Low-dose neuroleptic therapy and extrapyramidal side effects in schizophrenia: an effect size analysis

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Authors' objectives
To quantify the overall extrapyramidal side-effect improvement in patients treated with low doses of neuroleptics, compared with those receiving standard doses.

Searching
MEDLINE was searched from 1966 to 1994 using the MeSH terms 'schizophrenia', 'neuroleptic' and 'randomized controlled trial'. Reference lists of review articles and research studies were checked. The search was restricted to English language articles.

Study selection
Study designs of evaluations included in the review
Randomised double-blind controlled trials (RCTs), which randomised schizophrenic patients to standard-dose neuroleptic therapy (i.e. between 200 and 500 mg equivalents of chlorpromazine) or to a low dose (i.e. between 50 and 100 mg) of the same drug. Only trials where standard deviations were reported, or were available from the authors, were included. Length of follow-up ranged from 3 to 12 months.

Specific interventions included in the review
Neuroleptic therapy with fluphenazine decanoate (doses were converted to the equivalent of chlorpromazine). The standard dose was 500 mg/day (chlorpromazine equivalent) for all but one study, which was 230 mg/day. Low doses varied between 10, 20 and 50% of the standard dose.

Participants included in the review
Patients with a standardised diagnosis of schizophrenia (RDC, American Psychiatric Association DSM III) and/or schizoaffective disorder (details taken from the meta-analysis of effectiveness by the same authors, see Other Publications of Related Interest).

The mean age of the patients was 34 years with a mean history of disease of over 131 months.

Outcomes assessed in the review
Extrapyramidal side-effects assessed were akinesia, retardation, tardive dyskinesia, akathisia, muscle rigidity, facial rigidity.

The outcome measures used were Abnormal Involuntary Movements Scale, Simpson dyskinesia scale, and Simpson-Angus scale.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The effect size was calculated for each study; where multiple side-effect indicators were used, separate effect sizes were calculated and then averaged. The effect size was defined as the distance in standard deviation units between the average side-effect incidence in patients treated with low doses versus a control group. The overall mean effect size was calculated, weighting by sample size.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Five trials (218 patients), with 120 patients in the low-dose experimental groups and 98 patients in the standard-dose control groups.

The mean improvement in extrapyramidal side-effects in the low-dose group, compared to the standard-dose group, corresponds to an effect size of 0.30 (plus or minus 0.12). This represents a small-to-medium clinically-relevant effect size.

Authors' conclusions
The results support the view that extrapyramidal side-effects are fairly insensitive to differences in dosage. However, the small effect calculated could reflect the methodological characteristics of the clinical trials included. Follow-up may be too short, and chronically-ill patients could have been maintained on high-dose regimens before entering the trial.

The main clinical recommendation is to periodically assess the risk-benefit ratio of low- and standard-dose neuroleptic therapy in individual patients.

CRD commentary
No information on the validity criteria, or the way in which decisions on the suitability of studies were reached, was provided. The search strategy was relatively limited, including only English language publications. No attempt was made to search for unpublished literature, raising the possibility of publication bias. Very little details of the primary studies were provided, although the related publication by the same authors provided more (see Other Publications of Related Interest).

Four of the five included studies used the same standard-dose level (500 mg/day chlorpromazine equivalent), whilst the other study used a much lower standard dose (230 mg/day). The low-doses used in the studies also varied from 10 to 50% of the standard doses. Combining all of these studies which have differing absolute and relative dosage rates may be problematic. The authors acknowledge that within the studies a number of different side-effect scores have been pooled to provide a global estimate; this may affect the quality of the resultant pooled estimate, the clinical relevance of which is still unclear.

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.