Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience

Authors' objectives
To assess the efficacy of drugs used for treating psychosis, aggression and agitation in elderly patients with dementia.

Searching
MEDLINE and the Science Citation Index were searched from 1960 to 2000 for publications in the English language. Recent reviews and bibliographies of identified studies were also examined. The keywords were provided.

Study selection
Study designs of evaluations included in the review
Studies with fewer than ten patients were excluded. Studies in the review included randomised controlled trials (RCTs) both open and double-blind, non-randomised controlled trials, crossover studies and retrospective chart reviews. The duration of the included studies ranged from 1 to 52 weeks (mean: 10; median: 6).

Specific interventions included in the review
Studies of drug treatments were eligible for inclusion, whereas studies of educational interventions for physicians or carers were excluded. The included studies used haloperidol, other typical antipsychotics (acetophenazine, chlorpromazine, trifluoperazine, thiothixene, perphenazine, zuclopenthixol, tiapride, remoxipride, pimozide), atypical antipsychotics (risperidone, olanzapine, quetiapine), non-antipsychotics (mood stabilisers and antidepressants including carbamazepine, valproate and citalopram), placebo and other control medications. The included studies also used the following concomitant medications: anticholinergic agents, chloralhydrate, amobarbital, benztrpine, lorazepam, trazodone, phenobarbital, antidepressant, antipsychotics, paraldehyde, chlordiazepoxide, and supporting medication such as antibiotics and paracetamol.

Participants included in the review
Elderly people with a diagnosis of dementia or chronic brain dysfunction were eligible for inclusion. Studies reporting the age range were only included if the minimum age was 60 years; studies reporting the mean age were only included if the mean age was 60 years or over. Studies were excluded if the age was not defined. Studies were included if they did not focus on behavioural or psychotic disturbance, or if they included a large (not defined) proportion of patients with dementia related to movement disorders.

Outcomes assessed in the review
The inclusion criteria were not explicitly defined in terms of the outcomes. The review assessed improvement rates as reported in the individual studies. The included studies assessed improvement using the following measures: psychiatric symptom checklist, Brief Psychiatric Rating Scale, Clinical Global Impression, Sandoz Clinical Assessment-Geriatric, Nurse's Observation Scale, reduction in specified behaviour, behavioural pathology in Alzheimer's disease rating scale, Blessed Dementia Scale, Anxiety Status Inventory, Cohen-Mansfield Agitation Inventory, Caregiver Stress Inventory, Overt Aggression Scale, Missouri Inpatient Behaviour Scale, Neurobehavioural Rating Scale, aggressiveness scale, activities of daily living, Plutchik Geriatric Rating Scale, extrapyramidal symptoms, and other adverse effects. The studies considered improvement to be either a mean change in the score or a specified improvement (number of points) in the scale.

How were decisions on the relevance of primary studies made?
At least two authors assessed each study for inclusion according to the inclusion criteria.

Assessment of study quality
The authors described the study design and extent of blinding. The authors do not state how the papers were assessed.
for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following information were tabulated: sample size, drop-out rate, study design, primary diagnosis and aim of treatment, other medications, criteria for improvement, the number of patients evaluated, percentage improved, mean change on symptom score, and main adverse events by treatment group. The treatments were categorised as haloperidol, other typical antipsychotics, atypical antipsychotics, non-antipsychotics and placebo. Only studies reporting the number or percentage of patients improved were used to estimate the overall improvement. Only double-blind, placebo-controlled studies were used to calculate improvement for active treatment compared with placebo.

Methods of synthesis
How were the studies combined?
The mean (and standard deviation of the mean, SD) discontinuation rate and improvement rates were calculated for all treatment categories.

How were differences between studies investigated?
Differences between the studies were discussed in a narrative summary. The overall rate of improvement was calculated for double-blind placebo-controlled trials that compared antipsychotics (typical plus atypical) with placebo and reported improvement rates. The overall rate of improvement was calculated for studies published after 1990 that used atypical antipsychotics.

Results of the review
Forty-eight studies (3,697 patients) were included in the review.

Study characteristics: the studies varied considerably in sample size (range: 10 to 625 patients; mean: 78; median: 41), study design and the criteria used to measure improvement. Nineteen studies had less than 30 patients and 12 studies lasted less than 6 weeks. Over twenty measures were used to assess treatment effectiveness for psychosis and agitation. It appears that some studies used multiple treatment comparisons and were included more than once in the results.

Haloperidol (20 studies including 15 blinded RCTs): the mean discontinuation rate (17 studies) was 18.5% (SD 4.1), the mean duration of treatment was 9.1 weeks (SD 7.7), and the mean improvement rate (8 studies) was 62.6% (SD 25.7). Common adverse events were extrapyramidal symptoms, sedation and hypotension.

Other typical antipsychotics (23 studies including 12 blinded RCTs): 13 different antipsychotics were used. The mean discontinuation rate (19 studies) was 20.7% (SD 15.6), the mean duration of treatment was 7.1 weeks (SD 2.6), and the mean improvement rate (15 studies; all reported improvement with medication) was 59.7% (SD 16.1). Common adverse events were sedation, extrapyramidal symptoms and hypotension.

Atypical antipsychotics (10 studies including 3 blinded RCTs): the mean discontinuation rate (5 studies) was 22.4% (SD 10.4), the mean duration of treatment was 19.1 weeks (SD 17.0), and the mean improvement rate (5 studies; all reported improvement with medication) was 71.9% (SD 23.9). Common adverse events were sedation, extrapyramidal symptoms and orthostasis.

Non-antipsychotics (7 studies including one blinded RCT): the mean discontinuation rate (5 studies) was 12.0% (SD 5.2), the mean duration of treatment was 4.3 weeks (SD 1.7), and the mean improvement rate (2 studies) was 78.5% (SD 2.1). Common adverse events were sedation, ataxia and tremor.

Placebo (18 studies including 10 blinded RCTs): the mean discontinuation rate (12 studies) was 21.3% (SD 14.3), the mean duration of treatment was 8.0 weeks (SD 3.1), and the mean improvement rate (10 studies) was 33.9% (SD 19.3). Common adverse events were sedation and hypotension.
Double-blind placebo controlled trials (9 studies): the overall rate of improvement was 61% (SD 18%; median 65%) with antipsychotics compared with 35% (SD 20%; median 36%) with placebo.

Studies published after 1990 that used atypical antipsychotics (10 studies): the mean improvement rate was 72% (SD 24%; median 66%) with atypical antipsychotics compared with 34.3% (SD not stated; median 34.3%) with placebo.

Authors' conclusions
Conventional antipsychotics modestly improve psychosis and agitation in elderly patients with dementia. Newer treatments, such as atypical antipsychotics, are at least effective and have fewer adverse effects. The authors add that, currently, there is no ideal drug treatment available and that psychosocial management is an essential part of treatment.

CRD commentary
The review question was clear in terms of the intervention and participants. The inclusion criteria were not explicitly defined in terms of the study design or outcome. The included studies were limited to English language publications listed in two databases, which may have resulted in the omission of other relevant studies. In addition, no attempt was made to locate unpublished studies, thus raising the possibility of publication bias. At least two reviewers selected the studies for inclusion, but the methods used to extract the data were not described. Hence, the adequacy of the methods used cannot be judged. The validity assessment was limited to study design and degree of blinding.

The methodology of the meta-analysis was unclear and it was not always clear which data were used. Estimating improvement effects without weighting, as appeared to be the case in the review, can lead to bias since each study is weighted equally regardless of sample size. The studies were combined by estimating outcomes within treatments, which results in indirect rather than direct comparisons between different drugs. Statistical heterogeneity among the studies was not assessed or mentioned, although the wide standard deviations for the mean event rates for some outcomes indicate considerable variability among the studies. It was not clear whether the decision to analyse separately the studies on antipsychotics published since 1990 was made a priori or post hoc. The drop-out rates were high and the analysis was not conducted on an intention-to-treat basis. The quality of the evidence cannot be assessed since no validity assessment was performed and the results were not reported separately for the higher quality studies. The rates of adverse events per treatment were not reported.

In view of the limitations highlighted, the authors' conclusions do not appear to be adequately supported by the evidence presented in this review.

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Implications of the review for practice and research
Practice: The authors state that the treatment of choice for psychosis in patients with dementia is antipsychotics drugs. They go on to state that atypical antipsychotics are preferred because of lower adverse event rates and that non-psychotics should be reserved as second-line treatment. They recommend that drug treatments should be started with the lowest possible dose and increased gradually with regular monitoring for adverse events, and that non-pharmacological treatment should form part of the treatment for behavioural disturbances.

Research: The authors state that further large well-controlled studies are required to determine the relative effectiveness of atypical antipsychotics and non-antipsychotics.

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