Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder

The second-generation (atypical) antipsychotic drugs were introduced over a decade ago. Although they were intended to have greater efficacy and better tolerability (eg induction of motor side-effects) than the first-generation antipsychotics, their clinical effectiveness is still debated. In previous studies treatment response has been defined by the use of scales that measure the extent of psychopathology, and efficacy has been measured according to narrowly-defined criteria. A study was thus needed with the aim of measuring effectiveness which is a combination of efficacy and tolerability. Early-stage schizophrenia might also well respond differently to antipsychotic drugs. The EUFEST study then undertook with a pragmatic open randomized-controlled trial design to compare the effectiveness of second-generation antipsychotic drugs, with that of a low dose of haloperidol in first-episode schizophrenia. Funding was provided by AstraZeneca, Pfizer and Sanofi-Aventis.

A total of 50 sites in 13 European countries and Israel participated in the study. Eligible patients were aged 18-40 years and met the DSM-IV criteria for schizophrenia, schizophreniform disorder and schizoaffective disorder. Diagnoses were confirmed by the mini international neuropsychiatric interview plus (MINI plus). Patients were excluded if more than 2 years has passed since the onset of positive symptoms or antipsychotic drugs had been used for more than 6 weeks at any time.

Just over a thousand patients (1047) were assessed for eligibility and eventually 498 patients were randomly assigned by a web-based online system to haloperidol (1-4 mg per day; mean dose 3,0 mg per day; n=103), amisulpride (200-800 mg per day; mean dose 450,8 mg per day; n=104), olanzapine (5-20 mg per day; mean dose 12,6 mg per day; n=105), quetiapine (200-750 mg per day; mean dose 498,6 mg per day; n=104), or ziprasidone (40-160 mg per day; mean dose 107,2 mg per day; n=82). All randomized patients were followed up for 1 year. The primary outcome measure was all-cause treatment discontinuation. The treating physicians and their patients were not blinded to the assigned treatment. Statistical analysis was by intention to treat.

Baseline and follow-up data were obtained for demographics, diagnoses, present treatment setting, psychopathology (positive and negative syndrome scale - PANSS), severity of illness (clinical global impression scale - CGI), overall psychosocial functioning (global assessment of functioning - GAF), depression (Calgary depression scale for schizophrenia - CDSS), quality of life (Manchester short assessment of quality of life scale - MANSA), extrapyramidal symptoms (St Hans rating scale - SHRS), and sexual dysfunction (selected items from the Udvalg for Kliniske Undersogelser - UKU).

The number of patients who discontinued treatment for any cause within 12 months was 63 (Kaplan-Meier estimate 72%) for haloperidol, 51 (53%) for quetiapine, 31 (45%) for ziprasidone, 32 (40%) for amisulpride, and 30 (33%) for olanzapine. Comparisons with haloperidol showed lower risks for any-cause discontinuation with quetiapine (hazard ratio [HR] 0,52 [95% CI 0,35-0,76]), quetiapine (HR 0,52 [0,35-0,76]), ziprasidone (HR 0,51 [0,32-0,81]), amisulpride (HR 0,37, [0,24-0,57]), and olanzapine (HR 0,28 [0,18-0,43]). However, symptom reductions were virtually the same in all the groups, at around 60%.

Treatment discontinuation for any cause, as well as treatment discontinuation because of insufficient efficacy differed between treatment groups (p<0,0001), and was lower in patients on all of the second-generation antipsychotic drugs than in those taking haloperidol, although the difference between haloperidol and quetiapine was not significant on efficacy. Treatment discontinuation because of side-effects also differed between treatment groups (p=0,023), which was mostly attributable to better tolerability of olanzapine and quetiapine than that of haloperidol. Discontinuation of treatment for non-adherence did not differ significantly between treatment groups (p=0,241).

Regarding safety and tolerability the rates of admission to hospital did not differ significantly between groups. In summary a higher proportion of patients on haloperidol or ziprasidone had akathisia, haloperidol treated patients showed more signs of parkinsonism and a higher proportion of patients on haloperidol or amisulpride used anticholinergic drugs. Weight change from baseline was highest for olanzapine patients, and lowest for patients on haloperidol or ziprasidone. Amisulpride resulted in greater increases in prolactin values per month. Overall side-effects recorded in the EUFEST study were generally consistent with those from other studies.

The EUFEST trial suggests that clinically meaningful antipsychotic treatment of first-episode of schizophrenia is achievable, for at least 1 year. The study has shown that in patients with first-episode schizophrenia and schizophreniform disorder, treatment discontinuation over 12 months was significantly greater in patients given a low dose of haloperidol than in those assigned to treatment with second-generation antipsychotic drugs, with the lowest discontinuation with olanzapine. Overall the authors could not conclude that second-generation drugs are more efficacious than is haloperidol, since discontinuation rates are not necessarily consistent with symptomatic improvement.

In their discussion the authors also refer to the CATIE trial which had consistent results with the EUFEST trial when insufficient efficacy was the reason for discontinuation, and time to discontinuation was longer in the olanzapine group than in the perphenazine and quetiapine groups. The EUFEST trial also noted that olanzapine showed a longer time to discontinuation than did ziprasidone, which was different from what was reported in CATIE. Finally discontinuation rates with second-generation antipsychotic drugs were substantially lower in the EUFEST study.

Reference

1. *Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008;371:1085-1097*