

# TREATMENT OF COGNITIVE DEFICITS IN ALZHEIMER'S DISEASE: A PSYCHOPHARMACOLOGICAL REVIEW

Carlos Campos<sup>1</sup>, Nuno Barbosa F. Rocha<sup>1</sup>, Renata Teles Vieira<sup>2</sup>, Susana A. Rocha<sup>3</sup>,  
Diogo Telles-Correia<sup>4</sup>, Flávia Paes<sup>6</sup>, Tifei Yuan<sup>5</sup>, Antonio Egidio Nardi<sup>6</sup>, Oscar Arias-Carrión<sup>7</sup>,  
Sergio Machado<sup>6,8</sup> & Leonardo Caixeta<sup>2</sup>

<sup>1</sup>Polytechnic Institute of Porto, School of Health Technologies, Portugal

<sup>2</sup>Dementia Outpatient Unit, Hospital of the Clinics, Federal University of Goiás, Brazil

<sup>3</sup>Polytechnic Institute of Porto, School of Accounting and Administration of Porto, Portugal

<sup>4</sup>University of Lisbon, School of Medicine, Department of Psychiatry, Portugal

<sup>5</sup>Nanjing Normal University, China

<sup>6</sup>Panic and Respiration Laboratory, Institute of Psychiatry, Federal University of Rio de Janeiro,  
National Institute for Translational Medicine (INCT-TM), Rio de Janeiro, Brazil

<sup>7</sup>Unidad de Trastornos del Movimiento y Sueño (TMS), Hospital General Dr. Manuel Gea Gonzalez,  
Secretaria de Salud, México, DF, México

<sup>8</sup>Physical Activity Neuroscience, Physical Activity Postgraduate Program,  
Salgado de Oliveira University (UNIVERSO), Niterói, RJ, Brazil

received: 28.9.2015;

revised: 25.11.2015;

accepted: 21.12.2015

## SUMMARY

The growing and aging population has contributed to the increased prevalence of Alzheimer's disease (AD) and other types of dementia in the world. AD is a progressive and degenerative brain disease with an onset characterized by episodic memory impairments, although progressive deficits can be observed in several domains including language, executive functions, attention and working memory. The relationship between cognitive impairments and the topography and progression of brain neuropathology is well established. The pathophysiologic mechanisms and processes that underline the course of cognitive and clinical decline have been the theoretical support for the development of pharmacological treatments for AD. Cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) antagonists are the main drugs used in the management of global cognitive impairment and several studies also explore the effects of both in specific cognitive measures. Recent research trends also examine the effects of combination therapy using both compounds. This review aims to update practical recommendations for the treatment of global cognitive functioning and specific neurocognitive deficits in AD using ChEIs, NMDA antagonists and combination therapy with both drugs.

**Key words:** Alzheimer's disease - neurocognitive deficits - pharmacological treatment - cholinesterase inhibitors – memantine

**Abbreviations:** Ach = acetylcholine; AChE = acetylcholinesterase; AD = Alzheimer's disease; BChE = butyrylcholinesterase; ChAT = Choline acetyltransferase; ChEIs = cholinesterase inhibitors; Mg<sup>2+</sup> = magnesium ion; NMDA = N-methyl-D-aspartate antagonists; RCTs = randomized controlled trials

\* \* \* \* \*

## INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible brain disorder which slowly impairs memory and several cognitive functions. Typically, AD has an insidious onset which is manifested by subtle and intermittent deficits in episodic memory, followed by gradual impairment of declarative and nondeclarative memory. As the disease progresses over the years, severe AD becomes associated with deficits in multiple cognitive and behavioral domains (Schroeter et al. 2009, Shankar & Walsh 2009).

Age has a significant role on AD prevalence, with the chance for developing the disease doubling every five years after 65 (Kawas 2003, Nussbaum & Ellis 2003). The growing and aging population contributes to an increased prevalence of AD and other types of

dementia in the world. AD is the most common form of dementia (Blennow et al. 2006, Ferri et al. 2005) and recent estimates predict that the disease will affect more than 80 million individuals in 2040 (Brookmeyer et al. 2007, Reisberg 2006). The disease is associated with several economic and emotional costs to the society, to the patients and to their families (Brookmeyer et al. 2007, Ferri et al. 2005).

Several neurotransmitters have been associated with the course of AD (Francis 2005, Rudy et al. 2015, Strac et al. 2015, Tata et al. 2014). Current psychopharmacological strategies to treat cognitive and behavioral symptoms in AD are focused on these neurotransmitters systems. This review aims to report the pharmacokinetics, pharmacodynamics and efficacy of cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate antagonists (NMDA) for the treatment of cognitive impairment in AD.

**Table 1.** Assessment measures commonly used in clinical trials<sup>41,58,60,70,73,82</sup> and neurophysiological profiling<sup>9,10</sup>

Assessed Outcome	Scales/Tests
Global Cognitive Function (several cognitive domains included)	Alzheimer's Disease Assessment Scale – Cognitive (ADAS-cog) Mini-Mental State Examination (MMSE) Several Impairment Battery (SIB)
Specific Cognitive Domains	California Verbal Learning Test (CVLT) Rey Auditory Verbal Learning Test (RAVLT) Free and Cued Selective Reminding Test (FCSRT) Revised Wechsler Memory Scale (WMS) Benton Visual Retention Test (BVRT) Rey-Osterrieth Complex Figure (ROCF)
Memory	
Executive Functions	Wisconsin Card Sorting Task (WCST) - Flexibility Word color interference Stroop Test - Inhibition Tower of London, Drexel Version – Planning Trail Making Test B (TMT-B)
Language	Verbal Fluency Test (VBT) Boston Naming Test (BNT) Token Test – Comprehension
Attention and Working Memory	Digit Span – Verbal Corsi's Test – Visual
Visuospatial	Judgment of Line Orientation (JLO) Visual Object and Space Perception Battery (VOSPB)

## Neuropsychological Profile of AD

AD patients can be evaluated through the use of several neuropsychological measures applied to assess cognitive function (Table 1).

AD cognitive changes usually start by episodic memory impairment, with anterograde amnesia (the ineffective consolidation or storage of new information) being a clinical hallmark of the disease (Peña-Casanova et al. 2012, Weintraub et al. 2012). Several studies report reduced performance of patients with AD in episodic memory tests including free recall, recognition and paired-association learning (Salmon & Bondi 2009).

The disease progresses to other brain regions and additional cognitive symptoms emerge as the full process of dementia arises (Peña-Casanova et al. 2012, Weintraub et al. 2012). One of the affected domains is language, with a special focus on semantic knowledge impairment as corroborated by verbal fluency, object naming and semantic categorization tests (Weintraub et al. 2012). Verbal comprehension deficits at the semantic, syntactic and metaphorical level are also present in patients with AD (Bickel et al. 2000, Rapp & Wild 2011), although the ability to understand simple commands is usually preserved (Emery 2000).

Prefrontal cognitive functions are also impaired in AD (Waltz et al. 2004), with patients performing poorly on several executive functioning tests, including problem solving tasks that require mental manipulation (Weintraub et al. 2012). Patients also present impairments on working memory and attentional tasks, with deficits starting by being mild (Peña-Casanova et

al. 2012), but gradually affecting basic working memory and attentional tasks mechanisms (Perry & Hodges 1999). Lastly, simple language and motor skills are usually the last abilities affected in severe dementia (Peña-Casanova et al. 2012).

## Cholinergic Pathway and AD

Cholinergic neurons are mainly located in the basal forebrain (cell groups in medial septum, diagonal band of Broca and the nucleus basalis of Meynert) and innervate the neocortex and the hippocampus (Francis et al. 1999). It is suggested that in AD there is a progressive amyloid deposition that reaches the basal forebrain and interferes with cholinergic neurotransmission to the hippocampus, compromising the cognitive functions supported by this structure (Mohandas et al. 2009, Serrano-Pozo et al. 2011). Evidence indicates that the cholinergic system presents a prominent role in cognitive functioning, especially in attention, memory and emotion (Román & Kalaria 2006). Studies in AD have found loss of cholinergic neurons, particularly in the nucleus basalis of Meynert (Kim et al. 2013), as well as reduced levels of choline acetyltransferase (ChAT) activity, acetylcholine (ACh) synthesis and high-affinity choline in patients with AD (Francis et al. 1999, 1993). Decreased cholinergic function has been related to cognitive decline in patients with AD (Shinotoh et al. 2000) and cholinergic marker enzymes also appear to be correlated with the extent of the cognitive decline (Davis et al. 1999). Moreover, there is also evidence of ACh dysfunction in AD patients,

with reduced nicotinic (Court et al. 2001) and M2 muscarinic (Lai et al. 2001) presynaptic ACh receptors and possible disruption of M1 postsynaptic signaling (Tsang et al. 2007).

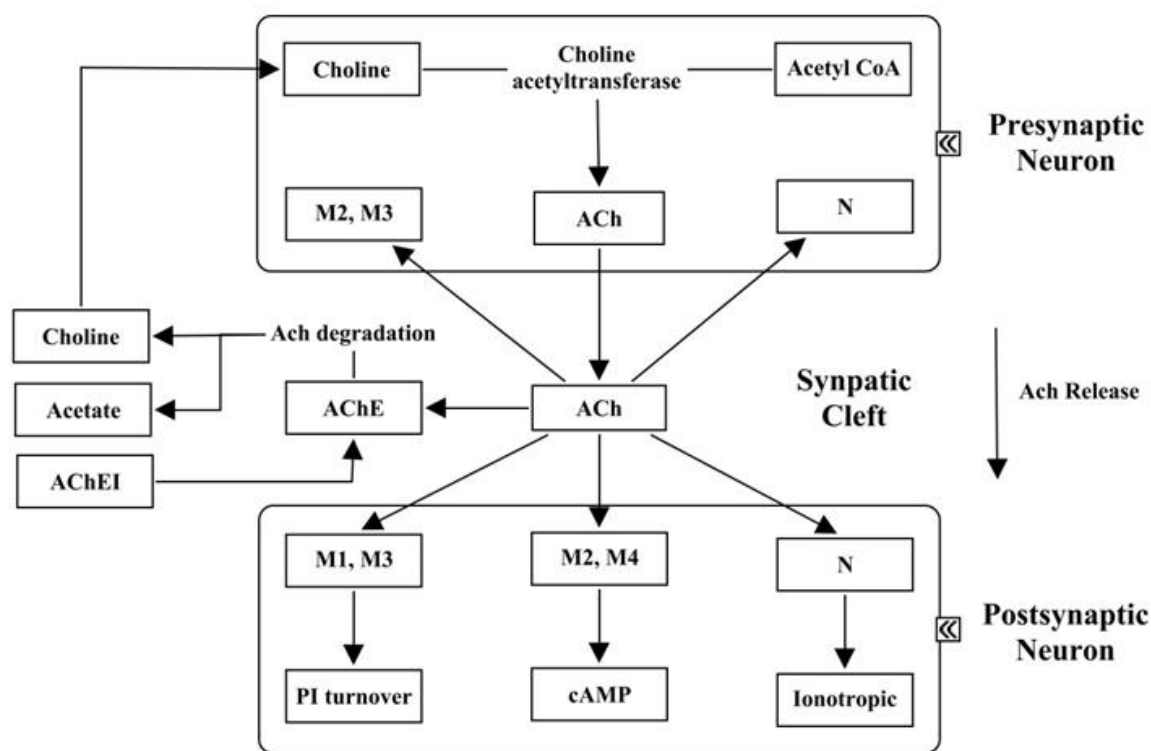
## Glutamatergic Neurotransmission and AD

The role of glutamate in AD is thought to be related with the abnormal build-up of this neurotransmitter in the synaptic cleft, induced by inefficient removal mechanisms (Francis 2003). As the basal levels of glutamate increase, so does the depolarization frequency of the postsynaptic membrane, displacing the magnesium ion ( $Mg^{2+}$ ) that blocks the NMDA receptor under physiological resting conditions (Danysz et al. 2000). Thereby, impaired LTP mechanisms in AD has been associated to NMDA signaling impairment (Battaglia et al. 2007), as the reduced efficiency the voltage-dependent  $Mg^{2+}$  block affects the detection of physiological signals by the NMDA receptors (Esposito et al. 2013). Furthermore, excessive pathological glutamate stimulation has been associated to increased excitotoxicity and may be a crucial factor that contributes to neuronal loss and cell death observed in AD (Lipton 2005, Ni et al. 2013). It has been suggested that the described dysregulation of LTP mechanisms may contribute to the cognitive impairment observed in AD (Danysz et al. 2000, Francis 2003).

There is evidence that in AD patients the number of glutamatergic neurons is significantly reduced, especially in the cerebral cortex and the hippocampus (Francis et al. 2012). Besides the consequences of neuronal loss, there is a possible dysfunction in the remaining glutamatergic neurons on several regions of the AD brain. Abnormal glutamate metabolism has been supported by findings of lower levels or reduced activity of glutamate transporters in several cortical regions (Kashani et al. 2008, Kirvell et al. 2006, Westphalen et al. 2003). Abnormalities in glutamate receptors and decreased NMDA subunits in critical areas to AD neuropathology have also been reported (Bi & Sze 2002, Mishizen-Eberz et al. 2004).

## CHOLINESTERASE INHIBITORS

ChEIs have been introduced in the treatment of AD for around 30 years and nowadays they are still crucial to target its symptoms (Birks 2012, Francis et al. 2012, Pepeu et al. 2013). Tacrine was the first licensed ChEI for severe AD, although it is not recommended nowadays since it has been associated with hepatotoxicity (Lam et al. 2009). Currently, donepezil, rivastigmine and galantamine are the three ChEI most commonly used in AD, targeting presynaptic cholinergic dysfunction (Birks 2012, Francis et al. 2012, Lam et al. 2009). The mechanism of action of ChEIs is represented in Figure 1.



ACh = acetylcholine; AChEI = acetylcholinesterase inhibitor; cAMP = cyclic adenosine monophosphate; CoA = coenzyme A; M = muscarinic receptors; N = nicotinic receptors; PI = phosphoinositol

**Figure 1.** Cholinergic neurotransmission and ChEI mechanism of action

ChEIs bind to and inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), enzymes that are responsible for the hydrolysis of acetylcholine at the synapse (Darvesh et al. 2003, Soreq & Seidman 2001). By inhibiting this enzyme, the levels of synaptic Ach increase, allowing the neurotransmitter to bind to cholinergic receptors (nicotinic and muscarinic) on the postsynaptic cells (Francis et al. 1993). This central inhibition mechanism allows this treatment to address cognitive deficits in AD (Table 2) (Birks 2012, Francis et al. 2012, Lam et al. 2009). These drugs have slightly divergent pharmacological properties and can be classified according to their cholinesterase inhibition time: reversible inhibitors, inhibition continues for seconds to minutes; pseudo-irreversible, inhibition lasts for hours; irreversible, permanent connection occurs, which implies that the body has to produce new enzymes for that function (Jann et al. 2002).

Clinical trials with ChEI have reported that patients using these drugs are more likely to leave the treatment in comparison to placebo due to side effects, which emphasizes the role of adverse effects on treatment compliance. In general, ChEI are associated with mild adverse effects (see Table 3 for more details) which are primarily gastrointestinal (e.g., nausea, vomiting and diarrhea) (Hansen et al. 2008, Lockhart et al. 2009), although other effects can also occur (e.g., abdominal pain, anorexia, dizziness and

headache, and insomnia) (Birks 2012). Moreover, donepezil appears to induce less adverse effects, which points out the need of a cautious and gradual titration routine (over 3 months) of galantamine and rivastigmine in order to assure drug tolerability (Birks 2012).

A meta-analysis performed by Birks (2012) found that ChEI had a beneficial effect on cognitive function and global clinical state 6 months or more after treatment in patients with AD. However, clinical improvements found in most of the studies are frequently subtle and sometimes simply consist of temporary stabilization, or even a slowing of cognitive decline when compared to patients with no treatment. Regarding the perpetuation of effects, some evidence indicates that the improvements accomplished by ChEI comparing to placebo are maintained for a 5-year period (Johannsen 2004).

Despite the different pharmacodynamics of the several ChEI, there is no evidence of any differences between them regarding efficacy (Birks 2012) and cost effectiveness (National Institute for Health and Care Excellence 2011). However, there are some indicators that have been associated with increase effects of ChEI treatment, including inexistence of comorbidities, early response after 3 months (Raschetti et al. 2005) and reduced short latency afferent inhibition or carotid artery thickness (Modrego et al. 2009). Hereinafter, specific characteristics of the main second generation ChEI will be presented.

**Table 2.** Pharmacokinetic parameters of the main ChEI

Drug	Inhibition	Elimination of half-life*	Half life of inhibition	Binding Protein	Metabolism
Tacrine	Reversible	Short (2.9-3.6h)	Short	Intermediate (55%)	Liver (CYP 1A2)
Galantamine	Reversible	Intermediate(7h)	Long (7h)	Low (17.7%)	Liver (CYP 2D6 e 3A4)
Rivastigmine (Also inhibits BChE)	Pseudo-Reversible	Short (1-2h) (Temporal decoupling)	Long (10h)	Intermediate (40%)	Synaptic (no action by P450)
Donepezil	Reversible	Long (70h)	Long	High (96%)	Liver (15%)** (CYP 2D6 e 3A4)

Adapted from Lam et al. <sup>43</sup>;

\* Terminal half-life of elimination after multiple oral doses in hours; \*\* Renal excretion of the drug intact (57%)

**Table 3.** Major adverse effects of ChEI

Symptoms	Donepezil (5–10 mg)	Galantamine (8–24 mg)	Rivastigmine (3–12 mg)
Nausea	++	+++	+++
Vomiting	+	++	+++
Diarrhea	++	+	++
Vertigo	+	++	+++
Weight Loss	+	+	++
Abdominal Pain	+	+	+
Constipation	+	+	+
Cardiovascular	-	-	-
CNS	-	-	-

\* Adapted from Hansen et al. <sup>47</sup> and Lockhart, Mitchell & Kelly <sup>48</sup>;

Incidence rate: - <5%; + up to 10%; ++ 10-20%; +++ 20-50%

## Donepezil

Donepezil is a reversible, noncompetitive and selective ChEI, approved in 1997 for the treatment of AD (Francis et al. 2012). This drug is a piperidine which presents selective activity for acetylcholinesterase (Wilkinson et al. 2004). In terms of administration, donepezil has long half-life (70 h), which means that it can be dosed once per day (Francis et al. 2012). Administered orally, donepezil reaches the C<sub>max</sub> (7.2 to 25.6 g/l) after 2.4 to 4.4 hours, with bioavailability of 90 to 100% (not affected by food). It is highly connected to proteins (approximately 93-96 %) and their state of equilibrium is reached between 14 and 22 days after repeated daily administration (Dooley & Lamb 2000).

Donepezil undergoes extensive first-pass metabolism in the liver by the action of the 3A4 and 2D6 isoenzymes cytochrome P450 (Jann et al. 2002, Scarpini et al. 2003). Regarding donepezil main metabolites, there is evidence that the CYP2D6 product displays similar pharmacological activity to the parent compound, while the CYP3A4 metabolite is inactive, which can play a significant role in the variability of clinical effects (Jann et al. 2002, Scarpini et al. 2003).

Guidelines recommend the use of donepezil for the management of cognitive decline of patients with mild to moderately severe AD (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011, Scottish Intercollegiate Guidelines Network 2006). Recommended dosage ranges from a minimum of 5mg/day (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011, Scottish Intercollegiate Guidelines Network 2006) to a maximum of 10 mg/day (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011), although some clinicians start the treatment with 2.5 mg/day in frail or side effects sensitive patients (American Psychiatric Association 2007). It is recommended to start the treatment orally with 5 mg, increasing to 10 mg after 1 month (National Institute for Health and Care Excellence 2011).

Overall, donepezil has a low incidence of serious side effects and is well tolerated, showing mainly mild adverse and transitional effects, which are more frequent for a 10 mg dose (Birks & Harvey 2009, Johannsen 2004), especially when there is rapid increase from 5 to 10 mg/day (Johannsen 2004). The most frequent side effects are nausea, vomiting and diarrhea, although fatigue and cramps can also appear (Birks & Harvey 2009, Johannsen 2004). There are also reports of syncope, so it is recommended precaution in its administration to patients with any type of bradycardia (Johannsen 2004).

The meta-analysis of Birks & Harvey (2009) provide evidence that donepezil improves the cognitive function of patients with mild or moderate AD treated for periods

of 12 and 24 weeks, with 5 or 10 mg/day. There is no evidence to suggest that the effects of donepezil are any less for those with severe dementia. Geldmacher et al. (2003) showed that patients with moderate to severe AD also benefit from treatment with donepezil. There are also studies showing the effectiveness of donepezil in patients with AD at the long-term, i.e., 5 years after the treatment (Dooley & Lamb 2000, Johannsen 2004). Few studies report donepezil effects on specific cognitive variables, although there is evidence indicating significant improvements on memory, attention, visuospatial skills, language, praxis and processing speed (Black et al. 2007, Cummings et al. 2010, Salloway et al. 2004, Winblad et al. 2006).

## Galantamine

Galantamine is a specific, competitive and reversible ChEI which has been approved for the treatment of AD since 2000 (Francis et al. 2012). It is a tertiary alkaloid (phenanthrene) which can be extracted from Amaryllidaceae (*Galanthus woronowi*, the Caucasian snowdrop) and daffodil bulbs or industrially synthesized (Harvey 1995). This drug has an affinity for both AChE and BChE, in spite of selectively inhibiting AChE to a much greater extent than BChE (Harvey 1995, Pacheco et al. 1995). In addition, galantamine is an allosteric modulator at nicotinic cholinergic receptor sites, potentiating cholinergic nicotinic neurotransmission and enhancing the effect of acetylcholine at these receptors, which provides this ChEI agent with a dual mechanism of action (Wattmo et al. 2013).

Galantamine reaches its C<sub>max</sub> in ½ to 2 hours, presents bioavailability between 85% and 100%, with only a 10% to 17% protein binding rate (Jann et al. 2002). The half-life of galantamine is 7 to 8 hours, therefore, to facilitate dosing and to increase compliance, a once-daily prolonged-release capsule of this drug was created (Brodaty et al. 2005). Plasma concentration is strongly correlated with dosage (Wattmo et al. 2013), although there is evidence of a decrease in plasma concentration in individuals with higher BMI and an increase when administration is completed with food (Jann et al. 2002). Regarding its metabolism, galantamine is mainly processed through liver isoenzymes (2D6 and 3A4), with its main metabolite being sanguinina (O-demetilGalantamine), which inhibits acetylcholinesterase around four times more than the galantamine (Bentué-Ferrer et al. 2003, Davis 2002). Furthermore, approximately 32% of the oral dose is excreted unchanged in the urine, which implies that an inferior dosage (16 mg/day) is needed for patients with hepatic or renal failure (Lockhart et al. 2009).

Several guidelines recommend the use of galantamine in the treatment of symptoms of patients with mild to moderately severe AD (American Psychiatric Association 2007, National Institute for Health and Care

Excellence 2011, Scottish Intercollegiate Guidelines Network 2006). The suggested dosage range from a minimum of 16mg/day (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011, Scottish Intercollegiate Guidelines Network 2006) to a maximum of 32 mg/day (American Psychiatric Association 2007), although most individuals intake between 16 and 24 mg/day (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011, Scottish Intercollegiate Guidelines Network 2006). Galantamine should be used with slow escalation to doses of up to 24 mg, starting with 8 mg and increasing every 4 weeks until maintenance treatment is reached (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011, Scottish Intercollegiate Guidelines Network 2006). There is a gradual increase of occurrence of adverse effects with increased dosage, with the most common adverse effects being nausea, vomiting and diarrhea (Loy & Schneider 2006). Other less common adverse effects include tremor, anorexia, weight loss, headaches, abdominal pain, dizziness and agitation (Loy & Schneider 2006).

Concerning galantamine efficacy on cognitive impairments of AD, results of a meta-analysis suggest that doses of 16 mg/d and above improve cognitive function of patients mildly to moderately cognitive impaired, for at least 6 months (Loy & Schneider 2006). Doses above 24 mg/day have been proven safe, although there is no evidence of additional benefits to treatment (Lockhart et al. 2009). The duration of efficacy is not clear even though there is a clinical trial reporting that cognitive performance remained improved in patients with mild AD after a 3-year follow-up (Richarz et al. 2014). There is also neurofunctional evidence of galantamine efficacy on cognition, with results suggesting that this compound has a long-term positive effect on brain perfusion and regional cerebral metabolic rate for glucose, with these results correlating with cognitive stabilization (Keller et al. 2011).

## Rivastigmine

Rivastigmine is a second-generation pseudo-irreversible acetylcholinesterase and butyrylcholinesterase inhibitor with a phenylcarbamate structure that has been approved for the treatment of AD since 1998 (Birks et al. 2009, Francis et al. 2012). Unlike others ChEI that are selective for the acetylcholine, rivastigmine shows equally potent inhibition of butyrylcholinesterase (Birks et al. 2009, Francis et al. 2012, Jann et al. 2002). This drug is considered a pseudo-irreversible inhibitor because it is actively metabolized by cholinesterase. Although the connection is irreversible, after binding to cholinesterase, the carbamate portion of rivastigmine is slowly hydrolysed, cleaved, conjugated to a sulphate and excreted (Jann et al. 2002, Onor et al. 2007). This

process makes rivastigmine half-life between 1 and 2 hours, with the duration of AChE inhibition occurring throughout 10 hours, making it necessary to have a twice-daily dosing (Francis et al. 2012). Administered orally, it reaches the C<sub>max</sub> in ½ to 2 hours with a bioavailability of 0,355 and a low (40%) binding to plasma proteins (Jann et al. 2002).

Rivastigmine also presents other benefits associated with its pharmacokinetics and pharmacodynamics. This drug is almost totally independent of hepatic metabolism, which makes it suitable for patients with renal or hepatic impairment (Jann et al. 2002). Moreover, the risk of interactions with other drugs is low, which has great relevance for patients with AD that are poly-medicated (Grossberg et al. 2000). The selective characteristics of the drug to the central nervous system and within it makes it a suitable choice for the treatment of AD (Kennedy et al. 1999, Polinsky 1998). Animal studies suggest that rivastigmine has higher efficiency inhibiting AChE in the cortex and hippocampus (brain regions most affected by AD) and preferentially inhibits the G1 enzymatic form of AChE, which predominates in the brain of patients with AD (Polinsky 1998).

Treatment guidelines for the treatment of AD suggest rivastigmine dosages between 6 and 12 mg/day (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011, Scottish Intercollegiate Guidelines Network 2006). It is usually recommended to start the treatment with 3 mg/day (1,5 mg twice), with dose being titrated upward every 4 weeks if necessary (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011). Rivastigmine patches are also administered, initially using a 4.6-mg patch per day, dosage which can be increased to a 9.5-mg patch per day after at least 4 weeks (National Institute for Health and Care Excellence 2011). The gradual exposition, either oral or transdermal, aims to identify more easily the precise dosage necessary and to decrease the gastrointestinal adverse effects (American Psychiatric Association 2007).

Meta-analyses from Birks et al (2009) have reported that the use of rivastigmine in daily 6-12 mg doses is associated with statistically significant benefits in terms of cognitive function in mild to moderate AD. Long term efficacy of rivastigmine treatment has also been described, with studies pointing out to benefits 2 and 5 years after treatment (Johannsen 2004).

Finally, rivastigmine appears to be associated with a low incidence of serious adverse effects, although it is necessary a fairly lengthy titration period (up to 12 weeks) to minimize adverse effects such as nausea, vomiting, diarrhea, abdominal pain, dizziness, headache and anorexia (Birks et al. 2009). Furthermore, when administered together with food, the C<sub>max</sub> decreases, which can reduce possible adverse gastrointestinal effects (Jann et al. 2002).

## NMDA RECEPTORS ANTAGONISTS - MEMANTINE

The only NMDA receptor currently approved (since 2002) for the treatment of AD is memantine (Francis et al. 2012). This drug is an uncompetitive, voltage-dependent, moderate-affinity NMDA receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate (National Institute for Health and Care Excellence 2011). This specificity to voltage dependency allows memantine to block the induction of signals based on elevated glutamate baseline levels, preventing the tonic pathological influx of Ca<sup>2+</sup> and oxidative stress in postsynaptic neurons, whilst allowing physiological transmission (Danysz et al. 2000, Francis 2009, Kosenko et al. 2014, Parsons & Gilling 2007, Parsons et al. 2007). Hence, cognitive function enhancements are supposed to be achieved through signal-to-noise ratio improvements, based on selective reduction of noise levels (Francis 2009).

Pharmacokinetically, memantine shows good oral absorption, with bioavailability of almost 100 % (not affected by food ingestion) and protein linking rate of approximately 45% (Jann et al. 2002). Dosage between 10 and 40 mg/day presents linear pharmacokinetics and after a single dose of 20 mg/day, C<sub>max</sub> reaches 22-46 mg/ml in 3 to 7 hours (Jann et al. 2002). Memantine presents elimination half-life of 60-100 hours and undergoes little metabolism (Lam et al. 2009). The elimination is mainly renal (75-90%) and reduced with alkalinization of the urine, but there are also removal through bile and feces (10-25%) (Davis 2002). Because memantine is removed primarily by the kidneys, lower dosages (e.g., 10 mg/day) should be considered in patients with compromised renal function (American Psychiatric Association 2007).

The Scottish Intercollegiate Guidelines Network (2006) stated that there was not sufficient evidence to recommend the use of memantine for the treatment of core or associated symptoms in people with AD. However, more recent guidelines state that memantine should be considered for the treatment of patients with moderate to severe AD, especially as there are no significant risks brought by its administration (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011). Memantine is well tolerated, with side effects being generally mild and of low incidence (Kumar 2004, McShane et al. 2009). Dizziness is the most common symptom and other possible side effects are headaches, insomnia, constipation, hypertension agitation and falls (Kumar 2004, McShane et al. 2009). Recommendations state that memantine should initially be given as 5 mg once daily and then increased in steps of 5 mg at weekly intervals (American Psychiatric Association 2007, National Institute for Health and Care Excellence 2011) to a maximum of 20 mg daily (National Institute for Health and Care Excellence 2011).

The positive effects of memantine over placebo on global cognitive function of patients with moderate to severe AD have been described reported (Molino et al. 2013, Rive et al. 2013). McShane et al. found that 20 mg/day caused a clinically noticeable reduction in cognitive deterioration over 28 weeks compared to placebo in these patients (McShane et al. 2009). There are also reports of significant effects of memantine in specific cognitive functions of patients with moderate to severe AD, including language, memory and praxis (Emre et al. 2008).

Conversely, the evidence of memantine in the treatment of mild to moderate AD is quite divergent (Schneider et al. 2011). There is a lack of evidence for memantine in mild AD and in patients with moderate AD there are very small effects on cognition and global change. However, while most studies report inferior results in comparison with the moderately severe to severe population, there is some evidence that supports reduced cognitive deterioration in the mild to moderate AD patients treated with memantine (McShane et al. 2009, Rive et al. 2013).

## COMBINATION THERAPY

Recently, the benefits of targeting both cholinergic or glutamatergic mechanisms in the treatment of AD have been investigated (Dantoine et al. 2006, Francis et al. 2012, Simoni et al. 2012). It is widely accepted that AD involves several pathological processes, which reinforces the hypothesis of superior combination therapy efficacy in comparison with monotherapy (Xiong & Doraiswamy 2005). There are not any drugs with a combined cholinergic–glutamatergic action that have been successful in the later stages of development; therefore, combination therapy is currently performed through the administration of one ChEI plus memantine (Francis et al. 2012).

There are several preclinical findings that justify the use of combination therapy. Both glutamatergic and Ach mechanisms display a critical role in the induction and maintenance of LTP, which emphasizes the role of both systems in cognitive function (Tai & Leung 2012). There is also evidence that both cholinergic and glutamatergic systems are affected by neuropathological process at the time of clinical diagnosis of AD, implying that treatment should consider the abnormalities in both systems (Francis et al. 2012).

However, clinical efficacy of combination therapy with ChEI and NMDA antagonists is still far from being fully established. The review by Molino et al. (2013) found no benefits of the association between these drugs in the treatment of moderate to severe AD. Another systematic review and meta-analysis suggests a small but significant benefit of memantine combination therapy on cognitive, global and behavior measures (Farrimond et al. 2012). Significant effects cognitive function of moderate to severe AD patients have also

been found by Muayqil and Camicioli (2012), although the authors recommend a caution interpretation of findings. By contrast, combination therapy has shown no significant benefits over AChEI monotherapy in patients with mild AD (Choi et al. 2011, Farlow et al. 2010, Porsteinsson et al. 2008). There is also evidence which suggest that combination therapy appears to be safe and well tolerated when compared to monotherapy (Muayqil & Camicioli 2012). In spite of some findings pointing out to benefits of ChEI and memantine combination therapy in the treatment of patients with moderate to severe AD, further blinded randomized controlled trials (RCTs) that replicate these results are necessary, comparing the combined results to the benefits granted by memantine and a ChEI monotherapy (Muayqil & Camicioli 2012).

## CONCLUSION/ PRACTICAL RECOMMENDATIONS

Considering the main international guidelines, the several systematic-reviews and meta-analyses for the efficacy of specific drugs, there is a growing body of evidence that supports the following recommendations:

- ChEI are mostly effective in the treatment of patients with mild to moderate AD;
- Effects of ChEI seem to remain in the same magnitude for a period of up to two years, although findings are less consisting regarding longer periods;
- There is no evidence of efficacy discrepancies between donepezil, rivastigmine and galantamine, although donepezil is associated with less adverse effects;
- Memantine is more suitable for the treatment of patients with moderate to severe AD;
- Irrespectively of the selected drug, treatment should start with low dosages and slowly increased according to the patient's tolerance;
- Combination therapy with ChEI and memantine could be administrated when patients do not respond to ChEI therapy, although there is not sufficient evidence that strongly supports this option;
- Cognition should be continuously assessed every 6 months using objective measures;
- Treatment should be maintained if improvement, stabilization or decreased progression of cognitive decline or functional behavior is observed. If these are not detected in the first 3 to 6 months, treatment should be replaced;
- The minimum period of treatment recommended to properly evaluate the therapeutic response is about 6 months and its maintenance depends on the response and tolerability presented by the patient;
- Pharmacokinetics of the administered drugs should be recognized by clinicians in order to prevent several adverse effects in patients with comorbidities (e.g. liver or renal failure).

Although therapeutic effects of the reported drugs are modest, they may be sufficient to improve the quality of life of both patients and family members. Further studies need to be developed in order to clarify maintenance treatment of patients with AD and the discontinuation of treatment. These studies should include long-term placebo-controlled studies comparing the different ChEI. Clinical trials and further analyzes are necessary for the clinician to decide the best treatment option (greater efficacy and less adverse effects) for each patient, taking into account the diagnosis, clinical comorbidities and possible drug interactions.

**Acknowledgements:** None.

**Conflict of interest:** None to declare.

## References

1. American Psychiatric Association: *Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias*, EUA, American Psychiatric Association, 2007.
2. Battaglia F, Wang HY, Ghilardi MF, Gashi E, Quartarone A, Friedman E et al: *Cortical plasticity in Alzheimer's disease in humans and rodents*. *Biol Psychiatry* 2007; 62:1405-1412.
3. Bentué-Ferrer D, Tribut O, Polard E & Allain H: *Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists*. *CNS Drugs* 2003; 17:947-963.
4. Bi H & Sze CI: *N-methyl-D-aspartate receptor subunit NR2A and NR2B messenger RNA levels are altered in the hippocampus and entorhinal cortex in Alzheimer's disease*. *J Neurol Sci* 2002; 200:11-18.
5. Bickel C, Pantel J, Eysenbach K & Schröder J: *Syntactic comprehension deficits in Alzheimer's disease*. *Brain Lang* 2000; 71:432-448.
6. Birks J: *Cholinesterase inhibitors for Alzheimer's disease*. *Cochrane Database Syst Rev* 2012; CD005593.
7. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M & Holt FE: *Rivastigmine for Alzheimer's disease*. *Cochrane Database Syst Rev* 2009; CD001191.
8. Birks J & Harvey RJ: *Donepezil for dementia due to Alzheimer's disease*. *Cochrane Database Syst Rev* 2009; CD001190.
9. Black SE, Doody R, Li H, McRae T, Jambor KM, Xu Y et al: *Donepezil preserves cognition and global function in patients with severe Alzheimer disease*. *Neurology* 2007; 69:459-469.
10. Blennow K, de Leon MJ & Zetterberg H: *Alzheimer's disease*. *Lancet* 2006; 368:387-403.
11. Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M & Damaraju CR: *Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease*. *Dement Geriatr Cogn Disord* 2005; 20:120-132.
12. Brookmeyer R, Johnson E, Ziegler-Graham K & Arrighi HM: *Forecasting the global burden of Alzheimer's disease*. *Alzheimers Dement* 2007; 3:186-191.

13. Choi SH, Park KW, Na DL, Han HJ, Kim EJ, Shim YS et al: Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. *Curr Med Res Opin* 2011; 27:1375-1383.
14. Court J, Martin-Ruiz C, Piggott M, Spurdin D, Griffiths M & Perry E: Nicotinic receptor abnormalities in Alzheimer's disease. *Biol Psychiatry* 2001; 49:175-184.
15. Cummings J, Jones R, Wilkinson D, Lopez O, Gauthier S, Waldemar G et al: Effect of donepezil on cognition in severe Alzheimer's disease: a pooled data analysis. *J Alzheimers Dis* 2010; 21:843-851.
16. Dantoine T, Auriacombe S, Sarazin M, Becker H, Pere JJ & Bourdeix I: Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. *Int J Clin Pract* 2006; 60:110-118.
17. Danysz W, Parsons CG, Mobius HJ, Stoffler A & Quack G: Neuroprotective and symptomatological action of memantine relevant for Alzheimer's disease--a unified glutamatergic hypothesis on the mechanism of action. *Neurotox Res* 2000; 2:85-97.
18. Darvesh S, Hopkins DA & Geula C: Neurobiology of butyrylcholinesterase. *Nat Rev Neurosci* 2003; 4:131-138.
19. Davis K: Current and Experimental Therapeutics of Alzheimer Disease, in *Neuropsychopharmacology: The Fifth Generation of Progress: An Official Publication of the American College of Neuropsychopharmacology*. Edited by 5th Lippincott Williams & Wilkins; 2002., 2002, pp 1243-1246.
20. Davis KL, Mohs RC, Marin D, Purohit DP, Perl DP, Lantz M et al: Cholinergic markers in elderly patients with early signs of Alzheimer disease. *JAMA* 1999; 281:1401-1406.
21. Dooley M & Lamb HM: Donepezil: a review of its use in Alzheimer's disease. *Drugs Aging* 2000; 16:199-226.
22. Emery VO: Language impairment in dementia of the Alzheimer type: a hierarchical decline? *Int J Psychiatry Med* 2000; 30:145-164.
23. Emre M, Mecocci P & Stender K: Pooled analyses on cognitive effects of memantine in patients with moderate to severe Alzheimer's disease. *J Alzheimers Dis* 2008; 14:193-199.
24. Esposito Z, Belli L, Toniolo S, Sancesario G, Bianconi C & Martorana A: Amyloid  $\beta$ , glutamate, excitotoxicity in Alzheimer's disease: are we on the right track? *CNS Neurosci Ther* 2013; 19:549-555.
25. Farlow MR, Alva G, Meng X & Olin JT: A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. *Curr Med Res Opin* 2010; 26:263-269.
26. Farrimond LE, Roberts E & McShane R: Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. *BMJ Open* 2012; 2: pii: e000917.
27. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M et al: Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; 366:2112-2117.
28. Francis PT: Glutamatergic systems in Alzheimer's disease. *Int J Geriatr Psychiatry* 2003; 18:S15-21.
29. Francis PT: The interplay of neurotransmitters in Alzheimer's disease. *CNS spectrums* 2005; 10:6-9.
30. Francis PT: Altered glutamate neurotransmission and behaviour in dementia: evidence from studies of memantine. *Curr Mol Pharmacol* 2009; 2:77-82.
31. Francis PT, Palmer AM, Snape M & Wilcock GK: The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry* 1999; 66:137-147.
32. Francis PT, Parsons CG & Jones RW: Rationale for combining glutamatergic and cholinergic approaches in the symptomatic treatment of Alzheimer's disease. *Expert Rev Neurother* 2012; 12:1351-1365.
33. Francis PT, Sims NR, Procter AW & Bowen DM: Cortical pyramidal neurone loss may cause glutamatergic hypoactivity and cognitive impairment in Alzheimer's disease: investigative and therapeutic perspectives. *J Neurochem* 1993; 60:1589-1604.
34. Geldmacher DS, Provenzano G, McRae T, Mastey V & Ieni JR: Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc* 2003; 51:937-944.
35. Grossberg GT, Stahelin HB, Messina JC, Anand R & Veatch J: Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. *Int J Geriatr Psychiatry* 2000; 15:242-247.
36. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG & Jonas DE: Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging* 2008; 3:211-225.
37. Harvey AL: The pharmacology of galanthamine and its analogues. *Pharmacol Ther* 1995; 68:113-128.
38. Jann MW, Shirley KL & Small GW: Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. *Clin Pharmacokinet* 2002; 41:719-739.
39. Johannsen P: Long-term cholinesterase inhibitor treatment of Alzheimer's disease. *CNS Drugs* 2004; 18:757-768.
40. Kashani A, Lepicard E, Poirer O, Videau C, David JP, Fallet-Bianco C et al: Loss of VGLUT1 and VGLUT2 in the prefrontal cortex is correlated with cognitive decline in Alzheimer disease. *Neurobiol Aging* 2008; 29:1619-1630.
41. Kawas CH: Clinical practice. Early Alzheimer's disease. *N Engl J Med* 2003; 349:1056-1063.
42. Keller C, Kadir A, Forsberg A, Porras O & Nordberg A: Long-term effects of galantamine treatment on brain functional activities as measured by PET in Alzheimer's disease patients. *J Alzheimers Dis* 2011; 24:109-123.
43. Kennedy JS, Polinsky RJ, Johnson B, Loosen P, Enz A, Laplanche R et al: Preferential cerebrospinal fluid acetylcholinesterase inhibition by rivastigmine in humans. *J Clin Psychopharmacol* 1999; 19:513-521.
44. Kim HJ, Moon WJ & Han SH: Differential cholinergic pathway involvement in Alzheimer's disease and subcortical ischemic vascular dementia. *J Alzheimers Dis* 2013; 35:129-136.
45. Kirvell SL, Esiri M & Francis PT: Down-regulation of vesicular glutamate transporters precedes cell loss and pathology in Alzheimer's disease. *J Neurochem* 2006; 98:939-950.
46. Kosenko EA, Solomadin IN, Tikhonova LA, Reddy VP, Aliev G & Kaminsky YG: Pathogenesis of Alzheimer disease: role of oxidative stress, amyloid-beta peptides,

- systemic ammonia and erythrocyte energy metabolism. *CNS & neurological disorders drug targets* 2014; 13:112-119.
47. Kumar S: Memantine: pharmacological properties and clinical uses. *Neurol India* 2004; 52:307-309.
  48. Lai MK, Lai OF, Keene J, Esiri MM, Francis PT, Hope T et al: Psychosis of Alzheimer's disease is associated with elevated muscarinic M2 binding in the cortex. *Neurology* 2001; 57:805-811.
  49. Lam B, Hollingdrake E, Kennedy JL, Black SE & Masellis M: Cholinesterase inhibitors in Alzheimer's disease and Lewy body spectrum disorders: the emerging pharmacogenetic story. *Hum Genomics* 2009; 4:91-106.
  50. Lipton SA: The molecular basis of memantine action in Alzheimer's disease and other neurologic disorders: low-affinity, uncompetitive antagonism. *Curr Alzheimer Res* 2005; 2:155-165.
  51. Lockhart IA, Mitchell SA & Kelly S: Safety and tolerability of donepezil, rivastigmine and galantamine for patients with Alzheimer's disease: systematic review of the 'real-world' evidence. *Dement Geriatr Cogn Disord* 2009; 28:389-403.
  52. Loy C & Schneider L: Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev* 2006; CD001747.
  53. McShane R, Areosa Sastre A & Minakaran N: Memantine for dementia. *Cochrane Database Syst Rev* 2009; CD003154.
  54. Mishizen-Eberz AJ, Rissman RA, Carter TL, Ikonomic MD, Wolfe BB & Armstrong DM: Biochemical and molecular studies of NMDA receptor subunits NR1/2A/2B in hippocampal subregions throughout progression of Alzheimer's disease pathology. *Neurobiol Dis* 2004; 15:80-92.
  55. Modrego PJ, Rios C, Pérez Trullen JM, García-Gómara MJ & Errea JM: Carotid intima-media thickness as a predictor of response to cholinesterase inhibitors in Alzheimer's disease: an open-label trial. *CNS Drugs* 2009; 23:253-260.
  56. Mohandas E, Rajmohan V & Raghunath B: Neurobiology of Alzheimer's disease. *Indian J Psychiatry* 2009; 51:55-61.
  57. Molino I, Colucci L, Fasanaro AM, Traini E & Amenta F: Efficacy of memantine, donepezil, or their association in moderate-severe Alzheimer's disease: a review of clinical trials. *ScientificWorldJournal* 2013; 2013:925702.
  58. Muayqil T & Camicioli R: Systematic review and meta-analysis of combination therapy with cholinesterase inhibitors and memantine in Alzheimer's disease and other dementias. *Dement Geriatr Cogn Dis Extra* 2012; 2:546-572.
  59. National Institute for Health and Care Excellence: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease., United Kingdom, National Institute for Health and Care Excellence, 2011.
  60. Ni R, Marutle A & Nordberg A: Modulation of  $\alpha 7$  nicotinic acetylcholine receptor and fibrillar amyloid- $\beta$  interactions in Alzheimer's disease brain. *J Alzheimers Dis* 2013; 33:841-851.
  61. Nussbaum RL & Ellis CE: Alzheimer's disease and Parkinson's disease. *N Engl J Med* 2003; 348:1356-1364.
  62. Onor ML, Trevisiol M & Aguglia E: Rivastigmine in the treatment of Alzheimer's disease: an update. *Clin Interv Aging* 2007; 2:17-32.
  63. Pacheco G, Palacios-Esquivel R & Moss DE: Cholinesterase inhibitors proposed for treating dementia in Alzheimer's disease: selectivity toward human brain acetylcholinesterase compared with butyrylcholinesterase. *J Pharmacol Exp Ther* 1995; 274:767-770.
  64. Parsons CG & Gilling K: Memantine as an example of a fast, voltage-dependent, open channel N-methyl-D-aspartate receptor blocker. *Methods Mol Biol* 2007; 403:15-36.
  65. Parsons CG, Stöfler A & Danysz W: Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system--too little activation is bad, too much is even worse. *Neuropharmacology* 2007; 53:699-723.
  66. Peña-Casanova J, Sánchez-Benavides G, de Sola S, Manero-Borrás RM & Casals-Coll M: Neuropsychology of Alzheimer's disease. *Arch Med Res* 2012; 43:686-693.
  67. Pepeu G, Giovannini MG & Bracco L: Effect of cholinesterase inhibitors on attention. *Chem Biol Interact* 2013; 203:361-364.
  68. Perry RJ & Hodges JR: Attention and executive deficits in Alzheimer's disease. A critical review. *Brain* 1999; 122(Pt 3):383-404.
  69. Polinsky RJ: Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. *Clin Ther* 1998; 20:634-647.
  70. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT & Group MM-M-S: Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res* 2008; 5:83-89.
  71. Rapp AM & Wild B: Nonliteral language in Alzheimer dementia: a review. *J Int Neuropsychol Soc* 2011; 17:207-218.
  72. Raschetti R, Maggini M, Sorrentino GC, Martini N, Caffari B & Vanacore N: A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease. *Eur J Clin Pharmacol* 2005; 61:361-368.
  73. Reisberg B: Diagnostic criteria in dementia: a comparison of current criteria, research challenges, and implications for DSM-V. *J Geriatr Psychiatry Neurol* 2006; 19:137-146.
  74. Richarz U, Gaudig M, Rettig K & Schauble B: Galantamine treatment in outpatients with mild Alzheimer's disease. *Acta Neurol Scand* 2014; 129:382-392.
  75. Rive B, Gauthier S, Costello S, Marre C & François C: Synthesis and comparison of the meta-analyses evaluating the efficacy of memantine in moderate to severe stages of Alzheimer's disease. *CNS Drugs* 2013; 27:573-582.
  76. Román GC & Kalaria RN: Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. *Neurobiol Aging* 2006; 27:1769-1785.
  77. Rudy CC, Hunsberger HC, Weitzner DS & Reed MN: The role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. *Aging and disease* 2015; 6:131-148.
  78. Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D et al: Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* 2004; 63:651-657.
  79. Salmon DP & Bondi MW: Neuropsychological assessment of dementia. *Annu Rev Psychol* 2009; 60:257-282.
  80. Scarpini E, Scheltens P & Feldman H: Treatment of Alzheimer's disease: current status and new perspectives. *Lancet Neurol* 2003; 2:539-547.

81. Schneider LS, Dagerman KS, Higgins JP & McShane R: Lack of evidence for the efficacy of memantine in mild Alzheimer disease. *Arch Neurol* 2011; 68:991-998.
82. Schroeter ML, Stein T, Maslowski N & Neumann J: Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. *NeuroImage* 2009; 47:1196-1206.
83. Scottish Intercollegiate Guidelines Network: Management of patients with dementia: A national clinical guideline, Edinburgh, Scottish Intercollegiate Guidelines Network, 2006.
84. Serrano-Pozo A, Frosch MP, Masliah E & Hyman BT: Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* 2011; 1:a006189.
85. Shankar GM & Walsh DM: Alzheimer's disease: synaptic dysfunction and Abeta. *Molecular neurodegeneration* 2009; 4:48.
86. Shinotoh H, Namba H, Fukushi K, Nagatsuka S, Tanaka N, Aotsuka A et al: Progressive loss of cortical acetylcholinesterase activity in association with cognitive decline in Alzheimer's disease: a positron emission tomography study. *Ann Neurol* 2000; 48:194-200.
87. Simoni E, Daniele S, Bottegoni G, Pizzirani D, Trincavelli ML, Goldoni L et al: Combining galantamine and memantine in multitargeted, new chemical entities potentially useful in Alzheimer's disease. *J Med Chem* 2012; 55:9708-9721.
88. Soreq H & Seidman S: Acetylcholinesterase--new roles for an old actor. *Nat Rev Neurosci* 2001; 2:294-302.
89. Strac DS, Muck-Seler D & Pivac N: Neurotransmitter measures in the cerebrospinal fluid of patients with Alzheimer's disease: a review. *Psychiatr Danub* 2015; 27:14-24.
90. Tai SK & Leung LS: Vestibular stimulation enhances hippocampal long-term potentiation via activation of cholinergic septohippocampal cells. *Behav Brain Res* 2012; 232:174-182.
91. Tata AM, Velluto L, D'Angelo C & Reale M: Cholinergic system dysfunction and neurodegenerative diseases: cause or effect? CNS & neurological disorders drug targets 2014; 13:1294-1303.
92. Tsang SW, Pomakian J, Marshall GA, Vinters HV, Cummings JL, Chen CP et al: Disrupted muscarinic M1 receptor signaling correlates with loss of protein kinase C activity and glutamatergic deficit in Alzheimer's disease. *Neurobiol Aging* 2007; 28:1381-1387.
93. Waltz JA, Knowlton BJ, Holyoak KJ, Boone KB, Back-Madruga C, McPherson S et al: Relational integration and executive function in Alzheimer's disease. *Neuropsychology* 2004; 18:296-305.
94. Wattmo C, Jedenius E, Blennow K & Wallin AK: Dose and plasma concentration of galantamine in Alzheimer's disease - clinical application. *Alzheimers Res Ther* 2013; 5:2.
95. Weintraub S, Wicklund AH & Salmon DP: The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med* 2012; 2:a006171.
96. Westphalen RI, Scott HL & Dodd PR: Synaptic vesicle transport and synaptic membrane transporter sites in excitatory amino acid nerve terminals in Alzheimer disease. *J Neural Transm* 2003; 110:1013-1027.
97. Wilkinson DG, Francis PT, Schwam E & Payne-Parrish J: Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging* 2004; 21:453-478.
98. Winblad B, Kilander L, Eriksson S, Minthon L, Båtsman S, Wetterholm AL et al: Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet* 2006; 367:1057-1065.
99. Xiong G & Doraiswamy PM: Combination drug therapy for Alzheimer's disease: what is evidence-based, and what is not? *Geriatrics* 2005; 60:22-26.

# Correspondence:

Dr. Nuno Barbosa F. Rocha  
 Polytechnic Institute of Porto, School of Health Technologies  
 Rua Valente Perfeito, 322 – 44, Porto, Portugal  
 E-mail: nrocha@estsp.ipp.pt