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The Potential Value of Early Long-Term use of Memantine to Delay the Onset of Alzheimer's Dementia in Genetically Loaded High Risk Individuals to Develop Alzheimer's Dementia with and Without Cardiovascular Risk Factors.

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Abstract:

Memantine is NMDA (N Methyl D Aspartate) antagonist used to manage dementia, it works by blocking the glutamate receptors that stimulate excito-toxic neuronal death that results from excessive calcium influx into the neurons which in turn causes mitochondrial suffocation and neuronal death. Memantine is an uncompetitive, low affinity, open-channel blocker that reduces the glutamate induced overstimulation of the receptors that results in neuronal damage. It is unlike potential neuroprotective agents that block virtually all NMDA receptor activity including blockade of those essential for normal neuronal functioning.

On the other hand, the pathology of dementia we are tackling here appears several years and may be decades earlier in structural and functional MRI studies before the development of the full-blown clinical picture of Alzheimer's Dementia. The use of Meantime in this paper is targeting the excito-toxic etiology mainly and the development of Alzheimer's Dementia. We used the term and definitions of critical numbers in a synonymous way to talk about brain reserve and to hypothesize the potential mechanism of Memantine in delaying the onset of symptoms of Alzheimer's Dementia if used as a monotherapy irrespective of other pathologies such as the neurofibrillary tangles and plaques formation. Meanwhile, in the same hypothesis we left a room for using memantine and other disease modifying agents to be combined and used to tackle more than one etiological factor in those individuals with genetic risk to develop Alzheimer's Dementia with and without cardiovascular risk factors.

The current thinking of health authorities around allocating resources might change dramatically if this hypothesis is tested and proved. This testing will require the suggested randomized clinical trials mentioned below to be carried out. The global financial burdens of managing established dementia cases are heavy with the direct and indirect costs. All of these costs are now growing exponentially with the growing population of the elderly with longer life spans associated with better health care. In fact, if left uncurbed, the economic cost of caring for Alzheimer's Dementia patients could consume the entire gross national product of the USA by the middle of this century.

One already existing way of reducing the costs of managing Alzheimer's Dementia is not approving reimbursement of medications without a Mini mental state examination (MMSE) score low enough to diagnose Dementia in order to avoid "unnecessary" or "not evidence-based prescribing" of Alzheimer's Dementia medications and finally to reduce national expenditure on Dementia management. This could change if our hypothesis is proved correct to allow prescribing Memantine – as monotherapy or combined with disease modifying agents - in the genetically loaded high risk individuals with and without cardiovascular risk factors before a full-blown picture of dementia. To be able to spot, measure and follow up this delay in the development and progression of the biological radiological markers in non-symptomatic high risk individuals we need to do clinical cognitive assessments, structural radiological and functional radiological periodic measurements for the radiological markers for a sufficient period of time probably 5 to 10 years follow up.

above hypothesis is tested and found to be correct, the commencement of prescribing Memantine as a monotherapy or in combination with other agents will not depend only on the clinical picture in a cross sectional assessment of established Dementia cases, or presence of symptoms of mild cognitive impairment (MCI). It will depend on presence of genetic risks detected earlier with and without cardiovascular risks and the presence of radiological structural and functional markers correlated with clinical cognitive assessments that will judge the degree of delay in the progression of the disease with Memantine.

Discussion

Symptoms of dementia have been described as progressive and irreversible for decades once the disease has been diagnosed. Do we have a chance to intercept the molecular changes early before individuals at high risk become clinically symptomatic patients?

As we now know - to an extent - the reason for this irreversibility is not intervening early enough to intercept the pathoetiological processes causing dementia. At the time of diagnosis, many neurons are already affected by the pathologies with subsequent brain substance loss and reduced brain reserve. Even years earlier certain brain region will show progressive atrophy and reduction in function as evidenced by functional and structural MRI before the emergence of the clinical symptoms.

Now we have the means to suspect that some individuals have high possibility to develop dementia based on genetic testing more than other individuals.
Can those who are tested and found to be genetically loaded for dementia or with less protective genetics with and without vascular risk factors benefit from the "early" and "long term" use of Memantine alone or in combination with other supplements or disease modifying agents? This is the core question of this hypothesis that needs to be tested.

It is important to mention here unlike the cholinesterase inhibitors, Memantine is a neuroprotective medication. Memantine is effective in the treatment of both mild and moderate-to-severe Alzheimer's disease and possibly vascular dementia (multi-infarct dementia). Given the high comorbidity between Alzheimer's disease and vascular dementia, the use of memantine might play a crucial role if used with those individuals with multiple risks to develop Alzheimer's disease (those who are genetically loaded with and without vascular risk factors).

The focus of this paper is to consider early and long-term use of Memantine with or without other disease modifying medications or supplements in those individuals who are at higher genetic risk to develop dementia by slowing down the decline in the brain reserve caused by the excite-toxicity and delaying the progression of the structural and functional radiological changes that appear decades earlier before it gets translated into clinical picture of dementia. This timely use theoretically will subsequently delay the decompensation of the brain due to enhanced cognitive reserve. In a later stage we can test this hypothesis on those with vascular risk factors only.

Many individuals show radiological markers before the full-blown clinical picture of Alzheimer's disease. It might be too late to wait and not to use a medication such as Memantine with or without disease modifying agents until radiological markers have appeared and progressed eroding the brains in those high-risk individuals to develop dementia.

With the development of medications with different mechanisms of action to tackle the different pathologies, we might have a chance to intervene earlier and we need to test this hypothesis.

If the inevitable is highly likely to happen as evidenced by existing genetic testing that might be compounded by cardiovascular risks especially if radiological markers are indicative of ongoing pathology of dementia, why wait so long until the number of
neurons functioning in the brain is below the critical number of neurons necessary to function without dementia symptoms.

In the slow progressive pathoetiological process of developing dementia, some brain neurons affected by Alzheimer's disease pathology can initially function in a dysfunctional way due to the presence of Dementia pathology, these are the ones that could be the target for a disease modifying agent. The second type of neurons are neurons that are affected by excitotoxicity and are functioning partially initially normally but due to ongoing excito-toxic effects and the oxidative processes of aging these neurons become affected and eventually are lost. By losing the second types neurons, our brains lose more brain reserve. This second type of neurons could be the target of Memantine in an attempt to enhance the brain reserve.

The combination of these two types of neurons including their mere number and summative level of functioning can give an idea about the brain reserve of this individual. Controlling the pathologies that influence these neurons can create a bigger brain reserve of a particular individual "individual specific brain reserve". The higher the brain reserve – referring to the individual differences in the anatomic substrate -, the better the cognitive reserve – referring to differences in the flexibility or adaptivity of cognitive networks or the ability of some individual brains to function better than others in the presence of brain pathology. The term cognitive reserve also describes resistance to the deterioration of cognitive functions in the dementias and other degradation of brain substance. Brain decompensates when brain reserve declines due to the progression of the dementia pathologies mentioned above and this would be followed by declining cognitive reserve then dementia clinical symptoms unfold.

As long as there is enough cognitive reserve, clinical symptoms of Dementia will not appear as fast, but with the accumulation of different brain pathologies including the neurofibrillary tangles, amyloid plaques, vascular insults and death of neurons by excitotoxicity and other reasons, quantitative brain reserve declines and different individuals will decompensate according to their individual cognitive reserve then clinical symptoms of dementia will unfold.

I hypothesize that, by reserving structure of the percentage of the brain neurons that die by excitotoxicity, we can delay the loss of brain reserve and subsequently help delaying the decompensation of the brain by summative brain insults and pathologies that finally result in dementia. The earlier to start this intervention the

better the outcome might be by delaying the onset of dementia.

Some of the acute clinical improvements of patients suffering from dementia following being managed by Memantine 20 mg daily include temporary improvements in some of the dementia symptoms, these improvements happen despite relatively short period of treatment. These acute improvements of some dementia symptoms when memantine is used, reflect molecular adjustments in viable neurons that are neither dead nor functioning normally but rather functioning in a dysfunctional way and those neurons are the target of Memantine when it is used in acutely symptomatic dementia patients in a relatively short period of management of several weeks.

This makes us think that, when the fluctuations of symptoms' severity tend to settle towards improvement with relatively short period of memantine treatment this means on molecular neuronal level Memantine can tip acutely the balance positively in these dysfunctional neurons to be functional or more functional. These are the dysfunctional percentage due to the excitotoxicity and they become more functional by reducing the effect of excitotoxicity that is noted clinically. This only slows down the dementia process until the brain decompensates due to reduced brain reserve resulting in reduced cognitive reserve. The temporary acute improvement in dementia symptoms is clinically noted because the brain reserve or the critical number of functional neurons increased not quantitatively but qualitatively in comparison to the number of dysfunctional neurons.

In other words, the two numbers (number of functional neurons and dysfunctional neurons) were very close to the extent that, memantine acute use made a difference clinically when both numbers were critical. So, the acute molecular effect of memantine could be observed clinically until brain decompensation occurs with the progression of the disease due to increase in the number of dysfunctional neurons compared to the number of the functional neurons.

Another example about the relevance of critical numbers of functional neurons and dysfunctional neurons but this time it is the chronic example of the progression of vascular insults in a group of patients with neurofibrillary tangles and amyloid plaques. This gradual progression of brain insults which further causes progression of dementia in a brain already riddled by Alzheimer's disease pathology could be attributed to decrease in functioning brain neurons (brain reserve) due to the vascular pathology and finally the onset of dementia develops in each individual according to the individual's cognitive reserve due to losing neurons below the "critical number" of neurons required for the brain to function normally Irrespective of the pathology that is causing loss of neurons (causing the brain reserve to decline). So, it is the number of the lost brain neurons and their rate of loss that decides the onset of symptoms of dementia. Appling this on specific locations in the brain and overall brain is important. The above explains some postmortem findings such as brains with extensive neurofibrillary tangles and amyloid plaques are found in individuals who did not suffer from Dementia symptoms in their life and other individuals with Dementia had less post mortem pathology. So, in the first group, and despite the extensive dementia pathology, cognitive reserve was high so those individuals did not develop Dementia and the second group despite the less pathology Dementia developed as their cognitive reserve was less.

The examples mentioned above are mentioned to clarify the idea that by using Memantine we can increase cognitive reserve. This time with Memantine used in individuals who are more likely to develop Dementia will hopefully on molecular level and subsequently clinically will delay the clinical onset of symptoms and will prolong the time lived with no/minimal symptoms and hopefully the critical number of functioning neurons required for the brain to function normally will be reserved longer in those individuals who will use Memantine early enough compared to those who will use it only when they are already symptomatic.

If theoretically Memantine is used earlier in groups of individuals with the risk profile mentioned above, and before being symptomatic, these acute changes on molecular level will not be translated into clinical improvements as those individuals are already having enough functional neurons in relatively significant numbers in the brain hence those individuals are asymptomatic and the disease is progressing yet silently. This does not mean that, the earlier use of memantine is not creating more brain reserve silently when used earlier by reducing the effects of excitotoxicity and as a result creating more cognitive reserve in brains with slow progressive dementia pathology. This is hopefully will help delaying brain decompensation and delaying the onset of dementia.

The general fluctuation of dementia symptoms in the diagnosed dementia cases with the established pathology reflects having dysfunctional brain neurons very close to the critical number of neurons required by the brain to show more symptoms of dementia because the brain reserve and subsequently the cognitive reserve have reached a critical level. The fluctuations of acute dementia symptoms happen in parallel with the fluctuations of the number of functional neurons. A simple infection or urinary tract infection (UTI) might cause delirium for instance in those patients with dementia because the brain reserve is very critically low, same infection might not cause delirium at all in same patient years earlier as their brain reserve was better with less brain pathology. Treating the UTI helps delirium to be cleared as functional brain neurons becomes more than the dysfunctional neurons.

Chronic excitotoxicity in Alzheimer's' disease. Along with other several detrimental factors, there is evidence for chronic excitotoxicity in Alzheimer's disease which may be driven by multiple complex factors including the sensitization of NMDA receptors, a decrease in glutamate reuptake capacity (intraneuronal) and increase in glutamate release (extra-neuronal). Also in Alzheimer's disease there is decrease activity in excitatory amino acid transporter 2 (EAAT2) which results in increased extra-synaptic glutamate which causes excitotoxicity (due to reduce reuptake).

Role of structural and functional MRI in evaluating the hypothesis / Neuroimaging studies of cognitive reserve. The following are just suggested examples and are not an exhaustive list for the possible tests that could be used to examine the hypothesis.

Hippocampal measures especially hippocampal atrophy rate best discriminates mild cognitive impairment (MCI) from controls.

Whole brain atrophy rate discriminates Alzheimer's disease from Mild cognitive impairment. Regional measures of hippocampal atrophy are the strongest predictors of progression of MCI to Alzheimer's disease.

Resting regional cerebral blood flow (rCBF) measurement can serve as a surrogate for AD pathology says one of the references used in this paper. The explanation is that, specific (rCBF) changes in AD pathology because (rCBF) becomes lower as the pathology advances.

The suggested studies to test this hypothesis are expected to be, prospective, comparative with relatively long term follow up of structural and regional brain functions including blood flow and/or oxygen utilization in two at risk / genetically loaded matched asymptomatic groups. One group is managed by Memantine with or without disease modifying agent and the control group without pharmacological intervention. Then to do base line assessment and further follow up every six, twelve, eighteen or twenty-four months. In these assessments we correlate the findings of functional and structural MRI with the cognitive findings in the two matched groups. If there is slowing down in the active group compared to the control group, then, there might be a very high possibility that the Memantine managed group might be less likely to develop the disease earlier compared to the control group. The reason would be the early and ongoing neuro-protective role of Memantine on the neurons and reduced excito-toxicity in comparison to the control group.

To further test the hypothesis a longitudinal prospective comparison trial could be conducted in two groups of patients with mild cognitive impairment (MCI) with medial temporal lobe atrophy, one group to be managed by Memantine and the control group not to be managed by memantine. If the Memantine group will develop the disease at a later stage compared to a control group without Memantine, that would be of further support to the hypothesis considering that, MCI is a closer stage to Alzheimer's dementia with pertinent radiological and cognitive findings, expectedly those individuals who are closer to decompensation - as the ratio between functional and dysfunctional neurons are very close- so, it would be easier to spot the change in the two groups tested.

The outcome of this work can pave the road to evidence-based practice to use Memantine in the future as a medication to slow down the development of dementia in genetically loaded at risk asymptomatic individuals with and without indicative structural and functional radiological findings and not only slowing down the progression of the disease in the diagnosed patients.
In critically appraising the hypothesis we need to consider some factors in testing this hypothesis. For instance, there are other reasons for increased cognitive reserve that need to be considered during matching the two comparative groups in these studies. These factors include and are not limited to Literacy, bilingualism and multilingualism, higher occupational and educational attainment, and engaging in leisure activities as those are associated with lower risk of incident dementia as these life exposure might enhance cognitive reserve.

Diet questionnaire is also an important factor in matching the two study groups as Martha et al, 2015. found that older individuals with APOE 4 variant gene who had once a week seafood diet or more had less Alzheimer's pathology compared to those with APOE 4 who did not have the same seafood dietary habits. The seafood consumption did not have same effect on the brain in individuals with no APOE 4 variant as the Alzheimer pathology was very minimal to pick up any differences.
Another challenging point is the difficulty to determine the exact percentage of the excitotoxicity contribution in the development of Alzheimer dementia compared to other pathologies.

Memantine if it is used in high risk individuals to develop Dementia who are asymptomatic compared with a normal group of people with no genetic risks to develop dementia may be equivocal with no apparent clinical differences in the short term meaning there is no symptom improvement simply because our active group of patients is genetically loaded yet asymptomatic and it might need decades for the symptoms to appear when their brain reserve declines enough to be symptomatic and subsequently the individual cognitive reserve declines below the critical level required for the brain to function with no dementia symptoms.

Another example that might make the picture clearer is Parkinson's disease and drug induced parkinsonism. In Parkinson's disease, dopaminergic neurons in the substantia nigra continue degenerating and patients becomes symptomatic when around 15 to 20% of neurons are only left. In drug induced extrapyramidal side effects EPSEs, they appear when around 80% of post synaptic dopaminergic receptors are blocked in the nigrostriatal pathway. So, irrespective of the pathology whether it is degeneration in Parkinson's disease or receptors blockade in EPSEs, the symptoms required roughly 80% dysfunction in the dopaminergic motor system. Can we apply the same on dementia, or can we say that, the percentage of the lost brain reserve that is required for patients to be symptomatic is – to an extent - independent of the pathology causing the decline in cognitive reserve. Based on that, and as excitotoxicity is a contributing factor in the development of dementia, can reducing excitotoxicity help delaying the onset of dementia even with not interfering directly with the process of forming the amyloid plaques and neurofibrillary tangles. This is a question that we need to answer.

Conclusion

Alzheimer's Dementia has multiple etiologies and one of them is excitotoxicity. Dementia symptoms appears when cognitive reserve is below a critical level required by the brain to function with no or minimal symptoms. The summative effect of these contributing pathologies affects the brain substrate (brain reserve) and this eventually is reflected on cognitive reserve (the ability of the brain to withstand brain insults before symptoms arise). Simply, by reducing excitotoxicity, we are taking one factor out of the etiological equation so that, if other pathologies remain active, it will take them longer time until dementia develops.

Brain reserve is "numbers" and "locations" of normally functioning neurons, using Memantine in high risk individuals can increase the brain reserve for those high-risk individuals if used before the development of the disease.

Using memantine in high risk individuals to develop dementia can reduce the global burden of the disease worldwide by delaying the

age of onset for the development of Dementia to an older age. This could be reflected in reducing the national health expenditure on Dementia and also will help older people to live healthier and longer with less health provision and less health providers around them which will be reflected in improving the quality of life (QoL) of the patients and their families.

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References

1. Neuroimaging of hippocampus atrophy in early recognition of Alzheimer's disease – a critical appraisal after two decades of research. Psychiatry research Neuroimaging 247:71-78. January 2016.
2. Senescence, prodromal dementia, electrophysiological biomarkers. Review article – journal of Neuroinformatics and Neuroimaging (2017) volume 2, issue 1. Juliana Dushanova.
3. The molecular basis of memantine action in Alzheimer's disease and other neurologic disorders: low- affinity non-compative antagonism. Lipton SA. Curr Alzheimer res, 2005.
4. MRI in the Practical Evaluation of Dementia: 'Beyond Exclusion' by Philip Scheltens
   View Philip Scheltens' presentation at the 8th International Conference on Alzheimer's disease and Related Disorders
5. Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. van Straaten EC, Scheltens P, Knol DL et al. Stroke 2003; 34: 1907-1912.
6. Wiesje M. van der Flier, PhD et al
   Stroke. 2005;36:2116
7. Neuroimaging and Early Diagnosis of Alzheimer Disease: A Look to the Future
   Jeffrey R. Petrella, MD, R. Edward Coleman, MD and P. Murali Doraiswamy, MD
   State of the Art article in Radiology 2003;226:315-336.
8. Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of the EADC
   G B Frisoni, P h Scheltens, S Galluzzi, F M Nobili et al.
   Journal of Neurology Neurosurgery and Psychiatry 2003;74:1371-1381 Oxford text book of old age psychiatry – 2nd edition.
9. Fish consumption, Brain Mercury, and Neuropathology in patients with Alzheimer's disease. Martha Clare Morris et al., JAMA, Feb 2 issue. 2015.