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Evaluation of the use of low-dose quetiapine and the risk of metabolic consequences: A retrospective review

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Abstract

Introduction: Quetiapine fumarate is an atypical antipsychotic approved for the treatment of schizophrenia, major depressive disorder, and bipolar disorder. Due to the sedative effects observed at low doses, prescribers use quetiapine to aid patients with sleep disturbances. Current evidence has established that quetiapine can cause negative changes in metabolic parameters, but it is unknown if these consequences also occur at low doses. Due to the use of quetiapine for sleep, the purpose of this study is to identify if metabolic effects are also a risk with the use of low-dose quetiapine.

Methods: Eligible subjects were identified through the Veterans Affairs electronic medical records as having an active prescription for quetiapine from June 30, 2012, through September 1, 2013. Subjects were then evaluated using inclusion and exclusion criteria for determination of study entrance. Descriptive statistics and *t* tests were utilized to identify clinical and statistical differences in outcomes.

Results: A total of 403 subjects were included in the final analysis. The average dose of quetiapine was 116.8 mg and average duration of therapy was 44 months. Increases were observed in systolic blood pressure (+1.95 mmHg; $P=.036$), diastolic blood pressure (+1.97 mmHg; $P=.001$), body mass index (+0.52; $P=.001$), weight (+1.88 kg; $P=.002$), and fasting blood glucose (+6.71 mg/dL; $P=.002$). Conversely, a decrease in total cholesterol (−10.06 mg/dL; $P<.001$) was recognized.

Discussion: As a result of the findings, there may be negative metabolic consequences with the use of low-dose quetiapine. Routine prescribing of low doses for sleep as a first-line medication should be avoided.

Keywords: quetiapine, low dose, insomnia, sleep, metabolic

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Introduction

Quetiapine fumarate is a second-generation (atypical) antipsychotic indicated for the treatment of schizophrenia and bipolar disorder and as adjunct therapy for major depressive disorder (MDD).[1] The mechanism by which quetiapine exerts its therapeutic effects, includes antagonism of dopamine type-2 (D_2) receptors and serotonin type-2 (5-HT_2) receptors.[2] A common adverse effect of quetiapine is orthostasis, which literature suggests may be attributed to antagonism of alpha type-1 (α_1) receptors.[3] It is proposed that antagonism of both the H_1 and 5-HT_2 receptors may result in the sedative effects often observed with this medication.[4]

Current evidence suggests that the minimum receptor binding occupancy required for efficacy in the treatment of psychosis must be at least 65% for D_2 receptors. It is

also theorized that occupancy of 80% should not be exceeded in order to reduce the risk of extrapyramidal side effects.[5] Translated to quetiapine, the literature suggests that a dose range of 400 mg to 800 mg would confer the targeted D_2 receptor antagonism.[6] The current recommended titration schedule of quetiapine is to start at 25 mg twice daily and titrate up by increments of 100 mg daily to at least 150 mg for MDD, 300 mg for bipolar disorder, and 400 mg for schizophrenia.[2] Minimum dosing in MDD is often considered to be low although patients may need upward of 300 mg as adjunct therapy for adequate control of symptoms. In some cases, patients do not reach the minimum effective dose needed to treat their psychiatric condition. Presumptive reasoning suggests this may be due to the rigorous titration schedule and tolerability issues; however, it can also be hypothesized that providers use this medication for the sedative effects observed even at low doses.[7-10]

Metabolic syndrome, defined as three or more of the following: impaired fasting blood glucose, hypertension, elevated triglycerides, decreased high-density lipoprotein (HDL), and increased waist circumference, is an effect observed with the use of many atypical antipsychotics. Metabolic consequences are recognized commonly with the use of quetiapine even though current literature suggests a moderate risk when compared to other second-generation antipsychotics.[11] Because metabolic parameters are observed to be negatively impacted with the use of quetiapine at recommended doses, it is hypothesized that these effects are not dose-dependent and may also occur at low doses. Current evidence is limited regarding the negative metabolic effects with low-dose quetiapine. A study conducted by Cates et al[12] evaluated the use of low-dose quetiapine (defined as doses less than or equal to 200 mg daily) and the risk of increased weight, body mass index (BMI), and waist circumference. Statistically significant changes in weight (+2.22 kg; $P = .037$) and BMI (+0.8 kg/m^2; $P = .048$) were observed; however, no significant change in waist circumference was identified (+1.02 cm; $P = .34$).[12] A similar study by Williams et al[13] evaluated changes in weight at 1, 6, and 12 months after the initiation of low-dose quetiapine (defined as doses less than or equal to 100 mg). Statistically significant increases in weight were identified at 6 months (+2.52 kg; $P < .001$) and 12 months (+4.8 kg; $P < .001$) postquetiapine initiation without any clear plateau of these effects with long-term use.[13] Due to the observed negative effects on weight and BMI, it is important to further evaluate the risks and include other metabolic parameters that may be implicated with the use of low-dose quetiapine.

The primary objective of this study is to evaluate the risks of developing metabolic consequences, including changes in blood pressure, lipids, blood glucose, weight, and BMI with the use of low-dose quetiapine, defined as 200 mg or less. Secondary objectives include an evaluation of changes in vital sign and laboratory measures in patients on concurrent antipsychotics as well as subjects on as-needed versus scheduled dosing of quetiapine.

Methods

Initial data was collected through the Veterans Affairs (VA) Computerized Patient Record System after approval was granted through the Ann Arbor VA Medical Center Institutional Review Board. Subject medical records were retrieved if there was an active prescription for quetiapine from June 30, 2012, through September 1, 2013, and were included in the initial screening process. Retrospective data collected for purposes of this study included sex, total daily dose of quetiapine, duration of use, fasting blood glucose (FBG), cholesterol panel, BMI, weight, blood pressure, concurrent antipsychotic use, and frequency of quetiapine use (ie, as needed or scheduled). Subjects were then reviewed to identify eligibility based upon inclusion criteria (Figure 1). Subjects were included in the initial analysis if they were 18 years of age or older, had a total daily dose of quetiapine that was 200 mg or less for at least 3 months in duration, and had metabolic laboratory parameters and vital signs drawn prior to the initiation of quetiapine as well as after discontinuation, if applicable. A minimum duration of 3 months was included due to the American Diabetes Association and American Psychiatric Association consensus guidelines suggesting that many of the metabolic parameters should be rechecked at 12 weeks of therapy.[14] Because refills are provided on a monthly basis at the Battle Creek VA Medical Center, 3 months of therapy was determined by identifying refill history through chart reviews.

All study data was recorded in a Microsoft Excel® spreadsheet (Redmond, WA) and were analyzed using Excel statistical functions. Descriptive statistics were used to identify means and ranges of qualitative data. Student *t* tests were used for independent variables to identify differences between groups. Paired *t* tests were used for dependent data to identify changes in labs from baseline with the use of low-dose quetiapine. Standard deviations of the mean were used to identify ranges of laboratory parameters. *P* values were considered significant if less than .05, and the sample size calculated to reach a power of 80% suggested a minimum of 384 patients.

Of the 1060 subjects who were prescribed quetiapine during the study dates listed, 457 subjects were excluded for total daily doses greater than 200 mg. Furthermore, 200 subjects were excluded from eligibility due to duration of use less than 3 months, absence of metabolic laboratory and vital sign parameters before initiation of quetiapine, and the absence of laboratory and vital sign parameters after the discontinuation of quetiapine.

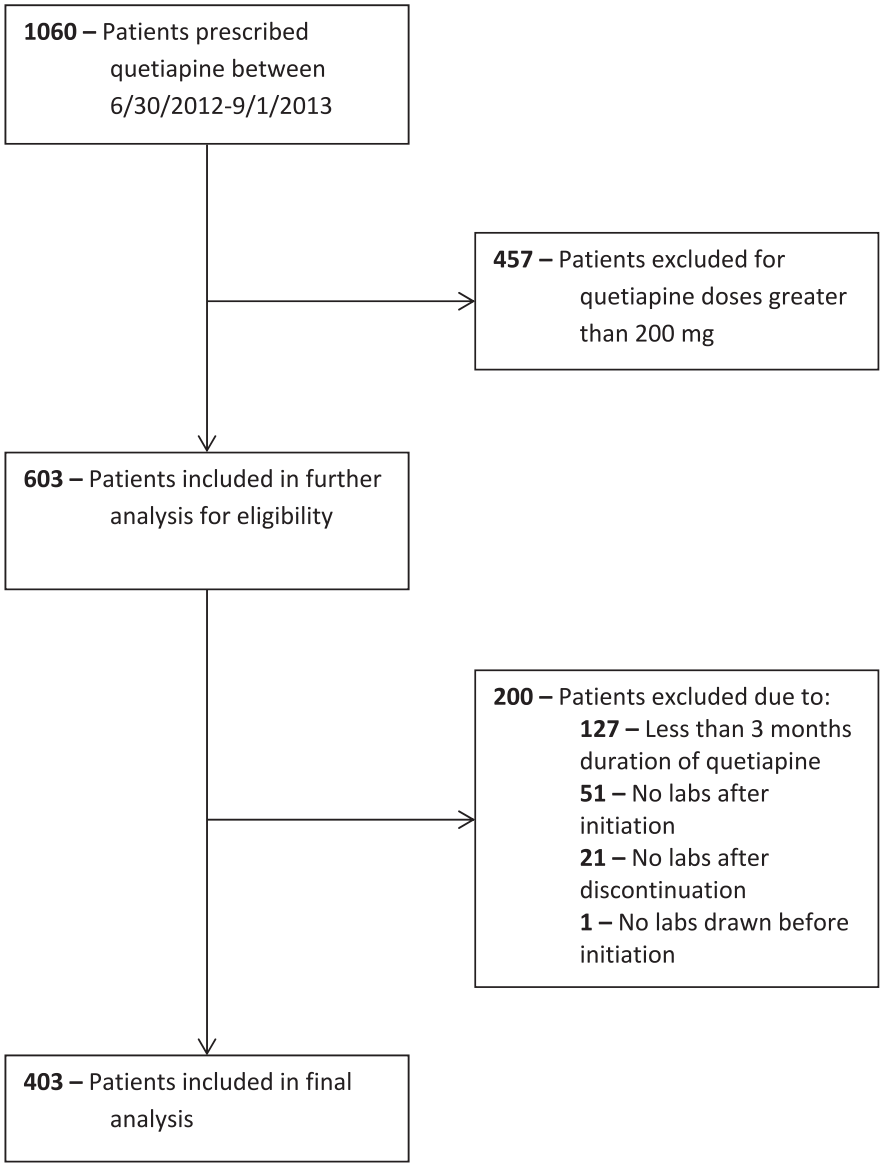


FIGURE 1: **Eligibility criteria**

Results

A total of 403 subjects met eligibility criteria and were included for analysis. Demographic data is represented in Table 1. Out of the 403 subjects included, 379 (94%) were male. It was identified that the average duration of use of low-dose quetiapine was 44 months, and the average daily dose of quetiapine was 116.8 mg.

Subjects prescribed low-dose quetiapine were observed to experience changes in all outcomes collected for analysis. Of the parameters identified, systolic blood pressure (+1.95 mmHg; $P = .036$), diastolic blood pressure (+1.97 mmHg; $P = .001$), BMI (+0.52; $P = .001$), weight (+1.88 kg; $P = .002$), and FBG (+6.71 mg/dL; $P = .002$) all had a statistically significant increase after the initiation of low-dose quetiapine. Conversely, total cholesterol had a statistically significant decrease after the initiation of low-dose quetiapine (−10.06 mg/dL; $P < .001$). Although not significant, LDL decreased (−8.73 mg/dL; $P > .05$), HDL increased (+0.21 mg/dL; $P = .729$), and triglycerides increased (+15.42 mg/dL; $P = .268$) (Table 2).

TABLE 1: **Baseline demographics**

Characteristic	Subjects (n = 403)
Sex, No. of male	379 (94%)
Average duration, months	44 (3-180)
Average dose, mg	116.8 (12.5-200)
Patients on concurrent antipsychotic, n	20 (5%)
Patients on as-needed scheduling, n	9 (2%)

TABLE 2: Changes in metabolic parameters

Parameters	Change From Baseline (n = 403)	*P* Value
Systolic blood pressure, mmHg	+1.95	.036[a]
Diastolic blood pressure, mmHg	+1.97	.001[a]
Body mass index, kg/m^2	+0.52	.001[a]
Weight, kg	+1.88	.002[a]
Fasting blood glucose, mg/dL	+6.71	.002[a]
Low-density lipoprotein, mg/dL	−8.73	.703
High-density lipoprotein, mg/dL	+0.21	.729
Triglycerides, mg/dL	+15.42	.268
Total cholesterol, mg/dL	−10.06	<.001[a]

[a]Statistically significant findings with a *P* value below .05.

For subjects prescribed a concurrent antipsychotic (n = 20) for at least 3 months in duration while also taking low-dose quetiapine, the only statistically significant difference that was observed was a decrease in LDL (−8.2 mg/dL; *P* = .015) when compared to subjects taking only low-dose quetiapine (n = 383). Despite lacking significance, there was a greater increase in diastolic blood pressure (+0.67 mmHg; *P* = .690), BMI (+0.54; *P* = .820), weight (+0.89 kg; *P* = .698), FBG (+8.9 mg/dL; *P* = .359), and triglycerides (+39.6 mg/dL; *P* = .523) when a concurrent antipsychotic was used with low-dose quetiapine. Systolic blood pressure decreased (−1.71 mmHg; *P* = .690) although this finding was not statistically significant (Figure 2).

For subjects prescribed quetiapine to take only when needed (n = 9) versus subjects who were scheduled to take quetiapine daily (n = 394), there were no statistically significant differences in any of the metabolic parameters identified when comparing the two groups together (Figure 3).

Discussion

With the frequent prescribing of low-dose quetiapine, safety concerns come to the forefront of patient

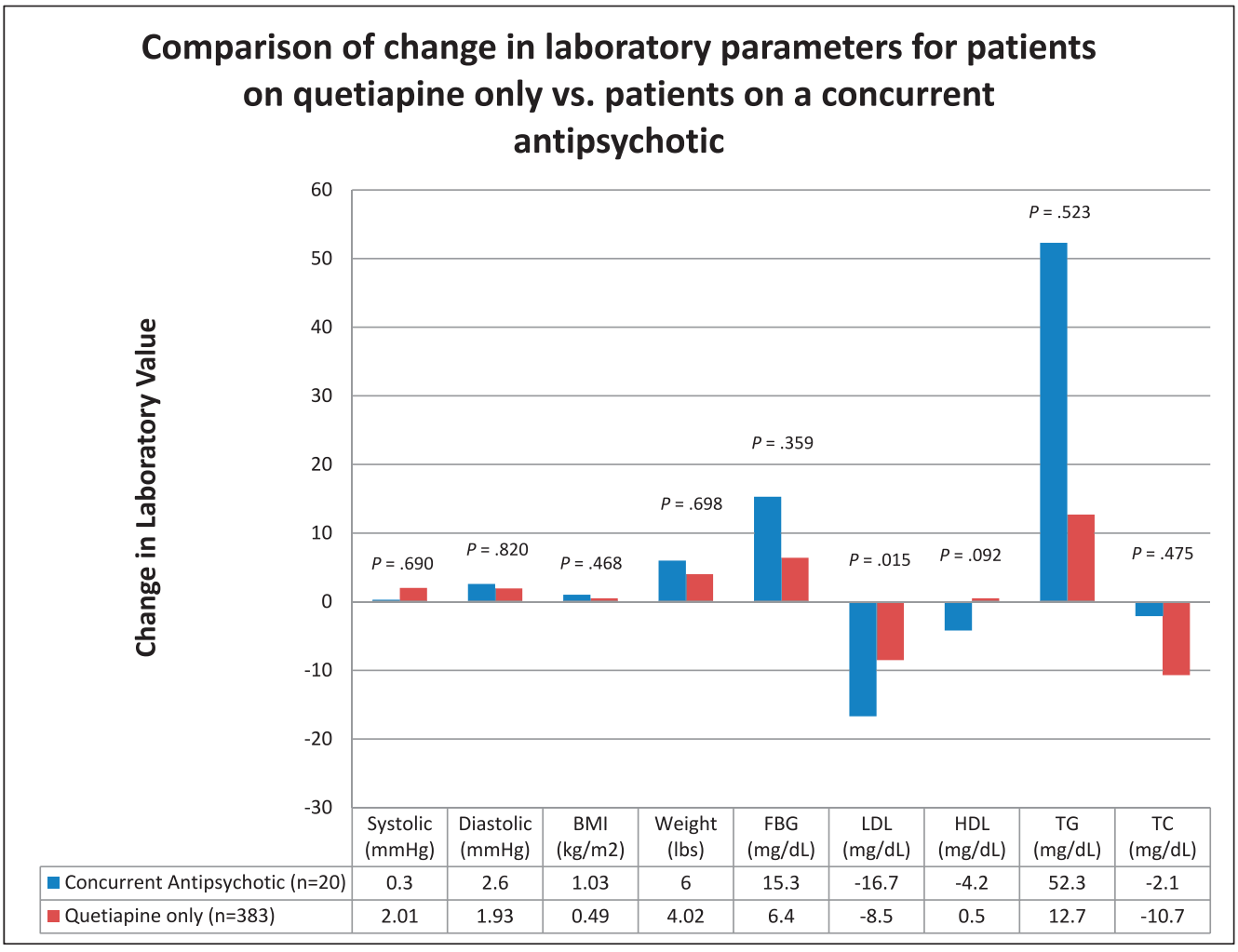
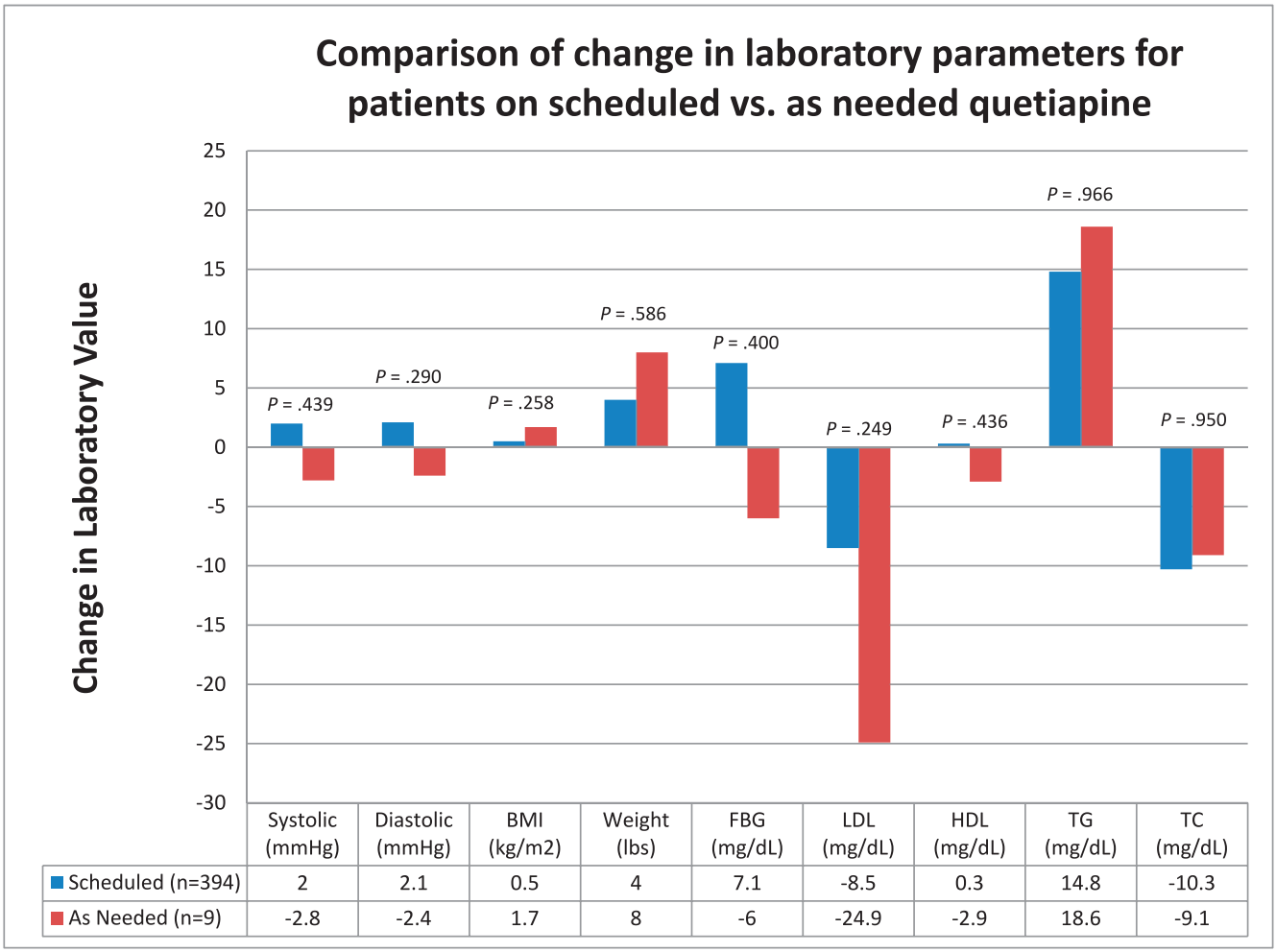


FIGURE 2: Concurrent antipsychotic use; BMI = body mass index; FBG = fasting blood glucose; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglycerides; TC = total cholesterol



	Systolic (mmHg)	Diastolic (mmHg)	BMI (kg/m2)	Weight (lbs)	FBG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	TC (mg/dL)
Scheduled (n=394)	2	2.1	0.5	4	7.1	-8.5	0.3	14.8	-10.3
As Needed (n=9)	-2.8	-2.4	1.7	8	-6	-24.9	-2.9	18.6	-9.1

FIGURE 3: Scheduled versus as-needed quetiapine; BMI = body mass index; FBG = fasting blood glucose; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglycerides; TC = total cholesterol

management. With regard to the primary end point of assessing the risk of increasing the occurrence of metabolic consequences with the use of low-dose quetiapine, a few statistically significant findings were identified. It was observed that systolic and diastolic blood pressure increased as well as BMI, weight, and FBG. Conversely, total cholesterol decreased with the use of low-dose quetiapine, and the other lipid levels were not observed to have a significant change in either direction. It is unknown why total cholesterol decreased, but it is hypothesized that patients were placed on lipid-lowering agents at some point during their treatment with low-dose quetiapine. It was discovered that the average length of therapy was just under 4 years in duration with a range of 3 months to 180 months. This was an unforeseen factor that may have had a significant impact on the results of this study as the authors did not anticipate subjects to be prescribed low-dose quetiapine for long durations.

Of the secondary end points, no significant changes were observed in patients prescribed low-dose quetiapine as needed compared to subjects on scheduled low-dose quetiapine. This could be due to patients taking their medication chronically even if prescribed to take only as needed. It was observed that refills were consistent during data collection, and this finding might offer a possible explanation for the reason there was no difference identified. For subjects prescribed concurrent antipsychotics in addition to low-dose quetiapine compared to subjects taking only low-dose quetiapine, a statistically significant decrease in LDL was observed favoring the subjects on a concurrent antipsychotic. Although not significant, it was also observed that triglycerides increased more in the concurrent antipsychotic group, which might offer an explanation as to why LDL significantly decreased.

There were a number of strengths and limitations associated with this study. Of the identified strengths, one very important advantage to note was that only one author collected patient data in order to maintain consistency. Likewise, there was a large subject cohort

of 403 patients that met eligibility criteria for this retrospective study. Unlike the studies conducted by Cates et al[12] and Williams et al,[13] this study included more metabolic parameters to identify changes, including the full lipid panel, both systolic and diastolic blood pressure, weight, BMI, and FBG. This study also included a larger patient population compared to the study by Cates and colleagues[12] as well as a larger dose inclusion compared to Williams and colleagues.[13] These changes allowed for more patient inclusion, which led to an ability to reach power.

With this study being a retrospective cohort design, a number of limitations were also observed. As previously mentioned, it was unanticipated as to how long the average patient would be prescribed low-dose quetiapine, thus allowing for confounding variables of pharmacologic and nonpharmacologic additions to patients' regimens that may have negatively impacted the results. In hindsight, it would have been appropriate to identify changes at prespecified lengths of therapy (eg, 1 month after initiation, 3 months, 6 months, and then annually). Other limitations identified include the realization that many patients were not eligible for study entrance due to inappropriate laboratory and vital sign monitoring. Many patients had to be excluded because they did not have any labs or vitals drawn before the initiation of quetiapine to serve as a baseline or, conversely, did not have labs or vitals drawn after discontinuation. In extreme cases, no labs were drawn after initiation of quetiapine. These limitations identify the need for regular monitoring and communication with patients in order to ensure effectiveness.

Conclusion

In conclusion, there is frequent prescribing of low-dose quetiapine, which could be due to the effect observed when treating patients with sleep disturbances. Although quetiapine can be used to treat patients with sleep issues, the results of this study suggest that the risk of metabolic consequences may outweigh the benefits. The benefits observed in the short term to aid in sleep may lead to greater complications long term and should be weighed heavily before initiating therapy. Because changes in metabolic parameters were identified, it is reasonable to suggest these outcomes are not dose-dependent. Consequently, further research needs to be conducted in order to account for the unforeseen confounding variables of this review in order to fully identify the breadth of changes in metabolic parameters with the use of low-dose quetiapine.

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