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European Neuropsychopharmacology 15 (2005) 75–84

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

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Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol

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Received 10 February 2004; accepted 15 June 2004

Abstract

In a randomized, double-blind trial, patients with acute bipolar mania received 1–6 mg/day of risperidone, 2–12 mg/day of haloperidol, or placebo for 3 weeks, followed by double-blind risperidone or haloperidol for 9 weeks. Of 438 patients, 154 were randomized to risperidone, 144 to haloperidol, and 140 to placebo. The mean±S.D. modal doses were 4.2±1.7 mg/day of risperidone and 8.0±3.6 mg/day of haloperidol during the initial 3-week phase and 4.1±1.8 and 7.4±3.7 mg/day during the 12-week period. At week 3, mean Young Mania Rating Scale (YMRS) score reductions from baseline were significantly greater in patients receiving risperidone than placebo ($p<0.001$). Differences between risperidone and haloperidol on this efficacy measure were not significant. Further reductions in YMRS scores were seen in patients receiving risperidone or haloperidol during the subsequent 9 weeks. No unexpected adverse events were reported. Extrapyramidal disorder and hyperkinesias, the most commonly reported adverse events with antipsychotic use, occurred less frequently with risperidone than haloperidol. We conclude that risperidone monotherapy was an effective and well-tolerated treatment for bipolar mania and that efficacy was maintained over the long term.

Keywords: Bipolar disorder; Haloperidol; Mania; Risperidone

1. Introduction

Bipolar disorder is a widespread illness associated with early mortality, a high degree of disability, and a large financial burden (Murray and Lopez, 1996; Sharma and Markar, 1994; Simon and Unutzer, 1999). It is ranked as the 9th highest cause of years lived with disability (disability adjusted life years) in the 18- to 44-year age group worldwide (World Health Report, 2001). Annual cost to society in the United Kingdom alone has been estimated at £2 billion (1999/2000 value; Gupta and Guest, 2002) and hospitalizations for manic episodes have been identified as the most costly element of care (Finnern et al., 2003). Treatment of the acute manic phase alone is often insufficient to allow the patient to return to full function and prevent the deleterious outcomes often observed in these patients, including loss of employment, criminal behavior, and suicide (Calabrese et al., 2003). Thus, treatments for acute mania that are effective and well tolerated in long-term use and that can return patients to full function and prevent relapse are needed.

Guidelines of the British Association of Psychopharmacology (Goodwin, 2003) and the American Psychiatric Association (2002) now recommend monotherapy with a

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doi:10.1016/j.euroneuro.2004.06.003

mood stabilizer or an antipsychotic or combination therapy with agents from either class for the treatment of acute mania. Agents such as lithium, sodium valproate, and carbamazepine are often used in the treatment of acute mania (Bauer et al., 1999; Frances et al., 1996; Goodwin, 2003; Kusumakar et al., 1997; Rush et al., 1999; Sachs et al., 2000) but may take up to 2 weeks to take effect. In clinical practice, therefore, a combination treatment with a mood stabilizer and an antipsychotic is often used.

Conventional antipsychotics are used in the treatment of bipolar disorder but are associated with a high incidence of extrapyramidal symptoms (EPS), which can occur in up to 40% of patients with bipolar disorder (Hunt and Silverstone, 1991; Mukherjee et al., 1986; Nasrallah et al., 1988). Thus, drugs with better safety and tolerability profiles are needed. Atypical agents have a lower liability for EPS than conventional antipsychotics (Kane, 1999; Leucht et al., 1999). Among the atypical antipsychotics, risperidone is of particular interest in the treatment of affective disorders because of its unique receptor binding profile, characterized by antagonism of the serotonin 5-HT_{2A}, dopamine D_2, and alpha-adrenergic$_{2c}$ receptors (Kalkman and Loetscher, 2003; Leysen et al., 1994). This receptor profile has been hypothesized to be relevant for the treatment of affective disorders (Pania and Gessab, 2002).

The efficacy of risperidone in combination with mood stabilizers in acute bipolar mania (Ghaemi and Sachs, 1997; Ghaemi et al., 1997; Sachs et al., 2002; Vieta et al., 1998, 2001a,b, 2002a; Yatham et al., 2003a) and as maintenance therapy (Ghaemi and Sachs, 1997; Vieta et al., 2001a; Yatham et al., 2003b) has been demonstrated in a number of clinical trials. Studies have also demonstrated the rapid antimanic effect of risperidone as monotherapy in acute bipolar mania (Hirschfeld et al., 2004; Segal et al., 1998; Vieta et al., 2002b). Achievement of sustained clinical remission as defined by Young Mania Rating Scale (YMRS) score ≤8 has been reported as early as 3 weeks in over 40% of patients treated with risperidone for an acute manic or mixed episode (Gopal et al., 2003).

In the present randomized, double-blind trial of risperidone monotherapy in patients experiencing an acute manic episode, we evaluated its efficacy and safety at 3 weeks in comparison with placebo and haloperidol and its sustained efficacy and safety at 12 weeks in comparison with haloperidol.

2. Experimental procedures

This was a randomized, double-blind, parallel-group, international multicenter clinical trial. After a 3-day washout of any prior psychotropic medication, patients experiencing an acute manic episode were randomly assigned to receive flexible doses of risperidone, haloperidol, or placebo for 3 weeks. Randomization was stratified by treatment site and presence or absence of psychosis at baseline. Patients were hospitalized initially for at least 7 days and were subsequently discharged only if they had a Clinical Global Impressions (CGI) severity score of ≤3. Based on investigators' judgment, after 3 weeks of treatment, patients continued double-blind treatment with haloperidol or risperidone as previously assigned, were given open-label risperidone, or were discontinued from the trial. Patients who had previously received placebo were switched to double-blind or open-label risperidone. Results from patients in the open-label risperidone group and data from the placebo group beyond 3 weeks are not included in this analysis.

2.1. Patients

Eligible patients were physically healthy, aged 18 years or older, and had bipolar I disorder according to DSM-IV criteria (American Psychiatric Association, 1994) and a history of at least one prior documented manic or mixed episode. All patients met DSM-IV criteria for a current manic episode, for which they were voluntarily hospitalized. All patients had a score of ≥20 on the Young Mania Rating Scale (YMRS) at screening and baseline and a Montgomery–Åsberg Depression Rating Scale (MADRS) of ≤20 at baseline. Comorbid depressive symptoms not meeting criteria for a mixed episode could be present.

Exclusion criteria included DSM-IV criteria for schizoaffective disorder or rapid cycling bipolar disorder, borderline or antisocial personality disorder, recent substance abuse or dependence, risk for suicidal or violent behavior, and history of poor antimanic response to antipsychotic monotherapy. Prior or concomitant therapies excluded were antidepressant or electroconvulsive therapy within 4 weeks before screening, antiparkinsonian drugs or beta-adrenergic blockers at baseline, clozapine within 1 month before screening, and depot antipsychotic medication within one treatment cycle before screening. Psychotropic drugs including mood stabilizers and antipsychotics taken within 3 days of study entry were excluded; patients taking them at screening completed a washout period of up to 3 days before randomization.

2.2. Medication

Patients in the risperidone group received a single 2-mg dose on day 1 which could be increased or decreased by the investigator by 1 mg daily beginning on day 2 to a minimum of 1 mg/day or a maximum of 6 mg/day on day 5. Patients in the haloperidol group received 4 mg on day 1 which could be increased or decreased by 2 mg daily to a minimum daily dose of 2 mg or a maximum daily dose of 12 mg on day 5. After day 5, flexible doses of 1–6 mg of risperidone and 2–12 mg for haloperidol were allowed. In the 9-week continuation phase, patients taking risperidone or haloperidol who continued double-blind therapy received