Can pharmacological treatment of behavioural disturbances in elderly patients with dementia lower the burden of their family caregiver?

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Family caregivers of a community-dwelling demented relative experience significant burden in their caregiving role. In particular, behavioural disturbances are expected to be responsible for high caregiver distress and burden. Above, in ~80% of the cases, institutionalization of the demented patients with dementia occurs as a result of a burdened caregiver.

Because of the impressive disruptive character of behavioural disturbances, most caregivers appeal for pharmacological intervention at a given moment, expecting instant suppression of the aberrant behaviour. Beside the antipsychotic drugs, the cholinesterase inhibitors are commonly used in the treatment of agitation, aggression, delusions, etc. Although in meta-analyses on the efficacy of both categories of drugs, only little evidence of their efficacy has been found and an important placebo effect has been reported that >90% of the demented elderly was treated at least once.

The aim of this study was to investigate if pharmacological treatment of behavioural disturbances of the demented can lower the burden and the time spent in the family caregiver irrespective of their effect on the demented himself.

A systematic literature search was performed by means of Medline, Embase, Cochrane DSR, Dare, CCTR and ACP Journal Club.

Based on this review, pharmacological treatment of demented elderly seems to lower caregiver burden (mean difference 0.27) and the time caregivers spent (mean difference 41.65 minutes).

Considering that family caregivers confronted with the troublesome behaviour of their demented relative will apply for pharmacological intervention, future research should particularly focus on the outcome measures of the caregivers’ well-being.

**Keywords.** Dementia, family medicine, geriatric medicine, meta-analysis, psychiatry.

Introduction

Family caregivers of a community-dwelling demented relative experience significant burden in their caregiving role.¹ Caregiving burden has previously been defined as a complex interaction of physical, psychosocial and economical economic problems experienced by the caregiver.² Large volumes of studies have explored the relation between the negative impact of caregiving on caregivers’ general well-being. Prevalence of depression and subjective burden is significantly higher in dementia caregivers than in peers or caregivers of other chronically ill relatives. Although much has been written about this observation, the mechanism of cause and consequence still remains unclear.³⁵ Patient, caregiver and the caregiving context contribute in a unique way to the onset of a negative impact of caregiving. In particular, behavioural disturbances are expected to be responsible for high caregiver distress and burden.⁶⁻⁸ Caregivers report the unexpected and unpredictable character of this troublesome behaviour as severely problematic. Moreover, a burdened or distressed caregiver is less able to deal with aberrant behaviour and in ~80% of the cases
institutions of the demented patients with dementia occurs as a result.9–11

Because of the impressive disruptive character of behavioural disturbances in the demented, most caregivers appeal for pharmacological intervention at a given moment, expecting instant suppression of the aberrant behaviour.12–14 Besides the antipsychotic drugs, the cholinesterase inhibitors are commonly used in the treatment of agitation, aggression, delusions, etc. Although in meta-analyses on the efficacy of both categories of drugs, only little evidence of their efficacy has been found and an important placebo effect has been reported >90% of the demented elderly was treated at least once.15–22 Besides, the use of these drugs in demented patients is marked by substantial side effects.16,23 Long-term use is therefore limited in this population. One meta-analysis found a small beneficial effect of cholinesterase inhibitors on caregivers’ experience of burden.24

Since the obviously persistent need in caregivers for pharmacological suppression of disturbing behaviour, redefining the outcome measures in pharmacological studies on this topic might be required.16,25–27 The fact that these behaviour-controlling drugs may have little or a short-term effect could possibly be of high relevance for the burdened caregiver.12,16,24 The aim of this study was to investigate if pharmacological treatment of behavioural disturbances of the demented can lower the burden and the time spent in the family caregiver irrespective of their effect on the demented himself.

The intervention was determined as the administration of a psychotropic drug versus a placebo. No specification of drug type was made: neuroleptic, antipsychotic, antidepressant and cognitive enhancement drugs were included.

Of all articles that were considered to be eligible, a hard copy was retrieved. If multiple articles used data of the same original trial, the most suitable in terms of outcome measures and study question was retained.

Quality judgement

Quality judgement of retrieved articles was based upon the modified version of the Delphi Criteria and performed by two independent reviewers.28 This instrument is developed as a consensus among experts on a generic criteria list for quality assessment in randomized controlled trials. Articles were eligible if randomization was performed, treatment allocation concealed, eligibility criteria specified, if assessor, care provider and caregiver were blinded and if primary outcome measures were described as point estimates and variability measures. Articles were coded on date of publication, authors, sample size and features, rating scales, treatment details and the final results according to a structured form.

When the quality of a report was debatable, a discussion between several independent reviewers was conclusive for inclusion or exclusion of the concerned article.

Methods

Literature

A systematic literature search was performed by means of Medline, Embase, Cochrane Database of Systematic Reviews, Dare, Cochrane Controlled Trial Register, and American College of Physicians Journal Club.

Keywords and MeSH terms that were searched were dementia, primary caregiver, cholinesterase inhibitors and psychotropic drugs.

Limitations of publication type were determined as randomized controlled trial, controlled trial and cohort design. No restriction of time was introduced.

Reference lists were checked to track additional relevant publications. Hand searching was performed with the aid of information on conferences and PhD manuscripts.

Inclusion criteria

Articles were initially eligible if they reported on a clinical trial of psychotropic medication to suppress disturbed behaviour in patients with dementia and when there was a caregiver-related outcome measure described as burden or caregiving time.

Population inclusion criteria were limited to community-dwelling elderly with dementia and the presence of a family caregiver.

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Analysis of data

Analysis of data was performed with the aid of Review Manager Software version 4.2 and based upon the theory described in the Cochrane Handbook of Systematic Reviews of Interventions version 4.2, 5 May 2005.

Publications were grouped along the drug category that was investigated. No distinction in substance was made for drugs of the same category. If dose-related comparisons were made, the highest tolerated dose versus placebo was used for analysis. In long-term follow-up studies, the observation at 6 months was used for analysis. For continuous outcome data, the standardized mean difference and its standard error were analysed. No articles with dichotomous outcome data were retrieved.

If necessary, the standard error was calculated from the mean difference, P-value, t-test or F-distribution. In Review Manager, the inverse generic technique was used to analyse the effect size of the intervention. This technique implies that the weight given to each study is chosen to be the inverse of the variance of the effect estimate. The advantage of this method lies in the possibility to estimate the effect size out of odds ratios, risk ratios and effect estimates and their confidence interval or exact P-value if more appropriate data are lacking. Only standard errors and estimates
of effects are required for this type of analysis. The forest plot graph was generated using the statistical software of STATA version 10, 2008.

Heterogeneity in published trials was as a P-value of chi-square of ≥0.1 or \( I^2 > 50\% \). In case of heterogeneity, a random model analysis was applied. A funnel plot was performed for both burden and time spent to determine if publication bias was present.

Results

Literature search

A total of 745 articles were retrieved after a first search. Out of this retrieval, 109 articles were found eligible based upon study design (controlled trial and cohort design) and outcome measures (burden and caregiver time spent). Searching through the reference lists of the retrieved articles yielded six more trials (Fig. 1).

Based upon abstract and, if unclear, the entire article, 15 articles were read thoroughly. Six studies did not include a control group (open-label design) and one article only reported percentages to describe mean changes after treatment. After this step, only eight articles met all inclusion criteria (Table 1).

A quality check for each article was performed with the Delphi Criteria and is described in Table 2.

Socio-demographic features were limited to age (\( k = 2 \)), gender (\( k = 2 \)) and relationship (\( k = 1 \)) with the patient. With respect to the mean caregiver and

<table>
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<tr>
<th>Mesh-terms and keywords</th>
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| dementS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] and (psychotropS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] or antidepressS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm]) or neuroleptS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] or hypnoticS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] or cholinesterase inhibitorsS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm]) and (family careS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] or home nursS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] or home care.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm] or primary careS.mp. [mp=t, ot, ab, tx, kw, ct, sh, hw, nm]) limit to (clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial or "review" or "review literature")

FIGURE 1  Flow chart of search strategy
Table 1  Overview of articles retrieved and read

<table>
<thead>
<tr>
<th>Design and participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Wimo et al.(^{30})</td>
<td>Subanalysis of RCT donepezil versus placebo, (n = 190)</td>
<td>Donepezil 5–10 mg 1 year versus placebo</td>
<td>RUD for caregiver time</td>
</tr>
<tr>
<td>Clipp and Moore(^{31})</td>
<td>449 patients and caregivers of RCT</td>
<td>Velacrine 150–225 mg versus placebo during 24 weeks</td>
<td>Caregiver time by CATS</td>
</tr>
<tr>
<td>Feldman et al.(^{32})</td>
<td>Subanalysis of RCT with dementing and caregivers, (n = 287)</td>
<td>Donepezil 5–10 mg versus placebo during 24 weeks</td>
<td>Caregiver time in minutes noted in diary; caregiver stress by CSS</td>
</tr>
<tr>
<td>Fillit et al.(^{33})</td>
<td>Matched control group among donepezil users and non-users, matching based upon status caregivers</td>
<td>Donepezil &gt; 9 months versus non-use</td>
<td>Burden by CBS, health status by SF-12</td>
</tr>
<tr>
<td>Teri et al.(^{34})</td>
<td>RCT with 149 patients-caregiver dyads, patients with dementia-related behavioural disturbances; caregivers: spouse or relative</td>
<td>Haloperidol 0.5 mg versus trazodone 50 mg versus behavioural management techniques, 16 weeks, all blinded to interviewer</td>
<td>Caregiver burden by SCB</td>
</tr>
<tr>
<td>Shikiar et al.(^{35})</td>
<td>(n = 546), subanalysis of RCT, dementing with MMSE between 10 and 26, primary caregiver present</td>
<td>26 weeks metrifonate 40/50 and 60/80 mg versus placebo</td>
<td>Caregiver burden by SCB, CATS</td>
</tr>
<tr>
<td>Cummings et al.(^{36})</td>
<td>24 weeks multicenter RCT, secondary analysis, (n = 978) probable alzheimer patients and their caregivers</td>
<td>galantamine 8/16/24 mg a day or placebo during 24 weeks</td>
<td>Caregiver distress by NPI-D</td>
</tr>
<tr>
<td>Sano et al.(^{37})</td>
<td>(n = 825) patients and caregivers in RCT, secondary analysis</td>
<td>Galantamine 24 mg 6 months or placebo</td>
<td>Allocation of caregiver time ACTS; Burden by RSSS</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; RUD, resource utilization in dementia; CSS, caregiver stress scale; CATS, cognitive assessment and treatment service; CBS, caregiver burden screen; SF-12, Short Form Health Scale-12; SCB, screen for caregiver burden; MMSE, mini mental state examination; ACTS, allocation of caregiver time; RSSS, Research School of Social Sciences.

Activity Survey, The Resource Utilization in Dementia and The Allocation of Caregiver Time Scale.\(^{43-45}\)

All scales estimate time spent in minutes a day. No component of subjective burden is included in these scales.

Test for heterogeneity and sensitivity analysis

In a preview of the data extracted from the included trials, heterogeneity among studies was not expected. Type of drug therapy varied, but participants and treatment conditions were comparable between trials. Patients all presented with mild-to-moderate cognitive impairment and behavioural disturbances.

All included studies used similar analysing techniques presented in mean differences between control and treatment groups. In all publications, a small beneficial, but mainly insignificant result in favour of the treatment arms was reported with broad overlap of confidence intervals. Sensitivity analysis by means of standardized mean differences and standard deviations if available did not change the result in a materially way. Excluding studies with small sample sizes did not affect the effect size. The robustness of the results was finally proved by changing the fixed effects model into a random effects model.

The absence of heterogeneity was confirmed for both outcomes with considerably high P-values.
Publication bias
Publication bias was tested with a funnel plot for both outcome measures burden and time spent. The inverse standard error of the effect estimate was plotted against the effect size. This method avoids an overestimation of the statistical power of a trial with a small sample size and a high number of events. No indication for publication bias was found.

Effect on burden
Subjective burden (burden and distress) in caregivers was assessed in different ways and with varying terminology (Table 1). All scales are validated and commonly used instruments. Five clinical trials reported on caregiver burden or distress. 

Four trials studied the efficacy of a cholinesterase inhibitor versus placebo on behavioural disturbances. 

One study compared haloperidol versus trazodone versus placebo (Fig. 2).

Except for the trial of Teri et al. and Fillit et al., study performance was based upon secondary analysis of existing databases as part of the safety and efficacy studies on drugs.

Mean ages and features of the patients were similar in all studies although it appeared impossible to make an exact pooling of data because of incomplete information. All studies showed a decrease in subjective burden. Teri et al. reported a placebo response of 31%.

Meta-analysis showed a slight but significant beneficial effect with a mean difference of 0.27 (95% CI 0.13–0.41, chi-square 2.98, $I^2 = 0\%$) of antipsychotic drug treatment on behavioural disturbances in demented on caregiver burden (Fig. 2).

The effect of cholinesterase inhibitors in behaviourally disturbed demented on caregiver burden shows a mean difference of 0.23 (95% CI 0.08–0.33).

Caregiver time spent
The time that caregivers spend on average in assisting patients with daily activities or supervision is assessed in minutes a day based upon a self-scoring evaluation (Table 2). Five trials compared the number of minutes a family caregiver of a drug-treated versus placebo-treated demented spent on caregiving tasks.

All trials investigated the efficacy of cholinesterase inhibitors in lowering caregiver time spent (Fig. 3).
All studies reported socio-demographic data on both caregiver and patient. Unfortunately, these data were useless for meta-analytic assessment due to incompleteness. All studies participated in the framework of a multicentre survey examining efficacy and safety of cognitive enhancing drugs. Publication was therefore based on secondary analysis. Meta-analysis of the time in minutes spent by the family caregiver favours the treatment arm in a significant way (mean difference 41.65 minutes/day, 95% CI 25.29–58.02, chi-square 3.73, $I^2 = 0\%$).

**Discussion**

Based on this review, pharmacological treatment of demented elderly seems to lower caregiver burden (mean difference 0.27). The time caregivers spent in caregiving and supervising also decreases (mean difference 41.65 minutes). Although only four of eight studies used an intention-to-treat analysis, effect sizes of treatment on outcome measures were comparable to the results in the other studies.

Caregivers usually put high confidence in pharmacological treatment of their demented relative. Particularly when this relative presents with a fast cognitive decline or with behavioural disturbances, caregivers expect an instant solution. However, because of the acute and unexpected character, caregivers usually put high confidence in pharmacological treatment of their demented relative. In this study, no subgroup analysis was performed, and fall-out rates were low (~20%). This relatively low fall-out rate is mainly due to the very short mean study duration (3–6 months).

It is known for both cognitive enhancers and antipsychotics that the treatment effect is best in mild to moderately demented patients. Aberrant behaviour due to the dementia process is a regular indication for prescription of cognitive enhancers. Scores on the behavioural instruments showed similar degrees of disturbed behaviour among the demented study population. Treatment conditions can therefore be considered as comparable between the different drug types.

The open-label studies (not included in the pooling) were performed with the explicit focus on caregivers’ burden or time spent in caregiving. In all five of these trials, the reported decline in caregiver burden reached statistical significance. However, the lack of a control group may have distorted the effect size in substantial way since an important placebo effect is noted in most controlled studies. Extra attention of a research group and medical personnel is known to positively influence caregivers’ and patients’ well-being. Particularly for caregivers, this might have more influenced the pharmacological treatment of their relative.

Some methodological issues limit the performance of studies on the effect of drug treatment in demented patients and their carers. Aberrant behaviour implies an acute situation and therefore inclusion in a placebo arm of a trial is not always feasible. Additionally, administration of antipsychotic drugs and cognitive enhancement drugs is both restricted in time due to side effects and declining clinical activity. On average, supported home care situations will take between 3 and 5 years of follow-up. It is unclear if longer lasting studies on drug treatment will evocate a more powerful effect on caregiver burden and time spent. Secondly, deciding to start drug treatment implies a moment of stopping them. Caregivers are faced with ethical dilemmas in these decisions. Besides the ‘start–stop’ dilemma, drug treatment also brings concerns about side effects and the extra burden of administration. These observations might limit the small beneficial effects on caregiver burden of drug treatment on the long term.

Thirdly, the treatment effect on caregivers might be very dependent on caregiver characteristics. It is known that caregivers with good coping strategies have a better prognosis in caregiving. These coping strategies rather than socio-demographic features seem to predict the impact of caregiving on the general well-being of the relative. Future studies are required to investigate which type of caregiver benefits from pharmacological treatment of his or her demented relative. In this study, no subgroup analysis was feasible since only very poor registration was performed in caregivers and the studies were a based upon a secondary analysis of an available dataset.
Finally, although drug treatment can dramatically reduce acute aberrant behaviour, teaching caregivers how to cope with these problems is of main importance. However, such training sessions require cooperative and physically capable caregivers since these are usually organized outside the caregivers’ home.

Caregivers as well as professionals usually have high expectations of pharmacological treatment as an instant solution for behavioural disturbances in patients with dementia. Although a minor but significant beneficial effect of drug treatment on caregiver burden was shown in this meta-analysis, results should be interpreted with caution. A short follow-up period, an important placebo effect and a preselection of caregivers mainly recruited from specialized care centres, might have resulted in an overestimation of the effect. Nevertheless, it seems justified under certain conditions to comply with caregivers’ requests for a pharmacological approach of aberrant behaviour in the demented relative. However, agreements between the clinician, the family caregiver and if possible the patient about how to cope with these problems is of main importance.56

Considering that family caregivers confronted with the troublesome behaviour of their demented relative will apply for pharmacological intervention, future research should particularly focus on the outcome measures of the caregivers’ well-being. On the other hand, a thorough assessment of side effects and benefits to the troublesome behaviour of their demented relative will apply for pharmacological intervention, future research should particularly focus on the outcome measures of the caregivers’ well-being. On the other hand, a thorough assessment of side effects and benefits to the troublesome behaviour of their demented relative.