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Quetiapine at high doses for the treatment of refractory schizophrenia

Dear Editor,

Selecting the appropriate dose of antipsychotic medication is essential for successful long-term treatment in people with schizophrenia. However, there is much debate in the literature about the correct dosing of antipsychotics. This is especially true for quetiapine, a second-generation antipsychotic which experts have advocated using doses above the maximum recommended by the FDA of 800 mg/day.(Kane et al., 2003)

In this letter we report on a 12-week open label trial of high dose quetiapine for subjects with documented treatment refractory schizophrenia. All subjects were titrated to the target dose of $1,200 \pm 200$ mg/day over a three-week period. Subjects were evaluated weekly with the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression Scale (CGI). Response was defined as $\geq 20\%$ decrease in total BPRS score from baseline. Other weekly measurements included vital signs, the Simpson Angus Scale (SAS), Barnes Akathisia Scale (BAS), and the Assessment of Involuntary Movements Scale (AIMS). Laboratory assessments and electrocardiogram monitoring were done at baseline and end of study. Statistical analysis was conducted using the Cochran-Mantel-Haenszel method for monotonic correlations between scores and time, using a summary χ^2 statistic for evidence of time by visit correlations, stratifying the analysis with subject.(Arndt et al., 1993) Within-subject Spearman correlation coefficients between symptom scores and time were calculated, and the mean of these correlations calculated. Dichotomous variables were evaluated with Fisher's exact test. All analysis was done using SAS® 9.1 (SAS Institute Inc., Cary, NC) using two-tailed tests at $\alpha = 0.05$.

Twelve subjects were recruited into this study. Eight were enrolled after not responding to treatment in a previous double-blind placebo controlled study(Conley et al., 2005); the remaining 4 meet the same inclusion criteria for this open label study as those in the double-blind study. Mean age for subjects was 50.3 ± 8.3 years old. One subject was female and 66% were African American. Previous antipsychotic therapy for subjects included: 4(33%) risperidone, 3(25%) fluphenazine, 2(17%) quetiapine, 1(8.3%) olanzapine, 1(8.3%) ziprasidone, and 1(8.3%) risperidone with fluphenazine. Subject's baseline symptom characteristics are listed in Table 1.

Four (33%) subjects withdrew due to lack of efficacy, (weeks 1, 3, 4 and 8), one subject was lost to follow-up (week 8) and one subject died after sustaining a physical injury that caused cardiac arrest (review by the data safety and monitoring board ruled the death was not attributed to the medication). Two subjects were stopped early after completing only 10 weeks of the study due to administrative reasons. The duration of time in the study for all participants was 58.1 ± 29.6 days. Five subjects received 1200 mg/day of medication. Six received 1400 mg/

day, but after experiencing hyperglycemia one subject was decreased to 1000 mg/day. One subject did not finish the titration phase.

Response to treatment was seen in 4(33%) subjects. However, only 1 subject had a corresponding endpoint CGI ≤ 3 . A decrease in symptoms over time was seen for BPRS total score, positive, negative, and anxiety/depression subfactors (see Table 1). (Guy, 1976) Extrapyramidal side effects, as assessed by the SAS, decreased during the study but BAS scores increased significantly over time. New adverse effects that occurred in > 2 subjects during the study included: somnolence 8(67%), headache 6(50%), constipation 5(42%), dry mouth 3(25%), dyspepsia 3(25%), lethargy 3(25%), and nausea 3(25%). No change in total cholesterol, fasting glucose, or TSH ($n = 10$) was seen during the study. One subject with a fasting glucose of 123 mg/dl at baseline developed diabetes mellitus during the study. Baseline prolactin ($n = 10$) decreased from 20.8 ± 19.7 ng/ml to 10.9 ± 6.4 ng/ml; ($\chi^2 = 5.52$, $df = 1$, $p = 0.02$). Weight ($n = 9$) increased from 106.1 ± 22.3 kg at baseline to 107.9 ± 20.3 kg at endpoint; ($\chi^2 = 6.28$, $df = 1$, $p = 0.01$). No clinically significant or statistical changes in ECG parameters were seen.

There are several limitations to this study. It was neither placebo-controlled nor blinded. Second, the study was small and only a third of the subjects were able to complete all 12-weeks of therapy. This was likely related to the long study duration (eight subjects had completed a 16 week study prior to this 12 week study) and the longer duration to reach targeted dose. Also, due to the high prevalence of older African American males, the results may not be generalizable to most clinical settings. It is also possible more subjects would have responded to a higher dose, a case series from (Pierre et al., 2005) found doses up to 2400 mg/day were required in treatment refractory patients. However, more studies are needed to determine the upper range as a recent study released by AstraZeneca (www.astrazenecaclinicaltrials.com/Article/526327.aspx) found no benefit in doses > 800 mg/day in a cohort of non-treatment refractory schizophrenia subjects.

The response rate of 33% in this study is compared to that seen in the landmark study by Kane et al., 1988, which found 30% refractory patients responded to clozapine. Other studies which rigorously defined treatment refractory populations have not shown this rate of response. (Breier et al., 1999; Lindenmayer et al., 2002) Therefore, these results suggest 1200 mg/day of quetiapine appears to be safe, tolerable, and may improve symptomatology in some patients with treatment refractory schizophrenia. Larger double-blind trials are needed to determine the efficacy of higher doses of quetiapine in treatment refractory schizophrenia.

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Table 1
Symptom and Movement Rating Scale Scores at Baseline and Week 12^a

Variable	Baseline (Mean ± SD)	Endpoint (Mean ± SD)	R ^b	χ ² (df = 1)	p-value
Symptom Scores					
BPRS Total	53.9 ± 10.8	49.8 ± 13.5	-0.22	8.73	0.003
CGI	4.9 ± 0.7	4.8 ± 1.0	-0.06	2.45	0.118
BPRS Factors ^c					
Positive	18.7 ± 4.6	16.3 ± 5.9	-0.31	19.45	< 0.001
Negative	8.5 ± 3.5	8.2 ± 3.7	-0.14	7.75	0.005
Activation	6.1 ± 3.2	5.9 ± 3.3	-0.03	0.38	0.54
Anxiety/Depression	12.4 ± 4.4	10.8 ± 3.7	-0.25	11.29	0.001
Hostility	9.1 ± 2.7	9.0 ± 3.3	-0.15	0.01	0.90
Movement Scores					
SAS	3.7 ± 7.4	1.3 ± 1.3	-0.15	4.11	0.043
BAS	0.50 ± 1.73	0.9 ± 2.0	0.20	7.54	0.006
AIMS	4.6 ± 7.45	4.0 ± 7.5	0.02	2.16	0.14

^a n = 12, except AIMS (n = 11)

^b Spearman correlation coefficients between symptom scores and time

^c Guy 1976

AIMS = Assessment of Involuntary Movements Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression Scale, SAS = Simpson Angus Scale