An Open-Label, Effectiveness Study of Long-Term Quetiapine Treatment

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ABSTRACT

The objective was to investigate the long-term clinical effectiveness of quetiapine in the treatment of patients with DSM-IV schizophrenia and schizoaffective disorder. Efficacy and tolerability were assessed in 78 patients over 6 months with Positive and Negative Syndrome (PANSS), Clinical Global Impressions (CGI), Simpson-Angus, and Abnormal Involuntary Movements scales. Patient satisfaction was evaluated with a self-report patient satisfaction questionnaire. PANSS positive, negative, and general psychopathology scores were significantly reduced ($P < 0.001$) together with significant improvements in CGI score ($P < 0.01$) compared to baseline. Patients reported increased satisfaction (36.5%), increased helpfulness (26.6%), and a reduction in side effects (31.7%) with quetiapine compared to prior therapy. Most adverse events reported were infrequent, mild, and transient in nature. All observed changes in the SAS except for salivation showed statistically significant improvement ($P < 0.05$) compared to baseline. Medication compliance was 74% on the average (visit by visit) and 85% of patients completed the study. In conclusion, long-term treatment with quetiapine was associated with positive efficacy and favorable tolerability, and high satisfaction ratings. These are important factors in determining treatment adherence and effectiveness.

INTRODUCTION

The current concept of clinical effectiveness of a drug treatment is one that encompasses patient acceptability together with the domains of efficacy, safety and tolerability, and functionality.[1,2] Acceptability reflects a patient's subjective experience of their medication that in turn influences adherence and thus, treatment outcome.[3] Furthermore, acceptability of treatment has been shown to be closely related to patient satisfaction.[4] Negative subjective response to treatment and side effects of conventional antipsychotics particularly extrapyramidal symptoms (EPS) play a major role in nonadherence.[4,5]

The assessment of satisfaction is particularly important for patients with

chronic diseases such as schizophrenia requiring long-term antipsychotic treatment and is influenced by the perception of the quality of life experienced whilst on medication.[6,7] Thus, a 6 month, phase IIIb, Canadian, multicenter, open-label, prospective, effectiveness study with quetiapine was undertaken.

METHODS

Data on 78 outpatients (18-65 years) with DSM-IV defined chronic schizophrenia or schizoaffective disorder switched to quetiapine monotherapy for 6 months were collected.[8] The study was approved by the University of Alberta Ethics Review Board and conducted in accordance with the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and the Declaration of Helsinki and subsequent revisions.

At screening, patients signed an informed consent and underwent a physical examination with ophthalmologic review together with laboratory assessment of hematological, thyroid, and liver indices and pregnancy test for all women of childbearing potential. Vital signs, weight, and height for calculation of Body Mass Index (BMI) were recorded.

Inclusion criteria included a Clinical Global Impression (CGI) score ≥ 3 and a Positive and Negative Syndrome Scale (PANSS) total score ≥ 45, with a score of ≥ 4 on 1 or more of the following items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), or suspiciousness/persecution (P6).[9,10]

Movement disorders were assessed with the Simpson-Angus (SAS) and Abnormal Involuntary Movements (AIMS) scales.[11,12] Patients' satisfaction was assessed using a 7-item self-report questionnaire developed by Hellewelle et al[13] that addresses domains of symptom relief, quality of life, activities of daily living; side-effects; treatment satisfaction and helpfulness; insight, adherence, and treatment preference (Table). Assessments were conducted at baseline and at weeks 8 and 24.

All previous antipsychotics were titrated down and discontinued over a 2-day period (or 1 dose interval for depot antipsychotics) before the initiation of quetiapine at 25 mg BID (baseline). The dose of quetiapine was then titrated to 300 mg/day within 4 days, after which the dose could be decreased or increased to a maximum of 800 mg/day by the investigator at any point during the study. Patients were seen every 4 weeks from baseline until study endpoint at 24 weeks.

The statistical analysis followed the Intent-to-Treat (ITT) principle using paired *t* tests applied to the efficacy, safety, and satisfaction data sets. The PANSS, CGI, SAS, and AIMS measures were compared at baseline, 8 and 24 weeks using repeated measures of variance (RM-ANOVA). Similar analyses were utilized for the laboratory and vitals data. Because the data in the patient satisfaction questionnaire was ranked specifying order of preference and was thus, ordinal and qualitative, before and after treatment pair-wise comparisons were performed with each patient serving as his or her own control.

RESULTS

Eighty-five percent of patients completed the study; 57.7% were male, mean age was 39 years (range, 19-65), and 65% were diagnosed as suffering from paranoid schizophrenia. Most patients were never married (57%) and 49% relied on a family member for primary support. Medication compliance was 74% on average (visit by visit).

The mean PANSS total score at baseline was 100.1 (SD = 0.70); total scores were statistically significantly reduced compared to baseline in posi-

Table. Patient Satisfaction Questionnaire.[13]

1.	**During the last month, how satisfied have you been with your antipsychotic medication?** Extremely satisfied - Very satisfied - Somewhat satisfied - Unsatisfied - Very unsatisfied
2.	**During the last month, how helpful do you think your medication has been?** Extremely helpful - Very helpful - Somewhat helpful - Unhelpful - Very unhelpful
3.	**During the last month, how would you rate the side effects of your medication?** None - Mild - Moderate - Severe
4a.	**Please list the things about the medication you are on now that you like:**
4b.	**Is there anything about the medication you are on now that you do not like?**
4c.	**Do you think the medication you are on now is better than other medications you have had in the past?** Yes - No
4d.	**Please say why you think your medication is or is not better.**
5.	**During the last 6 months, have you noticed any benefits in the following areas?** Yes - No
	• **Feel better (in general)**
	• **Feel happier**
	• **Feel more confident**
	• **Feel happier about relationships with friends and family**
	• **Feel more able to achieve something**
	• **Have a more positive outlook on life**
	• **Feel more energetic**
	• **Feel more relaxed**
	• **Feel more in-control of my thoughts**
	• **Feel more in-control of my actions**
	• **Feel better able to concentrate**
	• **Feel more able to cope with stress**
	• **Experienced an improvement in sex life**
	• **Feel less depressed**
	• **Feel less agitated**
	• **Feel less worried**
	• **Feel less suspicious of other people**
	• **Feel less restless**
	• **Feel less tense**
6.	**During the last 6 months, do you find it is easier?** Yes - No
	To eat more normally?
	To sleep more normally?
	To do things around the house?
	To prepare and cook meals?
	To go shopping for food and personal items
	To manage your own money?
7a.	**Do you think you need to take medication for your condition?** Yes - No
7b.	**Do you always take your medication as prescribed?** Yes - No
7c.	**Would you like to continue with your current medication?** Yes - No

tive (mean, –5.2; 95%, CI; –7.2 to –3.2; $P = 0.0001$) and negative (mean, –5.6; 95% CI; –7.6 to –3.51; $P = 0.0001$) symptoms and also in general psychopathology (mean, –10.2; 95% CI; –14.2 to –6.15; $P = 0.0001$). There was an overall improvement compared to baseline in CGI scores (mean, –0.36; 95% CI; –0.62 to –0.09; $P = 0.0086$).

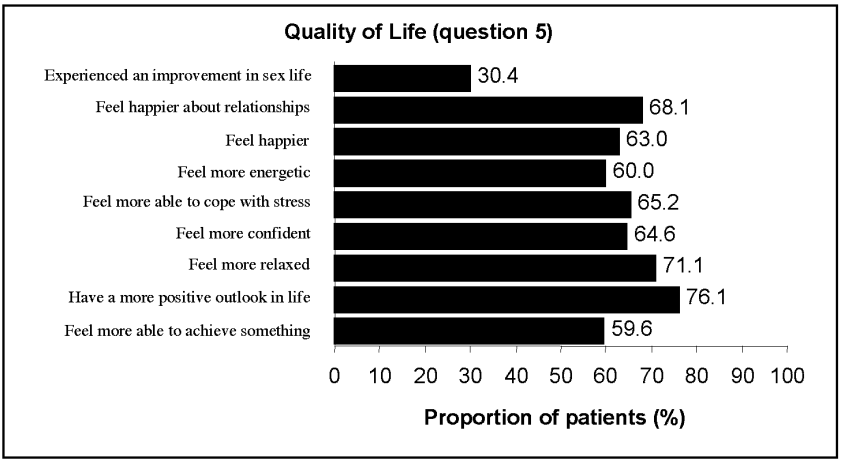
The incidence of subjectively reported adverse events (AEs) was very low. The most commonly reported (≥ 2%) AEs (dizziness, sedation, headache, agitation, dry mouth, insomnia) were infrequent, mild, and transient in nature. Of the 12 patients that discontinued the study due to an AE, the most commonly reported event was an aggravation of existing illness; no deaths occurred during the study. Extrapyramidal symptoms improved from baseline and abnormal involuntary movements seen at baseline did not show any deterioration. All observed changes in the SAS except for salivation showed statistically significant improvement ($P < 0.05$) compared to baseline. The total AIMS score was not found to be significantly different except for certain items; tongue (mean, –0.13; 95%CI; –0.24 to –0.02; $P = 0.019$) and incapacitation (mean, –0.16; 95%CI; –0.32 to 0.00; $P = 0.054$). Despite most patients being obese at baseline (mean BMI, 29.1 kg/m^2; SD = 8.3) there was an overall weight loss during the study (mean, –1.3kg; SD = 13.4). Physical examination and other vital signs showed no significant change at endpoint from baseline.

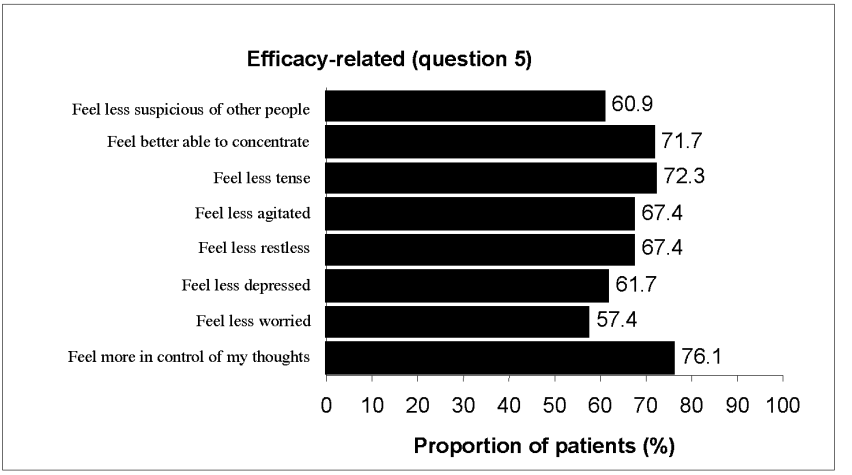
From the patient satisfaction questionnaire responses, there was a 36.5% increase in patient satisfaction ("Very" to "Extremely satisfied") compared to their previous medication at baseline (95% CI; 21.7-51.3); a reduction of 31.7% from baseline in reported side effects (95% CI; –16.6 to –46.9); and an increase of 26.6% from baseline in perceived helpfulness ("Very" to "Extremely helpful") (95% CI; 9.7-43.5) with quetiapine at endpoint. Results are summarized from the domains of quality of life measures, efficacy, and activities of daily living at endpoint in Figure.

DISCUSSION

The positive outcomes in terms of efficacy and tolerability, in this open-label study, are consistent with controlled clinical trial data on quetiapine particularly with respect to low EPS rates.[14,15] Quetiapine's neurotransmitter profile of antagonism at serotoninergic 5HT2, histamine H_1, and adrenergic α_1 receptors, accounts for the common AEs reported in the study.[16] The number of patients dropping out because of an exacerbation of symptoms may have reflected some caution on the part of investigators to pursue a rapid titration to higher doses, because the study was conducted at the time of quetiapine's introduction to Canada in 1998 and as such clinicians were relatively unfamiliar with the drug. The mean weight loss, though small, has been reported in other long-term studies with quetiapine particularly in switches from other antipsychotics that are known to be associated with significant weight gain such as olanzapine.[17,18]

Given the open-label nature of the study, caution is required in interpreting the patient satisfaction data, nonetheless patients' responses particularly in the domains of quality of life and activities of daily living are encouraging, since these were chronic and ill patients at baseline (mean PANSS, 100.1). Whilst patients were rapidly titrated down from their previous medication before initiation with quetiapine, which may have influenced baseline ratings, the literature suggests that switches to quetiapine are generally well tolerated no matter what strategies are employed.[19] Hellewell et al[13] found that 75% of patients on quetiapine reported being "Very" or "Extremely satisfied", and 96.6% pre-





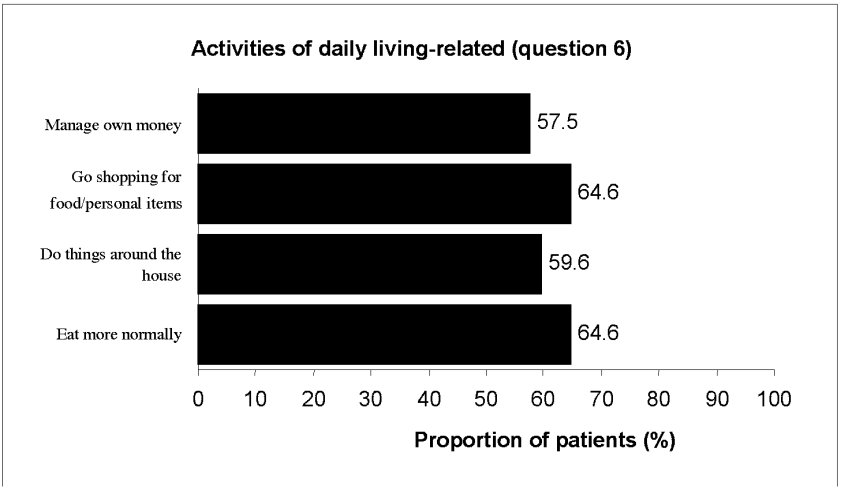


Figure. Summary of patient satisfaction questionnaire results at week 24 (endpoint).

ferred this medication to their previous antipsychotic. This high figure for treatment preference may have been due to the fact that this was a population of clinical trial patients (n = 129) in a 6-month open label extension study. Despite the importance of patient satisfaction particularly with respect to chronic psychiatric disorders such as schizophrenia where insight is frequently impaired, this aspect has not been systematically studied in many clinical trials.[20] Since no standard methodology exists to measure patient satisfaction it is difficult to compare findings from different studies employing a variety of scales measuring attitudes to medication, perception of side effects, or subjective well being rather than patient satisfaction.[21] In addition, many studies are short-term (6-12 weeks) switch studies that are likely to have positive results since patients are selected because of persistent symptoms and/or side effects with previous therapies. Whilst a similar patient selection bias likely existed in this study and further, it could be argued that the patient satisfaction questionnaire used is biased towards positive responses, nonetheless all measures of efficacy, tolerability, and satisfaction were maintained in this long-term study of 6 months duration.

There are numerous factors that influence patient satisfaction, but patients' perceptions of their treatment appear to be less related to severity of illness or symptom ratings and more strongly associated with adverse effects.[21] Tolerability may thus differentiate atypical antipsychotics to a greater extent then efficacy.[22,23] Persistence with initially prescribed antipsychotic treatment reflects these factors and an analysis of US managed care health claims data which reported that significantly fewer patients on quetiapine discontinued treatment over 12 months than patients on haloperidol, risperidone, and olanzapine.[24]

From the literature, there is an interesting variance between mental health professionals' expectations of patient satisfaction and the higher satisfaction that patients themselves report, suggesting that those things that are important to the patient may not necessarily be those things that clinicians have traditionally thought to be important.[21] Clearly, further long-term, effectiveness studies in real world patients need to be conducted given the relationships of patient satisfaction and acceptability to adherence, and thus, outcome.[25,26]

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