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BRAINSTORMS—Clinical Neuroscience Update

Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin 5HT2A and 5HT2C receptors

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ISSUE:

Pimavanserin, a novel agent approved for the treatment of Parkinson's disease psychosis, has potent actions as an antagonist/inverse agonist at serotonin 5HT2A receptors and less potent antagonist/inverse agonist actions at 5HT2C receptors.

Take-Home Points

- Pimavanserin is a selective 5HT2A/5HT2C receptor-acting agent and the only approved treatment for Parkinson's disease psychosis.
- Pimavanserin is the first example of a drug with antipsychotic actions that does not block dopamine D2 receptors.
- The antipsychotic actions of pimavanserin, particularly against visual hallucinations in Parkinson's disease psychosis, do not come at the expense of worsening motor symptoms in Parkinson's disease.

Introduction

Psychosis, defined as hallucinations and delusions, is present in up to half of patients with Parkinson's disease,[1–4] but there is debate about its cause. In some Parkinson's disease patients, Parkinson's disease psychosis (PDP) appears even before motor symptoms occur or before any treatment is given, and is thus a core non-motor feature of their Parkinson's disease;[1–5] in other patients with Parkinson's disease, PDP develops concomitantly with dementia, both the Alzheimer type and the Lewy body type, in which Lewy bodies of alpha synuclein accumulate not only in the substantia nigra, first to cause motor symptoms, but also in the cortex, later to cause dementia;[1–5] finally, PDP in yet other patients with Parkinson's disease seems to be caused or worsened by treatment with dopaminergic agents and improved by dose reduction of dopaminergic therapies.[1–4,6–8] Whatever the cause of PDP, it is clear that its onset is not good news, since it is associated with dementia[1–8] and predicts repeated hospitalizations,[9] nursing home placement,[10,11] and death.[12,13] Furthermore, the only previously available treatment for PDP, antipsychotics, can worsen motor symptoms and increase mortality in Parkinson's disease patients with dementia, many of whom have PDP.[2–4,14,15] Thus, there is urgent need for a safe and effective treatment for PDP.

From a pharmacologic perspective, PDP likely represents an imbalance between dopamine and serotonin systems in the brain.[2–4,6–8,16–31] Treatment of PDP, prior to the approval of pimavanserin, consisted of either lowering the doses of dopaminergic antiparkinsonian agents or adding antipsychotic agents, although the efficacy of antipsychotics for PDP has been poorly documented and is often associated with worsening of motor symptoms of Parkinson's disease.[2–4,6,32,33] Originally, the notion was that antipsychotics such as quetiapine or clozapine worked in PDP by blocking D2 dopamine receptors,[2–4,32,33] just as these drugs are thought to work in schizophrenia.[34] However, a novel line of investigation now suggests that it is actually the potent serotonin 5HT2A antagonist properties of quetiapine and clozapine,[34,35] not their weak D2 antagonist properties, that cause the apparent efficacy seen in Parkinson's disease. That is, pimavanserin—which lacks any potent D2 antagonist actions[36]—has now been proven effective in PDP.[37–40]

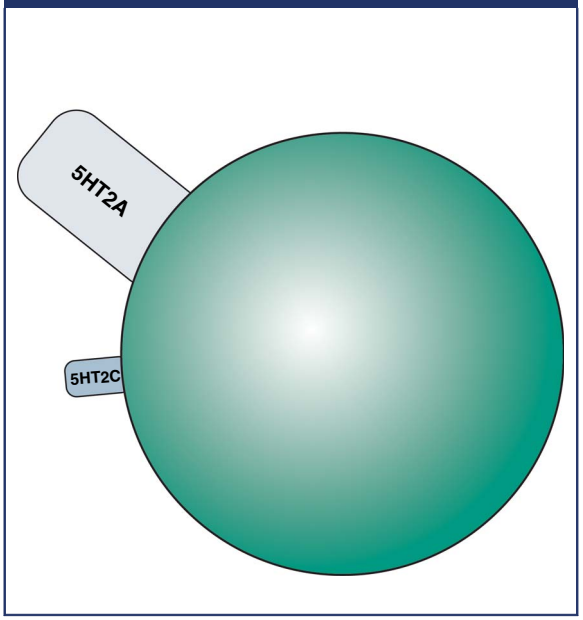
Pharmacologic Mechanism of Action of Pimavanserin

Pimavanserin has relatively selective pharmacologic actions, namely, potent interactions at serotonin 5HT2A receptors and around 40-fold less potent activity at 5HT2C receptors (Figure 1).[36] It is not clear whether pimavanserin acts only via 5HT2A receptors or via 5HT2C receptors as well, but the doses of pimavanserin required to treat PDP[37–40] suggest that the 5HT2C receptor actions of pimavanserin are indeed relevant to its therapeutic effects in PDP. That is, doses that essentially saturate the 5HT2A receptor[41,42] are not effective in PDP.[37–40] However, twice this dose is effective,[37–40] and this higher dose—the one that is approved for treatment of PDP by the FDA—not only saturates 5HT2A receptors,[42] but also recruits substantial if lesser degrees of occupancy of 5HT2C receptors.[36] This notion of dual activity at both 5HT2A and 5HT2C receptors for therapeutic efficacy of pimavanserin in PDP is consistent with animal studies of PDP, where the actions of pimavanserin on dopamine release are demonstrated at doses that engage both receptors as well.[43]

Another unresolved issue regarding the actions of pimavanserin is whether it acts as a more traditional *antagonist* at 5HT2A/2C receptors, or as a so-called *inverse agonist*.[34,36,44,45] The vast majority of drugs used in psychiatry are *antagonists*, ie, they block something. Usually they block the effects of an endogenous neurotransmitter, such as dopamine as in the case of treating schizophrenia. Drugs that have the opposite effects of agonists are *inverse agonists*. For example, from a behavioral point of view, a benzodiazepine *agonist* reduces anxiety, and a benzodiazepine *inverse agonist* causes anxiety. From a pharmacologic point of view, *antagonists* block the actions of agonists at their receptors, but they do so "silently," that is, without changing any intrinsic activity of that receptor from what that receptor is expressing in the absence of its agonist. On the other hand, an *inverse agonist* not only blocks the actions of agonists at the receptor the same as an *antagonist*, but also decreases the intrinsic activity that receptor has in the absence of its agonist. The point of differentiation pharmacologically is that *inverse agonists* reduce baseline (constitutive) activity at 5HT2A receptors in the absence of serotonin, whereas *antagonists* do not, ie, they are "silent."[34,44,45]

From a clinical point of view, the differentiation of an antagonist from an inverse agonist at 5HT2A receptors may be a distinction without a difference. Indeed, the same assay systems that suggest pimavanserin is an inverse agonist[36] also show that all the other atypical antipsychotics that interact at 5HT2A receptors are also inverse agonists.[46] Atypical antipsychotics have been traditionally called 5HT2A antagonists, not inverse agonists.[34] The clinical relevance of this all depends upon whether there is any baseline intrinsic activity of 5HT2A receptors in the living human brain in the absence of serotonin, and we do not have any convincing evidence of that. Thus, there is not yet any known clinically meaningful differentiation between inverse agonism and antagonism for pimavanserin and atypical antipsychotics in PDP, so it may be useful to continue to refer to them simply as antagonists.

Figure 1. Mechanism of action of pimavanserin. Shown here are the binding properties of pimavanserin, namely potent antagonist actions at serotonin 5HT2A receptors, sometimes called inverse agonist actions, and less potent antagonist/inverse agonist actions at 5HT2C receptors. Note that there is no notable binding to D2 dopamine receptors or any other neurotransmitter receptors.



Therapeutic Mechanism of Pimavanserin in PDP

Why does blocking 5HT2A/5HT2C receptors in PDP have antipsychotic efficacy without worsening motor symptoms? Although all traditional antipsychotics block D2 receptors[34] and all atypical antipsychotics block both D2 and 5HT2A receptors,[34] pimavanserin is the first 5HT2A/2C antagonist lacking D2 antagonist properties[46] that has been proven effective in psychosis, specifically PDP.[37–40] The antipsychotic efficacy of pimavanserin was at first surprising because long-standing dogma about the pharmacology of psychosis assumed it was due to excessive dopamine activity, and

the only way to treat psychosis was therefore to reduce dopamine activity. In PDP, that meant the early interventions were either to reduce dopaminergic therapy or to block D2 receptors with the addition of an antipsychotic; however, these treatments both have limited efficacy and also the propensity to make motor symptoms worse.[2–4,6–8,32,33] This put both PDP patients and their clinicians between a rock and a hard place when trying to balance simultaneously the treatment of both PDP and motor symptoms of Parkinson's disease.

Pharmacologists working within the traditional antipsychotic paradigm have long considered the 5HT2A antagonist actions of atypical antipsychotic agents to be responsible for reducing the incidence of drug-induced parkinsonism while simultaneously blocking D2 receptors,[34] but the evidence that 5HT2A receptors mediate antipsychotic actions was sparse.[34,47] Other selective 5HT2A antagonists were not convincing antipsychotics as monotherapies, although early preclinical and clinical studies of pimavanserin suggested that it could enhance the antipsychotic activity of risperidone.[48,49] Thus, it was a bit of a surprise that pimavanserin monotherapy, with its 5HT2A/2C antagonist properties, showed antipsychotic efficacy in PDP[37–40] without blocking D2 receptors.[46]

So, how does the selective 5HT2A/2C antagonism without D2 antagonism of pimavanserin exert its antipsychotic effects in PDP without worsening motor symptoms? It seems the answer to this may be that pimavanserin corrects the theoretical serotonin dopamine imbalance in PDP.[6–8,16–31] That is, the various causes of PDP are all hypothesized to act by the same ultimate common pharmacologic pathway, namely to cause an imbalance between serotonin and dopamine. The dopamine deficiencies of Parkinson's disease are well known and are obviously linked to motor symptoms.[1–6,17,18] Less well appreciated is that both serotonin and dopamine neurons degenerate in Parkinson's disease.[16,20–22] Although degeneration of dopamine neurons in the substantia nigra is linked to motor symptoms in Parkinson's disease,[1,6–8,17,18] loss of serotonin neurons is not.[16,20–22] Instead, loss of serotonin neurons is accompanied by a presumably compensatory upregulation of post synaptic 5HT2A receptors in the cerebral cortex, setting off an imbalance in the action of serotonin at these receptors.[23–27] That is, excessive stimulation of these receptors is thought to result in psychotic symptoms, especially visual hallucinations, which are the hallmark of PDP.[23–31,50] Indeed, hallucinogenic drugs cause striking visual hallucinations by stimulating these very same 5HT2A receptors.[50,51] Thus, there is robust pharmacologic rationale to explain why blocking hypothetically overstimulated 5HT2A receptors in PDP would reduce the hypothetical serotonergic imbalance, and thereby stop psychotic symptoms.[23–31,50,51] Also, 5HT2A receptors in the cortex regulate the downstream release of dopamine,[34] which has been hypothesized to have undergone a dorsal-to-ventral shift in the striatum in PDP.[8] Blocking these receptors could theoretically restore the correct balance by partially reversing this shift.[8,23–31]

Future

5HT2A receptors are also upregulated in dementia with Lewy bodies,[29] a condition where dementia precedes any motor symptoms, whereas in Parkinson's disease, the motor symptoms precede the dementia.[52–56] Visual hallucinations are a prominent feature in many patients who have dementia with Lewy bodies,[52–56] so it is rational to hypothesize that these psychotic symptoms might also be treatable with pimavanserin. Indeed, studies are underway to investigate this possibility. Psychotic symptoms also accompany the dementia of Alzheimer's disease,[1,34] whether comorbid with Parkinson's Disease or not, and could possibly be a therapeutic target for pimavanserin as well.[57] Finally, pimavanserin and all 5HT2A antagonists enhance slow-wave sleep,[58] and there may be therapeutic implications of this action as well.

References:

1. Cummings JL. Behavioral complications of drug treatment of Parkinson's disease. *J Am Geriatr Soc*. 1991; **39**(7): 708–716.
2. Chang A, Fox SH. Psychosis in Parkinson's disease: epidemiology, pathophysiology, and management. *Drugs*. In press. DOI: 10.1007/s40265-016-0600-5.
3. Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. *Curr Treat Options Neurol*. 2014; **16**(3): 281.
4. Goldman JG, Vaughan CL, Goetz CG. An update expert opinion on management and research strategies in Parkinson's disease psychosis. *Expert Opin Pharmacother*. 2011; **12**(13): 2009–2024.
5. Paponabarrage J, Martinez-Horta S, Fernández de Bobadilla R, *et al.* Minor hallucinations occur in drug-naïve Parkinson's disease patients, even from the premotor phase. *Mov Disord*. 2016; **31**(1): 45–52.
6. Vaillancourt DE, Schonfeld D, Kwak Y, Bohnen NI, Seidler R. Dopamine overdose hypothesis: evidence and clinical implications. *Mov Disord*. 2013; **28**(14): 1920–1929.
7. MacDonald AA, Mondhi O, Seergobin KN, Ganjavi H, Tamjeedi R, MacDonald PA. Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*. 2013; **28**(2): 153–160.
8. Joutsa J, Johansson J, Seppänen M, Nopenen 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.

9. Klein C, Prokhorov T, Miniovitz A, Dobronevsky E, Rabey JM. Admission of Parkinsonian patients to a neurological ward in a community hospital. *J Neural Transm (Vienna)*. 2009; **116**(11): 1509–1512.
10. Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology*. 1993; **43**(11): 2227–2229.
11. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc*. 2000; **48**(8): 938–942.
12. Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. *Neurology*. 1995; **45**(4): 669–671.
13. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson's disease? A prospective population-based long-term study. *Neurology*. 2010; **75**(14): 1270–1276.
14. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005; **294**(15): 1934–1943.
15. Ballard C, Isaacson S, Mills R, *et al*. Impact of current antipsychotic medications on comparative mortality and adverse events in people with Parkinson disease psychosis. *J Am Med Dir Assoc*. 2015; **16**(10): 898.
16. Birkmayer W, Birkmayer JD. Dopamine action and disorders of neurotransmitter balance. *Gerontology*. 1987; **33**(3–4): 168–171.
17. Ravina B, Marek K, Eberly S, *et al*. Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease. *Mov Disord*. 2012; **27**(11): 1392–1397.
18. Kordower JH, Olanaw CW, Dodiya HB, *et al*. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain*. 2013; **136**(Pt 8): 2419–2431.
19. Barone P. Neurotransmission in Parkinson's disease: beyond dopamine. *Eur J Neurol*.. 2010; **17**(3): 364–376.
20. Huot P, Fox. The serotonergic system in motor and non-motor manifestations of Parkinson's disease., *Exp Brain Res*. 2013; **230**(4): 463–476.
21. Halliday GM, Blumbergs PC, Cotton RGH, Blessing WW, Geffen LB. Loss of brainstem serotonin- and substance Pcontaining neurons in Parkinson's disease. *Brain Res*. 1990; **510**(1): 104–107.
22. Fox SH, Chuang R, Brotchie JM. Serotonin and Parkinson's disease: on movement, mood and madness. *Mov Disord*. 2009; **24**(9): 1255–1266.
23. Huot P, Hohnston TH, Darr T, *et al*. Increased 5HT2A receptors in the temporal cortex of parkinsonian patients with visual hallucinations. *Mov Disord*. 2010; **25**(10): 1399–1408.
24. Ballenger B, Strafella AP, van Eimeren T, *et al*. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol*. 2000; **67**(4): 416–421.
25. 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.
26. Kiferle L, Cervolo R, Petrozzi L, *et al*. Visual hallucinations in Parkinson's disease are not influenced by polymorphisms of serotonin 5HT2A receptor and transporter genes. *Neurosci Lett*. 2007; **422**(3): 228–231.
27. Albin RL, Koeppe RA, Bohnen NI, Wernette K, Kilbourn MA, Frey KA. Spared caudal brainstem SERT binding in early Parkinson's disease. *J Cereb Blood Flow Metab*. 2008; **28**(3): 441–444.
28. Ohno Y, Shimizu S, Tokudome K, Kunisawa N, Sasa M. New insight into the therapeutic role of the serotonergic system in Parkinson's disease. *Prog Neurobiol*. 2015; **134**: 104–121.
29. Cheng AVT, 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.
30. Politis M, Miccolini F. Serotonin in Parkinson's disease. *Behav Brain Res*. 2015; **277**: 136–145.
31. Birkmayer W, Danielczyk W, Neumayer E, Riederer P. Nucleus ruber and L-Dopa psychosis: biochemical post-mortem findings. *J Neural Transm*. 1974; **35**(2): 93–116.
32. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging*. 2008; **25**(8): 665–682.
33. Desmarais P, Massoud F, Filion J, Nguyen QD, Bajsarowicz P. Quetiapine for psychosis in Parkinson Disease and neurodegenerative parkinsonian disorders: a systematic review. *J Geriatr Psychiatry Neurol*. 2016; **29**(4): 227–236.
34. Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, UK: Cambridge University Press; 2013.
35. Hubbard D, Hacksell U, McFarland K. Behavioral effects of clozapine, pimavanserin and quetiapine in rodent models of Parkinson's disease and Parkinson's disease psychosis: evaluation of therapeutic ratios. *Behav Pharmacol*. 2013; **24**(7): 628–632.
36. Vanover KE, Weiner DM, Makhay M, *et al*. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N -(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. *J Pharmacol Exp Ther*. 2006; **317**(2): 910–918.
37. 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.
38. Hermanowicz S, Hermanowicz N. The safety, tolerability and efficacy of pimavanserin tartrate in the treatment of psychosis in Parkinson's disease. *Expert Rev Neurother*. 2016; **16**(6): 625–633.
39. Friedman JH. Pimavanserin for the treatment of Parkinson's disease psychosis. *Expert Opin Pharmacother*. 2013; **14**(14): 1969–1975.
40. Meltzer HY, Mills R, Revell S, *et al*. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. *Neuropsychopharmacology*. 2010; **35**(4): 881–892.
41. Vanover KE, Robbins-Weilert D, Wilbraham DG, *et al*. Pharmacokinetics, tolerability, and safety of ACP-103 following single or multiple oral dose administration in healthy volunteers. *J Clin Pharmacol*. 2007; **47**(6): 704–714.
42. Nordstrom A-L, Mansson M, Jovanovic H, *et al*. PET analysis of the 5-HT2A receptor inverse agonist ACP-103 in human brain. *Int J Neuropsychopharmacol*. 2008; **11**(2): 163–171.
43. Li Z, Ichikawa J, Huang M, Prus AJ, Dai J, Meltzer HY. 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.
44. Kenakin T. Inverse, protean, and ligand-selective agonism: matters of receptor conformation. *FASEB J*. 2001; **15**(3): 598–611.
45. Brink CB, Harvey BH, Bodenstein J, Venter DP, Oliver DW. Recent advances in drug action and therapeutics: relevance of novel concepts in G-protein-coupled receptor and signal transduction pharmacology. *Br J Clin Pharmacol*. 2003; **57**(4): 373–387.
46. Weiner DM, Burstein ES, Nash N, *et al*. 5-Hydroxytryptamine 2A receptor inverse agonists as antipsychotics. *J Pharmacol Exp Ther*. 2001; **299**(1): 268–276.
47. Laoutidis ZG, Luckhaus C. 5-HT2A receptor antagonists for the treatment of neuroleptic-induced akathisia: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2014; **17**(5): 823–832.
48. 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.

49. Meltzer HY, Elkis H, Vanover K, *et al*. Pimavanserin, a selective serotonin (5HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2 mg/day, but does not enhance efficacy of haloperidol 2 mg/day: comparison with reference dose risperidone, 6 mg/day. *Schizophr Res*. 2012; **141**(2–3): 144–152.
50. Sadzot B, Baraban JM, Glennon RA, *et al*. Hallucinogenic drug interactions at human brain 5-HT2 receptors: implications for treating LSD-induced hallucinogenesis. *Psychopharmacology (Berl)*. 1989; **98**(4): 494–499.
51. McClue SJ, Brazell C, Stahl SM. Hallucinogenic drugs are partial agonists of the human platelet shape change response: a physiological model of the 5-HT_2 receptor. *Biol Psychiatry*. 1989; **26**(3): 297–302.
52. Stinton C, McKeith I, Taylor JP, *et al*. Pharmacological management of Lew body dementia: a systematic review and meta-analysis. *Am J Psychiatry*. 2015; **172**(8): 731–742.
53. Boot BP. Comprehensive treatment of dementia with Lewy bodies. *Alzheimers Res Ther*. 2015; **7**(1): 45–52.
54. Hogan DB, Fiest KM, Roberts JI, *et al*. The prevalence and incidence of dementia with Lewy bodies: a systematic review. *Can J Neurol Sci*. 2016; **43**(Suppl 1): S83–S95.
55. Jacobson SA, Morshed T, Dugger BN, *et al*. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations. *Parkinsonism Relat Disord*. 2014; **20**(9): 1009–1014.
56. Petrova M, Mehrabian-Spasova S, Aarsland D, Raycheva M, Traykov L. Clinical and neuropsychological differences between mild Parkinson's disease dementia and dementia with Lewy bodies. *Dement Geriatr Cogn Dis Extra*. 2015; **5**(2): 212–220.
57. Price DL, Bonhaus DW, McFarland K. Pimavanserin, a 5-HT2A receptor inverse agonist, reverses psychosis-like behaviors in a rodent model of Alzheimer's disease. *Behav Pharmacol*. 2012; **23**(4): 426–433.
58. Ancoli-Israel S, Vanover KE, Weiner DM, Davis RE, van Kammen DP. Pimavanserin tartrate, a 5-HT(2A) receptor inverse agonist, increases slow wave sleep as measured by polysomnography in healthy adult volunteers. *Sleep Med*. 2011; **12**(2): 134–141.