the PRUDENT prescriber

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ADLARITY: ARICEPT REDUX

New Delivery System: Expect Same Paltry Efficacy

In March 2022 the FDA approved Adlarity (donepezil transdermal system) to treat Alzheimer's dementia. Adlarity will be available this fall.

- Dosage: Adlarity is a once weekly patch and available in two strengths. Patches are designed to release either 5 mg or 10 mg of donepezil every day. Patients already on donepezil tablets may directly switch to the equivalent dose of the patch. Apply patch to back or thigh. The buttocks will work but have 15% less absorption than application to the back.

- Mechanism of Action: As an acetylcholinesterase inhibitor, (AChEI) Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its

hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementia process.

- Pharmacokinetics: There is a delay in absorption on initiating this transdermal system. There is a gradual increase in serum concentrations over a week. Following multiple doses of Adlarity, a steady state is reached within three weeks.

- Storage: Adlarity patches should be stored at 2°C to 8°C. Patches should be allowed to come to room temperature before opening and applying.

- Efficacy: There are no new efficacy trials utilizing the Adlarity patch. Adlarity was brought to market based on the original Donepezil tablet studies.

- Side-Effects:
    - Headache (15% chance)
    - Application site itching (9% chance)
    - Muscle spasms (9% chance)
    - Insomnia (7% chance)
    - Abdominal pain (6% chance)
    - Constipation (6% chance)

These results were obtained in an open label study of healthy volunteers who were treated with 5mg and 10 mg doses of Adlarity or 10mg donepezil tablets over 15 weeks. No surprise! The patch route of administration had less nausea and diarrhea. Patch subjects complained more of headache and muscle cramps than those consuming the tablets.

- Warnings and precautions:

1. Application site reactions
2. Adlarity may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block. Syncopal episodes have been reported in association with the use of Donepezil
3. Adlarity may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding

- Cost: Adlarity 5mg and 10mg patches are flat priced at $123/month. Donepezil 5mg and 10 mg tabs, $9-$12/ month. Orally disintegrating 5mg and 10mg tabs $13-$14/ month. 23mg tabs, $27/month.

25 YEARS OF ARICEPT

What do the studies and clinical experience over the last quarter of a century teach us? With the assistance of the St. Mary's Hospital librarian in Grand Junction, we performed a literature review specifically looking at the efficacy and safety of Donepezil in mild, moderate, and severe Alzheimer's disease in clinical studies done since Aricept was approved in 1997. We examined 84 studies total from the Medline and Embase databases.
Here is a synopsis of the larger, "better" designed studies:

Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2006.

- Results: 23 trials were included, involving 5272 participants. Most trials were of 6 months or less duration. For cognition there was a statistically significant improvement for both 5 and 10 mg/day of Donepezil at 24 weeks compared with placebo on the ADAS-Cog scale.

- Conclusion: The results show some improvement in global clinical state (assessed by a clinician) in people treated with 5 and 10 mg/day of donepezil compared with placebo at 24 weeks. There were significantly more withdrawals before the end of treatment from the 10 mg/day (but not the 5 mg/day) donepezil group compared with placebo which may have resulted in some overestimation of beneficial changes at 10 mg/day. A variety of adverse effects were recorded, with more incidents of nausea, vomiting, diarrhea, muscle cramps, dizziness, fatigue, and anorexia in the 10 mg/day group compared with placebo.

Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomized clinical trials. BMJ. 2005;331(7512):321

- Results: 22 trials met the inclusion criteria. Follow-up ranged from six weeks to three years. 12 of 14 studies measuring the cognitive outcome by means of the 70-point Alzheimer's disease assessment scale showed differences ranging from 1.5 points to 3.9 points in favor of the respective cholinesterase inhibitors.

- Conclusion: Due to flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's disease is questionable.

Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148(5):379.

- Result: 96 publications representing 59 unique studies were eligible for this review. Both cholinesterase inhibitors and memantine had consistent effects in the domains of cognition and global assessment, but summary estimates showed small effect sizes. Outcomes in the domains of behavior and quality of life were evaluated less frequently and showed less consistent effects. Most studies were of short duration (6 months), which limited their ability to detect delay in onset or progression of dementia.

- Conclusion: Treatment of dementia with cholinesterase inhibitors and memantine can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment of dementia.

Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ. 2003;169(6):557

- Results: This meta-analysis identified 16 trials with 5159 patients that were treated with a cholinesterase inhibitor; 2795 received a placebo.

- Conclusion: The numbers needed to treat (NNT) for 1 additional patient to benefit were 7 for stabilization or better, 12 for minimal improvement or better and 42 for marked improvement; the number needed to harm (NNH) for 1 additional patient to experience an adverse event was 12.

Long-term Donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. Lancet. 2004;363(9427):2105.

- Results: Cognition averaged 0.8 MMSE (Mini-Mental State Examination) points better and functionality 1.0 BADLS (Basic Activities of Daily Living) point better with Donepezil over the first 2 years.

- Conclusion: No significant benefits were seen with Donepezil compared with placebo in institutionalization or progression of disability. No significant differences were seen between Donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg Donepezil.

Efficacy of Acetylcholinesterase Inhibitors on Cognitive Function in Alzheimer's Disease. *Review of Reviews Biomedicines* 2021, *9*(11), 1689

- Results: A review of the systematic reviews yielded 1773 articles that evaluated the efficacy of AChEI on cognitive function and/or general condition and/or behavioral disturbances of patients with mild to moderate AD.

- Conclusion: AChEI showed very low efficacy in improving cognition in patients with mild to moderate AD. No improvements in behavioral disturbances were found. Few high-quality reviews provide clear evidence of the effects of AChEI on cognition, global change, behavior, and mortality.

Donepezil: A Review of Pharmacological Characteristics and Role in the Management of Alzheimer's Disease. Clinical Medicine Insights: Therapeutics 2010:2 771–788

- Conclusion: These authors provide a thorough review of the variety of scales that measure outcomes representing the four key symptom domains in Alzheimer's dementia: cognitive, functional, behavioral, and clinical global assessments of change. They conclude that Donepezil treated patients may improve cognitively and show global clinical improvement in all disease stages. Effect on behavioral and psychiatric symptoms of the disease is more controversial. Cost benefit data are limited and the impact of Donepezil on patient relevant outcomes remains poorly understood. They call for more research on clinically meaningful outcomes and treatment benefits that are favored by patients and their caregivers.

Meta-analysis of Randomized Controlled Trial's on the Efficacy and Safety of Donepezil, Galantamine, Rivastigmine and Memantine for the Treatment of Alzheimer's disease. Frontiers in Neuroscience May 2019, volume 13.

- Results and Conclusion: These authors provide a magnus opus with graphic figures of odds ratios that demonstrate minimal positive effects for Donepezil and others that significantly favor placebo in the realms of cognitive, functional, behavioral, and clinical global assessments.

- Phil's Thoughts: Their conclusions however don't jive with their data.

Disease state changes and safety of long-term donepezil administration in patients with Alzheimer's disease: Japan – Great Outcome of Long-term trial with Donepezil (J-GOLD). Psychogeriatrics 2018; 18:402–411

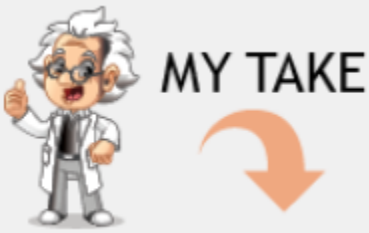
- Results and Conclusion: This is prospective observational study that followed 10,000 native Japanese with Alzheimer's dementia for as long as 48 months. The subjects of the study included dementia patients who received the drug for the first time (newly treated patients), as well as dementia patients who were already receiving the drug at the start of the study (continuously treated patients). The authors conclude, "Cognitive function decreased significantly after 24 months in

newly treated patients and after six months in continuously treated patients. The percentages of patients whose dementia severity improved or remained the same compared with baseline were 59.27% in 48 months in the newly treated patients and 57.09% at 48 months in the continuously treated patients.

- Phil's Thoughts: These results defy everything I know about the natural history of this disease. Then recall that the study was paid for by Eisai Co., the makers of Aricept in Japan, that there was no blinding, no control group and a significant drop out rate.

Bradycardia Due to Donepezil in Adults: Systematic Analysis of FDA Adverse Event Reporting System. Journal of Alzheimer's Disease 2021; 81(1): 297-307.

- Results and Conclusion: The authors from the University of South Florida mined the data from the FDA Adverse Event Reporting System (FAERS) specifically looking at the risk of bradycardia in patients who only took donepezil compared with the risk of those patients who took only over-the-counter medications, multiple arrhythmia drugs or other medications for Alzheimer's dementia. Patients administered donepezil were 4–11 times more likely to report bradycardia as an adverse event than patients administered memantine, galantine, and rivastigmine. When compared to a series of drugs that are commonly used to treat arrhythmias and have bradycardia as a side effect, bradycardia was found to be a more commonly observed adverse event in patients administered Do



- Please note my biases about Donepezil. I prescribed it only once under extreme duress. My geriatrician daughter-in-law (my guiding light in all things aging) has never prescribed Donepezil but has rescued several patients on Aricept from their bradycardias. My precious demented wife did well many days with trazadone, a little SSRI and a lotta love.

- Nonetheless, I did pick ten studies whose methods seemed to offer some hope for understanding Donepezil's effectiveness and side-effects.

- This entire body of research studies should be criticized for their short durations, their focus on assessment tools that often have little

relevance for the day to day lives of patients with dementia and their caregivers, and their frequent declarations that statistical significance is equivalent to clinical significance.

- I had trouble in interpreting the effect size of Donepezil in almost all these studies. Only the CMAJ study highlighted above talked about NNT. Most of the studies reported effect sizes that seemed minimal to nonexistent.

- There is no evidence that treatment with Donepezil in patients with Alzheimer's dementia is cost-effective.

- This literature review and recent communication with my geriatrician daughter-in-law upped my awareness of the significant potential of Donepezil to cause clinically important bradycardia.

- The natural history of Alzheimer's dementia with its prolonged downhill course but with its attendant short-term undulating better days and tougher days makes it difficult for researchers to understand cause and effect of drug interventions.

- The Alzheimer's Association that steam-rolled the FDA's approval of Aduhelm continues to recommend Donezepil. Unexpectedly UpToDate continues to recommend consideration of this drug for every Alzheimer's dementia patient. I simply do not understand how they can come to that conclusion.

- **I remain firm in my recommendation not to prescribe Donepezil or any of the AChEIs.**

Looking for previous versions of the Prudent Prescriber newsletter? Good news, 10 YEARS of monthly editions are now available on rmhp.org.

Prudent Prescriber
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