



Management of agitation in the acute psychotic patient — Efficacy without excessive sedation

Fernando Cañas *

Department of Psychiatry, Hospital “Dr. R. Lafora”, Madrid, Spain

KEYWORDS

Schizophrenia;
Atypical antipsychotics;
Acute agitation;
Intramuscular;
Sedation

Abstract Rapid-acting intramuscular (IM) formulations of atypical antipsychotics offer a significant advance over IM haloperidol in the short-term management of acute schizophrenic episodes. Several short-term open-label randomised studies, typically enrolling two- to three-hundred patients, have compared an atypical antipsychotic with haloperidol. These studies show that IM ziprasidone, IM olanzapine and IM aripiprazole are at least as effective and better tolerated than IM haloperidol, with lower extrapyramidal side effects. Successful transitions from an IM to oral formulation of the same agent have been performed in double-blind randomised trials assessing haloperidol, olanzapine, ziprasidone and aripiprazole. Avoiding over-sedation is now recognised as important, and randomised clinical trial data indicate that oral ziprasidone, quetiapine, and IM olanzapine have high dose-related sedative potential while oral risperidone and IM aripiprazole have low sedative potential. In summary, IM formulations of atypical antipsychotics are recommended as first-line treatment of acute agitation with subsequent transition to an oral formulation of the same agent for ongoing management.

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1. Introduction

Acute agitation associated with psychosis is a challenging presentation that requires early diagnosis, rapid intervention, and effective, well-tolerated treatment (Battaglia, 2005; Yildiz et al., 2003). Preferably, the treatment approach should provide specific calming effects, reducing agitation while not excessively sedating the patient. This is critical to allow continued interaction with and evaluation of the patient, as well as an accurate diagnosis. Consensus guidelines (Allen et al., 2001, 2005) emphasize that calming rather than over sedating the patient is a key goal in the initial management of agitation in the acute setting. Such considerations in the management of acute agitation associated with psychosis and,

more, specifically schizophrenia are reviewed in this article. An overview is also provided of the current treatment options for acute management of agitation associated with psychosis, focusing on intramuscular (IM) administration of antipsychotic agents.

2. Acute management: key considerations

Acute psychotic episodes are distressing periods that tend to recur throughout the course of illness in patients with schizophrenia. The acute phase of each relapse is generally short-lived after treatment intervention, lasting hours to days, with a subsequent period of troublesome but less severe symptoms usually lasting several weeks to months (stabilisation) (McEvoy et al., 1999). Relapses tend to be of similar or worse severity compared with the patient's initial or previous episode, with each relapse leading to additional morbidity in the form of residual positive, negative and

* Department of Psychiatry, Hospital “Dr. R. Lafora”, Cra. De Colmenar Viejo km 13,8, Madrid, Spain. Tel.: +34 91 586 7390.

E-mail address: fcanasd@hotmail.com

cognitive symptoms (Lieberman et al., 2001). This clinical deterioration mainly occurs during the first 5–10 years after a patient's first episode, after which the illness stabilises and relapses tend to occur less frequently. Hence, the long-term stabilisation of schizophrenia begins with effective management during the acute phase (Fig. 1). Agitation is a frequent symptom of schizophrenia, that mostly manifests during the acute episode, and can present as either motor or verbal activity that is inappropriate or excessive in nature.

One of the key goals of the treatment of agitation during an acute episode is to provide rapid and effective symptom relief, in order to minimise distress, because patients are at risk of harming themselves and others. It is, therefore, crucial for the psychiatrist to establish contact with the patient and develop a supportive therapeutic alliance in order to obtain details of clinical history and to conduct a risk evaluation (APA, 2004). Offering help and reassurance with a non-judgmental attitude and in a calm, slow, predictable manner is most likely to ensure patient cooperation. Lack of cooperation is a typical clinical manifestation of agitation that may result in suboptimal compliance, diagnosis and treatment. It is also essential that assessment takes place in a quiet setting to reduce stimulation. A recent US study that examined the relationship between the characteristics of patients hospitalised for acute psychiatric illness and subsequent involuntary readmission (Segal et al., 2002) found that diagnosis of psychosis was a primary predictor of involuntary return to the emergency psychiatric setting within 12 months. Hospitalisation was also observed to be too brief to meet adequately the needs of these seriously ill patients. Hence, acute management has a pivotal role in preventing the 'revolving door' syndrome and ensuring appropriate psychiatric care.

As the cornerstone of treatment for agitation associated with an acute episode, pharmacological intervention should be initiated as soon as is clinically feasible, provided that it will not interfere with diagnostic evaluation (APA, 2004; McEvoy et al., 1999). The newer atypical antipsychotics are strongly recommended as first-line agents (e.g. aripiprazole, olanzapine, risperidone, ziprasidone) due to their improved tolerability compared with the first-generation or conventional/typical antipsychotics (e.g. haloperidol, chlorpromazine) (McEvoy et al., 1999). Significant differences between the properties of the various atypical antipsychotics (Table 1) complicate the process of selecting an appropriate pharmacological agent for the individual patient and pose a

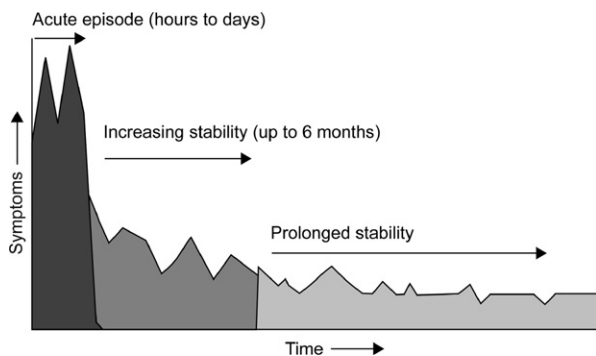


Figure 1 Long-term stabilisation of schizophrenia begins with acute management.

Table 1 Receptor activity of atypical antipsychotic drugs (Ohlsen and Pilowsky, 2005)

Drug	Receptor profile		
Risperidone	High affinity	5-HT _{2A}	Antagonist
	Moderate affinity	Dopamine D ₂	Antagonist
		Dopamine D ₁	Antagonist
Olanzapine	High affinity	5-HT _{2A}	Antagonist
	Minimal affinity	Dopamine D ₁	Antagonist
		Dopamine D ₂	Antagonist
Quetiapine	High affinity	5-HT _{1A}	Agonist
	Minimal affinity	5-HT _{2A}	Antagonist
		Dopamine D ₁	Antagonist
		Dopamine D ₂	Antagonist
Ziprasidone	High affinity	5-HT _{1A}	Partial agonist
		5-HT _{2A}	Agonist
		Dopamine D ₂	Antagonist
Aripiprazole	High affinity	5-HT _{1A}	Agonist
		5-HT _{2A}	Antagonist
		Dopamine D ₂	Partial agonist

particular challenge for physicians. The route of administration and need for controlling agitation/aggression are key considerations in the acute situation as treatment should ideally provide a rapid speed of onset, reliable delivery of the drug, high efficacy, a low incidence of adverse events and a calming effect without sedation. Patient preference, interaction with other medications and the ease of switching to a continuation antipsychotic within 24 h also need to be taken into account.

3. Intramuscular antipsychotics in the acute setting

To minimise the distress of agitation associated with an acute episode, treatment must be rapid-acting and effective, as well as being calming rather than sedative, to allow accurate patient assessment and provide symptom relief. Some of the newer atypical antipsychotics are available as oral solutions (aripiprazole and risperidone) or rapidly dissolving tablets (aripiprazole, olanzapine and risperidone), but it is the introduction of rapid-acting intramuscular (IM) formulations of atypical agents that represents the most significant advance in the short-term management of acute episodes (Daniel et al., 2004). Conventional antipsychotic agents such as haloperidol have been available as IM formulations for some time, but these drugs are associated with acute extrapyramidal symptoms (EPS; e.g. parkinsonism, akathisia, dystonia) that can worsen the distress and trauma of the acute episode. The patient's first experience of adverse effects can affect long-term compliance with therapy, and so must be considered when selecting initial treatments (McCreadie, 1996; Daniel et al., 2004).

Currently, IM formulations are only available for certain atypical antipsychotics. The IM formulation of ziprasidone was the first to be approved by the US FDA in 2002, followed by olanzapine in 2004. Clinical evidence relating to the efficacy of the IM formulation of aripiprazole, an atypical antipsychotic with a novel mechanism of action, has recently been published (Andrezina et al., 2006). Aripiprazole is pharmacologically distinct from other

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