JAMDA 16 (2015) 898.e1–898.e7

JAMDA

journal homepage: www.jamda.com

Original Study

Impact of Current Antipsychotic Medications on Comparative Mortality and Adverse Events in People With Parkinson Disease Psychosis

Clive Ballard MD [a,*], Stuart Isaacson MD [b], Roger Mills MD [c], Hilde Williams BSc [c], Anne Corbett PhD [a], Bruce Coate MSc [c], Rajesh Pahwa MD [d], Olivier Rascol MD [e], David J. Burn MD [f]

[a] *Wolfson Centre for Age-Related Diseases, King's College London, London, UK*
[b] *Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL*
[c] *ACADIA Pharmaceuticals, San Diego, CA*
[d] *University of Kansas Medical Center, Kansas City, KS*
[e] *Department of Clinical Pharmacology and Neurosciences, University UPS of Toulouse III, Toulouse, France*
[f] *Institute of Neuroscience, Newcastle University, Newcastle, UK*

Keywords:
Parkinson disease
antipsychotics
mortality
safety
psychosis

A B S T R A C T

Objectives: To establish the mortality risk and adverse events associated with the use of atypical antipsychotic medications in people with Parkinson disease psychosis (PDP) in a clinically defined trial cohort.
Design: Post hoc analysis of data from a multicenter, open-label extension study of pimavanserin comparing people taking and not taking current antipsychotics.
Setting: Primary and secondary care medical centers in the United States, Canada, Europe, and India.
Participants: A total of 459 people with PDP enrolled in the extension study. Participants were between ages 30 and 80 years, and had an established diagnosis of idiopathic Parkinson disease and moderate to severe psychosis.
Interventions: Participants were categorized into 2 groups: those receiving concomitant antipsychotic medications ("concurrent APD") and those who did not take antipsychotic medications at any time during the study ("no APD"). Participants were receiving 40 mg pimavanserin daily in addition to concurrent antipsychotics and Parkinson disease medications.
Main Outcome Measures: Safety assessments at 2 weeks; 1, 3, 6, 9, and 12 months; and every 6 months thereafter, including evaluation of adverse events (AEs), vital signs, weight, physical examinations, 12-lead electrocardiograms, clinical laboratory tests (serum chemistry, hematology, and urinalysis), and the Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS-II+III, activities of daily living and motor impairment, respectively). Differences between participants taking and not taking current antipsychotics were evaluated using incidence rate ratios (IRRs) with 95% confidence intervals (CIs).
Results: There was significant increase in the mortality rate for participants taking concurrent antipsychotics compared with the group not taking antipsychotic medications (IRR 4.20, 95% CI 2.13–7.96). Participants who received a concurrent antipsychotic were also significantly more likely to experience overall a serious AE (IRR 2.95, 95% CI 2.02–4.24), any antipsychotic-related event (IRR 1.66, 95% CI 1.18–2.29), cognition-related events (IRR 2.70, 95% CI 1.19–5.58), infections (IRR 1.97, 95% CI 1.17–3.16), and edema (IRR 2.61, 95% CI 1.09–5.59). The risk of falls, stroke, sedation, orthostatic hypotension, and thromboembolic events was also increased in these individuals but this was not significant.
Conclusions: This study highlights a significant risk of mortality, and severe AEs in patients with Parkinson disease receiving atypical antipsychotics. This is similar to or greater than the risks seen in people

The authors declare no conflicts of interest.

This study was funded by ACADIA Pharmaceuticals. The funder provided access to data and supported analysis and interpretation, and contributed to writing this manuscript.

Trial registration: Clinical Trials No. NCT00550238.

* Address correspondence to Clive Ballard, MD, Wolfson Centre for Age-Related Diseases, King's College London, Guy's Campus, London SE1 1UL, UK.
E-mail address: clive.ballard@kcl.ac.uk (C. Ballard).

http://dx.doi.org/10.1016/j.jamda.2015.06.021

with Alzheimer disease, although with a less clear-cut risk of stroke and a longer delay to increased mortality.

Parkinson disease (PD) affects approximately 7 to 10 million people worldwide,[1] with an estimated global cost of £41 billion per year for treatment and care. PD is characterized by progressive loss of motor function, psychiatric symptoms, autonomic dysfunction, and cognitive impairment related to underlying alpha-synuclein pathology. Psychosis is a common and distressing group of psychiatric symptoms affecting people with PD, usually manifesting as hallucinations and delusions. PD psychosis (PDP) affects more than 50% of people with PD[2] at some point in their condition, and occurs in up to 75% of people with PD dementia, where symptoms are particularly challenging for individuals and their carers.[2,3] In addition to the distress caused by PDP, these symptoms are associated with increased likelihood of institutionalization and mortality.

PDP presents a significant treatment challenge due to the lack of safe, effective, and licensed pharmacological treatments in cases in which reducing dopaminergic therapy has failed to have an impact on symptoms or led to worsening of motor function. As a result, atypical antipsychotics are frequently prescribed to these individuals. However, evidence of efficacy for currently available antipsychotics is limited. The best evidence is for clozapine, which has shown benefit in reducing psychotic symptoms without worsening of motor symptoms in 3 trials of 4-week duration.[4–6] A recent review of the evidence for the Movement Disorders Society supports this, and recommends clozapine for treatment of psychosis, but highlights the considerable limitations in the evidence-base and the need to continue to update guidance as ongoing trials of other treatments are completed.[7] Five placebo-controlled randomized controlled trials (RCTs) of quetiapine also have been published, but only one of these studies provided evidence of significant benefit.[8–12] A smaller number of preliminary RCTs with olanzapine have failed to demonstrate any advantage compared with placebo and worsened motor function.[13–15] Risperidone and aripiprazole were poorly tolerated in an open study[16,17] and have not been evaluated in an RCT.

Any benefits conferred by treatment with current atypical antipsychotics must be balanced against the potential harm associated with these drugs. The adverse impacts of medium- and long-term treatment have not been established in people with PD. Although a number of placebo-controlled RCTs of clozapine, quetiapine, and olanzapine in PD have been published, most have included fewer than 50 participants and the duration of most studies is only 4 weeks. In addition, studies to date have mainly been published as preliminary or short reports, and the reporting of adverse events (AEs) has been incomplete. Only 4 of the existing studies have included mortality as an outcome, with no overall pattern of increased risk, although 1 study of clozapine did report 6 deaths in 60 individuals during a 12-week open-label extension.[18] Only 1 study has provided information relating to cerebrovascular events, suggesting a possible increase associated with quetiapine.[8] There has been more consistent reporting of parkinsonism and sedation, with an indication of increased risk associated with antipsychotic use in comparison to placebo in patients with PD.[4,6,9,13,14,19,20] Safety outcomes from these existing studies are summarized in Table 1. Several open-label trials of longer duration have also been published with both clozapine and quetiapine.[21,22] Although the efficacy data have been superseded by the RCTs, the studies are useful in confirming worsening parkinsonism as an AE. The absence of matched comparison groups in any of the studies makes it impossible to interpret mortality data or other major AEs.

On the basis of the available evidence, no drugs have been approved for PDP in the United States, whereas in Europe clozapine has been approved as a second-line treatment, although paradoxically there is no recommended first-line treatment. In clinical practice, quetiapine is widely prescribed for people with PDP despite the very limited evidence of efficacy and the lack of long-term safety data. Clearly a better understanding of the risks associated with antipsychotic drugs in people with PD is urgently needed to inform clinical practice and provide an evidence base for clinical decision-making.

The limited information regarding the impact of current antipsychotics on adverse outcomes in people with PD is a serious concern, as in other neurodegenerative conditions, particularly Alzheimer disease (AD), the safety concerns are well documented. Evidence in people with AD shows a 1.5- to 1.8-fold increase in mortality, a 3-fold increase in stroke and related cerebrovascular events, and a significant increase in other thromboembolic events, parkinsonism, respiratory infection, extrapyramidal symptoms, and sedation associated with antipsychotic drug use in comparison with placebo.

Pimavanserin is a novel 5HT2A inverse agonist that has been developed to specifically target the underlying pathophysiology of psychotic symptoms, with clear evidence from a recent RCT of benefit in people with PDP.[23] Importantly, the development program for pimavanserin provides long-term open-label follow-up to monitor safety and tolerability. The program was designed to emulate real-world use, and a proportion of patients received concurrent antipsychotic medications during the course of their participation. This subset provides a unique opportunity to evaluate the safety of current antipsychotics in people with PD relative to those not treated with these medications using data collected from an AE reporting procedure with clinical trial quality and rigor. The analysis reported here results from a request from the Data Monitoring and Ethics Committee to evaluate the safety of current antipsychotics in this patient population.

Methods

Study Design and Participants

This is an analysis of data from a multicenter, open-label extension study in participants with PDP, designed to determine the long-term safety of pimavanserin 40 mg administered once daily (Clinical Trials No. NCT00550238). Tablets were manufactured by ACADIA Pharmaceuticals and packaged in compliance with good manufacturing practice. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki.

Participants were enrolled at 65 sites in the United States, 2 in Canada, 35 in Europe, and 12 in India. Eligible participants were people with PDP who fulfilled the published eligibility criteria.[24,25] Briefly, eligible participants were between age 30 and 80, had an established diagnosis of idiopathic PD, and moderate to severe psychosis. For this analysis, participants who had used antipsychotics before the first dose of open-label pimavanserin or within 30 days after the last dose of open-label pimavanserin were excluded.

Procedures

Study visits were conducted at 2 weeks; 1, 3, 6, 9, and 12 months; and every 6 months thereafter. Safety assessments were