

Haloperidol plus amitriptyline was superior to risperidone in a psychotic and depressive syndrome

Müller-Siecheneder F, Müller MJ, Hillert A, et al. *Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. J Clin Psychopharmacol* 1998 Apr;18:111–20.

Question

In patients with combined psychotic and depressive syndrome, is risperidone effective compared with haloperidol plus amitriptyline for improving psychotic and depressive symptoms?

Design

6 week randomised, double blind, controlled trial.

Setting

Clinical centres in Austria and Germany*.

Patients

123 patients (62% women) who were 19 to 63 years of age; had comorbid major depression with paranoid or hallucinatory symptoms, or both; scored ≥ 60 points on the Positive and Negative Syndrome Scale (PANSS) with ≥ 4 points scored on the positive symptoms subscale; and scored ≥ 15 points on the Bech-Rafaelsen Melancholia Scale (BRMES) with ≥ 3 points scored on its depression item. Diagnoses according to *DSM-III-R* were major depression with psychotic features (31%); schizoaffective disorder, depressive type (52%); schizoaffective disorder, bipolar type (2%); and schizophrenia or schizophreniform disorder with major depressive symptoms (15%). 14% of patients were also diagnosed with an Axis II disorder. Exclusion criteria included high suicidal risk and substantial physical disorder.

Intervention

Patients were allocated to a fixed dose escalation schedule of risperidone, range 2 to 12 mg/day (n = 62); or haloperidol, range 2.5 to 15 mg/day, plus amitriptyline, range 50 to 300 mg/day (n = 61). Daily medication doses were altered in response to side effects and clinical response.

Main outcome measures

Changes in psychotic and depressive symptoms, presence of extrapyramidal symptoms, and adverse effects at 6 weeks.

Main results

The difference in dropout rate between treatments was not statistically significant (32% for risperidone v 21% for haloperidol and amitriptyline, $p = 0.17$). Haloperidol and amitriptyline led to a greater decrease than risperidone in psychotic symptoms (mean decrease in Brief Psychiatric Rating Scale score 25.2 v 17.6, $p = 0.009$) and depressive symptoms (mean decrease in BRMES score 15.8 v 10.5, $p = 0.002$). Patients who were allocated to risperidone developed more extrapyramidal symptoms than those who were allocated to haloperidol and amitriptyline according to the total Extrapyramidal Symptom Rating Scale (EPSR) score (mean increase 6.2 v 3.2, $p = 0.03$), mainly because of a higher shift in the parkinsonian subscale score of the EPSR (mean increase 5.8 v 2.9, $p = 0.03$). The difference between treatments in the number of patients who reported adverse events was not statistically significant (66% for risperidone v 75% for haloperidol and amitriptyline; $p = 0.35$).

Conclusions

In patients who had a combined depressive and psychotic syndrome, haloperidol and amitriptyline led to greater reductions in depressive and psychotic symptoms than risperidone. Patients who received risperidone had more extrapyramidal symptoms than those who received haloperidol and amitriptyline. No substantial difference in other adverse events existed between treatments.

*Information provided by author.

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Commentary

Müller-Siecheneder *et al* developed 2 strands of thought on the management of patients with psychotic and depressive symptoms. Firstly, they adopted a target syndrome definition of psychosis and depression that allowed for the amalgamation of patients meeting a range of *DSM-III-R* diagnoses under 1 functional heading. Secondly, they tested their previous clinical observation that risperidone, an effective antipsychotic agent,¹ may have a clinically useful antidepressant effect.²

A previous meta-analysis suggested that an antidepressant and antipsychotic combination may not confer any additional advantage to the treatment of depressed subjects with delusions.³

The findings of this study show that it is unwise to substitute risperidone for the amitriptyline and haloperidol combination in patients who have the target syndrome of psychotic and depressive symptoms. Although the reduction in scores on positive symptoms of the PANSS did not differ substantially between the treatment groups, those treated with the combination of drugs had a greater reduction of scores on the negative symptoms and general psychopathology scales. Subgroup analysis showed that patients with major depression and psychotic features (*DSM-III-R* category 295.24/34) respond better to the combination treatment than to risperidone. Whether risperidone may be prescribed

instead for patients with *DSM-III-R* schizophrenic symptoms and depression needs further elucidation.

The patients who received the combination of drugs were also less likely to show an increase in parkinsonian symptoms than those who received risperidone, although as the authors note, the dose of risperidone prescribed may have been higher than current recommendations.¹

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1 Marder SR, Meibach RR. *Am J Psychiatry* 1994;151:825–35.

2 Hillert A, Maier W, Wetzel H, et al. *Pharmacopsychiatry* 1992;25:213–7.

3 Parker G, Roy K, Hadzi-Pavlovic D, et al. *J Affect Disord* 1992;24:17–24.