ORIGINAL RESEARCH PAPER | Medical Science | Volume : 6 | Issue : 11 | November 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

The Efficacy of Pimavanserin in the Treatment of Parkinson's Dependent Psychosis: A Review of the Literature

KEYWORDS

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ABSTRACT ***Objective***: *Parkinson's disease (PD) is a common degenerative disorder which at times presents as Parkinson's Dependent Psychosis (PDP). PDP presents with psychotic symptoms in 40% of people with PD.These psychotic symptoms are mainly delusions, hallucinations, illusions and thought disorder.PDP results in an increased caregiver burden leading to institutionalization and increased mortality.Typical and atypical antipsychotics are poorly tolerated. Pimavanserin has shown to be efficacious] and well tolerated.Hence, we felt the need to review the literature in this regard.*

Data sources: *An electronic search was done by us on the following database: www.pubmed.com. A combination of the following search terms 'Parkinson's dependent psychosis' and 'Pimavanserin' were used.*

Study selection: Only randomised clinical trials related to the use of Pimavanserin for the management of PDP in PD were selected.

Data extraction: *Two studies reported about the efficacy of Pimavanserin for PDP.The data of the two studies was extracted under the following headings –year of publication, author, title of article, aim, sample size, type of study, scales used and Pimavanserin usage (dose, frequency, duration, side-effects &efficacy).*

Data synthesis: *Both were foreign studies published between the years 2010-2016, and both of them received funding. One was a randomised, double-blind, placebo-controlled study of 6 weeks duration, while the other was aphase 2 multicenter study which was a randomized, double blind, placebo-controlled trial of 4 weeks duration, with a 4-week follow-up period.The first study was conducted on 60 patients (14 females + 46 males; mean age 70.9 years),and the second on 199 patients (69 females + 116 males; age >40 years). The Pimavanserin dosage was 20mg once daily in the first study, with possible increases to 40 or 60md OD on days 8th and 15th respectively, while in the second study it was 40mg OD.*

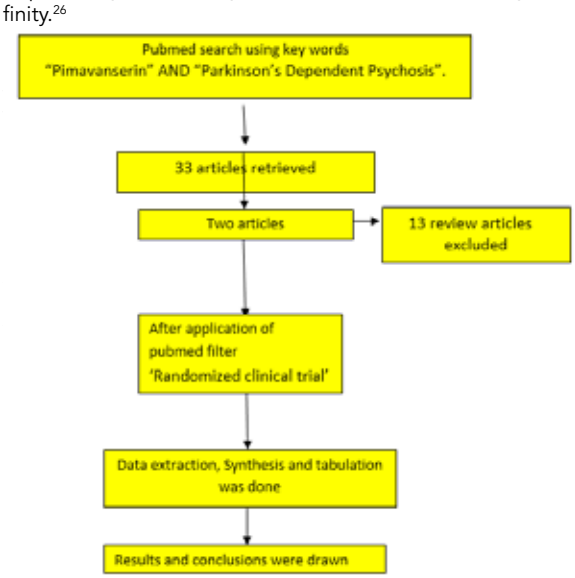
Conclusion: *Both studies concluded that Pimavanserin was efficacious and well tolerated bypatients with PDP. It also reduced care giver burden, improved sleep and had no motor impairment. Hence it is a viable alternative for treating psychosis in patients with PD.*

INTRODUCTION

In Parkinson's disease (PD),the basic pathology is neuro-degeneration in the pars compacta region of the substantia nigra, leading to reduced dopamine secretion.[1]PD presents with mainly motor, neuropsychiatric, sleep and autonomic nervous system disturbances.[2]PD at times presents with Parkinson's Dependent Psychosis (PDP).[3]PDP presents with psychotic symptoms in 40% of people with PD.[4]Delusions, hallucinations, misidentification of people and illusions are the common psychotic symptoms seen.[5]Alterationsand polymorphismsin the 5-HT receptor system play a role in the causation of dementiaand psychosisin PDP.[6-10]PDP results in an increased caregiver burden leading to institutionalization and increased mortality.[11]

Typical antipsychotics are not routinely used in the treatment of PDP as they worsen the motor symptoms of PD.[12,13] Atypical antipsychotics like Risperidone and Olanzapine are poorly tolerated.[11,14] Quetiapine seem better tolerated, but not efficacious.[15-23] Clozapine is shown to be efficacious without worsening the motor symptoms of PD but it has severe intolerable side effects.[11,12,15,24] Hence, there is need for an antipsychotic drug for PDP which is efficacious and has a favourable side effect profile.

Hallucinations and delusions seen in Parkinson's dependent psychosis are due to alterations and increased binding of the 5-HT2A receptors in the cerebral cortex, as suggested by studies.[6,7,25]Typical antipsychotics act as antagonists on the D2 receptors and worsen the motor symptoms of PD.[12,13]The atypical antipsychotics act as antagonists on the D2 and 5-HT2A receptors, and on other receptors as well, leading to adverse effects.[11,12,14-25] This is not seen with Pimavanserin, which has receptor selectivity for 5-HT2A receptors, acting as an inverse agonist. It does not have dopaminergic, adrenergic, muscarinic or histaminergic affinity.[26]



Data was extracted from the selected articles under the following headings: year of publication, author, title of arti-

Volume : 6 | Issue : 11 | November 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

cle, aim, sample size, type of study, scales used and Pimavanserin usage (dose, frequency, duration, side-effects and efficacy). The data was synthesised, tabulated and conclusions were drawn.

RESULTS

Year of publication

Both the studies were published during the period 2010 to 2014. One was in the year 2010,and the other one was in 2014.[4,27]

Locations of the studies

Both studies were foreign studies.[4,27]

Funding

Both the studies received funding.[4,27]

Study design The first study was a 6 week, randomised, double-blind, placebo-controlled study without follow-up andthe second study was a4 week, multi-centric, randomized, placebo-controlled, double-blind trial with a 4-week follow-up period.[4,27]

Sample size

The first study was conducted on 60 patients (14 females + 46 males; mean age 70.9 years) and the second on 199 patients (69 females + 116 males; age >40 years).[4,27]

Scales used

In the first study, Psychosis was assessed by the Scale for the Assessment of Positive Symptoms (SAPS), the Parkinson's Psychosis Rating Scale,and the Clinical Global Impression-Severity.[28,29,30]In addition, the Unified Parkinson's disease rating scale (UPDRS) Parts I, IV, and VI were used to assess the effects of treatment on mood, behaviour, and mentation; complications of therapy; and activities of daily living, respectively.[31]Daytime sleepiness was measured by the Epworth Sleepiness Scale.[32]

In the second study, psychosis was assessed by the SAPS-PD (Parkinson's disease-adapted SAPS).[33]Secondary outcomes included clinical global impression-severity (CGI-S) and improvement (CGI-I) scale scores.[30]Exploratory measures included the Zarit 22-item care giver burden scale (CBS), and scales for outcomes in Parkinson's disease-sleep (parts B and C) assessing night-time sleep quality (SCOPA-NS) and daytime wakefulness (SCOPA-DS).[34]A key secondary end point assessed Parkinsonism with the (UPDRS II and III)[35]

Pimavanserin

Dosage

In the first study, Pimavanserin was administered in the dosage of 20 mg on the first day, with possible increases to 40 or 60 mg daily doses on study days 8 and 15th, respectively, according to the individual clinical response.[27]

In the second study, Pimavanserin was administered in the dosage of 40 mg (two 20 mg tablets) once daily.[4]

Duration

In the first study, the drug was administered for four weeks, while in the second study, for six weeks.[4,27]

Frequency

The frequency was once daily in both the studies.[4,27]

Side effect profile

Pimavanserin was well tolerated in both the studies. In the first study, the side effects reported in 10% were oedema, increase in blood urea nitrogen, and somnolence, of which somnolence resolved on its own even with continuation of treatment.[27]In the second study, a mild increase in the QT interval was seen in the patients receiving Pimavanserin, but it was not associated with any cardiac adverse events.[4]

Efficacy of Pimavanserin

The first study concluded that Pimavanserin was efficacious and well tolerable by patients with PDP.[27] The second study also found Pimavanserin efficacious, with improvements in symptoms of psychosis, caregiver burden and sleep.[4]

Efficacy

The first study reported a statistically significant improvement in the scores on delusions (delusions of persecution & reference) and hallucinations (global ratings). There was no worsening of motor symptoms. There was also improvement in the thought disorder in patients with PDP.[27]

The second study also reported a statistically significant improvement in the global scores of hallucinations and delusions, along with a decrease in the caregiver- burden. There was no impairment of motor function. There was also improvement in sleep patterns.[4]

DISCUSSION

PD is a common degenerative disorder, and psychotic symptoms occur in 40% of PD patients.[4]The psychotic symptoms In PD are a the major reasons for institutionalisation of the patients, and increase in the burden of the caregivers.[11]Typical antipsychotics worsen the motor symptoms of PD.[12,13]The commonly used atypical antipsychotics such as Risperidone, Olanzapine, Clozapine, and Quetiapinehaveintolerable side effects.[11,12,14-25]

This review examined two studies reporting about the efficacy of Pimavanserin in the management of PDP. There is evidence from these studies that Pimavanserin is efficacious for the management of psychosis in PD. The maximum efficacy was for the control of

hallucinations and delusions. There was also improvement in sleep and decrease in caregiver burden. There was no worsening of the motor symptoms of Parkinsonism. This shows that there is evidence for the efficacy of Pimavanserin for the control of PDP in PD. It efficacious, safe and does not cause worsening of the motor symptoms of in PDP in PD.[4,27]

LIMITATIONS

Studies on Pimavanserin in PDP in PD were rare and difficult to locate, since it is a newly developed drug, hence we were able to find only two studies.[4,27]

STRENGTH OF THE STUDY

The review of literature was carefully evaluated for the efficacy of Pimavanserin in the treatment of PDP. A clearer picture emerges regarding the efficacy of Pimavanserin for the management of PDP in PD.

CONCLUSIONS

Pimavanserin, a selective 5HT2A inverse agonist, is efficacious and safe for patients with PDP in PD. It improved sleep with no motor impairment in patients with PDP. It also reduced care giver burden and decreased institutionalisation.[4,27] Hence, it is a viable alternative for treating psychosis in patients with PD. This has important implications for the pharmacotherapeutic management of PDP in PD.

Volume : 6 | Issue : 11 | November 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Table-1

Year	2010	2014
Author	Meltzer et al	Cummings et al
Study title	Pimavanserin, a Serotonin2A Receptor Inverse Agonist, for the Treatment of Parkinson's Disease Psychosis	Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial
Aim	To compare the tolerability and efficacy of Pimavanserin with placebo.	To assess safety and efficacy of Pimavanserin, a selective serotonin 5-HT2A inverse agonist, in people with Parkinson's dependent psychosis.
Sample size	60	199
Type of study	6 week, randomised, double-blind, placebo-controlled study without follow-up.	4 week, multi-centric, randomized, placebo-controlled, double-blind trial with a 4-week follow-up period.
Scales used	SAPS, PPRS, CGI-S, UPDRS Parts I,IV,VI, ESS.	SAPS-PD, CGI-S, CGI-I, CBS, SCOPA-DS, SCOPA-NS, UPDRS II,III.
Dosage	20mg on day one, with increments to 40mgand 60mg on days 8th and 15th, depending on response	40mg
Duration	4 weeks	6 weeks
Frequency	Once daily	Once daily
Side Effects	Oedema, somnolence, increase in blood urea nitrogen	Mild increase in QT interval without any cardiac adverse side effects
Results	Improvements in delusions, hallucinations, thought disorder. No worsening of motor symptoms.	Improvements in hallucinations, delusions, caregiver burden, sleep patterns. No motor impairment.
Conclusions	Pimavanserin is tolerable and efficacious.	Efficacious. Is a viable alternative for PDP

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Volume : 6 | Issue : 11 | November 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

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