Clinical Study

The weight profile of SEROQUEL over the long term

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Title: The long-term effect of quetiapine (Seroquel®) monotherapy on weight in patients with schizophrenia.

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Seroquel®
quetiapine fumarate 25 mg, 100 mg, 200 mg & 300 mg tablets

Study design

- Retrospective analysis of SEROQUEL monotherapy in placebo-controlled and open-label extension trials
- 427 patients with schizophrenia received a mean daily dose of 475 mg of SEROQUEL after one year of open-label treatment
  - —178 of the 427 patients were treated with SEROQUEL for a minimum of 6 months (mean duration = 18.6 months)
  - —Weight was recorded at baseline and end point
- Body weight was assessed by baseline body mass index (BMI) categories established by the National Heart, Lung, and Blood Institute of the National Institutes of Health
  - —BMI defines weight relative to height
- All concomitant antipsychotic medication was stopped prior to entry into clinical trials

Favorable weight profile unaffected by higher doses of SEROQUEL in this study

- SEROQUEL did not result in clinically significant mean weight gain at any dose
- No correlation between higher doses and long-term mean weight changes

Minimal treatment withdrawal

- Only 1 patient in 427 (0.22%) withdrew due to weight gain

In short-term studies, only dyspepsia, weight gain, and abdominal pain were reported at a significantly higher incidence with increasing doses of SEROQUEL.

Favorable weight profile over time

- Clinically insignificant weight changes over the long term (mean duration = 18.6 months) demonstrated by BMI categories

Weight changes from baseline to end point* by baseline BMI category

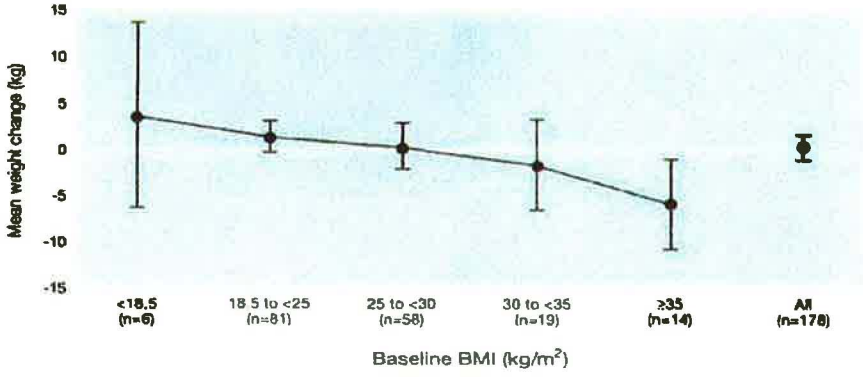
Baseline BMI (kg/m^2)	Number of patients	Mean daily dose at end point (mg)	Mean duration of treatment (days)	Mean weight change (kg)
<18.5	6	443	540	3.75
18.5 to <25	81	468	539	1.6
25 to <30	58	466	607	0.53
30 to <35	19	514	551	-1.53
≥35	14	483	543	-5.76
All	178	473	563	0.41

*Last recorded weight measurement

Little overall effect on weight across BMI categories

- SEROQUEL demonstrates a favorable weight profile in every weight category (from underweight to obese)

Mean change in weight by baseline BMI category



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The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

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INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI* < 18.5 *kg/m*^{2}*) and severely obese patients (BMI* ≥ 35 *kg/m*^{2}*).*

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Keywords
atypical antipsychotics *quetiapine*
schizophrenia *weight gain*
Body Mass Index *long-term therapy*

INTRODUCTION

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. Conventional antipsychotic agents have been prescribed extensively over the last 40 years to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms) (EPS) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment.[1,2] Such adverse effects of the older, typical antipsychotics caused great distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years.[3]

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, and are less likely to cause debilitating EPS than are the earlier antipsychotic agents.[1] However, there are marked differences between compounds: quetiapine, for example, has a particularly favourable EPS profile,[4] with an incidence of EPS no different from placebo across the entire dose range.[5]

Quetiapine also has a low propensity to cause hyperprolactinaemia or sexual dysfunction.[4] These properties suggest that quetiapine may be more acceptable to patients than alternative treatments.[6] Other side-effects, including a tendency to induce weight gain, have been observed to varying degrees with most atypical antipsychotics.[7] Weight gain may also adversely affect patients' quality of life and compromise treatment compliance.

The association between antipsychotic medication and weight gain has been recognized for more than 40 years.[8] Historically, weight gain has been linked to efficacy of antipsychotic medication, with increased weight being linked to a positive outcome. However, more recent research suggests this may not be the case.[9,10]

Weight gain is associated with increased morbidity and mortality in a wide range of conditions, including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems.[11,12] It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other side-effects commonly associated with antipsychotic medication.[13,14] If weight gain is considered unacceptable to the patient, then compliance may be compromised, potentially exacerbating the psychotic condition.

The extent to which antipsychotics are associated with weight gain varies considerably.[7,15] Weight gains of 4.45, 4.15, 2.10 and 2.16 kg have been observed following 10 weeks' treatment with clozapine, olanzapine, risperidone and quetiapine, respectively.[15,16] However, the true clinical significance of weight gain is observed in the context of long-term treatment. It is clear that long-term treatment with some antipsychotics (in particular clozapine and olanzapine) is associated with considerable increase in weight.[9,17] Given the growing importance of this issue, the present review assesses weight changes in patients with schizophrenia during long-term treatment with quetiapine monotherapy, focusing particularly on the potential effects exerted by dose or related to Body Mass Index (BMI).

METHODS

Weight data were analysed from controlled and uncontrolled clinical trials of quetiapine and the respective open-label extensions (OLE). Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase, where appropriate. Data from all patients who had a DSM-IV diagnosis of schizophrenia are included in the current review.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies, and treatment was with quetiapine monotherapy throughout both the double-blind and OLE periods of all studies.

Weight was assessed at baseline in most patients and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months. Consequently, the numbers of patients do not indicate the length of follow-up, and patients were not assessed following withdrawal of therapy. Baseline Body Mass Index (BMI) was available for most patients. For analysis, patients were grouped according to the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's standard categories for BMI.

STATISTICAL ANALYSIS

Weights were summarized using a last-observation-carried-forward approach within specified time intervals. Since the present exploratory analysis was designed only to highlight apparent contributors to weight change, rather than to provide a definitive analysis of predictors of weight change, no formal statistical analysis was performed on these data.

RESULTS

Weight data were analysed from 427 patients with schizophrenia from controlled and OLE studies in which only quetiapine was allowed as antipsychotic medication throughout the double-blind and open-label extension phase of each study. Patients received a mean daily quetiapine dose of 475 mg after one year of open-label treatment. Patient demographics are presented in Table 1.

Minimal overall weight change was observed over 18 months of treatment with quetiapine. The mean weight change from baseline was: 1.58 kg after 9–13 weeks (n=170); 0.26 kg after 14–26 weeks (n=165); 1.66 kg after 27–39 weeks (n=134); −1.53 kg after 40–52 weeks (n=41); and 1.94 kg after 53–78 weeks (n=146). (Note: patients did not necessarily have weight recorded at all timepoints.)

Table 1
Patient demographics

Number of patients (n)	427
Male/female (n)	277/150
Age, years (mean ± SD)	37.3 ± 10.8
Age distribution (N)	
<65 years	425
≥65 years	2
Weight, kg (mean ± SD)	75.21 ± 15.55
Weight distribution (n)	
Data not collected	28
<50 kg	5
50–70 kg	171
71–90 kg	164
>90 kg	59

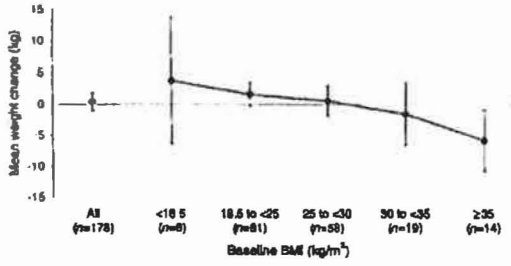

Figure 1
Mean change in weight, and associated 95% CI, from baseline to endpoint by baseline BMI category in patients treated with quetiapine monotherapy for at least 6 months (n=178). Mean treatment duration 18.6 months; mean daily dose 473 mg

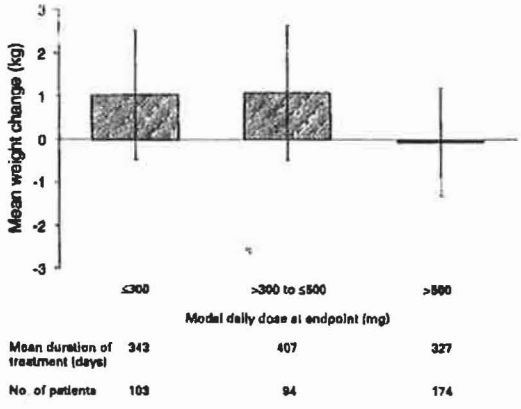

Figure 2
Mean change in weight, and associated 95% CI, from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy (endpoint is defined as final recorded weight measurement)

Effect of Baseline Body Mass Index

The mean change in weight from baseline to endpoint and associated 95% confidence intervals are shown in Figure 1 for each baseline BMI category for those patients who received at least 6 months' treatment with quetiapine (mean duration 18.6 months), and whose weight was recorded at baseline and endpoint. The mean dosage and duration of treatment are shown in Table 2 for each baseline BMI category. These data indicate that long term treatment with quetiapine has very little overall effect on weight, and the overlap of the 95% CIs with the zero change line allows quetiapine to be characterized as weight-neutral. Moreover, there is a tendency towards beneficial shifts in body weight in patients with BMI <18.5 kg/m^2 and in those with BMI ≥ 35 kg/m^2.

Longitudinal Analysis of Weight Change by Dose

Any effect of quetiapine dose on weight was investigated by analysing weight at baseline and endpoint for each of three dosage groups. The endpoint value was defined for each patient as the final recorded weight measurement that was taken. Patients were included in this analysis only if a baseline weight value had been obtained and if there was at least one other non-baseline value. Weight changes by dose group are presented in Figure 2, using the modal dose value for the last recorded weight value. These longitudinal data and associated 95% confidence intervals (CI) show there is no effect of quetiapine on weight at any dose, nor is there any correlation between increasing dose and mean long-term weight changes. These results are consistent with those from a short-term dose-ranging study reported previously.[5,16]

Effect of Gender

No clinically significantly different changes in weight from baseline to endpoint were observed between male and female patients on long term treatment with quetiapine. Weight changes of -0.58 kg and 1.94 kg were observed in male (n=108) and female (n=70) patients, respectively.

Withdrawals Due to Weight Gain

Only one patient withdrew (0.22%) as a result of an adverse event of weight gain.

DISCUSSION

Results of the present analysis show that, in clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight in the short term (8 weeks), and with an overall neutral effect on weight with long-term treatment. By comparison, an increase of approximately 12 kg has been reported after 12 months' treatment with olanzapine 12.5–17.5 mg/day.[17]

BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height, and our analysis of the weight change profile by baseline BMI shows that in the long term (18 months), weight changes in all but the severely obese (BMI >35 kg/m^2; Obesity Category II) are small, with 95% CIs overlapping the zero change line. Indeed, in this severely obese group, long-term quetiapine therapy was associated with a favourable weight loss. In addition, there was a trend towards beneficial weight gain in underweight patients (BMI <18.5 kg/m^2). Quetiapine appears therefore to be associated with potentially beneficial shifts in body weight towards normal values when individual BMI categories are considered.

Table 2
Weight changes from baseline to endpoint[a] by baseline BMI category in patients treated for at least 6 months with quetiapine monotherapy

Baseline BMI (kg/m^2)	n	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)
All	178	473	563	0.41
<18.5	6	443	540	3.75
≥18.5<25	81	468	539	1.6
≥25<30	58	466	607	0.53
≥30<35	19	514	551	−1.53
≥35	14	483	543	−5.76

[a]Final recorded weight measurement

Weight gain with certain antipsychotics (such as clozapine and olanzapine) has been associated with the development of diabetes.[18] In this context it is interesting to note that the addition of quetiapine to ongoing clozapine therapy in 65 patients significantly improved glycaemic status in the 20% of patients who had developed diabetes while on clozapine monotherapy.[19] Furthermore, these 65 patients had also experienced a 6.5 kg mean increase in weight during 6 months of clozapine monotherapy. Addition of quetiapine to the treatment regimen resulted in a mean weight loss of 4.2 kg over the subsequent 10 months.

Although various theories have been proposed, the precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated. It may be a multifactorial process, with involvement of serotonergic, histaminergic and/or adrenergic neurotransmission. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight,[9,15,16,20] have been shown to increase circulating leptin levels,[21,22] which correlate positively with increased BMI.

Antipsychotics also vary in the time course of their effect on weight gain. Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications.[23] In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics. In a retrospective analysis, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients showed continued increase in weight over a longer period (20 weeks).[7] In contrast, the present analysis demonstrates that quetiapine is associated with only a minimal change in weight that does not appear to be dose-related, does not increase over time, and does not appear to affect compliance. Indeed, in a recent study of patients' satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile was reflected in high levels of satisfaction and acceptance of long-term treatment, and a normalization of eating habits in 73% of the study population.[6] Given the association of weight gain with increased morbidity and mortality from hypertension and macrovascular disease,[11,12] and its detrimental impact on patients' well-being,[13,14] quetiapine's overall neutral or 'normalizing' effect on weight in the long term may have wider implications for patients' overall health, and associated healthcare costs.

In conclusion, weight changes in patients treated long term with quetiapine when used as monotherapy are neutral and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents. Combined with quetiapine's balanced combination of efficacy and tolerability, the present analysis suggests that quetiapine has a favourable benefit – risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

KEY POINTS

- While the impact of weight gain during long-term antipsychotic therapy is an important consideration when treating patients with schizophrenia, the extent to which individual agents are associated with weight gain varies considerably
- Long-term quetiapine monotherapy showed no overall effect on weight across the BMI spectrum, with 95% CIs encompassing zero weight change in all BMI categories apart from the severely obese (BMI ≥35 kg/m^2), in whom weight loss was observed. Any weight changes with quetiapine therapy showed no association with dose or gender
- Long-term monotherapy with quetiapine is associated with a potentially 'normalizing' effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients
- The combination of efficacy, good tolerability and an overall neutral long-term effect on weight suggests that quetiapine should be considered a first-choice antipsychotic in the long-term treatment of schizophrenia.