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Faster onset of antimanic action with haloperidol compared to second-generation antipsychotics. A meta-analysis of randomized clinical trials in acute mania

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Abstract
Background: there is a lack of scientific data regarding speed of action of antimanic treatments, a relevant issue in clinical practice. *Objective*: to assess differences in the speed of onset of antimanic efficacy between haloperidol (as most studied first-generation antipsychotic) and second-generation antipsychotics. *Experimental procedures*: meta-analysis of double-blind randomized clinical trials in acute mania, comparing treatment with haloperidol and with second-generation antipsychotics. Search was conducted in MEDLINE and CENTRAL databases (last search: September 2011). Differences in mania scale score reduction at week 1 were assessed. *Results*: 8 randomized clinical trials fulfilled inclusion criteria and 1 of them was excluded due to low methodological quality. 2037 Manic patients had been treated with antipsychotics in the 7 trials. Haloperidol was found to be significantly more efficacious in the reduction of the mania scale score at week 1. The effect size was small, the Standardized Mean Difference (SMD) being 0.17, with a 95% Confidence Interval ranging from 0.01 to 0.32. Haloperidol was significantly more efficacious than olanzapine (SMD: 0.40 [0.21, 0.59]) and ziprasidone (0.39 [0.18, 0.61]). A non-significant trend towards superiority of haloperidol was found over aripiprazole (SMD: 0.13 [−0.02, 0.19]). There were no significant differences between haloperidol and quetiapine (0.17 [−0.11, 0.44]), and haloperidol and risperidone (SMD: −0.10 [0.30, 0.09]). *Conclusions*: haloperidol shows a faster onset of antimanic action than second-generation antipsychotics. This difference may be related to D2 affinity. Haloperidol may be considered a treatment option in severely ill manic patients who require urgent relief of symptoms.

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1. Introduction

Mania is the main feature of Bipolar Disorder. According to the Diagnostic and Statistical Manual, 4th ed.-TR (DSM-IV-TR) (American Psychiatric Association, 1994), acute mania is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to require hospitalization in order to prevent harm to self or others.

In manic episodes, increased energy, disinhibition, inflated self-esteem, and irritability often lead to harmful consequences that go from job loss to breakup of couples, family or economic problems (risky investments, fool loans, or ridiculous purchases) with severe consequences for patients and their families (Goodwin and Jamison, 2007). In the most severe cases, due to the severity of the clinical picture or because of concurrent conditions such as substance abuse, aggressive behaviors may involve criminal offenses and even endanger the life of the patient or others (Large and Nielssen, 2011).

So, it looks clear that patients with acute bipolar mania require rapid and effective treatments that safely control this dangerous process (Keck et al., 2000). Acute mania frequently constitutes a medical emergency, requiring prompt intervention to avoid destructive and possibly life-endangering behavior (Belmaker, 2004).

There are currently a good number of treatments that have shown to be efficacious in treating acute mania, basically antipsychotics, lithium, and anticonsulvants such as valproate or carbamazepine (Nivoli et al., in press). The antimanic efficacy of these compounds is usually assessed in 3 (sometimes 4)-week trials. Most of the recent randomized clinical trials studying the efficacy of atypical antipsychotics in acute mania assess how early these drugs show superiority over placebo. However, it is surprising how little attention has been paid in the literature to the speed of the onset of action of these treatments. In fact, there is much more literature regarding this issue in the treatment of depression (Machado-Vieira et al., 2008). But acute mania seems to be a condition where not only the efficacy to achieve remission is important but also how rapid the most severe symptoms improve. A fast improvement of the most severe psychopathology is the best protection against the most dangerous consequences of acute mania. It is also likely to reduce direct (length of hospitalization) and indirect (the whole range of consequences) costs. Nevertheless, the information about which treatments may act faster is mainly limited to some comparisons between antipsychotics and lithium (Keck et al., 2009; Grunze et al., 2009) where the latter tends to act slower. Besides, some recommendations are made based on the first observation where a drug was superior over placebo, which mainly depends on the design of the study. For example, in the older olanzapine trials first assessment was at day 7 (Tohen et al., 2000), whereas in the more recent aripiprazole ones it was at day 2 (Keck et al., 2009). In any case, additional information regarding speed of onset of action would be an important factor for the best treatment choice for each patient, not only taking into account efficacy at week 3 or tolerability.

During the time that only typical antipsychotics (neuroleptics) were available, the advantages and disadvantages of neuroleptics compared to lithium were unclear (Tohen and Zarate, 1998). Some of the earlier comparative trials in the treatment of acute mania suggested superiority of neuroleptics over lithium, but a meta-analysis published in 1992 found lithium to be more effective but with the important limitation of having a slower onset of action (Janicak et al., 1992). Chlorpromazine and haloperidol are the best studied typical antipsychotics in the treatment of bipolar mania (Tohen and Vieta, 2009). Haloperidol has been compared as monotherapy to placebo, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and as add-on treatment to lithium. The literature suggests that haloperidol has antimanic properties and a faster onset of antimanic action compared to atypical antipsychotics (Tohen and Vieta, 2009). However, this suggestion has not been proven yet. In a previous meta-analysis on the efficacy of haloperidol alone or in combination for acute mania, no data regarding onset of action were available except for the comparison with risperidone where there were no significant differences (Cipriani et al., 2006). Recently, a meta-analysis by the same author showed haloperidol was one of the most efficacious antimanic drugs, showing superiority over aripiprazole, asenapine, quetiapine, and ziprasidone, and no differences with risperidone and olanzapine, among atypical antipsychotics. However, no analysis about speed of onset of action was performed (Cipriani et al., 2011). Finally, another recent meta-analysis did not find significant differences between haloperidol and second-generation antipsychotics (Yildiz et al., 2011).

In the last decade, several double-blind placebo-controlled trials, most of them sponsored by pharmaceutical companies in order to get the indication by the regulatory agencies, have yielded positive results supporting the antimanic efficacy of atypical antipsychotics (Vieta and Goikolea, 2005; Scherk et al., 2007). Olanzapine was the first atypical to be approved for the treatment of acute mania (2000) and has been followed by risperidone, quetiapine, ziprasidone, aripiprazole and asenapine. Thus, clinical guidelines, such as the WFSBP (Grunze et al., 2009) and the ISBD/Canadian Guidelines (Yatham et al., 2009), among others (Nivoli et al., in press) have progressively included atypicals as first line treatment options.

It is clear that choice of treatment should be guided by a balance in efficacy and tolerability. An adverse event that has been considered unique to bipolar patients is the potential risk of inducing depression. Zarate and Tohen reported an increased risk of relapse into depression and higher rates of discontinuation in patients with mania who received mood stabilizers combined with a typical antipsychotic compared with mood stabilizers alone (Zarate and Tohen, 2004). Other concerns about the safety of typical antipsychotics specific to mood disorders have been reported, specifically extrapyramidal symptoms (EPS) and tardive dyskinesia (Nasrallah et al., 1988). In fact, an analysis comparing patients with schizophrenia and patients with bipolar disorder indicated that the latter would be more sensitive to EPS when treated with haloperidol, but not with olanzapine (Cavazzoni et al., 2006). These considerations have led to haloperidol being considered a second or third-line option for acute mania, despite its proven efficacy. Moreover, long-term considerations are especially important in treatment decisions in bipolar disorder, and the long-term data on haloperidol are very