

ADJUNCTIVE TREATMENT OF ACUTE MANIA WITH RISPERIDONE VERSUS TYPICAL ANTIPSYCHOTICS: A RETROSPECTIVE STUDY

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Few studies have directly compared atypical antipsychotics (e.g. risperidone) with typical antipsychotics as adjunctive therapy in patients hospitalized for acute mania, especially during a lengthy hospital stay. Our retrospective, case-controlled study is a chart review of 64 patients with Diagnostic and Statistical Manual of Mental Disorders, 4th edition, defined bipolar I disorder (current episode, mania). Patients were divided into two groups according to the adjunctive medications used: the risperidone group (mood stabilizers plus risperidone) and the control group (mood stabilizers plus typical antipsychotics). Outcome at discharge, medications, adverse drug effects, and length of hospital stay were compared between groups, controlling for gender, age, number of prior admissions, and duration of illness. Results indicated no statistically significant differences between groups in the controlled factors, Global Assessment of Functioning and Clinical Global Impression-Improvement scores, and adverse drug events. Patients in the risperidone group used significantly lower doses of trihexyphenidyl than those in the control group ($p < 0.05$). Patients treated with risperidone had a shorter hospital stay than those treated with typical antipsychotics ($p < 0.01$). In conclusion, antipsychotics are effective as adjunctive agents in the treatment of acute mania. The use of risperidone, in particular, decreases the need for anticholinergics and may lead to a shorter hospital stay compared with typical antipsychotics.

Key Words: bipolar I disorder, risperidone, trihexyphenidyl, anticholinergics
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Bipolar disorder (manic-depressive illness) is a chronic episodic disorder with a lifetime prevalence of 0.8–1.6% [1–3]. Almost all patients with acute mania require rapid, effective treatment and hospitalization. The primary goal of treatment is to keep patients safe and to limit the economic, social, and personal costs of manic episodes. Monotherapy with mood stabilizers is still used as a first-line therapy and

is efficacious for the treatment of acute mania, but there is a delay in therapeutic onset of 1–2 weeks [4–8].

Because rapid control of acute mania is desired, adjunctive agents, including antipsychotics, clonazepam, lorazepam, verapamil, nimodipine, clonidine, and levothyroxine, are widely used [5,9–12]. Surveys of treatment practices for acute mania suggest that up to 90% of patients with acute mania are treated with a combination of mood stabilizers and antipsychotics [6,13–15]. Typical antipsychotics may produce undesirable side effects, such as induction of depressive symptoms, neuroleptic-induced dystonia, akathisia, extrapyramidal side effects (EPS), and a long-term risk of tardive dyskinesia (TD) [16,17]. These side effects occur more frequently in patients with

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affective disorders than in schizophrenics exposed to typical antipsychotic treatment. Atypical antipsychotics are generally better tolerated than typical antipsychotics because of the decreased risk of EPS and TD [6,18].

Most research regarding the use of antipsychotic drugs in the treatment of acute mania has focused on the safety, efficacy, and adverse effects of these drugs. To date, few studies have directly compared atypical antipsychotics with typical antipsychotics as adjunctive therapy in inpatient treatment of acute mania [19,20]. In our retrospective and paired-subject comparison study, we provide a controlled comparison of risperidone and typical antipsychotics in the treatment of acute mania.

MATERIALS AND METHODS

Patients

In this retrospective, case-controlled chart review, we surveyed the charts of inpatient units of Kaohsiung Medical University Chung-Ho Memorial (KMU) Hospital between July 1, 1999, and December 31, 2003. Patients with histories of bipolar I disorder with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)-defined diagnosis and at least two prior manic episodes were included in the study. Exclusion criteria included the presence of other psychotic disorders, substance abuse or dependence, and seizure disorders. Gender, age, number of prior admissions, and duration of illness were controlled.

During the study period, 146 patients who had bipolar I disorder (current episode, mania), were admitted to the acute psychotic ward of KMU Hospital. Of these, 39 patients had been treated with risperidone, in addition to mood stabilizers. Seven patients were excluded because they were discharged against advice. This study included 32 cases in which risperidone was used as adjunctive therapy (risperidone group). The control group comprised other cases in which typical antipsychotics (chlorpromazine, haloperidol, sulpiride [21], clotiapine, or thioridazine) were used as adjunctive therapy. Data that were equivocal or unavailable were excluded on a case-by-case basis. Medications were prescribed independently by the treating psychiatrists. All medications used during hospitalization were recorded. All patients were taking mood stabilizers.

Assessment

Length of hospital stay, adverse effects, Global Assessment of Functioning (GAF) [22] score at discharge, and Clinical

Global Impression-Improvement (CGI-I) [23] score at discharge were compared between groups. At the time of discharge, the GAF and CGI-I scores were rated by the psychiatrist responsible for treatment during admission.

The comparisons included frequency of drug use, type of drug prescribed, average dosages during hospitalization and discharge dosages. Dosages of all antipsychotics, including risperidone, were converted to approximate chlorpromazine (CPZe)-equivalent mg/day doses [24]. The serum concentrations of mood stabilizers were compared using the last possible steady-state level.

Drug adverse effects included EPS, tremor, and over-sedation. EPS included neuroleptic-induced parkinsonism, neuroleptic-induced dystonia, neuroleptic-induced akathisia, and TD. The presence or absence of drug adverse effects was recorded. If patients needed to take anticholinergics for drug adverse effects, the individual psychiatrist prescribed trihexyphenidyl.

Analyses

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA) and included analysis of variance for between-group comparisons, the Kruskal-Wallis test, the Mann-Whitney test, and appropriate *post hoc* tests.

RESULTS

Demographic data and severity of illness

There were no significant differences between groups in gender (Kruskal-Wallis $\chi^2 = 0.000$, $df = 1$, $p = 1.0$), age (Mann-Whitney $U = 506.5$, $Z = -0.074$, $p = 0.941$), duration of illness (Mann-Whitney $U = 509.0$, $Z = -0.040$, $p = 0.968$), and number of prior admissions (Mann-Whitney $U = 434.0$, $Z = -1.105$, $p = 0.269$) (Table 1).

Improvement at discharge

Patients in both groups were less severely ill at discharge than at admission. The differences in GAF scores (Mann-Whitney $U = 481.0$, $Z = -0.436$, $p = 0.663$) and CGI-I scores (*post hoc* analysis, Kruskal-Wallis $\chi^2 = 0.007$, $df = 1$, $p = 0.932$) at discharge were not statistically significant between groups (Table 2).

Adverse drug effects and trihexyphenidyl

In terms of adverse drug effects, there was no significant difference between patients treated with typical antipsychotics and those treated with risperidone (Kruskal-

Wallis $\chi^2 = 1.371$, $df = 1$, $p = 0.242$). In the risperidone group, 11 patients (34.4%) were treated with trihexyphenidyl and 21 (65.6%) were not. In the control group, 13 patients (40.6%) received trihexyphenidyl and 19 (59.4%) did not. The mean dosage of trihexyphenidyl was significantly lower in the risperidone group (1.6 mg/day) than in the control group (3.0 mg/day; Mann-Whitney $U = 374.5$, $Z = -2.020$, $p = 0.043$) (Table 2).

Medications

There was no statistical difference in CPZe equivalent doses between the risperidone and control groups (Mann-Whitney $U = 466.0$, $Z = -0.620$, $p = 0.535$). The average dosage of risperidone was 2.67 mg/day. There was no significant difference between groups in the use of single or multiple mood stabilizers (Kruskal-Wallis $\chi^2 = 0.680$, $df = 1$, $p = 0.410$). In the risperidone group, 17 patients (53.1%) were treated

with only lithium as a mood stabilizer. The mean plasma concentration of lithium was 0.63 mEq/L (12 hours after last dose). In the control group, 21 patients (65.6%) were treated with only lithium as a mood stabilizer. The mean plasma concentration of lithium was 0.67 mEq/L. The clonazepam doses during hospitalization were lower in the risperidone group than in the control group, although this difference was not significant (Mann-Whitney $U = 482.0$, $Z = -0.445$, $p = 0.656$) (Table 3).

Length of hospital stay

The mean hospital stay was 22.4 days in the risperidone group and 32.5 days in the control group. *Post hoc* testing showed that patients treated with risperidone had a significantly shorter hospital stay than those treated with typical antipsychotics (Mann-Whitney $U = 309.0$, $Z = -2.728$, $p = 0.006$).

Table 1. Demographic characteristics and clinical severity

Characteristics	Control group ($n = 32$)	Risperidone group ($n = 32$)	p
Age (yrs)*	40.2 \pm 14.2	40.4 \pm 14.2	0.941
Gender			1
Female	21 (65.6%)	21 (65.6%)	
Male	11 (34.4%)	11 (34.4%)	
Duration of illness (yrs)*	8.5 \pm 7.9	9.4 \pm 9.8	0.968
Prior admissions (yrs)*	2.8 \pm 3.1	3.5 \pm 3.2	0.269

*Mean \pm standard deviation.

Table 2. Outcome at discharge, drug adverse effects, and anticholinergics

Variable	Control group ($n = 32$)	Risperidone group ($n = 32$)	p
GAF score at discharge*	55.6 \pm 11.3	57.5 \pm 9.5	0.663
CGI-I score at discharge			0.932
Much improved	21 (65.6%)	22 (68.8%)	
Mildly improved	11 (34.4%)	10 (31.2%)	
Adverse effect			0.242
Present	20 (62.5%)	18 (56.3%)	
Absent	12 (37.5%)	14 (43.7%)	
Trihexyphenidyl			0.043
Not taking	13 (40.6%)	21 (65.6%)	
Taking	19 (59.4%)	11 (34.4%)	
Dose (mg/day)*	3.0 \pm 2.9	1.6 \pm 2.3	

*Mean \pm standard deviation. GAF = Global Assessment of Functioning; CGI-I = Clinical Global Impression-Improvement.

Table 3. Comparison of medications and dosages between groups

Variable	Control group (<i>n</i> = 32)	Risperidone group (<i>n</i> = 32)	<i>p</i>
Equivalence to CPZe dose (mg/day)*	203.3 ± 149.5	178.1 ± 102.9	0.535
Mood stabilizers			0.41
Single	24 (75.0%)	22 (68.8%)	
Multiple	8 (25.0%)	10 (31.2%)	
Clonazepam			0.656
Not taking	18 (56.3%)	18 (56.3%)	
Taking	14 (43.7%)	14 (43.7%)	
Dose (mg/day)*	1.5 ± 2.9	0.8 ± 1.2	
Plasma lithium concentrations			
Only lithium	21 (65.6%)	17 (53.1%)	
Mean (mEq/L)	0.67	0.63	

*Mean ± standard deviation. CPZe = chlorpromazine.

DISCUSSION

This case-controlled study compared the combination of mood stabilizers with either risperidone or typical antipsychotics in the treatment of acute mania in a clinical environment. This study analyzed treatment effects in patients routinely seen in clinical practice; treatment was based on clinical judgment rather than on a fixed protocol and all medications were monitored in detail. Case and control patients were carefully matched on gender, age, duration of illness, and number of prior admissions; each dose of medication, including mood stabilizers and antipsychotics, represent a good reference of clinical practice. The limitations were as follows: the subject numbers were relatively small, so there may have been a false-negative effect in group comparisons; the attending physicians who made judgments regarding medication dosing were not blinded to the medications given; only clinical global impressions were used as treatment outcome measures; and adverse effects of medications were reported by clinical description rather than assessed using systematic rating scales. However, we believe that this report reflects the conditions in a real clinical setting, and, hence, it deserves further discussion.

Given these limitations, the study yields interesting results. The clinical improvement at discharge was not significantly different between groups, although patients treated with risperidone had a shorter hospital stay than those treated with typical antipsychotics. In the current managed-care system, decreasing hospital stay is a welcome

benefit. The mean serum levels of lithium in this study were 0.63 and 0.67 mEq/L in the risperidone and typical antipsychotic groups, respectively. Several studies, including this one, have suggested that these levels are within the most common guideline for monotherapy maintenance therapeutic ranges [10,25,26]. The average dosage of risperidone during this admission was 2.67 mg/day, which is lower than the therapeutic dosage for acute exacerbations of schizophrenia (4–6 mg/day) [27]. Recent data support that, in the treatment of acute mania, atypical antipsychotics have a lower incidence of adverse effects than typical antipsychotics. Although there was no quantitative systemic assessment supporting a significant difference in adverse drug effects between the two groups, patients treated with risperidone received lower anticholinergic doses than those treated with typical antipsychotics (given according to the attending physician's judgment).

In conclusion, this chart review demonstrates that risperidone may lead to decreased hospital stay when used with mood stabilizers to treat manic episodes. Risperidone, in particular, decreases the need for anticholinergics and may be more effective than the typical antipsychotics.

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比較 risperidone 與典型抗精神病藥 作為躁症發作治療佐劑之效果： 一個回溯性研究

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到目前為止，只有少數的論文提到有關：在急性躁症住院患者的治療中，比較以非典型抗精神病藥 (如：risperidone) 與典型抗精神病藥為佐劑的效果；尤其直接比較兩者急性期住院天數的比較更稀少。我們是以病歷回溯性研究，去比較分析 64 位患有第一型雙極性情感疾患，依其使用抗精神病藥為佐劑的類型，分成兩組：一組為 risperidone 組 (使用情緒穩定劑加 risperidone)、另一組為控制組 (使用情緒穩定劑加典型抗精神病藥)。兩組均以性別、年齡、先前住院次數，及發病幾年為控制因子，去比較兩組個案的出院時的改善情形、住院中的藥物使用、藥物副作用，和住院天數。結果：在控制因子、GAF/CGI-I 分數 (出院時的改善情形) 和藥物副作用均無統計學上的差異，但是在 risperidone 組明顯地較控制組減少使用 trihexyphenidyl 的情形 ($p < 0.05$)，且在 risperidone 組明顯地減少急性期住院天數 ($p < 0.01$)。結論：抗精神病藥為一種有效抗急性躁症的佐劑，特別是 risperidone 使用可以減少抗乙醯膽鹼藥物使用外，亦可以減少急性期的住院天數。

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