Haloperidol decanoate doses of 200, 100, or 50 mg/month reduced symptomatic exacerbations more than a 25 mg/month dose in schizophrenia


QUESTION: In patients with schizophrenia, what are the rates of symptomatic exacerbation and adverse effects with 4 different doses of haloperidol decanoate?

Design
Randomised (unclear allocation concealment*), blinded (patients, clinicians, outcome assessors, and data collectors)**, controlled trial with 1 year of follow up.

Setting
6 sites in the US.

Patients
119 patients who met DSM-III criteria for schizophrenia or had schizoaffective disorder for ≥ 2 years, needed maintenance antipsychotic treatment, and had a baseline state of relative remission for ≥ 3 months during maintenance treatment with antipsychotic medication. Exclusion criteria were treatment with lithium or antidepressants, women of childbearing potential not using acceptable birth control methods, contraindications to haloperidol use, or a Brief Psychiatric Rating Scale (BPRS) score above a specific threshold on any of 4 psychotic items. 105 patients (88%) (mean age 39 y, 83% men) completed the 1 month titration phase.

Intervention
After stratification by sex and dose of prior maintenance treatment, patients were allocated to 4 different doses of haloperidol decanoate, 25 mg (n=25), 50 mg (n=28), 100 mg (n=26), and 200 mg (n=26), each given intramuscularly once per month for 1 year or until relapse. All patients were on a stable dose of antipsychotic medication for ≥ 3 months during admission, if side effects occur, cautious dosage reduction done under close medical supervision appears warranted. However, because none of the relapses justified a hospital admission, if side effects occur, cautious dosage reduction done under close medical supervision may be relatively safe.

Main outcome measures
Rates of symptomatic exacerbations and adverse events. Symptomatic exacerbation was defined by an increase of ≥ 2 scale points on any of 4 psychotic items on the BPRS (unusual thought content, conceptual disorganisation, hallucinations, or suspiciousness).

Main results
Compared with patients who received haloperidol decanoate, 25 mg/month, those who received doses of 50 mg/month (hazard ratio [HR] 0.30, 95% CI 0.12 to 0.76), 100 mg/month (HR 0.50, CI 0.11 to 0.78), and 200 mg/month (HR 0.19, CI 0.06 to 0.59) had lower rates of symptomatic exacerbation (table); no difference existed among the 50, 100, and 200 mg/month dose groups. Among patients having no symptomatic exacerbation who remained in the study for 1 year, no difference existed among groups on any psychopathology measure at 1 year. No difference existed among groups for rates of study withdrawal because of adverse effects.

Conclusion
In patients with schizophrenia, treatment with haloperidol decanoate doses of 200, 100, or 50 mg/month did not differ for rates of symptomatic exacerbation, and were associated with lower rates of symptomatic exacerbation and similar rates of adverse effects when compared with a 25 mg/month dose.

*See glossary.
†Information provided by author.

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COMMENTARY
Although several studies have compared the efficacy and tolerability of different dosages of antipsychotic medications for psychotic relapses, this has been addressed in few relapse prevention studies, and none compared various dosages of haloperidol. Thus, the study by Kane et al is relevant for clinical practice.

The use of a randomised double blind design makes this study appropriate to answer the research question. The methodological issues related to the study’s internal validity are minor and do not undermine the conclusions. Firstly, probably because of the small sample size, minor differences were seen among groups before randomisation, but confounding was prevented using appropriate covariance analyses. Secondly, the modest sample size may have limited power to find differences among the 3 higher dosage groups. Thus, incremental benefits of dosages ≥ 50 mg cannot be ruled out. Thirdly, the assessment of side effects was not detailed, and the study duration, although longer than usual efficacy studies, was still relatively short to assess some side effects (eg, tardive dyskinesia). Thus, the lack of differences in tolerability among the dosages should be interpreted cautiously.

The patients sampled are probably representative of those who are offered antipsychotics; however, 3 issues must be considered to assess generalisability. Firstly, patients included in such efficacy studies probably represent a subgroup of relatively cooperative patients who are not totally representative of the patients for whom such medications are used. Secondly, because most patients were men, the sex specificity of these results are not addressed. Thirdly, because patients had a relatively long duration of illness, the extent to which the conclusions apply to patients with more recent onset schizophrenia is unknown.

This study provides evidence for the efficacy of higher dosages of haloperidol (ie, ≥ 50 mg) but the optimal dosage range remains undefined. Using a higher dosage appears warranted. However, because none of the relapses justified a hospital admission, if side effects occur, cautious dosage reduction done under close medical supervision may be relatively safe.

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