Efficacy and safety of neuroleptics in behavioral disorders associated with dementia

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Authors' objectives
To compare the efficacy and safety of neuroleptics versus placebo in the treatment of behavioural disorders in patients with dementia.

Searching
MEDLINE was searched from 1966 to 1995 for publications in the English language. The keywords were 'antipsychotic agents', 'phenothiazines', or 'butyrophenones'; and 'dementia'; and 'behavior therapy' or 'behavior'. Additional material was identified by the manual cross-referencing of recent reviews and the retrieved papers, and by consulting experts.

Study selection
Study designs of evaluations included in the review
The included studies were randomised controlled trials (RCTs) of at least one antipsychotic drug with double-blind assessment and placebo-control, or comparisons with an active medication. The length of treatment had to be at least 4 weeks.

Specific interventions included in the review
Antipsychotics including acetophenazine, trifluoperazine, haloperidol, thioridazine, thiothixene, loxapine and oxazepam. The comparators included placebo, diazepam, thioridazine, haloperidol, cis(Z)-clopenthixol, chlormethiazole and diphenhydramine. The duration of treatment ranged from 3 to 12 weeks.

Participants included in the review
The participants were typically patients with primary dementia (greater than 70% of the patients) who were being treated for behavioural disorders. The diagnostic descriptors of the patients were as follows:

- organic brain syndrome with psychosis (n=64);
- schizophrenia (n=7);
- depression and psychosis (n=1);
- chronic brain syndrome with (senile) psychosis (n=73);
- nonpsychotic organic brain syndrome (n=24);
- senile dementia (n=77);
- presenile dementia (n=7);
- multi-infarct dementia (n=65);
- senility (n=56);
- senile arteriosclerosis (n=18);
- primary (degenerative) dementia (n=98);
- other organic dementia (n=5);
alcoholic dementia (n=1);
alcoholism (n=8);
Korsakoff (n=4);
head trauma (n=1);
dementia, Alzheimer and arteriosclerotic forms (n=74);
major strokes (n=4);
previous depression (n=1);
unknown (n=2);
unavailable (n=113);

primary (degenerative) dementia or Alzheimer's, multi-infact dementia or senile dementia (n=40).

Outcomes assessed in the review
The outcomes assessed were the proportion of respondents who were responders, had side-effects or dropped-out. In addition, behavioural outcomes were measured using the following scales: Motility Affect Cooperation Communication Scale; Psychotic Reaction Profile; Hamilton Rating Scale for Anxiety; Nurses’ Observation Scale for Inpatient Evaluation; global rating; Brief Psychiatric Rating Scale; Clinical Global Impression; psychiatric evaluation form; Gottfries-Cronholm Geriatric Rating Scale; Crichton Geriatric Rating Scale; Sandoz Clinical Assessment-Geriatric; Crichton Geriatric Behavioral Rating Scale; Behavior Rating Scale of the Clifton Assessments Procedures for the Elderly; verbal rating scale for agitation; Alzheimer Disease Assessment Scale; 'agression scale'; Cohen-Mansfield Agitation Inventory; and an unspecified scale.

How were decisions on the relevance of primary studies made?
Three raters were given a sample of the methods section of the 51 collected papers, to assess for adherence to the inclusion criteria. Each rater was given 13 to 15 papers to rate individually plus 10 randomly selected papers to test inter-rater reliability. The raters were blinded to the authors, date, journal and place of publication of the papers.

Assessment of study quality
A quality-rating scale was used that scored each study on the following attributes: study patients, trial design, results, analysis and overall quality. Each could be rated as either 0 (not reported), 1 (poor), 2 (satisfactory) or 3 (good). Three raters were given the methods and results sections, with all identifiers removed, to assess for quality.

Data extraction
The data were extracted by three raters from the results section of each paper. The raters were blinded to the authors, date, journal and place of publication of the papers. The doses were converted to standardised units using the defined daily dose (DDD) methodology. The DDD is the mean daily dose of a medication when prescribed for its major indication. The mean dose of a neuroleptic, or the midpoint of the range of doses used in each clinical trial, was correlated to each of the major outcome variables (efficacy, side-effect rate and drop-out rate) using both raw and placebo-adjusted rates. A Pearson correlation coefficient was also calculated.

Methods of synthesis
How were the studies combined?
The method of DerSimonian and Laird (see other Publications of Related Interest no.1) with the modification by Velanovich (see other Publications of Related Interest no.2) was used to combine the study effect sizes. The summary event rates were calculated using this technique, which weights the individual studies by their sample size and
variance, to yield a pooled mean point estimate and 95% confidence level. This approach used a random-effects model.

How were differences between studies investigated?
The homogeneity of the studies was tested, prior to their combination, using the method of Breslow and Day (see Other Publications of Related Interest no.3); this calculates a Q value that follows a chi-squared distribution. The pooled, weighted mean percentages of patients who improved were calculated for subgroups of the neuroleptics, according to chemical structure (i.e. butyrophenones and phenothiazines) and degree of potency (low, moderate, moderate-to-high, and high). A sensitivity analysis was conducted to assess the effect of quality on the outcomes by (1) eliminating the poor papers and recalculating; and (2) weighting each paper by quality and recalculating.

Results of the review
Sixteen RCTs involving 734 patients were included; there were 499 neuroleptic-treated patients, 112 active controls, and 123 placebo-treated patients.

Comparative analysis: the pooled mean percentage of patients who improved was 61% (95% confidence interval, CI: 47, 75) for all neuroleptics, and 34% (95% CI: 18, 50) for placebo. No differences in efficacy existed between the different potencies of the neuroleptics. The therapeutic effect (neuroleptic minus placebo) was 26% (95% CI: 14, 38; Z=4.26, p<0.0001). Phenothiazines were more efficacious than placebo (therapeutic effect 22%, 95% CI: 5, 39, p=0.01), but they were not significantly different from the butyrophenone (i.e. haloperidol). The butyrophenone demonstrated no significant improvement over other neuroleptics.

Treatment-emergent side-effects were more common for neuroleptics than placebo (mean difference 25%, 95% CI: 13, 37). The pooled mean drop-out rates were not different (mean difference 4%, 95% CI: -7, 14). Neither weighting by clinical trial quality, nor the exclusion of poor-quality trials, changed the results.

Authors’ conclusions
Neuroleptics have small but significantly efficacy over placebo in this population, and the efficacy rate is equivalent to the side-effect rate. A comparison of different neuroleptics showed they have similar efficacy, side-effects and drop-out rates.

CRD commentary
This was a very thorough meta-analysis on the efficacy and safety of neuroleptics. The inclusion criteria appeared to be complete and well chosen, and the quality of the studies was assessed in a proper manner. The available studies have been well documented and analysed. The results were controlled by several sensitivity analyses, demonstrating the robustness of the outcomes.

The search was restricted to one database (MEDLINE) and English language publications, and the authors did not attempt to assess the possible impact of publication bias. The results may therefore be biased.

The authors reported that much of the literature on pharmacotherapies for behavioral disorders suffers from major flaws. These included a lack of a homogeneous population of well-characterised dementia patients, and inappropriate study designs. Only one study was rated as having ’good’ quality for the purposes of this analysis by all 3 raters. These flaws limited the relevance of the outcomes of this analysis.

Implications of the review for practice and research
The authors state that further studies to determine more specific drug-responsive behaviours are needed to maximise the benefits of these drugs.

Funding
Alzheimer Society of Canada.

**Bibliographic details**

**PubMedID**
9818639

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antipsychotic Agents /adverse effects /therapeutic use; Dementia /complications /psychology; Humans; Mental Disorders /drug therapy; Patient Dropouts; Placebos; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**
11998001935

**Date bibliographic record published**
30/11/1999

**Date abstract record published**
30/11/1999

**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.