Haloperidol, risperidone and olanzapine are similarly effective for first-episode non-affective psychosis but have differing side effects


Q Are first and second generation antipsychotics equally effective and safe for people with first-episode non-affective psychosis?

METHOD

- Design: Randomised controlled trial.
- Allocation: Unclear.
- Blinding: Unclear.
- Follow-up period: Six weeks (treatment period only).
- Setting: One outpatient and one inpatient clinic at a university hospital, Cantabria, Spain; enrolment February 2001 to February 2005.
- Patients: 182 adults (15–60 years old; 93% antipsychotic naive) with non-affective psychotic disorder (DSM-IV) and psychotic symptoms of moderate severity or greater (Scale for the Assessment of Positive Symptoms). Exclusions: DSM-IV mental retardation, DSM-IV drug dependence, or >6 weeks’ total lifetime adequate antipsychotic treatment.
- Intervention: Haloperidol (3–9 mg/day; mean modal dose 5.4 mg/day), risperidone (3–6 mg/day; mean modal dose 4 mg/day), or olanzapine (5–20 mg/day; mean modal dose 15.3 mg/day).
- Outcomes: Response (>=40% reduction in Brief Psychiatric Rating Scale score), adverse events including treatment-emergent akathisia (Barnes Akathisia Scale global score >3) and akathisia (Barnes Akathisia Scale global score >2).
- Patient follow-up: 95% included in last observation carried forward analyses.

MAIN RESULTS

All treatments showed similar effectiveness in inducing response by the sixth week (% responders: 57.1% with haloperidol vs 52.5% with risperidone vs 63.6% with olanzapine; p = 0.476). Haloperidol increased parkinsonism compared with the second generation antipsychotics (46.6% with haloperidol vs 5.5% with olanzapine vs 24.6% with risperidone; p < 0.001). Haloperidol also increased akathisia (55.4% with haloperidol vs 26.2% with risperidone vs 5.5% with olanzapine; p < 0.001). Olanzapine increased weight gain compared to the other antipsychotics (% people with >4 kg weight gain: 47% with olanzapine vs 23% with risperidone vs 9% with haloperidol; p < 0.001). Olanzapine and haloperidol increased somnolence compared with risperidone (46% with olanzapine vs 46% with haloperidol vs 23% with risperidone; p = 0.012).

CONCLUSIONS

Haloperidol, risperidone and olanzapine are similarly effective for first-episode non-affective psychosis. Haloperidol increases parkinsonism and akathisia, while olanzapine increases weight gain. Both olanzapine and haloperidol increase somnolence.

Commentary

There is a continuum between explanatory and pragmatic trials and physicians should critically appraise the design of randomised trials to check whether the results are applicable to everyday patients. This may be a rather difficult exercise because often trials have pragmatic aspects nested into traditional designs. Crespo-Facorro and colleagues designed a study with a very practical objective, that is to establish the effectiveness and safety of first- versus second-generation antipsychotics in the acute treatment of individuals with first-episode non-affective psychosis. Individuals with different diagnoses were pooled together, reflecting that under ordinary circumstances, first-episode patients with psychosis typically receive antipsychotic treatment even before a diagnosis is formulated. Dose regimens were very reasonable for individuals who had never been exposed to antipsychotics before, and the lack of blindness allowed researchers to manage drugs as if they were under ordinary circumstances.

These practical aspects, very innovative in the field of antipsychotic trials, coexisted with other less practical features. First, only a moderate number of patients were included in each treatment arm, and this may have negative consequences. It may leave uncertainty as to whether these patients truly resemble those seen in practice, and it may create imbalances between the three cohorts, as can be hypothesised by noting that more than 70% of those allocated to haloperidol, but less than 54% of those allocated to olanzapine, had a diagnosis of schizophrenia. Second, the primary outcome was not a pragmatic measure. In everyday practice physicians rarely establish the success of treatments on the basis of a certain score on a rating scale; by contrast, clinicians employ more pragmatic outcomes such as treatment switching, hospitalisation, or even dropping out of the trial itself. Finally, six weeks of follow-up sadly leaves unanswered the practical question of whether the metabolic consequences associated with the long-term use of second-generation antipsychotics have the potential to surpass the negative impact of motor side effects associated with the use of first-generation antipsychotics.

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