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# Efficacy and safety of quetiapine for depressive symptoms in patients with schizophrenia

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**Objective** To investigate the efficacy and safety of quetiapine for depressive symptoms in patients with schizophrenia.
**Method** Thirty-nine patients fulfilling DSM-IV-TR diagnostic criteria for schizophrenia and had depressive symptoms were studied in a prospective 6-week open-label design using quetiapine monotherapy. The brief psychiatric rating scale (BPRS), 17-item Hamilton depression rating scale (HAMD-17), Simpson–Angus rating scale, and the Barnes Akathisia rating scale (BARS) were used to assess patients at baseline, week 1, 2, 4, and 6.
**Results** Thirty patients (76.9%) completed this study. The dose of quetiapine at endpoint was 583 (±235 SD) mg/day. Treatment with Quetiapine was associated with significantly reduced depressive symptoms (HAMD-17 total score and BPRS depression/anxiety subscale) from the first week of treatment. Changes of mean score from baseline to endpoint were $7.8 \pm 6.2$ for HAMD-17 total score and $3.4 \pm 3.6$ for BPRS depression/anxiety subscale (LOCF, $n = 39$, $p < 0.001$). Quetiapine was well tolerated, with minimal extrapyramidal symptoms and non-significant increase in body weight (mean increase of 0.8 kg).
**Conclusions** While the interpretation of findings from the open-label design of this study warrants appropriate caution, the results suggest that quetiapine may be an effective and tolerable treatment for depression in patients with schizophrenia. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — quetiapine; schizophrenia; depression

## INTRODUCTION

Depressive symptoms are common in patients suffering from schizophrenia with some studies reporting a prevalence of up to 75% in the course of schizophrenia (Koreen *et al*., 1993; Mauri *et al*., 2000).

The presence of significant depressive symptoms in schizophrenia is associated with poorer response to medications (Himmelhoch *et al*., 1981), higher rates of relapse and rehospitalization (Sands and Harrow, 1999), and poor social and vocational functioning (Mandel et al., 1982) and worse overall outcomes (Falloon *et al*., 1978). In addition, poorly controlled depressive symptoms have been reported to affect patient's quality of life, that is, lower satisfaction with daily living, finances, health, and social life (Conley *et al*., 2007; Norholm and Bech, 2006).

The significance of depression in schizophrenia is sustained by the high rate (10–15%) of suicide among patients suffering from schizophrenia (Roy, 1990). Although a recent meta-analysis estimated that 4.9% of schizophrenics commit suicide in their lifetime, it is still an unacceptably high incidence (Palmer *et al*., 2005). In addition, the presence of depressive symptoms in schizophrenia increases suicidal risk (Zisook *et al*., 1999; De Hert *et al*., 2001). Therefore, effective treatment of depression in schizophrenia appears critical to improvement in outcome, quality of life, and reduction of suicide rate in this chronic and disabling disorder.

Recently, the introduction of newer antipychotics (second generation or atypical antipsychotics) has added a new dimension of treating depressive symptoms in patients with schizophrenia. Recent studies have reported reduction in depressive symptoms in patients with schizophrenia and schizoaffective disorder when treated with atypical agents such as clozapine, risperidone, olanzapine, ziprasidone, and quetiapine (Daniel *et al*., 1999; Keck *et al*., 2000; Siris,

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2000; Dollfus *et al*., 2005; Mauri *et al*., 2007). Additionally, these agents are associated with less neuroleptic-induced extrapyramidal side effects that may overlap with depressive symptomatology (Siris, 2000).

In this study, we were specifically interested in the effect of quetiapine on depressive symptoms in schizophrenia. Quetiapine is a novel dibenzothiazepine antipsychotic with affinity for multiple neurotransmitter receptors including serotonin, dopamine, histamine, and adrenergic receptors (Goldstein, 1999). It shares with clozapine a low affinity for dopamine D2 receptors and resembles the other atypical antipsychotics in exhibiting a greater 5-hydroxytryptamine (HT)-2A than dopamine D2 receptor antagonism, suggesting that it might be potentially useful for mood symptoms (Jones *et al*., 2001; Nemeroff *et al*., 2002).

There is some evidence that supports the use of quetiapine for mood symptoms in schizophrenia. In one brief report, quetiapine was superior to placebo in improving depressive signs and symptoms in patients with schizophrenia (Arvanitis *et al*., 1997). In a study of partial responders to conventional antipsychotic agents, the switch to quetiapine produced a significant reduction in the positive and negative syndrome scale (PANSS) depression factor which was interpreted to be a direct effect on depressive symptoms (Emsley *et al*., 2003). A recent analysis of data from the open-label extension phases of three randomized clinical trials demonstrated that quetiapine was effective for the treatment of depressive and anxiety symptoms in long-term treatment (Kasper, 2004). However, not all studies have been positive which some reporting lack of effect and even inducing depressive symptoms in patients with schizophrenia (Mauri *et al*., 2008; Mergui *et al*., 2005). Thus, while there is support for the use of quetiapine for depressive symptoms in schizophrenia, the findings are not consistent and further studies are clearly warranted.

In this study, we examined the efficacy and safety of quetiapine on depressive symptoms in patients with schizophrenia in a 6-week open-label design naturalistic treatment study.

## METHODS

### *Study design and patient population*

This study was a 6-week prospective open-label clinical trial that was conducted at three university hospital sites. Eligible subjects (male and female; 18–65 years) met DSM-IV-TR (APA, 2000) criteria for schizophrenia or schizophreniform disorder (clinical diagnosis), and had depressive symptoms ($\geq$8) on the 17-item Hamilton depression rating scales (HAMD-17) (Hamilton, 1960) at both the screening visit and on the day of quetiapine administration (baseline). Exclusion criteria included an unstable medical or neurological disorder, clinically significant laboratory abnormalities on screening, current substance or alcohol dependence and pregnancy. Written informed consent was obtained from each patient or guardian or legal representative. The study protocol was approved by Institutional Review Board at each participating hospital.

During screening period (1–3 days), current medications (14 patients received risperidone, 7 olanzapine, 4 amisulpride, 3 aripiprazole, and 2 ziprasidone) were tapered. Following the screening period, quetiapine was initiated at 100–800 mg/day (baseline) and titrated upwards in response to the clinical status of the patient by the treating psychiatrist. Potent cytochrome P450 inhibitors or inducers, antidepressants, mood stabilizers, and other antipsychotic agents were prohibited. Benztropine in doses up to 3 mg/day and limited use of benzodiazepines (lorazepam $\leq$ 3 mg/day equivalent) as concomitant medications were allowed.

### *Efficacy and safety assessment*

Primary outcome measures; Patients were assessed at baseline, week 1, 2, 4, and 6 using HAMD-17 and brief psychiatric rating scale (BPRS) depression/anxiety subscale score (depressive mood, guilt feelings, somatic concern, and anxiety) (Guy, 1976).

Extrapyramidal side effects were assessed using the Simpson–Angus rating scale (SARS) total (Simpson and Angus, 1970) and Barnes Akathisia rating scale (BARS) global scores (Barnes, 1989) at each visit. All assessments were performed by independent raters (psychiatry residents trained to conduct these assessment by the PI).

Laboratory tests performed on all patients at screening included complete blood count (with differential, hematocrit, and platelet count), blood chemistries, urinalysis, pregnancy test for women of childbearing potential, and an electrocardiogram. A physical examination, including body weight measurement, and blood pressure and pulse rate were measured at each visit.

### *Statistical analyses*

All statistical analyses were performed using the Statistical Analysis System software package (Version



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6.0) (SAS Institute, Cary, North Carolina, 1999). All statistical tests were two-tailed, with $\alpha$ set at 0.05.

Change in depressive symptoms (pre–post quetiapine) was assessed by using the HAMD-17 total score and BPRS depression/anxiety subscale score. Changes of mean scores from baseline to endpoint (last observation carried forward [LOCF]) and from baseline to each week (observed cases [OC]) were assessed using the paired *t*-test. Mean changes over time were analyzed using repeated measures of ANOVA with the Greenhouse–Geisser correction.

Also, change in psychotic symptoms (pre–post quetiapine) was evaluated utilizing the BPRS total score and analyzed according to the above methods.

Safety measures such as SARS, BARS, and body weight were analyzed by means of the paired *t*-test for OCs from baseline to each week.

## RESULTS

### *Patient characteristics and treatment*

A total of 42 patients were enrolled. Of these, three patients were excluded from the analysis (two patients for protocol violation, one patient for depressive symptom improvement over 50% during screening period). The data of remaining 39 patients were included in the analysis, and the demographic and clinical characteristics of patients are summarized in Table 1.

Mean age of patients in this study was 34.9 (SD 9.7) with slightly more females than males (59%). The primary diagnosis for most subjects was schizophrenia (97.4%) (with the rest diagnosed with schizophreniform disorder). Mean duration of illness was 5.1 years (SD 4.8). Fourteen patients (35.9%) were short-term (less than 1 month) inpatients who had been hospitalized for the treatment of acute psychotic symptoms. Patients had moderate psychotic symptoms (mean BPRS total score of 49.1 (SD 15.9) and mild depressive symptoms (mean HAMD-17 total score of 16.3 (SD 6.4) at baseline. The numbers of patients with mild depression (scores of 8–19), moderate (scores of 20–24), and severe (scores greater than 25) on HAMD-17 were 29 (74.4%), 5(12.8%), and 5(12.8%), respectively. These cutoff points selected in this study were similar to that used in previous studies (Endicott *et al*., 1981; Shelton *et al*., 2007).

Mean starting dosage of quetiapine was $314.3 \pm 184.8$ mg/day (range 100–800 mg/day) and mean dosage at endpoint was $583.3 \pm 235$ mg/day (range 100–1000 mg/day).

Of the 39 patients, 30 patients (76.9%) completed the 6-week study and 9 patients (23.1%) did not complete the study due to being lost to follow up (5) and lack of efficacy (4).

Table 1. Demographic and clinical characteristics of patients ($n = 39$)

| Variables | Mean ± SD (%) |
|---|---|
| Age | $34.9 \pm 9.7$ |
| Gender | |
| Male | 16 (41.0) |
| Female | 23 (59.0) |
| Marriage | |
| Married | 12 (30.8) |
| Single | 24 (61.5) |
| Divorced/separated/widowed | 3 (7.7) |
| Socioeconomic status | |
| High | 1 (2.6) |
| Middle | 34 (87.2) |
| Low | 4 (10.3) |
| Job | |
| Employed | 10 (25.6) |
| Unemployed | 29 (74.4) |
| patient status | |
| Inpatients | 14 (35.9) |
| Outpatients | 25 (64.1) |
| Primary diagnosis | |
| Schizophrenia | 38 (97.4) |
| Paranoid | 24 (61.5) |
| Undifferentiated | 14 (35.9) |
| Schizophreniform disorder | 1 (2.6) |
| Age of onset (years) | $30 \pm 9.9$ |
| Duration of illness (years) | $5.1 \pm 4.8$ |
| Number of hospitalization | $1.5 \pm 1.4$ |
| BPRS total scores | $49.1 \pm 15.9$ |
| BPRS depression/anxiety scores | $12.2 \pm 3.7$ |
| HAMD-17 total scores | $16.3 \pm 6.4$ |
| SARS total scores | $0.2 \pm 0.7$ |
| BARS global scores | $0.1 \pm 0.3$ |
| Body weight | $68.1 \pm 14.2$ |
| Baseline | $68.9 \pm 15.3$ |
| Endpoint | |
| Quetiapine dosage (mg/day) | |
| Baseline | $314.3 \pm 184.8$ |
| Endpoint | $583.3 \pm 235$ |

BPRS: brief psychiatric rating scale, HAMD-17: 17-item Hamilton depression rating scale, SARS: Simpson–Angus rating scale, BARS: Barnes Akathisia rating scale.

### *Efficacy*

Patients showed a significant improvement in their BPRS total scores over the 6-week treatment period with quetiapine ($F(4, 116) = 18.68$, $p < 0.001$). BPRS total scores showed a significant reduction from baseline to endpoint (LOCF; mean $11.4 \pm 14.3$, $n = 39$, $p < 0.001$). Visit-wise analyses showed a significant reduction of psychotic symptoms from the second week (visit 2) following the initiation of quetiapine ($p < 0.001$).

There was a significant reduction of depressive symptoms as measured by HAMD-17 total scores over treatment period ($F(4, 116) = 28.71$, $p < 0.001$) or from baseline to endpoint (LOCF; mean 7.8, $n = 39$,



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$p < 0.001$). The effect of quetiapine in improving depressive symptoms was significant from first week (Visit 1) of treatment (OC; $p < 0.001$) (Figure 1).

Similarly, there was a significant reduction of depressive symptoms as measured by the BPRS depression/anxiety subscale score over the treatment period ($F(4,116) = 16.85$, $p < 0.001$). Quetiapine treatment was associated with a significant improvement in depression and anxiety symptoms as measured by the change in BPRS depression/anxiety subscale scores from baseline to endpoint (LOCF; mean 3.4, $n = 39$, $p < 0.001$). Visit-wise analyses showed a significant reduction of symptoms in the BPRS depression/anxiety subscale scores both early and late in the course of treatment with quetiapine (OC; week 1 and 2: $p < 0.005$, week 4 and 6: $p < 0.001$) (Figure 2).

### *Tolerability*

Overall there were no serious adverse events observed during the course of the study and quetiapine was well tolerated. Common side effects reported were dry mouth, somnolence, headache, extrapyramidal symptoms, akathisia, and leg pain, but they were mild and did not require discontinuation of quetiapine.

Over the course of trial, about 9.4% of patients had a total score $> 1$ on SARS which decreased over the course of the study (mean SARS score; $0.21 \pm 0.73$ at baseline, $0.07 \pm 0.25$ at endpoint). Only one patient had a rating $> 2$ (mild) on the global severity item of the BARS, and which decreased over the course of study (mean global BARS score; $0.1 \pm 0.31$ at baseline, $0.03 \pm 0.18$ at endpoint) (Figure 3).

The initial average body weight of all subjects was 68.1 kg (SD = 14.2), and at week 6 the mean weight was 68.9 kg (SD = 15.3). There was an increase of weight about 0.8 kg (SD = 3.5 kg) over the course of treatment which was not statistically significant ($t = -1.27$, df = 28, $p = 0.215$).

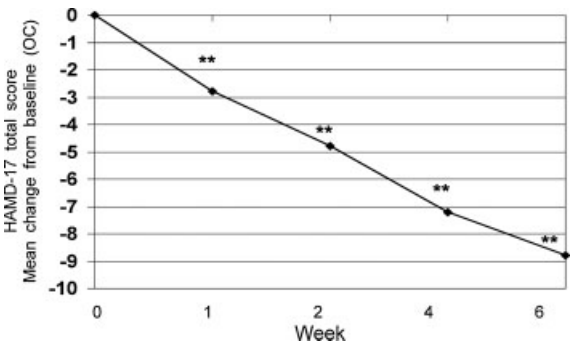


Figure 1. Changes in 17-item Hamilton depression rating scales total scores ($N = 39$) $^{**}p < 0.001$ HAMD-17: 17-item Hamilton depression rating scales, OC: observed case

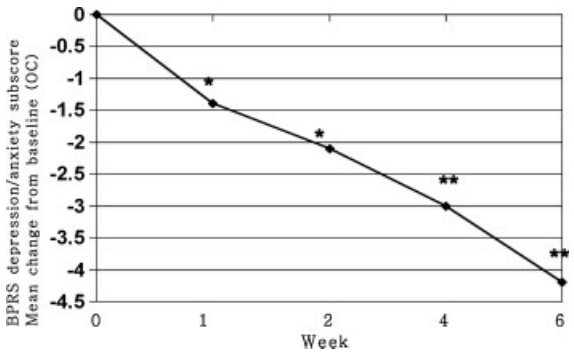


Figure 2. Changes in brief psychiatric rating scale depression/anxiety subscale scores ($N = 39$) $^{*}p < 0.005$, $^{**}p < 0.001$ BPRS: brief psychiatric rating scale, OC: observed case

## DISCUSSION

Over the past two decades, the focus of treatment of schizophrenia has evolved from the reduction of positive symptoms to a global improvement which includes negative symptoms, cognitive symptoms, and affective symptoms. As discussed earlier, these clusters of symptoms directly impact the overall functioning and quality of life in patients with schizophrenia. Thus, therapeutic interventions aimed at treating depressive symptoms in patients with schizophrenia are important to the goal of improving individual patients' quality of life and compliance with therapy. In this study, we investigated the effect of quetiapine on depressive symptoms in patients with schizophrenia.

The findings from this 6-week prospective open-label study suggest that quetiapine is effective and safe not just for psychotic symptoms but also depressive symptoms that were present in these patients with schizophrenia. The mean change of depressive symptoms were 7.8 points on the HAMD-17 total score and 3.4 on the BPRS depressive/anxiety subscale scores with the effect of quetiapine evident from the first week of treatment.

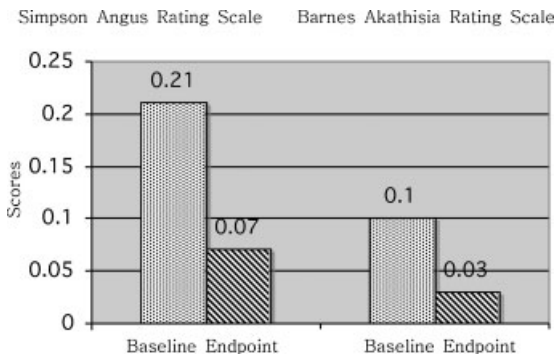


Figure 3. The tolerability of quetiapine as measured by Simpson–Angus rating scale and Barnes Akathisa rating scale observed cases (baseline $n = 39$, endpoint $n = 30$)



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These findings are consistent with previous studies reporting the effect of quetiapine on depressive symptoms in patients with acute or chronic schizophrenia (Arvanitis *et al*., 1997; Khouzam, 2000; Emsley *et al*., 2003; Kasper, 2004). Emsley *et al*. compared the efficacy of quetiapine with haloperidol for patients with a history of partial response to conventional antipsychotic, and reported that quetiapine produced a greater reduction in depression scores (PANSS depression factor) than haloperidol ($-1.6$ vs. $-0.54$) (Emsley *et al*., 2003). Patients with higher depression scores (PANSS depression factor score of $\geq 8$) showed greater reduction of mean scores ($-2.24$ vs. $-1.27$, for quetiapine and haloperidol, respectively). The present study also showed similar findings where HAMD-17 scores were significantly reduced in patients with moderate to severe depression relative to mild depression ($t = 4.73$, $\mathrm{df} = 28$, $p < 0.001$). Analysis of data from the open-label extension phases of three randomized clinical trials showed that the mean change in BPRS depression/anxiety subscale score was $-1.13$ and $-1.33$ for acute and long-term phases, respectively (Kasper, 2004). The differences of improvement among studies might be due to the differences in population characteristics (gender, depression severity, and disease stage) or treatment characteristics (dosage differences, dosing schedule).

Among atypical antipsychotics, quetiapine may have a lower rate of extrapyramidal symptoms (Casey, 1996). This study showed similar results as about 9.4% of patients had a total score $> 1$ on SARS and only 1 patient had a rating $> 2$ (mild) on the global severity item of the BARS. These extrapyramidal symptoms were easily managed during the course of treatment with conventional doses of anticholinergics or benzodiazepines; both SARS total and BARS global scores decreased over the course of the treatment.

Among side-effects of atypical antipsychotics, weight gain has gained a lot of attention recently, as it is associated with increased risk of diabetes and cardiovascular disease, medication noncompliance and poor quality of life (Allison *et al*., 2003; Solomon and Manson, 1997; Weiden *et al*., 2004). Recent reviews suggested that mean weight gain is highest with clozapine and olanzapine, moderate with quetiapine and lowest with aripiprazole and ziprasidone (Brecher *et al*., 2007; Haddad and Sharma, 2007). In the present study, quetiapine induced a minimal weight change (under 1 kg) during this short-term exposure which is similar to previous findings.

Studies including the present study have suggested that quetiapine may be effective in controlling depression without leading to a manic or hypomanic state in patients with schizophrenia. However, several previous reports presented cases of manic induction associated with quetiapine treatment (Atmaca *et al*., 2002; Biancosino *et al*., 2003; Lykouras *et al*., 2003; Mishra *et al*., 2004; Pacchiarotti *et al*., 2003). Thus, caution is needed when administering quetiapine for the treatment of schizophrenia or schizoaffective disorder and more studies are needed to confirm its effect on manic induction.

The results of this study should be interpreted with caution in light of the limitations such as its open-label design, small sample size, and flexible dosing schedule. We used a flexible dosing design to enable clinicians to titrate each patient to a dosage that was optimal for that patient thereby maximizing the patient's level of efficacy while minimizing intolerability. Also, flexible dosing mimics clinical practice more closely than fixed dosing and may, therefore, allow for better generalization of the findings of this study to real-world clinical practices.

In summary, the findings of this 6-week open-label prospective study supports the effectiveness and tolerability of quetiapine in reducing depressive symptoms in patients with schizophrenia. However, further randomized double-blind placebo-controlled studies are needed to address the question of whether this effect is specific to depressive symptoms.

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## REFERENCES

Allison DB, Mackell JA, McDonnell DD. 2003. The impact of weight gain on quality of life among persons with schizophrenia. *Psychiatr Serv* **54**(4): 565–567.

Arvanitis LA, Miller BG, Kowalcyk BB. 1997. Efficacy of ''Seroquel'' (quetiapine fumarate) in affective symptoms of schizophrenia. *Scientific Abstracts of the 36th Annual Meeting of the American College of Neuropsychopharmacology*, Honolulu, Hawaii.

Atmaca M, Kuloglu M, Buyukbayram A, Tezcan E. 2002. Quetiapine-associated and dose-related hypomania in a woman with schizophrenia. *Eur Psychiatry* **17**(5): 292–293.

Barnes TR. 1989. A rating scale for drug-induced akathisia. *Br J Psychiatry* **154**: 672–676.

Biancosino B, Marmai L, Facchi A, Rossi E, Grassi L. 2003. Quetiapine may induce mania: a case report. *Can J Psychiatry* **48**(5): 349–350.

Brecher M, Leong RW, Stening G, Osterling-Koskinen L, Jones AM. 2007. Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry* **68**(4): 597–603.

Casey DE. 1996. Side effect profiles of new antipsychotic agents. *J Clin Psychiatry* **11** (Suppl 57): 40–45. Discussion 46–52.

Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. 2007. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res* **90**(1–3): 186–197.

Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. 1999. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. *Neuropsychopharmacology* **20**(5): 491–505.

De Hert M, McKenzie K, Peuskens J. 2001. Risk factors for suicide in young people suffering from schizophrenia: a long-term follow-up study. *Schizophr Res* **47**(2–3): 127–134.

Dollfus S, Olivier V, Chabot B, Deal C, Perrin E. 2005. Olanzapine versus risperidone in the treatment of post-psychotic depression in schizophrenic patients. *Schizophr Res* **78**(2–3): 157–159.

Emsley RA, Buckley P, Jones AM, Greenwood MR. 2003. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *J Psychopharmacol* **17**(2): 210–215.

Endicott J, Cohen J, Nee J, Fleiss J, Sarantakos S. 1981. Hamilton depression rating scale. Extracted from regular and change versions of the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* **38**(1): 98–103.

Falloon I, Watt DC, Shepherd M. 1978. A comparative controlled trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia. *Psychol Med* **8**(1): 59–70.

Goldstein JM. 1999. Quetiapine fumarate (Seroquel): a new atypical antipsychotic. *Drugs Today (Barc)* **35**(3): 193–210.

Guy W. 1976. *ECDEU Assessment Manual for Psychopharmacology*, Revised (DHEW Publication No. ADM 76–338), Superintendent of Documents, Washington, DC, U.S. Government Printing Office.

Haddad PM, Sharma SG. 2007. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs* **21**(11): 911–936.

Hamilton M. 1960. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry* **23**: 56–62.

Himmelhoch JM, Fuchs CZ, May SJ, Symons BJ, Neil JF. 1981. When a schizoaffective diagnosis has meaning. *J Nerv Ment Dis* **169**(5): 277–282.

Jones HM, Travis MJ, Mulligan R, *et al*. 2001. In vivo 5-HT2A receptor blockade by quetiapine: an R91150 single photon emission tomography study. *Psychopharmacology (Berl)* **157**(1): 60–66.

Kasper S. 2004. Quetiapine is effective against anxiety and depressive symptoms in long-term treatment of patients with schizophrenia. *Depress Anxiety* **20**(1): 44–47.

Keck PE Jr, Strakowski SM, McElroy SL. 2000. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. *J Clin Psychiatry* **61** (Suppl 3): 4–9.

Khouzam HR. 2000. Treatment of depressive mood in schizophrenia with the atypical antipsychotic quetiapine. *Depress Anxiety* **11**(2): 80–82.

Koreen AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. 1993. Depression in first-episode schizophrenia. *Am J Psychiatry* **150**(11): 1643–1648.

Lykouras L, Oulis P, Hatzimanolis J. 2003. Manic symptoms associated with quetiapine treatment. *Eur Neuropsychopharmacol* **13**(2): 135–136.

Mandel MR, Severe JB, Schooler NR, Gelenberg AJ, Mieske M. 1982. Development and prediction of postpsychotic depression in neuroleptic-treated schizophrenics. *Arch Gen Psychiatry* **39**(2): 197–203.

Mauri MC, Laini V, Barone R, et al. 2000. ''Postpsychotic depression'' and residual schizophrenia in a mental health hospital. *Encephale* **26**(6): 21–26.

Mauri MC, Moliterno D, Rossattini M, Colasanti A. 2008. Depression in schizophrenia: comparison of first- and second-generation antipsychotic drugs. *Schizophr Res* **99**(1–3): 7–12.

Mergui J, Jaworowski S, Lerner V. 2005. Quetiapine-associated depression in a patient with schizophrenia. *Clin Neuropharmacol* **28**(3): 133–135.

Mishra A, Moore PB, Hobbs R. 2004. Does quetiapine have mood altering properties? *J Psychopharmacol* **18**(2): 281–284.

Nemeroff CB, Kinkead B, Goldstein J. 2002. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry* **13** (Suppl 63): 5–11.

Norholm V, Bech P. 2006. Quality of life in schizophrenic patients: association with depressive symptoms. *Nord J Psychiatry* **60**(1): 32–37.

Pacchiarotti I, Manfredi G, Kotzalidis GD, Girardi P, Tatarelli R. 2003. Quetiapine-induced mania. *Aust N Z J Psychiatry* **37**(5): 626.

Palmer BA, Pankratz VS, Bostwick JM. 2005. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* **62**(3): 247–253.

Roy A. 1990. Relationship between depression and suicidal behavior in schizophrenia, In *Depression in Schizophrenia*. DeLish LE (Ed.). American Psychiatric Press: Washington DC; 41–58.

Sands JR, Harrow M. 1999. Depression during the longitudinal course of schizophrenia. *Schizophr Bull* **25**(1): 157–171.

Shelton RC, Prakash A, Mallinckrodt CH, et al. 2007. Patterns of depressive symptom response in duloxetine-treated outpatients with mild, moderate or more severe depression. *Int J Clin Pract* **61**(8): 1337–1348.

Simpson GM, Angus JW. 1970. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* **212**: 11–19.

Siris SG. 2000. Depression in schizophrenia: perspective in the era of ''Atypical'' antipsychotic agents. *Am J Psychiatry* **157**(9): 1379–1389.

Solomon CG, Manson JE. 1997. Obesity and mortality: a review of the epidemiologic data. *Am J Clin Nutr* **66** (Suppl 4): 1044S–1050S.

Weiden PJ, Mackell JA, McDonnell DD. 2004. Obesity as a risk factor for antipsychotic noncompliance. *Schizophr Res* **66**(1): 51–57.

Zisook S, McAdams LA, Kuck J, *et al*. 1999. Depressive symptoms in schizophrenia. *Am J Psychiatry* **156**(11): 1736–1743.




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