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Short Communications

Impact of pimavanserin on prescribing practices in parkinson disease

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ABSTRACT

Introduction: Parkinson disease psychosis (PDP) is a common complication of PD. Until 2016, the only drugs available to treat PDP in the U.S. were antipsychotics with variable degrees of dopamine-receptor antagonism (DRA) that may worsen PD motor symptoms. We evaluated the impact that pimavanserin, a selective serotonin receptor inverse agonist/antagonist atypical antipsychotic (AAP) with no known DRA, had on PDP treatment practices in a commercially insured population.

Methods: We included adults diagnosed with PD who filled at least one AAP prescription from 2016 to 2022. AAP dispensings were categorized into (1) pimavanserin, (2) clozapine and quetiapine (i.e., PDP-"preferred" mixed receptor antagonist AAPs), and (3) the remaining AAPs (i.e., PDP-"nonpreferred" mixed receptor antagonist AAPs). Trends in quarterly dispensing rates per 1000 persons treated were compared across categories. Secondary analyses focused on the 65+ subpopulations insured by Medicare Advantage programs.

Results: Dispensing rates varied between 4 and 697/1000 persons treated for pimavanserin, 1434–1821 for preferred, and 394–746 for nonpreferred AAPs. Pimavanserin dispensings surpassed the nonpreferred category after quarter 3 of 2018. However, preferred AAPs, particularly quetiapine, remained the most dispensed category in the sixth year after pimavanserin's approval. We observed similar trends among Medicare Advantage enrollees.

Conclusion: The availability of pimavanserin was followed by a decline in the use of the most harmful AAPs in persons living with PD. Quetiapine remained the most prescribed AAP. Comparative safety and effectiveness studies are needed to define the relative risks and benefits of treatment options in PDP.

1. Introduction

Parkinson disease psychosis (PDP) ultimately affects at least 60% of persons living with PD and is characterized by visual and auditory hallucinations, delusions, and behavioral disturbances and frequently co-occurs with PD dementia.[1] The etiology of PDP is unclear,[2] but degeneration of the adrenergic (locus coeruleus), cholinergic (nucleus basalis of Meynert), and serotonergic (dorsal raphe nuclei) systems are suspected.[1] PDP may be precipitated or worsened by anti-parkinsonian dopaminergic drugs and psychoactive medications, environmental factors, infection, visual dysfunction, and sleep disturbance.[1].

PDP is associated with a higher risk of mortality, hospitalization, caregiver burden, and institutionalization.[1,3] Following treatment of any predisposing or precipitating factors, treatment with antipsychotics is recommended for persistent and impairing symptoms.[2,4] Each antipsychotic has varying degrees of affinity and binding properties towards dopaminergic, serotonergic, and muscarinic receptors, which influence both off-target benefits and adverse effects.[5,6] In particular, drugs which bind to dopamine D2 receptors [5,6] can potentially worsen motor symptoms in individuals with PD, making it a significant concern for this population.[1,2,4].

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Quetiapine, a multi-acting receptor-targeted AAP with low dopaminergic D2-receptor antagonism (DRA),[5–7] is widely prescribed to persons with PDP due to its accessibility and sedating properties but has uncertain effectiveness for treating PDP.[8] Randomized clinical trial (RCT) data and clinical guidelines support the use of clozapine, another multi-acting receptor-targeted AAP with low DRA [5–7] for PDP. However, clozapine carries a risk of agranulocytosis, which can be fatal if undetected and thus has blood monitoring recommendations. Nevertheless, clozapine and quetiapine have been shown to have minimal motor adverse effects in prior clinical trials among people with PD.[9–15] Pimavanserin, a selective serotonin (5-HT2A) receptor inverse agonist/antagonist without known DRA properties or affinity for other receptors, is a newer medication that the Food and Drug Administration (FDA) has approved for treating PDP in the U.S.[1,8], with emerging data on its effectiveness. As a result, current recommendations from the International Movement Disorders Society classify pimavanserin and clozapine as "clinically useful," and quetiapine as "possibly useful" for the treatment of psychosis in PD.[8] The American Geriatrics Society (AGS) Beers Criteria® continually recommend against the use of all antipsychotics except for pimavanserin, clozapine, and quetiapine, in persons with PD due to potential drug-disease interactions (i.e., worsening of motor symptoms).[16] In countries where pimavanserin is unavailable, such as the United Kingdom, quetiapine and clozapine are the sole medications recommended for the pharmacological management of hallucinations and delusions in persons with PD.[17].

The extent to which clinical practice reflects the available evidence and guideline recommendations is an important component of population health but is not currently known for PDP treatment. We examined AAP dispensing trends in a PD population sample from a large U.S. database of commercially insured individuals from 2016 (when pimavanserin first became available) to 2022.

2. Methods

2.1. Ethical compliance and data availability statement

The Office of Regulatory Affairs of the University of Pennsylvania (Philadelphia, Pennsylvania) granted an Institutional Review Board exemption for this study. Optum's de-identified Clinformatics® Data Mart Database (CDM) used in this study requires individual or institutional purchase.

2.2. Data source

We used the 2016–2022 CDM (OptumInsight: Eden Prairie, Minnesota). CDM is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans across the U.S. Available data include demographic information (e.g., age, sex, etc.), medical encounters, and pharmacy prescription claims. CDM represents the commercially insured population in the U.S., including adults 65+ years with Medicare Advantage, allowing for a large-scale study of chronic medication use.

2.3. Study population and exposure of interest

We first identified persons with at least one AAP prescription with at least one day's supply during the study period (May 1, 2016–June 31, 2022) in the database using national drug codes from Lexicon Plus (Oracle Corporation: Austin, Texas). We then restricted the data to persons whom 1) had at least one PD diagnosis code from a physician or advanced practice provider previously, 2) had at least one prescription for anti-parkinsonism medications within six months of that diagnosis, and 3) were at least 40 years old at their first PD diagnosis captured in the database. We excluded persons with a concurrent diagnosis of atypical parkinsonism, dementia with Lewy bodies, amyotrophic lateral sclerosis, bipolar disorder, or schizophrenia, as these persons have distinct symptoms and unique treatment needs/responses. AAP dispensings for the remaining individuals were deduplicated within each year and grouped into three different categories for analyses: 1) pimavanserin (i.e., PDP-FDA-indicated selective 5-HT2A receptor inverse agonist/antagonist AAP), 2) clozapine and quetiapine (i.e., PDP-off-label, guideline-supported mixed receptor antagonist AAPs, hereby referred to as the "preferred AAPs" [8,16,17]), and 3) the remaining AAPs (i.e., PDP-off-label, safety-warned, mixed receptor antagonist AAPs, including aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, risperidone, ziprasidone, hereby referred to as the "nonpreferred AAPs" [8,16,17]).

2.4. Statistical analyses

All analyses were performed using SAS v9.4 and Microsoft Excel. We tracked quarterly AAP dispensing trends in each of the three categories of interest from the second quarter of 2016 (when pimavanserin first became available) through the second quarter of 2022, the last year of CDM data available at our institution. Dispensing rates were calculated and standardized quarterly as the number of prescription claims for each AAP category per 1000 individuals with PD treated with AAPs. We also estimated the annual rates of new users (i.e., persons initiating an AAP category of interest without dispensings of any AAPs within six months prior) receiving each AAP category per 1000 persons with PD newly initiating AAPs. We repeated our analyses in the subpopulation of qualifying AAP users with PD who were 65 and older and receiving benefits from a Medicare Advantage plan.

3. Results

We identified 45,397 individuals ages 40 and older with a qualifying PD diagnosis and at least one AAP dispensing during the study period. As shown in Fig. 1, from 2016 to 2022, nonpreferred AAPs' annual average dispensing rates declined from 607 to 394 claims/1000 treated persons with PD, as pimavanserin dispensing rates increased from 4 to 612. The dispensing of pimavanserin surpassed that of nonpreferred AAPs in the fourth quarter of 2018 (536 vs. 504 claims/1000 treated persons, respectively). However, prescriptions for preferred AAPs (>90% of which were for quetiapine) remained the most prescribed AAP category for PDP between 2016 and 2022, fluctuating between 1453 and 1522 prescriptions claims/1000-treated-persons. During our study period, the annual number of new initiators increased from 77 to 175 for pimavanserin, slightly decreased from 693 to 659 for preferred AAPs, and reduced from 229 to 166 for nonpreferred AAPs per 1000 persons with PD newly started on AAPs (Supplemental Table 1).

Restricting our sample to those ages 65 and older yielded 39,513 persons with a qualifying PD diagnosis who filled 102,095 prescriptions for an AAP during the study period and revealed similar results as our overall sample (Fig. 2). Preferred AAPs remained the most prescribed category, driven primarily by quetiapine prescriptions. The use of pimavanserin increased, surpassing that of nonpreferred AAPs in the fourth quarter of 2018. Similarly, the number of new initiators increased for the pimavanserin from 82 to 175, slightly reduced for preferred AAPs from 695 to 670, and decreased from 223 to 155 for nonpreferred AAPs per 1000 individuals with PD newly treated with AAPs from 2016 to 2022 (Supplemental Table 1).

4. Discussion

In this study, we examined the dispensing trends of AAPs among individuals being actively treated for PD in a large database of commercially insured people in the U.S. We observed that once pimavanserin, the first selective 5-HT2A inverse agonist/antagonist AAP with no known affinity to dopaminergic or other receptors became available, dispensing of the most potentially harmful AAP group declined.

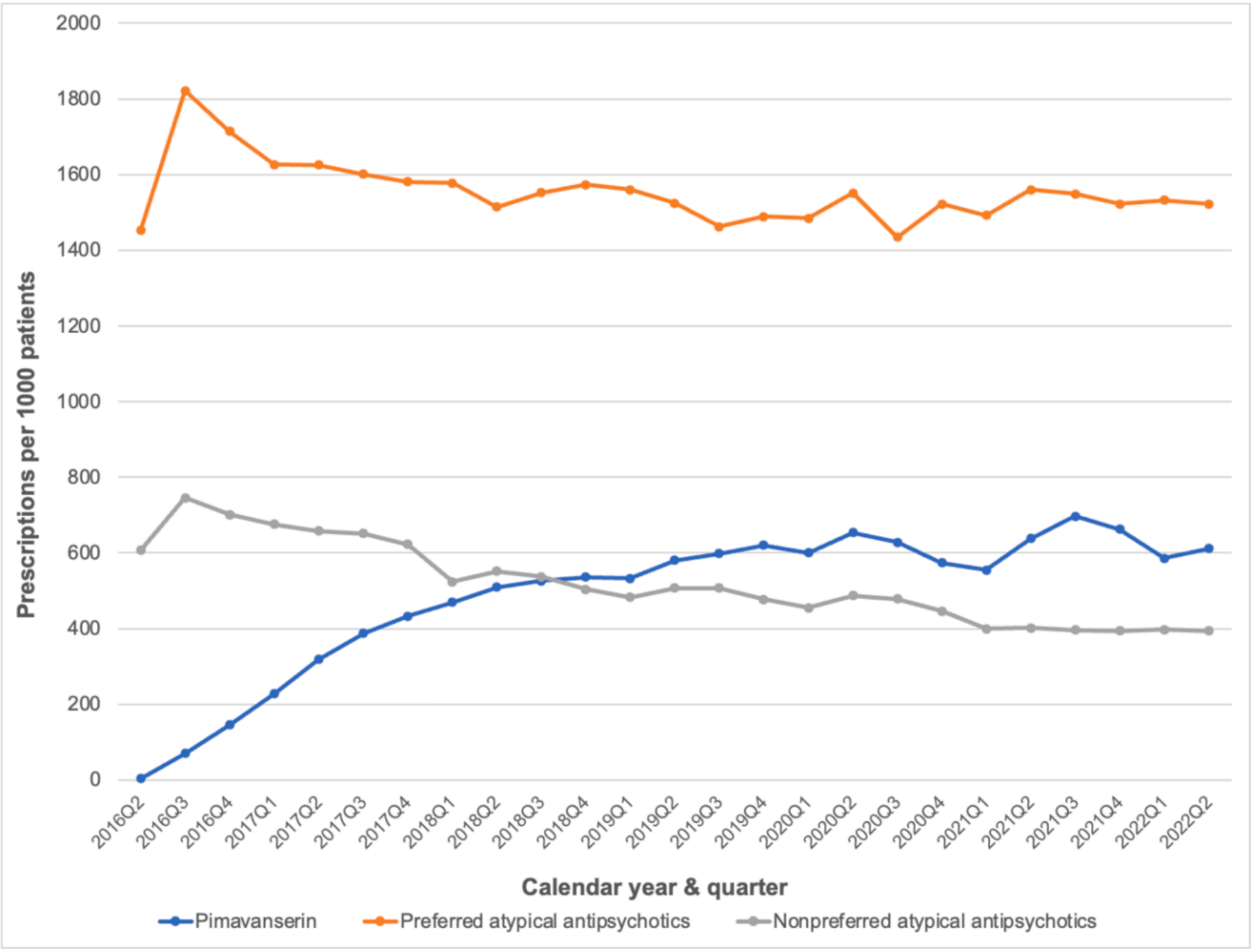

Fig. 1. Prescription distributions per 1000 patients by atypical antipsychotic group, 2016–2022.

Nonpreferred AAPs frequently appear on numerous clinician safety lists and advisories, including the AGS Beers Criteria®,[16] the European EU (7)-PIM list,[18] or the STOPP/START criteria [19] due to concerns regarding their adverse effects related to their mixed receptor affinities, particularly in older adults, a group that largely includes individuals with PD. Prior work has indicated an increased prevalence of documented falls and fractures over a 6-month follow-up period among institutionalized new users of the nonpreferred AAPs as compared to pimavanserin, with a number needed to harm 29.6.[20] From a PD population safety perspective, a 33 % decrease in dispensings of the nonpreferred AAPs is an encouraging finding, regardless of the many potential factors that drive, enable, and support the observed trends.

In our sample, quetiapine, a drug with limited evidence of efficacy for PDP,[8] remained the most prescribed AAP despite the introduction of an FDA-indicated alternative and the existence of a guideline-recommended alternative. There are many possible contributors to this observation. Quetiapine is widely accessible and has evidence of minimal extrapyramidal adverse effects. [5,6] Its known soporific effects may directly reduce hallucinations through increased sleep duration and may reduce caregiver experiences of disruptive nocturnal behavior through sedation. Greater widespread use of clozapine likely remains limited by concerns over its safety and its monitoring recommendations. Pimavanserin, like many new therapies, is distributed by specialty pharmacies and has a prior authorization requirement that consumes non-reimbursable prescriber personnel resources. Even with patient support programs, the final out-of-pocket cost of pimavanserin may be prohibitive to some patients, especially those who already have significant medical care expenses resulting from multiple medications for various comorbidities, a need to see several specialists, and home nursing care expenses due to psychosis itself.[21,22] Additionally, the long half-lives of pimavanserin and its major active N-demesthylated metabolite may raise concerns related to the length of time prior to observable benefit, drug clearance, adverse effects, and drug-drug interactions.[23] Finally, there is no level I evidence, such as in a randomized controlled trial comparing the effectiveness and safety of clozapine, pimavanserin and quetiapine.[1].

This study evaluated AAPs' dispensing and initiation rates in a large sample of commercially insured individuals with PD over time. We found that the market entry of a new and effective drug with a theoretically safer adverse effect profile was followed by a reduction in the use of the most harmful treatment options. Strengths of the study include a large, population-representative longitudinal dataset that combines clinical care documentation with prescription fill data. However, our study also had limitations. Our findings are limited by our inability to capture discrete data on factors that may influence documented diagnosis and medical decision-making, such as clinical symptoms, patients' and caregivers' personal beliefs, preferences and financial situations, and physician knowledge/ability. Moreover, we did not require a diagnosis of psychosis preceding the antipsychotic prescription. While pimavanserin prescriptions require a documented diagnosis of psychosis, we might have inadvertently captured quetiapine prescriptions intended solely for another indication (e.g., insomnia, major depressive disorder), which in turn inflated the rate of quetiapine prescriptions. However, there is currently no specific diagnosis code for

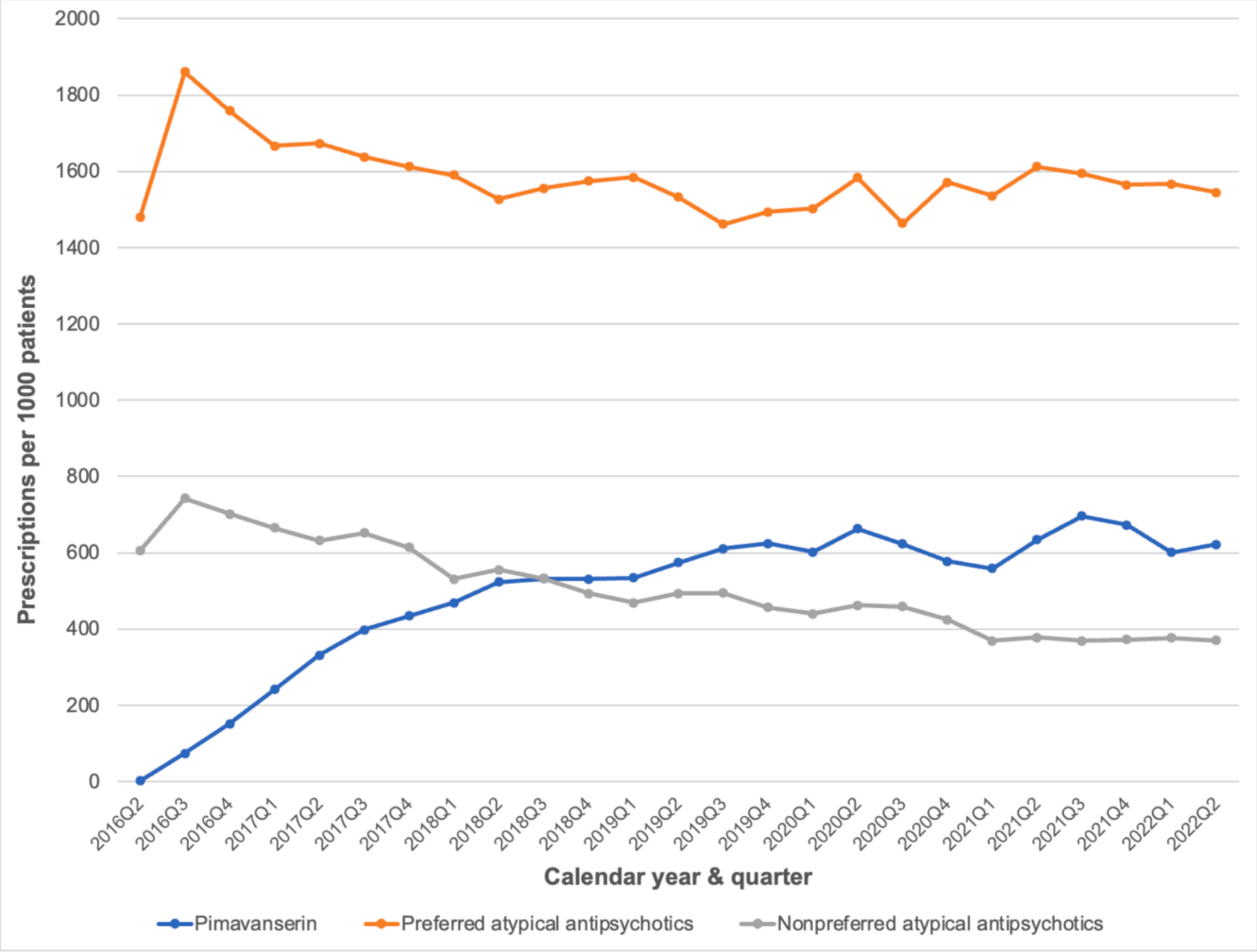

Fig. 2. Prescription distributions per 1000 patients 65+ at PD diagnosis by atypical antipsychotic group, 2016–2022.

PDP, and hallucinations and delusions are frequently under-coded in claims data.[24] Lastly, commercially insured people tend to be wealthier and have better access to new therapies. Thus, our findings might not be generalizable. Despite these limitations, our data suggest that sizeable populations of older U.S. adults with PD now receive all categories of AAPs and are thus able to be examined in specific drug-drug, drug-drug-drug, and drug-disease interaction studies. Head-to-head comparison studies using real-world data in emulated target trials are needed to assess the safety and effectiveness of clozapine, quetiapine, and pimavanserin to better understand the relative risks and benefits of psychosis treatment options in the PD population.

Author contributions

T.P.P.N., V.L., D.W., and A.W.W. designed the research. T.P.P.N. performed the research. T.P.P.N., and A.W.W. analyzed the data. T.P.P.N. and V.L. wrote the manuscript; all other authors revised important content of the manuscript. All authors reviewed and approved the manuscript.

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None.

CRediT authorship contribution statement

Thanh Phuong Pham Nguyen: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Vy Le:** Writing – original draft, Conceptualization. **Daniel Weintraub:** Writing – review & editing, Writing – original draft, Resources, Conceptualization. **Allison W. Willis:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2025.100317.

References

[1] D. Weintraub, Management of psychiatric disorders in Parkinson's disease: Neurotherapeutics - Movement Disorders Therapeutics, Neurotherapeutics 17 (4) (2020) 1511–1524.
[2] K.J. Wilby, E.G. Johnson, H.E. Johnson, M.H.H. Ensom, Evidence-based review of pharmacotherapy used for Parkinson's disease psychosis, Ann. Pharmacother. 51 (8) (2017) 682–695.
[3] J. Cummings, S. Isaacson, R. Mills, H. Williams, K. Chi-Burris, A. Corbett, R. Dhall, C. Ballard, Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial, Lancet 383 (9916) (2014) 533–540.
[4] K. Kyle, J.M. Bronstein, Treatment of psychosis in Parkinson's disease and dementia with Lewy Bodies: A review, Parkinsonism Relat. Disord. 75 (2020) 55–62.
[5] S. Siafis, H. Wu, D. Wang, A. Burschinski, N. Nomura, H. Takeuchi, J. Schneider-Thoma, J.M. Davis, S. Leucht, Antipsychotic dose, dopamine D2 receptor occupancy and extrapyramidal side-effects: a systematic review and dose-response meta-analysis, Mol. Psychiatry 28 (8) (2023) 3267–3277.
[6] D.A. Sykes, J. Lochray, H.M.F. Comfort, P. Jain, S.J. Charlton, Exploring the kinetic selectivity of antipsychotics for dopamine D₂ and 5-HT_{2A} receptors: implications for the prevalence of EPS and receptor occupancy, bioRxiv (2021), 2021.11.14.468520.
[7] I.M. Lako, E.R. van den Heuvel, H. Knegtering, R. Bruggeman, K. Taxis, Estimating dopamine D(2) receptor occupancy for doses of 8 antipsychotics: a meta-analysis, J. Clin. Psychopharmacol. 33 (5) (2013) 675–681.
[8] K. Seppi, K. Ray Chaudhuri, M. Coelho, S.H. Fox, R. Katzenschlager, S. Perez Lloret, D. Weintraub, C. Sampaio, C. the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine, Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review, Mov. Disord. 34 (2) (2019) 180–198.
[9] P. Pollak, F. Tison, O. Rascol, A. Destee, J.J. Pere, J.M. Senard, F. Durif, I. Bourdeix, Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J. Neurol. Neurosurg. Psychiatry 75 (5) (2004) 689–695.
[10] Parkinson Study Group, Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease, N. Engl. J. Med. 340 (10) (1999) 757–763.
[11] W.G. Ondo, R. Tintner, K.D. Voung, D. Lai, G. Ringholz, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Mov. Disord. 20 (8) (2005) 958–963.
[12] J.M. Rabey, T. Prokhorov, A. Miniovitz, E. Dobronevsky, C. Klein, Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration, Mov. Disord. 22 (3) (2007) 313–318.
[13] P. Shotbolt, M. Samuel, C. Fox, A.S. David, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatr. Dis. Treat. 5 (2009) 327–332.
[14] H.H. Fernandez, M.E. Trieschmann, M.A. Burke, C. Jacques, J.H. Friedman, Long-term outcome of quetiapine use for psychosis among Parkinsonian patients, Mov. Disord. 18 (5) (2003) 510–514.
[15] D. Merims, M. Balas, C. Peretz, H. Shabtai, N. Giladi, Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis, Clin. Neuropharmacol. 29 (6) (2006) 331–337.
[16] By the American Geriatrics Society Beers Criteria Update Expert Panel, American Geriatrics Society 2023 updated AGS Beers Criteria(R) for potentially inappropriate medication use in older adults, J Am Geriatr Soc 71(7) (2023) 2052-2081.
[17] National Institute for Health and Care Excellence, Parkinson's disease in adults, 2017. https://www.nice.org.uk/guidance/ng71/resources/parkinsons-disease-in-adults-pdf-1837629189061. (Accessed February 11 2025).
[18] A. Renom-Guiteras, G. Meyer, P.A. Thurmann, The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries, Eur. J. Clin. Pharmacol. 71 (7) (2015) 861–875.
[19] D. O'Mahony, A. Cherubini, A.R. Guiteras, M. Denkinger, J.B. Beuscart, G. Onder, A. Gudmundsson, A.J. Cruz-Jentoft, W. Knol, G. Bahat, N. van der Velde, M. Petrovic, D. Curtin, STOPP/START criteria for potentially inappropriate prescribing in older people: version 3, Eur Geriatr Med 14 (4) (2023) 625–632.
[20] K. Rajagopalan, N. Rashid, D. Gopal, D. Doshi, Falls and fractures among nursing home residents treated with pimavanserin versus other atypical antipsychotics: analysis of medicare beneficiaries with Parkinson's disease psychosis, Drugs Real World Outcomes (2024).
[21] E.L. Reynolds, G. Gallagher, C.E. Hill, M. Banerjee, A. Mante, G.J. Esper, B. C. Callaghan, Costs and Utilization of New-to-Market Neurologic Medications, Neurology 100 (9) (2023) e884–e898.
[22] K.M. Bozymski, D.K. Lowe, K.M. Pasternak, T.L. Gatesman, E.L. Crouse, Pimavanserin: A novel antipsychotic for Parkinson's disease psychosis, Ann. Pharmacother. 51 (6) (2017) 479–487.
[23] M.P. Cruz, Pimavanserin (Nuplazid): a treatment for hallucinations and delusions associated With Parkinson's Disease, P T 42 (6) (2017) 368–371.
[24] A.G. Hamedani, D. Weintraub, A.W. Willis, Medicare claims data underestimate hallucinations in older adults with dementia, Am. J. Geriatr. Psychiatry 30 (3) (2022) 352–359.