Deuterated dextromethorphan/quinidine for agitation in Alzheimer's disease

Rita Khoury*

Alzheimer's disease (AD) is the most common type of neurodegenerative disorder; it affects around 47 million individuals worldwide (Prince et al., 2013). AD rose from the 12th most burdensome disease in the United States in 1990 to the sixth in 2016 in terms of disability-adjusted life years (Alzheimer's Disease, Facts and Figures 2021). The burden carried by patients and their caregivers is substantially related to neuropsychiatric symptoms, notably agitation as the disease progresses. To date, there is no Food and Drug Administration (FDA)-approved treatment for agitation in AD. The American Psychiatric Association recommends pharmacotherapy in case of failure of non-pharmacological options. While antidepressants such as trazodone or citalopram can be used as first line agents, antipsychotics may be warranted in case of severe agitation. Antipsychotics carry however a black box warning regarding the increased risk of cerebrovascular events and mortality in patients with dementia. Hence, their use needs to be limited. Several agents are currently being investigated to fill the gap of finding a treatment for agitation in AD. Compounds in the pipeline include pimavanserin and brexpiprazole, both of which are antipsychotics. Newer "safer" compounds that are being studied include cannabinoid derivatives, and dextromethorphan/quinidine. Drug design is a long and expensive process. It is often associated with unexpected unfavorable tolerability and safety profile halting the development of a new product. Deuteration recently emerged as a new and cost-effective technique that aims at repurposing old medications and advancing their development in clinical trials to garner quick FDA approval. It consists of the selective replacement of hydrogen (protium) with deuterium, naturally occurring and stable isotope of hydrogen. This structural substitution increases the metabolic stability of the molecule and extends the metabolic half-life of the drug, improving its safety and tolerability (Schmidt, 2017). AVP-786 is the deuterated form of dextromethorphan/quinidine that emerges as a promising well-tolerated treatment option for agitation in AD. With two completed phase III trials investigating this compound, there is still insufficient evidence to obtain FDA approval of the deuterated form. The latest clinical evidence on dextromethorphan/quinidine and its deuterated form for this indication will be discussed herein.

Dextromethorphan/quinidine or AVP-923 (*Neudexta*): Neudexta or AVP-923 is a compound that is FDA approved for the treatment of pseudobulbar affect, a dysfunction of emotional expression characterized by involuntary outbursts of crying or laughing disproportionate or unrelated to mood, occurring in patients with various underlying neurologic disorders including multiple sclerosis. It is composed of 20 mg of dextromethorphan and 10 mg of quinidine sulfate. Only dextromethorphan is the active component in the central nervous system. Quinidine inhibits CYP2D6 hepatic enzyme that catalyzes the metabolism of dextromethorphan. Thus, coadministration of a small dose of quinidine with dextromethorphan decreases the metabolism of the latter, leading to an increase in the concentration of free dextromethorphan by 25-fold. Free dextromethorphan will then effectively reach the brain to exert its neurological and psychiatric effects (Pope et al., 2004).

In a unique 10-week phase II clinical trial (NCT0158440) in subjects with moderate to severe AD, dextromethorphan/quinidine (administered at the dose of 30/10 mg twice daily for 152 subjects) was associated with a statistically significant decrease in agitation as measured by the neuropsychiatric inventory-agitation and aggression scale, compared to placebo (127 subjects); $P < 0.001$. Adverse events demonstrated in this trial included falls (8.6% *vs.* 3.9% in placebo), diarrhea (5.9% *vs.* 3.1% in placebo), urinary tract infections (5.3% *vs.* 3.9% in placebo), and dizziness (4.6% *vs.* 2.4% in placebo). Serious adverse events occurred in 7.9% of those receiving dextromethorphan/quinidine compared to 4.7% of those on placebo. 11.2% of those receiving the drug discontinued the study compared to 7.1% of those receiving placebo (5.3% and 3.1% owing to adverse events, in the two groups, respectively). No significant impact on Qtc prolongation or cognition were shown.

Deuterated dextromethorphan/quinidine or AVP-786: Following the successful findings in the phase II trial with AVP-923, the FDA granted a fast-track designation to the deuterated sister compound, AVP-786 (**Figure 1**) to be directly investigated in phase III trials for the indication of agitation in AD. Deuteration of dextromethorphan/quinidine was shown to reduce the amount of quinidine needed to reach an effective plasma concentration of free dextromethorphan, thus reducing drug-drug interaction and cardiac side effects usually associated with quinidine. Aside from the pharmacokinetic alteration, deuteration of dextromethorphan was not shown to affect the selectivity and affinity for the receptors in the brain that are implicated in the neuropsychiatric effects .

The two completed phase III trials with AVP-786 showed contradictory findings. The full dataset from both studies is not published yet in any peer-reviewed journals. According to press releases from the pharmaceutical company (Avanir Pharmaceuticals), TRIAD-1 (NCT02442765) showed statistically significant effect of the experimental drug on decreasing agitation in a sample of 410 individuals with moderate to severe AD (with one of two doses used). TRIAD-2 (NCT02442778) failed however to replicate this finding in a similar population of 522 patients (Avanir pharmaceuticals press releases). Discrepancy in the findings can be explained by differences in the study design used: Researchers in TRIAD-1 adopted the sequential parallel comparison design that involves 2 stages of randomization to drug versus placebo. The first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo non-responders from stage 1 are re-randomized and included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences without increasing sample size (Boessen et al., 2012). TRIAD-2 however was a conventional parallel randomized controlled trial. This study design is known to require a larger sample size to enhance the likelihood to detect a change in

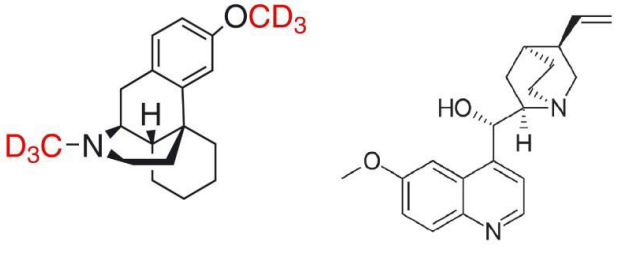

Figure 1 | **Representation of deuterated dextromethorphan/quinidine.**
From left to right, deuterated dextromethorphan and quinidine chemical structures are shown. Structures are adapted from Wikimedia Public Domain.

signal/outcome. Otherwise, both trials used the Cohen-Mansfield Agitation Inventory to assess for agitation severity as the primary outcome, whereas the initial phase II trial with dextromethorphan/quinidine used the neuropsychiatric inventory-agitation and aggression instrument.

Unfortunately, without the full publication of the methods, statistical analyses, and results of TRIAD-1 and 2, the scientific community is unable to further compare the two studies and critically analyze for discrepancies. Given the mixed results, the company is planning future phase III trials with the deuterated compound, per the FDA recommendation. Surprisingly, the conventional parallel design and not the sequential parallel comparison design model will be adopted in all future trials announced by Avanir pharmaceuticals.

Discussion: There are currently 7 other agents in clinical trials for this indication. Brexpiprazole (antipsychotic) at the dose of 2 mg only was associated with significant anti-agitation effect, compared to placebo (Grossberg et al., 2020). A confirmatory trial is currently in progress. Both AX-05, (a combination of dextromethorphan and bupropion) and nabilone (a cannabinoid derivative) were recently shown to have a significant anti-agitation effect in phase II trials. Phase III trials are thus planned (Cummings, 2021). Other products being investigated are lumateperone, pimavanserin, dronabinol, lithium and prazosin (Khoury et al., 2021).

Designing a successful clinical trial for a medication to garner regulatory approval for treating agitation in AD remains a big challenge. Agitation is a very heterogeneous disorder, across different stages of dementia. Researchers are recommended to objectively define agitation, using the latest International Psychogeriatric Association definition, as well as using standardized tools to measure agitation in clinical trials. The Cohen-Mansfield Agitation Inventory emerges as a practical instrument given its concordance with the IPA definition for agitation. Concomitant use of psychotropic medications including cognitive enhancers need to be addressed in the statistical analysis. Innovative study designs are encouraged to minimize placebo response, in addition to using technology-based interventions to enhance treatment adherence (O'Gorman et al., 2020).

From a pharmacodynamic perspective, dextromethorphan binds mainly to the sigma-1 receptors, N-methyl-D-asparate receptors, the α3β4 nicotinic acetylcholine receptors, the serotonin transporters and norepinephrine transporters. However, the exact role of these receptors in the pathophysiology of agitation is not well-understood. The neurochemical abnormalities associated with AD agitation include decreased acetylcholine and serotonin neurotransmission, leading to loss of cortical inhibition. In AD, neurofibrillary tangles (tau deposits) are seen early in the nucleus basalis of Meynert with cholinergic projections to several regions implicated in agitation including the cingulate cortex and amygdala. With the progression of the disease, there is a loss of serotoninergic neurons in the raphe and their cortical projections, notably to the frontal cortex and amygdala. Degeneration of serotonin pathways may also diminish cholinergic neurotransmission, exacerbating agitation (Rosenberg et al., 2015).

The biological effects of dextromethorphan on agitation would be better elucidated by including imaging procedures with ligand binding in future planned trials.

Although dextromethorphan/quinidine and its deuterated form do not share the same liabilities of antipsychotics, they are associated with a significant increased risk of falls, in addition to the risk of drug-drug interaction with medications that are metabolized by CYP2D6 such as antidepressants. Although, a small dose of quinidine is used in the deuterated form, physicians should be wary of the risk of QTc prolongation, when prescribed with other medications in poly-medicated older individuals.

Conclusion: Deuterated dextromethorphan/quinidine emerges as new investigational compound for agitation in moderate to severe AD. No solid recommendation can be made for this compound at this point, with only one successful phase III trial (TRIAD-1) and without the publication of the methods, analyses, and results of the completed trials in peer-reviewed journals. Further well-designed, large, robust trials with AVP-786 are additionally needed to ascertain the efficacy and safety of this compound for this highly needed indication in neuropsychiatry.

Rita Khoury*
Department of Psychiatry and Clinical Psychology; Saint George Hospital University Medical Center-Beirut, Lebanon. Adjunct Faculty, Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine, St. Louis, MI, USA
***Correspondence to:** Rita Khoury, MD, rita.khoury@idraac.org.
https://orcid.org/0000-0003-2481-6816 (Rita Khoury)
Date of submission: May 6, 2021
Date of decision: July 5, 2021
Date of acceptance: July 16, 2021
Date of web publication: September 17, 2021

https://doi.org/10.4103/1673-5374.324842
How to cite this article: *Khoury R (2022) Deuterated dextromethorphan/quinidine for agitation in Alzheimer's disease. Neural Regen Res 17(5):1013-1014.*

Open peer reviewers: *Kenji Hashimoto, Chiba University, Japan; Jolanta Dorszewska, Poznan University of Medical Sciences, Poland.*

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P-Reviewers: Hashimoto K, Dorszewska J; C-Editors: Zhao M, Liu WJ, Li JY; T-Editor: Jia Y