What Do We Really Know About the Treatment of Delirium with Antipsychotics? Ten Key Issues for Delirium Pharmacotherapy

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Despite the significant burden of delirium among hospitalized adults, no pharmacologic intervention is approved for delirium treatment. Antipsychotic agents are the best studied but there are uncertainties as to how these agents can be optimally applied in everyday practice. We searched Medline and PubMed databases for publications from 1980 to April 2012 to identify studies of delirium treatment with antipsychotic agents. Studies of primary prevention using pharmacotherapy were not included. We identified 28 prospective studies that met our inclusion criteria, of which 15 were comparison studies (11 randomized), 2 of which were placebo-controlled. The quality of comparison studies was assessed using the Jadad scale. The DRS (N = 12) and DRS-R98 (N = 9) were the most commonly used instruments for measuring responsiveness. These studies suggest that around 75% of delirious patients who receive short-term treatment with low-dose antipsychotics experience clinical response. Response rates appear quite consistent across different patient groups and treatment settings. Studies do not suggest significant differences in efficacy for haloperidol versus atypical agents, but report higher rates of extrapyramidal side effects with haloperidol. Comorbid dementia may be associated with reduced response rates but this requires further study. The available evidence does not indicate major differences in response rates between clinical subtypes of delirium. The extent to which therapeutic effects can be explained by alleviation of specific symptoms (e.g. sleep or behavioral disturbances) versus a syndromal effect that encompasses both cognitive and noncognitive symptoms of delirium is not known. Future research needs to explore the relationship between therapeutic effects and changes in pathophysiological markers of delirium. Less than half of reports were rated as reasonable quality evidence on the Jadad scale, highlighting the need for future studies of better quality design, and in particular incorporating placebo-controlled work. (Am J Geriatr Psychiatry 2013; 21:1223–1238)

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Delirium is a complex neuropsychiatric syndrome that is commonly encountered across healthcare settings.[1] Historically, treatment has focused on identifying and addressing underlying causes, but increasingly delirium is being considered as an entity that warrants therapeutic consideration in its own right. Central to this is the recognition that for many patients with delirium the course of illness is frequently persistent with an independent impact on functional capacity, morbidity, and mortality.[2] As such, therapeutic effort is directed at minimizing the impact of delirium and its symptoms upon outcomes.

However, the challenge of managing delirium in everyday practice involves applying imperfect evidence regarding effectiveness while recognizing the potential for adverse effects. Good quality evidence to support delirium pharmacotherapy from placebo-controlled studies is lacking and no agent is licensed for the treatment of delirium. As a consequence, clinical practice is informed by lower-quality evidence and empiricism. Not surprisingly, there is considerable variation in practices that reflect how needs differ according to the heterogeneity of delirium as a syndrome, the variety of populations and settings in which delirium occurs, limitations in our knowledge base, and a range of attitudinal inconsistencies.[3] The past decade has witnessed increased research into delirium pharmacotherapy that supports pharmacological interventions used prophylactically as well as for incident delirium and this is reflected in recent therapeutic guidelines.[4] This information remains limited in scope, however, mainly addressing issues of efficacy in particular populations and with limited exploration of the many factors (e.g., comorbid dementia, specific clinical subtypes) that are relevant to treatment choice in any individual patient. As a consequence, how this information should be best applied to allow for optimal management in everyday practice remains uncertain. This article focuses upon the role of antipsychotic agents in the treatment of a delirium episode and explores key issues for consideration by treating clinicians and by researchers (see Fig. 1).

FIGURE 1. Ten key issues for delirium pharmacotherapy.

1. What is the overall evidence to support the efficacy of pharmacotherapy in delirium?
2. Which agent should be the treatment of first choice?
3. How do antipsychotics impact upon delirium symptom profile?
4. What is the principal mechanism of action for antipsychotic agents in delirium?
5. How should treatment response be measured?
6. What are optimal dose ranges and how should these be titrated?
7. What is the optimal timing and duration of treatment?
8. Do clinical subtypes differ in responsiveness?
9. What is the relevance of comorbid dementia for treatment?
10. What is the risk for adverse effects?

METHODS

We conducted a search of Medline from January 1980 to the present using the key words *delirium*, *antipsychotics*, and *treatment*. This review considers prospective studies in detail but also includes other information that can inform issues beyond efficacy analysis (surveys of preferred practice, retrospective studies, treatment guidelines, etc.). Review articles were also examined to identify further studies and where necessary additional information was sought through direct communication with the authors.[5–8] Specific studies for consideration in detail were selected according to five criteria; (i) Treatment study (not prophylaxis), (ii) Prospective design, (iii) At least 10 participants (in any treatment arm), (iv) Use of standardized criteria for diagnosing delirium, and (v) Clear criteria for reporting outcomes. Our summary of these studies is complemented by less formal evidence from other studies.

The quality of evidence was assessed by calculating Jadad scores[9] for each comparison study. This widely used instrument[10] allows for the objective assessment of study quality by rating randomization procedures, method of blinding, and account of withdrawals and dropouts. Scores range from 0 to 5, with scores of 2 or less indicative of poor quality evidence. Antipsychotic doses were compared by conversion to haloperidol dose equivalents.[11]

RESULTS

The search identified 28 prospective studies—13 single agent and 15 comparison studies, of which 11