5-HT_{2A} receptors and Parkinson's disease psychosis: a pharmacological discussion

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“Although postmortem and imaging studies support an involvement of 5-HT_{2A} receptors in PD psychosis and VHs, there still is a need to optimize drugs that interact with this target and that will reduce symptoms to a greater extent than that what is currently obtained with pimavanserin, and that will do so safely.”

First draft submitted: 8 October 2018; Accepted for publication: 17 October 2018; Published online: 19 November 2018

Keywords: 5-HT_{2A} • Parkinson's disease • psychosis • serotonin • visual hallucinations

Blockade of the serotonin 2A (5-HT_{2A}) receptor is an approach that was shown to be effective at alleviating Parkinson's disease psychosis, in a Phase III clinical trial. However, the benefit conferred by this approach in the clinic appears to be relatively modest. Here, we briefly speculate on why this might be and reflect on possible ways to modulate this target that would confer greater antipsychotic effect to parkinsonian patients.

Visual hallucinations (VHs), the most common form of psychotic manifestation in Parkinson's disease (PD) are experienced by as many as 52% of PD patients 15 years after initiation of therapy [1], while as many as 75% of patients experience VHs over a 20-year span [2]. The pathophysiology of VHs in PD is complex, and likely to be combination of neurodegenerative changes and effects of antiparkinsonian medication [3]. Few drugs have proven effective to reduce VHs and psychosis in PD and, according to an evidence-based medicine review by the International Parkinson and Movement Disorder Society [4] and its recent update <https://www.movementdisorders.org/MDS-Files1/Resources/PDFs/EBM-NMS-Final-Paper-August-2018.pdf>, only clozapine is 'useful' for the treatment of PD psychosis, while quetiapine and pimavanserin are both 'possibly useful'. Whereas clozapine and quetiapine both bind to several targets [5], pimavanserin is selective for 5-HT_{2A} and serotonin 2C (5-HT_{2C}) receptors [6], making an interaction with these targets its putative mechanism of action.

An antipsychotic effect of modulating 5-HT_{2A} receptors is supported by a postmortem study which demonstrated increased 5-HT_{2A} receptors in the inferolateral temporal cortex of PD patients with VHs [7]. A positron emission tomography study in PD patients with VHs also discovered higher 5-HT_{2A} receptor levels in the inferolateral temporal cortex, in addition to the prefrontal cortex and the ventral visual pathway [8]. These studies, by finding elevated 5-HT_{2A} receptors in several brain areas, notably the inferolateral temporal cortex, suggest that neurotransmission mediated by 5-HT_{2A} receptors may be abnormal in VHs in PD.

In the literature, pimavanserin is referred to as a 5-HT_{2A} inverse agonist [6], meaning that it reduces the constitutive activity of its target [9], the 5-HT_{2A} receptor. In a Phase III clinical trial, pimavanserin reduced PD psychosis, however the effect was modest [10]. Thus, using the at the time novel scale for assessment of positive symptoms adapted for PD (SAPS-PD), pimavanserin diminished PD psychosis by approximately 13%, while the placebo arm experienced approximately 6% reduction. Prior to this study that demonstrated an antipsychotic effect, three previous Phase III trials had failed to demonstrate efficacy [11].

Important questions emanate from the results obtained with pimavanserin in these Phase III trials, for example, to what extent is 5-HT_{2A} receptor modulation an effective way to reduce VHs in PD? The *postmortem* and positron emission tomography studies cited above, coupled with the modest effect of pimavanserin, suggest that the 5-HT_{2A} receptor represents a target that bears therapeutic potential in PD psychosis. Based on the mechanism of action of

pimavanserin, a follow-up question is: is inverse agonism at the 5-HT_{2A} receptor the best way forward, or could greater benefit be achieved by interacting differently with the target? Indeed, drugs that modulate 5-HT_{2A} receptors differently led to different effects on psychosis-like behaviors (PLBs), in experimental parkinsonism. Thus, the 5-HT_{2A} partial agonist R-3,4-methylenedioxymethamphetamine (R-MDMA) [12] did not significantly, despite a trend, alter the severity of PLBs, although it reduced duration of on-time with disabling PLBs [13], while the highly-selective 5-HT_{2A} neutral antagonist pruvanserin [14] provided approximately 50% reduction of PLBs [15], both in the parkinsonian nonhuman primate. It is noteworthy that the antipsychotic effect of pimavanserin or of other selective 5-HT_{2A} inverse agonists has not been assessed in the parkinsonian primate and that the extent to which this strategy might (or not) have reduced PLBs in this species is uncertain. Speculatively, given the important reduction of PLBs conferred by pruvanserin in the primate, it is possible, although unproven, that the maximal benefit might be achieved with 5-HT_{2A} neutral antagonism, whereas partial and inverse agonism might lead to too little or too much modulation of the activity of the receptor, respectively. Further studies are needed to test this hypothesis. As of 8 October 2018, no 5-HT_{2A} partial agonist or neutral antagonist has been registered on <https://clinicaltrials.gov> for end points related to PD psychosis.

Another possibility to explain the modest efficacy of pimavanserin might pertain to its seldom acknowledged action at 5-HT_{2C} receptors. Thus, pimavanserin harbors approximately 40 × selectivity for 5-HT_{2A} receptors over 5-HT_{2C} receptors, at which it also acts as an inverse agonist [6]. Blockade of 5-HT_{2C} receptors was shown to enhance mesocorticolimbic dopamine transmission [16], which could possibly offset the antipsychotic action of 5-HT_{2A} blockade. The extent to which pimavanserin interacts with 5-HT_{2C} receptors in the brain of PD patients has not been published, although the drug is marketed as a selective 5-HT_{2A} ligand and, for that reason the 5-HT_{2C}-centered argument put forward in this paragraph remains hypothetical.

Alternately, perhaps an interaction with 5-HT_{2A} receptors is an approach that will end up being effective to alleviate psychosis in a subset of PD patients with specific characteristics, which still have to be identified. Further research is needed that will refine our understanding of PD psychosis and of individual patients' response to develop such a personalized approach.

In addition to the actions at 5-HT_{2A} and possibly 5-HT_{2C} receptors discussed above, other considerations remain with pimavanserin, but because pimavanserin is the sole selective 5-HT_{2A} modulator that was tested for PD psychosis in the clinic, whether these would also apply to other agents modulating 5-HT_{2A} receptors remains unknown. Thus, the positive Phase III trial with pimavanserin lasted 6 weeks, and whether tachyphylaxis would occur after the 6-week time point or if the benefit would be maintained is uncertain [10]. Furthermore, concerns regarding the safety of pimavanserin have been raised <https://edition.cnn.com/2018/04/09/health/parkinsons-drug-nuplazid-invs/index.html>, and the US FDA is currently reviewing the evidence supporting the use of the drug [17]. Recently, a single-center retrospective study reported that mortality rates are not different between pimavanserin and quetiapine in the parkinsonian population [18], although the use of antipsychotics in PD, including quetiapine, is usually associated with higher mortality rates [19].

Collectively, the studies presented briefly here indicate that inverse agonism of 5-HT_{2A} receptors has a limited benefit on PD psychosis and VHS. Other strategies, for example, 5-HT_{2A} partial agonism and neutral antagonism, showed promising effects in the parkinsonian primate, the latter being seemingly more effective than the former, but their effectiveness, or lack thereof, remains to be determined in the clinic. Although postmortem and imaging studies support an involvement of 5-HT_{2A} receptors in PD psychosis and VHS, there still is a need to optimize drugs that interact with this target and that will reduce symptoms to a greater extent than that what is currently obtained with pimavanserin, and that will do so safely.

Financial & competing interests disclosure

P Huot has research support from Parkinson Canada, Fonds de Recherche Québec – Santé, the Natural Sciences and Engineering Research Council of Canada, the Weston Brain Institute and the Michael J Fox Foundation for Parkinson's Research. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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