

Dementia agents

Two small groups of symptomatic medicines for dementia: the cholinesterase inhibitors, which raise synaptic acetylcholine, and memantine, which blocks the open NMDA receptor channel. Their labels are explicit that neither group alters the underlying disease, and for the cholinesterase inhibitors the mechanism predicts almost every adverse effect worth knowing.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/dementia-agents>

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Quick revision

One Liner: These medicines treat symptoms. The regulatory labels say so in as many words, and a page written for families and students has to say so too.

1. Donepezil, rivastigmine and galantamine all work by inhibiting the enzyme that hydrolyses acetylcholine, so more transmitter survives at the synapse. [1][2][4]
2. The donepezil label states that there is no evidence that donepezil alters the course of the underlying dementing process. [1]
3. The memantine label is equally direct: there is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease. [3]
4. Gastrointestinal upset and weight loss are not incidental here; the galantamine label calls them a predictable consequence of its pharmacological properties. [2]
5. Cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. [2][1]
6. Additive bradycardia, which may result in syncope, has been reported when rivastigmine is combined with beta blockers including atenolol. [4]
7. An antimuscarinic prescribed for bladder symptoms, such as oxybutynin or tolterodine, works directly against a cholinesterase inhibitor. [4]
8. Memantine is excreted predominantly unchanged in urine, so anything that alkalinises urine reduces its elimination and raises plasma levels. [3]
9. Antipsychotics used for behavioural symptoms carry a boxed warning of increased mortality in elderly patients with dementia-related psychosis. [6]

Overview

1. Four drugs make up the treated part of dementia pharmacology, and only two mechanisms separate them. Donepezil is indicated for dementia of the Alzheimer's type, galantamine for mild to moderate dementia of the Alzheimer's type, and memantine for moderate to severe dementia of the Alzheimer's type. Rivastigmine is licensed in Europe for the symptomatic treatment of mild to moderately severe Alzheimer's dementia and, uniquely in this group, for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease. [1][2][3][4]
2. What the labels claim is narrow and worth quoting rather than paraphrasing, because families read pages like this one. The donepezil label says there is no evidence that the drug alters the course of the underlying dementing process, the galantamine label makes the same statement about galantamine, and the memantine label states that there is no evidence it prevents or slows neurodegeneration. The European rivastigmine text goes further in a practical direction: if after three months of maintenance treatment the rate of decline in dementia symptoms is not altered favourably, treatment should be discontinued. [1][2][3][4]
3. The cholinesterase inhibitors are a good example of a class whose adverse effects can be predicted from first

principles. Raising acetylcholine everywhere, not only in the cortex, produces gut stimulation, vagal slowing of the heart, bronchial and bladder effects, and increased gastric acid. Memantine sits apart: it acts on glutamatergic rather than cholinergic transmission, is cleared by the kidney rather than the liver, and its commonest reported adverse effects are dizziness, headache, confusion and constipation rather than the cholinergic diarrhoea of the other three. [4][2][3]

Classification and drug examples

Intro: Two mechanisms, and the split is clean. Everything on the left of this classification shares one enzyme target and therefore one adverse-effect profile; the single agent on the right shares almost none of it.

1. Name: Cholinesterase inhibitors

1. Note: Three agents that increase the concentration of acetylcholine by reversibly inhibiting its hydrolysis. They differ in half-life, in route, and in how they are cleared, but their toxicity is largely interchangeable.

1. Name: Donepezil

Aricept

1. Route: Oral

1. Note: Postulated to exert its therapeutic effect by enhancing cholinergic function, achieved by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Its elimination half-life of about 70 hours is by far the longest in the group. [1]

2. Name: Rivastigmine

Exelon

2. Route: Oral and transdermal patch

2. Note: An acetyl- and butyrylcholinesterase inhibitor of the carbamate type, and the only member available as a patch. It forms a covalently bound complex that temporarily inactivates its target enzymes, and it is the only agent here licensed for dementia in Parkinson's disease. United States patch labelling carries the same disclaimer as the rest of the class, stating there is no evidence that rivastigmine alters the course of the underlying dementing process. [4][7]

3. Name: Galantamine

Razadyne

3. Route: Oral

3. Note: A tertiary alkaloid described in its United States prescribing information as a competitive and reversible inhibitor of acetylcholinesterase. Its label reports a dose-related increase in the risk of syncope, and excess deaths in two trials conducted in mild cognitive impairment. [2] [1][2][4]

2. Name: NMDA receptor antagonists

2. Note: A single agent with a wholly different target, reserved for more advanced disease and carrying none of the cholinergic burden.

Name: Memantine

Namenda

Route: Oral

Note: A low to moderate affinity uncompetitive open-channel NMDA receptor antagonist that binds preferentially to NMDA receptor-operated cation channels. Hepatic cytochrome P450 does not play a significant role in its metabolism. [3] [3]

Mechanism of action

Summary: Cholinesterase inhibitors slow the breakdown of acetylcholine released by surviving cholinergic neurones, which is why their benefit is symptomatic and depends on neurones that are still working. Memantine instead blocks the open channel of the NMDA receptor, on the hypothesis that persistent activation of that receptor by glutamate contributes to the symptoms of Alzheimer's disease.

Target: Acetylcholinesterase and butyrylcholinesterase, and the NMDA receptor-operated cation channel

Cidal Static: Symptomatic only; no label in this class claims an effect on the underlying disease process

Kill Kinetics: Effect persists only while the drug is present, and is reassessed against the observed rate of decline

1. Step: 1

1. Title: Acetylcholine is preserved rather than replaced

1. Detail: Rivastigmine is described as facilitating cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. That qualifier carries the whole limitation of the class: the drug can only make better use of transmitter that surviving neurones still release. [4]

2. Step: 2

2. Title: Reversible inhibition of acetylcholinesterase

2. Detail: Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function, accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase.

Galantamine is characterised as a competitive and reversible inhibitor of the same enzyme. [1][2]

3. Step: 3

3. Title: Dual enzyme inhibition by the carbamate

3. Detail: Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase, forming a covalently bound complex that temporarily inactivates them. In cerebrospinal fluid from fourteen treated patients, inhibition of butyrylcholinesterase activity was similar to that of acetylcholinesterase. [4]

4. Step: 4

4. Title: The same enzyme is inhibited outside the brain

4. Detail: Nothing confines these drugs to cortical synapses. The resulting peripheral cholinergic excess produces the gastrointestinal effects, the vagotonic slowing of the sinoatrial and atrioventricular nodes, the bronchial caution in asthma and obstructive pulmonary disease, and increased gastric acid secretion. [2][4]

5. Step: 5

5. Title: Open-channel blockade of the NMDA receptor

5. Detail: Persistent activation of central NMDA receptors by the excitatory amino acid glutamate has been hypothesised to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to act as a low to moderate affinity uncompetitive open-channel antagonist binding preferentially to NMDA receptor-operated cation channels, and its label adds that there is no evidence it prevents or slows neurodegeneration. [3]

Major clinical uses

1. Drug: Donepezil

1. Organism: Not applicable

1. Indication: Dementia of the Alzheimer's type

1. Line: first-line cholinesterase inhibitor

1. Note: The broadest cholinesterase inhibitor indication of the three, and the longest half-life, which makes once-daily administration straightforward. The label attaches no claim about the course of the disease. [1]

2. Drug: Galantamine

2. Organism: Not applicable

2. Indication: Mild to moderate dementia of the Alzheimer's type

2. Line: alternative cholinesterase inhibitor

2. Note: Its licence stops at moderate disease. Two randomised placebo-controlled trials of two years' duration in subjects with mild cognitive impairment recorded thirteen deaths among 1,026 subjects on galantamine against one among 1,022 on placebo, which is why the drug is not used outside its indication. [2]

3. Drug: Rivastigmine

3. Organism: Not applicable

3. Indication: Symptomatic treatment of mild to moderately severe Alzheimer's dementia

3. Line: alternative cholinesterase inhibitor, oral or transdermal

3. Note: The patch formulation matters where swallowing is difficult or where a carer administers treatment. European labelling requires that therapy is started only if a caregiver is available who will regularly monitor the patient's intake of the medicine. [4]
4. Drug: Rivastigmine
4. Organism: Not applicable
4. Indication: Symptomatic treatment of mild to moderately severe dementia in idiopathic Parkinson's disease
4. Line: the only licensed option in this group
4. Note: The distinguishing indication of the class. Its label also warns that, like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms, with worsening tremor observed in this population. [4][7]
5. Drug: Memantine
5. Organism: Not applicable
5. Indication: Moderate to severe dementia of the Alzheimer's type
5. Line: used where disease is more advanced
5. Note: Indicated at the stage where the cholinesterase inhibitors are licensed least, and tolerated by patients in whom cholinergic gastrointestinal or cardiac effects are the limiting problem. [3]

Pharmacokinetics

1. Drug: Donepezil
1. Route: Oral
1. Absorption: Oral
1. Csf Penetration: Not applicable
1. Metabolism: Cytochrome P450 isoenzymes 2D6 and 3A4, with glucuronidation
1. Elimination: About 57% of radioactivity recovered in urine, roughly 17% as unchanged drug
1. Half Life: About 70 hours
1. Dose Adjust: The long half-life means steady state and the resolution of adverse effects both take time [1]
2. Drug: Galantamine
2. Route: Oral
2. Absorption: Oral
2. Csf Penetration: Not applicable
2. Metabolism: CYP2D6 and CYP3A4 are the major isoenzymes involved
2. Elimination: About 20% of the dose excreted unchanged in urine over 24 hours
2. Half Life: About 7 hours
2. Dose Adjust: Exposure rose by 37% in moderate and 67% in severe renal impairment; clearance fell by about 25% in moderate hepatic impairment [2]
3. Drug: Rivastigmine
3. Route: Oral and transdermal
3. Absorption: Rapid and complete after oral administration; food delays it
3. Csf Penetration: Readily crosses the blood-brain barrier
3. Metabolism: Cholinesterase-mediated hydrolysis; the major cytochrome P450 isoenzymes are minimally involved
3. Elimination: Renal excretion of metabolites is the major route; unchanged drug is not found in urine
3. Half Life: About 1 hour in plasma after an oral dose
3. Dose Adjust: Exposure more than doubles in mild to moderate hepatic impairment and in moderate renal impairment [4]
4. Drug: Memantine
4. Route: Oral
4. Absorption: Oral, with or without food
4. Csf Penetration: Not applicable

- 4. Metabolism: Partial hepatic metabolism; the microsomal P450 system plays no significant role
- 4. Elimination: Excreted predominantly, about 48%, unchanged in urine
- 4. Half Life: About 60 to 80 hours
- 4. Dose Adjust: A reduced target dose is recommended in severe renal impairment, defined in the label as a creatinine clearance of 5 to 29 mL/min [3]
- 1. No dose regimens appear on this page. Starting, titrating, continuing or stopping any of these medicines is a decision for the treating clinician, working from a current prescribing reference and from the person's own circumstances.
- 2. The clearance routes split neatly along mechanism lines: donepezil and galantamine are cytochrome substrates, rivastigmine bypasses the cytochromes almost entirely through enzymatic hydrolysis, and memantine leaves largely unchanged in the urine. [1][2][4][3]

Adverse effects

- 1. Effect: Cholinergic gastrointestinal effects
 - 1. Detail: Nausea, vomiting and diarrhoea are dose-related and occur particularly when treatment is started or the dose is raised. The most common adverse reactions reported for donepezil are nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. [4][1]
- 2. Effect: Anorexia and weight loss
 - 2. Detail: The galantamine label describes nausea, vomiting, diarrhea, anorexia and weight loss as a predictable consequence of the drug's pharmacological properties. Weight should be monitored during treatment with a cholinesterase inhibitor, in a group of patients who are already losing weight from the disease itself. [2][4]
- 3. Effect: A different profile with memantine
 - 3. Detail: Its most common adverse reactions, occurring in at least 5% of patients and more often than on placebo, are dizziness, headache, confusion and constipation. Constipation rather than diarrhoea is a useful marker that this agent is not a cholinomimetic. [3]
- 1. Effect: Bradycardia, heart block and syncope
 - 1. Detail: Cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, which may manifest as bradycardia or heart block in patients with and without known conduction abnormalities, and syncopal episodes have been reported. Galantamine showed a dose-related rise in the risk of syncope, from 0.7% on placebo to 2.2% at the highest dose studied.
 - 1. Action: Care is required in sick sinus syndrome and in sino-atrial or atrio-ventricular block; recognition of a new bradycardia or a fall belongs with the treating clinician, not with a dose change made at home. [1][2][4]
- 2. Effect: Peptic ulceration and gastrointestinal bleeding
 - 2. Detail: Because they increase cholinergic activity these drugs may raise gastric acid secretion, and rivastigmine labelling advises care in patients with active gastric or duodenal ulcers. The galantamine label directs close monitoring for active or occult gastrointestinal bleeding, especially in those at increased risk of ulcers such as patients with a history of ulcer disease or those using concurrent non-steroidal anti-inflammatory drugs.
 - 2. Action: A concurrent NSAID converts a background ulcer risk into a monitored one; the combination is a prompt to review the analgesic rather than to accept the bleeding risk silently. [4][2]
- 3. Effect: Seizures
 - 3. Detail: Cholinomimetics are believed to have some potential to cause generalised convulsions, though seizure activity may also be a manifestation of Alzheimer's disease itself. Cholinomimetics may equally induce or exacerbate urinary obstruction.
 - 3. Action: Caution is advised in patients already predisposed to either problem, and the distinction between drug effect and disease progression is a clinical judgement. [1][4]
- 4. Effect: Oesophageal rupture after severe vomiting
 - 4. Detail: Some cases of severe vomiting on rivastigmine were associated with oesophageal rupture, appearing

particularly after dose increments or at high doses. Dehydration from prolonged vomiting or diarrhoea can itself be associated with serious outcomes.

4. Action: Severe or persistent vomiting on a cholinesterase inhibitor is a reason for urgent medical review rather than for persevering. [4]

5. Effect: Overdose from patch medication errors

5. Detail: UK regulators reported medication errors with the rivastigmine transdermal patch, most commonly failure to remove the old patch and application of more than one patch at the same time, some resulting in overdose and hospital admission. Reported features include nausea, vomiting, diarrhoea, hypertension and hallucinations, and bradycardia or syncope associated with malaise or falls.

5. Action: The regulator's advice is that in suspected overdose all patches are removed immediately and no further patch is applied for the next 24 hours. [5]

1. Drug: Donepezil

1. Effect: An elimination half-life of about 70 hours, so both accumulation to steady state and the washout of an adverse effect are slow compared with the rest of the class. [1]

2. Drug: Galantamine

2. Effect: Excess deaths in trials outside its licensed indication: thirteen deaths among 1,026 subjects with mild cognitive impairment against one among 1,022 on placebo across two two-year trials. [2]

3. Drug: Rivastigmine patch

3. Effect: Application site reactions, which may progress to allergic contact dermatitis; suspicion arises where the reaction spreads beyond the patch, becomes more intense, or fails to improve within 48 hours of removal. [4]

4. Drug: Memantine

4. Effect: Accumulation when urine is alkalinised, because conditions that raise urine pH decrease its urinary elimination and increase plasma levels. [3]

Contraindications, precautions and interactions

1. Rivastigmine is contraindicated in hypersensitivity to the active substance, to other carbamate derivatives, or to any excipient, and also where there is a previous history of application site reactions suggestive of allergic contact dermatitis with the patch. [4]

2. Memantine is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipient used in the formulation. [3]

1. Care is needed in sick sinus syndrome and in conduction defects, including sino-atrial and atrio-ventricular block, because of the vagotonic effect on the conducting system. [4]

2. Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. [4][2]

3. As cholinesterase inhibitors, these drugs are likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia, so their use is relevant information for an anaesthetist. [1][4]

4. Patients with a body weight below 50 kg may experience more adverse reactions on rivastigmine and may be more likely to stop treatment because of them. [4]

5. Galantamine is licensed only for mild to moderate dementia of the Alzheimer's type, and the excess mortality seen in its mild cognitive impairment trials is the reason for not extending its use to that group. [2]

1. With: Beta blockers and other rate-limiting drugs

1. Effect: Additive effects leading to bradycardia, which may result in syncope, have been reported with combined use of various beta blockers including atenolol and rivastigmine. Caution extends to other bradycardic agents such as class III antiarrhythmics, calcium channel antagonists and digitalis glycosides. [4]

2. With: Antimuscarinic (anticholinergic) medicines

2. Effect: Cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications, with oxybutynin and tolterodine named as examples. The two treatments oppose each other at the same receptor. [1][4]

3. With: Other cholinomimetic drugs and succinylcholine
3. Effect: A synergistic effect may be expected when a cholinesterase inhibitor is given with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists, and rivastigmine should not be given concomitantly with other cholinomimetic substances. [1][4]
4. With: Antipsychotics and other QT-prolonging medicines
4. Effect: Because bradycardia is itself a risk factor for torsade de pointes, combining rivastigmine with QT-prolonging or torsade-inducing medicines, including several antipsychotics, warrants caution and may require electrocardiographic monitoring. [4]
5. With: Drugs that alkalinise the urine
5. Effect: Alteration of urine pH towards the alkaline may lead to accumulation of memantine with a possible increase in adverse effects; carbonic anhydrase inhibitors and sodium bicarbonate are the examples given. [3]
6. With: Other NMDA antagonists
6. Effect: Combined use of memantine with amantadine, ketamine or dextromethorphan has not been systematically evaluated and such use should be approached with caution. [3]

Comparison tables

Title: What actually separates the four agents

Caption: Mechanism, clearance and the practical distinguishing feature. Choice of agent, and the decision to continue or stop it, rest with the treating clinician.

1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: mechanism
2. Label: Mechanism
3. Key: clearance
3. Label: Main clearance route
4. Key: distinguishing
4. Label: Distinguishing feature
1. Drug: Donepezil
1. Mechanism: Reversible acetylcholinesterase inhibition
1. Clearance: CYP2D6 and CYP3A4, with glucuronidation
1. Distinguishing: Half-life of about 70 hours; licensed across dementia of the Alzheimer's type [1]
2. Drug: Rivastigmine
2. Mechanism: Carbamate inhibition of acetyl- and butyrylcholinesterase
2. Clearance: Cholinesterase-mediated hydrolysis, metabolites renally excreted
2. Distinguishing: The only patch, and the only agent licensed for Parkinson's disease dementia [4]
3. Drug: Galantamine
3. Mechanism: Competitive, reversible acetylcholinesterase inhibition
3. Clearance: CYP2D6 and CYP3A4, about a fifth excreted unchanged
3. Distinguishing: Documented dose-related syncope; excess deaths in mild cognitive impairment trials [2]
4. Drug: Memantine
4. Mechanism: Uncompetitive open-channel NMDA receptor antagonism
4. Clearance: Renal, about 48% unchanged
4. Distinguishing: No cholinergic burden; accumulates when urine is alkaline [3]

High-yield exam pearls

1. Pearl: Every adverse effect of a cholinesterase inhibitor can be derived from one sentence: there is more

acetylcholine everywhere, not just in the cortex.

1. Why: Gut cramping and diarrhoea, vagal bradycardia, bronchoconstriction, bladder contraction and gastric acid secretion all follow from the same mechanism, so the profile does not need memorising separately. [4][2]
2. Pearl: A cholinesterase inhibitor and an antimuscarinic prescribed for urinary urgency cancel each other out.
2. Why: The rivastigmine label names oxybutynin and tolterodine as the anticholinergic medicines whose activity may be interfered with, which makes this the cleanest pharmacological antagonism in geriatric prescribing. [4]
3. Pearl: Rivastigmine is distinguished by inhibiting butyrylcholinesterase as well as acetylcholinesterase, and by being a carbamate that forms a temporary covalent complex.
3. Why: It explains why the drug bypasses the cytochrome system that handles donepezil and galantamine, and why its plasma half-life is short despite a long pharmacodynamic effect. [4]
4. Pearl: Memantine is renally cleared and largely unmetabolised, so renal function and urine pH matter far more than any cytochrome interaction.
4. Why: It is the counterpoint to the cholinesterase inhibitors in almost every respect, and the pharmacokinetic contrast is what examiners test. [3]
5. Pearl: An older patient on a beta blocker who begins a cholinesterase inhibitor has two drugs slowing the heart.
5. Why: Additive bradycardia leading to syncope is documented for rivastigmine with beta blockers, and a fall in a patient with dementia has consequences out of proportion to the arrhythmia itself. [4]

Common exam traps

1. Trap: Describing these medicines as slowing or treating Alzheimer's disease.
1. Correction: The donepezil and galantamine labels each state there is no evidence the drug alters the course of the underlying dementing process, and the memantine label states there is no evidence it prevents or slows neurodegeneration. The European rivastigmine indication is worded as symptomatic treatment. [1][2][3][4]
2. Trap: Treating memantine as another cholinergic drug because it is used in the same disease.
2. Correction: It is an uncompetitive open-channel NMDA receptor antagonist. Its reported adverse effects are dizziness, headache, confusion and constipation, and it carries none of the vagotonic or gastrointestinal cholinergic liability. [3]
3. Trap: Assuming a drug with a cognitive indication must be safe in mild cognitive impairment as well.
3. Correction: Two two-year randomised trials of galantamine in mild cognitive impairment recorded thirteen deaths on the drug against one on placebo, and the indication remains mild to moderate dementia of the Alzheimer's type. [2]
4. Trap: Reaching for an antipsychotic to manage behavioural symptoms without weighing the mortality warning.
4. Correction: Antipsychotic labelling carries a boxed warning that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, with a risk of death in drug-treated patients between 1.6 and 1.7 times that in placebo-treated patients, and these drugs are not approved for that use. [6]
5. Trap: Assuming a transdermal formulation is the safer option because it avoids the gut.
5. Correction: The commonest medication errors with the rivastigmine patch were failure to remove the previous patch and application of more than one at a time, and some of these resulted in overdose requiring hospital admission. [5]

Self-test questions

1. Question: Which statement most accurately reflects what the labels for donepezil, galantamine and memantine claim about disease course?
 1. None of them claims to alter the underlying disease process
 2. All three are stated to slow neurodegeneration
 3. Only memantine is stated to slow neurodegeneration
 4. Only the cholinesterase inhibitors are stated to slow neurodegeneration
1. Explanation: The donepezil and galantamine labels both state there is no evidence the drug alters the course of the underlying dementing process, and the memantine label states there is no evidence it prevents or slows

neurodegeneration in patients with Alzheimer's disease. [1][2][3]

2. Question: An 82-year-old taking donepezil is started on tolterodine for urinary urgency. What is the pharmacological problem?

1. The antimuscarinic opposes the cholinergic action of the cholinesterase inhibitor
2. Tolterodine inhibits the renal excretion of donepezil
3. The combination causes additive serotonergic toxicity
4. Tolterodine induces the enzyme that metabolises donepezil

2. Explanation: Cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications, and tolterodine is named among those medicines. The two agents act in opposite directions on the same receptor system. [1][4]

3. Question: Which cardiac effect follows directly from the mechanism of a cholinesterase inhibitor?

1. Bradycardia and atrioventricular block from vagotonic effects on the conducting system
2. Sinus tachycardia from reflex sympathetic activation
3. Atrial fibrillation from direct atrial myocyte toxicity
4. Hypertensive crisis from noradrenaline release

3. Explanation: Cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block, and syncopal episodes have been reported. The galantamine label records a dose-related increase in the risk of syncope. [2][1]

4. Question: Which agent in this class is licensed for dementia associated with idiopathic Parkinson's disease?

1. Rivastigmine
2. Donepezil
3. Galantamine
4. Memantine

4. Explanation: European labelling for rivastigmine covers the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease, in addition to Alzheimer's dementia. Its label also warns that it may exacerbate extrapyramidal symptoms. [4]

5. Question: A patient on memantine is prescribed a carbonic anhydrase inhibitor. What is the expected consequence?

1. Reduced urinary elimination of memantine and higher plasma levels
2. Increased hepatic metabolism of memantine
3. Displacement of memantine from plasma protein binding
4. Loss of memantine efficacy through receptor competition

5. Explanation: Memantine is excreted predominantly unchanged in urine, and conditions that raise urine pH decrease its urinary elimination, resulting in increased plasma levels. Carbonic anhydrase inhibitors and sodium bicarbonate are given as examples of drugs that alkalinise urine. [3]

6. Question: Which combination most clearly increases the risk of gastrointestinal bleeding in a patient on galantamine?

1. A concurrent non-steroidal anti-inflammatory drug
2. A concurrent proton pump inhibitor
3. A concurrent beta blocker
4. A concurrent carbonic anhydrase inhibitor

6. Explanation: The label directs close monitoring for active or occult gastrointestinal bleeding, especially in patients at increased risk of ulcers, such as those with a history of ulcer disease or those using concurrent non-steroidal anti-inflammatory drugs. [2]

Frequently asked questions

1. Question: Do these medicines stop dementia getting worse?

1. Answer: No, and their own labels say so. The donepezil and galantamine prescribing information each state there is

no evidence the drug alters the course of the underlying dementing process, and the memantine label states there is no evidence it prevents or slows neurodegeneration. What they offer is symptomatic benefit, which is also how the European rivastigmine indication is worded. [1][2][3][4]

2. Question: How is it decided whether treatment is still worth continuing?

2. Answer: By reassessment against the observed course rather than by assumption. European rivastigmine labelling states that maintenance treatment can continue for as long as a therapeutic benefit exists, that the benefit should be reassessed regularly, and that treatment should be discontinued if after three months of maintenance the rate of decline in dementia symptoms is not altered favourably. That judgement belongs to the treating clinician. [4]

3. Question: Why do these drugs so often cause nausea, diarrhoea and weight loss?

3. Answer: Because the enzyme they inhibit is not confined to the brain. More acetylcholine in the gut means more motility and secretion. The galantamine label is blunt about it, listing weight loss alongside nausea, vomiting, diarrhea and anorexia as effects predictable from the drug's pharmacology, and rivastigmine labelling notes these effects are dose-related and commonest when treatment is started or increased. [2][4]

4. Question: What should be checked before adding a cholinesterase inhibitor to an older person's existing medicines?

4. Answer: Two categories stand out. Rate-limiting cardiac drugs, because additive bradycardia leading to syncope has been reported with beta blockers and caution extends to calcium channel antagonists, class III antiarrhythmics and digitalis glycosides. And antimuscarinics, because a cholinesterase inhibitor interferes with their activity and the pair work against each other. Reviewing and reconciling those medicines is a clinician's task. [4][1]

5. Question: Are antipsychotics an appropriate way to manage agitation in dementia?

5. Answer: They carry a specific warning that belongs alongside this class. Antipsychotic labelling states that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, quantified as between 1.6 and 1.7 times the risk seen with placebo, with a death rate of about 4.5% against about 2.6% over a typical ten-week trial, and these medicines are not approved for that indication. [6]

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