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# SIDE EFFECTS OF APPROVED ANTIDEMENTIVES

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***SUMMARY***

*The aim of this review is to describe side effects of five antidementives which are approved by the United States Food and Drug Administration (FDA); four acetylcholinesterase inhibitors and one glutamate - or N–metyl-D–aspartat receptor antagonist - memantine. The antidementives are well tolerated and undesired effects are rare; except hepatotoxicity of tacrine and gastrointestinal side effects of donepezil, rivastigmine, galantamin and tacrine that result from acetylcholinesterase inhibition. Nausea, diarrhea, vomiting, and weight loss are the most common side effects of the acetylcholinesterase inhibitors. Significant cholinergic side effects can occur in patients receiving higher doses; often they are related to the rate of initial titration of medication. Memantine is the first noncholinesterase inhibitor indicated for Alzheimer's disease. The side effects which may occur during the treatment with memantine are constipation, dizziness, headache and confusion. These effects if appears are mild end transient.*

***Key words:*** *Alzheimer's disease – donepezil – galantamine – memantine – rivastigmine - side effects - tacrine*

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## INTRODUCTION

Five antidementive drugs are approved by the United States Food and Drug Administration (FDA) for Alzheimer's disease (AD) (Agronin 2008, Folnegović-Šmalc et al. 2002, Mimica & Folnegović-Šmalc 2004). Three of them are acetylcholinesterase inhibitors (AChEI) approved for the treatment of mild to moderate AD and one of them for treatment of all three stages of AD (Jann & Small 2005, Agronin 2008). Memantine is approved for the treatment of moderate to severe AD, defined as an Mini Mental State Examination (MMSE) score of less than 15 (Lieberman & Tasman 2006, Agronin 2008).

The AChEI increase the levels of acetylcholin (ACh) in the brain, but they also can increase ACh levels in the periphery causing the potential side effects which include the increased secretion of gastric acid, increased bronchial secretions, vagotonic effects on the heart that can exacerbate bradyarrhythmias, and the potentation of the effects of succinylcholine in anesthesia (Agronin 2008). The most common gastrointestinal side effects (Müller & Fürstl 2001) related to cholinergic mechanisms include nausea, vomiting, anorexia and diarrhea (Yaari et al. 2008). Anorexia and weight loss may be clinically significant problems over the longer term which should be monitored and the medication must be reduced or discontinued to assess if appetite returns (Lieberman & Tasman 2006). The most common side effects of AChE inhibitors are shown on Table 1.

The side effects may be managed using slow titration and administration with food (Agronin 2008). When the side effects occur, they usually decrease after a few days or they may be relieved by maintenance of the present dose level, by omitting one or more doses or by temporarily decreasing dosage (Yaari et al. 2008). The procedure with side effects are shown on Table 2.

The initiation of treatment with AChEI should be avoided in individuals with active peptic ulcer disease, unstable bradycardia, acute pulmonary

disease or congestive heart failure, and may be appropriate when the latter medical conditions have been stabilized. Precautions with AChE inhibitors because of increasing central and peripheral cholinergic stimulation are shown on Table 3.

**Table 1.** Side effects of acetilcholinesterase inhibitors (AChEI)

| DRUG | SIDE EFFECTS |
|---|---|
| Tacrine | Nausea, vomiting, diarrhea, dyspepsia, myalgia, anorexia, dizziness, confusion, insomnia, rare agranulocytosis, reversible hepatotoxicity manifested by elevated transaminases |
| Donepezil | Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia, dizziness, abdominal pain, myasthenia, rhinitis, weight loss, anxiety, syncope |
| Rivastigmine | Nausea, vomiting, anorexia, dizziness, abdominal pain, diarrhea, malaise, fatigue, asthenia, headache, sweating, weight loss, somnolence, syncope. Rarely, severe vomiting with esophageal rupture |
| Galantamine | Nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain, dizziness, tremor, syncope |

According to Yaari et al. 2008

**Table 2.** What to do about side effects of antidementives?

| | |
|---|---|
| 1. | Wait, use slower dose titration, consider lowering dose, switching to a different agent or adding an appropriate augmenting agent; |
| 2. | If you are switching one AChEI to another because of side effects, stop the original agent and allow the side effects to subside before starting the new agent; |
| 3. | For patient with intolerable side effects, generally allow a washout period with resolution of side effects prior to switching to another cholinesterase inhibitor; |
| 4. | Many side effects cannot be improved with an augmenting agent. |

AChEI = acetilcholinesterase inhibitor According to Stahl 2005 and Agronin 2008

**Table 3.** Precautions with acetilcholinesterase inhibitors (AChEI) because of increasing central and peripheral cholinergic stimulation

| AChEI may: | |
|---|---|
| 1. | Due to increased gastric acid secretion increase the risk of gastrointestinal bleeding, particularly in patients with ulcer disease or those taking anti–inflammatories; |
| 2. | Produce bradycardia or heart block in patients with or without cardiac impairment; |
| 3. | Exacerbate asthma or other pulmonary disease; |
| 4. | Cause urinary outflow obstruction; |
| 5. | Increase risk for seizures; |
| 6. | Prolong the effects of succinylcholine – type muscle relaxants. |

According to Stahl 2005 and Lieberman & Tasman 2006

All AChEI can be taken safely in combination with the glutamate - receptor antagonist memantine (Agronin 2008). Memantine causes side effects due to excessive actions at N-metil-D-aspartat (NMDA) receptors. The side effects during the treatment with memantin have a low incidence and are well-tolerated (Stahl 2005). Reported side effects by patients treated with memantine were similar to that occurring in patients assigned to placebo (Lieberman & Tasman 2006).

The aim of this lecture is to describe side effects of five antidementives which are approved by the United State Food and Drug Administration (FDA); four acetylcholinesterase inhibitors and one glutamate - or N–metyl-D–aspartat receptor antagonist - memantine.

## TACRINE

Tacrine is a reversible AChEI which was the first one approved in 1992, for mild to moderate AD (Agronin 2008). Due to peripheral inhibition of acetylcholinesterase and peripheral inhibition of butyrylcholinesterase tacrine can cause gastrointestinal side effects. Central inhibition of AChE may contribute to nausea, vomiting, weight loss and sleep disturbances. Nausea, diarrhea, vomiting, appetite loss, increased gastric acid secretion, dyspepsia, weight loss, myalgia, rhinitis and rash are notable side effects. Dangerous side effects are liver toxicity and rare seizures (Stahl 2005). Tacrine is no longer widely used because induces liver transaminase elevations what does not happens with the newer AChEI (Agronin 2008). The possibility of hepatotoxicity requires constant monitoring of liver function tests during its prescribed use (Jann & Small 2005). Transaminases may be elevated within 6 to 12 weeks and reversed within 6 weeks of discontinuing medication. Patients may be able to tolerate tacrine if it is reintroduced, but it is now rarely prescribed (Lieberman & Tasman 2006). In Croatia it is not registered and due to this very rarely prescribed (Folnegović-Šmalc et al. 2006, Mimica 2007, Vuksan-Ćusa et al. 2007). If liver transaminase elevation occurs, the dose should be maintained or reduced. If tacrine is discontinued for longer than 4 weeks, the medication must be restarted at the initial dose of 10 mg four times a day with monitoring of liver enzymes. If gastrointestinal problems occur, tacrine can be given with food, but a decrease in drug bioavailability may occur (Jann & Small 2005). Weight gain and sedation are reported but not expected (Stahl 2005).

Due to the hepatotoxicity, tacrine fell out of favor and is generally no longer used (Yaari et al. 2008).

## DONEPEZIL

Donepezil is the second reversible AChEI that is FDA approved for treating mild, moderate and severe AD (Agronin 2008). Donepezil is highly selective for AChE versus butyrylcholinesterase (Jann & Small 2005). Peripheral inhibition of AChE can cause gastrointestinal side effects (Stahl 2005, Uzun et al. 2005). Central inhibition of AChE may contribute to nausea, vomiting, weight loss and sleep disturbances. Notable side effects are nausea, diarrhea, vomiting, appetite loss, increased gastric acid secretion, weight loss, insomnia, dizziness, muscle cramps, fatigue, depression and abnormal dreams. Donepezil may cause more sleep disturbances than some other cholinesterase inhibitors. To reduce insomnia donepezil is recommend to be used in daytime. Best augmenting agents for side effects are hypnotics or trazodone which may improve insomnia. Dangerous side effects are rare seizures and rare syncope. Weight gain and sedation are reported but not expected (Stahl 2005). Donepezil does not produce hepatotoxicity. Gastrointestinal problems with donepezil are dose-dependent. Patients with peptic ulcer disease or other gastrointestinal illnesses should be carefully monitored (Jann & Small 2005). Donepezil has no significant effects on liver function and no significant drug-drug interactions (Agronin 2008). Side effects are usually mild and transient, resolving during continued donepezil treatment without the need for dose modifications and did not result in significant dropout rate during clinical trials (Jann & Small 2005, PDR 2001). Clinicians typically use a 4 to 6 week dose increase with donepezil to minimize adverse side effects (Jann & Small 2005). Side effects occur more frequently in female patients and with advancing age (PDR 2001).

## RIVASTIGMINE

Rivastigmine, the third AChEI, is a reversible AChE and butyrylcholinesterase inhibitor approved from the FDA in 2000, for the treatment of mild to moderately symptoms of AD (Jann & Small 2005, Agronin 2008). Rivastigmin has an indication for dementia associated with Parkinson disease too (Agronin 2008). Rivastigmine is considered a second-generation type of AChEI based on its different pharmacological profile compared to tacrine and donepezil. Rivastigmine does not cause hepatotoxicity. Gastrointestinal problems can occur in a dose-dependent manner. Patients with peptic ulcer disease or other gastrointestinal illnesses should be carefully

monitored. Side effects were usually mild and transient and did not result in significant dropout rate during clinical trials. Reanalysis of the electrocardiograph (ECG) from the clinical trial revealed no significant differences between rivastigmine and placebo in heart rate and PR, QRS and QTc intervals. Drug interactions with rivastigmine have not been reported with digoxin, warfarin, diazepam or fluoxetine. A retrospective analysis of the clinical trials did not find an increase in adverse side effects in patients who received various medications, including β-blockers, antihypertensives and other drugs. It is highly recommended that food be given with rivastigmine (Jann & Small 2005).

Peripheral inhibition of AChE and peripheral inhibition of butyrylcholinesteraze can cause gastrointestinal side effects (Stahl 2005, Uzun et al. 2005). Central inhibition of AChE may contribute to nausea, vomiting, weight loss and sleep disturbances. Notable side effects are nausea, diarrhea, vomiting, appetite loss, increased gastric acid secretion, headache, dizziness, fatigue, asthenia, sweating. Rivastigmine may cause more gastrointestinal side effects than some other cholinesterase inhibitors, especially if not slowly titrated. Dangerous side effects are rare seizures and rare syncope. Weight gain and sedation are reported but not expected (Stahl 2005)**.** Rivastigmine may cause severe vomiting with esophageal rupture which may occur if rivastigmine therapy is resumed without re-titrating the drug to full dosing (Stahl 2005). The risk of side effects can be minimized with slow titration and administration with meals. The side effects do become less frequent over the course of treatment (Agronin 2008). Metabolism of rivastigmine is essentially extra–hepatic and is unlikely to have significant pharmacokinetic interactions. Adverse effects are primarily gastrointestinal and occurred in the high dose (6 - 12 mg/day) group. The FDA approval letter requested that the manufacturer do further analyses to better characterize these effects, especially weight loss and anorexia (Yaari et al. 2008).

Recently is developed rivastigmine transdermal patch witch may have the ability to reduce side effects (Cummings et al. 2007). Rivastigmine patch have an efficacy similar to the oral capsules of rivastigmine (Lefèvre et al. 2008). Nausea and vomiting seems to be linked to peak plasma concentration of the drug (Cummings & Winblad 2007). A transdermal patch of rivastigmine obtain a lower peak of concentration with less gastro – intestinal side effects (Salmon 2008). The target dose 9,5 mg/24 h rivastigmine patch provided similar efficacy like the highest rivastigmine capsule doses with three times fewer reports of nausea and vomiting (Winblad & Machado 2008). The skin tolerability profile of rivastigmine patch is generally good (Winblad et al. 2007a, Winblad & Machado 2008). The skin side effects included itch and shingles on the application area (Winblad et al. 2007a, Winblad et al. 2007b). The rivastigmine patch may sign the next generation of dementia treatment (Winblad & Machado 2008).

## GALANTAMINE

Galantamine is the fourth reversible AChEI (Agronin 2008). In 2001, galantamine is approved by the FDA for mild to moderate AD (Jann & Small 2005). Peripheral inhibition of acetylcholinesterase can cause gastrointestinal side effects (Stahl 2005, Uzun et al. 2005). Central inhibition of acetylcholinesterase may contribute to nausea, vomiting, weight loss and sleep disturbances. Notable side effects are nausea, diarrhea, vomiting, appetite loss, increased gastric acid secretion, weight loss, headache, dizziness, fatigue, depression. Dangerous side effects are rare seizures and rare syncope. Weight gain and sedation are reported but not expected (Stahl 2005). The side effects were mild and transient and did not produce a significant dropout rate during clinical studies (Jann & Small 2005). Ketoconazole, erythromycin, and paroxetine are concomitant medications that may potentially increase the levels of galantamine, although a dose reduction of galantamine is not always necessary; instead, closer patient monitoring is warranted (Agronin 2008). Rivastigmine does not produce elevations in liver transaminases or cause hepatotoxicity. Gastrointestinal problems can occur with rivastigmine in a dose-dependent manner. Patients with peptic ulcer disease or other

gastrointestinal illnesses should be carefully monitored (Jann & Small 2005). Adverse events were more frequent earlier in the course of treatment and during the dosage titration from 16-24 mg/day and higher (Yaari et al. 2008).

## MEMANTINE

In 2003, the FDA approved memantine for the treatment of moderate to severe AD (Jann & Small 2005). Memantine is currently the only FDA - approved glutamate - or NMDA-receptor antagonist for the treatment of AD. It is only one of two agents approved for moderate to severe AD (Agronin 2008). Memantine appears to be relatively well tolerated (Lieberman & Tasman 2006). Notable side effects are dizziness, headache and constipation (Stahl 2005, Uzun et al. 2005). Dangerous side effects included rares seizures. Weight gain and sedation are reported but not expected. Memantin must be use cautiously if co-administering with other NMDA antagonists such as amantadine, ketamine and dextromethorphan (Stahl 2005). Memantine can be used as monotherapy or can be safely combined with an AChEI. Initial sedation and/or confusion tend to be mild and transient in many patients (Agronin 2008). There are minimal drug-drug interactions with memantine (Yaari et al. 2008). Patient on combination therapy memantine-donepezil has fewer side effects than those on donepezil alone, particularly gastrointestinal side effects (Agronin 2008). Memantine does not produce hepatic transaminase increases or hepatotoxicity. Memantine is mainly renally excreted. Although data in renally impaired patients are not available, drug doses should be reduced in patients with mild to moderate renal impairment. Memantine is not recommended for patients with severe renal impairment (Jann & Small 2005). In general memantine is well tolerated (Yaari et al. 2008).

## CONCLUSIONS

Tacrine is no longer widely used due to its side effects profile. Cholinergic side effects generally occur early in the course of treatment with AChEI (donepezil, rivastigmine, galantamine) and are related to initiating or increasing medication. They tend to be mild and self–limited. Medications should be restarted at lowest doses after temporarily stopping. Patients tend to become tolerant to the adverse events rapidly. Rivastigmine patch because of clinical utility and patient acceptability can mark the next generation of dementia treatment. Memantine is well tolerated and is associated with very mild side effects. Generally speaking commonly used antidementives are well tolerated and safe.

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