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Latrepirdine, a potential novel treatment for Alzheimer's disease and Huntington's chorea

Marwan N Sabbagh and **Holly A Shill**
Banner Sun Health Research Institute, The Cleo Roberts Center for Clinical Research, 10515 West Santa Fe Drive, Sun City, AZ 85351, USA

Marwan N Sabbagh: marwan.sabbagh@bannerhealth.com

Abstract

Latrepirdine (Dimebon) is a novel compound currently under development by Medivation Inc and Pfizer Inc for the treatment of Alzheimer's disease and Huntington's chorea. Originally developed and marketed as an antihistamine in Russia, it has potential for the treatment of neurodegenerative diseases. Early research suggested that the mechanism of action is centered on AChE inhibition and NMDA antagonism. Newer research casts some doubt regarding these early findings and other mechanisms of action have been proposed and investigated. In phase II clinical trials, latrepirdine demonstrated clinically relevant improvements in patients with Alzheimer's disease and Huntington's chorea. At the time of publication, phase III clinical trials had been initiated. Given the robustness of the phase II clinical data, latrepirdine has a high likelihood of success in phase III trials and in subsequently being granted regulatory approval.

Introduction

Alzheimer's disease is a neurodegenerative disease that is the leading cause of dementia in the elderly [578486], [1045750], affecting 1 in 13 individuals over the age of 65 [1045750]. In 2000, there were 5.3 million Americans with Alzheimer's disease [578486]. The disease is characterized by the extracellular accumulation of β-amyloid (Aβ) plaques, which consist of peptides of 38 to 42 amino acids that are cleaved from amyloid precursor protein by β- and γ-secretase, and neurofibrillary tangles, which consist of hyperphosphorylated tau protein filaments. These molecular changes are accompanied by progressive cell loss, especially in cholinergic neurons in the basal forebrain region [1045914], [1053824]. Several inciting events (eg, trauma, genetics and environment factors) have been proposed as triggers of the cascade of pathological events that ultimately leads to the cognitive decline that characterizes Alzheimer's disease [1059495].

The accumulation of Aβ peptides in the brain disrupts the synthesis and release of ACh [1045914], and may play a pivotal role in the pathophysiological process of Alzheimer's disease [1053823]. Existing therapies for Alzheimer's disease attempt to provide

Correspondence to: Marwan N Sabbagh, marwan.sabbagh@bannerhealth.com.

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Disclosure
Marwan N Sabbagh has worked as principle investigator on clinical trials assessing latrepirdine.

symptomatic relief via cholinergic mechanisms or by altering NMDA receptor mechanisms [1045921]. At the time of publication, no disease-modifying (ie, a drug specifically indicated to change the course, biology or trajectory of the disease) or anti-amyloid therapies were available.

An increasing body of data suggests that mitochondrial dysfunction may play a central and early role in the pathobiology of Alzheimer's disease. Aβ peptides associate with the mitochondria can destabilize mitochondrial membranes, suppress ACh synthesis and inhibit respiratory chain complexes [1045917]. Mitochondrial abnormalities linked to Alzheimer's disease include: decreased glucose metabolism, increased production of reactive oxygen species and oxidative stress, abnormal mitochondrial calcium homeostasis and increased mitochondrial DNA mutations [1045920].

Huntington's chorea is an autosomal-dominant neurodegenerative disease characterized by progressive motor, psychiatric and cognitive decline [1046085]. The age of diagnosis is typically in the mid-40s, affecting individuals during one of the most productive times of their lives [1053831]. On average, patients survive for 15 to 20 years from the time of diagnosis. Prevalence is 4 to 10 per 100,000 individuals, with an estimated 150,000 individuals at risk of this disease based on family history [1053831]. The basic pathophyisology of Huntington's chorea is well understood; the associated gene, *HUNTINGTIN,* was identified more than two decades ago [1046090] and was later understood to be an expansion of a CAG trinucleotide repeat. One mechanistic pathway for neuronal death involves excitotoxicity mediated by glutamate and the NMDA receptor [1046091]. Another major pathway involves calcium homeostasis and mitochondrial dysfunction [1046080]. Lastly, pathways related to direct toxicity of the trinucleotide-repeat-induced aggregates and transcriptional dysregulation (eg, accumulation of proteins that may be toxic) may be relevant [1046097], [1046105].

Prior to the approval of AChE inhibitors (AChEIs; eg, donepezil) and the NMDA receptor inhibitor memantine (approved for moderate-to-severe Alzheimer's disease only), there was no effective pharmacotherapy for Alzheimer's disease [1053832]. These agents are associated with detectable symptomatic improvement and may have a modest effect on the progression of Alzheimer's disease from mild cognitive impairment to disabling dementia and death [1045922], [1045923]. The therapeutic limitations of AChEIs and the steadily increasing prevalence of the disease have led to increased preclinical and clinical research aimed at developing better medications for the treatment of patients with Alzheimer's disease. At the time of publication, several agents were in development, with some discovered serendipitously, some designed based on evolving knowledge of the pathophysiology of Alzheimer's disease and some identified from epidemiological research [1053832], which include: nicotinic ACh receptor agonists (eg, pozanicline [Abbott Laboratories] and ispronicline [Targacept Inc/AstraZeneca plc]), AMPA receptor modulators (eg, CX-717 [Cortex Pharmaceuticals Inc]), soluble receptors for advanced glycation end product inhibitors (eg, PF-4494700 [Pfizer Inc]), γ-secretase inhibitors (eg, semagacestat [Eli Lilly & Co]), immunotherapy (eg, bapineuzumab [Pfizer Inc/JANSSEN Alzheimer Immunotherapy] and solanezumab [Eli Lilly]) and cholesterol-lowering drugs (eg, simvasatin) [1045924], [1045925]. Because it is highly unlikely that any individual agent will provide a cure for Alzheimer's disease, future treatment is likely to involve polypharmacy, with newer medications given in combination with AChEIs and with one another. Moreover, polypharmacy for the treatment of Alzheimer's disease has already been initiated with the add-on use of memantine as adjunctive therapy to AChEIs [1053939].

The only approved drug for the treatment of Huntington's chorea is tetrabenazine, a monoamine-depleting agent. The main benefit of this agent is in control of chorea, but

tetrabenzine can worsen psychiatric and cognitive function [1046531]. Therefore, a major unmet need in Huntington's chorea is drugs that benefit cognitive performance or psychiatric status, or slow the progression of the disease.

Preclinical studies support the use of NMDA receptor inhibitors, such as riluzole, amantadine and memantine, in the treatment of Huntington's chorea [368140], [1046107], [1046108], [1046111]. However, there are limited clinical trials of these agents. Treatment with amantadine mediated motor symptoms of Huntington's chorea, but it was not evaluated as a neuroprotective agent and had no beneficial effect on the cognitive or neuropsychiatric components [1046114], [1046443]. Open-label pilot trials supported the use of memantine, but definitive double-blind clinical trials have not been conducted [854862], [1046493]. A double-blind trial assessed riluzole in patients with Huntington's chorea during a 3-year period, with no evidence of neuroprotective or symptomatic benefits [854862]. Therefore, the clinical relevance of NMDA receptor blockade remains unclear.

Mitochondrial pathways in Huntington's chorea have been proposed as a means to provide neuroprotection because cellular and animal models of Huntington's chorea support impairment of mitochondrial function [442348], [1046497]. Patients with Huntington's chorea often lose weight as an early symptom, which is believed to be related to mitochondrial impairment [1046512]. In addition, brain and serum biomarkers of oxidative stress are further evidence of impaired mitochondrial function [1046513], [1046518]. Unfortunately, clinical trials of antioxidant-type therapies have not provided positive results. The ethyl-eicosapentaenoic acid AMR-101 (Amarin Corp plc) was assessed as a neuroprotective agent in patients with Huntington's chorea with no evidence of slowing progression of the disease [1046521]. Similarly, treatment with coenzyme Q10 did not slow progression in a double-blind trial [1046526]. A smaller, double-blind trial of high dose creatine (HD-02 [Avicena Group plc]) demonstrated no meaningful slowing of progression at 1 year [1046528]. These results highlight a lack of an effective agent targeting mitochondrial pathways in Huntington's chorea.

Latrepirdine (Dimebon), under development by Medivation Inc and Pfizer Inc, was originally marketed and used in Russia as a treatment for allergies [622333]. Based on positive preclinical data, latrepirdine is currently under investigation for the potential treatment of Alzheimer's disease and Huntington's chorea [622333], [628047], [940230]. The mechanism of action of latrepirdine in the CNS has not been elucidated, with a range of evidence to support different actions. These include actions at receptors targeted by launched drugs, such as the serotonin and NMDA receptors [980967], and indications that this compound may act on the mitochondrial pathways outlined in the previous paragraphs [927598], [928254]. At the time of publication, phase III clinical trials had been initiated in patients with Huntington's disease [1030076], [1029785] and with Alzheimer's disease [904943].

Synthesis

Latrepirdine was synthesized by condensation of 2-methyl-5-vinyl-pyridine (MVP) and 2,8-dimethyl-2,3,4,5- tetrahydro-1*H*-pyrido[4,3-*b*]indole (γ-carboline derivative) under basic conditions. 3-Bromopicoline was converted to 1-(6-methyl-pyridin-3-yl)-ethanol by adding acetaldehyde to the ate-complex intermediate. The resultant alcohol was transformed to the chloride, then dehydrohalogenated with potassium hydroxide in *N*-methylpyrrolidine at 50°C to produce MVP. The starting γ-carboline was synthesized from p-tosylhydrazine hydrochloride and *N*-methyl-4-piperidone in large-scale and in high yield (90%). A mixture of starting carboline and potassium phosphate was treated successively with dimethyl acetamide and MVP. The resultant slurry was stirred at 100°C for 24 h, then cooled to 40 to

60°C (water was added slowly over 1 h), followed by stirring at room temperature for 2 h to produce latrepirdine in 80% yield [WO-2009111540]. Similar methods were published in SU-01138164.

Preclinical development

In vitro

Latrepirdine was initially identified as an antihistamine agent with inhibitory activity at the H_1 receptor. Latrepirdine demonstrated antihistamine activity that was 292-, 74-, 21- and 1.5-fold greater than diazoline, diphenhydramine, phencarol and promethazine, respectively [1031269], [1045558]. Latrepirdine efficiently inhibited (10 μM resulted in > 90% inhibition) norepinephrine (α_{1A}, α_{1B}, α_{1D} and α_{2A}), histamine (H_1 and H_2) and serotonin (5-$HT_{2C'}$, 5-$HT_{5A'}$ and 5-HT_6) receptors [980967]. Significant inhibition (10 μM resulted in 70 to 80% inhibition) was also observed for dopamine (D_1, D_{2S} and D_3), imidazoline (I_2) and serotonin (5-HT_2 and 5-HT_{2B}) receptors [980967]. Another study demonstrated that latrepirdine bound to the human and rat 5-HT_6 recpetor with a K_i value of 26 and 119 nM, respectively [1045568]. In homogenates of the cortex, hypothalamus and basal ganglia, latrepirdine (0.1 μM) inhibited the deamination of dopamine and benzylamine; the deamination of serotonin was also inhibited in the hypothalamus, but this was not significant. At higher concentrations (1 to 10 μM), these effects were not observed [1031269], [1045558]. In addition, latrepirdine is a potent and reversible inhibitor of AChE and butyrylcholine esterase (IC_{50} = 42 and 7.9 μM, respectively) [622451].

In 1321N1 human astrocytoma cells, 5-HT mediates a concentration-dependent accumulation of cAMP; this accumulation was inhibited in a dose-dependent manner by treatment with latrepirdine, indicating that latrepirdine was mediating the 5-HT_6 receptor [1045568].

The effect of latrepirdine treatment on cerebellar granule cells cultured with Aβ (25 μM) was analyzed [622451], [927596], [927598], [927599]. Latrepirdine (25 μM) increased survival of neurons by approximately 45% [927599], and latrepirdine (20 to 100 μM) also inhibited mitochondrial permeability transition induced by Aβ [927598]. Consistent with these findings, latrepirdine also reduced mitochondrial impairment induced by Aβ [1054004]. Furthermore, latrepirdine increased the threshold of inductors to mitochondrial pore transition, making mitochondria more resistant to lipid peroxidation [928254].

Latrepirdine (0.1 to 100 nM) induced neurite outgrowth from cortical, hippocampal and spinal cord neurons, with effects comparable in magnitude with those achieved with maximally effective concentrations of brain-derived neurotrophic factor [1031263]. Latrepirdine (0.01 to 500 nM) also increased cortical neuron process and branch length in a concentration-dependent manner and increased the number of mitochondrial clusters per neuron [1031263].

TDP43 (TAR DNA binding protein of 43 kDa) accumulates as inclusion bodies in neurodegenerative diseases, such as Alzheimer's disease and Huntington's chorea [1045567]. Treatment with latrepirdine (5, 10 and 20 μM) prevented aggregation of TDP43 in SHSY5Y cell culture; this effect was concentration dependent (45, 60 and 70% reduction in TDP43 inclusions compared with controls for 5-, 10- and 20-μM concentrations, respectively) [1045567].

In murine neuroblastoma cell culture (N2a), treatment with latrepirdine either decreased or had no effect on Aβ levels [1022141].

In rat cerebellar neurons, latrepirdine (1 to 20 μM) potentiated AMPA receptor activity (average increase of 42%), but this effect was not observed at higher concentrations (40 to 50 μM) [1031271]. NMDA receptor activity was inhibited by latrepirdine by up to 25% (IC_{50} range of 6 to 90 μM depending on the neuron tested); the most efficient inhibition (IC_{50} range 6 to 10 μM) was in neurons that were only weakly inhibited by memantine. The investigators stated that this result implied that latrepirdine was likely to bind to the site on the NMDA receptor that is also the target for histamine, and not that of memantine [1031271]. In addition, in a neuronal cell culture obtained from a mouse model of Huntington's chorea (YAC128), latrepirdine blocked NMDA receptor current with an IC_{50} value of 10 μM; in a comparison with wild-type culture, no selectivity for NR2B receptor subtypes was observed [980967].

In calcium channels in cerebellar granule cells, latrepirdine treatment (5 to 200 μM) inhibited potential-dependent currents by an average of 20%, which was observed 1 to 3 min post-application [927599]; this calcium channel antagonist activity was quantified in isolated rat smooth-muscle tissue, demonstrating an IC_{50} value of 57 μM [622451]. In mouse neuronal cell cultures from both wild-type and YAC128 mice, latrepirdine treatment blocked high-voltage activated calcium channels with an IC_{50} value of 50 μM [980967]. In addition, in the YAC128 neuron-cell culture, treatment with a 50-μM dose of latrepirdine exerted a 'calcium-stabilizing' effect; this effect was not observed in cultures from wild-type mice or at a lower latrepirdine dose (10 μM) [980967].

In an *in vitro* assay modeling Huntington's chorea using glutamate-induced toxicity, a 50-μg dose of latrepirdine demonstrated significant neuroprotective effects; these effects were not observed at lower doses (10 and 20 μM) [980967].

In vivo

The antihistamine function of latrepirdine was demonstrated in guinea pigs [1057242]. The anti-anaphylactic effect of latrepirdine was favorable compared with the antihistamine phencarol, and was more effective than the OTC antihistamine ketotifen at doses of 2.5 to 5 mg/kg [1057242].

The first *in vivo* analysis of latrepirdine in the CNS was in studies in rats [1031269], [1045558]. Rats were treated with a single-dose of latrepirdine (15 mg/kg ip); 1 h post-dose, the activity of the monoamine oxidase (MAO) responsible for deaminating dopamine was altered by −13, −22 and +37% from baseline levels in the hypothalamus, basal ganglia and cerebral cortex, respectively. Similar changes were also observed for the MAO responsible for deaminating serotonin (−22 and +15% in the basal ganglia and cerebral cortex, respectively). In the cortex, norepinephrine and dopamine levels increased by 32 and 84%, respectively, and, in the basal ganglia, homovanillic acid (the principle metabolite of dopamine) levels were decreased by 24% [1031269], [1045558].

In an *ex vivo* analysis of rat brain slices, latrepirdine (0.1 to 30 mg/kg ip) dose-dependently inhibited binding of the selective 5-HT_6 antagonist [^{125}I]SB-271046 [1045568]. This effect was significant at 10 and 30 mg/kg ($p < 0.05$ versus vehicle control), with an ID_{50} value of 7.8 mg/kg [1045568].

In a rat model of memory dysfunction resulting from ACh hypofunction caused by intracerebral injections of the ACh neurotoxin AF64A (3 nmol/ventricle), treatment with latrepirdine (1 mg/kg ip, qd) improved learning and memory in an active avoidance conditioning protocol, offsetting the cholinergic deficit to an extent comparable with that of treatment with the AChEI tacrine (1 mg/kg ip, qd) [622451], [927595]. This response was significant for both agents compared with vehicle control animals ($p < 0.05$) [927595].

Similar improvements in learning and memory were demonstrated in experiments using the rat Morris water maze test [622433]. Rats pretreated with AF64A received daily oral doses of latrepirdine, donepezil, memantine or placebo for 3.5 weeks. Rats treated with latrepirdine, donepezil or memantine demonstrated comparable improvement in learning and memory compared with placebo; in rats that received latrepirdine or memantine, this improvement in memory remained after treatment was terminated [622433].

The affect of treatment with latrepirdine on memory consolidation, reconsolidation and recovery was studied in 1-day-old chicks trained in weak or strong passive avoidance tasks using taste-aversive colored beads [927588]. Treatment with latrepirdine (0.1 to 5 mg/kg ip, 5 min prior to weak training) significantly improved avoidance behavior compared with untreated controls when tested 24 h after the training (72 versus 29%; $p < 0.05$). This affect was dose dependent and comparable with that achieved with the noncompetitive NMDA antagonist dizocilpine and the AMPA receptor agonist cyclothiazine. The administration of latrepirdine 4 h after weak training also improved avoidance behavior (57 versus 24%; $p < 0.05$ versus untreated control); this effect was not observed after strong training. The impaired avoidance behavior of anisomycin-treated (80 μg) chicks was significantly improved with concomitant latrepirdine treatment either 30 or 5 min prior to training (53 and 57%, respectively; $p < 0.05$ versus untreated controls) [927588].

In a rat social recognition model (in which adult rats are exposed to a juvenile rat and later tested for recognition), treatment with latrepirdine (1 to 30 mg/kg ip) enhanced recognition of the familiar juvenile; this was significant at 10 and 30 mg/kg ($p < 0.05$ versus vehicle control) [1045568]. At the 30-mg/kg dose, latrepirdine also inhibited investigative behavior when a novel juvenile was introduced, indicating that this effect may not be attributed solely to memory improvement [1045568].

In the SAMP 10 (senescence-accelerated mouse prone 10) mouse model of senescence, untreated, 16-month-old mice demonstrated behavior and memory deficiency, exploratory behavior impairment, and increased levels of anxiety [1045566]. Chronic latrepirdine treatment (1.5 mg/kg/day po, for 5 months) offset these senescent changes and improved exploratory behavior in the open field test, reduced anxiety in the maze test, and improved function in the maze and passive-avoidance tests [1045566].

Latrepirdine (10 μg) demonstrated efficacy in a mouse model of synucleinopathy [1031262]. Transgenic mice bred to develop amyloid deposits, loss of motor neurons and astrogliosis in the spinal cord were treated with latrepirdine beginning at the age of 3 (before onset of clinical symptoms) or 6 (when clinical symptoms are obvious) months. Both treatment groups performed significantly better than age-matched control littermates; at 12 months old, animals that had received 6 months of treatment had a substantial decrease in the number of amyloid inclusions and reduced astrogliosis compared with age-matched and 6-month-old control littermates [1031262]. In addition, latrepirdine also had an unexpected effect on amyloid plaques [1022141]. Acute treatment with latrepirdine increased levels of Aβ in the isolated nerve terminals of TgCRND8 mice and in the interstitial fluid of the brains of Tg2576 mice. An increase in Aβ levels was unexpected because an elevation of Aβ levels is not readily associated with a clinically beneficial Alzheimer's disease drug [1022141].

The potential anti-aging property of latrepirdine was examined in female mice [928251], [928254]. Aged mice (21 months old) treated with latrepirdine (1.5 mg/kg/day po) for 14 months appeared more active and healthy than untreated control mice; the treated mice had reduced hair loss (66% reduction), cataract formation (55% reduction) and weight loss (11%

reduction). The oldest experimental mice lived for approximately 2 months longer than untreated mice, although the average lifespan increase (5%) was not significant [928251].

In mice, an injection of NMDA (1 μg) into the lateral ventricle resulted in hyperactivity [622451]. When these mice were pretreated with latrepirdine (ip), the development of convulsions and death was prevented; the ED_{50} value was 42 mg/kg [622451]. However, in rats tested with a novel object recognition (NOR) task, treatment with latrepirdine (0.05, 0.5 and 5 mg/kg po) increased the amount of time rats spent exploring the novel object compared with a familiar one ($p < 0.05$) [1054016]. There was no evidence of change in extracellular ACh levels in the hippocampus or prefrontal cortex. In addition, latrepirdine was 200-fold weaker in binding to the NMDA receptor than memantine (K_i = 105 and 0.54 μM, respectively) [1054016]. These data indicated that doses of latrepirdine that enhance cognition in the rat NOR task do not alter the extracellular ACh levels in two brain regions associated with learning and memory [Giorgetti M, Gibbons JA, Bernales S, Alfaro IE, Drieu La Rochelle C, Cremers T, Altar A, Wronski R, Hutter-Paier B, Protter AA: unpublished data].

In mice with TNFα-induced disorders of sphingolipids, treatment with latrepirdine (0.2 mg/kg) protected lipids against disorders in the mouse brain [1057213].

Studies examining latrepirdine in the treatment of myocardial infarction were also conducted [1057236], [1057237], [1057238]. In cats, treatment with latrepirdine (7.5 mg/kg) improved the response of the cat myocardium to ischemia; however, this agent was not as effective as treatment with the β-blocker propranolol, the calcium channel blocker finoptin or the antiarrhythmic agent amiodarone [1057236]. In dogs and cats treated with latrepirdine (2.5 mg/kg iv), a moderate coronary vasodilatory effect was observed, without exerting an effect on myocardial contractility [1057237].

Toxicity

In SHSY5Y cell culture, treatment with latrepirdine (1 to 60 μM) for 1 day did not cause any toxic effects [1045567]. In addition, in cerebellar granular cells, treatment with latrepirdine (25 to 50 μM) did not affect mature neurons [927596], [927598], [927599]; however, at higher doses (100 μM), neurotoxic effects were observed [927596], [927598]. In 2-day-old cultures of cerebellar granular cells, latrepirdine treatment even at low doses (< 25 μM) was toxic [927599].

In female rats, the LD_{50} value for single-oral-dose latrepirdine was approximately 1200 mg/kg. Furthermore, single-dose latrepirdine (800 mg/kg po) increased embryonic preimplantation death, although doses of 150 to 300 mg/kg (representing 150- to 300-fold greater than the therapeutic dose in humans) did not exert embryotropic effects [1031268].

In rats, guinea pigs and dogs, treatment with latrepirdine (1 and 5 mg/kg) for 2 months did not produce any toxic effects; at higher doses (10 and 70 mg/kg) some moderate and reversible structural changes were observed in the liver and kidneys [1057240]. The administration of latrepirdine (150 and 300 mg/kg) during pregnancy did not reveal any embryolethal or teratogenic effects [1057240].

In guinea pigs, latrepirdine administered intragastrically, subcutaneously and intravenously was less toxic than phencarol (1.28-, 1.78- and 1.43-fold, respectively) and ketotifen (1.78-, 1.68- and 5-fold, respectively) [1057242]. In addition, when mice were treated with latrepirdine (0.2 mg/kg), no change in the sphingolipids spectrum was observed in brain sections [1057213].

Metabolism and pharmacokinetics

Studies in rabbits and rats were undertaken to assess the kinetics, absorption and tissue distribution of latrepirdine [1031270]. The administration of latrepirdine (30 and 50 mg/kg po in rabbits and rats, respectively) revealed an absolute bioavailability of 70 and 53% in rabbits and rats, respectively. The absorbance was dependent on the route of administration and on the dose (AUC = 1.2, 3.56, 4.06 and 3.6 μg·h/ml for rabbits at 10 mg/kg iv and 30 mg/kg po, and for rats at 30 mg/kg ip and 50 mg/kg po, respectively), with a C_{max} value reported for the 30-mg/kg dose in rabbits of 1.65 μg/ml. The $t_{1/2}$ value in rats and rabbits ranged from 1.02 to 2.04 h. Latrepirdine (50 mg/kg po) demonstrated good tissue and brain penetration in rats, with uptake in most vascularized organs (spleen, liver, kidneys and lungs) occurring within 90 min of ingestion, which was 2- to 3-fold greater than in the blood serum [1031270].

In rats treated with single-dose latrepirdine (0.05 mg/kg po), detected levels of latrepirdine were consistently higher (up to 10-fold increase) in brain than plasma [Giorgetti M, Gibbons JA, Bernales S, Alfaro IE, Drieu La Rochelle C, Cremers T, Altar A, Wronski R, Hutter-Paier B, Protter AA: unpublished data]. In addition, when rats were treated at the same single-dose levels of latrepirdine (0.05, 0.5 and 5.0 mg/kg po) as in the NOR study (described in the *Preclinical development, In vivo* section), a dose-dependent increase in brain and plasma concentration was observed (1.67, 14.0 and 172 nM for plasma and 0.15, 1.03 and 13.9 nM for brain with the 0.05-, 0.5- and 5.0-mg/kg doses, respectively) [Giorgetti M, Gibbons JA, Bernales S, Alfaro IE, Drieu La Rochelle C, Cremers T, Altar A, Wronski R, Hutter-Paier B, Protter AA: unpublished data].

A phase I, placebo-controlled, parallel-assignment, multicenter clinical trial assessed concomitant treatment with latrepirdine (gradual within-patient dose titration) and donepezil (10 mg qd) in patients (n = 24) with Alzheimer's disease [1021782]. In the first group, the latrepirdine dose titration consisted of 2.5 mg (tid) for 7 days, followed by 10 mg (tid) for 7 days and finally 20 mg (tid) for 7 days. The titration for the second group was faster: 10 mg (tid) for 7 days, followed by 20 mg (tid) for 7 days. The coadministration of latrepirdine and donepezil did not cause any changes in the C_{max} or AUC values of either agent [1021782]. At the time of publication, a phase I, open-label, single-group-assignment, extension trial (ClinicalTrials.gov identifier: NCT00704782; DIM13) was ongoing in patients (expected n = 21) with Alzheimer's disease.

Clinical development

Phase I

A phase I, open-label, single-center, 8-week clinical trial assessed latrepirdine (20 mg po, tid) in patients (n = 14) with mild-to-moderate Alzheimer's disease [622451]. During patient evaluation, orientation, memory and speech were assessed. Latrepirdine treatment was associated with improvements in cognitive functions, anxiety, depression, tearfulness and headache as measured by the Hasegawa Dementia scale and the Bukatina scale. Assessments of cognitive function continued for 8 weeks following termination of latrepirdine treatment; deterioration in cognitive function from the end of the trial was observed at this time point [622451].

At the time of publication, a further 12 phase I clinical trials were listed as completed, ongoing or recruiting participants on the NIH clinical trials registry. The six completed clinical trials were: (i) a randomized, open-label, crossover-assignment, single-center trial (NCT00827034; B1451020), which assessed single-doses of the anticoagulant warfarin (25 mg po) alone or on day 12 of treatment with latrepirdine (10 mg on days 1 to 7 and 20 mg

on days 8 to 17 po, tid) in healthy volunteers (expected n = 14); (ii) a non-randomized, open-label, parallel-assignment, multicenter trial (NCT00831532; B1451018), which assessed single-dose latrepirdine (5 mg po) in healthy volunteers and patients with mild-to-severe hepatic impairment (expected n = 23); (iii) a randomized, double-blind, placebo-controlled, parallel-assignment, single-center trial (NCT00825084; B1451014), which assessed latrepirdine as single-dose escalation (5, 10 and 20 mg po) and multi-dose titration (10 mg on days 1 to 7 and 20 mg on days 8 to 14 po, tid) in Japanese and Western healthy volunteers (expected n = 48); (iv) a randomized, double-blind, placebo-controlled, crossover-assignment, single-center trial (NCT00907322; B1451036), which assessed single-dose latrepirdine (20, 40 and 60 mg po) in healthy volunteers (expected n = 12); (v) a randomized, double-blind, placebo-controlled, crossover-assignment, single-center trial (NCT00831506; B1451021), which assessed the antiarrythmic agent digoxin (0.125 mg po, qd) alone and in combination with latrepirdine (10 mg days on 1 to 7 and 20 mg days on 8 to 14 po, tid) in healthy volunteers (expected n = 12); and (vi) a randomized, open-label, crossover-assignment, single-center trial (NCT00788047; B1451022), which assessed single-doses of the cough suppressant dextromethorphan (30 ml po) alone or on day 12 of treatment with latrepirdine (20 mg po, tid for 14 days) in healthy volunteers (expected n = 14).

One clinical trial was listed as ongoing, and was described as a randomized, double-blind, placebo-controlled, crossover-assignment, multicenter trial (NCT00829816; DIM17) assessing latrepirdine (20 mg po, tid) in patients (expected n = 44) with Alzheimer's disease on a stable dose of memantine or memantine plus donepezil. The five clinical trials recruiting participants were: (i) a randomized, double-blind, active-controlled, crossover-assignment, single-center trial (NCT00990613; B1451038), which assessed latrepirdine as an oral formulation (10 mg) and a transdermal formulation (5 mg and another to be determined dose) in healthy volunteers (expected n = 20); (ii) a non-randomized, open-label, crossover-assignment, single-center trial (NCT00931073; B1451017), which assessed single-dose latrepirdine (10 mg po) alone or on day 4 of treatment with ketoconazole (400 mg po, qd for 11 days) or omeprazole (40 mg po, qd for 12 days) in volunteers (expected n = 24) with cytochrome P450 subtype 2D6 extensive or poor metabolizer status, based on genotyping; (iii) a randomized, open-label, crossover-assignment, single-center trial (NCT00988624; B1451023), which assessed single-dose latrepirdine (10 mg po) and four latrepirdine modified-release tablets (10 mg po) in healthy volunteers (expected n = 20); (iv) a non-randomized, open-label, parallel-assignment, multicenter trial (NCT00824590; B1451019), which assessed single-dose latrepirdine (20 mg po) in volunteers (expected n = 20) with normal renal function or severe renal impairment; and (v) a randomized, double-blind, placebo- and active-controlled, crossover-assignment, single-center trial (NCT00975481; B1451037), which assessed single-dose latrepirdine (20, 40 and 60 mg po) and alprazolam (1 and 3 mg po) in healthy recreational polydrug users (expected n = 30).

Phase II

Alzheimer's disease—A phase II, randomized, double-blind, placebo-controlled, parallel-assignment, multicenter, 26-week clinical trial (NCT00377715; DIM02) assessed latrepirdine (20 mg po, tid) in patients (n = 183) with mild-to-moderate Alzheimer's disease [924919], [925211], [926134], [927591], [1031264], [1045557]. Concomitant treatment with other antidementia drugs was not permitted, and the baseline parameters were similar and matched without any significant differences between the latrepirdine and placebo groups. The primary outcome measure of the trial was the Alzheimer's disease assessment scale – cognitive subscale (ADAS-cog), which improved by approximately two points from baseline in the latrepirdine cohort compared with a decrease of two points in the placebo cohort at week 26 ($p < 0.0001$). Other outcomes included the mini-mental state evaluation

(MMSE), which improved in the latrepirdine cohort compared with placebo ($p < 0.0001$); the clinician's interview-based impression of change plus caregiver input (CIBIC-plus), which improved by 0.66 points compared with worsening by 0.33 points in the placebo cohort; the Alzheimer's disease cooperative study – activities of daily living (ADCS-ADL), which improved from baseline compared with placebo ($p < 0.002$); and the neuropsychiatric inventory (NPI), which also improved compared with placebo ($p < 0.006$) [926134].

This clinical trial was extended by 26 weeks in patients (n = 134) who re-consented to continue the trial in their originally randomized groups, leading to 1 year of double-blind treatment [924919], [925211], [926134], [1031264], [1045557]. Through 52 weeks of total treatment, the latrepirdine-treated group continued to show significant positive benefit in the placebo-corrected difference on all outcome measures: ADAS-cog (−6.9; $p < 0.0001$ versus placebo), MMSE (2.1; $p = 0.0002$ versus placebo), CIBIC-plus (−0.7; $p = 0.0014$ versus placebo), ADCS-ADL (4.4; $p = 0.0014$ versus placebo) and NPI (−3.3; $p = 0.0201$ versus placebo) [926134]. In the CIBIC-plus analysis, 69% of latrepirdine-treated patients were judged to be improved or unchanged after 1 year [926134]. These benefits were observed in both mild (MMSE baseline score > 18) and moderate (MMSE baseline score ≤ 18) patients, with moderate patients demonstrating the greatest benefit [1031264]. For example, on the ADAS-cog, the mean drug-placebo difference at week 52 was 5.4 for patients with mild disease ($p = 0.0027$ versus placebo) and 9.7 points for patients with moderate disease ($p < 0.0001$ versus placebo) [1031264]. Analyses of the ADAS-cog subdomains comparing all patients receiving latrepirdine with placebo revealed improvements in: memory (word recall [−0.5; $p = 0.04$], word recognition [−1.62; $p = 0.03$] and remembering instructions [−0.24, $p = 0.10$]); orientation (−0.88; $p = 0.01$); constructional and ideational praxis (−0.47; $p = 0.005$ and −0.47; $p = 0.006$, respectively); and language (following commands [−0.65; $p < 0.0001$], naming objects [−0.78; $p < 0.0001$], word finding [−0.39; $p = 0.005$], comprehension [−0.24; $p = 0.15$] and overall language [−0.62; $p = 0.0002$]) [925211]. In addition, caregivers of the patients receiving latrepirdine reported considerably less distress than those receiving placebo (−2.2; $p = 0.04$) [1045557]. Additional analysis of these data revealed that the group treated with latrepirdine had a reduction of time required by caregivers [926134].

This clinical trial was extended by a further 6 months in an open-label design, where all participating patients (n = 104) received latrepirdine (20 mg po, tid), including those formerly receiving placebo [1031261], [1045574]. The data were analyzed using a natural history staggered start (NHSS) approach, which uses the difference in the severity of disease at baseline to reflect a staggered initiation of the drug; in addition, the trial was a staggered-start design because of the group previously receiving placebo. The NHSS approach was used because this approach is less subject to dropout bias and provides a larger disease-modifying estimate than the staggered start approach. Patients originally treated with placebo demonstrated treatment benefit from latrepirdine (reduction in ADAS-cog of 0.96 from week 52), but did not reach the same level as patients originally treated with latrepirdine who maintained a 3.01 point advantage at week 78. The investigators compared the staggered start data with the NHSS data, and concluded that the majority of the affect of latrepirdine treatment in patients with Alzheimer's disease was caused by disease modification. Patients treated with latrepirdine remained at or near their initial baseline level throughout the 18-month treatment on all efficacy outcome measures [1031261].

Huntington's chorea—At the time of publication, a phase I/IIa, non-randomized, open-label, single-group-assignment clinical trial (NCT00387270; DIM03; DIMOND), which assessed latrepirdine (10 and 20 mg po, tid for 7 days) in patients (expected n = 9) with Huntington's chorea was listed on the NIH clinical trials registry as completed. However, no data have been published from this trial.

A phase II, randomized, double-blind, placebo-controlled, parallel-assignment, multicenter clinical trial (NCT00497159; DIM05; DIMOND) assessed latrepirdine (20 mg po, tid for 90 days) in patients (n = 91) with mild-to-moderate Huntington's chorea [1057407]. At day 90, mean MMSE scores were improved in the latrepirdine group compared with placebo (one point improvement; p = 0.03); however, no difference was observed using the ADAS-cog. An improvement in the unified Huntington's disease rating scale was observed, but this was not significant [1057407].

Phase III

Alzheimer's disease—At the time of publication, five phase III, randomized, double-blind, placebo-controlled, parallel-assignment, multicenter clinical trials of latrepirdine were ongoing in patients with Alzheimer's disease. Details were listed on the NIH clinical trials registry, but data were not available. The first of these trials (NCT00675623; DIM14; CONNECTION) was investigating latrepirdine (5 and 20 mg po, tid for 6 months) in patients (expected n = 525) with mild-to-moderate Alzheimer's disease. The second trial (NCT00838110; B1451027) was evaluating latrepirdine (10 mg po, tid for 1 week, followed by 20 mg po, tid for either 12 or 26 weeks) in patients (expected n = 750) with mild-to-moderate Alzheimer's disease; a phase III, non-randomized, open-label, single-group-assignment, multicenter, extension (NCT00939783; B1451029) of this trial was also ongoing. The third trial (NCT00912288; B1451006) was assessing latrepirdine (10 mg po, tid for 1 week, followed by 20 mg po, tid for 25 weeks) in patients (expected n = 576) with moderate-to-severe Alzheimer's disease. The fourth trial (NCT00829374; DIM18) was assessing latrepirdine (5 and 20 mg po, tid for 1 year) in patients (expected n = 1050) with mild-to-moderate Alzheimer's disease receiving concurrent donepezil. The fifth trial (NCT00954590; DIM19) was assessing latrepirdine (20 mg po, tid for 6 months) in patients with moderate-to-severe Alzheimer's disease.

Huntington's chorea—At the time of publication, a phase III, randomized, double-blind, placebo-controlled, parallel-assignment, multicenter clinical trial (NCT00920946; DIM20; HORIZON) to assess latrepirdine (20 mg po, tid for 6 months) was recruiting patients (expected n = 350) with Huntington's chorea [1054173].

Side effects and contraindications

In the phase I, safety and pharmacokinetic clinical trial, which assessed the coadministration of latrepirdine (2.5 to 20 mg tid) and donepezil (10 mg qd) in patients with Alzheimer's disease, no serious adverse events or deaths occurred [1021782]. All adverse events that occurred in the latrepirdine groups were mild in severity, except one fall and one case of neuralgia, which were not considered to be related to the trial drugs. Adverse events reported in at least two patients receiving latrepirdine and more frequently than in the placebo group were fatigue, abdominal distention, dizziness, fall, hyperkalemia and nightmares. The patients with a shortened titration period did not report more adverse events than those on the prolonged titration regimen [1021782].

In the phase I, open-label, single-center clinical trial that assessed latrepirdine in patients with mild-to-moderate Alzheimer's disease, no pathological changes in the hematological or biochemical parameters were observed [622451]. A reduction in leukocyte count was observed at the fourth week of the trial, but this had resolved by the eighth week [622451].

In the phase II clinical trial in patients with Alzheimer's disease, latrepirdine was well tolerated [925211], [926134], [1031264], [1045557]. Adverse events that occurred more frequently in the latrepirdine group compared with the placebo group at week 26 were: dry mouth (14 versus 1%), depressed mood (14 versus 5%), insomnia (9 versus 4%), asthenia (5

versus 2%), hyperkalemia (5 versus 0%), hyperhidrosis (5 versus 1%), motor dysfunction (5 versus 2%) and dyspnea (3 versus 0%) [926134]. At 52 weeks, a similar profile was observed, but the adverse events also included angina pectoris (5 versus 2%), polyuria (5 versus 0%), atrial flutter (3 versus 0%), elevated bilirubin (3 versus 1%) and musculoskeletal pain (3 versus 0%). More serious adverse events occurred in the placebo than the latrepirdine group (11 patients compared with 3, respectively; $p = 0.03$) [926134].

In the phase II clinical trial in patients with Huntington's chorea, latrepirdine and placebo were tolerated equally, with 87 compared with 82% completing the trial, respectively [1057407]. The most common adverse event was fall, occurring in 16% of the placebo group and 9% of the latrepirdine group. Headache was the most common latrepirdine-associated side effect observed in 15% of patients compared with 7% receiving placebo. Other adverse events that occurred in at least 5% of patients were dizziness, nausea, chorea, depression, nasopharyngitis, somnolence, irritability, increased QTc interval and diarrhea; the difference in occurrence between cohorts was not significant for any of these events [1057407].

Patent summary

Latrepirdine was originally claimed in SU-01138164, which was filed in April 1963, but not published until February 1985; there is no record that this patent was granted.

A new use for latrepirdine was claimed by Medivation in WO-09715225. The patent claims the treatment of neurodegenerative disorders, particularly Alzheimer's disease, and was granted as US-06187785, US-07071206 and EP-00876818, which all expire in October 2016. This application was also granted in Russia as RU-02106864, which expires in October 2015.

Further new use cases claimed by Medivation include: WO-2005055951 (claiming use as a geroprotective agent); WO-2007041697, WO-2007087425 and WO-2008036410 (claiming the treatment of particular CNS disorders); WO-2008036410 (claiming treatment of amyotrophic lateral sclerosis); WO-2008069963 (claiming treatment of cognitive dysfunction); WO-2008073231 (claiming treatment of disorders of cerebral circulation); WO-2008147551 (claiming treatment of injury-related mild cognitive impairment, macular degeneration, spinal cord injury and multiple sclerosis); WO-200905771 (claiming treatment of mood disorders) and WO-2009039420 (claiming treatment of ocular diseases). In addition, Medivation claimed a combination of latrepirdine with donepezil for the treatment of Alzheimer's disease in WO-2008051599, and a combination with the atypical antipsychotic risperidone for the treatment of schizophrenia in WO-2009017836. Medivation has also claimed compounds related to latrepirdine in WO-2009055828, and the synthesis of latrepirdine in WO-2009111540. At the time of publication, no regional patents had been granted for these applications.

Latrepirdine was claimed in WO-2008112238 by Grey Fox LLC for the treatment of pain. Alla Chem LLC has filed three product cases for compounds related to latrepirdine, WO-2008123796, WO-2008123800 and WO-2009082268; D2E LLC filed WO-2009038764, another product case for related compounds. At the time of publication, all of these applications were pending grant.

Current opinion

Latrepirdine is a potential novel treatment for Alzheimer's disease and Huntington's chorea. Given the robustness of the phase II clinical data, this compound has a high likelihood of success in phase III trials and subsequently in being granted regulatory approval. Therefore,

it is possible that latrepirdine could be the next drug approved to treat Alzheimer's disease and, likely, Huntington's chorea. In this context, latrepirdine would be likely to be described as a symptomatic treatment for Alzheimer's disease, although the clinical data presented to date suggest that the compound may also have disease-modifying properties. Part of the attractiveness of latrepirdine is the multiple potential mechanisms of action, although the true mechanism of action has not been clearly identified. The potential actions include mitochondrial-potentiating effects, anti-excitotoxic effects, effects on serotonin receptors (5-HT_6 antagonist) and channel-regulating effects. Data suggest that the clinical benefit of latrepirdine is not via cholinesterase inhibition or NMDA-receptor antagonism. Some researchers would consider the lack of a clearly identified mechanism of action to be a detriment; however, in this setting, the rich pharmacology is likely to be a benefit, as multiple mechanisms of action could be exerted simultaneously. In addition, the side effects and safety profile are well established because of the previous use of latrepirdine as an allergy medication [1057240]. Because the compound is being developed and perhaps marketed as a symptomatic treatment for Alzheimer's disease, approval for latrepirdine will avoid the difficult issues of defining disease-modifying endpoints for clinical trials.

Latrepirdine is likely to be used in an adjunctive treatment in both Alzheimer's disease and Huntington's chorea. The compound will probably be safe in conjunction with AChEIs and even potentially with NMDA receptor antagonists, such as memantine, but added efficacy with these drugs remains to be determined. At the time of publication, little published evidence of drug-drug interaction with approved treatments for Alzheimer's disease existed; the results from ongoing trials will be of great interest in this regard. Because the compound is likely to be approved as a symptomatic treatment, latrepirdine may also be used as an adjunct to future disease-modifying treatments. Given the data that have been presented to date, the robustness of the clinical effect is evident, but further research is required to determine whether the compound possesses a disease-modifying property.

As mentioned previously, polypharmacy is likely to be inevitable for the treatment of Alzheimer's disease given the complexity of the biology of the disease; however, it is unknown whether emerging drugs are likely to have drug-drug interactions. In the future, expert panels that create practice guidelines (as has been done with hypertension, diabetes and atherosclerotic heart disease) will need to be convened to provide guidance to practitioners on how to approach the treatment of Alzheimer's disease.

The safety and tolerability of latrepirdine appears to be excellent. Further clinical trial data are needed; however, there is little evidence that ongoing hematological or metabolic monitoring will be required; these findings make this drug attractive from a development standpoint. Nevertheless, postmarketing surveillance, as is customary for all new medications, would be required to continue to ensure that the safety profile observed in clinical trials is maintained in clinical practice.

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