noted in terms of any other outcomes.

The unclear benefits of antipsychotics need to be weighed against the concern over serious harm caused by these drugs.6–18 Common side-effects are due to anticholinergic activity and α-receptor blockade, and include confusion, cognitive and functional decline, sedation, hypotension, orthostasis, dizziness, falls, urinary
incontinence, voiding problems, and increased risk of urinary infections. Although the anticholinergic effects of atypical antipsychotics are milder than are those of other major tranquillisers, they are still present and contribute to substantial morbidity. Extrapyramidal effects include parkinsonism, dystonia, and oropharyngeal dysphagia leading to an increased risk of pneumonia. Increased risks of potentially fatal complications, including stroke, seizures, venous thromboembolism, QT prolongation, and ventricular arrhythmias, have been shown. The risk of sudden cardiac death is increased more than 2·4-times with both typical and atypical antipsychotic drugs. Neuroleptic malignant syndrome is a rare but potentially fatal disease that is associated with all classes of antipsychotic medication. Although the risks increase with the dose and duration of treatment, even short-term treatment (≤10 weeks) has been associated with a 70% increased risk of mortality in elderly patients with dementia. Another important danger is the potential for inadvertent chronic administration of antipsychotics after in-hospital initiation during an episode of delirium. 20 (34%) of 59 patients who began receiving antipsychotics during an episode of delirium continued to receive these drugs without a clear indication after hospital discharge. Finally, many patients with delirium have underlying dementia, and the risk of antipsychotic side-effects, including death, is substantially increased in patients with dementia. These factors sway the risk to benefit balance away from the off-label use of antipsychotics for treatment of delirium.

Another important limitation of previous studies of antipsychotics in delirium is the outcome measure used. Present measures of delirium severity tend to over-emphasise hyperactive symptoms (eg, agitation and hallucinations); therefore, patients with hyperactive delirium tend to receive higher delirium severity scores than do patients with the hypoactive form. After antipsychotic treatment, the severity score can be reduced, from which the investigators might have concluded treatment success. However, in reality, with treatment these patients might have been changed to a hypoactive delirium that was not diagnosed, or the severity score could have fallen owing to the bias in the measures. Inaccurate measurement probably accounts for the worse clinical outcomes in one of the studies assessed in the systematic literature review and the lack of improvement in clinical outcomes in the other five studies. Thus, all of these studies need to be interpreted with caution. Improved delirium severity measures that focus more on the key symptoms of delirium, such as attentional deficits rather than behavioural disorders, are needed to advance the field.

What are the alternatives to antipsychotic treatment? First and foremost, the clinician must address reversible contributors to delirium. Too often, this crucial step is neglected when the focus is on pharmacological treatment. Without assiduous attention to this step, the patient will not improve. Next, removal or reduction of psychoactive drugs, particularly sedating and anticholinergic agents, should be considered in every patient. Finally, non-pharmacological, multicomponent intervention strategies can be used for prevention and management of agitated patients without the use of physical or chemical restraints. The Hospital Elder Life Program (HELP) and other multicomponent risk-factor interventions for delirium are effective through the use of non-pharmacological strategies (including mobilisation, sleep enhancement, orientation, therapeutic activities, and environmental modification) by trained volunteers.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Population</th>
<th>Intervention (control) groups</th>
<th>Results</th>
<th>Jadad score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Page et al</td>
<td>Prevention, treatment</td>
<td>Haloperidol (placebo)</td>
<td>No difference in number of delirium-free or coma-free days; no difference in mortality rate</td>
<td>6</td>
</tr>
<tr>
<td>Hakim et al</td>
<td>Treatment</td>
<td>Risperidone (placebo)</td>
<td>Reduced incidence of delirium; no difference in length of stay in ICU or hospital</td>
<td>6</td>
</tr>
<tr>
<td>Wang et al</td>
<td>Prevention</td>
<td>Haloperidol (placebo)</td>
<td>Reduced incidence of delirium; no difference in length of stay, incidence of complications, or mortality rate</td>
<td>6</td>
</tr>
<tr>
<td>Girard et al</td>
<td>Treatment</td>
<td>Haloperidol or ziprasidone (placebo)</td>
<td>No difference in number of delirium-free or coma-free days; no difference in mortality rate</td>
<td>6</td>
</tr>
<tr>
<td>Larsen et al</td>
<td>Prevention</td>
<td>Olanzapine (placebo)</td>
<td>Reduced incidence of delirium, but greater delirium duration and severity</td>
<td>6</td>
</tr>
<tr>
<td>Prakanrattana et al</td>
<td>Prevention</td>
<td>Risperidone (placebo)</td>
<td>Reduced incidence of delirium; no difference in length of stay, number of days in ICU, or incidence of complications</td>
<td>6</td>
</tr>
<tr>
<td>Kalswaart et al</td>
<td>Prevention</td>
<td>Haloperidol (placebo)</td>
<td>No difference in incidence of delirium, but reduced delirium duration and severity; reduced length of stay</td>
<td>6</td>
</tr>
</tbody>
</table>

*ICU=intensive-care unit. *The modified Jadad score (6 points) included randomisation or balanced allocation (1 point), description of method for group assignment (1 point), double-blinding (1 point), description of double-blinding (1 point), description of withdrawals and dropouts (1 point), and sample size ≥100 patients (1 point).
and an interdisciplinary geriatric team. Delirium rooms are promising options for management of agitated patients with delirium. Although these multicomponent interventions are more labour intensive than simple prescription of a medication, their risk to benefit ratio is highly favourable, and HELP has been shown to be cost-effective.

Present evidence does not support the use of antipsychotics for prevention or treatment of delirium. Although more rigorous trials might shed new light in the future, the evidence for benefit is inconsistent or lacking at present. The risk of bias in measurement of delirium incidence and severity as outcomes is high in published trials; therefore, the results must be interpreted with caution. Moreover, these trials have failed to show an improvement in other clinical outcomes closely associated with delirium. Finally, the risk of harm from antipsychotics, including fatal complications, is substantial in elderly patients. On balance, for the population as a whole, the risks clearly outweigh the benefits of treatment with antipsychotics. Treatment should thus be reserved only for the small proportion of patients with severe agitation and distress who pose a substantial risk of harm or interruption of essential medical therapy.

What would it take to reduce use of antipsychotics for delirium? In view of their widespread use, large-scale efforts would be required, such as those being used to decrease antipsychotic use in nursing homes. Such efforts should include comprehensive, multimedia training of all health-care professionals and awareness campaigns about the hazards of antipsychotic drugs in elderly people. Incentives against prescribing will be required if a true effect is to be had. Strategies might target physicians’ order-entry systems; for example, safety screening questions before allowing prescription of an antipsychotic or implementation of single or 24 h dose limits for frail elderly patients. System-wide strategies might include public posting of antipsychotic prescribing rates in elderly patients by hospital, scrutiny of prescribing rates by accrediting organisations, and other quality-improvement initiatives.

First, do no harm. As William Osler stated, “One of the first duties of the physician is to educate the masses [patients, families, caregivers, nurses] not to take medicine”. This proverb seems to apply to the overuse of antipsychotics for delirium. The prevention and management of delirium must focus on approaches that address underlying causes and manage behavioural disturbances non-pharmacologically in order to enhance recovery, maximise functional status, and improve clinical outcomes. Certainly, in the case of delirium, antipsychotic drugs are unlikely to be the answer.

Declarations of interest
We declare no competing interests.

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