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Galantamine beyond Alzheimer's disease—a fact or artefact?

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Abstract

Galantamine is US-Food and Drug Administration FDA-approved for mild-to-moderate Alzheimer's disease. However, its unique pharmacological portfolio speaks to the idea of a pluripotent agent with a broad therapeutic potential. Here, authors briefly discuss these off-label clinical indications synthesizing the extant evidence.

Introduction

Originally derived from the snowdrop *Galanthus nivalis*, galantamine was developed in the Union of Soviet Socialist Republics (USSR) by Mashkovsky and Kruglikova-Lvova in the 1950s and industrialized by the Bulgarian Paskov in 1959. It is a phenanthrene alkaloid and similar in structure to codeine. It was originally marketed as Nivalin and used to treat paralytic and neuropathic conditions. After the cholinergic hypothesis of Alzheimer's disease (AD) was proposed and accepted in the early 1980s, interest turned to using cholinesterase inhibitors to treat dementia.[1] Patent problems delayed the introduction of galantamine to treat AD. It was first licensed to treat AD in Austria in 1994 and then in Europe and the United States in 2000.[2]

Galantamine Pharmacology

Galantamine reversibly and competitively inhibits centrally active acetylcholinesterase, making more acetylcholine available. Increased availability of acetylcholine compensates in part for degenerating cholinergic neurons in neocortex that regulate memory. It also modulates nicotinic receptors ($\alpha_4\beta_2$ and α_7), which enhance actions of acetylcholine. Nicotinic modulation may also enhance the actions of other neurotransmitters by increasing the release of dopamine, norepinephrine, serotonin, Gamma-amino-butyric acid (GABA), and glutamate.[3]

However, it does not inhibit butyrylcholinesterase (cf. rivastigmine). Galantamine may release growth factors or interfere with amyloid deposition with putative neuroprotection through antiapoptotic and antioxidant actions.[4] It may take up to 6 weeks before any improvement in baseline memory or behavior is evident and months before any stabilization in degenerative course is apparent.

Posology: 16–24 mg/d (÷2 doses) preferably *with* food.

adverse drug reactions (ADRs): Gastrointestinal; headaches, dizziness, and insomnia.

Kinetics: $t_{1/2}$ = 7 hours. Metabolized by cytochrome (CYP) 450 2D6 and 3A4.

Of related interest, Memogain is an inactive prodrug of galantamine. It has more than 15-fold higher bioavailability in the brain than the same doses of galantamine. In the brain, Memogain is enzymatically cleaved to galantamine, thereby regaining its pharmacological activity as a cholinergic enhancer. In animal models of drug-induced amnesia, Memogain produced several-fold larger cognitive improvement than the same doses of galantamine, without exhibiting any significant levels of gastrointestinal side effects that are typical for the unmodified drug.[5]

Methods: EMBASE, Ovid MEDLINE, PubMed, Scopus, Web of Science, and Cochrane Database of Systemic Reviews were searched for all relevant studies of galantamine clinical uses up to date of October 2020.

Clinical Indications

Galantamine is FDA-approved for mild-to-moderate Alzheimer's disease. However, its unique pharmacological portfolio speaks to the idea of a pluripotent agent with a broad therapeutic potential. Here, we briefly discuss these off-label clinical indications while examining the extant evidence.

Alzheimer's disease

This is currently the only legitimate indication of galantamine.[6-7] A recent meta-analysis[8] of 36 randomized controlled trials (RCTs) on efficacy and safety of available antidementia agents suggested that galantamine is beneficial for stabilizing or slowing the decline in cognitive function, functional outcome, behavior outcome, and global assessment change in AD patients. This favorable performance of galantamine spanned mild-to-moderate, moderate-to-severe, and severe AD. Authors concluded that galantamine should be the first choice for AD.

Vascular dementia

In a Cochrane database and systematic review,[9] efficacy of galantamine has been tested in two randomized-controlled trials for the treatment of vascular dementia and for a mixed population of AD patients with evidence of cerebrovascular disease on scanning. Results suggested some advantage over placebo in areas of cognition and global clinical state. In both included trials, galantamine produced higher rates of gastrointestinal side effects.

ADHD

As a cognitive enhancer, one double-blind, placebo-controlled trial of galantamine was conducted in adults diagnosed with attention-deficit/hyperactivity disorder (ADHD). In this 12-week study, there was no effect of the drug compared to placebo on any of the relevant outcome measures.[10]

Autism

Cholinergic stimulation of central serotonergic subsystem with galantamine may enhance language and communication in autistic adults as shown in three cases.[11] A prospective open-label trial of galantamine in autism spectrum disorder (ASD) showed it was well tolerated and beneficial for interfering behaviors, particularly aggression, behavioral dyscontrol, and inattention.[12] Recently, an RCT showed galantamine was effective and safe augmentative strategy to risperidone for alleviating some of autism-related symptoms.[13]

Bipolar mood disorder

In a systematic review, including three studies of galantamine, as a neurotransmitter modulator, evidence points to no effect of galantamine for all aspects of bipolar disorder.[14] In a proof-of-concept study, treatment with galantamine-ER was associated with improved cognition in bipolar patients and with increases in neuronal viability and normalization of lipid membrane metabolism in the left hippocampus.[15] Galantamine might have specific benefits for episodic memory but not processing speed in these patients.[16-17]

Cancer chemotherapy–induced cognitive changes

Chemotherapy-induced cognitive impairment (CICI), also called chemobrain or chemofog, is currently recognized as a relatively common adverse effect of chemotherapeutic agents typically administered to treat various types of solid tumors, mainly breast, lung, prostate, and ovarian cancers. Several pharmacologic and nonpharmacologic interventions have been evaluated as potential therapies for cognitive decline and CICD, which may be used as adjuncts during conventional chemotherapeutic treatment. Philpot et al[18] reported that cyclophosphamide- and doxorubicin-induced spatial memory deficits in mice were successfully prevented by coadministering the acetylcholine esterase inhibitors donepezil and galantamine together with chemotherapy.

Down's syndrome

Galantamine is a scavenger of reactive oxygen species and possesses a neuroprotective effect by lowering the oxidative neuronal damage, through the prevention of the activation of P2X7 receptors; protection of mitochondrial membrane potential; and prevention of the membrane fluidity disturbances.[19]

While preclinical studies have reported improvement of behavioral deficits in the Ts65Dn mouse model of Down's syndrome (DS), translation to human clinical trials to improve cognition in individuals with DS has had a poor success record. Treatment of trisomic mice with galantamine resulted in a significant improvement in olfactory learning.[20] Olfactory learning has been demonstrated to be a sensitive tool for evaluating deficits in associative learning in mouse models of DS, and galantamine might have therapeutic potential for improving cognitive abilities.

Organophosphate poisoning

Organophosphate compounds are commonly used as insecticides. These agents inhibit cholinesterases, especially acetylcholinesterase, and accumulate acetylcholine causing muscarinic, nicotinic, and central nervous system manifestations. Currently, drugs such as atropines, oximes, and benzodiazepines are used to treat these symptoms. But these drugs are associated with certain drawbacks and have found to be ineffective in preventing the delayed symptoms. Mechanistically, galantamine can be an effective choice in the management of organophosphate toxicity.[21] The mechanism is based on reversible competitive inhibiting property of galantamine on acetylcholinesterase without affecting butylcholinesterase. The drug can prevent the delayed cognitive effects and neurodegeneration by acting as a nicotinic allosteric potentiating ligand. It can cross the blood–brain barrier and inhibit acetylcholinesterase in the brain reversibly and decrease the incidence of central nervous system manifestations such as convulsions. The drug is associated with good pharmacokinetic profile, minimal side effects, and has been found to be effective as a pretreatment and post-treatment agent.

Schizophrenia

Schizophrenia is, in part, a cognitive illness. There are no approved medications for cognitive impairments associated with schizophrenia (CIAS) and primary negative symptoms. Cholinergic and glutamatergic systems, alpha-7 nicotinic acetylcholine (α-7nACh) and *N*-methyl-D-aspartate (NMDA) receptors, kynurenic acid (KYNA), and mismatch negativity have been implicated in the pathophysiology of CIAS and negative symptoms. Galantamine is a positive allosteric modulator at the α4β2 and α7nACh receptors. Memantine is a noncompetitive NMDA receptor antagonist. Galantamine and memantine alone and in combination were effective for cognition in animals and people with AD. There is evidence from a small open-label study that the galantamine–memantine combination may be effective for CIAS with kynurenine pathway metabolites as biomarkers to

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Table 1. Galantamine Clinical Uses in Psychiatry.

Indication	Level of Evidence[a]
1- Alzheimer's disease[b]	Level I
2- Vascular dementia	Level I
1- ADHD	Level I (negative)
3- Autism	Level I
2- Bipolar mood disorder	Level I (negative)
3- Cancer chemotherapy–induced cognitive changes	Level III
4- Down's syndrome	Level III
5- Organophosphate poisoning	Level III
6- Schizophrenia	Level III
7- Smoking cessation	Level I
8- Stroke	Level III
9- TBI	Level II-1

Level I: Evidence obtained from at least one properly designed randomized-controlled trial.
Level II-1: Evidence obtained from well-designed controlled trials without randomization.
Level II-2: Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
Level II-3: Evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
[a]US preventiveservices taskforce (USPSTF) rankings (1998).
[b]Only FDA indication.

detect the severity of cognitive impairments.[22] Given that there are no available treatments for cognitive impairments and primary negative symptoms in schizophrenia, testing of this "five-pronged strategy" (quintuple hypotheses: dopamine, nicotinic-cholinergic, glutamatergic/NMDA, GABA, and KYNA) is a "low-risk high-gain" approach that could be a major breakthrough in the field. The galantamine–memantine combination has the potential to treat positive, cognitive, and negative symptoms, and targeting the quintuple hypotheses concurrently may lead to a major scientific advancement—from antipsychotic treatment to antischizophrenia treatment.

Smoking cessation

An RCT suggested that galantamine reduces nicotine intake, but it is unlikely that galantamine improves cognitive performance in otherwise healthy, treatment-seeking smokers.[23] Galantamine attenuated some of the subjective effects of intravenous nicotine and improves performance on a Go No-Go task in abstinent cigarette smokers in a double-blind, placebo-controlled, crossover study.[24] Galantamine reduced smoking in a 24-week randomized, placebo-controlled, multicentric clinical trial in recently detoxified alcohol-dependent patients.[25]

Stroke

Administration of galantamine had a beneficial effect on chronic poststroke aphasia and was more prominent in subcortical dominant lesions.[26] Galantamine has been shown to provide in vivo neuroprotection and memory recovery against global cerebral ischemia, even when administration begins 3 hours post ischemia.[27]

TBI

Posttraumatic brain injury administration of galantamine was found to decrease traumatic brain injury TBI-triggered blood–brain barrier permeability (tested 24 h post injury), attenuate the loss of both GABAergic and newborn neurons in the ipsilateral hippocampus, and improve hippocampal function (tested 10 d after termination of the drug treatment). Specifically, significant improvements in the Morris water maze, novel object recognition, and context-specific fear memory tasks were observed in injured animals treated with galantamine.[28] Galantamine has shown efficacy for the treatment of electroconvulsive therapy (ECT-) and TBI-induced cognitive impairments.[29] Acetylcholinesterase inhibitors have shown a great potential in the treatment of chronic phase TBI, improving fatigue, memory, attention, and initiative. However, there were no significant differences between the drugs galantamine, rivastigmine, and donepezil.[30]

Conclusion

This overview has casted some light on galantamine pharmacological portfolio and its therapeutic potential. Having said so, the hitherto level of evidence supporting the use of galantamine in all these indications is highly variable (Table 1), and, hence, sound clinical acumen, manipulating all other viable treatment options at hand, would dictate its judicious and proper use and placement in real-life psychiatric practice and psychopharmacotherapy algorithms. Sound evidence-base supports use of galantamine for AD, vascular dementia (VasD), ASD (adjuventia), and smoking cessation. A modicum of evidence exists for galantamine use in CICI, organo-phosphate (OP) poisoning, schizophrenia, poststroke aphasia, and TBI. No evidence supports galantamine use in ADHD or BMD.

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