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Study concept and design: Dashtipour.

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Abstract (word count = 250)

Objective: To determine the efficacy and tolerability of quetiapine as compared to placebo or other interventions for psychosis in parkinsonism.

Design: Systematic review

Participants: Subjects with a diagnosis of parkinsonism participating in randomized controlled trials (RCTS) investigating the efficacy and tolerability of quetiapine on psychotic symptoms within a defined follow-up period.

Measurements: PubMed, Cochrane Register of Controlled Trials, and EMBASE were searched for articles published from January 1991 to October 2017. The process adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses format. Study methodology, patient- and treatment-level data were independently extracted and summarized using descriptive statistics. Studies underwent quality assessment for risk of bias.

Results: 17,615 unique records were identified and seven RCTs (total of 241 subjects) met inclusion criteria. Five RCTs were placebo-controlled and two compared quetiapine against clozapine. Mean study duration was 12 weeks and mean daily quetiapine dose was 103 mg per day (range of 12.5 mg to 300 mg). In four of five placebo-controlled RCTs, quetiapine failed to demonstrate significant improvement of PP compared to placebo. In two clozapine-comparator RCTs, quetiapine was better tolerated but no more effective than clozapine. Across all RCTs, mean completion rates for quetiapine, clozapine, and placebo were 66%, 68.5%, and 66%, respectively. Quetiapine did not significantly worsen motor function.

Conclusion: The efficacy and completion rate of quetiapine in RCTs for psychosis in parkinsonism is no better than placebo or clozapine. Based on new information, clinicians must re-evaluate traditional viewpoints on the use of quetiapine for psychosis in parkinsonism.

Keywords: Parkinson Disease, parkinsonism, hallucinations, quetiapine, psychosis

INTRODUCTION

The most common neurodegenerative form of parkinsonism is Parkinson disease (PD) which is a clinical syndrome characterized by lesions in the basal ganglia, predominantly in the substantia nigra. Parkinson disease makes up approximately 80% of cases of parkinsonism and it is recognized that non-motor symptoms are prominent {1,2}. Much current clinical research surrounds the frequency and impact of non-motor symptoms on patients with parkinsonism, including Parkinson disease psychosis (PDP) which is common but frequently underrecognized and undertreated {3}. Psychotic symptoms will develop in up to 60% of patients with PD and in up to 75% of patients with PD and concurrent dementia {3,4}.

The care of patients with PDP is associated with significant healthcare utilization. In a Medicare survey of claims data from 2000 to 2010, patients with PDP had higher all-cause costs and resource utilization {3}. The highest annual cost differentials were found in long-term care costs ($31,178 for PDP vs $14,461 for PD without psychosis), skilled nursing facility costs ($6601 for PDP vs $2067 for PD without psychosis), and inpatient costs ($10,125 for PDP vs $6024 for PD without psychosis). Long-term care utilization and expenditures were also significantly higher for PDP patients, spending an average of approximately 179 days in long-term care, compared with 83 days for patients with PD without psychosis.

The presence of psychotic symptoms is not only an independent cost-driving factor, but also intrusive to the patient's daily life and a significant determinant of increased caregiver burden, sometimes exceeding that imposed by the motor symptoms that are classically associated

with PD {5,6}. In a community-based PD sample, minor symptoms of PDP (e.g., illusions, sense of presence, passage hallucinations) were associated with more depressive symptoms and worse quality of life {7}. The presence of hallucinations and psychotic symptoms are also an independent risk factor for nursing home placement and mortality in PD patients {8,9}. When patients with PDP are admitted to long-term care (LTC) facilities, their associated disruptive behaviors can have a significant effect on LTC personnel and other LTC residents.

Balancing control of the motor and psychiatric symptoms of parkinsonism has historically been challenging because of a paucity of evidence-based strategies. Quetiapine is indicated for the treatment of schizophrenia and bipolar disorder, however it is commonly used off-label for the management of psychosis in parkinsonism. For patients with this condition, quetiapine dosing is titrated from 12.5 mg nightly up to a range of 50 to 150 mg per day {10}. Quetiapine is similar in structure to clozapine and has antagonist activity at histamine, muscarinic, and serotonin 5-HT_{2A} receptors, with minimal affinity for dopaminergic D2 receptor {11}. In the American Academy of Neurology evidence-based practice parameter on the treatment of psychosis in PD, quetiapine was classified as Level C (i.e., possibly effective) {12}. A task force of the International Parkinson and Movement Disorder Society concluded in an evidence-based report that because of conflicting data on the efficacy of quetiapine and study methodology concerns (e.g., small sample size, low-quality rating), there is insufficient evidence for quetiapine for the treatment of PDP {13}. A joint task force of the European Federation of Neurological Societies and the Movement Disorder Society – European Section recommends quetiapine as possibly useful {14}. Subsequent to the publication of these evidence-based statements, the use of quetiapine and other antipsychotics in patients with PD has been found to be associated with an increased risk of mortality (quetiapine hazard ratio of 2.16 [95% CI, 1.88-

2.48] over nonuse) {15} in a Veteran Administration PD population, and a new molecular entity, pimavanserin, was FDA approved for the treatment of PDP. Given these new developments, it is important to re-evaluate the role of quetiapine in the treatment of psychosis in patients with parkinsonism.

METHODS

Literature Search Strategy and Data Sources

The literature search strategy was designed to identify randomized controlled trials (RCTs) of quetiapine in the treatment of psychosis in patients with parkinsonism. The literature search was performed using these databases: PubMed, Cochrane Central Register of Controlled Trials, and EMBASE. The search used the keyword "quetiapine.'' We limited our search to English language-only articles published from January 1991 to October 2017. Additionally, we manually searched the reference lists of identified publications for additional studies to supplement our electronic search.

Study Selection

Two reviewers (JC, LM) performed the literature research in parallel and independently. Reviewers discussed and selected articles to be included. Studies were included in the qualitative review if they: 1) were randomized and controlled with either placebo or an active comparator, 2) enrolled subjects with a diagnosis of parkinsonism, 3) assessed the efficacy of quetiapine on psychotic symptoms, and 4) evaluated adverse effects including motor outcomes. When disagreement arose between screeners on studies to be included in the final synthesis, a third reviewer resolved the discrepancy.

The first level of screening examined the title and abstract of publications for inclusion or exclusion. At the second level of screening, the full text of publications were retrieved and reviewed for inclusion or exclusion. Reference lists were also screened to identify additional studies. At the final level of screening, data were extracted from the final list of RCTs.

Data Extraction and Quality Assessment

Study methodology, patient, and treatment-level data were extracted from full text publications under predefined headings. Each study underwent quality assessment for risk of bias based on Cochrane metrics {16}. The quality assessment for RCTs systematically addressed seven types of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.

RESULTS

Studies Identified

The systematic literature search identified seven studies on the efficacy of quetiapine in treating psychosis in parkinsonism (including PD psychosis, dementia with Lewy bodies, dementia with parkinsonian features) (Figure 1). Five of the RCTs compared quetiapine to placebo {17-22}, and two RCTs compared quetiapine to clozapine {23,24}. A summary of the RCT results is provided in Table 1. The seven unique RCTs included a total of 241 subjects with parkinsonism and psychosis. Quetiapine at doses between 12.5 mg and 300 mg per day (mean daily dose of 103 mg) administered from four to 22 weeks (mean duration of 12 weeks) failed to significantly reduce psychotic symptoms in subjects with parkinsonism compared to placebo or

clozapine when objectively assessed on the BPRS, the most frequently reported scale in these RCTs. In the two clozapine-comparator controlled studies, quetiapine demonstrated no advantage over clozapine in terms of efficacy or adverse effects and in one of the studies {23}, hallucination and delusion scores favored clozapine over quetiapine. Overall, the mean completion rates for all groups were poor and rates did not differ between quetiapine and placebo-treated subjects. Across all RCTs, the completion rates for quetiapine, clozapine, and placebo were 66%, 68.5%, and 66%, respectively. Among the two RCTs comparing the efficacy of quetiapine to clozapine, the completion rates were more favorable compared to clozapine, (80% and 68.5%, respectively) {23,24}.

Overall, adverse effects reported in quetiapine-treated subjects include, confusion, dizziness, headache, orthostatic hypotension, somnolence, and worsening parkinsonism. Although individual RCTs reported quetiapine-associated worsening of parkinsonism, the overall data demonstrates quetiapine does not significantly worsen motor function as measured by UPDRS motor scores. The systematic quality assessment revealed that all RCTs were subject to high risk of attrition bias due to incomplete outcome data (Table 2).

Details of Studies

Fernandez et al. performed a randomized, double-blind, placebo-controlled study on the use of quetiapine for subjects with PD and visual hallucinations {17}. Subjects were randomly assigned to treatment arms and initiated at 25 mg of quetiapine or matching placebo at bedtime. Dosage increased by 25 mg increments every 3 to 7 days until reaching a maximum dosage of 150 mg, or the complete cessation of nocturnal hallucinations. The primary dependent variable was the length of REM sleep, measured by polysomnography. The quetiapine group increased in

the length of their REM sleep (mean increase = 13.6 min), and the placebo group decreased in REM sleep (mean decrease = 28.3 min), but the difference between groups was not statistically significant. Hallucination severity was self-reported in one item of the Brief Psychiatric Rating Scale (BPRS), which presents a series of psychiatric symptoms rated on a 7-point scale in which larger scores indicated greater severity. Although the quetiapine group experienced greater reduction in hallucination severity (mean reduction 1.32, *SD* = 1.13) than the placebo group (mean reduction 0.04, *SD* = 0.82), *P*=0.02, the change in total BPRS scores was not statistically different between groups. There were no statistically-significant differences between quetiapine and placebo in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores or in the number of adverse events experienced by either group. The completion rate was only 68.75% (11 out of 16 subjects), with 50% of the quetiapine group and 87.5% of the placebo group finishing the study. Notable reasons for termination from the quetiapine group were lack of efficacy in treating hallucinations (experienced by two subjects), and one subject who dropped out because of an adverse event, drowsiness.

A randomized, double-blind, placebo-controlled, parallel group study by Kurlan et al. assessed the effect of quetiapine on agitation and psychosis on subjects with dementia, PD, or Alzheimer's disease with PD features {18}. Quetiapine and placebo groups started treatment at a dosage of 25 mg of quetiapine or placebo. Dosage was increased, as necessary, up to an additional 25 mg every 2 days and up to an absolute limit of 150 mg twice daily. Quetiapine efficacy was assessed using the BPRS, and motor function was assessed using the motor subscale of the UPDRS. Statistical analysis failed to find any statistically significant difference between quetiapine and placebo groups on efficacy, adverse events, or change in UPDRS. The study-wide completion rate was 75% (30 out of 40 subjects). The quetiapine group had 85%

completion, and the placebo group had 65% completion. The authors reported that the most common reasons for dropout were concern over placebo (one in each treatment group), effectiveness of medication (two in the placebo arm, one in the quetiapine arm), and adverse effects (three in the placebo arm, one in the quetiapine arm).

Ondo et al. conducted a double-blind, placebo-controlled, 2:1 randomized, parallel trial to evaluate the efficacy of quetiapine in treating hallucinations in subjects with PD {19}. The first three weeks of treatment were two doses of quetiapine per day—one in the afternoon, one at night—titrating up to 50 mg per dose. Weeks 4-6 of treatment maintained two doses per day while titrating up to a maximum of 200 mg per dose. Hallucinations were assessed with the BPRS and the Baylor PD Hallucination Questionnaire. On the Baylor PD Hallucination Questionnaire, subjects in the quetiapine group had a non-significant trend toward improvement (P=0.20). The quetiapine group and placebo had comparable outcomes regarding the change in total BPRS score and change in the score on the BPRS hallucination item. The main adverse events in the drug group were sedation (40%), and subjective worsening in PD (19%) although there was no statistically-significant worsening of parkinsonism on the UPDRS motor scores. Twenty-six out of 31 subjects (83.87%) completed the study, with 80.95% completion from the quetiapine group and 80% from the placebo group. Reasons for dropout from the quetiapine group included serious unrelated illness, lack of effectiveness, and noncompliance. The placebo group had two dropouts from unrelated serious illness.

Rabey et al. performed a double-blind, placebo-controlled RCT on the efficacy of quetiapine on drug-induced psychosis in subjects with PD {20}. All the subjects in this study had been successfully treated with dopaminergic medication for at least 2 years prior to recruitment. Subjects had psychotic symptoms (hallucinations and/or delusions), which significantly affected

the subject's quality life. Subjects were randomly assigned to either the quetiapine or placebo group for 12 weeks of treatment. Both groups began with one 12.5 mg dose of quetiapine or placebo per day. Over a titration period of up to 4 weeks, dosage increased until the psychotic symptoms resolved or side effects became severe. The outcomes experienced by the quetiapine group and placebo group were comparable, and the differences were not statistically significant. There were no statistically significant differences in the UPDRS motor scores from baseline to final point of assessment in either group. The most commonly occurring adverse event was somnolence, seen in seven subjects from the quetiapine group and two subjects from the placebo group. The study-wide completion rate was 55.17% (32 of 58 subjects), with 50.00% completion in the quetiapine group and 60.71% completion in the placebo group. The most common reason for dropout was a lack of therapeutic response, which occurred in 10 of 15 dropouts in the quetiapine group and 9 of 11 dropouts in the placebo group. Three subjects in the quetiapine group discontinued treatment due to side effects, of which two were due to somnolence.

Shotbolt et al. conducted a double-blind placebo-controlled RCT to evaluate the efficacy of quetiapine for psychosis in PD {21,22}. The study period lasted 12 weeks, during which subjects were started on a daily dose of 25 mg of quetiapine or placebo and titrated through the first 6 weeks up to a maximum dosage of 50 mg in the morning and 100 mg at night. The primary dependent variable was the time remaining in treatment at the time of dropout. This outcome was based on the theory that "patients would drop out if their psychosis failed to improve or deteriorated and would stay in if their symptoms were improving." On average, subjects in the quetiapine group dropped out sooner than those in the placebo group, but this difference was not statistically significant. The secondary assessment measures were the UPDRS total score, UPDRS Motor score, BPRS, Neuropsychiatric Inventory (NPI), and Baylor PD

hallucination scale; none of these measures showed statistically significant changes between baseline and final observation. The quetiapine group had three adverse events—all drowsiness—followed by dropout, and the placebo group also had three adverse events—two cases of drowsiness, one case of confusion—followed by dropout.

Clozapine has improved psychosis in PD in two multicenter, placebo-controlled trials and is commonly used in clinical practice {25,26}. We identified two RCTs that compared quetiapine to clozapine and met inclusion criteria {23,24}. Merims et al. randomly assigned subjects with psychosis and PD to receive treatment with quetiapine or clozapine and assessed outcomes with the delusion and hallucination items of the NPI and the Clinician Global Improvement-Change Scale (CGI-C) {23}. Although the hallucination frequency was reduced for both the treatment groups, the baseline-to-final-assessment difference was statistically significant for only the clozapine group. Subjects in the clozapine group experienced a statistically-significant reduction in the frequency of delusions whereas subjects assigned to quetiapine actually increased delusion frequency, but not to a consistent degree. The change in CGI-C scores were comparable between the two treatment arms. The article lists UPDRS total score but not the motor score; however, the authors state, “We did not observe any worsening in parkinsonian symptoms as measured by the UPDRS […] in any of the treatment arms.” Only 59.26% of the subjects (16 out of 27) completed the study: 69.23% of the quetiapine group and 50.00% of the clozapine group. Lack of treatment efficacy was the most common cause for dropout from the quetiapine group, and a decreased leukocyte count was the most common cause for dropout from the clozapine group.

In the second RCT that compared quetiapine to clozapine, Morgante et al. randomly assigned subjects with psychosis in PD to either quetiapine or clozapine treatment to assess

effect on hallucinations, suspiciousness, and hostility {24}. Outcome measurements included the BPRS, Clinician Global Improvement-Severity Scale (CGI-S), Abnormal Involuntary Movement Scale (AIMS), and the total score of the UPDRS. Although the outcome assessors were blinded to the treatment assignments, the subjects were informed about the drug they were receiving. The starting dose was 25 mg per day of quetiapine or 6.25 mg per day of clozapine. Dosage was titrated by a neurologist aware of the treatment conditions, with maximum doses of 200 mg daily of quetiapine or 50 mg daily of clozapine. Post-treatment scores on the BPRS, CGI-S, and AIMS were improved compared to baseline for both the quetiapine and the clozapine groups. Overall, the UPDRS scores remained unchanged, however a mild worsening of parkinsonism was observed in three patients treated with quetiapine (greater than 100 mg per day). The efficacy of both drugs was comparable, as the differences between quetiapine and clozapine groups were not statistically significant. Both groups experienced a small number of adverse events, but no inferential statistics were provided comparing quetiapine to clozapine. The majority of the subjects, 88.89% (40 out of 45) completed the 12-week study: 90.91% of the quetiapine group, 86.96% of the clozapine group. One subject in the quetiapine group withdrew because of sedation, and another subject withdrew due to a “confusional state.” Dropout in the clozapine group was attributed to sedation, dizziness, and severe hypotension.

DISCUSSION

The aim of this comprehensive systematic literature review is to qualitatively evaluate the efficacy and safety (including effects on motor function) of quetiapine as compared to placebo or other interventions for the treatment of psychosis in parkinsonism. Our methodology aimed to

gather data for all forms of parkinsonism and we found that the published RCT evidence is dominated by investigations of patients with psychosis and idiopathic PD.

In a network meta-analysis, Iketani et al. report that the utility of quetiapine for the treatment of psychosis (assessed by BPRS) in patients with idiopathic PD is inferior to that of placebo and that use of quetiapine was likely to lead to deterioration of motor function {27}. The meta-analysis by Iketani et al was confined to RCTs of subjects with idiopathic PD. Additionally, the meta-analysis included only four unique (i.e., non-redundant reports) RCTs of quetiapine which comprised a total of 138 subjects. In our current study, we analyzed data from seven unique studies with a total of 241 subjects with parkinsonism and psychosis (including PD psychosis, dementia with Lewy bodies, dementia with parkinsonian features) who were randomized to receive either quetiapine or a comparator (placebo or clozapine). Quetiapine at doses between 12.5 mg and 300 mg per day (mean daily dose of 103 mg) administered from four to 22 weeks (mean duration of 12 weeks) failed to significantly reduce psychotic symptoms in subjects with parkinsonism compared to placebo or clozapine when objectively assessed on the BPRS, the most frequently reported scale in these RCTs. Overall, in four of five placebo-controlled RCTs, quetiapine failed to significantly improve psychosis. In two clozapine-comparator controlled studies, quetiapine demonstrated no advantage over clozapine in terms of efficacy or adverse effects and in one of the studies, hallucination and delusion scores favored clozapine over quetiapine.

Across all RCTs, mean completion rates for all groups were similarly poor. The RCT completion rates for quetiapine and placebo were no different and this suggests that dropouts cannot be substantively attributed to quetiapine dose titration methodologies. However, completion rates for quetiapine were more favorable compared to clozapine. Overall, adverse

effects reported in quetiapine-treated subjects include, confusion, dizziness, headache, orthostatic hypotension, somnolence, and worsening parkinsonism. Despite reports of worsening parkinsonism, the overall data demonstrates quetiapine does not significantly worsen motor function as measured by UPDRS motor scores. The regularity of discontinuations due to adverse effects associated with quetiapine in subjects with psychosis and parkinsonism indicates that use of quetiapine in this population may not be as well tolerated as traditionally believed. The most common adverse effects leading to quetiapine discontinuation were confusion and somnolence.

In 2008, a task force of the International Parkinson and Movement Disorder Society published a critique of rating scales for the assessment of psychosis in PD and recommended four scales for use in clinical studies: the Brief Psychiatric Rating Scale (BPRS), Neuropsychiatric Inventory (NPI), Positive and Negative Syndrome Scale (PANSS), and the Scale for Assessment of Positive Symptoms (SAPS) {28}. The task force labeled these scales as "recommended" with the caveat that none contained all the basic content, mechanistic and psychometric properties to be deemed adequate for capturing the entire phenomenology of PD psychosis and that none have undergone formal psychometric evaluation in patients with psychosis and PD. Given the limitations of the recommended scales, the task force also recommended using the Clinician Global Improvement-Change Scale (CGI-C) as a secondary outcome scale to complement the more detailed psychosis rating scales. We found that of the seven RCTs in our study, six utilized the BPRS as a primary outcome and all utilized the CGI-C as a secondary outcome. This is consistent with the task force recommendations and representative, at that time, of best practice for clinical research in psychosis with PD. Despite this, the RCTs failed to reveal any statistically significant differences between quetiapine and placebo or clozapine for efficacy.

The failure to detect a statistically significant difference could also have been due to underpowering of the RCTs and the overall poor completion rates for treated and placebo groups in some studies. Additionally, none of the psychosis rating scales utilized in the quetiapine RCTs (i.e., Baylor PD Hallucination Questionnaire, BPRS, NPI) have undergone psychometric evaluation in the parkinsonism population {28} and it is possible that the lack of detecting significant differences between quetiapine and placebo or clozapine may be due to issues of instrument reliability, validity, and/or sensitivity. Given the psychometric limitations of the rating scales utilized in the seven RCTs, we believe that performing a quantitative analysis (i.e., meta-analysis) would only have yielded quantitatively indeterminant results and would not substantively alter any clinically relevant conclusions reached by our qualitative study.

Quetiapine has traditionally been widely prescribed for the treatment of psychosis in patients with PD due to clinical impressions of efficacy and tolerability. Use of quetiapine, unlike clozapine, does not requires mandated laboratory monitoring and, unlike other antipsychotics, is not generally associated with worsen of motor function. Generally, quetiapine is considered to be well tolerated. We found that the RCT completion rate of quetiapine-treated subjects was no better than placebo. However, rates were better than that for clozapine-treated subjects. Additionally, the psychosis rating scales utilized to measure efficacy outcomes in the quetiapine RCTs have not been deemed psychometrically suitable for this utility. Given our negative findings and the emerging data of increased mortality in PD patients treated with quetiapine and other antipsychotics as well as the recent introduction of a novel antipsychotic pimavanserin for treatment of psychosis in PD, the overall treatment landscape for psychosis in

parkinsonism has evolved to a point in which clinicians must recalibrate the traditional clinical impression of quetiapine efficacy and tolerability for psychosis in parkinsonism.

CONCLUSION

Quetiapine has not demonstrated better efficacy compared to placebo or clozapine for treatment of psychosis in parkinsonism. Overall, quetiapine is not associated with significant worsening of motor function. However, the RCT completion rates of quetiapine-treated subjects are no better than placebo with treatment-emergent somnolence the most common reason for study discontinuation.

REFERENCES

1. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. Nat Rev Dis Primers 2017;17013.

2. Rajput AH, Offord KP, Beard CM, Kurland LT. Epidemiology of parkinsonism: incidence, classification, and mortality. Ann Neurol 1984;16:278-282.

3. Hermanowicz N, Edwards K. Parkinson's disease psychosis: symptoms, management, and economic burden. Amer J Manag Care 2015;10 Suppl:s199-206.

4. Aarsland D, Ballard C, Larsen JP, et al. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. Int J Geriatr Psychiatry 2001;5:528-36.

5. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. Parkinsonism Rel Disord 2015;6:629-34.

6. Winter Y, von Campenhausen S, Brozova H, et al. Costs of Parkinson's disease in eastern Europe: a Czech cohort study. Parkinsonism Rel Disord 2010;1:51-6.

7. Mack J, Rabins P, Anderson K, et al. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. Amer J Geriatr Psychiatry 2012;2:123-32.

8. Aarsland D, Larsen JP, Tandberg E, et al. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 2000;8:938-42.

9. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. What predicts mortality in Parkinson disease?: a prospective population-based long-term study. Neurology 2010;14:1270-6.

10. Chen JJ. Treatment of psychotic symptoms in patients with Parkinson disease. Ment Health Clin 2017;6:262-70.

11. Hacksell U, Burstein ES, McFarland K, et al. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. Neurochem Res 2014;10:2008-17.

12. Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;7:996-1002.

13. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;S42-80.

14. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol 2013;1:5-15.

15. Weintraub D, Chiang C, Kim HM, et al. Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease. JAMA Neurol 2016;5:535-41.

16. Higgins JPT, Altman DG, Sterne JAC. Table 8.5.a The Cochrane Collaboration's tool for assessing risk of bias. In: Higgins JPT, Green S eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011]. The Cochrane Collaboration, 2011.

17. Fernandez HH, Okun MS, Rodriguez RL, et al. Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study. Int J Neurosci 2009;12:2196-205.

18. Kurlan R, Cummings J, Raman R, et al. Quetiapine for agitation or patients with dementia and parkinsonism. Neurology 2007;17:1356-63.

19. Ondo WG, Tintner R, Voung KD, et al. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov Disord 2005;8:958-63.

20. Rabey JM, Prokhorov T, Miniovitz A, et al. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. Mov Disord 2007;3:313-8.

21. Shotbolt P, Samuel M, Fox C, et al. A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. Neuropsychiatr Dis Treat 2009;327-32.

22. European Medicines Agency. EU Clinical Trials Register, Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2004-002608-13/GB. Accessed October 17, 2017.

23. Merims D, Balas M, Peretz C, et al. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol 2006;6:331-7.

24. Morgante L, Epifanio A, Spina E, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol 2004;4:153-6.

25. Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. Lancet 1999;9169:2041-2.

26. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med 1999;10:757-63.

27. Iketani R, Kawasaki Y, Yamada H. Comparative utility of atypical antipsychotics for the treatment of psychosis in Parkinson's disease: a systematic review and bayesian network meta-analysis. Biol Pharm Bull 2017;40:1976-1982.

28. Fernandez HH, Aarsland D, Fénelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. Mov Disord 2008;23(4):484-500.

29. Martinez-Martin P, Leentjens AF, de Pedro-Cuesta J, et al. Accuracy of screening instruments for detection of neuropsychiatric syndromes in Parkinson's disease. Mov Disord 2016;31(3):270-9.

LEGENDS

Figure 1. Study selection.

Table 1. Quetiapine for Treatment of Psychosis in Subjects with Parkinsonism: Summary of Randomized Clinical Trial Results

Table 2. Assessment of Risk of Bias