Pharmacological Treatment of Apathy in Neurodegenerative Diseases: A Systematic Review

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Key Words

Apathy · Neurodegenerative disease · Dementia ·
Pharmacotherapy · Systematic review

Abstract

Objective: To evaluate the efficacy of pharmacological treatment of apathy in patients with neurodegenerative diseases.

Methods: Systematic review of studies assessing the effects of pharmacological treatment on apathy in neurodegenerative diseases. **Results:** Thirty-five studies were included: 2 meta-analyses, 13 randomized controlled trials (RCTs), 14 open-label studies, 5 case series, and 1 single case study. Eight studies included apathy as a primary outcome. A cholinesterase inhibitor was investigated in 24 studies, methylphenidate in 5, and other medications in 6 studies. Most RCTs of cholinesterase inhibitors reported a small but statistically significant improvement of apathetic symptoms. **Conclusions:** Although some medications are promising candidates for further study, there is as yet insufficient evidence that pharmacological treatment improves apathetic symptoms in patients with neurodegenerative disease. Large-scale, placebo-controlled RCTs with apathy as a primary outcome measure are needed to establish the potential benefit of pharmacological treatment of apathy.

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Introduction

Apathy is defined as a lack of motivation characterized by diminished goal-oriented behavior and cognition, and diminished emotional concomitant to goal-directed behavior [1]. It is common in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Apathy is the most frequently reported behavioral syndrome in dementia, with an estimated prevalence of 42–92% [2–6]. In PD, apathy is reported in 17–70% of patients [7–10].

Apathy is increasingly considered a distinct syndrome instead of a symptom of neuropsychiatric disorders. Its neuroanatomical and neurochemical substrates are still largely unknown, although limbic structures and striato-thalamo-cortical circuits are thought to be involved [11]. Apathy decreases the quality of life of patients with AD and their caregivers and is associated with caregiver distress; apathy in AD patients increases the likelihood of institutionalization [12–17]. In patients with PD, apathy is associated with more severe cognitive dysfunction and a decreased ability to perform activities of daily living (ADL) [8, 18–20]. For these reasons, apathy is increasingly considered a potential target for treatment. Although non-pharmacological interventions have been tested as therapy for apathy – such as multisensory stim-

Table 1. Levels of evidence and grades of recommendation

Level	Explanation
<i>Levels of evidence</i>	
1	One or more randomized controlled trials (RCT) (or systematic review of trials) of sufficient size to ensure a low risk of false-positive or false-negative results (narrow confidence interval)
2	Good quality cohort studies or low-quality RCT (e.g. too small, <80% follow-up)
3	Case-control studies, including systematic reviews of case-control studies
4	Case series, and poor-quality cohort and case-control studies
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'
<i>Grades/strengths of recommendations</i>	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies OR extrapolations from level 1 studies
C	Level 4 studies OR extrapolations from level 2 or 3 studies
D	Level 5 evidence OR troublingly inconsistent or inconclusive studies of any level
Summarized from Oxford Centre for Evidence-Based Medicine 2001 [25].	

ulation, protocollized activity therapy, communication therapy, and massage therapy – to date, results have been either inconclusive or negative [21–24]. However, the pharmacological treatment of apathy has not yet been critically evaluated. Therefore, the aim of this study is to systematically review the evidence for pharmacological treatment of apathy in patients with neurodegenerative diseases.

Methods

Search Strategy and Selection Criteria

The Pubmed database was searched up to June 2008 using the keyword 'apathy', applying the following limits: 'humans', 'clinical trial', 'meta-analysis', 'practice guideline', and 'randomized controlled trial'. Abstracts of the retrieved articles were screened for relevance. Criteria for inclusion in the review were: (i) the study population involved patients with a neurodegenerative disease; (ii) the study objective was to evaluate the effects of a pharmacological treatment; (iii) apathy was reported as a primary or secondary outcome; and (iv) the article was written in English,

Dutch, German, or French. Further articles for inclusion were identified by searching the references of retrieved articles and by checking the Cochrane library. There were no limitations regarding study design, and thus the review included meta-analyses, randomized controlled trials (RCTs), open-label studies, and case studies. Studies that were included in a meta-analysis were not also included separately as RCTs.

All articles were read in full and their level of evidence and outcome were assessed by 2 of the authors (R.D., A.W.). If there was a difference of opinion, a consensus meeting was held with the last author (A.L.) to discuss the disagreement and to reach a final decision. Studies were classified by their level of evidence following the system of the Oxford Centre for Evidence-Based Medicine [25, 26]. Grades of recommendation were also scored with this classification (table 1).

Results

Literature Search

The initial search yielded 136 articles. Of these, 23 articles were selected on basis of title and abstract and the remainder were excluded because the study population did not suffer from a neurodegenerative disease ($n = 46$), the study did not investigate pharmacotherapy ($n = 59$), or the article was written in a language other than English, German, French or Dutch ($n = 8$). Another 32 potentially relevant articles were identified from the references of the included articles, 19 of which were excluded because the study population did not suffer from a neurodegenerative disease ($n = 1$), the study did not investigate a pharmacological intervention ($n = 2$), or apathy was not a primary or secondary outcome ($n = 16$). Three studies known by the authors, but not retrieved by the search, were also included. Four studies were not considered individually because they were included in 2 meta-analyses. In total, 35 studies were included in the review.

Appraisal of Studies

Of these 35 studies, only 9 had the treatment of apathy in a neurodegenerative disease as primary outcome, whereas the other 26 studies included apathy as a secondary outcome variable, often as part of a broader measure of neuropsychiatric symptoms, such as the Neuropsychiatric Inventory (NPI) [27]. The review included 2 meta-analyses, 13 RCTs, 14 open-label studies, and 6 case studies. Cholinesterase inhibitors were investigated in 24 studies, methylphenidate in 5 studies, and other drugs (paroxetine, amantadine, memantine, levodopa, tianeptine, and *Ginkgo biloba* extract) in 6 studies (1 study each). Both meta-analyses, 9 of the 13 RCTs, and 9 of the 14 open-label studies involved patients with AD; the other

studies included patients with dementia with Lewy bodies (DLB) (n = 3), frontotemporal dementia (FTD) (n = 4), vascular dementia (n = 2), and PD (n = 3). Two studies included both patients with AD and vascular dementia, and 1 study did not define the type of dementia (table 2).

Study recommendations were graded according to the criteria of the Oxford Centre for Evidence-Based Medicine (table 1) [25], and where possible, effect sizes were calculated with Cohen's d [28]. Both meta-analyses and 11 of the 13 RCTs were classified as grade A. None of these studies included apathy as a primary outcome variable. The remaining 2 RCTs were classified as grade B, and the open-label studies and the case studies were classified as grade C (table 2).

Meta-Analyses

Cummings et al. [29] performed a meta-analysis of the combined data from 2 previously published double-blind, multicenter, placebo-controlled RCTs involving 672 patients treated with the cholinesterase inhibitor metrifonate [30, 31]. After 26 weeks, treatment with metrifonate (30 or 60 mg daily) resulted in a significant reduction in the average score on the NPI apathy item ($p = 0.019$), with 51% of the metrifonate-treated versus 36% of the placebo-treated patients achieving a reduction of at least 30% ($p = 0.020$).

Herrmann and colleagues [32] performed a meta-analysis of 3 large placebo-controlled RCTs examining the effectiveness of the cholinesterase inhibitor galantamine. Two of these trials had been published before [33, 34]. The meta-analysis included 2,033 patients with mild to moderate AD treated for 13, 22, or 26 weeks with doses varying from 16–32 mg daily. Apathy was assessed, as a secondary outcome variable, using the NPI apathy item. There was no significant difference in outcome between treatment with galantamine or placebo.

RCTs

Thirteen RCTs assessed the effects of pharmacological treatment on apathy, of which 1 evaluated apathy as a primary outcome, measured with the Apathy Evaluation Scale (AES) [35, 36]. The other 12 studies included apathy as a secondary outcome, mostly measured with the NPI apathy item. Seltzer et al. [37] used another validated scale, the Apathy Scale (AS), to measure apathy as a secondary outcome [38]. Ten studies involved a cholinesterase inhibitor, 1 study involved methylphenidate, 1 paroxetine, and 1 *Ginkgo biloba* extract. Of the cholinesterase inhibitors, donepezil was used in 6 studies, metrifonate in 2, and galantamine and rivastigmine in 1 each.

Donepezil was the most-studied cholinesterase inhibitor. Feldman et al. [39] reported that donepezil produced a significantly greater reduction in NPI apathy score than placebo in 290 patients with AD but failed to report the p value. The same database was used for 2 sub-analyses [40, 41]. Gauthier et al. [41] included the same 290 patients and found significant treatment differences on the NPI apathy score ($p = 0.0018$), whereas Feldman et al. [40] found a significant improvement in NPI apathy score with donepezil in 145 patients with more severe AD ($p = 0.012$), operationalized as a score between 5 and 12 on the Mini Mental State Examination (MMSE) [42]. Tariot et al. [43] did not find donepezil to improve apathy (assessed using the NPI apathy item) in 208 nursing home patients with AD, whereas Holmes et al. [44] reported a significant reduction in NPI apathy score after 12 weeks of open-label treatment with donepezil in 134 patients with AD ($p < 0.001$). No results were reported for the subsequent randomization phase. Seltzer et al. [37] found no difference in scores on the AS between treatment with donepezil and placebo in 253 patients with AD.

Kaufer [45] and Dubois et al. [46] both studied the effect of metrifonate in patients with AD. The former reported a significant improvement in apathy (NPI apathy item) in 408 patients treated with metrifonate compared with placebo ($p = 0.03$) [45], whereas in the latter study ($n = 605$), a significant improvement ($p = 0.048$, compared with placebo) in the NPI apathy score of patients treated with a high (60–80 mg) but not low (40–50 mg) dose of metrifonate was reported [46].

Of the other pharmacological treatments, McKeith et al. [47] reported an improvement in NPI apathy score after 23 weeks of treatment with rivastigmine (6–12 mg) in 120 patients with DLB; however, no p value was mentioned. Erkinjuntti et al. [48] reported that galantamine significantly improved the NPI apathy score of 592 patients with vascular dementia ($p < 0.0001$). In a recent study, Herrmann et al. [35] found methylphenidate (10 mg, b.i.d.) to improve apathy (measured with the AES) compared with placebo in 13 apathetic patients with AD. In their study of 10 patients with FTD, Deakin et al. [49] defined a NPI-4 score to measure apathy based on factor analysis of the full NPI. This NPI-4 score represented a sub-score consisting of the items disinhibition, apathy, aberrant motor behavior and euphoria. The authors did not find paroxetine to significantly improve apathy compared with placebo [49]. A study by Scripnikov et al. [50] examined the effects of *Ginkgo biloba* extract (EGb 761) in 400 patients with vascular dementia and AD. One of the largest drug-placebo differences in favor of EGb 761

Table 2. Characteristics and outcome of studies included in the review, by design and in chronological order

Study	Grade of recommendation	Population	Sample size	Intervention	Duration	Apathy as a primary or secondary objective	Measure-ment instrument	Outcome	Effect size
<i>Meta-analyses</i>									
Cummings et al., 2001 [29]	A	Mild to moderate AD	672	Metrifonate (30–60 mg or 50 mg fixed dose/day) or placebo	26 weeks	Secondary	NPI	Significant reduction in NPI apathy item with metrifonate ($p = 0.019$)	
Herrmann et al., 2005 [32]	A	Mild to moderate AD	2,033	Galantamine (16–24 mg/day) versus placebo	13, 22, and 26 weeks	Secondary	NPI	Reduction in NPI-4 score ($p = 0.009$), but no significant reduction in NPI apathy item, with galantamine	–0.09
<i>Double-blind randomized controlled trials, placebo-controlled</i>									
Kaufer et al., 1998 [45]	A	AD	408	Metrifonate (30–60 mg) or placebo	26 weeks	Secondary	NPI	Significant reduction in NPI apathy score with metrifonate ($p = 0.03$)	
Dubois, 1999 [46]	A	Mild to moderate AD	605	Metrifonate (40–80 mg/day) or placebo	26 weeks	Secondary	NPI	NPI apathy score improved significantly with 60–80 mg metrifonate only ($p = 0.048$)	
McKeith et al., 2000 [47]	A	DLB	120	Rivastigmine (6–12 mg/day) or placebo	23 weeks	Secondary	NPI	Improvement in NPI apathy score with rivastigmine	
Feldman et al., 2001 [39]	A	Moderate to severe AD	290	Donepezil (5–10 mg/day) or placebo	24 weeks	Secondary	NPI	Significant reduction in NPI apathy scores with donepezil	
Tariot et al., 2001 [43]	A	AD nursing home patients	208	Donepezil (5–10 mg/day) or placebo	24 weeks	Secondary	NPI-NH	No significant differences between donepezil and placebo	
Erkinjuntti et al., 2002 [48]	A	VaD	592	Galantamine (24 mg/day) or placebo	26 weeks	Secondary	NPI	Significant reduction in NPI apathy scores with galantamine ($p < 0.0001$)	
Gauthier et al., 2002 [41]	A	Moderate to severe AD	290	Donepezil (5–10 mg/day) or placebo	24 weeks	Secondary	NPI	Significant reduction in NPI apathy scores with donepezil ($p = 0.0018$)	
Deakin et al., 2004 [49]	B	FTD	10	Paroxetine (40 mg/day) or placebo	9 weeks	Secondary	NPI	No significant improvement in NPI-4 score ($p = 0.913$)	0.71
Holmes et al., 2004 [44]	A	Mild to moderate AD	134	Donepezil (10 mg/day) or placebo	24 weeks	Secondary	NPI	Significant reduction in NPI apathy score with donepezil ($p < 0.0001$)	
Seltzer et al., 2004 [37]	A	Early-stage AD	153	Donepezil (10 mg/day) or placebo	24 weeks	Secondary	AS	No difference between donepezil and placebo	
Feldman et al., 2005 [40]	A	Severe AD	145	Donepezil (5–10 mg/day) or placebo	24 weeks	Secondary	NPI	Significant reduction in NPI apathy scores with donepezil ($p = 0.0116$)	
Scribnikov et al., 2007 [50]	A	AD and VaD	400	<i>Ginkgo biloba</i> extract (240 mg/day) or placebo	22 weeks	Secondary	NPI	Significant reduction in NPI apathy scores with <i>Ginkgo biloba</i>	
Herrmann et al., 2008 [35]	B	AD	13	Methylphenidate (20 mg/day) or placebo	5 weeks	Primary	AES	Greater reduction in AES score with methylphenidate than placebo ($p = 0.045$)	–0.63
<i>Open-label studies</i>									
Kaufer et al., 1996 [61]	C	AD	28	Tacrine (40–160 mg/day)	24 weeks	Secondary	NPI	No significant improvement in NPI apathy score ($p = 0.06$)	
Galynker et al., 1997 [63]	C	Dementia (AD & VaD)	27	Methylphenidate (10–20 mg/day)	3–14 days	Primary	SANS	Negative symptoms improved	
Kaufer et al., 1998 [62]	C	AD	40	Tacrine (40–160 mg/day)	24 weeks	Secondary	NPI	Significant reduction in NPI apathy score ($p < 0.02$)	

Mega et al., 1999 [56]	C	AD	86	Donepezil (10 mg/day)	8 weeks	Secondary	NPI	Significant decrease in NPI apathy score in 41% of patients (p = 0.004)
McKeith et al., 2000 [53]	C	DLB	11	Rivastigmine (3–12 mg/day, average 9.6 mg/day)	12 weeks	Secondary	NPI	Decrease in NPI apathy score of 63%
Czernecki et al., 2002 [52]	C	PD	51	Levodopa	–	Primary	AS	Significant reduction in AS score (p = 0.0026)
Dartigues et al., 2002 [54]	C	Mild to moderate AD	696	Rivastigmine (6–12 mg/day)	26 weeks	Secondary	NPI	No change in NPI apathy score
Edwards et al., 2004 [59]	C	DLB	25	Galantamine (8–24 mg/day)	24 weeks	Secondary	NPI	Significant reduction in NPI-4 score (p = 0.003)
Tanaka et al., 2004 [57]	C	Mild to moderate AD	70	Donepezil (5 mg/day)	12 weeks	Secondary	NPI	Improvement in apathy in 30% of patients (p < 0.01), but significant worsening in 10% of patients
Cummings et al., 2005 [55]	C	Moderate to severe AD nursing home patients	173	Rivastigmine (3–12 mg/day)	26 weeks	Secondary	NPI-NH	Decrease in NPI-NH apathy score by 60% (p < 0.001)
Brodaty et al., 2006 [60]	C	Mild to moderate AD	345	Galantamine, (average dose 15.2 ± 2.7 mg/day)	26 weeks	Secondary	Behavior assessment scale	Stable or improvement of apathy in 87% of patients
Gauthier et al., 2007 [51]	C	Mild to moderate AD	2,119	Rivastigmine (6–12 mg/day)	26 weeks	Primary	CGI-C	Improvement in CGI-C apathy scores in 62.6% of patients
Levin, 2007 [65]	C	PD	18	Tianeptine (37.5 mg/day)	13 weeks	Secondary	BDI	No change
Rockwood et al., 2007 [58]	C	AD	101	Donepezil (5 or 10 mg)	24 weeks	Secondary	TOPS checklist, NPI	Apathy scores improved
<i>Case reports</i>								
Marin et al., 1995 [70]	C	FTD	7 (1 FTD)	Amantadine (300 mg/day)	104 weeks	Primary	Observation	More talkative, improved initiation
Lancôt and Herrmann, 2000 [71]	C	DLB	7	Donepezil (5–10 mg/day)	8 weeks	Secondary	NPI	Improvement in NPI apathy score in 4 patients
Jansen et al., 2001 [66]	C	Depressed or apathetic geriatric patients	5 (2 dementia)	Methylphenidate (10 mg/day) or placebo in a 5-week randomized block design	5 weeks	Primary	AES-clinician, AES-informant	No significant improvement
Chatterjee et al., 2002 [68]	C	PD	1	Methylphenidate (10 mg/day)	–	Primary	UPDRS item 4 and observation	Motivation and initiative improved
Padala et al., 2007 [69]	C	Depression, PTSD, VaD	4 (1 VaD)	Methylphenidate (20 mg/day)	4 weeks	Primary	AES	Improvement in apathy and its sub-domains
Swanberg, 2007 [72]	C	FTD	3	Memantine (20 mg/day)	13 weeks	Secondary	NPI	Apathy score improved

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; VaD = vascular dementia; FTD = frontotemporal dementia; PD = Parkinson's disease; PTSD = post-traumatic stress disorder; NPI = Neuropsychiatric Inventory; NPI-NH = NPI nursing home version; AS = Apathy Scale; AES = Apathy Evaluation Scale; SANS = Scale for the Assessment of Negative Symptoms; CGI-C = Clinical Global Impression of Change scale; BDI = Beck Depression Inventory; TOPS checklist = top symptoms checklist; UPDRS = unified Parkinson's disease rating scale.

was found for the NPI apathy score, but the significance level was not reported.

Open-Label Studies

Fourteen open-label studies were retrieved, of which 9 included patients with AD; the other 5 studies included patients with DLB, PD, and both AD and vascular dementia. The studies of Gauthier et al. [51] and Czernecki et al. [52] included apathy as a primary outcome variable, measured with the Clinical Global Impression of Change scale (CGI-C) and the AS, respectively. Eleven studies used a cholinesterase inhibitor: rivastigmine ($n = 4$), donepezil ($n = 3$), galantamine ($n = 2$), and tacrine ($n = 2$). The remaining 3 open-label studies used methylphenidate, levodopa therapy, and tianeptine, 1 each respectively.

Of the studies investigating rivastigmine, McKeith et al. [53] reported a 63% reduction in the NPI apathy score of 11 patients with DLB, and Dartigues et al. [54] ($n = 696$) reported a significant improvement in NPI apathy score after 12 weeks ($p = 0.011$) but not after 6 months of treatment. Cummings et al. [55] found a 60% improvement in NPI apathy score in 173 patients with AD ($p < 0.001$), and Gauthier et al. [51] found that 62.6% of 2,119 patients with AD showed improvement of apathy, measured as primary outcome with the CGI-C.

Donepezil was investigated in 3 open-label studies. Mega et al. [56] reported a significant improvement in apathy in 41% of 86 patients with AD and apathy ($p = 0.004$). While Tanaka et al. [57] reported that 30% of 70 patients with AD showed an improvement in total NPI score and the NPI apathy score after donepezil treatment ($p < 0.01$), apathy became significantly worse in 10% of the patients. Rockwood et al. [58] ($n = 101$) reported that donepezil consistently improved apathy, but these authors failed to mention the significance of the finding.

Two open-label studies examined the effect of galantamine. Edwards et al. [59] examined 25 patients with DLB and observed a significant improvement in the scores of a NPI-4 subscale, which included delusions, hallucinations, apathy, and depression ($p = 0.003$). Brodaty et al. [60] reported that 6 months of galantamine treatment stabilized or improved the apathy scores of 87% of 345 patients with AD.

Kaufer et al. [61, 62] investigated tacrine in 2 open-label studies involving patients with AD. In the first study ($n = 28$), apathy, as measured with the NPI, was one of the most responsive symptoms, although the improvement did not reach statistical significance ($p = 0.06$) [61]. In the second study, in which 28 of the 40 patients came from

the previous study, a significant reduction in NPI apathy score was detected ($p < 0.02$). Apathy improved equally in patients with mild, moderate, or severe dementia [62]. In a pilot study, Galynker et al. [63] investigated the effect of methylphenidate on negative symptoms, including apathy, in 27 patients with AD or vascular dementia. Negative symptoms were measured with the Scale for the Assessment of Negative Symptoms (SANS) [64]. Results showed that the negative symptoms of patients with dementia appeared to be responsive to treatment with methylphenidate [63]. Czernecki et al. [52] studied the effects of levodopa on motivation in non-demented, non-depressed patients with PD with response fluctuations, comparing patients in 'on' and 'off' states to controls and using the AS to measure apathy. While patients with PD were apathetic, their apathy responded to levodopa treatment ($p = 0.0026$). Levin [65] focused on the use of tianeptine in 18 patients with PD. While core symptoms of depression measured with the Beck Depression Inventory improved, those of apathy did not.

Case Studies

Six case studies investigated the effect of pharmacological treatment of apathy, of which 3 studies focused on methylphenidate. Notable was that 4 studies assessed apathy as a primary outcome. The patients had various neurodegenerative diseases, including PD, (vascular) dementia, FTD, DLB, and AD. Jansen et al. [66] used the AES as outcome measure for apathy and reported a treatment-associated improvement in AES-clinician score and AES-informant score; however, the improvements were not significant ($p = 0.077$ and $p = 0.086$, respectively). Chatterjee and Fahn [68] studied methylphenidate in 1 patient with PD, measuring apathy with item 4 (motivation/initiative) of part I of the UPDRS [67]. They found methylphenidate to improve motivation/initiative, with scores decreasing from 3 to 0 (0 = none; 4 = complete loss of motivation). Padala and colleagues [69] reported an improvement in apathy (AES scores) of 18.3% in a patient with vascular dementia. One case, part of a series involving patients with apathy, reported that amantadine, in combination with bupropion or levodopa, improved observed initiative and communication (the patient became more talkative) in a man with frontal lobe dementia [70]. Lanctôt and Herrmann [71] studied the effects of treatment with donepezil on neuropsychiatric symptoms in 7 patients with DLB, of which 4 patients showed an improvement in NPI apathy score. A case series of 3 patients with FTD using memantine reported an improvement in NPI apathy score [72].

Discussion

This is the first systematic review of the pharmacological treatment of apathy in patients with neurodegenerative diseases. Of the 35 articles included, 2 meta-analyses and 11 RCTs provided grade A evidence, and 2 RCTs provided grade B evidence. The grading of quality was based on the general design and methodology of the studies. However, apathy was a primary outcome in only 1 RCT. From this it may be concluded that there is a lack of high-quality research that focuses specifically on apathy.

Among pharmacological treatments, cholinesterase inhibitors have been studied the most. Of the 2 meta-analyses, 1 reported positive (metrifonate) and the other (galantamine) reported no effects of these agents on apathy. Of the 9 RCTs with cholinesterase inhibitors, 3 derived from the same trial [39–41] and another 2 derived from the same study [61, 62]. Six studies reported positive effects (metrifonate, galantamine, and donepezil), 2 no effect (donepezil), and 2 did not report on the significance of their findings (rivastigmine, donepezil). Of the 11 open-label studies with cholinesterase inhibitors, 5 reported a significant improvement in apathy, while 6 reported inconsistent effects or did not report the significance of the findings. Given the lack of a placebo condition, an open-label design is not the most appropriate for studying the effects of drugs on apathy. Many of the included articles did not contain enough information to calculate the size of the effect on apathy, and for those that did, the effect sizes were small, which makes the clinical relevance of the effects doubtful. This is in line with a review of the treatment of neuropsychiatric symptoms of dementia by Sink et al. [73], who also concluded that effect sizes were mostly modest and that positive effects on neuropsychiatric symptoms were trivial.

Concerning the other drugs that were used apart from cholinesterase inhibitors, a single RCT provided evidence for a positive effect of *Ginkgo biloba* extract, and 1 small RCT and 3 case reports suggested that methylphenidate was beneficial. No conclusions could be drawn about the other medications investigated. Taken together, the meta-analyses and RCTs with cholinesterase inhibitors yielded inconclusive results so that it is not possible to draw firm conclusions about the efficacy of cholinesterase inhibitors for the treatment of symptoms of apathy in patients with neurodegenerative diseases. However, several studies provided some promising indications, in particular, for the effectiveness of cholinesterase inhibitors and methylphenidate, although this needs thorough investi-

gation in the future. These results are in line with the conclusion of Boyle and Malloy [3], who stated that cholinesterase inhibitors reduce the neuropsychiatric symptoms of AD, with apathy showing the most consistent improvement, and that other activating neuropsychotropic agents may be useful in the treatment of apathy.

This review had several limitations. The first is that the conclusions drawn necessarily depend on the quality of the studies included. Although apathy is a common symptom of many neurodegenerative diseases, few RCTs have investigated apathy as a primary outcome. Most studies have focused on cognitive deterioration, with apathy as a secondary outcome, or on neuropsychiatric symptoms in a broad sense as measured by the NPI, with apathy being one of several outcome variables investigated. For identifying the effectiveness of the interventions, the studies used 2 different types of ratings. Some used a composite measure of frequency and severity, such as the NPI, while others have used scales that only rate severity, such as the AES [36]. How this differential approach influences the outcome of the studies is not known. In addition, in the absence of generally accepted diagnostic criteria, most of the rating instruments used in the studies have not been validated in this specific population. Studies focusing on apathy as a primary outcome were generally case studies; only 1 small RCT focused on apathy as primary outcome [35]. Moreover, most of these studies involved patients with AD, varying widely in disease stage and severity. From earlier research, it is known that apathy is correlated with the severity of cognitive problems in community-based older adults [16]. In dementia, the occurrence and severity of apathy increase with disease severity and persist during the more advanced stages of dementia [6]. The role of disease severity in treatment response of apathetic symptoms is as yet unknown, but some studies have reported differential responses in different severity stages [62]. Studies of pharmacological treatment of apathy in other neurodegenerative diseases were under-represented. Many of the studies included were small, lacked a control group, and did not control for concomitant psychotropic medication. In some studies, apathy was part of a cluster of several NPI items, yet the validity of such an 'apathy' cluster is unclear. All these issues make a generalization of the results questionable.

Another limitation is that our results may have been influenced by publication bias. We retrieved only studies that explicitly reported apathy. While many studies have used the NPI, scores on NPI sub-items are usually only reported if there is a general effect on the NPI. This may

have led to non-retrieval of negative studies, with a consequent overestimation of the effect of pharmacological treatment.

In this systematic review, we evaluated the evidence base for pharmacological treatment of apathy in patients with neurodegenerative diseases. We found limited and inconsistent evidence for the efficacy of any specific drug in treating apathy in these patients and hence could not draw firm conclusions about their efficacy. Although research is hampered by the lack of generally accepted criteria for apathy as a syndrome [74], cholinesterase inhibitors and methylphenidate may be the best candidates for further study. Future research should include high-quality RCTs with apathy as a primary outcome. To facilitate this research, reliable and validated diagnostic criteria for apathy and validated scales that differentiate between ap-

athy, depression, and executive dysfunction are a prerequisite. In addition, studies need to address different individual neurodegenerative diseases to be able to generalize results to other forms of dementia. Moreover, studies should take potential differences in treatment response between patients with different severity stages of disease into consideration. Study of the potential of pharmacological treatment of apathy in neurodegenerative disease is warranted because effective treatment would improve the quality of life of both patients and their caregivers.

Acknowledgement

This study was sponsored in part by the Stichting Internationaal Parkinson Fonds.

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