Exploring the Dual Facets of Memantine: A Neurological and Pharmacological Analysis

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Abstract: Memantine protects cultured neurons from excitotoxin-induced cell-death; it attenuated loss of cholinergic neurons in the CNS induced by injection of NMDA into the basal forebrain of rats. It has been shown that memantine induced production of brain-derived neurotrophic factor (BDNF), a substance shown to promote survival and differentiation of CNS neuron. Due to the preclinical effects of memantine owing to its anti-ischemic and anti-excitotoxic properties, recent clinical effi cacy has been demonstrated in patients with advanced dementia of vascular origins. Therefore, it has been employed in different trials, in vascular dementia, showing a potential benefi t and no unbearable side effects. Different studies underline the possible role of memantine in Parkinson Disease.

Keywords: memantine, NMDA, glutamate, degeneration

Glutamate is the principal excitatory neurotransmitter in the brain and is active in about one-third of all the synapses in the central nervous system. Although glutamate is a crucial mediator of physiological communication between neuronal cells, under certain conditions activation of glutamate receptors kills neurones—a term called “excitotoxicity” (Rothman et al. 1987). It has been implied that excitotoxicity is involved in many types of acute and chronic CNS neurodegenerative disorders and is connected with Ca2+ overload (Choi et al. 1995). Disturbance of glutamate homeostasis probably plays a pivotal role in neuropathology triggered by other factors such as: energy defi cits, free radicals formation, etc. that facilitate the neurotoxic potential of endogenous glutamate (Danysz et al. 2000).

Glutamate activates three major types of ionotropic receptors, namely a-amino-3- hydroxy-5-methyl4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) and several types of metabotropic receptors. AMPA receptors are probably involved in all forms of fast glutamatergic neurotransmission (Danysz et al. 2000). There are four known subunits GluR1 to GluR4 which form functional receptors as tetrameric subunit assemblies. All AMPA receptors are permeable to Na+ and K+ while complexes lacking GluR2 subunits are also permeable to Ca2+. NMDA-sensitive ionotropic glutamate receptors are coupled to high conductance cationic channels permeable to Na+, K+, and Ca2+ (Danysz et al. 2000).

The NMDA channel is blocked in a use- and voltage dependent manner by Mg2+ and many exogenous agents. NMDA receptors are only activated following depolarisation of the postsynaptic membrane which physiologically follows AMPA receptor stimulation which relieves blockade by Mg2+. This unique feature and the high Ca2+ permeability renders NMDA receptors inherently suitable as mediators of synaptic plasticity (e.g. learning and memory). Similar to Mg2+, uncompetitive NMDA receptor antagonists such as ketamine, dextromethorphan, memantine, phencyclidine and (+)-5-methyl-10,11-dihydro-5Hdibenzocyclohepten-5,10-imine meleate (+)MK-801 block the NMDA channel in the open state, although the blocking kinetics and voltage dependence of this effect vary considerably (Danysz et al. 2000).

Glutamate and NMDA receptors are involved in long-term potentiation (LTP), a fundamental process for memory consolidation, whereby brief high-frequency stimulation leads to an increased response after subsequent activation. NMDA receptors are involved in mediating the postsynaptic components of LTP in the hippocampus e.g. in the Schaffer collateral projection from CA3 to CA1 (Danysz et al. 1995; Parsons et al. 1998; Fischer et al. 1977).

Under normal physiological resting conditions, the ion channels of the NMDA receptors are blocked by magnesium ions in a voltage-dependent manner. The small amounts of glutamate that are released

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are not suffi cient to displace the magnesium ions and remove the blockade of the NMDA receptor channels; there is a so-called "low background noise". During normal synaptic activity, larger concentrations of glutamate are released, the postsynaptic membrane is depolarised, the magnesium blockade is transiently inactivated, calcium ions enter the cell and a signal is generated. Under conditions of impaired metabolism, there is a sustained release of glutamate, and excessive glutamate activity is associated with excitotoxicity. The magnesium ions are lost from the NMDA receptors—allowing a continuous infl ux of calcium ions into the cell-creating a high level of background noise and impairing the recognition of signals, resulting from physiological activation of the receptor. High intracellular concentrations of calcium eventually lead to neuronal degeneration and cell death.

Memantine blocks NMDA receptor channels in cultured neurons in a voltage-dependent manner as measured by patch clamp technique (Chen et al. 1997; Blanpied et al. 1997; Borman et al. 1989). The effects of memantine were not reversed by exposure to glycine 100 micromol/L (Borman et al. 1989).

Memantine induces open-channel blockade of NMDA receptors (Ambrozi et al. 1988) and is 'partially trapped' in NMDA receptor channels (Chen et al. 1999; Frankiewicz et al. 1999). Memantine could be washed from approximately one-sixth of channels during *in vitro* experiments (Frankiewicz et al. 1999). Memantine protects cultured neurons from excitotoxin-induced cell death (Parsons et al. 1993; Krieglstein et al. 1996; Erdo et al. 1991; Weller et al. 1993; Pellegrini et al. 1993).

Memantine exerts neuroprotective effects in several models of brain injury. The drug attenuated loss of cholinergic neurons in the CNS induced by injection of NMDA into the basal forebrain of rats (Wenk et al. 1997).

Memantine also attenuated neuronal injury in various rat models including traumatic brain injury (Rao et al. 2001), ischaemic stroke induced by occlusion of cerebral (Gorgiilii et al. 2000; Dogan et al. 1999) or carotid arteries (Seif eJ NasI' et al. 1990; Heim et al. 1995), a photo-induced thrombotic model of cerebral focal ischaemia (Stieg et al. 1999) and quinolinic acid-induced hippocampal damage (Keilhoff et al. 1992).

At a dosage of 5–50 mg/kg in rats, memantine induced production of brain-derived neurotrophic factor (BDNF), a substance shown to promote survival and differentiation of CNS neurons, and trkB, a tyrosine kinase receptor for BDNF (Keilhoff et al. 1992). mRNA for BDNF and trkB was
detected in limbic cortex slices by *in situ* hybridisation (Lundbeck AIS, 2002).

Clinical Therapy

Due to its preclinical effects, above described, memantine, late in 2003, was approved by the FDA as a drug for AD treatment. Memantine is indicated for the treatment of moderate to severe Alzheimer's disease, refl ecting a license extension granted by the European Commission in October 2005 to include the moderate AD patient population.

Post-mortem orepidemiological studies suggest a strong association between glutamate dysfunction and Alzheimer's disease. Some

authors observed co-localisation of glutamatergic neurones and pathological alterations (neurofi brillary tangles and senile plaques) in post-mortem analysis of the brains of Alzheimer's patients (Braak et al. 1993; Francis et al. 1993). In Alzheimer's disease there is an increase of glutamate, caused by a decrease of uptake and/or increase of release. There is a decrease in astroglial glutamate carrier EAA2 in the frontal cortex of post-mortem samples from brains of Alzheimer's patients (Li et al. 1997). In vitro constituents of senile plaques stimulate microglia to produce an unknown neurotoxin having agonistic properties at NMDA receptors (Giulian et al. 1995; Klegeris et al. 1997). Beta-amyloid peptide either activates NMDA receptors or enhances their sensitivity (Goodwin et al. 1995); in fact, beta-amyloid (1–40) stimulates nitric oxid (NO) production by microglia (Goodwin et al. 1995)—NO is known to enhance glutamate release and to inhibit uptake (Brorson et al. 1995). Beta-amyloid peptide enhances the toxicity of glutamate in *in vitro* test (Mattson et al. 1992; Wu et al. 1995) and augments NMDA receptor mediated transmission (Cullen et al. 1996). In vivo injection of beta-amyloid produces long lasting depression of EPSPs in the hippocampus, which is an expression of ongoing mild excitotoxicity. It is prevented by the NMDA receptor antagonist 3-(2-carboxypiperazin4-yl)propyl-1-phosphonic acid (CPP) (Cullen et al. 1996).

In multi centre placebo-controlled trials, memantine has demonstrated effi cacy and safety in AD patients. The N-methyl-D-aspartate (NMDA) antagonist memantine has been shown to be effective in moderately-severe to severe AD. 252 patients were enrolled, with equal numbers (n = 126) receiving either memantine 20 mg/day or placebo for 28 weeks. Effi cacy was assessed using the clinician's interview-based impression of change (NYU CIBICplus), the modified Alzheimer's Disease Cooperative Study activities of daily living (ADCS-ADLsev) inventory, the severe impairment battery (SIB), and functional assessment staging (FAST) (Reisberg et al. 2003; Reisberg et al. 2000). In Study Two, 166 patients were enrolled to the study and randomised to receive either memantine 10 mg/day or placebo for 12 weeks. The primary effi cacy endpoints were measured using the Clinical Global Impression of Change (CGI-C) and the Behavioural Rating Scale for Geriatric Patients (BGP). The modifi ed D-scale (Arnold/Ferm) was used to assess basic activities of daily living as a secondary endpoint. Both studies demonstrated that patients treated with memantine show improvements in the three main AD domains: function, cognition and global response. Memantine was well tolerated in both studies, being the incidence of adverse events (AEs) and serious AEs was similar in both groups (Winblad et al. 1999). In conclusion, memantine treatment offered functional improvements and reduced care dependence for patients with moderately-severe to severe AD.

Another well designed study, involving patients with moderate-to-severe Alzheimer's disease, who were randomly assigned to receive placebo or 20 mg of memantine daily for 28 weeks has been conducted (Bleich et al. 2003). 252 patients were enrolled. Of these, 181 (72%) completed the study and were evaluated at week 28. 71 patients discontinued treatment prematurely (42 taking placebo and 29 taking memantine). Patients receiving memantine had a better outcome than those receiving placebo, according to the results of the clinical global impression (P = 0.06 with the last observation carried forward, P = 0.03 for observed cases), of the activities of daily living (P = 0.02 with the last observation carried forward, P = 0.003 for observed cases), and the Severe Impairment Battery (P 0.001 with the last observation carried forward, P = 0.002 for observed cases). Memantine was not associated with a signifi cant frequency of adverse events. The conclusions of the authors are well stigmatized by the following sentence: "Antiglutamatergic treatment reduced clinical deterioration in moderate-to-severe Alzheimer's disease, a phase associated with distress for patients and burden on caregivers, for which other treatments are not available" (Bleich et al. 2003).

It has been demonstrated a favourable effect of memantine, even in the association with cholinesterase inhibitors. A 24-week, randomised, doubleblind, parallel-arm, placebo controlled trial was performed in 37 US centres to study the safety and effi cacy of memantine in

patients with moderate to severe AD treated with donepezil (Hartmann et al. 2003). Inclusion criteria of the study were: a diagnosis of probable AD by NINCDS-ADRDA, MMSE (5–14), MRI or CT scan consistent with probable AD, and 6-month daily AChEI (donepezil) therapy (stable dose for the past 3 months). Primary outcome assessments were: cognition and function in daily living. A pharmacokinetic study in 24 healthy volunteers showed no pharmacokinetic or pharmacodynamic interactions and the combination was well tolerated. The global effect was in general favourable to the population who received both the drugs.

A postmarketing surveillance study was performed in Germany to assess the tolerability of memantine in combination with an AChEI (84% donepezil and 15% rivastigmine) based on 200 questionnaires. The results demonstrate that combining memantine with a commonly used AChEI is safe and superior to the AChEI alone in moderate to severe AD (Tariot et al. 2003; Tariot et al. 2004; Knopman, 2005; Pomara et al. 2004; Sudhir, 2004).

To investigate, the cognitive effect of the memantine, a group of scientists (Schmitt et al. 2006) executed a post-hoc exploratory reanalysis of a 24 week randomized, double-blind, placebocontrolled, parallel group clinical trial comparing memantine to placebo in patients with moderate to severe AD receiving treatment with cholinesterase inhibitor, donepezil. These post-hoc analyses support the benefi cial effects of memantine on cognition observed in a previously reported clinical trial. The results suggested an effect of memantine on memory, language, and praxis in patients with moderate to severe AD and support the effi cacy of memantine for the treatment of cognitive defects in AD (Schmitt et al. 2006). A very recent work (Jones et al. 2007) confi rmed the statistically signifi cant benefi ts of memantine given twice-daily to treat moderate to severe AD have already been shown by multiple studies in pivotal AD domains (function, cognition and global performance) (Winblad et al. 2006). No clinically relevant differences in adverse effects or vital signs were observed between the different dosing schedules (Jones et al. 2007).

Memantine and Vascular Dementia

In course of a cerebrovascular event, there is a run-down of energy in neurons. There are number of microdialysis studies indicating that there is also a consistent increase in extracellular glutamate concentration. In humans, there is also an increase in cerebrospinal fl uid (CSF) and plasma content of glutamate in patients with progressive, but not stable stroke. Thus, other factors may increase neuronal vulnerability to physiological levels of glutamate by, for example, a decrease of resting membrane potential or intracellular buffering of Ca2+ ions. Apart from glutamate, oxidative stress, inflammatory reactions and breakdown of the blood-brain barrier may also play a pivotal role.

The toxic effects of glutamate are mediated largely through N-methyl- D-aspartate (NMDA) receptors. Activation of NMDA-associated channels leads to the passage of sodium and chloride into the cell followed by the obligatory movement of water resulting in cytotoxic oedema. If calcium is present early, it tends to pass through the channel into the cell where it recruits second messengers, with concomitant activation of kinases and proteases that eventually lead to irreversible injury. This is believed to be the underlying mechanism behind delayed glutamate toxicity. Glutamate excitotoxicity can lead to a state of self-amplifi cation, followed by an increase of intracellular calcium. These events lead to a second messenger activation, giving rise to changes that make the cell more permeable to additional calcium entry and further glutamate release. Glutamate release also gives rise to oxygen free radical production, which maintains the further release of glutamate.

Controversial are the results from animal studies: often short delays (1–3 days) for analysis of infarct size are used. There are data showing that some treatments delay, but do not really prevent neuronal death. Therefore, the protective effects are seen when analyzed at three days but not 7–28 days after insult. Infarct volume or cell damage is not always predictive of functional outcome. There is signifi cant strain and vendor variability of infarct size and neuroprotective efficacy of NMDA receptor antagonists, adding

to the already large methodological diversity (Mortimer et al. 1991; Orgogozo et al. 2002).

Physiological NMDA receptor activity, however, is also essential for normal neuronal function; potential neuroprotective agents that block virtually all NMDA receptor activity will very likely have unacceptable clinical side effects. For this reason many NMDA receptor antagonists have disappointingly failed advanced clinical trials for a number of diseases including stroke and neurodegenerative disorders such as Huntington's disease. In contrast, studies by Lipton (2004) were the fi rst to show that memantine preferentially blocks excessive NMDA receptor activity without disrupting normal activity (Orgogozo et al. 2002).

Based on the hypothesis of glutamate-induced neurotoxicity (excitotoxicity) in cerebral ischemia, different studies examined the effi cacy and tolerability of memantine, an uncompetitive N-methylD-aspartate antagonist, in the treatment of mild to moderate vascular dementia.

In a multicenter, 28-week trial carried out in France, 321 patients received 10 mg/d memantine or placebo twice a day; 288 patients were valid *for* intent-to-treat analysis. Patients had to meet the criteria *for* probable vascular dementia and have a Mini-Mental State (MMSE) score between 12 and 20 at inclusion. The 2 primary end points were the cognitive subscale of the Alzheimers Disease Assessment Scale (ADAS-cog) and the global Clinician's Interview Based Impression of Change (CIBIC-plus) (Wilkock et al. 2002).

After 28 weeks, the mean ADAS-cog scores were signifi cantly improved relative to placebo. In the intention-to-treat population, the memantine group mean score had gained an average of 0.4 points, whereas the placebo group mean score had declined by 1.6 points (95% confi dence interval, 0.49 to 3.60). The response rate for CIBIC-plus, defi ned as improved or stable, was 60% with memantine compared with 52% with placebo (P = 0.227, intention to treat). Among the secondary effi cacy parameters, which were analyzed in the per-protocol subset, MMSE was signifi cantly improved with memantine compared with deterioration with placebo (P = 0.003) (Wilkock et al. 2002).

Another work has been conducted on the topic. The aim of the reported trial was to investigate the safety and effi cacy of memantine in mild to moderate vascular dementia (VaD) (Jarvis et al. 2002).

It was a 28-week, double-blind, parallel, randomized controlled trial of memantine 20 mg daily versus placebo, in probable VaD which was conducted in 54 centres in the U.K. Primary effi cacy parameters were cognition and the clinical global impression. A total of 579 patients were randomized and 548 patients with at least one post baseline effi cacy assessment qualifi ed for the intent-to-treat analysis. At endpoint, memantine was shown to improve cognition relative to placebo in VaD: the change of cognition scores from baseline differed by a mean of −1.75 points (95% confi dence intervals −3.023 to −0.49) and a median of 2 points between the two groups, while clinical general impression on the global status rating scores showed no signifi cant differences between treatment groups.

Demaerschalk and Wingerchuk (2007) examined in a complete meta-analysis eight relevant systematic reviews and randomized controlled trials were identifi ed and served as the principal sources of information. The best evidence to date revealed that donepezil 5 mg/d [number needed to treat (NNT) = 10] was the most effective and best tolerated [number needed to harm (NNH) = 50] of the available agents. Galantamine 24 mg/d

(NNT = 7) was also effective but less well tolerated (NNH = 7). Due to insuffi cient evidence, rivastigmine could not yet be recommended for the treatment of vascular dementia. Memantine appeared to be safe and well tolerated but did not demonstrate effectiveness across all cognitive outcomes and clinical global measures. Acetylcholinesterase inhibitors and NMDA receptor antagonists, in general, displayed promise as treatments for patients with vascular dementia and vascular cognitive impairment. The most effective, evidence-based treatments were donepezil and galantamine

Memantine and Parkinson's Disease

Because of its peculiar pharmacological properties, memantine is proposed to be benefi cial, as it blocks excessive NMDA receptors activation, without interfering with their physiological activity.

An anti-parkinsonian activity has been described for memantine, in animal models of Parkinson's disease and in parkinsonian patients (Merello et al. 1999). In addition, memantine prevents cell death induced by 1-methyl-4-phenyl1,2,3,6- tetrahydropyridine (Kucheryanu and Kryzhanovskii, 2000).

Therefore, an Italian group (Giustizieri et al. 2007) focused our attention onto the action of this drug on the dopamine neurons of the substantia nigra *pars compacta* (SNc), whose progressive degeneration is a hallmark of Parkinson's disease. Indeed, several lines of evidence indicate an overstimulation of glutamate receptors, especially of the NMDA subtype, as the main cause of the progressive loss of this neuronal population (Gardoni and Di Luca, 2006).

Memantine has been showed not only to increase the fi ring rate of the dopamine neurons, but also changed occasionally their fi ring mode, from tonic to bursting behavior. This change in the fi ring pattern may have important functional implications, as burst fi ring of the dopamine neurons has been associated to increased release of dopamine in the areas of nigral projection (Floresco et al. 2003; Phillips et al. 2003).

According to the observations of Giustizieri et al. (2007), memantine does not affect the basal fi ring activity of the dopamine neurons in physiological conditions, while, in conditions of metabolic stress, a signifi cant effect of memantine emerges, resulting in recovery of fi ring activity of previously silenced dopamine neurons. This property may be particularly relevant in terms of fi ring dependent dopamine release and in relation to prevention of neuronal loss in Parkinson's disease. The activity of complex I of the mitochondrial respiratory chain is reduced in dopamine neurons of parkinsonian patients (Schapira, 2001), and drugs acting as inhibitors of complex I, like rotenone or 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine induce dopamine neurons degeneration (Przedborski and Vila, 2003). A recent report by Liss and colleagues (2005) proposed that the selective vulnerability of the SNc dopamine neurons in Parkinson's disease is casually correlated with the opening of Katp conductances in these neurons; thus, the presence of functional Katp channels promotes the selective loss of SNc dopamine neurons in both a genetic model of Parkinson's disease and in response to mitochondrial complex I inhibition. At present, the mechanism through which Katp channel opening contributes to dopamine neurons degeneration is still unclear. There is evidence that increasing neuronal excitability protects dopamine neurons from degeneration (SalthunLassalle et al. 2004), for this reason Liss and colleagues (2005) proposed that drugs acting at KATP channels of SNc dopamine neurons, should cause a recovery from their functional silencing, thus providing a clinical benefi t in the treatment of Parkinson's disease.

Indeed, memantine has been shown to prevent cell death associated to Parkinson's disease (Merello et al. 1999; Kucheryanu and Kryzhanovskii, 2000), although prevention of excitotoxic neuronal damage through an uncompetitive inhibition of NMDA receptors has been proposed as its underlying mechanism of action. Giustizieri et al. results (2007) results show that memantine does inhibit NMDA responses in the SNc, however, memantine may also result benefi cial in Parkinson's disease patients because it reduces dopamine neurons silencing through closure of Katp conductances.

Quite balancing the preclinical studies, there are not so consistent data in Parkinson patients in a clinical perspective. An open-fashion study, involving 14 parkinsonian patients with motor fl uctuations taking L-dopa, has been conducted (Rabey et al. 1992); these patients were given a supplement of memantine 30 mg/day. After one month, 10 patients completed the treatment (4 discontinued it due to abdominal pain, psychomotor agitation, confusion and dizziness). In 5 patients, the main parkinsonian features improved signifi cantly (1 point or more on the Webster scale). In 6 patients, "off " episodes improved (from daily mean of 273 minutes, to 172 minutes). In summary, the authors postulated

that memantine addition to parkinsonian features, could form a basis for novel therapeutic strategies directed to neutralize the effects of glutamate at striatal and subthalamic levels.

Another work has been conducted quite later (Merello et al. 1999); the aim was to evaluate the effect of Memantine on cardinal symptoms of Parkinson's disease and on the latency, duration, and magnitude of the response to a single dose of L-Dopa and on drug-induced dyskinesias. Twelve Hoehn-Yahr III-IV patients with idiopathic Parkinson's disease with motor fl uctuations and drug-induced dyskinesias were randomized to the NMDA antagonist memantine or placebo in a cross-over design. A single-dose L-Dopa challenge was performed after each medication arm. A signifi cant drug effect on the Unifi ed Parkinson's Disease Rating Scale motor score was observed in "off " and "on" states (F(1,11) = 13.5; p 0.003). No signifi cant effect on drug-induced dyskinesias was seen. The results suggest that memantine may improve parkinsonian symptoms independently of dopaminergic drugs and, in contrast to recent fi ndings with amantadine, it has no effect on druginduced dyskinesias.

Very recently, a new study has been conducted to determine the effect of memantine on Parkinson Disease (Seeman et al. 2007), considering that memantine is reported to improve symptoms in moderate cases of Alzheimer's disease and Parkinson's disease, but is also known to trigger psychosis in some Parkinson patients. Because these clinical features suggested a possible dopamine component of memantine action, we measured the potency of memantine on the functional high-affi nity state of dopamine D2 receptors, or D2(High). Using [(3)H]domperidone to label D2 receptors, the memantine dissociation constant at D2(High) was 917 +/− 23 nM for rat striatal D2 receptors and 137 +/− 19 nM for human cloned D2Long receptors. The memantine dissociation constant for striatal N-methyl-D-aspartate (NMDA) receptors labeled by [(3)H] MK 801 was 2200 +/− 400 nM. Memantine stimulated the incorporation of [(35)S]GTPgamma-S into D2-expressing Chinese Hamster Ovary cells with a dissociation constant of 1200 +/− 400 nM. Memantine, between 200 and 2000 nM, directly acted on D2(High) to inhibit the release of prolactin from isolated anterior pituitary cells in culture. Because the memantine potencies at NMDA receptors and dopamine D2(High) receptors are of a similar order of magnitude, it is likely that the clinical features of memantine can be attributed to its action at both types of receptors.

Conclusions

Memantine protects cultured neurons from excitotoxin-induced cell-death. Memantine exerts neuroprotective effects in several models of brain injury. The drug attenuated loss of cholinergic neurons in the CNS induced by injection of NMDA into the basal forebrain of rats. It has been shown that memantine induced production of brain-derived neurotrophic factor (BDNF), a substance shown to promote survival and differentiation of CNS neuron. Due to the preclinical effects of memantine owing to its anti-ischemic and anti-excitotoxic properties, recent clinical effi cacy has been demonstrated in patients with advanced dementia of vascular origins. Therefore, it has been employed in different trials, in vascular dementia, showing a potential benefi t and no unbearable side effects.

Memantine has a small benefi cial, clinically detectable effect on cognitive function and functional decline measured at 6 months in patients with moderate to severe Alzheimer's Disease (AD). In patients with mild to moderate dementia, the small benefi cial effect on cognition was not clinically detectable in those with vascular dementia and barely detectable in those with AD. It is well tolerated (McShane et al. 2007).

Main results can be summarized as follows:

1. Moderate to severe AD. Two out of three six month studies show a small benefi cial effect of memantine. Pooled data indicate a benefi cial effect at six months on cognition (2.97 points on the 100 point SIB, 95% CI 1.68 to 4.26, P 0.00001), activities of daily living (1.27 points on the 54 point ADCS-ADLsev, 95% CI 0.44 to 2.09, P = 0.003) and behaviour (2.76 points on the 144 point NPI, 95% CI 0.88 to 4.63, P = 0.004), supported by clinical

impression of change (0.28 points on the 7 point CIBIC+, 95% CI 0.15 to 0.41, P 0.0001).

2. Mild to moderate AD. Pooled data from three unpublished studies indicate a marginal benefical effect at six months on ITT cognition (0.99 points on the 70 point ADAS-Cog, 95% CI 0.21 to 1.78, P = 0.01) which was barely detectable clinically (0.13 CIBIC+ points, 95% CI 0.01 to 0.25, P = 0.03) but no effect on behaviour, activities of daily living or OC analysis of cognition.
3. Mild to moderate vascular dementia. Pooled data from two six month studies indicated a small benefi cial effect of memantine on cognition (1.85 ADAS-Cog points, 95% CI 0.88 to 2.83, P = 0.0002), and behaviour (0.84 95% CI 0.06 to 0.91, P = 0.03) but this was not supported by clinical global measures.
4. Patients taking memantine were slightly less likely to develop agitation (134/1739, 7.7% versus 175/1873, 9.3% OR 0.78, 95% CI 0.61 to 0.99, P = 0.04). This effect was slightly larger, but still small, in moderate to severe AD (58/506 [12%] vs 88/499 [18%]; OR = 0.6, 95% CI 0.42 to 0.86, P = 0.005). There is no evidence either way about whether it has an effect on agitation which is already present.

Importantly, however, it does appear that the dementia caused by brain vascular disease may share similar anatomic substrates with AD, supporting the notion of a common substrate to dementia.

Different studies suggest that memantine should be studied in a wider and broader population, even in Parkinson Disease, but results are quite experimental. It might be postulated that many studies should be designed to define the real clinical relevance of the laboratory and pre-clinical observations.

References

Ambrozi, L. and Danieczyk, W. 1988, May. Treatment of impaired cerebral function in psychogeriatric patients with memantine—results of a phase II double-blind study. *Pharmacopsychiatry*, 21(3):144–6.

Blanpied, T.A., Boeckman, F.A., Aizenman, E. et al. 1997, Jan. Trapping channel block of NMDA-activated responses by amantadine and memantine. *J. Neurophysiol*., 77(I):309–23.

Bleich, S., Wiltfang, J., Kornhuber, J., Reisberg, B., Doody, R. and Möbius,
H.J. 2003. Memantine in Moderate-to-Severe Alzheimer's Disease. *N. Engl. J. Med*., 349:609–10.

Bormann, J. 1989, Aug 3. Memantine is a potent blocker of N.-methylDaspartate (NMDA) receptor channels. *Eur. J. Pharmacol*., 166(3):591–2.

Braak, H., Braak, E. and Bohl, J. 1993. Staging of Alzheimer related cortical destruction. *Eur. Neurol*., 33:403–8.

Brorson, J.R., Bindokas, Y.P., Iwama, I., Marcuccilli, C.J., Chisholm, J.C. and Miller, R.J. 1995. The Ca2+ infl ux induced by beta-amyloid peptide 25–35 in cultured hippocampal neurons results from network excitation. *J. Neurobiol*., 26:325–38. chapira, A.H. 2001. Causes of neuronal death in Parkinson's disease. *Adv. Neurol*., 86:155–62.

Chen, H-S. and Lipton, S.A. 1997, Feb 15. Mechanism of memantine block of NMDA-activated channels in rat retinal ganglion cells: uncompetitive antagonism. *J. Physiol*., 499(Pt I):27–46.

Choi, D.W. 1995. Calcium: still center-stage in hypoxicischemic neuronal death. *Trends Neurosci*., 18:58–60.

Cullen, W.K., Wu, J.Q., Anwyl, R. and Rowan, M.J. 1996. Beta amyloid produces a delayed NMDA receptor-dependent reduction in synaptic transmission in rat hippocampus. *Neuroreport*., 8:87–92.

Danysz, W., Zajaczkowski, W. and Parsons, C.G. 1995. Modulation of learning processes by ionotropic glutamate receptor ligands. *Behav. Pharmacal*., 6:455–74.

Danysz, W., Parsons, C.G., Mobius, H.J., Stoffl er, A. and Quack, G. 2000. Neuroprotective and Symptomatological Action of Memantine Relevant for Alzheimer's Disease—A Unifi ed Glutamatergic Hypothesis on the Mechanism of Action. *Neurotoxicity Res*., 2:85–97.

Demaerschalk, B.M. and Wingerchuk, D.M. 2007, Jan. Treatment of vascular dementia and vascular cognitive impairment. *Neurologist*, 13(1):37–41.

Dogan, A., Eras, M.A., Rao, VLR. et al. 1999. Protective effects of memantine against ischemia-reperfusion injury in spontaneously hypertensive rats. *Acta. Neurochir (Wien)*., 141(10):1107–13.

Erdo, S.L. and Schafer, M. 1991, Jun 6. Memantine is highly potent in protecting cortical cultures against excitotoxic cell death evoked by glutamate and N.-methyJ.-D-aspartate. *Eur. J. Pharmacol*., 198(2–3):215–7.

Fischer, P-A., Jacobi, P., Schneider, E. et al. 1977. Effects of intravenous administration of memantine in Parkinsonian patients (in Ger-23 man].
Arzneimittelforschung, 27(II)(7):1487–9.

Floresco, S.B., West, A.R., Ash, B., Moore, H. and Grace, A.A. 2003. Afferent modulation of dopamine neuron fi ring differentially regulates tonic and phasic dopamine transmission. *Nat. Neurosci*., 6:968–73.

Francis, P.I., Sims, N.R., Procter, A.W. and Bowen, D.M. 1993. Cortical pyramidal neurone loss may cause glutamatergic hypoactivity and cognitive impairment in Alzheimer's disease—investigative and therapeutic perspectives. *J. Neurochem*., 60:1589–604.

Frankiewicz, T. and Parsons, C.G. 1999, Sep. Memantine restores long term potentiation impaired by tonic N-methyl-D-aspartate (NMDA) receptor activation following reduction of Mg2+ in hippocampal slices. *Neuropharmacology*, 38(9):1253–9.

Gardoni, F. and Di Luca, M. 2006. New targets for pharmacological intervention in the glutamatergic synapse. *Eur. J. Pharmacol.*, 545:2–10.

Giulian, D., Haverkamp, L.J., Li, L., Karshin, W.L., Yu, L., Tom, D., Li, X. and Kirkpatrick, J.B. 1995. Senile plaques stimulate microglia to release a neurotoxin found in Alzheimer brain. *Neurochem. Int*., 27:119–37.

Giustizieri, M., Cucchiaroni, M.L., Guatteo, E., Bernardi, G., Mercuri, N.B. and Berretta, N. 2007, May 11. Memantine Inhibits ATP-Dependent K+ Conductances in Dopamine Neurons of the Rat Substantia Nigra Pars Compacta JPET Fast Forward. Published on, as DOI:10.1124/ jpet.107.122036.

Goodwin, J.L., Demura, E. and Cunnick, J.E. 1995. Microglial release of nitric oxide by the synergistic action of beta-amyloid and IFN-gamma. *Brain Res*., 692:207–14.

Gorgiilii, A., Kins, T., Cobanoglu, S. et al. 2000. Reduction of edema and infarction by memantine and MK-80l after focal cerebral ischaemia and reperfusion in rat. *Acta. Neurochir (Wien)*, 142(11):1287–92.

Hartmann, S. and Mobius, H. 2003. Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy. *Int. Clin. Psychopharmacol*., 18:81–5.

Heim, C. and Sontag, K.H. 1995. Memantine prevents progressive functional neurodegeneration in rats. *J. Neura.l Transm*, 46(Supp1):17–30.

Jarvis, B. and Figgitt, D.P. 2003. Memantine. *Drugs and Aging*, 20(6):465–76.

Jones, R.W., Bayer, A., Inglis, F. et al. 2007, January. Safety and tolerability of once-daily versus twice-daily memantine: a randomised, doubleblind study in moderate to severe Alzheimer's disease. *Int. J. Geriatr. Psychiatr.*, http://www3.interscience.wiley.com/cgi–bin/ jhome/4294.

Keilhoff, G. and Wolf, G. 1992, Sep 4. Memantine prevents quinolinic acid-induced hippocampal damage. *Eur. J. Pharmacol*., 219(3):451–4.

Klegeris, A. and McGeer, P.L. 1997. Beta-amyloid protein enhances macrophage production of oxygen free radicals and glutamate. *J. Neurosci. Res*., 49:229–35.

Knopman, D. 2005. San Francisco. Where We Stand With Symptomatic Treatments For Alzheimer Disease. *American Academy of Neurology*, 1KP003:1–34.

Krieglstein, J., Lippert, K. and Poch, G. 1996. Apparent independent action of nimodipine and glutamate antagonists to protect cultured neurons against glutamate-induced damage. *Neuropharmacology*, 35(No. J2):1737–42.

Kucheryanu, V.G. and Kryzhanovskii, G.N. 2000. Effect of glutamate and antagonists of Nmethyl- D-aspartate receptors on experimental parkinsonian syndrome in rats. *Bull Exp. Biol. Med.*, 130:629–32.

Li, S., Mallory, M., Alford, M., Tanaka, S. and Masliah, E. 1997. Glutamate transporter alterations in Alzheimer disease are possibly associated with abnormal APP expression. *J. Neuropathal. Exp. Neurol*., 56:901–11.

Liss, B., Haeckel, O., Wildmann, J., Miki, T., Seino, S. and Roeper, J. 2005. K-ATP channels promote the differential degeneration of dopaminergic midbrain neurons. *Nat. Neurosci*., 8:1742–51.

Lundbeck AlS, H. 2002. Summary of product characteristics. Ebixa (memantine hydrochloride). H. Lundbeck AIS, Valby, Denmark l–13.

Mattson, M.P., Cheng, B., Davis, D., Bryant, K., Lieberburg, 1 and Rydel, R.E. 1992. Beta-amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. *J. Neurosci*., 12:376–89.

McShane, R., Areosa Sastre, A. and Minakaran, N. Memantine for dementiaThe Cochrane Library The Cochrane Database of Systematic Reviews 2007 Issue 1.

Merello, M., Nouzeilles, M.I., Cammarota, A. and Leiguarda, R. 1999. Effect of memantine (NMDA antagonist) on Parkinson's disease: a doubleblind crossover randomized study. *Clin. Neuropharmacol*., 22:273–6.

Mortimer, J.A., VanDuijn, C.M., Chandra, V., Fratiglioni, L., Graves, A.B., Heyman, A., Jorm, A.E., Kokmen, E., Kondo, K., Rocca, W.A., Shalat, S.L., Soinien, S.L. and Hofman, A. 1991. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case control studies. *Int. J. Epidemiol.*, 20(Suppl 2):S28–S35.

Orgogozo, J.M., Rigaud, A.S., Stoffl er, A., Mobius, H.J. and Forette, F. 2002. Effi cacy and Safety of Memantine in Patients With Mild to Moderate Vascular Dementia. A Randomized, Placebo-Controlled Trial (MMM 300) Stroke 33:1834–9.

Parsons, C.G., Gruner, R., Rozental, J. et al. 1993, Dec. Patch clamp studies on the kinetics and selectivity of N.-methyl-D aspartate receptor antagonism by memantine (l-amino-3,5-dimethyJadamantan). *Neuropharmacology*, 32(12):1337–50.

Parsons, C.G., Danysz, W. and Quack, G. 1998. Glutamate in CNS disorders as a target for drug development. An update. *Drug News Perspect*, 11:523–69.

Pellegrini, J.W. and Lipton, S.A. l993. Delayed administration of memantine prevents N-methyl-D-aspartate receptor-mediated neurotoxicity. *Ann. Neurol*., 33(4):403–7.

Phillips, P.E., Stuber, G.D., Heien, M.L., Wightman, R.M. and Carelli, R.M. 2003. Subsecond dopamine release promotes cocaine seeking. *Nature*, 422:614–8.

Pomara, N., Peskind, E.R., Potkin, S.G. et al. 2004. Memantine monotherapy is effective and safe for the treatment of mild to moderate Alzheimer's Disease: a randomized controlled trial. *Neurobiol. Aging*, 25:1.

Przedborski, S. and Vila, M. 2003. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model: a tool to explore the pathogenesis of Parkinson's disease. *Ann. N.Y. Acad. Sci.*, 991:189–98.

Rabey, J.M., Nissipeanu, P. and Korczyn, A. 1992. D Effi cacy of memantine, an NMDA receptor antagonist, in the treatment of Parkinson's disease. *Journal of Neural Transmission*, 4(4):277–82.

Rao, VLR., Dogan, A., Todd, K.G. et al. 2001, Aug 17. Neuroprotection by memantine, a non-competitive NMDA receptor antagonist after traumatic brain injury in rats. *Brain Res*., 911(1):96–100.

Reisberg, B., Mobius, H.J., Stomer, A. et al. 2000, July 20–25. Long-term treatment with the NMDA antagonist memantine; results of a 24-week, open-label extension study in moderately severe to severe Alzheimer's disease [abstract]. 8th International Conference on Alzheimer's Disease and Related Disorders, Stockholm.

Reisberg, B., Doody, R., Stamer, A. et al. 2003. A randomized, placebo-controlled study of memantine, an uncompetitive NMDA ant-agonist, in patients with moderate to severe Alzheimer's disease. *N. Engl. J. Med*., 348:1333–41.

Rothman, S.M. and Olney, J.W. 1987. Excitotoxicity and the NMDA receptor. *Trends Neurosci*., 10:299–302.

Salthun-Lassalle, B., Hirsch, E.C., Wolfart, J., Ruberg, M. and Michel, P.P. 2004. Rescue of mesencephalic dopaminergic neurons in culture by low-level stimulation of voltage-gated sodium channels. *J. Neurosi*, 24:5922–30.

Schmitt, F., van Dyck, C., Wichems, C., Olin, J. and for the Mem MD 02 Study Group, 2006. Cognitive Response to memantine in moderate to severe Alzheimer Disease patients already receiving donepezil: an exploratory reanalysis. *Alzh. Dis. Ass. Dis*., 20(4):255–62.

Seeman, P., Caruso, C. and Lasaga, M. 2007, Nov 13. Memantine agonist action at dopamine D2(High) receptors. *Synapse*, 62(2):149–53.

Seif eJ. NasI', M., Peruche, B., Rossberg, C. et al. 1990, Aug 21. Neuroprotective effect of memantine demonstrated in vivo and in vitro. *Eur. J. Pharmacol*., J. 85(1):19–24.

Stieg, P.E., Sathi, S., Warach, S. et al. 1999, Jun 30. Neuroprotection by the NMDA receptor-associated open-channel blocker memantine in a photothrombotic model of cerebral focal ischemia in neonatal rat. *Eur. J. Pharmacol*., 375(1–3):115–20.

Sudhir, k. 2004. Memantine: pharmacological properties and clinical uses. *Neurology India*, 52(3):307–9.

Tariot, P., Farlow, M., Grossberg, G. et al. 2003, May. Memantine/donepezil dual therapy is superior to placebo/donepezil

therapy for treatment of moderate to severe Alzheimer's disease. Poster presented at the American Psychiatric Association Annual Meeting, San Francisco, U.S.A.

Tariot, P.N., Farlow, M.R., Grossberg, G.T., Graham, S.M., McDonald, S. and Gergel, I. 2004. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *Jama*, 291:317–24.

Weller, M., Finiels-Marlier, F. and Paul, S.M. 1993. NMDA receptormediated glutamate toxicity of cultured cerebellar, cortical and mesencephalic neurons: neuroprotective properties of amantadine and memantine. *Brain Res*., 613:143–8.

Wenk, G.L., Zajaczkowski, W. and Danysz, W. 1997, Feb. Neuroprotection of acetylcholinergic basal forebrain neurons by memantine and neurokinin B. *Behav. Brain Res*., 83 (1–2):129–33.

Wilcock, G., Mobius, H.J. and Stoffler, A. 2002. on behalf of the MMM 500 group A double-blind, placebo-controlled multi centre study of memantine in mild to moderate vascular dementia (MMM500). *International Clinical Psychopharmacology*, 17:297–305.

Winblad, B., Mobius, H.J. and Stoffl er, A. 2002. Glutamate receptors as a target for Alzheimer's disease—are clinical results supporting the hope? *J. Neural. Transm*., 62(Suppl):217–25.

Winblad, B., Jones, R.W., Wirth, Y. et al. 2006, September. Meta-analysis of clinical trial data with memantine in moderate to severe Alzheimer's disease. *Poster presented at EFNS*.

Wu, J.Q., Anwyl, R. and Rowan, M.J. 1995. Beta-amyloid selectively augments NMDA receptor-mediated synaptic transmission in rat hippocampus. *Neuroreport*., 6:2409–13.