

Drug therapy and disease management: An opinion

The Impact of Memantine and One-on-One Caregiver Contact on Antipsychotic Medication Prescribed to Elderly Veterans with Dementia: Potential Global Care Strategy

To cite: Farinde A, Aruoma OI. The Impact of Memantine and One-on-One Caregiver Contact on Antipsychotic Medication Prescribed to Elderly Veterans with Dementia: Potential Global Care Strategy. *Arch Med Biomed Res.* 2014;1(4):163-168. doi: 10.4314/ambr.v1i4.6

Publication history

Received: October 6, 2014
Accepted: October 8, 2014

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CrossRef Link

<http://dx.doi.org/10.4314/ambr.v1i4.6>

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Dementia is described as a progressive neurological disorder that can produce cognitive decline and behavioral and neuropsychiatric symptoms with disease progression. Given that dementia is an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform every day activities, people who are diagnosed with dementia can ultimately be placed on either typical or atypical antipsychotic medications to manage the onset of behavioral and neuropsychiatric symptoms.¹⁻³ Dementia is caused by damage to brain cells which interferes with the ability of brain cells to communicate with each other. When brain cells cannot communicate normally, thinking, behavior and feelings can be affected and this impacts the distinct regions responsible for different functions such as memory, judgment and movement. While antipsychotic medications can be effective in minimizing these disturbances, they are also well known to be associated with an increased risk of mortality resulting from infections or cardiovascular related occurrences in the elderly population. Alzheimer's disease accounts for 60 to 80 percent of cases. Vascular dementia, which occurs after a stroke, is the second most common dementia type. Anything that damages blood vessels anywhere in the body can damage blood vessels in the brain, depriving brain cells of vital food and oxygen. Blood vessel changes in the brain are linked to vascular dementia. However, conditions such as thyroid problems and vitamin deficiencies can cause symptoms of dementia but these may be reversible. Cerebral vasculitis responds to aggressive treatment with immunosuppressive drugs. In rare cases, treatable infectious disorders can cause dementia. Some drugs, vitamin deficiencies, alcohol abuse, depression, and brain tumors can cause neurological deficits that resemble dementia. Most of these causes respond to treatment. In a healthcare administration

setting providing care for the elderly, the premise is to combine the use of cognitive enhancers (e.g. a cholinesterase inhibitor such as donepezil, galantamine and rivastigmine and antagonists of the N-methyl-D-aspartate (NMDA) receptor, such as memantine, **Figure 1**) with one-on-one therapy in order to have proper compliance and modulation of the dose of the antipsychotic medications prescribed within this special population. A cholinesterase inhibitor is a cognitive enhancer that is used to manage the cognitive decline that can be associated with dementia. Memantine is a noncompetitive antagonist of the NMDA receptor (**Figures 2**) that is thought to have neuroprotective effects for the management of dementia.^{4,5} Memantine is used to treat the symptoms of Alzheimer's disease, a condition that slowly destroys the memory and the ability to think, learn, communicate and handle daily activities. Memantine is in a class of medications called NMDA receptor antagonists that works by decreasing abnormal activity in the brain. Memantine may improve the ability to think and remember or may slow the loss of these abilities in people who have AD. However, memantine will not cure AD or prevent the loss of these abilities at some time in the future. The appropriate management of dementia is a complex process that requires the initiation of intervention that are designed to offer optimal therapeutic benefits for patients and avoid any potential for harm. Such can be managed by a one-on-one caregiver contact and can include the adoption of psychosocial interventions that can include redirection or multisensory stimulation.⁶ The use of antipsychotic medications can present with negative side effects, and researchers and providers are continuously striving to find alternative treatments or modalities that will remove or minimize these potential harmful effects on elderly patients.⁷ Dementia is recognized as a major public health concern because of the

manifestations of the illness, the significant caregiver burden, and the associated financial costs.^{8,9} Before individuals reach the final stage of the disease, they can experience and be faced with the complete loss of capacity to engage in social functioning, diminished intellectual functioning, and language skills and hence may become unable to perform the normal activities of daily living and become functionally impaired when it comes to performing the key activities of life.¹⁰ Besides the development of cognitive and functional impairments, individuals with a diagnosis of dementia can begin to display inappropriate behaviors that may ultimately require constant supervision in order to avoid self-harm or harm to others.¹¹ The presence of agitation aggression, and combativeness can cause significant distress for caregivers and support staff, further demonstrating the importance of the requirement of the effective treatment of dementia.¹¹

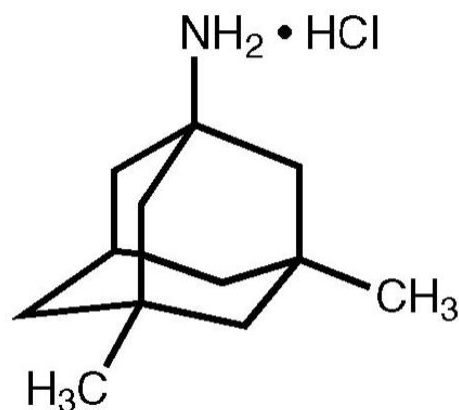


Figure 1: Namenda® (memantine hydrochloride) is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula: The molecular formula is C₁₂H₂₁N·HCl with the structure shown above and the molecular weight is 215.76. Memantine HCl occurs as a fine white to off-white powder and is soluble in water.

To manage the cognitive decline, dementia patients are typically placed on a cholinesterase inhibitor which serves to manage cognitive decline via the inhibition of acetylcholinesterase, the enzyme that is responsible for the hydrolysis of the

neurotransmitter acetylcholine.^{10,12,13} The changes that can be observed cognitive capacity are assessed with standardized inventories such as the Mini-Mental State Examination.¹⁴⁻¹⁶

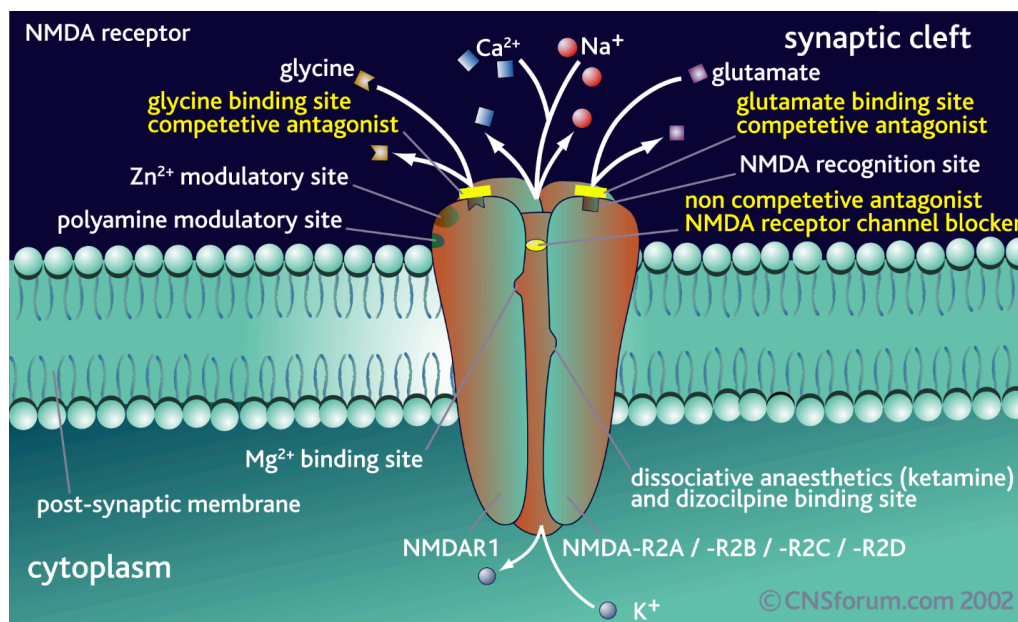


Figure 2: Depicting the mechanism operative for an NMDA antagonist. The NMDA receptor can be modulated by a number of antagonists, including competitive antagonists at the glycine and glutamate binding sites and non-competitive NMDA receptor channel blockers. Since NMDA receptor activation is dependent on the binding of both glycine and glutamate, the binding of an antagonist at either of these sites prevents activation and opening of the channel.

There is lack of awareness and understanding of dementia in most countries, resulting in stigmatization, barriers to diagnosis and care, and impacting caregivers, families and societies physically, psychologically and economically. One possible avenue towards reducing the amount of prescribed antipsychotic medication is one-on-one therapy. Recent evidence suggests that implementation of one-on-one caregiver contact can reduce neuropsychiatric symptoms and verbally disruptive behavior in dementia.¹⁷ However, while one-on-one contact appears promising, the effect of one-on-one caregiver contact on possible

reductions in prescribed antipsychotic medication in patients with dementia has not been explored. Additionally, NMDA antagonists represent a second avenue for reducing the amount of prescribed antipsychotic medication. NMDA antagonists block the glutamate receptors in the brain, which is beneficial in dementia because glutamate can become a neurotoxin in dementia.¹⁸ While one-on-one caregiver contact and NMDA antagonists represent promising areas towards reducing antipsychotic medications prescribed to elderly patients with dementia, no studies to date have explored the possibility that a co-therapy of one-on-one caregiver contact

might be associated with a reduction in prescribed antipsychotic medication. Veterans represent an important population for study because veterans in the United States (and undoubtedly globally) are aging, and thereby increasing pressures on the helping sciences to find solutions to ameliorate unnecessary suffering, morbidity, and mortality associated with prescribed antipsychotic medication for dementia.^{18,19} This holds universally and applies to the aging population. Memantine is considered to be an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) type of glutamate receptors (**Figure 1**) that is located throughout the brain. Glutamine is the primary excitatory amino acid in the central nervous system and is viewed to be the contribution to the pathogenesis of Alzheimer's disease by the overstimulation of numerous glutamate receptors that can produce excitation. Memantine binds to the intra-pore magnesium site and serves to function as an effective receptor blocker. Many dementias are progressive, meaning symptoms start out slowly and gradually get worse. So for the caregiver, if a person is experiencing memory difficulties or other changes in thinking skills, this should not be ignored. A prompt professional evaluation may detect a treatable condition. And even if symptoms suggest dementia, early diagnosis allows a person to get the maximum benefit from available treatments. Dementia, a progressive neurodegenerative disease can be overwhelming not only for the people who have it, but also for their caregivers and families. There is lack of awareness and understanding of dementia in most countries, resulting in stigmatization, barriers to diagnosis and care, and impacting caregivers, families and societies physically, psychologically and economically. With progression of the disease there is the potential development

of neurological and psychiatric disturbances.

Parkinson's disease (PD) has a multitude of non-motor symptoms including psychosis, cognitive impairment and dementia, mood disturbances, fatigue, apathy, and sleep disorders. Psychosis and dementia, in particular, greatly affect quality of life for both patients and caregivers and are associated with poor outcomes. Current treatments for PD dementia are mostly derived from those utilized in Alzheimer's disease, focusing mainly on cholinesterase inhibitors and memantine. Antipsychotic medications can be initiated in elderly patients with these symptoms but initiation must be based on a risk versus benefit assessment since antipsychotic medications have the potential to increase the risk of mortality and infection in this vulnerable population. There exist a degree of complexity in the relationship between dementia and depression in terms of definitions, epidemiology, related concepts, treatment, and emerging biomarkers.^{20,21} Damiani et al²¹ reviewed the applicability of dementia clinical guidelines to older patients, to patients with one or several comorbidities and concluded that dementia clinical guidelines poorly address treatment for older patients with comorbidities, regardless of their quality hence questioning the application of modern clinical practice. This raises the need for more research to assess wellness and cognitive deficits.

The combined use of cognitive enhancers in the form of a cholinesterase inhibitor and memantine along with caregiver one-on-one contact (e.g. multisensory stimulation or redirection) has the potential to decrease antipsychotic medication burden as well as the harm^{8,22}. The various cholinesterase inhibitors have similar effects on memory and cognitive function. So the decision about what medicine to use may be based on side effects, dosing schedules and ease

of use, individual response to a particular medicine, or other factors. Additional information can be obtained from the US based National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov) and the National Institute on Aging Alzheimer's Disease Education and Referral Center (www.nia.nih.gov/alzheimers) as well as from respective governmental health departments and from the World Health Organization (WHO) and Alzheimer's Disease International publications as listed and found in the following website: (http://www.who.int/mental_health/publications/dementia_report_2012/en/). The set of WHO reports are expected to facilitate governments, policy-makers, and other stakeholders to address the impact of dementia as an increasing threat to global health, an outcome that is anticipated to stimulate promotion of the awareness of dementia as a public health and social care priority worldwide. It is of paramount importance for physicians, caregivers, nurses, pharmacists and other public healthcare professionals in order to produce evidence and recommendations to not only strengthen patient-centered clinical practice but to provide longitudinal studies, aimed at detecting the effectiveness of treatment of dementia in patients with varying comorbidities.

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