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Systematic Literature Review of Quetiapine for the Treatment of Psychosis in Patients With Parkinsonism

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Systematic Literature Review of Quetiapine for the Treatment of Psychosis in Patients With Parkinsonism

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11

12 **Systematic Literature Review of Quetiapine for the Treatment of Psychosis in Patients with**
13 **Parkinsonism**

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69 Drafting of the manuscript: Chen, Hua, Massihi.

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- 72 Study supervision: Chen, Dashtipour.
- 73

74 **Abstract** (word count = 250)

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

77 **Design:** Systematic review

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

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

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

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

97

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

99

100 **INTRODUCTION**

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

109 The care of patients with PDP is associated with significant healthcare utilization. In a
110 Medicare survey of claims data from 2000 to 2010, patients with PDP had higher all-cause costs
111 and resource utilization {3}. The highest annual cost differentials were found in long-term care
112 costs (\$31,178 for PDP vs \$14,461 for PD without psychosis), skilled nursing facility costs
113 (\$6601 for PDP vs \$2067 for PD without psychosis), and inpatient costs (\$10,125 for PDP vs
114 \$6024 for PD without psychosis). Long-term care utilization and expenditures were also
115 significantly higher for PDP patients, spending an average of approximately 179 days in long-
116 term care, compared with 83 days for patients with PD without psychosis.

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

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

126 Balancing control of the motor and psychiatric symptoms of parkinsonism has
127 historically been challenging because of a paucity of evidence-based strategies. Quetiapine is
128 indicated for the treatment of schizophrenia and bipolar disorder, however it is commonly used
129 off-label for the management of psychosis in parkinsonism. For patients with this condition,
130 quetiapine dosing is titrated from 12.5 mg nightly up to a range of 50 to 150 mg per day {10}.
131 Quetiapine is similar in structure to clozapine and has antagonist activity at histamine,
132 muscarinic, and serotonin 5-HT_{2A} receptors, with minimal affinity for dopaminergic D2 receptor
133 {11}. In the American Academy of Neurology evidence-based practice parameter on the
134 treatment of psychosis in PD, quetiapine was classified as Level C (i.e., possibly effective) {12}.
135 A task force of the International Parkinson and Movement Disorder Society concluded in an
136 evidence-based report that because of conflicting data on the efficacy of quetiapine and study
137 methodology concerns (e.g., small sample size, low-quality rating), there is insufficient evidence
138 for quetiapine for the treatment of PDP {13}. A joint task force of the European Federation of
139 Neurological Societies and the Movement Disorder Society – European Section recommends
140 quetiapine as possibly useful {14}. Subsequent to the publication of these evidence-based
141 statements, the use of quetiapine and other antipsychotics in patients with PD has been found to
142 be associated with an increased risk of mortality (quetiapine hazard ratio of 2.16 [95% CI, 1.88-

143 2.48] over nonuse) {15} in a Veteran Administration PD population, and a new molecular entity,
144 pimavanserin, was FDA approved for the treatment of PDP. Given these new developments, it is
145 important to re-evaluate the role of quetiapine in the treatment of psychosis in patients with
146 parkinsonism.

147

148 **METHODS**

149 *Literature Search Strategy and Data Sources*

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

157

158 *Study Selection*

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

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

170

171 *Data Extraction and Quality Assessment*

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

178

179 **RESULTS**

180 *Studies Identified*

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

189 clozapine when objectively assessed on the BPRS, the most frequently reported scale in these
190 RCTs. In the two clozapine-comparator controlled studies, quetiapine demonstrated no
191 advantage over clozapine in terms of efficacy or adverse effects and in one of the studies {23},
192 hallucination and delusion scores favored clozapine over quetiapine. Overall, the mean
193 completion rates for all groups were poor and rates did not differ between quetiapine and
194 placebo-treated subjects. Across all RCTs, the completion rates for quetiapine, clozapine, and
195 placebo were 66%, 68.5%, and 66%, respectively. Among the two RCTs comparing the efficacy
196 of quetiapine to clozapine, the completion rates were more favorable compared to clozapine,
197 (80% and 68.5%, respectively) {23,24}.

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

204

205 *Details of Studies*

206 Fernandez et al. performed a randomized, double-blind, placebo-controlled study on the
207 use of quetiapine for subjects with PD and visual hallucinations {17}. Subjects were randomly
208 assigned to treatment arms and initiated at 25 mg of quetiapine or matching placebo at bedtime.
209 Dosage increased by 25 mg increments every 3 to 7 days until reaching a maximum dosage of
210 150 mg, or the complete cessation of nocturnal hallucinations. The primary dependent variable
211 was the length of REM sleep, measured by polysomnography. The quetiapine group increased in

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

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

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

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

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

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

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

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

285 Clozapine has improved psychosis in PD in two multicenter, placebo-controlled trials and
286 is commonly used in clinical practice {25,26}. We identified two RCTs that compared
287 quetiapine to clozapine and met inclusion criteria {23,24}. Merims et al. randomly assigned
288 subjects with psychosis and PD to receive treatment with quetiapine or clozapine and assessed
289 outcomes with the delusion and hallucination items of the NPI and the Clinician Global
290 Improvement-Change Scale (CGI-C) {23}. Although the hallucination frequency was reduced
291 for both the treatment groups, the baseline-to-final-assessment difference was statistically
292 significant for only the clozapine group. Subjects in the clozapine group experienced a
293 statistically-significant reduction in the frequency of delusions whereas subjects assigned to
294 quetiapine actually increased delusion frequency, but not to a consistent degree. The change in
295 CGI-C scores were comparable between the two treatment arms. The article lists UPDRS total
296 score but not the motor score; however, the authors state, “We did not observe any worsening in
297 parkinsonian symptoms as measured by the UPDRS [...] in any of the treatment arms.” Only
298 59.26% of the subjects (16 out of 27) completed the study: 69.23% of the quetiapine group and
299 50.00% of the clozapine group. Lack of treatment efficacy was the most common cause for
300 dropout from the quetiapine group, and a decreased leukocyte count was the most common cause
301 for dropout from the clozapine group.

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

304 effect on hallucinations, suspiciousness, and hostility {24}. Outcome measurements included the
305 BPRS, Clinician Global Improvement-Severity Scale (CGI-S), Abnormal Involuntary Movement
306 Scale (AIMS), and the total score of the UPDRS. Although the outcome assessors were blinded
307 to the treatment assignments, the subjects were informed about the drug they were receiving. The
308 starting dose was 25 mg per day of quetiapine or 6.25 mg per day of clozapine. Dosage was
309 titrated by a neurologist aware of the treatment conditions, with maximum doses of 200 mg daily
310 of quetiapine or 50 mg daily of clozapine. Post-treatment scores on the BPRS, CGI-S, and AIMS
311 were improved compared to baseline for both the quetiapine and the clozapine groups. Overall,
312 the UPDRS scores remained unchanged, however a mild worsening of parkinsonism was
313 observed in three patients treated with quetiapine (greater than 100 mg per day). The efficacy of
314 both drugs was comparable, as the differences between quetiapine and clozapine groups were not
315 statistically significant. Both groups experienced a small number of adverse events, but no
316 inferential statistics were provided comparing quetiapine to clozapine. The majority of the
317 subjects, 88.89% (40 out of 45) completed the 12-week study: 90.91% of the quetiapine group,
318 86.96% of the clozapine group. One subject in the quetiapine group withdrew because of
319 sedation, and another subject withdrew due to a “confusional state.” Dropout in the clozapine
320 group was attributed to sedation, dizziness, and severe hypotension.

321

322 **DISCUSSION**

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

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

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

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

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

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

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

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

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

396

397 **CONCLUSION**

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

403

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480

481 **LEGENDS**

482 Figure 1. Study selection.

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

485 Table 2. Assessment of Risk of Bias