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Randomized controlled trials for Alzheimer disease and Parkinson disease

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1. ABSTRACT

The continuous increase in elderly and oldest-old population, and subsequent rise in prevalence of chronic neurological diseases like Alzheimer's disease (AD) and Parkinson's disease (PD), are a major challenge for healthcare systems. These two conditions are the most prevalent neurodegenerative diseases in older persons and physicians should engage treatment for these patients. In this field, Randomized Clinical Trials (RCTs) specifically focused on elderly populations are still lacking. The aim of this study was to identify RCTs conducted among AD and PD and to examine the difference between mean age of enrollment and incidence of these two neurodegenerative diseases. We found that the scenario is different between PD and AD. In particular, the enrollment for PD trials seems to include younger persons than AD, although the incidence of both diseases is similar and highest after 80 years old. The consequence of these results could influence conclusive guidelines of treatment in older parkinsonian patients.

2. BACKGROUND

The continuous increase in elderly and oldest-old population, and subsequent rise in prevalence of chronic neurological diseases like AD and PD, are a major challenge for healthcare systems.

In this field, randomized clinical trials (RCTs) specifically focused on elderly populations are still lacking. Multimorbidity, clinical complexity, age-related changes in body composition and physiology and polypharmacy generally prevent the inclusion in such studies (1).

The reasons are well-known. Elderly patients have more disability and co-morbidities than younger persons and the age-related changes in body composition and physiology lead to a higher rate and intensity of adverse events.

Many neurological diseases are highly prevalent in older persons (2,3). Alzheimer's disease (AD) is the sixth leading and fastest growing cause of death worldwide, and the only one of the top 10 causes with no means of prevention or cure (2). Most people only live for 8 to 10 years after a diagnosis of AD, and between 5% and 10% of those with AD are in their 30s, 40s, and 50s when diagnosed (2). Parkinson's disease (PD) is an age-related neurodegenerative disorder that affects as many as 1-2% of persons aged 60 years and older (3). With the aging of the population, the prevalence of PD is expected to increase dramatically in the future (4). PD is an age-related disease, rare before 50 years of age and with a prevalence of up to 4% in the highest age groups. Some studies report a higher prevalence of PD in men than in women, although other studies found no significant differences between sexes (4). Interestingly, signs of parkinsonism are frequently found on neurologic examination in older people without an overt PD (5).

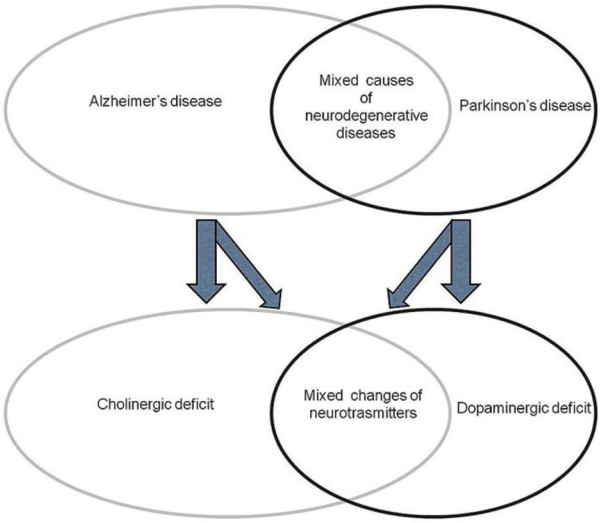

Figure 1. Neurotransmitter deficit in PD, AD and mixed pathology.

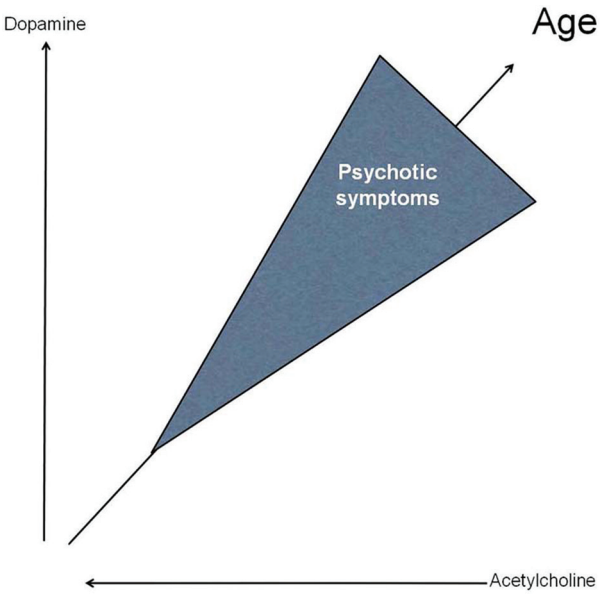

Figure 2. Dopamine and acetylcholine effect on psychotic symptoms in PD and AD.

These signs are often regarded as benign (5). However, data regarding their prevalence and relation to disability in older persons showed that they were associated with increased risk of falling (6) and with higher levels of disability in performing both physical and instrumental activities of daily living (7).

Changes in cognition and locomotion emerge simultaneously in elderly persons at the first neurological/geriatric visit and this could be a sign of mixed neurodegenerative diseases or AD with parkinsonism or PD with cognitive impairment (Figure 1) (8).

Recently, it has been proposed the definition of "motoric cognitive risk" syndrome for a condition with cognitive impairment and reduced walking speed. This is an isolated pre-dementia condition, that could be a marker of a specific disease where cognitive and motor systems are compromised in older persons (9). This condition, such as other mixed diseases (10), could be related to an alteration in both dopamine and acetylcholine neurotransmitters, which are involved in PD and AD, respectively (Figure 1). In fact, treatment for PD and AD include drugs that act on dopamine or acetylcholine, and their balance is the main core of the motor and cognitive symptoms for both these neurodegenerative diseases (Figure 2) (11). A stable clinical condition in PD can be obtained only balancing motor and psychotics symptoms through a careful dopamine pharmacological dose adjustment. In AD the most effective pharmacological treatment is administration of antipsychotics, especially atypical, that do not increase extrapyramidal symptoms, leading to a reduction of falls and mobility-disability.

Thus, the aim of this paper was to analyze the appropriateness of the RCTs conducted among neurodegenerative diseases in older persons, in terms of comparison between mean age of enrollment and mean age of incidence of these diseases.

3. RESULTS OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN THE COCHRANE REVIEWS AND OTHER SYSTEMATIC REVIEWS AND META-ANALYSES FOR ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

Figure 3 shows the prevalence of the PD and AD across decades of persons older than 65 years old. The prevalence for both diseases increases with aging with a peak after 85 years old. We calculated the mean age of RTCs in AD and PD across the most recent meta-analyses and systematic reviews (Figure 4). The mean age of RTCs for AD is 75 years old, while mean age for PD is 67.5 years old.

3.1. RCT in AD

Table 1 shows the mean age, numbers, gender and main outcomes of subjects enrolled in the RCTs carried out in AD for cognitive, behavioral and psychological symptoms of dementia (BPSD). Overall, the mean age of these studies is in line with the incident and prevalent mean age of this disease, as shown in Figure 4. The sample size of these RCTs also reached a sufficient number of participants avoiding population bias. Namely, the mean age of enrolled subjects was greater than 70 years old and even higher (>80 years old) for studies addressing behavioral and sleep disorders.

3.1.1. RCT in AD: Cognitive symptoms

Thirteen randomized, double blind, placebo-controlled trials for evaluation of cognitive symptoms in

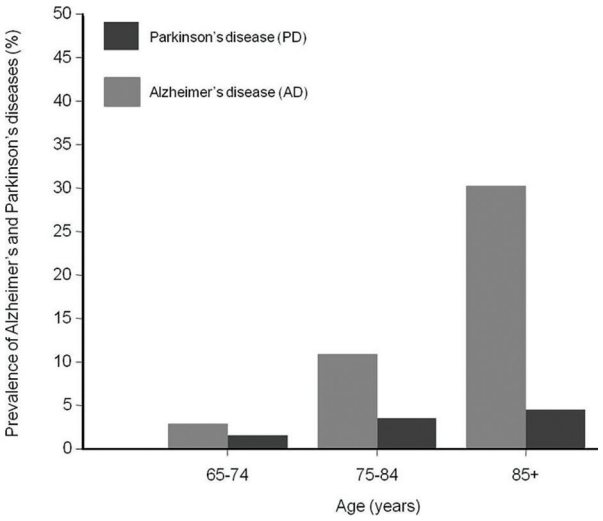

Figure 3. Prevalence of the PD and AD across decades of persons older.

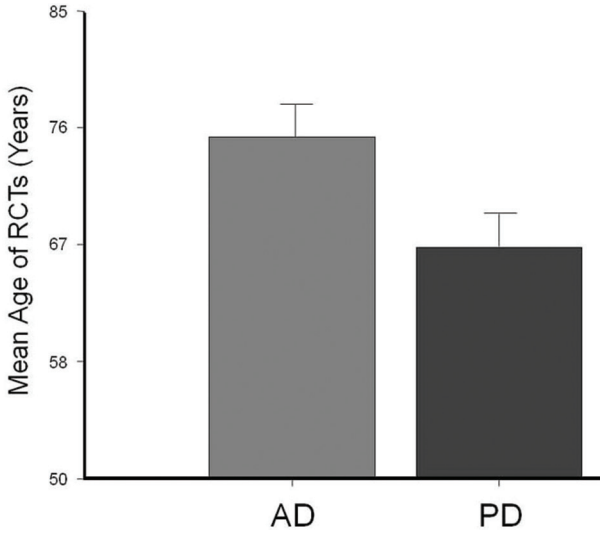

Figure 4. Mean age of Randomized Clinical Trials in AD and PD.

AD were identified in the literature and recently reported in a systematic review conducted by Cochrane Database. They demonstrated that administration of donepezil, galantamine or rivastigmine at the recommended dose to people with mild, moderate or severe Alzheimer-type dementia for a period of 6 months or 1 year was associated with improvement in cognitive function. The variation in the 70-point Alzheimer's disease assessment scale-cognition (ADAS-Cog) was on average -2.7 points (95% CI -3.0. to -2.3.) (12).

3.1.2. RCT in AD: BPSD

All RCTs were identified in the most recent literature and included in previous meta-analyses and systematic reviews. Overall, they showed that cholinesterase inhibitors (ChEIs) and atypical antipsychotics improved Neuropsychiatric Inventory (NPI) total scores (ChEIs: standardized mean difference (SMD) −0.1.2; 95% CI −0.2.3 to −0.0.2; atypical antipsychotics: SMD −0.2.1; 95% CI −0.2.9 to −0.1.2). However, other commonly used drugs like antidepressants (95% CI −0.3.5 to 0.3.7) and memantine (95% CI −0.2.7 to 0.0.3) did not. ChEIs and atypical antipsychotics increased the risk of dropouts due to adverse events (ChEIs: risk ratio (RR) 1.6.4; 95% CI 1.1.2 to 2.4.2; atypical antipsychotics: RR 2.2.4; 95% CI 1.5.3 to 3.2.6) and on incidence of adverse events (ChEIs: RR 1.0.8; 95% CI 1.0.1 to 1.1.7; atypical antipsychotics: RR 1.1.7; 95% CI 1.0.5 to 1.3.1). For typical antipsychotics, no study was included for testing this specific outcome. Therefore, as suggested by many authors, ChEIs and atypical antipsychotics could improve neuropsychiatric symptoms in AD patients, but adverse events should be considered when these drugs are prescribed, especially in very old patients (27).

3.1.3. RCT in AD: Sleep disorders

A recent Cochrane Database systematic review reported that there is a lack of evidence to help guided drug treatment of sleep problems in AD (28). Namely, they found that no RCTs have been performed despite the large number of drugs that are widely prescribed for sleep problems in AD, like the benzodiazepines and non-benzodiazepine hypnotics. As such, there is still a considerable uncertainty about the balance of benefits and risks associated with these common treatments. Melatonin was not found as beneficial to AD patients with moderate to severe dementia and sleep problems. There is some evidence to support the use of a low dose (50 mg) of trazodone, although larger trials would be needed to reach a more definitive conclusion and focus risks and benefits. No evidence of any effect of mirtazapine on sleep in patients with mild to moderate dementia due to AD was found. As such, McCleery *et al.* concluded that this is an area with a high need for pragmatic trials, particularly on those drugs that are in common clinical use for sleep problems in AD (28). Systematic assessment of adverse effects is essential in clinical trials, particularly when including very old patients with a high risk of negative outcomes.

3.2. RCT in PD

Table 2 shows the mean age, number, gender and main outcomes of participants to the RCTs realized in PD for both motor and non-motor symptoms. Contrary to AD, the mean age of RCT testing the efficacy of several drugs for motor symptoms in PD does not match the real age of onset of this disease, as showed in Figure 3 and Figure 4. In fact, the mean age of participants in these studies is nearly 60 years old, while the peak of incidence of the disease appears at least two decades after. Moreover, there are very few studies testing the effects of these drugs on sleep disorders.

Table 1. RCT in AD

	Mean age (years)	Participants (n)	Men (%)	Main outcome (scale)
Cognitive symptoms				
Birks J *et al.* 2006 (12)				
DON vs RIV/Bullock	75.9 (±6.7)	998	n.a.	SIB/GDS/ADCS-ADL/MMSE/NPI
DON-302	51-94	473	180	ADAS-Cog/CIBIC plus
DON-304	71.7 (8.3)	818	348	ADAS-Cog/CIBIC plus/CDR-SB/QoL/IDDD
DON -311	n.a.	208	37	NPI-NH/MMSE/CDR-SB
DON-402	74	153	71	mADAS-Cog/MMSE/CDR/CMBT
DON-Feldman	51-94	292	115	CIBC plus/MMSE/SIB/DAD/IADL/NPI
DON-Nordic	49-88	286	102	GBS/MMSE/PDS/GDS
GAL-INT-1	72.7 (7.6)	653	n.a.	ADAS-Cog/ADAS-CGIC/DAD
GAL-USA-1 Raskind	70.3 (±1.6) to 71.1 (±1.5)	636	242	ADAS-Cog/ADAS-CGIC/DAD
GAL-USA-10 Tariot	76.0 (±0.6) to 77.7 (±0.4)	978	353	ADAS-Cog/ADAS-CGIC/ADCS-ADL
RIV-B303	72 (45-95)	725	297	ADAS-Cog/CIBIC-plus/PDS/GDS/CAS/MMSE
RIV-B304	n.a.	678	n.a.	ADAS-Cog/CIBIC-plus/PDS/GDS/CAS/MMSE
RIV-B351	74.5 (45-89)	702	309	ADAS-Cog/CIBIC-plus/PDS/GDS/CAS/MMSE
RIV-B352	74.5 (45-89)	699	273	ADAS-Cog/CIBIC-plus/PDS/GDS/CAS/MMSE
Muayquil T *et al.*, 2012 (13)				
Tariot *et al.* 2004 (14)				
Placebo	75.5 (±8.73)	201	33% (67)	ADCS/ADL
Treatment	75.5 (±8.45)	203	37% (73)	ADCS/ADL
Portsteinsson *et al.*, 2008 (15)				
Placebo	76 (±8.43)	216	49.5% (107)	ADCS/ADL
Treatment	74.9 (±7.64)	217	46.1% (100)	ADCS/ADL
Howard *et al.*, 2012 (16)				
Placebo	77.2 (±7.5)	73	30% (22)	BADLS
Treatment	77.5 (±9)	73	33% (24)	BADLS
Memantine	76.2 (±8.9)	76	39% (30)	BADLS
Dantoine *et al.*, 2006 (17)	77.4 (±7.5)	86	42% (28)	MMSE
Shua-aim *et al.*, 2008 (18)	78.3 (±5.7)	16	43.7% (7)	n.a.
Olin *et al.*, 2010 (19)	78.4 (±7.99)	117	26.7% (22)	MMSE
Riepe *et al.*, 2007 (20)	74.2 (±8.88)	95	46.3% (44)	ADAS-Cog
Farlow *et al.*, 2010 (21)				
ChEI	74.7 (±7.7)	126	41.3% (52)	MMSE
ChEI and memantine	77.2 (±8.18)	135	43% (58)	MMSE
Choi *et al.*, 2011 (22)				
ChEI	74.7 (±7.7)	84	16.7% (14)	MMSE
ChEI and memantine	75.0 (±7.3)	88	21.4% (22)	MMSE
Atri *et al.*, 2008 (23)				

(Cont...)

Table 1. *(Continued)*

	Mean age (years)	Participants (n)	Men (%)	Main outcome (scale)
ChEI	75.5 (±0.7)	122	42% (51)	BDS
ChEI and memantine	71.5 (±0.9)	116	47% (54)	BDS
Hartmann and Mobius, 2003 (24)	74	158	49% (77)	n.a.
Lopez *et al.*, 2009 (25)				
ChEI	74.6 (±8.5)	387	33% (126)	n.a.
ChEI and memantine	72.8 (±10.2)	140	36% (51)	n.a.
Schneider et al, 2011 (26)				
ChEI	76.0 (±6.69)	86	55.8% (48)	MMSE
ChEI and memantine	74.0 (±8.63)	73	57.5% (42)	MMSE
BPSD				
Wang J *et al.*, 2015 (27)	73.3 to 85.6	11656	n.a.	
Sleep disorders				
McCleery J *et al.*, 2014 (28)				
Camargos *et al.*, 2014	81 (±7.5)	30	10	nTST
Dowling *et al.*, 2008	86 (±8)	50	7	sleep time
NCT00325728	76	66	42	nTST
Serfaty *et al.*, 2002	84.2 (±7.6)	25	9	sleep time
Singer *et al.*, 2003	77.4 (±8.9)	157	69	nTST

Table 2. RCT in PD

	Mean age (years)	Participants (n)	Men (%)	Main outcome (scale)
Motor symptoms				
Stowe R *et al.*, 2010 (29)				
COMTI (E): Celomen	61	301	43% (129)	Clinician rated disability
COMTI (E): ComQol	67	270	56% (151)	Clinician rated disability
COMTI (E): Filomen	62	326	66% (216)	Clinician rated disability
COMTI (E): Int-02	64	162	62% (101)	Clinician rated disability
COMTI (E): Interntl	55	30	53% (16)	Clinician rated disability
COMTI (E): Japan	63	341	45% (127)	Clinician rated disability
COMTI (E): Largo	64	456	59% (271)	Clinician rated disability
COMTI (E): Nomecomt	63	171	55% (94)	Clinician rated disability
COMTI (E): Seesaw	63	205	65% (133)	Clinician rated disability
COMTI (E): South Korea	57	197	40% (79)	Clinician rated disability
COMTI (E): Uk/Irish	65	300	63% (109)	Clinician rated disability
COMTI (T): China	67	49	82.5% (33)	Clinician rated disability
COMTI (T): Europe	63	177	56% (99)	Clinician rated disability
COMTI (T): TFSG 1	65	161	65% (105)	Clinician rated disability
COMTI (T): TFSG 3	63	215	69% (149)	Clinician rated disability
COMTI (T): TIPS 1	63	154	62% (95)	Clinician rated disability

(Contd..)

Table 2. *(Continued)*

	Mean age (years)	Participants (n)	Men (%)	Main outcome (scale)
COMTI (T): TIPS 2	67	97	64% (62)	Clinician rated disability
COMTI (T): US/Canada	64	202	69% (139)	Clinician rated disability
DA (B): Germany	65	40	57.5% (23)	On/off time
DA (B): Japan	63	222	49% (109)	Motor complications
DA (B): Rotteredam	59	23	43% (10)	Clinician rated disability
DA (B): South Africa	65	40	52.5% (21)	Levodopa dose
DA (C): Spain	61	43	58% (25)	Clinician rated disability
DA (C): Uk	62	37	N.A.	Clinician rated disability
DA (C): USA 1	63	188	66% (122)	Clinician rated disability
DA (C): USA 2	N.A.	218	N.A.	Clinician rated disability
DA (Pe): North America	63	376	64% (239)	Clinician rated disability
DA (Pe): Aust/Germ	60	78	65% (51)	Clinician rated disability
DA (Pr): CLEOPATRA	64	302	61% (183)	Clinician rated disability
DA (Pr): Denmark	63	69	58% (40)	Clinician rated disability
DA (Pr): Europe	64	354	65% (230)	Clinician rated disability
DA (Pr): H Kong/Taiw	60	150	69% (104)	Clinician rated disability
DA (Pr): US/Canada	63	360	65% (235)	Clinician rated disability
DA (Pr/B): Interntl	63	247	63% (156)	Clinician rated disability
DA (R): EASE-PD	66	393	63% (246)	Clinician rated disability
DA (R): France/Eng	63	46	61% (28)	Clinician rated disability
DA (R): UK/Israel	63	68	60% (41)	Clinician rated disability
DA (R): USA	N.A.	149	N.A.	Clinician rated disability
MAOBI (R): Isra/Hun	57	70	56% (39)	Clinician rated disability
MAOBI : LARGO	64	460	62% (286)	Clinician rated disability
MAOBI (R): PRESTO	64	472	65% (305)	Clinician rated disability
MAOBI (S): Norw/Fin	66	38	53% (20)	Clinician rated disability
MAOBI (S): USA	62	96	N.A.	Clinician rated disability
MAOBI (ZS): USA	65	140	64% (89)	On/off time
MAONI (ZS): USA/UK	N.A.	163	N.A.	Clinician rated disability
Grey R *et al.*, 2014 (30)				
3-way (levodopa vs dopamine agonist vs MAOBI)	71	1058	65% (686)	PDQ-39 mobility score
2-way (levodopa vs dopamine agonist)	71	348	65% (225)	PDQ-39 mobility score
2-way (dopamine agonist vs MAOBI)	62	214	66% (141)	PDQ-39 mobility score
Levodopa vs levodopa sparing comparison				
Levodopa group	71	528	64% (338)	PDQ-39 mobility score
Levodopa-sparing	71	878	61% (538)	PDQ-39 mobility score
Levodopa-sparing comparison (dopamine agonist vs MAOBI)				

(Contd..)

Table 2. *(Continued)*

	Mean age (years)	Participants (n)	Men (%)	Main outcome (scale)
Dopamine agonist	69	459	62% (284)	PDQ-39 mobility score
MAOBI	69	460	68% (315)	PDQ-39 mobility score
"Non-motor symptoms"				
Wang HF *et al.*, 2015 (31)				
Mc Keith *et al* (32)				
Rivastigmine	73.9 (6.5)	59	31	MMSE
Placebo	73.9 (6.4)	61	37	MMSE
Aarsland *et al* (33)				
Donepezil - placebo	71 (3.9)	14	13	MMSE
Placebo - donepezil	71 (3.9)	14	13	MMSE
Emre et al (34)				
Rivastigmine	72.8 (6.7)	362	234	MMSE
Placebo	72.4 (6.4)	179	117	MMSE
Leroi *et al* (35)				
Donepezil	66.2 (9.3)	7	6	MMSE
Placebo	74.7 (7.9)	9	4	MMSE
Ravina *et al* (36)				
Donepezil - placebo	75 (9.8)	9	9	MMSE
Placebo - donepezil	72.1 (8.1)	10	6	MMSE
Aarsland *et al* (37)				
Memantine	76.9 (6.1)	34	27	MMSE
Placebo	76.2 (5.8)	38	27	MMSE
Leroi *et al* (38)				
Memantine	76.7 (7.8)	11	4	MMSE
Placebo	74.7 (7.9)	14	9	MMSE
Emre *et al* (39)				
Memantine	76.7 (7.8)	11	4	MMSE
Placebo	74.7 (7.9)	14	9	MMSE
Dubois *et al* (40)				
Donepezil 5 mg	72 (6.83)	195	127	MMSE
Donepezil 10 mg	70.8 (7.46)	182	137	MMSE
Placebo	72.9 (6.48)	173	112	MMSE
Mori *et al* (41)				
Donepezil 5 mg	77.9 (6.8)	32	16	MMSE
Donepezil 10 mg	78.6 (6.1)	36	4	MMSE
Placebo	78.6 (4.7)	32	9	MMSE
Pagano *et al.*, 2014 (42)				
Emre *et al.*				
Rivastigmine	72.7 (± 6.6)	541	64.9%	MMSE/UPDRS motor score

(Contd..)

Table 2. *(Continued)*

	Mean age (years)	Participants (n)	Men (%)	Main outcome (scale)
Ravina *et al.*				
Donepezil	73.5 (± 8.95)	22	86.3%	MMSE/UPDRS motor score
Chung *et al.*				
Donepezil	68.3 (± 10.8)	23	65.2%	MMSE/UPDRS motor score
Dubois *et al.*				
Donepezil	71.6 (± 6.9)	335	39.4%	MMSE/UPDRS motor score
Morgante *et al.*, 2004 (43)				
Quetiapine	70 (± 10.1)	20	10	BPRS/CGI-S/UPDRS III/AIMS
Clozapine	69 (± 10.7)	20	10	BPRS/CGI-S/UPDRS III/AIMS

3.2.1. RCT in PD: Motor symptoms

RCTs showed that levodopa is the most important drug for treatment of motor symptoms in PD. However, compared to placebo, adjuvant therapy, with dopamine agonist, reduces off-time, levodopa dose, and improves unified Parkinson's disease rating scale (UPDRS) scores in PD patients who develop motor complications on levodopa therapy. It is well established that treatment with levodopa is at the expense of increased dyskinesia and many other side-effects. Many authors showed that the risk of motor complications with levodopa therapy significantly increased when the dosage is higher than 400 mg/die (44).

Indirect comparisons suggest that dopamine agonist therapy may be more effective than catechol-O-methyltransferase inhibitors (COMTI) and monoamine oxidase type B inhibitors (MAOBI) therapy, which have comparable efficacy. However, as indirect comparisons should be interpreted with caution, direct head-to-head randomized trials assessing the impact of these different drug classes on overall patient-rated quality of life are needed (30). Adequate clinical trials including more people at advanced age, as showed by incidence age of this disease, should be carried out. They should not consider a class-effect, but select singular drugs, especially the dopamine agonist, where the reported adverse effects, such as impulse control disorders (ICDs), are different for each specific drug (45).

3.2.2. RCT in PD: Non-motor symptoms

RCTs showed that cholinesterase inhibitors and memantine slightly improve global impression scale in PD; however, only cholinesterase inhibitors enhance cognitive function. Besides, all the drugs have good safety outcomes (31). The limited number of trials precluded the generalization of these outcomes, especially in very old PD patients (42).

Clozapine and quetiapine are the only two drugs whose use can be recommended in PD with psychotic symptoms (43). These two drugs are quite different each other, but dosage and side-effects are well known even in older persons (43) and this allows a safe use and prescription.

4. DISCUSSION

We found that the scenario is different between PD and AD. In particular, the enrollment for PD trials seems to include younger persons than AD, although the incidence of both diseases is similar and highest after 80 years old.

PD generally affects mobility, although in the last decade non-motor manifestations and the bradikinetic form with increased falls have been recognized as relevant symptoms affecting mobility-disability and quality of life. Classically, the disease is diagnosed after the appearance of typical motor symptoms and non-motors symptoms are usually not recognized at the moment of the diagnosis. However, many older persons show minor neurological signs, including those indicative of parkinsonism, that are considered age-related, and a standardized evaluation for the diagnosis of PD is not made, even in very old persons. The diagnosis of PD could be hence under-estimated in older persons. This may be the main limitation of enrollment of older PD patients in RTCs. Multimorbidity is the main factor limiting the inclusion of older persons in RTCs, but in most cases a missed diagnosis of PD is the reason for excluding very old patients in such studies.

In PD, levodopa remains the drug of reference, although, when the dosage is increased to more than 400 mg/day, the onset of typical side-effect should be taken into account after few years (44). Therefore, treatment with levodopa should be avoided or delayed in younger subjects, preferring other non-ergot dopamine-agonist with a more favorable pharmacological profile as first-line therapy. The effectiveness of AchEi on cognitive performance in PD is well-established, while only two

drugs, clozapine and quetiapine, should be used for psychotics symptoms in advanced PD.

For AD the level of evidence is different from PD. In fact, the analyzed RTCs have shown an higher mean age of enrollment compared to PD, especially when psychiatric symptoms of AD were studied. In this case the most important open question is the precocity of the diagnosis, for preventing the deposition of the amyloid, but in this direction the neuroimaging techniques are promising to establish an early diagnosis, even in older persons (46). Actually, only standard-dose treatment with donepezil, galantamine or rivastigmine produced improvements in cognitive function in AD. Psychotics symptoms could be treated with atypical antipsychotics instead of typical ones, although cardiovascular side-effects should be carefully evaluated.

The problem of missing RCTs in older persons is now well known in many chronic diseases, as well emphasized by Cherubini *et al.* (47), evaluating RTCs for heart failure. These authors showed that among 251 trials investigating treatments for heart failure, 64 (25.5%) excluded patients by an arbitrary upper age limit. Such exclusion was significantly more common in trials conducted in the European Union than in the United States (32.3% vs 16.2%) and in drug trials sponsored by public institutions compared those by private entities (35.6% vs 13.9%). They also found that 109 trials (43.4.%) on heart failure had one or more poorly justified exclusion criteria that could limit the inclusion of older individuals.

This observation has now allowed to create, at least in Europe, a network for studying the lack of evidence in older persons, focused on the most prevalent chronic diseases, with the aim of avoiding off-labels use of many drugs commonly prescribed in clinical practice. One example is the PREDICT consortium, established by the European Community, and aimed at identifying, addressing and resolving the issues related to the exclusion of older people from RCTs using full range of relevant scientific and clinical disciplines (48).

In conclusions, a selection or population bias exists for RTCs in PD, as expected, since they generally enroll younger patients in comparison of the mean age of incidence of the disease. This could not permit to have a conclusive guideline for caring older persons with PD.

For AD the situation is different, because mean age of enrollment is almost a decade higher than PD although, the peak of incidence in age is similar among these two diseases.

To avoid biases and to improve usefulness of RCT results in clinical practice, a multidisciplinary approach, involving also geriatricians, is recommended for establishing appropriate inclusion criteria and promoting enrolment of older persons.

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