Review Article

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Movement disorders associated with acetylcholinesterase inhibitors in Alzheimer's dementia: A systematic review

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Abstract:

BACKGROUND: Acetylcholinesterase inhibitors (AChEIs) are widely used in Alzheimer's disease (AD). This study aims to systematically review the literature about movement disorders (MDs) associated with AChEIs for AD, which include donepezil, galantamine, rivastigmine, tacrine, and ipidacrine.

METHODOLOGY: Two reviewers conducted a comprehensive review of relevant studies across six databases, without language restrictions, covering publications from 1992 to 2024.

RESULTS: Overall, 74 studies containing 92 cases were found of MDs related to ACHEIs. The MDs found were Pisa syndrome in 33 patients, parkinsonism in 31, myoclonus in 11, dystonia in 10, dyskinesia in 6, and extrapyramidal symptoms in 1. Regarding the medications, the abnormal movements were associated with donepezil in 62 cases, rivastigmine in 15, galantamine in 10, and tacrine in 5. No case of ipidacrine-induced MD was found. Overall, the most commonly affected sex was the female, accounting for 61.9% of the cases. The mean and median age was 74.1 (standard deviation: 8.9) and 75 years (range: 49–93 years). The MD occurred within 6 months of the starting of AChEI in approximately 70% of the patients. Furthermore, the full recovery of the MD after the main management was noticed within 6 months in about 80% of the patients. About 86.3% of the individuals fully recovered after treatment, which included AChEI discontinuation, dose adjustment, and prescription of additional therapy.

CONCLUSIONS: The occurrence of tacrine-induced tremor indicated a potential predisposition to movement disorders associated with AChEI therapy. Based on the drug class side effect profile, it is possible that future studies may observe abnormal movements with other AChEIs.

Keywords:

Adverse effect, donepezil, drug-induced, extrapyramidal symptom, galantamine, movement disorder, rivastigmine

Introduction

Acetylcholinesterase inhibitors (AChEIs), also known as cholinesterase inhibitors, are widely prescribed in clinical practice for dementia. Physostigmine was the first medication assessed as a potential therapeutical option for Alzheimer's disease (AD), but it was later discontinued due to significant side effects.[1] The first AChEI to receive the United States (US) Food and Drug Administration (FDA) approval for the treatment of AD was tacrine, and later, donepezil, galantamine, rivastigmine, and the compound donepezil/memantine were introduced.[2] Noteworthy, memantine is not an AChEI. It exhibits a low-affinity antagonist action at glutamatergic N-methyl-D-aspartate (NMDA) receptors which is also described as voltage-dependent.[2] Furthermore, in 2013,

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the commercialization of tacrine ceased due to easy access to other AChEIs and concerns about safety due to hepatoxicity.[3]

In 2021, donepezil was allocated at the 131st position among the 300 most frequently prescribed medications in the USA, with 4,435,098 prescriptions to 1,278,743 different patients, according to the Medical Expenditure Panel Survey released by the US Government. Donepezil development started in 1983 with Japanese chemist Hachiro Sugimoto at the Eisai Co. Ltd.[4] In 1996, the FDA approved donepezil under the brand Aricept®, co-marketed with Pfizer Inc.[4] In November 2010, the first generic donepezil formulation was prepared by Ranbaxy Lab Ltd.[4]

Galantamine is an alkaloid synthesized from flowers of the genus *Galanthus*, which has the *Galanthus nivalis*, also known as the "snowdrop," as the most well-known and widespread of the species in this genus.[5] In 1952, Proskurnina and Yakovleva from the Union of Soviet Socialist Republics isolated galantamine for the first time from bulbs of *G. nivalis*, and the cholinesterase inhibitor properties of this compound were identified.[6] In 1959, the first synthetical production of galantamine began, but only in the 1990s, galantamine full-scale synthesis was upscaled and optimized.[7]

Rivastigmine has a unique formulation with a transdermal patch, which significantly increases tolerance of the therapy with less adverse events such as vomiting and nausea. Furthermore, it is the only AChEI approved for treating Parkinson's disease dementia (PDD).[8] The first patent of rivastigmine was published in 1985, but it was only in the late 1990s that rivastigmine was tested in clinical trials.[9] Interestingly, rivastigmine is a semisynthetic derivative of physostigmine.

In 1949, tacrine was first synthesized by Adrient Albert in Australia.[10] Besides inhibiting acetylcholinesterase, tacrine can also affect histamine N-methyltransferase, which plays an important role on regulating behaviors and the circadian rhythm. Furthermore, although tacrine was discontinued from the market for clinical treatment, this medication still has significant importance in the pharmacological studies for the PD animal models since tacrine can induce abnormal jaw movements in mice.[11]

Ipidacrine was first synthesized by the National Research Center for Biologically Active Compounds in Russia. The literature about ipidacrine is limited, and most of the published manuscripts are in Russian. Ipidacrine is a modified chemical structure from tacrine, which reversibly inhibits acetylcholinesterase. The effect of ipidacrine on butyrylcholinesterase (BChE), an enzyme involved in the mechanism of tacrine, is scarce.[12] For a complete pharmacological overview of AChEIs used for AD, consider reading supplementary material [Supplementary Table 1].

Among the most commonly described adverse events associated with AChEIs are associated with increased stimulation of the cholinergic system, including abdominal discomfort, anxiety, blurred vision, diarrhea, dizziness, dry mouth, headache, insomnia, nausea, and vomiting.[13] Furthermore, postmarketing reports revealed rare occurrences of hemolytic anemia, neuroleptic malignant syndrome, pancreatitis, rhabdomyolysis, Stevens–Johnson syndrome, toxic epidermal necrolysis, and QTc prolongation.[14] In this context, movement disorders (MDs) secondary to AChEIs were rarely described in the literature. To the author's knowledge, there is no review in the literature specifically assessing this group of medications. Therefore, the present study aims to assess the reports of MDs associated with AChEIs used for AD (donepezil, donepezil/memantine, galantamine, rivastigmine, tacrine, and ipidacrine). We will assess demographic characteristics, the time for occurrence of the MD, and the management of the AChEI-induced MD.

Methodology

A literature search across databases was conducted to find cases on MDs related to AChEIs that were reported in electronic format between January 1992 and June 2024. The databases searched included ScienceDirect, Scientific Electronic Library Online, PubMed, Latin American and Caribbean Health Sciences Literature, Google Scholar, and Excerpta Medica. The searching terms were "tremor, tics, stuttering, restlessness, restless legs syndrome, parkinsonism, myokymia, myoclonus, movement disorder, hypokinetic, hyperkinetic, extrapyramidal, dystonia, dyskinesia, chorea, bradykinesia, ballism, ataxia, and akathisia." These keywords were merged with "donepezil, galantamine, rivastigmine, tacrine, and ipidacrine [Supplementary Table 2]." The evaluation adhered to the protocols established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 [Supplementary Table 3].[15]

The eligibility criteria included case reports, case series, original research articles, editorials, bulletins, and poster presentations published from January 1992 to June 2024, with no restrictions on language, to ensure a thorough review. In cases where the non-English literature surpassed the authors' language abilities (Spanish and French) or when the English abstract provided insufficient information, as observed in articles written in Japanese and Russian, the Google Translate service was employed.[16]

The authors independently examined the titles and abstracts of all articles identified in the initial search. Any disagreements among the authors were addressed through discussion. Cases where the cause of MD was already known and the motor symptoms remained unchanged or were unrelated to AChEIs were excluded. Furthermore, cases that could not be accessed electronically, despite formal requests to the authors, were removed. Cases involving multiple factors contributing to the MD were evaluated based on the likelihood of the event occurring, using the Naranjo algorithm.

A total of 2,453 articles were located; 1,684 were considered inappropriate, while 695 were either irrelevant to the topic, duplicates, not available electronically, or lacked adequate data [Figure 1]. Data extraction was performed. When possible, we collected details on the author, department, year of publication, country of occurrence, number of affected patients, AChEI indications including off-label uses, the duration from the first AChEI dose to the emergence of MDs, the interval from AChEI cessation to symptom improvement, patient status at follow-up, and significant findings related to clinical history and management. The data were extracted by two independent authors and later verified for accuracy.

Categorical variables were displayed as percentages. Continuous variables were summarized using mean, standard deviation (SD), median, and range. Statistical analysis was conducted using Microsoft Excel Spreadsheet Software version 16.0 (Microsoft Corp, Redmond, WA, USA).

The clinical characteristics and definitions of MDs such as tics, restless legs syndrome, stuttering, myoclonus, parkinsonism, dystonia, dyskinesia, ataxia, chorea,

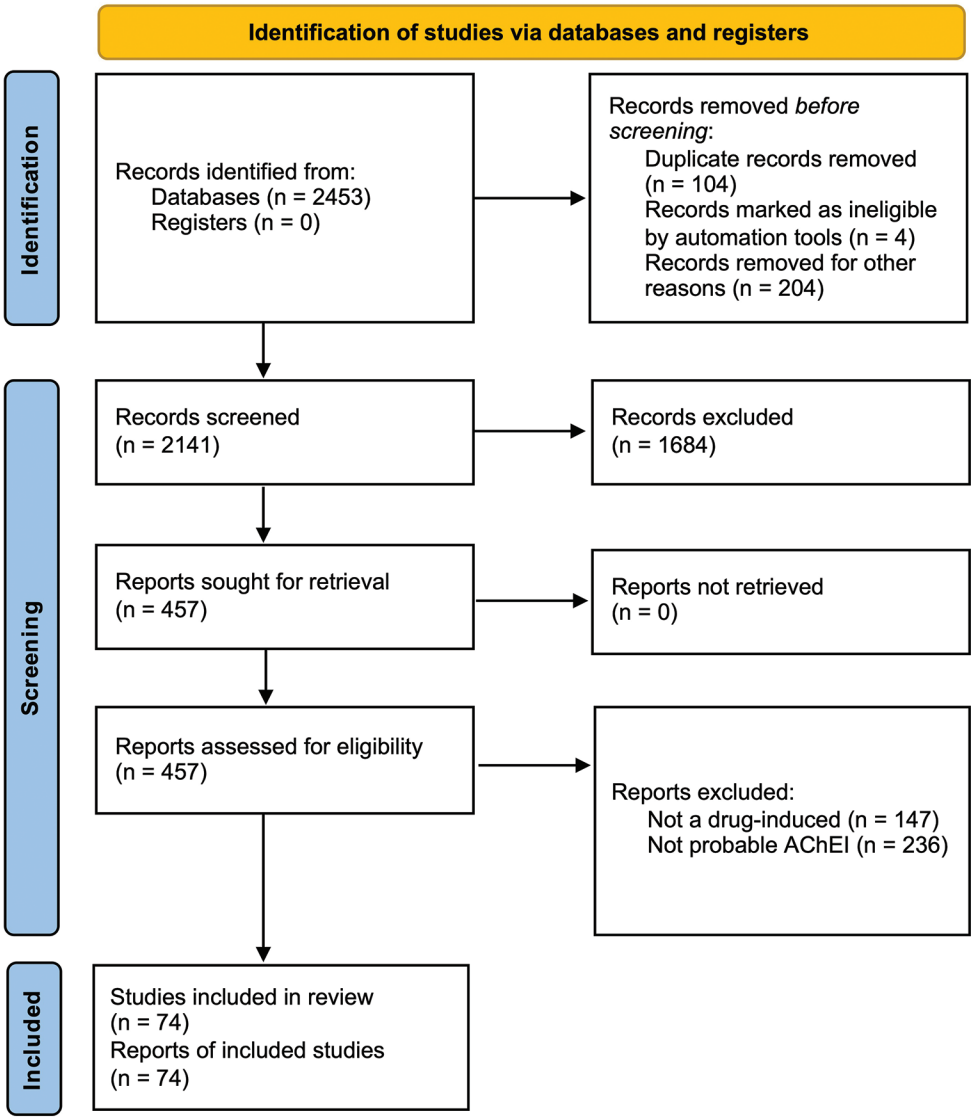

Figure 1: Flowchart of the screening process

and ballism were derived from the work of Rissardo *et al*.[17] The evaluation of psychiatric disorders was based on the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).[18] The probability of attributing an adverse drug reaction to the medication, as opposed to other variables, was determined using the Naranjo algorithm.[19] The onset of the MD was defined as the interval beginning with the administration of AChEIs up to the point when the MD became evident. Recovery from the MD was characterized as the time frame from the initial treatment, which may involve stopping AChEIs, until the complete alleviation of the abnormal movements, for example.[17]

Results

Seventy-four studies containing 92 cases were assessed about AChEI-associated MDs [Supplementary Table 4]. The MDs found were 33 cases of Pisa syndrome, 31 parkinsonism, 11 myoclonus, 10 dystonia, 6 dyskinesia, and 1 extrapyramidal symptom. Regarding the medications, 62 cases were associated with donepezil, 15 rivastigmine, 10 galantamine, and 5 with tacrine [Table 1]. No case of MD was found with ipidacrine.

Donepezil was the most frequently implicated drug in MDs, accounting for 67.39% of cases associated with AChEI use. The MD most commonly described with donepezil was Pisa syndrome, which occurred in 37.1% of the reports. The other abnormal movements observed were 21 patients with parkinsonism, 8 dystonia, 7 myoclonus, and 3 dyskinesia. About 88.2% of the individuals achieved recovery at the follow-up. The worst prognosis was observed with donepezil-induced parkinsonism, of which only 71.4% achieved full recovery.

Galantamine-induced MDs had the worst reported prognosis, in which only 75% of the individuals recovered. Furthermore, the individuals with MDs associated with galantamine were slightly younger than the other groups. The mean age at the occurrence of the MD was 73.9 (SD: 9.7), 74.1 (SD: 8.9), 74.1 (SD: 8.9), and 74.3 (SD: 9.1) years old, for galantamine, rivastigmine, tacrine, and donepezil, respectively.

For rivastigmine, we found cases related to the oral and patch formulations of the medication. It was the only medication still in use in the market that had more cases of rivastigmine-induced parkinsonism than rivastigmine-induced Pisa syndrome. Furthermore, it is interesting that the mean MD onset time was 28.9 weeks, but the recovery time was short, which was 2.1 weeks. Full recovery was observed in 80% of the individuals.

To the best of the author's knowledge, there is no case reported in the literature on ipidacrine-induced MDs. The latest case, in which tacrine was the main cause of MD, was published in 1999.[94] Interestingly, 80% of the cases of tacrine-associated MD were parkinsonism, and the remaining 20% were myoclonus.

In general, the most frequently reported drug with AChEI-associated MD was donepezil. The sex most commonly affected was the female, accounting for 61.9% of the cases. The mean and median age were 74.1 (SD: 8.9) and 75 years (range: 49–93 years). The MD occurred within 6 months of the starting of AChEI in approximately 70% of the patients [Figure 2]. Furthermore, the full recovery of the MD after management was noticed within 6 months in about 80% of the patients [Figure 3].

Discussion

General

AD is recognized as one of the most prevalent neurodegenerative disorders leading to dementia, predominantly affecting the older people population. In the US alone, it is estimated that approximately 4.5 million individuals are living with AD, making it a significant public health concern. This condition not only impacts the quality of life for those diagnosed but is also one of the leading causes of mortality, ranking among the top ten causes of death in older adults.[92]

AD is characterized by progressive cognitive decline, memory loss, and changes in behavior, which can severely affect daily functioning and independence. As the disease advances, individuals may experience challenges with language, problem-solving, and even basic activities of daily living.

Overall, understanding AD and the available treatment options is crucial for patients, caregivers, and healthcare providers, as the disease poses significant challenges in managing care and improving the quality of life for those impacted.

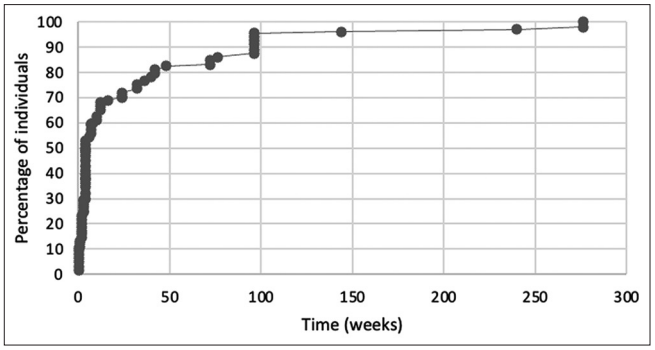

Figure 2: Movement disorder onset. The figure describes the percentage of individuals with Acetylcholinesterase inhibitor (AChEI)-associated movement disorder versus the time between the AChEI's start and the movement disorder's development in weeks

Table 1: Summary of acetylcholinesterase inhibitor-associated movement disorder

	Cases (%)	Sex	Age (years)	Dose	MD onset[a]	MD recovery[b]	FU[c]
Donepezil							
DIP	21 (33.8)	Female: 11 Male: 3 U: 7	Range: 68–89 Mean: 75.8	Mean: 11.6 mg/day	Range: 1 day–3 years Mean: 23.7	Range: 5 days–2 months Mean: 2.7 weeks	71.4% (10/14)
DTN	8 (12.9)	Female: 8 Male: 0 U: 0	Range: 67–81 Mean: 76.3	Mean: 5.7 mg/day	Range: 5 days–1.5 years Mean: 17.3	Range: 1 week–2 months Mean: 3.7 weeks	100% (5/5)
DKN	3 (4.8)	Female: 0 Male: 3 U: 0	Range: 70–81.5 Mean: 77.6	Mean: 4.3 mg/day	Range: 3 weeks–6 months Mean: 10 weeks	Range: 5 days–1.5 weeks Mean: 1.2 weeks	100% (3/3)
MCL	7 (11.2)	Female: 3 Male: 3 Unknown: 1	Range: 49–93 Mean: 69.1	Mean: 13.75 mg/day	Range: 4 days–2 years Mean: 19.2 weeks	Range: 1 day–1 week Mean: 0.3 week	100% (6/6)
PS	23 (37.1)	Female: 17 Male: 6 Unknown: 0	Range: 57–89 Mean: 73.8	Mean: 7.3 mg/day	Range: 1 day–5 years Mean: 35.3 weeks	Range: 3 days–6 months Mean: 4.8 weeks	91.3% (21/23)
Total	62 (100)	Female: 39 Male: 15 Unknown: 8	Range: 49–93 Median: 75.5 Mean: 74.3 SD: 9.1	Range: 4–30 mg/day Median: 6.6 mg/day Mean: 8.5 mg/day SD: 5.8	Range: 1 day–5 years Median: 4 weeks Mean: 26.6 years SD: 45.7	Range: 1 day–6 months Median: 2 weeks Mean: 3.5 weeks SD: 4.8	88.2% (45/51)
Galantamine							
PS	5 (50)	Female: 5 Male: 0 Unknown: 0	Range: 57–75 Mean: 68.8	Mean: 10.6 mg/day	Range: 2 weeks–5.7 years Mean: 116.4 weeks	Range: 2–6 weeks Mean: 3 weeks	80% (4/5)
DKN	1 (10)	Female: 0 Male: 1 Unknown: 0	Range: 70 Mean: 70	Mean: 16 mg/day	Range: 2 weeks Mean: 2 weeks	Range: NA Mean: NA	0% (0/1)
MCL	3 (30)	Female: 1 Male: 2 Unknown: 0	Range: 69–87 Mean: 78.6	Mean: 18.6 mg/day	Range: 1 month–4 months Mean: 10 weeks	Range: 2–3 weeks Mean: 2.5 weeks	100% (2/2)
EPS	1 (10)	Female: 1 Male: 0 Unknown: 0	Range: 89 Mean: 89	Mean: NA	Range: NA Mean: NA	Range: NA Mean: NA	NA
Total	10 (100)	Female: 7 Male: 3 Unknown: 0	Range: 57–89 Median: 73.5 Mean: 73.9 SD: 9.7	Range: 8–24 mg/day Median: 16 mg/day Mean: 14.8 mg/day SD: 5.5	Range: 2 weeks–5.7 years Median: 10 weeks Mean: 75.5 weeks SD: 124	Range: 2–6 weeks Median: 2 weeks Mean: 2.8 weeks SD: 1.6	75% (6/8)
Rivastigmine							
DIP	6 (40)	Female: 2 Male: 1 Unknown: 3	Range: 71–88 Mean: 77	Mean: 5.5 mg/day (PO)	Range: 1 day–3 months Mean: 6.3 weeks	Range: 1 day–1 week Mean: 0.5 week	66.6% (2/3)
PS	5 (33.3)	Female: 2 Male: 3 Unknown: 0	Range: 57–80 Mean: 72	Mean: 7.8 mg/day (PO)	Range: 5 days–2 years Mean: 49.3 weeks	Range: 3 days–1 month Mean: 1.8 weeks	66.6% (2/3)
DKN	2 (13.3)	Female: 2 Male: 0 Unknown: 0	Range: 81 Mean: 81	Mean: 6 mg/day (PO) and 13.3 mg/cm^2 (patch)	Range: 3 months–9 months Mean: 24 weeks	Range: 6 days–3 months Mean: 6.4 weeks	100% (2/2)
DTN	2 (13.3)	Female: 2 Male: 0 Unknown: 0	Range: 61–75 Mean: 68	Mean: 6 mg/day (PO) and 10 mg/cm^2 (patch)	Range: 1 month Mean: 4 weeks	Range: 1–2 days Mean: 0.2 weeks	100% (2/2)

Contd...

Table 1: Contd...

	Cases (%)	Sex	Age (years)	Dose	MD onset[a]	MD recovery[b]	FU[c]
Total	15 (100)	Female: 8 Male: 4 Unknown: 3	Range: 57–88 Median: 76 Mean: 74.1 SD: 8.9	Range: 1.5–12 mg/day (PO) and 10–13 mg/cm^2 (patch) Median: 6 mg/day (PO) and 11.5 mg/cm^2 (patch) Mean: 6.6 mg/day (PO) and 11.5 mg/cm^2 (patch) SD: 3.2 (PO) and 2.1 (patch)	Range: 1 day–2 years Median: 12 weeks Mean: 28.9 weeks SD: 35.5	Range: 1 day–3 months Median: 0.8 week Mean: 2.1 weeks SD: 3.8	80% (8/10)
Tacrine							
DIP	4 (80)	Female: 2 Male: 1 Unknown: 1	Range: 67–87 Mean: 75.3	Mean: 26.6 mg/day	Range: 3 days–2 months Mean: 3.1 weeks	Range: 1 day–1 month Mean: 1.7 weeks	100% (3/3)
MCL	1 (20)	Female: 1 Male: 0 Unknown: 0	Range: 68 Mean: 68	Mean: 40 mg/day	Range: 1 day Mean: 1 day	Range: 1 day Mean: 1 day	100% (1/1)
Total	5 (100)	Female: 3 Male: 1 Unknown: 1	Range: 67–87 Median: 70 Mean: 73.5 SD: 9.2	Range: 10–50 mg/day Median: 30 mg/day Mean: 30 mg/day SD: 18.2	Range: 1 day–2 months Median: 0.7 weeks Mean: 2.3 weeks SD: 3.7	Range: 1 day–1 month Median: 0.5 Mean: 1.3 SD: 1.8	100% (4/4)
Total AChEI							
General data	92 (100)	Female: 57 Male: 23 Unknown: 12	Range: 49–93 Median: 75 Mean: 74.1 SD: 8.9	NA	Range: 1 day–5.7 years Median: 4 weeks Mean: 30.9 weeks SD: 57.9	Range: 1 day–6 months Median: 1.75 weeks Mean: 4.2 weeks SD: 4.7	86.3% (63/73)

[a]MD onset: Time between the beginning of the AChEI and the occurrence of the movement disorder, [b]MD recovery: Time between the diagnosis of the movement disorder and the full recovery, [c]Percentage of individuals with full recovery of the movement disorder and other adverse effects related to the AChEI after the management, which also will be described the number of reports between brackets. AChEI: Acetylcholinesterase inhibitor, DIP: Drug-induced parkinsonism, DKN: Dyskinesia, DTN: Dystonia, EPS: Extrapyramidal symptom, FU: Follow-up, MCL: Myoclonus, MD: Movement disorder, NA: Not available/not reported/not applicable, PO: Per oral/per mouth, PS: Pisa syndrome, SD: Standard deviation

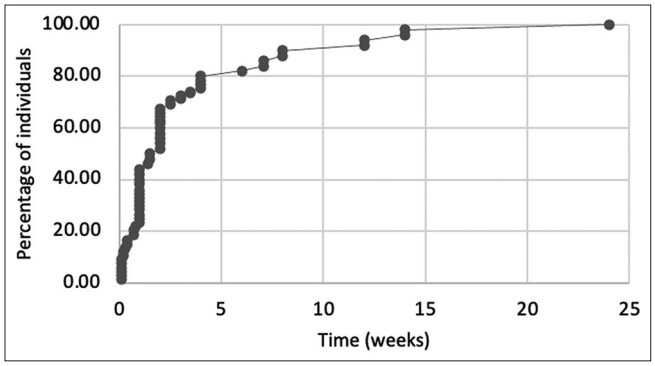

Figure 3: Movement disorder recovery. The figure describes the percentage of individuals with Acetylcholinesterase inhibitor-associated movement disorder that fully recovered versus the time between the management and the full recovery

Kose *et al*. assessed the Japanese Adverse Drug Event Report database to establish whether the side effects of medications used to treat AD are different. The target drugs were donepezil, rivastigmine, galantamine, and memantine. The authors observed that individuals taking donepezil have a slow onset of adverse effects when compared to other AChEIs (galantamine and rivastigmine).[95]

Bittner *et al*. evaluated the neuropsychiatric side effects associated with AChEIs in patients with AD and PDD. The authors found that patients in use of AChEIs more commonly have anorexia, decreased appetite, insomnia, and humor abnormalities.[96] Noteworthy, other studies have reported that the use of cholinesterase inhibitors, either alone or in combination with memantine, is associated with a reduction in neuropsychiatric symptoms.[97] Interestingly, Bittner *et al*. also found that decreased appetite and anorexia are dose-dependent side effects since they are more commonly observed in individuals taking high doses than lower doses of AChEIs. It is worth mentioning that donepezil was more frequently associated with sleep structural abnormalities when compared to galantamine, and this finding was statistically significant.[96]

For further details of abnormal movements reported with AChEIs in clinical trials, read Table 2.[24,31,34,79,98]

Table 2: Abnormal movement percentages reported in clinical trials with acetylcholinesterase inhibitors

Abnormal movement	*n*[a]	Sample size	Percentage	Note	Reference
Worsening of PD symptoms	2	8	25	Patients with PD receiving donepezil 5 mg for hallucinations and delusions	Fabbrini *et al*.[24]
Worsening of PD symptoms	3	26	11.5	Patients with PDD receiving rivastigmine 8 mg/day (mean)	Gurevich *et al*.[79]
Worsening of PD symptoms	19	182	10.4	Patients with PDD receiving donepezil 10 mg/day	Dubois *et al*.[31]
Worsening of PD symptoms	20	195	10.3	Patients with PDD receiving donepezil 5 mg/day	Dubois *et al*.[31]
Tremor	14	195	7.2	Patients with PDD receiving donepezil 5 mg/day	Dubois *et al*.[31]
Tremor	13	182	7.1	Patients with PDD receiving donepezil 10 mg/day	Dubois *et al*.[31]
Tremor	1	62	1.6	Patients with dementia, including LBD, AD, PDD	Chebotareva and Levin[34]
Tremor	131	16,995	0.8	Patients in use of AChEI	Kröger *et al*.[98]
Tremor	3	529	0.6	Patients with AD in use of donepezil 5–10 mg/day	Carrasco *et al*.[99]
Myoclonus	32	16,995	0.2	Patients in use of AChEI	Kröger *et al*.[98]
Restlessness	1	529	0.2	Patients with AD in use of donepezil 5–10 mg/day	Carrasco *et al*.[99]
Parkinsonism	1	529	0.2	Patients with AD in use of donepezil 5–10 mg/day	Carrasco *et al*.[99]

[a]Number of individuals reported with abnormal movement in the clinical trial. AD: Alzheimer's disease, PD: Parkinson's disease, AChEI: Acetylcholinesterase inhibitor, PDD: Parkinson's disease dementia, LBD: Lewy body dementia

Parkinsonism

Donepezil was already widely studied regarding safety and effectiveness in the management of AD. Noteworthy, the clinical trials revealed that donepezil has dose-dependent side effects that occur more frequently with 10 mg/day than with 5 mg/day.[100] Another interesting fact about donepezil is that side effects in individuals with end-stage renal disease more commonly occur during uptitration. However, there are no pharmacokinetic studies showing that donepezil is affected by renal function.[37]

On the other hand, donepezil-associated parkinsonism was scarcely described in the literature. Tremor, bradykinesia, and rigidity were observed with a short time of onset in individuals with mild dementia in the use of low-dose donepezil and also taking antipsychotics such as risperidone[25] and tiapride.[22] Kang and Kim reported a patient with donepezil-induced parkinsonism in who dopamine transporter activity was not decreased, suggesting drug-induced parkinsonism than PD.[32]

Bourke and Druckenbrod described a patient with PD and likely PDD that donepezil 5 mg/day for 2 weeks was prescribed, and the patient had significant worsening of symmetric resting tremor and bradykinesia.[20]

Onofrj and Thomas described a case of donepezil overdose, in which the aide of a patient with Lewy body dementia did not clearly understand the physician's instructions and gave 25 mg of donepezil within 15 h. At the presentation, the authors noticed severe abnormal forward bending of the lower spine when standing. Donepezil was withdrawn, and the motor symptoms improved within 5 days.[26] Furthermore, Rozzini *et al*. reported a patient with worsening motor symptoms and Lewy body dementia after taking high doses of donepezil for a long period of time.[28] Therefore, these two case reports can support the hypothesis that high doses of donepezil are associated with parkinsonism, independently of donepezil use time. This can be partially explained by the total accumulation of the medication in acute or chronic patterns, leading to a disbalance of the dopaminergic and cholinergic systems in the basal nuclei. However, especially in patients with long-term donepezil, the aging effect cannot be excluded as the worsening of PD symptoms.

The affinities of the different isoforms of AChE vary among the AChEIs. G1 AChE is commonly associated with cognition and sensorial systems, on the other hand, G4 AChE is frequently related to movement and awareness. G1 and G4 isoforms are both affected by donepezil. However, animal models revealed that, mainly in the striatum, donepezil has more affinity to the G4 isoform than G1.[101] Noteworthy, it is believed that due to the aging process, there is an increased affinity to G4 than G1 in the striatum (21:1) and in the temporal cortex (1.7:1).[102] Hence, movement abnormalities are more frequently modulated than cognitive function due to the increased G4 affinity, and this is mostly observed in the striatum. Therefore, donepezil-associated MD is likely related to increased donepezil levels and changes in G4 isoforms, mainly in patients with PD whose NMDA receptors are more likely to fire due to decreased inhibitory mechanisms.

An interesting fact to mention is that AChEI was already associated with worsening gait, but other studies have revealed improvement in gait, especially in individuals with PD.[103] Chung *et al*. investigated the effect of AChEI on the gait of patients with PD. The fall frequency per day on placebo was 0.25 ± 0.08 (scanning electron microscopy) compared with 0.13 ± 0.03 on donepezil ($P < 0.05$). However, near falls were not significantly different between phases.[104] Apparently,

the gait and balance impairment in PD may be explained by the progression of this neurodegenerative disease to the brainstem pedunculopontine nucleus neurons, which is an area rich in acetylcholine.[105] Similar findings have already been observed in animal models, in which lesions in the pedunculopontine nucleus and the cuneiform nucleus led to gait impairment.[106]

Tacrine-induced tremor model

Tacrine associated with PD was highly reported in the literature because of the PD tremor predominant animal model with tacrine. We performed a repeat analysis with only the animal studies in the PubMed database. We found 29 studies with tacrine-induced tremulous jaw movement. For a complete description of the studies of tacrine-induced tremulous jaw movements, please refer to supplementary material [Supplementary Table 5].

Collins *et al*. performed a study with galantamine in rats and assessed the effect of adenosine A (2A) antagonists.[136] The authors noticed that galantamine can induce tremulous jaw movement in a dose-dependent fashion, and the movements occur in the 3–7 Hz frequency range, similar to PD tremors. Scopolamine improved the abnormal movements dose-dependently, suggesting that galantamine may induce abnormal movements through muscarinic acetylcholine receptors. The authors also observed that 2A antagonists can significantly improve tremulous jaw movements.

Dyskinesia

Tardive dyskinesia (TD) is among the most worrisome adverse events related to antipsychotic therapy.[45] Orofacial movements are the most commonly affected. One of the proposed mechanisms for TD is the disbalance between the cholinergic and the dopaminergic systems.[46] It is believed that AChEI used in the management of AD may increase acetylcholine and lead to cholinergic hyperstimulation, causing abnormal movements such as TD.[45]

Tanaka *et al*. reported a case of donepezil-induced athetosis.[45] Nozaki *et al*. reported a case of donepezil-associated choreoathetosis, and they hypothesized that there is a level of acetylcholine to modulate the dopaminergic system in the striatum.[46] The decreased levels of AChEI may lead to suppression of the dopaminergic system, causing increased sensitivity of postsynaptic dopamine receptors, which, even with lower levels of dopamine, can lead to choreiform movements. Furthermore, Nozaki *et al*. explained that abnormal movements would likely improve by prescribing biperiden that is an M1-selective muscarinic acetylcholine receptor antagonist causing the levels of dopamine to decrease in the striatum, which may lead to a return in the equilibrium between dopamine and acetylcholine.[46] In animal models, the fact that antagonism of M1 leads to extracellular dopamine dropping in the striatum can support this hypothesis.[137]

Diaz and Rosales reported rivastigmine-induced chorea and its recurrence with drug re-challenge.[86] The authors proposed the same hypothesis as those of Nozaki *et al*. for the explanation of chorea related to rivastigmine.[46] Concurrent medications may also reduce the threshold for the development of dyskinetic reactions. Interestingly, organophosphate poisoning can result in extrapyramidal symptoms in a similar pattern as with AChEIs.[86] Hsieh *et al*. hypothesized that there is a genetic determinant for the development of abnormal movements with AChEIs, which can be supported by the fact that not all individuals develop MDs with AChEI therapy.[138] Other authors believe that the cortico-striato-pallido-thalamo-cortical loop is influenced at multiple levels, leading to an overall decrease in dopamine levels.[139]

Tacrine-induced orofacial dyskinesia was observed in animal models. Mohan *et al*. assessed chewing movements, tongue protrusions, and orofacial bursts after tacrine therapy, and they also observed the effect of ethanolic extract of coriander (*Coriandrum sativum* L., Apiaceae). The authors reported a significant improvement in the abnormal movements and inflammatory markers with coriander.[140] Interestingly, although by unclear mechanism, Mohan *et al*. demonstrated the appearance of dyskinetic movements associated with AChEI.

Caroff *et al*. studied the effect of donepezil on TD, and in their case series, donepezil was shown to be effective in suppressing TD.[141] Cubo *et al*. assessed the effect of donepezil in Huntington's chorea, and the authors found no significant result.[142]

Myoclonus

Beagle *et al*. reported a cumulative probability of developing seizures after AD onset of 13.4%. Furthermore, they described that patients with AD have the lowest percentage of developing myoclonus when compared to patients with Lewy body dementia and frontotemporal dementia. The cumulative myoclonus probability in patients with AD within 9 years is around 15%.[143] Hauser *et al*. reported an incidence of seizures or myoclonus in 10% of the patients with AD, which was ten times higher than expected in a reference population. Interestingly, seizures occurred in any stage of AD, but myoclonus was often a late manifestation.[144]

Rissardo and Fornari Caprara systematically reviewed the literature regarding AChEIs and

myoclonus.[52] The authors found only six cases of donepezil/galantamine-induced myoclonus, which was multifocal in most individuals. The most frequently reported treatment was discontinuing the AChEI. All the individuals recovered within 3 weeks.[52] The authors also proposed that jerks associated with AChEIs are likely related to an increase in acetylcholine. There are reports in animal models of myoclonus associated with picrotoxin improved with decreased levels of acetylcholine.[145] In this way, in individuals with cognitive impairment in the use of AChEIs, acetylcholine levels are increased, and they are more susceptible to developing jerks. Furthermore, dopamine levels but not norepinephrine were increased in the cortex and dorsal hippocampus in animal models with high doses of donepezil.[146] Furthermore, they observed that the most common AChEIs associated with myoclonus was donepezil, which can be explained by the fact that donepezil, compared to galantamine and rivastigmine, has lower selectivity to acetylcholinesterase.[52,147]

Hernández-Fernández *et al*. reported a case of belly dancer dyskinesia associated with galantamine. Electromyographic (EMG) recording from trapezius, scalene, and inferior intercostal muscles revealed a cluster of involuntary, irregular, and pseudorhythmic activity, especially after the phase-type forced contraction of the muscles being tested.[74] Drug-induced belly dancer dyskinesia is one of the most frequently reported secondary causes of belly dancer dyskinesia, and it is more commonly related to dopaminergic blocking agents.[148]

Abilleira *et al*. reported a case of tacrine-induced myoclonus.[93] Svejdová *et al*. reported that nonepileptic myoclonus was induced in baboons (Papio papio) by 7-methoxytacrine, a tacrine derivative. Myoclonus is likely related to the cholinergic system since it can be caused by atropine and blocked by physostigmine.[149] Therefore, tacrine may have an antagonist effect on muscarinic acetylcholine receptors.[150]

Dystonia

Ikeda *et al*. reported a case of donepezil-induced cervical anterocollis dystonia in a patient with AD.[43] The authors revealed persistent muscle contraction discharges on both sides of the sternocleidomastoid, anterior scalenus, and trapezius muscles at rest on the surface EMG, which disappeared after the full recovery of the anterocollis. Ikeda *et al*. proposed that the decreased dopaminergic neurotransmission and excessive cholinergic neurotransmission are likely related to the development of donepezil-induced dystonia in a similar mechanism that occurs to the development of drug-induced Pisa syndrome. Furthermore, they explained that cervical dystonia secondary to donepezil should be differentiated from dropped head syndrome (DHS), in which DHS is characterized by severe neck extensor muscle weakness that is easily correctable with passive neck extension.

Drug-induced dystonia is commonly observed with antipsychotics, and the mechanism proposed for dystonia secondary to antipsychotics is related to dopamine D2 receptors. However, AChEIs do not directly influence dopamine; instead, they may cause an imbalance between dopamine and acetylcholine, leading to a relative hypodopaminergic state causing dystonia. Magnuson *et al*. reported a patient in use of risperidone that developed dystonia only after the addition of donepezil.[38] The emergence of extrapyramidal symptoms after the addition of donepezil in a patient with dementia on risperidone suggests more than changes in just the acetylcholine–dopamine ratio. In patients with abnormal movements with AChEIs, a possible alternative for the management of cognitive impairment is memantine, a medication that is a noncompetitive NMDA receptor antagonist.[42] While dystonia is an uncommon side effect of cholinesterase inhibitors, healthcare providers need to recognize this occurrence due to the rising population of dementia patients and the expanding application of cholinesterase inhibitors for their treatment.

Pavlis *et al*., Dhikav and Anand reported a case of rivastigmine-induced dystonia.[87,88] The authors explained that this AChEI has nonlinear pharmacokinetics and inhibits both acetylcholinesterase and BChE. They hypothesized that the increased muscle tone likely occurred due to an increased cholinergic activity due to the anticholinesterase action in the striatum.

Pisa syndrome

In a comprehensive survey conducted by Stübner *et al*., a significant population of psychiatric patients was examined to investigate the prevalence of Pisa syndrome. Out of a total of 45,000 psychiatric patients surveyed, only 17 individuals were found to have developed this condition, indicating a rare occurrence within this demographic.[151]

Similarly, Yassa *et al*. undertook a thorough analysis of all newly admitted psychogeriatric patients over a 5-year span. Their findings revealed an overall prevalence rate of 8.3% for Pisa syndrome, with a notable gender disparity: 6.4% of men were affected compared to 9.3% of women.[152]

In addition, Vanacore *et al*. reported on the occurrence of Pisa syndrome induced by AChEIs in a specific subgroup. In their study, which involved 7395 AChEI-treated patients suffering from mild to moderate AD, three patients exhibited symptoms of Pisa syndrome. This led to the estimation that the incidence of this condition

among the cohort was approximately two cases per 10,000 patients on an annual basis.[57]

Pisa syndrome was already associated with different medications, especially with long-term antipsychotic therapy. AChEIs are one of the most common classes of drugs associated with Pisa syndrome. It is suggested that the cause of Pisa syndrome is the disbalance between the cholinergic and dopaminergic systems. Zannas *et al*. reported a 2:1 (female:male) ratio in the reported cases of Pisa syndrome associated with AChEI, with a mean-onset age of approximately 75 years.[153] Some authors proposed that the older people population is at risk due to the sensitivity of the cholinergic system, but the fact that AChEIs are more commonly prescribed to this population may also influence the results and lead to significant confounding variables.[154]

Galantamine was historically believed to be more strongly associated with Pisa syndrome than donepezil and rivastigmine.[71] However, animal studies revealed that galantamine affects AChEI and the allosteric potentiating ligand for the nicotinic acetylcholine receptor. Interestingly, galantamine was found to facilitate striatal dopamine release by acting as an allosteric potentiating ligand (APL) at the alpha-4 nicotinic acetylcholine receptor.[155] Noteworthy, Pisa syndrome is more commonly associated with drugs that block dopamine receptors. Furthermore, Ago *et al*. assessed galantamine-induced motor abnormalities in rat models, and the authors observed that the abnormal movements improved with muscarinic antagonists but not with nicotinic antagonists. Furthermore, they noticed that galantamine showed a weaker antagonistic effect against the muscarinic receptor than donepezil.[156]

Another possible explanation for Pisa syndrome secondary to AChEIs is a disruption in the body schema. Some authors believe that the visuospatial dysfunction assessed by Benton's judgment line orientation test was a strong and significant predictor for developing Pisa syndrome.[157]

Withdrawing or reducing the dose of the causative drug is recommended for individuals with Pisa syndrome associated with medications. The most common management for AChEI-induced Pisa syndrome was AChEI discontinuation. However, Hsu *et al*. reported improvement in Pisa syndrome symptoms after tapering off rivastigmine without discontinuation.[83] Some patients with Pisa syndrome and long-term antipsychotics have significant improvement in motor symptoms with anticholinergic medications.[158] Nevertheless, anticholinergic medication may worse cognitive function in individuals with AD.

Amantadine was already reported to improve Pisa syndrome in patients with AD.[159] However, some authors did not find any effectiveness in the motor symptoms in this group of individuals.[152] AChEI withdrawal markedly ameliorated Pisa syndrome in most patients. Furthermore, Chen *et al*. suggested the prescription of memantine in case of the occurrence of Pisa syndrome associated with AChEIs.[70] Mouse experiments support this hypothesis in that memantine significantly reduced extrapyramidal side effect induced by haloperidol, compared to galantamine and donepezil, through its antagonistic effect on the NMDA receptor.[160] Nevertheless, Zannas *et al*. found a similar strong association with memantine compared to AChEIs.[153]

We included Pisa syndrome as a different disorder from the dystonia section, but some authors believe that Pisa syndrome is a form of tardive dystonia.[43]

Future studies

There is a significant need for better data description in cases of drug-induced MDs. Authors should provide a full description of the MDs, including basic characteristics of the phenomenology, because even if the abnormal movement was wrongly diagnosed, a second reading specialist can change the diagnosis or bring it up in discussions in conferences and meetings.

The adverse reporting databases of the FDA Adverse Event Reporting System (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda) and World Health Organization's VigiAccess (https://www.vigiaccess.org/) should include a more detailed demographic description of the cases, and the full explanation of the adverse event should be included. These modifications are essential for improving the quality of the current databases and increasing the knowledge and possible adverse events associated with medications.

Limitations

A comprehensive and systematic review was conducted to gather all reported cases of MDs associated with the use of AChEIs. The majority of the material collected consisted of case reports and case series, which limited the possibility of performing a meta-analysis. One notable challenge in this type of research is the variability in the quality of case reports; often, essential information is incomplete or inadequately documented, complicating the analysis.

In addition, the presence of other medications being taken by some patients introduces a potential for

confounding factors, which means that establishing a clear cause-and-effect relationship between AChEIs and the onset of abnormal movements can be difficult. To address these complexities, we applied the Naranjo algorithm, ensuring that only cases classified as "probable" were included in our study, thereby enhancing the reliability of our findings.

It is also worth noting that many of the published reports did not originate from specialists in MDs. This could potentially lead to significant discrepancies in the outcomes reported. Interestingly, the primary medical departments responsible for publishing these cases were internal medicine and psychiatry, highlighting an interdisciplinary approach to the observation of these MDs.

A potential limitation of this study is that while AD is the most common neurodegenerative condition requiring symptomatic treatment with AChE inhibitors, but these drugs were also prescribed for Lewy body dementia and PDD with cognitive impairment. These underlying disorders themselves could contribute to the MDs reported, independent of AChE-inhibitor treatment. To mitigate this limitation, patients with Lewy body dementia and PDD were included only if a probable causality was established using the Naranjo algorithm. In addition, only cases demonstrating a worsening of the preexisting MD were considered. However, since none of the reports included neuropathological confirmation, the possibility of misdiagnosis in the selected cases cannot be entirely ruled out.

Conclusions

In summary, the most frequently observed MDs linked to AChEIs include Pisa syndrome, parkinsonism, myoclonus, dystonia, dyskinesia, and various extrapyramidal symptoms. Among these medications, donepezil stands out as the most commonly reported AChEI associated with abnormal movements. Notably, donepezil is also the medication most often prescribed for AD.

The underlying mechanisms that lead to these unusual MDs following AChEI treatment remain largely elusive. However, it is suggested that Pisa syndrome, characterized by abnormal postural alignment, may stem from a disruption in the delicate balance between dopamine and acetylcholine levels in the brain.

In addition, there is an interesting connection with tacrine, another AChEI, which has been linked to the occurrence of tremulous jaw movements in patients. This phenomenon has inspired the development of a PD-tremor animal model, aimed at investigating the tremor-inducing effects of tacrine observed in human subjects.

Author contributions

J. P. R. and A. L. F. C. conceived and designed the methodology of the literature review; J. P. R. and A. L. F. C. extracted and collected the relevant information and drafted the manuscript; A. L. F. C. supervised the article selection and reviewed and edited the manuscript; J. P. R. and A. L. F. reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

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All data generated and/or analyzed during this study are included in this published article [and its supplementary information files].

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Acetylcholinesterase inhibitors used for Alzheimer's disease therapy

Drug	Donepezil	Memantine/donepezil	Galantamine	Rivastigmine	Tacrine	Ipidacrine
PubChem CID	3152	NA	11760356	11398409	2723754	604519
Canonical SMILES	COC1=C (C=C2C(=C1) CC (C2=O) CC3CCN (CC3) CC4=CC=CC=C4) OC	NA	C[NH+]1CCC23C=CC (CC2OC4=C (C=CC(=C34) C1) OC) O.[Br−]	CCN (C) C(=O) OC1=CC=CC (=C1) C (C) N (C) C.CN (C) CC (C1=CC=C (C=C1) OC) C2(CCCCC2) O	C1CCC2=NC3=CC= CC=C3C(=C2C1) N.Cl	C1CCC2=C (C1) C(=C3CCCC3=N2) N
Systematic name	(RS)-2-[(1-Benzyl-4-piperidyl) methyl]-5,6-dimethoxy2,3-dihydroinden-1-one	NA	(4aS,6R,8aS) 5,6,9,10,11,12-Hexahydro3-methoxy-11-methyl-4aH-[1] benzofuro[3a, 3,2-ef][2] benzazepin-6-ol	(S)-N-Ethyl-N-methyl3-[1-(dimethylamino) ethyl] phenyl carbamate	1,2,3,4-tetrahydroacridin -9-amine	2,3,5,6,7,8-hexahydro-1H-cyclopenta[b] quinolin-9-amine
FDA approval	1996	2014	2001	2007	1993, and discontinued 2013	NA
Indication	AD	AD	AD	AD, PDD	AD	AD
Off-label indications	PDD, DLB, comorbid vascular dementia	NA	PDD, DLB, comorbid vascular dementia	DLB, comorbid vascular dementia	NA	NA
Dosage and forms	Tablet: 5 mg; 10 mg; 23 mg. Tablet, oral disintegrating: 5 mg; 10 mg	Capsule ER: 7 mg/10 mg; 14 mg/10 mg; 21 mg/10 mg; 28 mg/10 mg	Tablet: 4 mg; 8 mg; 12 mg. Capsule, ER: 8 mg; 16 mg; 24 mg. Oral solution: 4 mg/mL	Capsule: 1.5 mg; 3 mg; 4.5 mg; 6 mg. Transdermal patch: 4.6 mg/24hr; 9.5 mg/24hr; 13.3 mg/24hr	NA	NA
Mechanism of action	Noncompetitive inhibitor of AChE	Combined Memantine: Uncompetitive NMDAR antagonist	Competitive inhibitor of AChE	Pseudo-irreversible inhibitor of AChE and BChE	Inhibitor of AChE and BChE	Inhibitor of AChE
Metabolism	Cytochromes P450 3A4 and 2D6	Memantine: Undergoes partial hepatic metabolism	Cytochromes P450 3A4 and 2D6	Capturing by cholinesterases or eliminated without modification	Cytochromes P450 1A2	NA
Bioavailability	100%	NA	90%	36%	30%	NA
Peak plasma	3–4 h	Memantine ER: 18 h (with food); 25 h (fasting)	1 h	1 h (PO), 8 h (patch)	0.8 h	1 h
Distribution	Protein bound 96%, Vd 12–16 L/kg	Protein bound (memantine ER): 45%, Vd (memantine ER) 9–11 L/kg	Protein bound 18%; Vd 175 L	Protein bound 40%; Vd 1.8 L/Kg	Protein bound 55%; Vd 14.4 (IV), 49.1 (PO)	Protein bound 55%; Vd: NA
Elimination	Half-life: 70 h; excretion: Urine (57%), feces (17%)	Half-life (memantine): 60–80 h; excretion (memantine): Predominantly in urine (48% unchanged)	Half-life: 7 h; excretion urine	Half-life: 1.5 h (PO), 3 h (patch); excretion: urine (97%)	Half-life: 3 h (PO), 2.8 (IV); excretion: Urine	Half-life: 0.7 h; excretion: Urine

AChE: Acetylcholinesterase, AD: Alzheimer's disease, BChE: Butyrylcholinesterase, DLB: Dementia with Lewy bodies, ER: Extended-release, NA: Not available/not reported/not applicable, NMDAR: N-methyl-D-aspartate receptor, PDD: Parkinson's disease dementia, Vd: Volume distribution

Supplementary Table 2: FreeText and MeSH search terms in the US National Library of Medicine

Search term	Query	Results
	Donepezil	
(donepezil) AND (akathisia)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("akathisias"[All Fields] OR "psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "akathisia"[All Fields])	27
(donepezil) AND (ataxia)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("ataxia"[MeSH Terms] OR "ataxia"[All Fields] OR "ataxias"[All Fields])	7
(donepezil) AND (ballism)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("dyskinesias"[MeSH Terms] OR "dyskinesias"[All Fields] OR "ballism"[All Fields])	76
(donepezil) AND (bradykinesia)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields] OR "bradykinesia"[All Fields])	9
(donepezil) AND (chorea)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("chorea"[MeSH Terms] OR "chorea"[All Fields] OR "choreas"[All Fields])	5
(donepezil) AND (dyskinesia)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("dyskinesiae"[All Fields] OR "dyskinesias"[MeSH Terms] OR "dyskinesias"[All Fields] OR "dyskinesia"[All Fields])	81
(donepezil) AND (dystonia)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("dystonia"[MeSH Terms] OR "dystonia"[All Fields] OR "dystonias"[All Fields] OR "dystonic disorders"[MeSH Terms] OR ("dystonic"[All Fields] AND "disorders"[All Fields]) OR "dystonic disorders"[All Fields])	19
(donepezil) AND (extrapyramidal)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND "extrapyramidal"[All Fields]	31
(donepezil) AND (hyperkinetic)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("hyperkinetic"[All Fields] OR "hyperkinetics"[All Fields])	0
(donepezil) AND (hypokinetic)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields] OR "hypokinetic"[All Fields])	4
(donepezil) AND (movement disorder)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("movement disorders"[MeSH Terms] OR ("movement"[All Fields] AND "disorders"[All Fields]) OR "movement disorders"[All Fields] OR ("movement"[All Fields] AND "disorder"[All Fields]) OR "movement disorder"[All Fields])	281
(donepezil) AND (myoclonus)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("myoclonus"[MeSH Terms] OR "myoclonus"[All Fields])	14
(donepezil) AND (myokymia)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("myokymia"[MeSH Terms] OR "myokymia"[All Fields] OR "myokymias"[All Fields])	0
(donepezil) AND (parkinsonism)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields])	323
(donepezil) AND (restless legs syndrome)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("restless legs syndrome"[MeSH Terms] OR ("restless"[All Fields] AND "legs"[All Fields] AND "syndrome"[All Fields]) OR "restless legs syndrome"[All Fields])	3
(donepezil) AND (restlessness)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "restlessness"[All Fields] OR "restless"[All Fields])	29
(donepezil) AND (stuttering)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("stammerers"[All Fields] OR "stammers"[All Fields] OR "stutterer"[All Fields] OR "stutterer s"[All Fields] OR "stutterers"[All Fields] OR "stuttering"[MeSH Terms] OR "stuttering"[All Fields] OR "stammer"[All Fields] OR "stammering"[All Fields] OR "stutter"[All Fields] OR "stuttered"[All Fields] OR "stutters"[All Fields] OR "stutterings"[All Fields])	1
(donepezil) AND (tics)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("tics"[MeSH Terms] OR "tics"[All Fields])	5
(donepezil) AND (tremor)	("donepezil"[MeSH Terms] OR "donepezil"[All Fields] OR "donepezil s"[All Fields]) AND ("tremor"[MeSH Terms] OR "tremor"[All Fields] OR "tremors"[All Fields] OR "tremoring"[All Fields] OR "tremorous"[All Fields])	29
	Galantamine	
(galantamine) AND (akathisia)	("galantamine"[MeSH Terms] OR "galantamine"[All Fields] OR "galantamin"[All Fields] OR "galantamine s"[All Fields]) AND ("akathisias"[All Fields] OR "psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "akathisia"[All Fields])	15

Contd...

Supplementary Table 2: Contd...

Search term	Query	Results
	Galantamine	
(galantamine) AND (ataxia)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“ataxia”[MeSH Terms] OR “ataxia”[All Fields] OR “ataxias”[All Fields])	1
(galantamine) AND (ballism)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “ballism”[All Fields])	44
(galantamine) AND (bradykinesia)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “bradykinesia”[All Fields])	7
(galantamine) AND (chorea)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“chorea”[MeSH Terms] OR “chorea”[All Fields] OR “choreas”[All Fields])	4
(galantamine) AND (dyskinesia)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“dyskinesiae”[All Fields] OR “dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “dyskinesia”[All Fields])	46
(galantamine) AND (dystonia)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“dystonia”[MeSH Terms] OR “dystonia”[All Fields] OR “dystonias”[All Fields] OR “dystonic disorders”[MeSH Terms] OR (“dystonic”[All Fields] AND “disorders”[All Fields]) OR “dystonic disorders”[All Fields])	8
(galantamine) AND (extrapyramidal)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND “extrapyramidal”[All Fields]	15
(galantamine) AND (hyperkinetic)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“hyperkinetic”[All Fields] OR “hyperkinetics”[All Fields])	0
(galantamine) AND (hypokinetic)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “hypokinetic”[All Fields])	5
(galantamine) AND (movement disorder)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“movement disorders”[MeSH Terms] OR (“movement”[All Fields] AND “disorders”[All Fields]) OR “movement disorders”[All Fields] OR (“movement”[All Fields] AND “disorder”[All Fields]) OR “movement disorder”[All Fields])	90
(galantamine) AND (myoclonus)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“myoclonus”[MeSH Terms] OR “myoclonus”[All Fields])	3
(galantamine) AND (myokymia)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“myokymia”[MeSH Terms] OR “myokymia”[All Fields] OR “myokymias”[All Fields])	0
(galantamine) AND (parkinsonism)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“parkinson disease”[MeSH Terms] OR (“parkinson”[All Fields] AND “disease”[All Fields]) OR “parkinson disease”[All Fields] OR “parkinsons”[All Fields] OR “parkinson”[All Fields] OR “parkinson s”[All Fields] OR “parkinsonian disorders”[MeSH Terms] OR (“parkinsonian”[All Fields] AND “disorders”[All Fields]) OR “parkinsonian disorders”[All Fields] OR “parkinsonism”[All Fields] OR “parkinsonisms”[All Fields] OR “parkinsons s”[All Fields])	110
(galantamine) AND (restless legs syndrome)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“restless legs syndrome”[MeSH Terms] OR (“restless”[All Fields] AND “legs”[All Fields] AND “syndrome”[All Fields]) OR “restless legs syndrome”[All Fields])	0
(galantamine) AND (restlessness)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation”[All Fields] OR “restlessness”[All Fields] OR “restless”[All Fields])	15
(galantamine) AND (stuttering)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“stammerers”[All Fields] OR “stammers”[All Fields] OR “stutterer”[All Fields] OR “stutterer s”[All Fields] OR “stutterers”[All Fields] OR “stuttering”[MeSH Terms] OR “stuttering”[All Fields] OR “stammer”[All Fields] OR “stammering”[All Fields] OR “stutter”[All Fields] OR “stuttered”[All Fields] OR “stutters”[All Fields] OR “stutterings”[All Fields])	0
(galantamine) AND (tics)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“tics”[MeSH Terms] OR “tics”[All Fields])	3
(galantamine) AND (tremor)	(“galantamine”[MeSH Terms] OR “galantamine”[All Fields] OR “galantamin”[All Fields] OR “galantamines”[All Fields]) AND (“tremor”[MeSH Terms] OR “tremor”[All Fields] OR “tremors”[All Fields] OR “tremoring”[All Fields] OR “tremorous”[All Fields])	20
	Rivastigmine	
(rivastigmine) AND (akathisia)	(“rivastigmin”[All Fields] OR “rivastigmine”[MeSH Terms] OR “rivastigmine”[All Fields]) AND (“akathisias”[All Fields] OR “psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation”[All Fields] OR “akathisia”[All Fields])	17

Contd...

Supplementary Table 2: Contd...

Search term	Query	Results
	Rivastigmine	
(rivastigmine) AND (ataxia)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("ataxia"[MeSH Terms] OR "ataxia"[All Fields] OR "ataxias"[All Fields])	1
(rivastigmine) AND (ballism)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("dyskinesias"[MeSH Terms] OR "dyskinesias"[All Fields] OR "ballism"[All Fields])	47
(rivastigmine) AND (bradykinesia)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields] OR "bradykinesia"[All Fields])	9
(rivastigmine) AND (chorea)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("chorea"[MeSH Terms] OR "chorea"[All Fields] OR "choreas"[All Fields])	7
(rivastigmine) AND (dyskinesia)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("dyskinesia"[All Fields] OR "dyskinesias"[MeSH Terms] OR "dyskinesias"[All Fields] OR "dyskinesia"[All Fields])	51
(rivastigmine) AND (dystonia)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("dystonia"[MeSH Terms] OR "dystonia"[All Fields] OR "dystonias"[All Fields] OR "dystonic disorders"[MeSH Terms] OR ("dystonic"[All Fields] AND "disorders"[All Fields]) OR "dystonic disorders"[All Fields])	9
(rivastigmine) AND (extrapyramidal)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND "extrapyramidal"[All Fields]	23
(rivastigmine) AND (hyperkinetic)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("hyperkinetic"[All Fields] OR "hyperkinetics"[All Fields])	0
(rivastigmine) AND (hypokinetic)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields] OR "hypokinetic"[All Fields])	3
(rivastigmine) AND (movement disorder)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("movement disorders"[MeSH Terms] OR ("movement"[All Fields] AND "disorders"[All Fields]) OR "movement disorders"[All Fields] OR ("movement"[All Fields] AND "disorder"[All Fields]) OR "movement disorder"[All Fields])	253
(rivastigmine) AND (myoclonus)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("myoclonus"[MeSH Terms] OR "myoclonus"[All Fields])	5
(rivastigmine) AND (myokymia)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("myokymia"[MeSH Terms] OR "myokymia"[All Fields] OR "myokymias"[All Fields])	0
(rivastigmine) AND (parkinsonism)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields])	313
(rivastigmine) AND (restless legs syndrome)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("restless legs syndrome"[MeSH Terms] OR ("restless"[All Fields] AND "legs"[All Fields] AND "syndrome"[All Fields]) OR "restless legs syndrome"[All Fields])	2
(rivastigmine) AND (restlessness)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "restlessness"[All Fields] OR "restless"[All Fields])	21
(rivastigmine) AND (stuttering)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("stammerers"[All Fields] OR "stammers"[All Fields] OR "stutterer"[All Fields] OR "stutterer s"[All Fields] OR "stutterers"[All Fields] OR "stuttering"[MeSH Terms] OR "stuttering"[All Fields] OR "stammer"[All Fields] OR "stammering"[All Fields] OR "stutter"[All Fields] OR "stuttered"[All Fields] OR "stutters"[All Fields] OR "stutterings"[All Fields])	0
(rivastigmine) AND (tics)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("tics"[MeSH Terms] OR "tics"[All Fields])	2
(rivastigmine) AND (tremor)	("rivastigmin"[All Fields] OR "rivastigmine"[MeSH Terms] OR "rivastigmine"[All Fields]) AND ("tremor"[MeSH Terms] OR "tremor"[All Fields] OR "tremors"[All Fields] OR "tremoring"[All Fields] OR "tremorous"[All Fields])	25
	Tacrine	
(tacrine) AND (akathisia)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("akathisias"[All Fields] OR "psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "akathisia"[All Fields])	5
(tacrine) AND (ataxia)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("ataxia"[MeSH Terms] OR "ataxia"[All Fields] OR "ataxias"[All Fields])	1

Contd...

Supplementary Table 2: Contd...

Search term	Query	Results
	Tacrine	
(tacrine) AND (ballism)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("dyskinesias"[MeSH Terms] OR "dyskinesias"[All Fields] OR "ballism"[All Fields])	47
(tacrine) AND (bradykinesia)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields] OR "bradykinesia"[All Fields])	1
(tacrine) AND (chorea)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("chorea"[MeSH Terms] OR "chorea"[All Fields] OR "choreas"[All Fields])	2
(tacrine) AND (dyskinesia)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("dyskinesiae"[All Fields] OR "dyskinesias"[MeSH Terms] OR "dyskinesias"[All Fields] OR "dyskinesia"[All Fields])	50
(tacrine) AND (dystonia)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("dystonia"[MeSH Terms] OR "dystonia"[All Fields] OR "dystonias"[All Fields] OR "dystonic disorders"[MeSH Terms] OR ("dystonic"[All Fields] AND "disorders"[All Fields]) OR "dystonic disorders"[All Fields])	0
(tacrine) AND (extrapyramidal)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND "extrapyramidal"[All Fields]	8
(tacrine) AND (hyperkinetic)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("hyperkinetic"[All Fields] OR "hyperkinetics"[All Fields])	1
(tacrine) AND (hypokinetic)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields] OR "hypokinetic"[All Fields])	1
(tacrine) AND (movement disorder)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("movement disorders"[MeSH Terms] OR ("movement"[All Fields] AND "disorders"[All Fields]) OR "movement disorders"[All Fields] OR ("movement"[All Fields] AND "disorder"[All Fields]) OR "movement disorder"[All Fields])	58
(tacrine) AND (myoclonus)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("myoclonus"[MeSH Terms] OR "myoclonus"[All Fields])	3
(tacrine) AND (myokymia)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("myokymia"[MeSH Terms] OR "myokymia"[All Fields] OR "myokymias"[All Fields])	0
(tacrine) AND (parkinsonism)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields])	73
(tacrine) AND (restless legs syndrome)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("restless legs syndrome"[MeSH Terms] OR ("restless"[All Fields] AND "legs"[All Fields] AND "syndrome"[All Fields]) OR "restless legs syndrome"[All Fields])	1
(tacrine) AND (restlessness)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "restlessness"[All Fields] OR "restless"[All Fields])	7
(tacrine) AND (stuttering)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("stammerers"[All Fields] OR "stammers"[All Fields] OR "stutterer"[All Fields] OR "stutterer s"[All Fields] OR "stutterers"[All Fields] OR "stuttering"[MeSH Terms] OR "stuttering"[All Fields] OR "stammer"[All Fields] OR "stammering"[All Fields] OR "stutter"[All Fields] OR "stuttered"[All Fields] OR "stutters"[All Fields] OR "stutterings"[All Fields])	0
(tacrine) AND (tics)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("tics"[MeSH Terms] OR "tics"[All Fields])	0
(tacrine) AND (tremor)	("tacrine"[MeSH Terms] OR "tacrine"[All Fields] OR "tacrin"[All Fields] OR "tacrine s"[All Fields] OR "tacrines"[All Fields]) AND ("tremor"[MeSH Terms] OR "tremor"[All Fields] OR "tremors"[All Fields] OR "tremoring"[All Fields] OR "tremorous"[All Fields])	47
	Ipidacrine	
(ipidacrine) AND (akathisia)	("amiridine"[Supplementary Concept] OR "amiridine"[All Fields] OR "ipidacrine"[All Fields]) AND ("akathisias"[All Fields] OR "psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "akathisia"[All Fields])	0
(ipidacrine) AND (ataxia)	("amiridine"[Supplementary Concept] OR "amiridine"[All Fields] OR "ipidacrine"[All Fields]) AND ("ataxia"[MeSH Terms] OR "ataxia"[All Fields] OR "ataxias"[All Fields])	1

Contd...

Supplementary Table 2: Contd...

Search term	Query	Results
	Ipidacrine	
(ipidacrine) AND (ballism)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “ballism”[All Fields])	6
(ipidacrine) AND (bradykinesia)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “bradykinesia”[All Fields])	0
(ipidacrine) AND (chorea)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“chorea”[MeSH Terms] OR “chorea”[All Fields] OR “choreas”[All Fields])	0
(ipidacrine) AND (dyskinesia)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“dyskinesiae”[All Fields] OR “dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “dyskinesia”[All Fields])	7
(ipidacrine) AND (dystonia)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“dystonia”[MeSH Terms] OR “dystonia”[All Fields] OR “dystonias”[All Fields] OR “dystonic disorders”[MeSH Terms] OR (“dystonic”[All Fields] AND “disorders”[All Fields]) OR “dystonic disorders”[All Fields])	0
(ipidacrine) AND (extrapyramidal)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND “extrapyramidal”[All Fields]	0
(ipidacrine) AND (hyperkinetic)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“hyperkinetic”[All Fields] OR “hyperkinetics”[All Fields])	0
(ipidacrine) AND (hypokinetic)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “hypokinetic”[All Fields])	0
(ipidacrine) AND (movement disorder)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“movement disorders”[MeSH Terms] OR (“movement”[All Fields] AND “disorders”[All Fields]) OR “movement disorders”[All Fields] OR (“movement”[All Fields] AND “disorder”[All Fields]) OR “movement disorder”[All Fields])	10
(ipidacrine) AND (myoclonus)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“myoclonus”[MeSH Terms] OR “myoclonus”[All Fields])	0
(ipidacrine) AND (myokymia)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“myokymia”[MeSH Terms] OR “myokymia”[All Fields] OR “myokymias”[All Fields])	0
(ipidacrine) AND (parkinsonism)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“parkinson disease”[MeSH Terms] OR (“parkinson”[All Fields] AND “disease”[All Fields]) OR “parkinson disease”[All Fields] OR “parkinsons”[All Fields] OR “parkinson”[All Fields] OR “parkinson s”[All Fields] OR “parkinsonian disorders”[MeSH Terms] OR (“parkinsonian”[All Fields] AND “disorders”[All Fields]) OR “parkinsonian disorders”[All Fields] OR “parkinsonism”[All Fields] OR “parkinsonisms”[All Fields] OR “parkinsons s”[All Fields])	4
(ipidacrine) AND (restless legs syndrome)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“restless legs syndrome”[MeSH Terms] OR (“restless”[All Fields] AND “legs”[All Fields] AND “syndrome”[All Fields]) OR “restless legs syndrome”[All Fields])	0
(ipidacrine) AND (restlessness)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation”[All Fields] OR “restlessness”[All Fields] OR “restless”[All Fields])	0
(ipidacrine) AND (stuttering)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“stammerers”[All Fields] OR “stammers”[All Fields] OR “stutterer”[All Fields] OR “stutterer s”[All Fields] OR “stutterers”[All Fields] OR “stuttering”[MeSH Terms] OR “stuttering”[All Fields] OR “stammer”[All Fields] OR “stammering”[All Fields] OR “stutter”[All Fields] OR “stuttered”[All Fields] OR “stutters”[All Fields] OR “stutterings”[All Fields])	0
(ipidacrine) AND (tics)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“tics”[MeSH Terms] OR “tics”[All Fields])	0
(ipidacrine) AND (tremor)	(“amiridine”[Supplementary Concept] OR “amiridine”[All Fields] OR “ipidacrine”[All Fields]) AND (“tremor”[MeSH Terms] OR “tremor”[All Fields] OR “tremors”[All Fields] OR “tremoring”[All Fields] OR “tremorous”[All Fields])	2

Supplementary Table 3: Preferred reporting items for systematic reviews and meta-analyses 2020 checklist

Section and topic	Item #	Checklist item	Location where item is reported
		Title	
Title	1	Identify the report as a systematic review	1
		Abstract	
Abstract	2	See the PRISMA 2020 for abstracts checklist	1
		Introduction	
Rationale	3	Describe the rationale for the review in the context of existing knowledge	1–2
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses	1–2
		Methods	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	2–4
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	2–4
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	2–4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	2–4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	2–4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect	2–4
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	2–4
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	2–4
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results	2–4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5])	2–4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	2–4
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses	2–4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used	2–4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression)	2–4
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results	2–4
Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases)	2–4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	2–4
		Results	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	4–8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	4–8
Study characteristics	17	Cite each included study and present its characteristics	4–8

Contd...

Supplementary Table 3: Contd...

Section and topic	Item #	Checklist item	Location where item is reported
		Results	
Risk of bias in studies	18	Present assessments of risk of bias for each included study	4–8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots	4–8
Results of syntheses	20a	For each synthesis, briefly summaries the characteristics and risk of bias among contributing studies	4–8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	4–8
	20c	Present results of all investigations of possible causes of heterogeneity among study results	4–8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	4–8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	4–8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	4–8
		Discussion	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	8–14
	23b	Discuss any limitations of the evidence included in the review	8–14
	23c	Discuss any limitations of the review processes used	8–14
	23d	Discuss the implications of the results for practice, policy, and future research	8–14
		Other information	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	No registration
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	No registration
	24c	Describe and explain any amendments to information provided at registration or in the protocol	No registration
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review	None
Competing interests	26	Declare any competing interests of review authors	None
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: Template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	Supplementary material

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. PRISMA: Preferred reporting items for systematic reviews and meta-analyses

Supplementary Table 4: Literature review of movement disorders associated with donepezil, galantamine, rivastigmine, tacrine, and ipidacrine

Donepezil-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Donepezil-induced parkinsonism								
Bourke and Druckenbrod[20]	1	80/female	PDD	5 mg/day	2 weeks	NA	PR. Improved but still present symptoms included shuffling, bradykinesia, stiffness, and tremor	Shuffling, bradykinesia, stiffness, tremor
Magnuson *et al*.[21]	1	79/female	AD	10 mg/day	2 weeks	2 months	FR. Donepezil dose was reduced	Parkinsonian features and dyskinetic movements
Arai[22]	1	79/female	Dementia	3 mg/day increased to 5 mg/day 2 weeks later	3 weeks	10 days	FR. Gait disturbance improved and regained the ability to walk without assistance	Expressionless face, stooped posture, bradykinesia, four-limb rigidity
Carcenac *et al*.[23]	3	NA	NA	NA	NA	NA	2 FR and 1 PR	Patients developed gait disorder
Fabbrini *et al*.[24]	2	NA	NA	NA	NA	NA	NA	2 out of 8 patients with PD had worsening with donepezil therapy for hallucinations and delusions
Liu *et al*.[25]	1	80/female	AD	5 mg/day	2 weeks	1 week	FR	Parkinsonian features with severe rigidity
Onofrj and Thomas[26]	1	73/female	DLB	25 mg/day	1 day	5 days	FR	Camptocormia
Morita *et al*.[27]	1	75/female	DLB	NA	NA	NA	FR. Donepezil was discontinued. Trihexyphenidyl worsened parkinsonian symptoms	Patient presenting with severe rigidity and akinesia
Rozzini *et al*.[28]	1	70/female	DLB	20 mg/day	2 years	4 weeks	FR	Rigidity, bradykinesia, hypomimia, inability to walk
Brucki and Nitrini[29]	1	82/male	AD	10 mg/day	3 years	NA	NA	Levodopa did not improve camptocormia
Song *et al*.[30]	1	76/female	MCI	5 mg/day	2 days	7 days	Donepezil was discotninued	Donepezil-induced jaw tremor
Dubois *et al*.[31]	1	NA	NA	NA	NA	NA	NA	Study assessing donepezil in the management of PDD
Kang and Kim[32]	1	69/male	MCI	10 mg/day	6 weeks	NA	PR. Donepezil was discontinued	Dopamine transporter imaging was normal
Rangseekajee *et al*. (2016)[33]	1	59/female	AD	23 mg/day	2 weeks	NA	PR. Donepezil was discontinued	Titrated donepezil up to 15 mg/day for 3 months without any adverse events. On the following visit, it was increased the dose to 23 mg/day, then the husband noticed her tremor 2–3 weeks later
Chebotareva and Levin[34]	1	NA	NA	NA	NA	NA	NA	1 out of 62 individuals had worsening of tremors
Mukherjee[35]	1	72/female	AD	NA	NA	NA	NA	Erroneously ingestion of 43 mg instead of 20 mg/day. Rapid-onset global rigidity and subsequent altered sensorium
Segal *et al*.[36]	1	70/male	Dementia	NA	NA	NA	FR. Donepezil dose was not modified	Camptocormia. It can be explained by citalopram and donepezil. Unclear description of neurological examination
Wang *et al*.[37]	1	68/female	AD	10 mg/day	1 month	20 days	FR	Masked face, bradykinesia, hypophonia, posture instability

Contd...

Supplementary Table 4: Contd...

Donepezil-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Donepezil-induced dystonia								
Magnuson *et al.*[38]	2	77 (mean)/2 females	AD	5 mg/day (mean)	7 weeks (mean)	NA	Donepezil dose was not changed	Cervical dystonia, retrocollis. Cervical dystonia, toticollis
Hasegawa *et al.*[39]	1	67/female	DLB	5 mg/day	18 months	NA	Donepezil was discontinued	Cervical dystonia, anterocollis
Negoro[40]	1	79/female	AD	NA	4 weeks	2 weeks	FR. Donepezil was discontinued	NA
Oh *et al.*[41]	1	79/female	PDD	10 mg/day	1 month	1 week	FR. Donepezil was switched to memantine	Cervical dystonia, anterocollis
Yagi *et al.*[42]	1	70/female	AD	5 mg/day	1 month	4 weeks	FR. Donepezil was switched to memantine	Cervical dystonia, torticollis
Ikeda *et al.*[43]	1	81/female	AD	5 mg/day	10 months	2 months	FR. Donepezil was switched to memantine	Cervical dystonia, anterocollis
Li *et al.*[44]	1	87/female	AD	5 mg/day	5 days	NA	FR. Donepezil was discontinued	Cervical dystonia, left-side torticollis
Donepezil-induced dyskinesias								
Tanaka *et al.*[45]	1	70/male	AD	5 mg	6 months	5 days	FR. Donepezil was discontinued	Athetosis
Nozaki *et al.*[46]	2	81.5 (mean)/2 males	AD	4 mg/day (mean)	3 weeks (mean)	1.5 weeks (mean)	FR. Donepezil discontinuation and biperiden started	Chorea. Only donepezil discontinuation did not improve symptoms
Donepezil-induced myoclonus								
Bougea *et al.*[47]	1	80/female	AD	30 mg/day	25 days	1.5 days	FR. Donepezil was discontinued	Myoclonus in both upper and lower extremities
Whateley *et al.*[48]	1	93/female	AD	10 mg/day	7 weeks	2 days	FR. Donepezil was discontinued	Multifocal myoclonic nonsynchronous, affecting all four limbs at rest
Amlang *et al.*[49]	1	67/male	NA	NA	4 weeks	1 day	FR. Donepezil was discontinued; clonazepam was started	Multifocal myoclonic movements of head, face, upper extremities, and trunk
Eroğlu *et al.*[50]	1	84/male	Dementia	10 mg/day	2 years	1 week	FR. Donepezil dose was maintained, and quetiapine was changed	Case with concerning for atypical neuroleptic malignant syndrome
Ramsey *et al.*[51]	1	50/NA	Dementia	NA	4 days	NA	FR. Donepezil was discontinued	Case showing concerning for possible serotonin syndrome due to polypharmacy
Rissardo and Fornari Caprara[52]	1	61/female	MCI	5 mg/day	4 weeks	1 day	FR. Donepezil was discontinued; clonazepam was started	Multifocal myoclonus of distal limbs and face; myoclonus worsened with action
Delirrad *et al.*[53]	1	49/male	Intoxication	NA	NA	NA	NA	Mistakenly ingested 200 mg of donepezil. Multifocal myoclonus. He also experienced rhabdomyolysis
Donepezil-induced Pisa syndrome								
Kwak *et al.*[54]	2	63 (mean)/2 females	2 AD	5 mg/day (mean)	2.5 months (mean)	2.5 weeks (mean)	FR. Discontinuation of donepezil improved PS, but it recurred with rivastigmine	NA
Miyaoka *et al.*[55]	1	57/male	1 AD	5 mg/day	1 month	7 days	FR. Donepezil was discontinued	NA
Villarejo *et al.*[56]	2	74.5 (mean)/2 females	1 AD and 1 PDD	7.5 mg/day (mean)	1 month (mean)	8 days (mean)	FR. Donepezil was discontinued	One of the patients had risperidone dose–adjusted

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Supplementary Table 4: Contd...

Donepezil-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Donepezil-induced Pisa syndrome								
Vanacore *et al*.[57]	3	80.6 (mean)/3 females	3 AD	6.6 mg/day (mean)	1 month (mean)	2 weeks (mean)	3 FR. Donepezil was discontinued in one case. Donepezil was changed to rivastigmine in other case	In one case donepezil was changed to rivastigmine, but the patient did not improve. Rivastigmine was discontinued, and the patient full recovery
Huvent-Grelle *et al*.[58]	2	75.5 (mean)/2 females	2 AD	NA	2 years (mean)	2 weeks (mean)	1 FR and 1 PR. Donepezil was discontinued in both cases	In one case, rivastigmine was changed to donepezil, and Pisa syndrome occurred
Ogihara *et al*.[59]	2	68.5 (mean)/2 females	1 AD and 1 DLB	5 mg/day (mean)	8 months (mean)	3.5 weeks (mean)	FR. Donepezil was discomntinued	NA
Huvent-Grelle *et al*.[60]	2	89 (mean)/2 males	2 AD	NA	10.5 months (mean)	1 week (mean)	2 FR. Donepezil was discontinued in one case. Donepezil was switched to rivastigmine	NA
Shinfuku *et al*.[61]	1	71/female	DLB	5 mg/day	1 year	NA	PR. Donepezil was discontinued	Patient showed mild improvement within 6 months
Ioannidis *et al*.[62]	1	74/female	AD	NA	1 day	1 week	FR. Donepezil was discontinued	Acute Pisa syndrome after administration of a single dose of donepezil
Selvaraj *et al*.[63]	1	66/female	Dementia	10 mg/day	3 weeks	1 week	FR. Donepezil was discontinued	
Pollock *et al*.[64]	1	87/male	AD	10 mg/day	2 years	3 months	FR. Donepezil was discontinued	Discontinuation and reduction of donepezil was a better approach than the use of anticholinergics which could further impair cognition
Mukku *et al*.[65]	1	60/male	AD	10 mg/day	3 months	3 days	FR. Donepezil was discontinued	
Bruggeman *et al*.[66]	1	68/female	AD	NA	5 years	6 months	FR. Donepezil was discontinued	Video-recorded
Ueda *et al*.[67]	2	79 (mean)/1 female and 1 male	1 AD and 1 DLB	10 mg/day (mean)	2.75 weeks (mean)	3.5 months (mean)	FR Donepezil was discontinued	In one patient pramipexole and levodopa were increased, and the recovery time was longer
Waykar *et al*.[68]	1	75/female	AD	10 mg/day	6 months	1 week	FR. Doneepezil was switched to memantine	
Galantamine-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Galantamine-induced Pisa syndrome								
Cossu *et al*.[69]	1	72/female	AD	8 mg/day	1 month	NA	PR. Galantamine was discontinued, and the patient did not improve	Patient required scheduled botulinum toxin for improvement
Huvent-Grelle *et al*.[59]	2	75 (mean)/ female	2 AD	NA	5.75 years (mean)	2 weeks (mean)	FR. Galantamine was discontinued	In one case galantamine was switched to rivastigmine
Chen *et al*.[70]	1	65/female	AD	16 mg/day	6 months	6 weeks	FR. Galantamine was switched to memantine	Memantine can be an alternative to AChEI-induced Pisa syndrome

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Supplementary Table 4: Contd...

Galantamine-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Galantamine-induced Pisa syndrome								
Mimura *et al*.[71]	1	57/female	AD	8 mg/day	2 weeks	2 weeks	FR. Galantamine was discontinued	Pisa syndrome occurred after donepezil switched to galantamine
Galantamine-induced dyskinesia								
Bhanji and Gauthier[72]	1	70/male	DLB	16 mg/day	2 weeks	NA	PR. Galatamine was switched to donepezil	New-onset lower limb dyskinesia, not specifically described
Galantamine-induced myoclonus								
Colebatch and Bacsi[73]	1	69/female	Dementia	16 mg/day	NA	NA	NA	Multifocal myoclonus affecting upper and lower limbs
Hernández-Fernández *et al*.[74]	1	80/male	AD	24 mg/day	1 months	3 weeks	FR. Galantamine was discontinued; valproic acid and clonazepam were started	Respiratory myoclonus, also known as diaphragmatic flutter
Luna *et al*.[75]	1	87/male	Dementia	16 mg/day	4 months	2 weeks	FR. Galantamine was discontinued	Multifocal myoclonus
Galantamine-induced extrapyramidal symptoms								
Suzuki *et al*.[76]	1	89/female	AD	Intoxication. 264 mg once	NA	NA	FR. Patient needed intensive care unit level of care	Restlessness, tremors, sweating, diarrhea, pharyngeal gurgling, and severe hypoxia
Rivastigmine-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Rivastigmine-induced parkinsonism								
Heinze *et al*.[77]	1	88/female	AD	6 mg/day	7 weeks	1 week	Rivastigmine was discontinued	Parkinsonian symptoms
Richard *et al*.[78]	1	71/female	PDD	3 mg/day	1 day	1 day	FR. Rivastigmine was discontinued	Single-dose of rivastigmine
Gurevich *et al*.[79]	3	NA	NA	NA	NA	NA	NA	Effect of rivastigmine on tremor in patients with PDD
Clerici *et al*.[80]	1	72/male	DLB	7.5 mg/day	3 months	NA	PR. Improvement of parkinsonian symptoms	Tremor, camptocormia, postural instability - with severe gait difficulty and repeated falls
Rivastigmine-induced Pisa syndrome								
Huvent-Grelle *et al*.[58]	1	79/male	AD	NA	2 years	NA	Died	NA
Wang and Chiu[81]	1	77/male	MCI	9 mg/day	2 weeks	3 days	Rivastigmine dose was reduced	Dose-dependent Pisa syndrome
Leelavathi *et al*.[82]	1	80/male	AD	12 mg/day	18 months	NA	NA. Rivastigmine was switched to donepezil	Pisa syndrome secondary to the rivastigmine oral and patch forms
Hsu *et al*.[83]	1	57/female	AD	9 mg/day	19 months	1 month	FR. Rivastigmine dose was reduced	Patient with early-onset AD
Chao *et al*.[84]	1	67/female	AD	1.5 mg/day	5 days	1 week	FR. Rivastigmine was discontinued	
Rivastigmine-induced dyskinesia								
Porta-Etessam *et al*.[85]	1	81/female	AD	6 mg/day	9 months	3 months	FR. Rivastgimine was discontinued	Orofacial dyskinesia
Diaz and Rosales[86]	1	81/female	AD	13.3 mg/cm^2 24 h	3 months	6 days	FR. Rivastigmine was discontinued	Choreiform movements

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Supplementary Table 4: Contd...

Galantamine-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Rivastigmine-induced dystonia								
Pavlis *et al*.[87]	1	61/female	AD	6 mg/day	NA	2 days	FR. Rivastigmine was discontinued	Cervical dystonia, retrocollis
Dhikav and Anand[88]	1	75/female	AD	10 mg/cm^2 24 h	1 month	1 day	FR. Rivastigmine was discontinued and diazepam was started	Cervical dystonia. Recurrence with rivastigmine rechallenge
Tacrine- and ipidacrine-associated movement disorders								
Reference	***n***	**Age/sex**	**AChEI indication**	**AChEI dose**	**MD onset**	**MD recovery**	**FU**	**Commentary**
Tacrine- and ipidacrine-induced parkinsonism								
Ott and Lannon[89]	1	67/female	Dementia	20 mg/day	2 months	1 month	FR. Tacrine was continued, and levodopa was started	Pakrinsonian features. When tacrine dose was increased, tremors and bradykinesia reappeared
McSwain and Forman[90]	1	87/male	PDD	50 mg/day	3 days	1 day	FR. Tacrine was discontinued	Akinesia/bradykinesia, masked facies, shuffling gait, and lead-pipe rigidity
Maany[91]	1	72/female	Dementia	10 mg/day	1 weeks	1 week	FR. Tacrine dose was maintained	Severe akinesia, shuffling gait, masked facies, slurred speech, and pronounced rigidity and cogwheel signs
Cabeza-Alvarez *et al*. (1999)[92]	1	NA	Dementia	NA	NA	NA	NA	NA
Tacrine- and ipidacrine-induced myoclonus								
Abilleira *et al*.[93]	1	68/female	AD	40 mg	1 day	1 day	FR. Tacrine was discontinued, and clonazepam was started	Generalized myoclonus. EEG was normal. Myoclonus reappeared with tacrine rechallenge

FU: Follow-up, MD: Movement disorder, AChEI: Acetylcholinesterase inhibitor, NA: Not available/not reported/not applicable, AD: Alzheimer's disease, DLB: Dementia with Lewy bodies, FR: Full recovery, PR: Partial recovery, PDD: Parkinson's disease dementia, MCI: Mild cognitive impairment

Supplementary Table 5: Tacrine-induced tremulous jaw movements rat model studies in PubMed

Reference	Population	Intervention	Comparison	Outcome	Note
Carriero *et al*.[107]	27 rats	Tacrine	Placebo	Tacrine-induced TJMs were dose-dependent. Increased pauses were observed, which was correlated with akinesia	TJMs induced by tacrine in rats appear to share some characteristics with Parkinsonian tremor and akinesia
Cousins *et al*.[108]	164 rats	Apomorphine, SKF 38393, L-DOPA, amantadine, and benztropine	Placebo	All interventions reduced tacrine-induced TJMs	Apomorphine, bromocriptine, and benztropine were more potent than amantadine and L-DOPA
Finn *et al*.[109]	113 rats	Muscimol	Placebo	Muscimol in the entopeduncular nucleus failed to suppress tacrine-induced TJMs. But, it was suppressed with muscimol in the SNr	Striatonigral GABA projections are involved in the generation of TJMs
Mayorga *et al*.[110]	41 rats	Tacrine	Placebo	Tacrine-induced TJMs were dose-dependent. Scopolamine improves TJMs. TJMs local frequency range of 3–7 Hz	TJMs induced by tacrine in rats appear to share some characteristics with Parkinsonian tremor
Trevitt *et al*.[111]	63 rats	Clozapine, thioridazine, risperidone, and haloperidol	Placebo	Clozapine suppressed tacrine-induced TJMs. Haloperidol did not suppress TJMs. Thioridazine and risperidone suppressed TJM only with doses that caused lever-pressing disappearance	Clozapine in rats is related to the unique behavioral and motor effects of clozapine
Cousins *et al*.[112]	6 rats	Tacrine	Placebo	Tacrine-induced TJMs within 3–7 Hz frequency	Temporalis is a major contributor to the muscle activity that underlies TJMs
Trevitt *et al*.[113]	133 rats	Clozapine, thioridazine, and haloperidol	Placebo	Clozapine reduce TJMs. Thioridazine and haloperidol can suppress at higher levels	Tests of jaw movement activity and lever pressing after repeated administration may be useful for assessing atypical antipsychotic drugs
Cousins *et al*.[114]	89 rats	Hemicholinium	Placebo	Hemicholinium in the VLS improved tacrine-induced TJMs, but it did not in the DMS. There was correlation with acetylcholine level and tacrine-induced TJMs	Dialysis methods could be used to monitor the relation between striatal acetylcholine and TJMs
Trevitt *et al*.[115]	84 rats	Olanzapine	Placebo	Olanzapine reduced TJMs. Also, repeated olanzapine reduced TJMs in a dose range similar to or slightly higher than that which suppressed lever pressing	Olanzapine demonstrated a profile similar to clozapine
Carlson *et al*.[116]	59 rats	Diphenhydramine, doxepin, and mepyramine	Placebo	Only diphenhydramine produced a significant reduction in TJMs	Diphenhydramine suppresses TJMs through a mechanism that does not depend upon antagonism of histamine H1 receptors
Carlson *et al*.[117]	55 rats	Mianserin	Placebo	Systemic injection of mianserin improved tacrine-induced TJMs. The same effect was observed with mianserin injection in the SNr	Antipsychotics may act both on striatal muscarinic receptors and nigral serotonin receptors to suppress jaw movement activity
Simola *et al*.[118]	NA	SCH58261 and SCHBT2	Placebo	Infusion of SCHBT2 in VLS reduced TJMs. SCHBT2 in DMS was less effective in TJMs and did not improve tremor	A2A antagonists effectively reduce the magnitude of tacrine-induced TJMs, mainly by an action in VLS
Betz *et al*.[119]	112 rats	Quetiapine	Placebo	Quetiapine decreased tacrine-induced TJMs and lever pressing. Repeated quetiapine dose was ineffective. But, quetiapine was effective for 14 days	Quetiapine showed a profile somewhat similar to clozapine and olanzapine. Atypical antipsychotics that act on 5-HT or muscarinic receptors have intrinsic antiparkinsonian actions that work in opposition to the motor effects produced by dopamine antagonism

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Supplementary Table 5: Contd...

Reference	Population	Intervention	Comparison	Outcome	Note
Ishiwari *et al.*[120]	64 rats	Pimozide	Placebo	Pimozide failed to suppress tacrine-indued TJMs	NA
Salamone *et al.*[121]	25 rats	Pergolide, ropinirole, and CY-208243	Placebo	Pergolide, ropinirole, and CY-208243 improved tacrine-induced TJMs, in decreased order of effect	Rank order of potency for suppressing cholinomimetic-induced jaw movements in rats is related to the potency for producing antiparkinsonian effects in humans
Simola *et al.*[122]	NA	SCH58261	Placebo	SCH58261 dose-dependently reduced tacrine-induced TJMs	Ineffectiveness of SCH58261 in blocking pilocarpine-stimulated perioral tremor suggests that the antitremorigenic effects of A (2A) antagonists are not related to a direct action on muscarinic receptor
Zazpe *et al.*[123]	NA	F-97013-GD	Placebo	F-97013-GD suppressed tacrine-induced TJMs. Buspirone and 8-OH-DPAT also suppressed tacrine-induced TJMs	5HT-1A receptors play a role in the regulation of tacrine-induced TJM and suggest that their activation may reduce the extrapyramidal side effects, and treat parkinsonian tremor
Tronci *et al.*[124]	NA	ST1535	Placebo	ST1535 reduced tacrine-induced TJMs	ST1535, in association with a low dose of L-DOPA, displayed antiparkinsonian activity similar to that produced by a full dose of L-DOPA without exacerbating abnormal motor side effects
Miwa *et al.*[125]	36 rats	Zonisamide	Placebo	Zonisamide suppressed tacrine-induced TJMs, and this effect was not lost under conditions of monoamine-depletion or dopaminergic blockade	Anti-tremor effects of zonisamide may be achieved by a nondopaminergic mechanism
Vanover *et al.*[126]	11 rats	ACP103	Placebo	ACP103 reduced tacrine-induced TJMs	NA
Kasture *et al.*[127]	NA	Mucuna pruriens	Placebo	Mucuna pruriens reduced tacrine-induced TJMs	NA
Miwa *et al.*[128]	36 rats	Zonisamide	Placebo	Zonisamide suppressed the tacrine-induced c-Fos expression in the cortex, the dorsal striatum, and the nucleus accumbens	Anti-TJM effect of zonisamide may not relate to suppression of neural activity specifically in primary tremor-generating sites, but may be due to a more broad inhibitory effect on tremor-related structures such as the cortex or the striatum
Trevitt *et al.*[129]	50 rats	Caffeine, 8-cyclopentyl theophylline, SCH58261	Placebo	Caffeine, 8-cyclopentyl theophylline, SCH58261 did not reduce tacrine-induced TJMs, and in the case of SCH58261 significantly increased TJMs compared to tacrine alone	Antagonism at A (1) receptors may be more important for the reduction of tremor. Also, dopamine antagonist-induced tremor models and acetylcholine agonist-induced tremor models are not entirely similar
Pinna *et al.*[130]	NA	ANR94	Placebo	ANR94 reduced tacrine-induced TJMs	
Miwa *et al.*[131]	36 rats	Zonisamide, ethosuximide, lomerizine, amiloride, mibefradil, and NCC550396	Placebo	Only zonisamide and NCC550396 significantly suppressed TJMs when given at a nonsedating dose	T-type calcium channels in the central nervous system may be a suitable target for treating parkinsonian tremor

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Supplementary Table 5: Contd...

Reference	Population	Intervention	Comparison	Outcome	Note
Koganemaru *et al*.[132]	64 rats	Cabergoline and rotigotine	Placebo	Dose-dependently reduced in TJMs by pretreatment. c-Fos-positive cells were significantly attenuated by cabergoline, while rotigotine-suppressed	c-Fos-positive cells were assessed in the medial striatum, nucleus accumbens core, and nucleus accumbens. Rotigotine suppressed c-Fos expression in two regions except the nucleus accumbens core
Schintu *et al*.[133]	NA	Tacrine	Placebo	Global p11 knockout mice develop fewer jaw tremors in response to tacrine	Selective deletion of p11 in cholinergic acetyltransferase neurons reduces tacrine-induced TJMs
Ingale and Kasture[134]	NA	n-butanol extract of P. incarnata flowers	Placebo	Butanolic extract reduced tacrine-induced TJMs	
Johnson *et al*.[135]	45 rats	Caffeine, 8-cyclopentyl theophylline, and SCH 58261	Placebo	Generally suppress low-dose tacrine-induced TJMs	Biphasic effect of adenosine A2A receptor antagonists

DMS: Dorsomedial striatum, NA: Not available/not reported/not applicable, SNr: Substantia nigra pars reticulate, TJM: Tremulous jaw movements, VLS: Ventrolateral striatum, L-DOPA: Levodopa, DPTA: Dipropylaminotetralin hydrobromide, GABA: Gamma-aminobutyric acid.