CNS Spectrums

www.cambridge.org/cns

Perspectives

Cite this article: Cummings JL, Devanand DP, and Stahl SM (2020). Dementia-related psychosis and the potential role for pimavanserin. *CNS Spectrums* https://doi.org/10.1017/S1092852920001765

Received: 26 May 2020
Accepted: 24 July 2020

Key words:
Alzheimer's; Parkinson's; Vascular; Frontotemporal; Lewy

Author for correspondence:
Jeffery L. Cummings,
Email: jcummings@cnsinnovations.com

CAMBRIDGE UNIVERSITY PRESS

Dementia-related psychosis and the potential role for pimavanserin

Jeffery L. Cummings[1*], D. P. Devanand[2] and Stephen M. Stahl[3]

[1]Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada at Las Vegas (UNLV) and Cleveland Clinic, Lou Ruvo Center for Brain Health, Las Vegas, Nevada, USA, [2]Department of Psychiatry, Columbia University Medical Center, New York, New York, USA, and [3]Department of Psychiatry, University of California, San Diego, La Jolla, California, USA

Abstract

Dementia-related psychosis (DRP) is prevalent across dementias and typically manifests as delusions and/or hallucinations. The mechanisms underlying psychosis in dementia are unknown; however, neurobiological and pharmacological evidence has implicated multiple signaling pathways and brain regions. Despite differences in dementia pathology, the neurobiology underlying psychosis appears to involve dysregulation of a cortical and limbic pathway involving serotonergic, gamma-aminobutyric acid ergic, glutamatergic, and dopaminergic signaling. Thus, an imbalance in cortical and mesolimbic excitatory tone may drive symptoms of psychosis. Delusions and hallucinations may result from (1) hyperactivation of pyramidal neurons within the visual cortex, causing visual hallucinations and (2) hyperactivation of the mesolimbic pathway, causing both delusions and hallucinations. Modulation of the 5-HT_{2A} receptor may mitigate hyperactivity at both psychosis-associated pathways. Pimavanserin, an atypical antipsychotic, is a selective serotonin inverse agonist/antagonist at 5-HT_{2A} receptors. Pimavanserin may prove beneficial in treating the hallucinations and delusions of DRP without worsening cognitive or motor function.

Introduction

No pharmacological agents are approved by the U.S. Food and Drug Administration (FDA) to treat dementia-related psychosis (DRP). Pimavanserin, an atypical antipsychotic that acts as a selective serotonin inverse agonist/antagonist at 5-HT_{2A} receptors (and to a lesser extent, at 5-HT_{2c} receptors), is the only FDA-approved treatment for hallucinations and delusions associated with Parkinson's disease (PD) psychosis.[1,2] A phase 2 study of pimavanserin in Alzheimer's disease (AD) psychosis met its primary end point at week 6 (mean change in the Neuropsychiatric Inventory-Nursing Home version psychosis score of −3.76 points [SE 0.65] for pimavanserin and −1.93 points [SE 0.63] for placebo; P=0 .045) with an acceptable tolerability profile and no worsening of cognition or motor function.[3] Pimavanserin is being investigated (NCT03325556 and 2017-002227-13) for treating hallucinations and delusions associated with DRP across five common neurodegenerative dementias: AD dementia, PD dementia, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia (VaD).[4-6] This article discusses the emerging understanding of the neurobiology of psychosis, the current state of knowledge about the neurobiology of psychotic symptoms in dementia syndromes, and the hypothesized role of pimavanserin in treating DRP.

Approximately 7.9 million people in the United States have dementia, with this number projected to rise as the elderly population grows.[7-9] Although AD dementia is most common in the United States (60%-80% of cases), other forms of dementia include PD dementia, DLB, FTD, and VaD. While distinctive features characterize each form of dementia, broad symptom overlap is observed.[10]

Dementia is a syndrome characterized by a decline in one or more cognitive domains (eg, memory, language, executive function, problem-solving, attention, and social cognition) sufficiently severe to compromise daily function.[11] Besides the well-recognized cognitive deficits characteristic of dementia, noncognitive symptoms (often referred to as behavioral and psychological symptoms of dementia or neuropsychiatric symptoms [NPS]) are estimated to occur in up to 90% of individuals during the course of dementia. NPS include behavioral symptoms (such as agitation, aggression, disinhibition, elation, and irritability), aberrant motor behavior, anxiety, apathy, appetite changes, depression, sleep disturbances, and symptoms of psychosis.[12]

Although some dementia patients display no or only a few noncognitive symptoms, multiple NPS commonly occur simultaneously.[12] The Agitation Definition Work Group of the International Psychogeriatric Association defines agitation as occurring in patients with a cognitive impairment or dementia syndrome; exhibiting behavior consistent with emotional distress;

Table 1. Prevalence ranges for psychosis, delusions, and hallucinations in AD dementia, VaD, DLB, PD Dementia, and FTD

	Alzheimer's Disease Dementia	Vascular Dementia	Dementia with Lewy Bodies	Parkinson's Disease Dementia	Frontotemporal Dementia
Overall psychosis prevalence	30%	15%	75%	50%	10%
Delusions prevalence	10%-39%	14%-27%	40%-57%	28%-50%	2.3%-6%
Hallucinations prevalence	11%-17%	5%-14%	55%-78%	32%-63%	1.2%-13%

manifesting excessive motor activity, verbal aggression, or physical aggression; and evidencing behaviors that cause excess disability and are not solely attributable to another disorder.[13] In contrast, DRP is defined by delusions or hallucinations occurring after the onset of cognitive decline, persisting for at least 1 month, and not better explained by delirium or some other mental illness.[11] Both hallucinations and delusions are associated with behavioral symptoms such as physical and verbal aggression in patients with dementia.[14–16]

Prevalence estimates for psychosis range from 10% for FTD to 75% for DLB (Table 1).[16–30] In the United States, an estimated 2.34 million people suffer from DRP.[16–30] Visual hallucinations occur in all forms of dementia and are commonly observed in PD dementia and DLB.[31,32] Delusions are also observed in all forms of dementia, most commonly paranoid delusions (eg, theft or spousal infidelity) and misidentifications, though the latter is sometimes considered a type of memory deficit rather than psychosis.[31,33] DRP varies within and across patients in the psychotic symptoms manifested and in the severity of symptoms during the course of illness.[33] DRP is more frequently observed in patients with more advanced dementia. DRP has consistently been associated with greater caregiver burden and more rapid progression to severe dementia, institutionalization, and death.[34–38]

Many forms of dementia, aside from VaD, result from neurodegenerative disease and are associated with various proteinopathies characterized by protein misfolding and aggregation. Aberrant aggregated proteins in AD produce β-amyloid plaques and neurofibrillary tangles (hyperphosphorylated tau aggregates).[39,40] In DLB and PD dementia, Lewy bodies and Lewy neurites, composed primarily of phosphorylated α-synuclein aggregates, accumulate preferentially in limbic brain regions.[41–43] FTD may be associated with either aggregated tau protein or aggregated trans-activator regulatory DNA-binding 43 (TDP-43) protein.[44]

Post-mortem analyses have revealed most dementia patients exhibit mixed pathology comprising abnormal protein aggregates plus vascular changes.[45,46] In one study of community-dwelling adults, 56% of dementia patients were diagnosed with multiple underlying pathologies (AD in combination with either PD/DLB, infarctions representing vascular brain injury, or both).[46] After adjusting for age, individuals with multiple diagnoses were deemed to be nearly three times more likely to develop dementia as those with a single underlying pathology.[46] In a separate study, database analyses revealed that 59% to 68% of patients with AD neuropathology also displayed Lewy body pathology or vascular brain injury.[45]

Neurobiology of Psychosis

The underlying mechanisms behind psychosis in dementia are unknown. The neurobiology of psychosis has primarily been examined in studies of patients with schizophrenia and animals investigated in pharmacological probe paradigms.[47] Taken together, the evidence suggests alterations in multiple signaling pathways—including dopaminergic, gamma-aminobutyric acid (GABA)ergic, glutamatergic, and serotonergic neurotransmission—may contribute to psychosis.[48] Excess dopamine signaling in the mesolimbic pathway, which projects from the ventral tegmental area (VTA) to the nucleus accumbens, has been demonstrated to promote positive symptoms, primarily delusions and hallucinations.[49] Under basal conditions, GABAergic interneurons provide inhibitory regulation of the activity of cortical pyramidal neurons. Inhibition of N-methyl-D-aspartate (NMDA) receptors reduces the inhibitory activity of GABAergic interneurons, resulting in glutamatergic hyperfunction. In rodent models, NMDA receptor antagonism or cortical and hippocampal NMDA receptor deletion results in psychotic-like behaviors.[50,51] Similarly, ketamine-induced NMDA antagonism significantly increases positive symptoms in haloperidol-treated patients diagnosed with schizophrenia.[52] Glutamatergic projections from the prefrontal cortex provide tonic control of dopaminergic neurons in the VTA. Microdialysis and electrical stimulation rodent models reveal that glutamatergic hyperfunction increases burst firing of dopaminergic neurons in the VTA, stimulating the mesolimbic pathway.[53,54]

These findings are supported by basic pharmacological intervention studies showing that multiple signaling pathways contribute to psychosis. These observations include dopamine D2 receptor activation via psychostimulants, glutamate NMDA receptor inhibition via dissociative anesthetics, and serotonin 5-HT_{2A} receptor activation via psychedelics, all of which have been reported to precipitate psychotic symptoms.[55] Methamphetamine, which is a substrate for the dopamine transporter (DAT), increases the firing rate of cultured rat dopamine neurons, triggering an excitatory response at dopamine concentrations lower than those required for D2 autoreceptor activation.[56] Both methamphetamine and the DAT inhibitor cocaine, which increases extracellular dopamine levels via uptake inhibition, induce paranoid delusions as well as auditory and tactile hallucinations in stimulant-dependent individuals.[57,58] Ketamine, a noncompetitive NMDA receptor antagonist, significantly increases hallucinations and delusions in schizophrenic patients following administration of subanesthetic doses and increases regional cerebral blood flow to the anterior cingulate cortex, while decreasing blood flow to the hippocampus and primary visual cortex.[59,60] In addition, subanesthetic doses of ketamine induces acute auditory verbal hallucinations and paranoid delusions in control subjects without psychosis in a reduced-stimulation environment.[61] Administration of the serotonin 5-HT_{2A} receptor agonist lysergic acid diethylamide (LSD) to healthy volunteers results in increased cerebral blood flow and enhanced resting-state functional connectivity in the visual cortex, which strongly correlates with visual hallucinations.[62] Administration of the 5-HT_{2A} receptor agonist psilocybin to hallucinogen-naïve adults precipitates mystical delusions that persist at 14-month follow-up in 60% of subjects.[63] In a separate study in

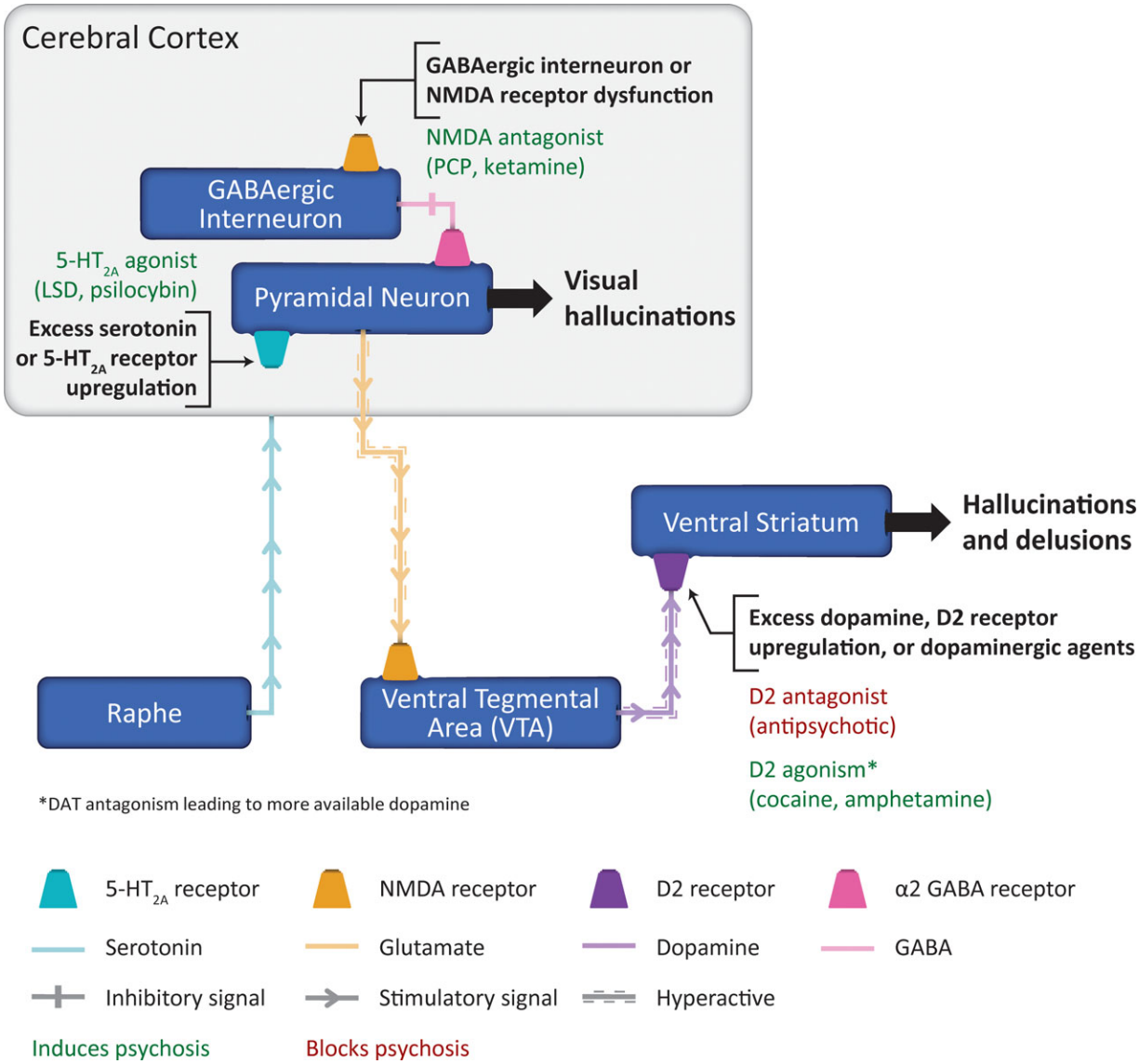

Figure 1. Hypothesized cortical–limbic psychosis pathway and proposed mechanism of disease for DRP. Neurobiological and pharmacological evidence suggests that hallucinations and delusions are precipitated by overactivation of the mesolimbic pathway, while visual hallucinations are mediated via overactivation of the visual cortex. Dissociative anesthetic-induced (ie, PCP, ketamine) glutamate NMDA receptor antagonism, psychedelic-induced (ie, LSD, psilocybin) serotonin 5-HT_{2A} receptor agonism, and psychostimulant-induced (ie, amphetamine, cocaine) dopamine D2 receptor agonism/DAT antagonism have all been reported to precipitate hallucinations and delusions. In contrast, antipsychotic-mediated D2 and 5-HT_{2A} antagonism treat both hallucinations and delusions. GABAergic interneuron or NMDA receptor dysfunction, and excess serotonin or 5-HT_{2A} receptor upregulation in the cerebral cortex can result in sustained activation of pyramidal neurons and may lead to hyperactive glutamatergic signaling to the VTA, resulting in excess dopamine or D2 receptor upregulation in the ventral striatum, triggering hallucinations and delusions in DRP.[55–56,70–87]

healthy human volunteers, psychotic symptoms that closely mimicked those observed in first-episode schizophrenic patients (including sensory misperceptions and thought-process disruption) occur within 20 to 30 minutes of psilocybin administration. Pretreatment with the 5-HT_{2A} receptor antagonist ketanserin inhibits psilocybin-induced psychosis in a dose-dependent manner, while pretreatment with the D2 receptor antagonist haloperidol does not affect psilocybin-induced hallucinations, further supporting the idea that certain symptoms of hallucinogen-induced psychosis (such as visual hallucinations) result from 5-HT_{2A} agonism, while others (such as auditory hallucinations) are more strongly linked to the D2 receptor.[64] Additional support for multifactorial signaling stems from the observation that conventional antipsychotics exert their effects primarily via D2 receptor inhibition, while atypical antipsychotics act as serotonin–dopamine antagonists, inhibiting both D2 and 5-HT_{2A} receptors.[65]

Taken together, neurobiological and pharmacological evidence points to a common, interconnected cortical–limbic psychosis pathway (Figure 1). Both the occurrence of hallucinogen 5-HT_{2A} receptor effects in the prefrontal and visual cortices, and the observation that loss of serotonin nerve terminals in the prefrontal and visual cortices of patients with PD psychosis leads to upregulation of 5-HT_{2A} receptors in the cortex support this hypothesis. A possible convergence of many of these pathways into 5-HT_{2A}-modulated systems is suggested by the observation that the 5-HT_{2A} receptor is affected by essentially all atypical antipsychotics, which led to the development of pimavanserin, a

5-HT_{2A}-selective inverse agonist/antagonist.[66] In preclinical rodent studies, pimavanserin reduced both amphetamine- and NMDA receptor antagonist-induced hyperactivity when combined with haloperidol or haloperidol and risperidone, respectively.[67] Additionally, pimavanserin was shown to reverse psychosis-like behaviors in rodent models of PD psychosis without impairing motor performance or interfering with the efficacy of PD medications.[68] Finally, pimavanserin increased dopamine release in the medial prefrontal cortex but not in the nucleus accumbens, suggesting pimavanserin may be beneficial for cognitive, negative, and psychotic symptoms.[69]

Changes in Dementia that may Result in Psychosis Pathway Dysfunction

The cortical–limbic psychosis pathway provides numerous points where dysfunction could trigger delusions and/or hallucinations. The pathology and dysfunction across the dementias leading to delusions and/or hallucinations may be different in specific dementias but each is positioned to affect the function of the cortical–limbic system thought to mediate psychosis. The evidence for dysfunction which could disrupt the cortical–limbic psychosis pathway in each dementia is described below.

PD dementia

While dopamine depletion in the dorsal striatum due to loss of nigrostriatal neurons results in the characteristic motor symptoms of PD, serotonin dysfunction is thought to be the underlying cause of PD psychosis. Post-mortem analyses indicate Lewy body and Lewy neurite deposition in the raphe nucleus magnus, obscurus, and pallidus, and the gigantocellular nucleus of the medullary lateral reticular formation nuclei (which comprise the serotonergic caudal brainstem complex) precedes deposition in dopaminergic midbrain neurons.[88] In addition, significant decreases in serotonin, the serotonin transporter (SERT), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) are observed in the caudate in post-mortem analyses of PD patients.[72] During the early stages of PD, SERT expression is diminished in the forebrain, but preserved in the caudate, and increased serotonergic uptake is observed in the thalamus and raphe nuclei, indicating a shift toward mesolimbic and mesocortical dysfunction.[73,74] As PD progresses, SERT expression in the caudate decreases and is correlated with disease stage.[75] In PD patients with visual hallucinations, upregulation of 5-HT_{2A} receptors has been observed using positron emission tomography in the inferolateral temporal cortex—in complex visual processing—as well as other portions of the ventral visual pathway, including the bilateral inferior occipital gyrus and right fusiform gyrus.[76,77] 5-HT_{2A} receptor upregulation may represent a compensatory mechanism by which the brain attempts to counteract reductions in serotonin levels.[77] In a double-blind, randomized, placebo-controlled phase 3 study of the efficacy of pimavanserin in the treatment of hallucinations and delusions associated with PD psychosis, a post-hoc subgroup analysis revealed patients with cognitive impairment (Mini-Mental State Examination scores 21-24) demonstrate a significantly greater improvement in Scale for the Assessment of Positive Symptoms-PD scores from baseline to week 6 with pimavanserin as compared to placebo-treated patients (P=0.002), suggesting pimavanserin may exhibit a more robust effect in cognitively impaired patients.[89]

Imaging studies demonstrate that PD dementia is associated with more widespread cortical cholinergic depletion than that observed in patients with PD who do not exhibit dementia.[90,91] Modulation of cholinergic activity has been reported to decrease hallucinations and delusions in PD dementia patients. Treatment with the acetylcholinesterase inhibitor donepezil significantly reduces hallucinations and paranoid ideation, as well as overall rating scale scores for PD psychosis.[92] At present, the underlying mechanism for these effects is unknown. Serotonin has been reported to inhibit acetylcholine release from cortical cholinergic nerve terminals[93] and 5-HT receptor inverse agonism/antagonism may represent another therapeutic strategy to modulate cortical cholinergic activity.

Dementia with Lewy bodies

In DLB, the density of Lewy bodies in limbic areas (highest density in the amygdala) is significantly higher than in neocortical areas.[94] As in PD, serotonin dysfunction is thought to be the underlying cause of psychosis in DLB. Cortical 5-HT_2 binding differs between patients with DLB with and without hallucinations. Significant deficits in 5-HT_2 binding are observed in cortical layers III and V (deep cortical layers that contain pyramidal neurons) in patients who did not experience hallucinations, whereas a 5-HT_2 binding deficit was observed only in one upper cortical layer in patients who did experience hallucinations, suggesting 5-HT_2 receptor preservation in the temporal cortex may contribute to hallucinations in this population.[78] This hypothesis is further supported by the observation that serotonergic receptor binding and 5-HIAA levels were significantly decreased in nonhallucinating vs hallucinating patients with DLB in a neurochemical analysis of the temporal cortex. In the same study, downregulation of choline acetyltransferase activity was observed in the temporal and parietal cortices, particularly in those experiencing hallucinations.[79] Treatment with the cholinesterase inhibitor rivastigmine decreased delusions and hallucinations in patients with DLB compared to placebo.[95] The mechanism underlying the efficacy of cholinesterase inhibition in the treatment of DLB remains unresolved. However, hallucinations in patients with DLB have been proposed to result from imbalances between the serotonergic and cholinergic inputs to the cortex, suggesting restoration of the balance between the two inputs may account for this effect.[96]

AD dementia

Although serotonergic signaling is altered in AD, it may not be the primary dysfunction contributing to psychosis. When compared to healthy controls, significant reductions in 5-HT_2 receptor binding and expression have been observed in the frontal, temporal, and cingulate cortices, as well as the amygdala and hippocampus, in patients with AD.[97–101] In a study of psychopathology in late-onset AD patients, the 5-HT_{2A} receptor polymorphism 102-T/C was significantly associated with visual and auditory hallucinations, and the 5-HT_{2C} receptor polymorphism Cys23Ser was significantly associated with visual hallucinations, implicating neurodegeneration in the biology of the psychotic symptoms of individuals expressing these genetic variations. However, the 5-HT_{2A} 102-T/C polymorphism reduces 5-HT_{2A} receptor expression while the 5-HT_{2C} Cys23Ser polymorphism leads to functional downregulation of the 5-HT_{2C} receptor.[102–104]

Concomitant serotonergic and cholinergic deficits have been observed in the frontal and temporal cortices in AD patients as compared to healthy controls, and the ratio of serotonin to acetylcholinesterase in the temporal cortex is correlated with psychosis in

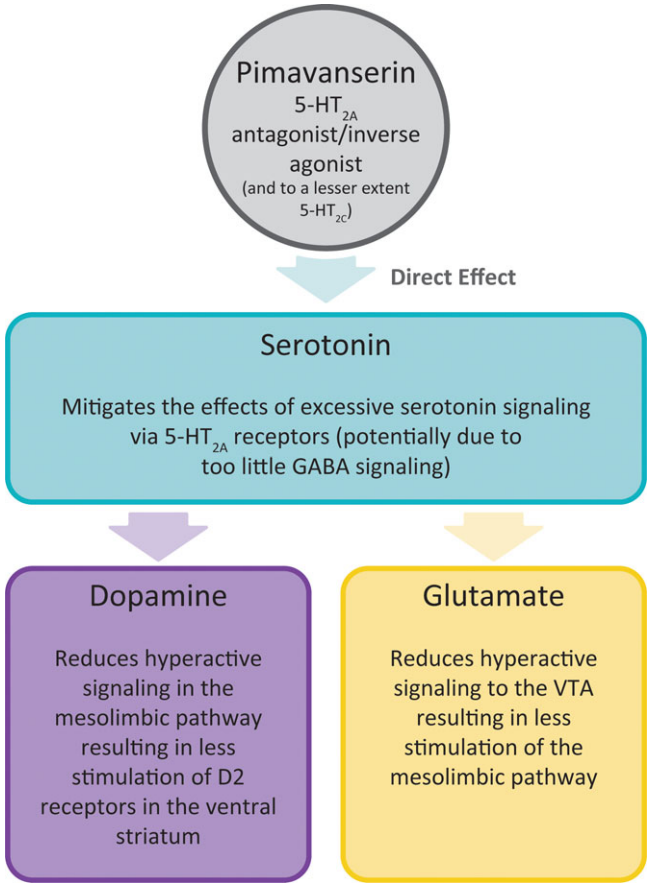

Figure 2. Pimavanserin-mediated 5-HT$_{2A}$ receptor inhibition: hypothesized modulation of signaling through a variety of neurotransmitters. Through 5-HT$_{2A}$ antagonism/reverse agonism, pimavanserin is proposed to act as a targeted serotonergic modulator of circuits, mitigating the effects of GABAergic deficits and excess serotonergic signaling, while also reducing hyperactive glutamatergic signaling and mesolimbic pathway activation.

female patients.[105] Cholinesterase inhibitors used in the treatment of AD may improve hallucinations and delusions in some patients.[106]

There is evidence of GABAergic and glutamatergic dysfunction in AD which might disrupt the cortical–limbic psychosis pathway. Significant reductions in GABA concentrations in numerous cortical areas, including the temporal, frontal (orbitofrontal and premotor cortex), parietal, and occipital cortices, are observed in biopsy and autopsy specimens obtained from AD patients.[107-111] Alterations in NMDA-mediated glutamatergic signaling appears to vary throughout the course of AD. Under normal circumstances, glutamate regulates the inhibitory tone of these GABA neurons; amyloid appears to increase the sensitivity of these receptors to glutamate, leading to glutamatergic hyperactivation and GABAergic neuronal degeneration. During the later stages of disease progression, excessive GABAergic neuronal degeneration results in NMDA receptor hypofunction.[80] Evidence of GABAergic or glutamatergic dysfunction has yet to be directly associated with psychosis in AD. Treatment of AD patients with the NMDA receptor antagonist memantine, which was shown to inhibit the excitotoxic effects of NMDA glutamate receptors, has occasionally been reported to worsen or induce new visual hallucinations in AD patients.[81]

Frontotemporal dementia

Deficiencies in the serotonergic system have been reported in imaging studies, post-mortem tissue analyses, and cerebrospinal fluid studies of patients with FTD. Decreased 5-HT$_{2A}$ receptor expression has been observed in the orbitofrontal, frontal medial, and cingulate cortices of such patients.[82] Data regarding how GABAergic and glutamatergic signaling are affected in FTD are incomplete; however, loss of glutamatergic pyramidal cells and GABAergic neurons in the upper layers of the frontal and temporal cortices has been reported.[83] MRI studies have revealed widespread limbic atrophy in FTD,[112,113] suggesting disruption of the cortical–limbic psychosis pathway may occur. However, data regarding dysfunction specific to psychosis in this population are not yet reported, possibly because psychosis is less common in FTD.

Vascular dementia

Serotonergic dysfunction is present in VaD, with increased 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor binding observed in the temporal cortex of post-mortem tissue samples from multi-infarct VaD patients.[84] The relationship between this increased receptor binding and psychosis is unknown. Data regarding the roles of GABAergic and glutamatergic signaling in VaD is lacking.

Neurotransmission alterations across dementias

While the strength of the evidence varies across these dementias, all have been associated with alterations in neurotransmission which

have the potential to impact the cortical–limbic psychosis pathway. Each of these conditions is highly heterogeneous and the likelihood an individual patient will develop psychosis varies greatly. Further research is required to confirm how etiological factors, such as the anatomical locations of neurodegeneration, compensatory mechanisms, and genetic influences contribute to the development of psychosis.

Proposed Mechanism for DRP

The proposed mechanism for DRP is believed to involve a common cortical–limbic psychosis pathway (Figure 1). Cortical GABAergic interneuron or NMDA receptor dysfunction is hypothesized to result in loss of inhibitory tone, leading to hyperactivity of glutamatergic neurons that signal to the VTA. Alternatively, excessive signaling via 5-HT_{2A} receptors on pyramidal glutamate neurons can lead to hyperactive glutamatergic neurons that signal to the VTA. Sustained hyperactive glutamatergic signaling then leads to mesolimbic dopamine pathway hyperactivation, resulting in hallucinations and delusions. Excess signaling via 5-HT_{2A} receptors in the visual cortex may be responsible specifically for visual hallucinations.[64–66,70,72–87]

The cortical–limbic psychosis pathway can be triggered in a variety of different ways across dementias based on which neurons are lost or damaged and which signaling pathways become disordered but appears to be responsive to serotonin modulation. Cortical GABA interneuron dysfunction, excess serotonin, cortical 5-HT_{2A} receptor upregulation, excess striatal dopamine, striatal D2 receptor upregulation, and excess glutamate signaling all have the potential to contribute to pathway dysfunction.

Proposed Mechanism of Action of Pimavanserin

Across the underlying causes of cortical–limbic psychosis pathway hyperactivation, 5-HT_{2A} receptor antagonism represents a common point of regulation and for treatment intervention with antipsychotics.[66] Pimavanserin is a selective serotonin inverse agonist/antagonist at 5-HT_{2A} receptors, with 40-fold less activity at 5-HT_{2C} receptors and no affinity for dopaminergic, histaminergic, muscarinic, or adrenergic receptors, and is proposed to act as a targeted serotonergic modulator of circuits (Figure 2).[66] Pimavanserin is thought to reduce the activity of these receptors to below basal levels and regulate the effects of both cortical GABAergic deficits and excess cortical serotonergic signaling. This is posited to decrease visual hallucinations and attenuate glutamate signaling to the VTA and mesolimbic pathway, further decreasing delusions and hallucinations.

Summary

DRP is a commonly occurring phenomenon across dementias, yet no pharmacological agents are currently approved by the FDA for DRP treatment. Commonly used typical and atypical antipsychotics have an increased risk of death and other treatment-limiting side effects.[114,115] While the etiology of DRP is unknown, neurobiological and pharmacological evidence supports a common, interconnected cortical–limbic psychosis pathway mediating DRP, which may be modified via 5-HT_{2A} receptor inverse agonism/antagonism. The only FDA-approved agent to treat hallucinations and delusions associated with PD psychosis, pimavanserin (proposed to act as a targeted serotonergic modulator of circuits), is being investigated to treat DRP in a phase 3 trial completed in 2019.[5] The selectivity of pimavanserin presents a potential novel mechanism for the management of hallucinations and delusions associated with DRP.[66,89]

Acknowledgments. The authors received editorial assistance in the preparation of this manuscript from Arbor Scientia, Inc., which was supported by Acadia Pharmaceuticals Inc., San Diego, CA. Dr. Cummings is supported by Keep Memory Alive (KMA), National Institute of General Medical Sciences (NIGMS) grant P20GM109025, National Institute of Neurological Disorders and Stroke (NINDS) grant U01NS093334, and National Institute of Aging (NIA) grant R01AG053798. Dr. Devanand is supported by the NIA.

Disclosures. Dr. Cummings has provided consultation to Acadia, Actinogen, Alkahest, Allergan, Alzheon, Avanir, Axsome, BiOasis, Biogen, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, Foresight, Genentech, Green Valley, Grifols, Otsuka, Resverlogix, Roche, Samumed, Samus, Signant, Third Rock, Toyama, and United Neuroscience pharmaceutical and assessment companies. Dr. Cummings has stock options in Prana, Neurokos, Adamas, MedAvante-ProPhase, Anovis, and BiOasis.

Dr. Devanand has provided consultation to Acadia, BXcel, Corium, Eisai, Genentech, and Grifols.

Dr. Stahl has served as a consultant to Acadia, Alkermes, Allergan, Arbor Pharmaceuticals, Axovant, Axsome, Celgene, Concert, Clearview, EMD Serono, Eisai Pharmaceuticals, Ferring, Impel NeuroPharma, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen, Lilly, Lundbeck, Merck, Otsuka, Pfizer, Sage Therapeutics, Servier, Shire, Sunovion, Takeda, Taliaz, Teva, Tonix, Tris Pharma, and Vifor Pharma; he is a board member of Genomind; he has served on speakers bureaus for Acadia, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, Takeda and Vertex; and he has received research and/or grant support from Acadia, Avanir, Braeburn Pharmaceuticals, Eli Lilly, Intra-Cellular Therapies, Ironshore Pharmaceuticals, ISSWSH, Neurocrine, Otsuka, Shire, Sunovion, and TMS NeuroHealth Centers.

References

1. *NUPLAZID® [package insert]*. San Diego, CA: Acadia Pharmaceuticals Inc.; 2019.
2. Cummings J, Isaacson S, Mills R, *et al.* Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;**383**(9916):533–540.
3. Ballard C, Banister C, Khan Z, *et al.* Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study. *Lancet Neurol.* 2018;**17**(3):213–222.
4. Acadia Pharmaceuticals Inc. Analyses of pimavanserin studies evaluating treatment in Alzheimer's disease psychosis and parkinson's disease psychosis published in the journal of prevention of Alzheimer's disease suggest potential for treating dementia-related psychosis. Acadia Pharmaceuticals website. http://ir.acadia-pharm.com/phoenix.zhtml?c=125180&p=irol-newsArticle&ID=2366704. Updated September 2018. Accessed June 2019.
5. Relapse prevention study of pimavanserin in dementia-related psychosis. ClinicalTrials.gov identifier: NCT03325556. https://clinicaltrials.gov/ct2/show/NCT03325556. Updated April 21, 2020. Accessed July 2020.
6. EU Clinical Trials Register. Clinical trials for 2017-002227-13. https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-002227-13. Accessed July 2020.
7. Goodman RA, Lochner KA, Thambisetty M, *et al.* Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement*. 2017;**13**(1):28–37.
8. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*. 2013;**80**(19):1778–1783.

9. Plassman BL, Langa KM, Fisher GG, *et al.* Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology*. 2007;**29**(1–2):125–132.
10. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement*. 2017, 2017;**13**(4):325–373.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Arlington, VA: American Psychiatric Association; 2013.
12. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol*. 2012;**3**:73
13. Cummings J, Mintzer J, Brodaty H, *et al.* Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *Int Psychogeriatr*. 2015;**27**(1):7–17.
14. Gilley DW, Wilson RS, Beckett LA, Evans DA. Psychotic symptoms and physically aggressive behavior in Alzheimer's disease. *J Am Geriatr Soc*. 1997;**45**(9):1074–1079.
15. Leonard R, Tinetti ME, Allore HG, Drickamer MA. Potentially modifiable resident characteristics that are associated with physical or verbal aggression among nursing home residents with dementia. *Arch Intern Med*. 2006;**166**(12):1295–1300.
16. Lopez OL, Becker JT, Sweet RA, *et al.* Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2003;**15**(3):346–353.
17. Ballard C, Neill D, O'Brien J, *et al.* Anxiety, depression and psychosis in vascular dementia: prevalence and associations. *J Affect Disord*. 2000;**59**(2):97–106.
18. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. I: disorders of thought content. *Br J Psychiatry*. 1990;**157**:72, 92–76, 74.
19. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. II: disorders of perception. *Br J Psychiatry*. 1990;**157**:76, 92–81, 74.
20. Johnson DK, Watts AS, Chapin BA, Anderson R, Burns JM. Neuropsychiatric profiles in dementia. *Alzheimer Dis Assoc Disord*. 2011;**25**(4):326–332.
21. Lyketsos CG, Lopez O, Jones B, *et al.* Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA*. 2002;**288**(12):1475–1483.
22. Lyketsos CG, Steinberg M, Tschanz JT, *et al.* Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry*. 2000;**157**(5):708–714.
23. Leroi I, Voulgari A, Breitner JC, Lyketsos CG. The epidemiology of psychosis in dementia. *Am J Geriatr Psychiatry*. 2003;**11**(1):83–91.
24. Ballard C, Saad K, Patel A, *et al.* The prevalence and phenomenology of psychotic symptoms in dementia sufferers. *Int J Geriatr Psychiatry*. 1995;**10**(6):477–485.
25. Nagahama Y, Okina T, Suzuki N, *et al.* Classification of psychotic symptoms in dementia with Lewy bodies. *Am J Geriatr Psychiatry*. 2007;**15**(11):961–967.
26. Aarsland D, Ballard C, Larsen JP, McKeith I. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. *Int J Geriatr Psychiatry*. 2001;**16**(5):528–536.
27. Ballard C, Holmes C, McKeith I, *et al.* Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry*. 1999;**156**(7):1039–1045.
28. Lee W, Tsai C, Gauthier S, Wang S, Fuh J. The association between cognitive impairment and neuropsychiatric symptoms in patients with Parkinson's disease dementia. *Int Psychogeriatr*. 2012;**24**(12):1980–1987.
29. Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: prevalence and review. *Dement Geriatr Cogn Disord*. 2008;**25**(3):206–211.
30. Mourik JC, Rosso SM, Niermeijer MF, *et al.* Frontotemporal dementia: behavioral symptoms and caregiver distress. *Dement Geriatr Cogn Disord*. 2004;**18**(3–4):299–306.
31. Fenelon G, Soulas T, Zenasni F, Cleret de Langavant L. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. *Mov Disord*. 2010;**25**(6):763–766.
32. McKeith IG, Boeve BF, Dickson DW, *et al.* Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;**89**(1):88–100.
33. Devanand DP, Jacobs DM, Tang MX, *et al.* The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry*. 1997;**54**(3):257–263.
34. Haupt M. Psychotherapeutic intervention in dementia. *Dementia*. 1996;**7**(4):207–209.
35. Lim L, Zhang A, Lim L, *et al.* High caregiver burden in young onset dementia: what factors need attention? *J Alzheimers Dis*. 2018;**61**(2):537–543.
36. Naimark D, Jackson E, Rockwell E, Jeste DV. Psychotic symptoms in Parkinson's disease patients with dementia. *J Am Geriatr Soc*. 1996;**44**(3):296–299.
37. Peters ME, Schwartz S, Han D, *et al.* Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. *Am J Psychiatry*. 2015;**172**(5):460–465.
38. Scarmeas N, Brandt J, Albert M, *et al.* Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol*. 2005;**62**(10):1601–1608.
39. Rovelet-Lecrux A, Hannequin D, Raux G, *et al.* APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet*. 2006;**38**(1):24–26.
40. Hyman BT, Phelps CH, Beach TG, *et al.* National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012;**8**(1):1–13.
41. Goldman JE, Yen SH, Chiu FC, Peress NS. Lewy bodies of Parkinson's disease contain neurofilament antigens. *Science*. 1983;**221**(4615):1082–1084.
42. Colom-Cadena M, Pegueroles J, Herrmann AG, *et al.* Synaptic phosphorylated alpha-synuclein in dementia with Lewy bodies. *Brain*. 2017;**140**(12):3204–3214.
43. Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol*. 2000;**10**(3):378–384.
44. Nelson PT, Dickson DW, Trojanowski JQ, *et al.* Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;**142**(6):1503–1527.
45. Brenowitz WD, Keene CD, Hawes SE, *et al.* Alzheimer's disease neuropathologic change, Lewy body disease, and vascular brain injury in clinic- and community-based samples. *Neurobiol Aging*. 2017;**53**:83–92.
46. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;**69**(24):2197–2204.
47. Gründer G, Cumming P. Chapter 7—the dopamine hypothesis of schizophrenia: current status. In: Abel T, Nickl-Jockschat T, eds. *The Neurobiology of Schizophrenia*. San Diego, CA: Academic Press; 2016:109–124.
48. Hirvonen J, Hietala J. Dopamine receptor imaging in schizophrenia: focus on genetic vulnerability. In: Seeman P, Madras B, eds. *Imaging of the Human Brain in Health and Disease*. San Diego, CA: Elsevier Inc.; 2014:341–360.
49. Watanabe T, Morimoto K, Nakamura M, Suwaki H. Modification of behavioral responses induced by electrical stimulation of the ventral tegmental area in rats. *Behav Brain Res*. 1998;**93**(1–2):119–129.
50. Zhou Z, Zhang G, Li X, *et al.* Loss of phenotype of parvalbumin interneurons in rat prefrontal cortex is involved in antidepressant- and propsychotic-like behaviors following acute and repeated ketamine administration. *Mol Neurobiol*. 2015;**51**(2):808–819.
51. Nakazawa K, Zsiros V, Jiang Z, *et al.* GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology*. 2012;**62**(3):1574–1583.
52. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology*. 1995;**13**(1):9–19.
53. Almodovar-Fabregas LJ, Segarra O, Colon N, *et al.* Effects of cocaine administration on VTA cell activity in response to prefrontal cortex stimulation. *Ann N Y Acad Sci*. 2002;**965**:157–171.

54. Karreman M, Moghaddam B. The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. *J Neurochem*. 1996;**66**(2):589–598.
55. Rolland B, Jardri R, Amad A, *et al.* Pharmacology of hallucinations: several mechanisms for one single symptom? Biomed Res Int. 2014;**2014**:307106
56. Ingram SL, Prasad BM, Amara SG. Dopamine transporter-mediated conductances increase excitability of midbrain dopamine neurons. *Nat Neurosci*. 2002;**5**(10):971–978.
57. Mahoney JJ, 3rd., Kalechstein AD, De La Garza R, 2nd., Newton TF. Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. *Am J Addict*. 2008;**17**(2):83–98.
58. McKetin R, Baker AL, Dawe S, Voce A, Lubman DI. Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Res*. 2017;**251**:349–354.
59. Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport*. 1995;**6**(6):869–872.
60. Krystal JH, Karper LP, Seibyl JP, *et al.* Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;**51**(3):199–214.
61. Powers AR, 3rd, Gancsos MG, Finn ES, Morgan PT, Corlett PR. Ketamine-induced hallucinations. *Psychopathology*. 2015;**48**(6):376–385.
62. Carhart-Harris RL, Muthukumaraswamy S, Roseman L, *et al.* Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proc Natl Acad Sci U S A*. 2016;**113**(17):4853–4858.
63. Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol*. 2008;**22**(6):621–632.
64. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*. 1998;**9**(17):3897–3902.
65. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th ed. New York, NY: Cambridge University Press; 2013.
66. Hacksell U, Burstein ES, McFarland K, Mills RG, Williams H. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. *Neurochem Res*. 2014;**39**(10):2008–2017.
67. Gardell LR, Vanover KE, Pounds L, *et al.* ACP-103, a 5-hydroxytryptamine 2A receptor inverse agonist, improves the antipsychotic efficacy and side-effect profile of haloperidol and risperidone in experimental models. *J Pharmacol Exp Ther*. 2007;**322**(2):862–870.
68. McFarland K, Price DL, Bonhaus DW. Pimavanserin, a 5-HT2A inverse agonist, reverses psychosis-like behaviors in a rodent model of Parkinson's disease. *Behav Pharmacol*. 2011;**22**(7):681–692.
69. Li Z, Ichikawa J, Huang M, *et al.* ACP-103, a 5-HT2A/2C inverse agonist, potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. *Psychopharmacology (Berl)*. 2005;**183**(2):144–153.
70. Kometer M, Schmidt A, Jancke L, Vollenweider FX. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on alpha oscillations, N170 visual-evoked potentials, and visual hallucinations. *J Neurosci*. 2013;**33**(25):10544–10551.
71. Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectrums*. 2018;**23**(3):187–191.
72. Kish SJ, Tong J, Hornykiewicz O, *et al.* Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. *Brain*. 2008;**131**(Pt 1):120–131.
73. Albin RL, Koeppe RA, Bohnen NI, *et al.* Spared caudal brainstem SERT binding in early Parkinson's disease. *J Cereb Blood Flow Metab*. 2008;**28**(3):441–444.
74. Joutsa J, Johansson J, Seppanen M, Noponen T, Kaasinen V. Dorsal-to-ventral shift in midbrain dopaminergic projections and increased thalamic/raphe serotonergic function in early Parkinson disease. *J Nucl Med*. 2015;**56**(7):1036–1041.
75. Kerenyi L, Ricaurte GA, Schretlen DJ, *et al.* Positron emission tomography of striatal serotonin transporters in Parkinson disease. *Arch Neurol*. 2003;**60**(9):1223–1229.
76. Ballanger B, Strafella AP, van Eimeren T, *et al.* Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol*. 2010;**67**(4):416–421.
77. Huot P, Johnston TH, Darr T, *et al.* Increased 5-HT2A receptors in the temporal cortex of parkinsonian patients with visual hallucinations. *Mov Disord*. 2010;**25**(10):1399–1408.
78. Cheng AV, Ferrier IN, Morris CM, *et al.* Cortical serotonin-S2 receptor binding in Lewy body dementia, Alzheimer's and Parkinson's diseases. *J Neurol Sci*. 1991;**106**(1):50–55.
79. Perry EK, Marshall E, Kerwin J, *et al.* Evidence of a monoaminergic-cholinergic imbalance related to visual hallucinations in Lewy body dementia. *J Neurochem*. 1990;**55**(4):1454–1456.
80. Olney JW, Wozniak DF, Farber NB. Excitotoxic neurodegeneration in Alzheimer disease. New hypothesis and new therapeutic strategies. *Arch Neurol*. 1997;**54**(10):1234–1240.
81. Monastero R, Camarda C, Pipia C, Camarda R. Visual hallucinations and agitation in Alzheimer's disease due to memantine: report of three cases. *J Neurol Neurosurg Psychiatry*. 2007;**78**(5):546
82. Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology*. 2006;**66**(1):17–22.
83. Ferrer I. Neurons and their dendrites in frontotemporal dementia. *Dement Geriatr Cogn Disord*. 1999;**10**(Suppl 1):55–60.
84. Elliott MS, Ballard CG, Kalaria RN, *et al.* Increased binding to 5-HT1A and 5-HT2A receptors is associated with large vessel infarction and relative preservation of cognition. *Brain*. 2009;**132**(Pt 7):1858–1865.
85. Govindpani K, Calvo-Flores Guzman B, Vinnakota C, *et al.* Towards a better understanding of GABAergic remodeling in Alzheimer's disease. *Int J Mol Sci*. 2017;**18**(8):1
86. Lakhan SE, Caro M, Hadzimichalis N. NMDA receptor activity in neuropsychiatric disorders. *Front Psychiatry*. 2013;**4**:52
87. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997;**18**(4):351–357.
88. Braak H, Del Tredici K, Rub U, *et al.* Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;**24**(2):197–211.
89. Cummings J, Ballard C, Tariot P, *et al.* Pimavanserin: potential treatment for dementia-related psychosis. *J Prev Alzheimers Dis*. 2018;**5**(4):253–258.
90. Bohnen NI, Kaufer DI, Ivanco LS, *et al.* Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Arch Neurol*. 2003;**60**(12):1745–1748.
91. Kuhl DE, Minoshima S, Fessler JA, *et al.* In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. *Ann Neurol*. 1996;**40**(3):399–410.
92. Fabbrini G, Barbanti P, Aurilia C, *et al.* Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. *Neurol Sci*. 2002;**23**(1):41–43.
93. Lanctôt KL, Herrmann N, Mazzotta P. Role of serotonin in the behavioral and psychological symptoms of dementia. *J Neuropsychiatry Clin Neurosci*. 2001;**13**(1):5–21.
94. Rezaie P, Cairns NJ, Chadwick A, Lantos PL. Lewy bodies are located preferentially in limbic areas in diffuse Lewy body disease. *Neurosci Lett*. 1996;**212**(2):111–114.
95. McKeith I, Del Ser T, Spano P, *et al.* Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet*. 2000;**356**(9247):2031–2036.
96. Perry EK, Marshall E, Thompson P, *et al.* Monoaminergic activities in Lewy body dementia: relation to hallucinosis and extrapyramidal features. *J Neural Transm Park Dis Dement Sect*. 1993;**6**(3):167–177.
97. Blin J, Baron JC, Dubois B, *et al.* Loss of brain 5-HT2 receptors in Alzheimer's disease. In vivo assessment with positron emission tomography and [18F]setoperone. *Brain*. 1993;**116**(Pt 3):497–510.
98. Cross AJ, Crow TJ, Ferrier IN, *et al.* Serotonin receptor changes in dementia of the Alzheimer type. *J Neurochem*. 1984;**43**(6):1574–1581.

99. Crow TJ, Cross AJ, Cooper SJ, *et al.* Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. *Neuropharmacology*. 1984;**23**(12B):1561–1569.
100. Perry EK, Perry RH, Candy JM, *et al.* Cortical serotonin-S2 receptor binding abnormalities in patients with Alzheimer's disease: comparisons with Parkinson's disease. *Neurosci Lett*. 1984;**51**(3):353–357.
101. Jansen KL, Faull RL, Dragunow M, Synek BL. Alzheimer's disease: changes in hippocampal N-methyl-D-aspartate, quisqualate, neurotensin, adenosine, benzodiazepine, serotonin and opioid receptors—an autoradiographic study. *Neuroscience*. 1990;**39**(3):613–627.
102. Holmes C, Arranz MJ, Powell JF, Collier DA, Lovestone S. 5-HT2A and 5-HT2C receptor polymorphisms and psychopathology in late onset Alzheimer's disease. *Hum Mol Genet*. 1998;**7**(9):1507–1509.
103. Polesskaya OO, Sokolov BP. Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *J Neurosci Res*. 2002;**67**(6):812–822.
104. Okada M, Northup JK, Ozaki N, *et al.* Modification of human 5-HT(2C) receptor function by Cys23Ser, an abundant, naturally occurring amino-acid substitution. *Mol Psychiatry*. 2004;**9**(1):55–64.
105. Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M, *et al.* Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. *Neuropsychologia*. 2005;**43**(3):442–449.
106. Cummings JL, McRae T, Zhang R, Donepezil-Sertraline Study G. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. *Am J Geriatr Psychiatry*. 2006;**14**(7):605–612.
107. Ellison DW, Beal MF, Mazurek MF, Bird ED, Martin JB. A postmortem study of amino acid neurotransmitters in Alzheimer's disease. *Ann Neurol*. 1986;**20**(5):616–621.
108. Gueli MC, Taibi G. Alzheimer's disease: amino acid levels and brain metabolic status. *Neurol Sci*. 2013;**34**(9):1575–1579.
109. Lowe SL, Francis PT, Procter AW, *et al.* Gamma-aminobutyric acid concentration in brain tissue at two stages of Alzheimer's disease. *Brain*. 1988;**111**(Pt 4):785–799.
110. Perry TL, Yong VW, Bergeron C, Hansen S, Jones K. Amino acids, glutathione, and glutathione transferase activity in the brains of patients with Alzheimer's disease. *Ann Neurol*. 1987;**21**(4):331–336.
111. Sasaki H, Muramoto O, Kanazawa I, *et al.* Regional distribution of amino acid transmitters in postmortem brains of presenile and senile dementia of Alzheimer type. *Ann Neurol*. 1986;**19**(3):263–269.
112. Meyer S, Mueller K, Stuke K, *et al.* Predicting behavioral variant frontotemporal dementia with pattern classification in multi-center structural MRI data. *Neuroimage Clin*. 2017;**14**:656–662.
113. Boccardi M, Sabattoli F, Laakso MP, *et al.* Frontotemporal dementia as a neural system disease. *Neurobiol Aging*. 2005;**26**(1):37–44.
114. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry*. 2006;**14**(3):191–210.
115. US Food and Drug Administration. *FDA Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances*. Silver Spring, MD: US Food and Drug Administration; 2005.