Dosing Quetiapine in Drug-Naive First-Episode Psychosis: A Controlled, Double-Blind, Randomized, Single-Center Study Investigating Efficacy, Tolerability, and Safety of 200 mg/day vs. 400 mg/day of Quetiapine Fumarate in 141 Patients Aged 15 to 25 Years

Gregor E. Berger, M.D., F.M.H.Psych., F.R.A.N.Z.C.P.; Tina-Marie Proffitt, Ph.D.; Mirabel McConchie, M.Sc.; Melissa Kerr, M.Sc.; Connie Markulev, M.Sc.; Hok Pan Yuen, M.Sc.; Colin O'Donnell, M.B., B.Ch., M.R.C.Psych.; Dan Lubman, Ph.D.; Andrea Polari, M.D.; Stephen Wood, Ph.D.; G. Paul Amminger, M.D.; and Patrick D. McGorry, M.D., Ph.D., F.R.A.N.C.P.

Objective: To assess dosing, efficacy, and tolerability of quetiapine fumarate in drug-naive first-episode psychosis.

Method: We present a prospective, randomized, controlled, single-center, double-blind, fixed-dose, 4-week comparison study of 200 mg/day versus 400 mg/day of quetiapine in 141 drug-naive acutely ill first-episode psychosis patients (diagnosed according to DSM-IV) aged 15 to 25 years. The double-blind 4-week trial (Part 1) was followed by a single-blind, naturalistic, flexible-dose 8-week period (Part 2). The main outcome measures were symptomatic change, functioning, and tolerability. Data were collected from July 2003 until January 2006.

Results: The estimated time trends of the linear mixed-effects modeling indicated that efficacy between the 2 treatment groups in Part 1 was similar for most outcome measures except for 5 measures: the Scale for the Assessment of Negative Symptoms (SANS) anhedonia-asociality subscale ($p = .011$), the Social and Occupational Functioning Assessment Scale ($p = .020$), the Global Assessment of Functioning scale ($p = .070$), the SANS affective flattening or blunting subscale ($p = .051$), and the Udvalg for Kliniske Undersogelser total ($p = .056$), suggesting that the 200-mg group improved more for the SANS anhedonia-asociality subscale, whereas the 400-mg group showed a slight deterioration. Social and global functioning also improved more in the 200-mg group than in the 400-mg group. Part 2 of the study revealed that, independent of the initial target dose, when clinicians were able to adjust the dose flexibly, the dose at 12 weeks was similar between groups and averaged 268 mg/day.

Conclusion: Our study in acutely ill drug-naive first-episode psychosis patients suggests that quetiapine is a safe and well-tolerated antipsychotic medication. In contrast to multiepisode patients, dosing should be more conservative in untreated new-onset cases. An initial dose of 250 to 300 mg/day of quetiapine is proposed as a primary target dose in drug-naive first-episode psychosis patients.

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Corresponding author and reprints: Gregor E. Berger, M.D., The Schloessli Clinic, Department of Research and Education, Schlösslistrasse 8, CH-8618 Oetwil am See, Switzerland (e-mail: bergerg@mac.com).

Quetiapine fumarate demonstrates clinical efficacy and good tolerability over a wide dose range (300 mg/day to 750 mg/day) in schizophrenia.[1,2] Early controlled studies included mainly multiepisode schizophrenia patients and suggest that doses greater than 250 mg/day are more effective than lower doses.[1,3] Quetiapine's good tolerability led to the recommendation of its use as

a first-line drug.[4,5] However, dose recommendations for drug-naive first-episode psychosis patients are mainly from open-label small-scale studies.[4,6–8] In clinical practice, a wide dose range beyond dose recommendations from controlled clinical trials is used.[9] However, McEvoy et al.[10] used elbow rigidity as a proxy to determine the neuroleptic threshold and demonstrated that drug-naive first-episode schizophrenia patients require about 50% lower doses of haloperidol in comparison to multiepisode schizophrenia patients. It is unknown whether a reduced dose requirement is also true for second-generation antipsychotic medications. There is some evidence that low doses of risperidone are at least as effective as medium doses of risperidone in drug-naive first-episode psychosis patients but have a better tolerability profile.[11,12] To our knowledge, no controlled randomized study has investigated whether drug-naive first-episode psychosis patients also need lower doses of quetiapine, potentially resulting in better tolerability (e.g., less sedation, dizziness, and hypotension) and better treatment adherence. The objectives of this study were to assess efficacy and tolerability of 200 mg/day versus 400 mg/day of quetiapine as the initial target dose in drug-naive first-episode psychosis. Our hypotheses were that both doses would be equally effective but that the lower dose (200 mg/day) would have better tolerability and result in better treatment adherence (lower dropout rates). Furthermore, we wanted to investigate whether the initial target dose has any carryover effects.

METHOD

Study Design and Inclusion and Exclusion Criteria

We present a prospective, randomized, controlled, single-center, double-blind, fixed-dose, 4-week comparison study of 200 mg/day versus 400 mg/day of quetiapine, investigating its efficacy, tolerability, and safety in 141 drug-naive first-episode psychosis patients aged 15 to 25 years. The double-blind 4-week trial (Part 1) was followed by a single-blind, naturalistic, flexible-dose 8-week period (Part 2). At the end of Part 1 (28–31 days of randomized treatment with 200 or 400 mg/day), research assistants obtained the sealed unblinding envelopes from the clinical trials pharmacy and passed these on to the treating psychiatrist at a scheduled medical review that occurred after the week 4 research assessment and that the research assistant did not attend. The treating psychiatrist then proceeded to adjust the dose of quetiapine as he or she deemed appropriate, providing the patient with the new prescription, which the clinical trials pharmacy dispensed. The patient was instructed not to reveal to the research assistant the dose that he or she was taking. In addition, the treating doctor was required to write only the new dose in the file (i.e., the dose prescribed at the commencement of Part 2) and not the dose the patient had been receiving during the double-blind randomization phase. During Part 2, the treating psychiatrist could increase the dose in weekly 100-mg steps, as clinically indicated according to treatment response. Treatment response was assessed naturalistically by the clinician's experience. If no treatment response was achieved at 700 mg/day of quetiapine, the dose was maintained over a period of 2 weeks and the patient was then switched to another atypical antipsychotic (either risperidone or olanzapine). The research assistants who performed the study assessments remained blind to the prescribed dose of quetiapine until study completion.

The first participant signed the consent form on July 21, 2003. The last patient completed the trial (including Part 2) on January 6, 2006. The study was approved by the Melbourne Health Research and Ethics Committee and conducted in compliance with Good Clinical Practice guidelines (available at: http://www.ich.org/LOB/media/MEDIA482.pdf). Involuntary patients (sections 9 and 12 of the Victorian Mental Health Act, Australia [available at: http://www.health.vic.gov.au/mentalhealth/mh-act/index.htm]) could also be approached to be a part of this study. If an initially involuntary patient was eligible and agreeable to participate in the trial, the appropriate authorities (Victorian Civil and Administrative Tribunal) provided additional written informed consent within 48 hours, which is consistent with the Australian guidelines for the treatment of early psychosis[13,14] and did not cause any extra delay in the initiation of treatment.

Inclusion criteria for this study are based on the inclusion criteria for the Early Psychosis Prevention and Intervention Centre (EPPIC), a subprogram of ORYGEN Youth Health.[15] Male and female patients from 15 to 25 years of age, outpatients or inpatients, undergoing a first episode of psychosis defined as daily psychotic symptoms for longer than 1 week that cannot be explained by other factors (e.g., organic in the context of temporal lobe epilepsy, or drug-induced psychotic episodes that remitted within 7 days without antipsychotic medication) are eligible for EPPIC. These criteria represent the standard of practice whereby most psychiatrists would start antipsychotic treatment and which has been implemented as best practice in the context of the Australian treatment guidelines for early psychosis.[13] Patients must have 1 or more of the following symptoms, each present for at least 1 week on a daily basis according to the manual of the extended Brief Psychiatric Rating Scale (BPRS), version 4[16]: somatic concerns (≥ 6), guilt (≥ 6), suspiciousness (≥ 5), hallucinations (≥ 5), unusual thought content (≥ 4), bizarre behavior (≥ 4), and/or conceptual disorganization (≥ 4). Patients included in the study met criteria for 1 of the following DSM-IV diagnoses: schizophreniform psychosis, schizophrenia, schizoaffective disorder, delusional disorder, major depression with psychotic features, or psychosis not otherwise specified. In order to

make the primary diagnosis for patients, the Structured Clinical Interview for DSM-IV, Research Version, Patient Edition (SCID-I/P)[17] was completed at the week 3 assessment. In cases in which this was not possible because of a patient's time constraints or a patient's being too unwell to complete the interview, the primary diagnosis was obtained from a chart review of clinical notes taken during the index admission assessment and subsequent medical reviews. No diagnosis was obtained for the patients who withdrew consent for the study.

Exclusion criteria were previous treatment with antipsychotic medication (more than 1 week), presence of concurrent manic syndrome, mental retardation (IQ lower than approximately 70), organic disorders presenting with a psychotic syndrome (e.g., human immunodeficiency virus encephalopathy), epilepsy (febrile convulsions in childhood acceptable), a clinically significant physical illness (e.g., terminal cancer), history of brain surgery, history of brain infarct, concomitant medications that prolong the QT interval, a 20% deviation from normal-range laboratory values at baseline (e.g., potassium abnormalities), participation in any other studies involving investigational or marketed products concomitantly or within 30 days prior to entry into the study, having donated blood or blood products within the 4 weeks prior to start of study drug, and pregnant or lactating women, or women of childbearing potential not using an acceptable method of contraception. Female patients at risk for pregnancy had to guarantee using an acceptable method of contraception (such as oral contraceptive or other recognized method if successfully used prior to onset of psychosis).

Randomization Procedure and Medication Dispensing

Patients who gave written informed consent and met all eligibility criteria were randomly allocated, in a 1:1 ratio, to receive either 200 mg/day or 400 mg/day of quetiapine for a period of 4 weeks. A computer-generated, block-balanced randomization list was generated and kept centrally. Sealed envelopes with the randomization key were kept in the clinical trials pharmacy in case of any serious adverse events. Blister packs were dispensed weekly for the first 4 weeks. Administration was double-blind during the initial 4 weeks of the trial (Part 1). Each blister pack contained enough medication for 1 week of treatment (plus 3 days' worth of additional quetiapine to cover variance in appointment times) with either 200 mg (100-mg tablet b.i.d.) or 400 mg (100-mg tablet in the morning/300-mg tablet at night) of equally sized quetiapine tablets per day. For each subject, 4 labeled blister packs were supplied. Labeling of study supplies was in compliance with applicable regulatory requirements. Although the protocol allowed for patients to be started on the 200-mg or 400-mg (double-blind, randomized) quetiapine dose, most psychiatrists titrated the dose up to 200 mg at the treating doctors' discretion, typically from a starting dose of 25 mg to 50 mg. The titration period was never longer than 7 days in accordance with the study protocol.

After completion of Part 1 (the double-blind, randomized, fixed-dose trial period), participants received commercial packs of quetiapine as prescribed by the treating psychiatrist for an additional 8 weeks (Part 2). The clinical trials pharmacist or his or her representative labeled and dispensed each individual blister pack from the commercial packs of quetiapine with name, date of birth, and dosage direction as prescribed by the treating psychiatrist.

Study Visits and Clinical Evaluation

A total of 6 face-to-face study visits were conducted (baseline assessment prior to commencement of the trial medication, followed by assessments at weeks 1, 2, 3, 4, and 12). We further performed monitoring phone calls at week 6, 8, and 10 to review and document adverse events. A window of ± 3 days was permitted for visits 2 through 5. A window of ± 7 days was permitted for visit 6. All raters undertook systematic psychopathology training in the context of annual rater workshops at the ORYGEN Research Centre; the ratings demonstrated good reliability, with intraclass coefficients of agreement ≥ 0.8, and all were within 20% of the standard scores.

Symptomatology and global functioning measures. Symptomatology ratings were done at all time points and were the BPRS, extended version 4,[16] the Scale for the Assessment of Negative Symptoms (SANS),[18] the Young Mania Rating Scale (YMRS),[19] the Calgary Depression Scale for Schizophrenia (CDSS),[20] the Clinical Global Impressions (CGI) scale,[21] the Global Assessment of Functioning scale (GAF),[22] and the Social and Occupational Functioning Assessment Scale (SOFAS).[23]

Tolerability and safety measures. Adverse events were assessed at all time points using a semistructured interview for the assessment of side effects of psychotropic medication, the Udvalg for Kliniske Undersogelser (UKU).[24] We did not use the Simpson-Angus scale for extrapyramidal side effects, as a previous controlled clinical trial[25] provided good correlation between the Simpson-Angus total score and the total score of the first 5 UKU neurologic items (Spearman correlation, 0.67). We also assessed attitudes toward medication using the Medication Adherence Rating Scale (MARS).[26] We further measured weight (body mass index) at baseline, week 4, and week 12. We took blood at baseline and at week 12, performing a full blood examination, urea and electrolyte levels, thyroid function test, liver function test, and glucose level (random). Female patients performed a serum pregnancy test at baseline or if clinically indicated during the trial period. We assessed vital signs: pulse and arterial blood pressure (sitting and standing).

Substance use measures. We considered substance use as a major confounding factor. In addition to the

substance use diagnosis from the SCID interview, we performed the Alcohol, Smoking and Substance Involvement Screening Test (a World Health Organization publication available at: http://www.who.int/substance_abuse/activities/assist/en/index.html) to assess substance abuse in the last 3 months prior to study inclusion.

Adverse events. All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship, were recorded adhering to Good Clinical Practice standards.

Concomitant Therapy

Any medication other than the study drugs specified in the protocol was considered concomitant medication and was recorded. Antipsychotic medication other than study medication used during the study period resulted in the patient being withdrawn from the study (except if prescribed for behavioral control as permitted by the study protocol). Patients meeting criteria for major depressive disorder (according to DSM-IV) were permitted to receive sertraline (50–200 mg/day). Use of anticholinergic medication, benzodiazepines (diazepam, lorazepam, temazepam), zolpidem, and zopiclone was permitted as clinically indicated and was recorded.

Data Analysis

Sample size justification. It was estimated that 50 completers (Monte Carlo simulations) per treatment group have a power of greater than 0.90 to detect various dose relationships, using a standard deviation of 15 for change in BPRS total score, resulting in a power of greater than 0.80 for pairwise comparison of parameters of interest. At the primary end point of the study (Part 2), i.e., after study completion and data verification, we counted 47 completers in each group.

Method of analysis. Table 1 presents the data for the treatment groups on demographic and primary efficacy measures at baseline. Note that statistical tests have not been used to compare the 2 groups in terms of their demographic and baseline characteristics. Such tests are deemed inappropriate for comparison of baseline characteristics (http://www.consort-statement.org/Explanation/examples15.htm).

Primary outcome analyses (Part 1)—efficacy. Of the 141 patients initially randomly assigned, the final intent-to-treat (ITT) population consisted of 126 patients who had 1 dose of study medication and had at least 1 post-baseline evaluation (Figure 1, CONSORT flowchart). We applied linear mixed-effects modeling (also called multilevel modeling or hierarchical modeling). For each measure, this method enables us to estimate the time trend for each treatment group over the 4 weeks and then to compare the groups in terms of time trend. As long as a subject has data for at least 2 time points, the subject can be included in the analysis (2 time points are enough to estimate the time trend). Additionally, change from baseline in each outcome variable at primary endpoint (week 4) was analyzed by a 2-way analysis of covariance (ANCOVA) model, extracting effects due to baseline psychopathology, gender, diagnostic grouping (affective versus nonaffective), duration of untreated psychosis, and illicit substance use as covariates to test for treatment difference between 200 mg/day and 400 mg/day of quetiapine for each outcome measure. Our primary outcome measures were change over time on the total and subscale scores of the BPRS (extended version 4), SANS, YMRS, CDSS, CGI, GAF, and SOFAS. Change scores were calculated for each outcome variable by subtracting baseline from follow-up score at each follow-up assessment time point for each patient. All statistical tests of significance were performed as 2-sided tests. Values of test statistics were considered statistically significant if $p < .05$.

We further compared response and remission rates between the 2 doses for each time point between baseline and week 4, as well as overall response rate. Response between baseline and any time point up to week 4 was defined by the following criteria: (1) at least a 20% reduction in BPRS total score as compared to baseline and (2) a CGI global improvement rating of at least minimally improved. A patient could switch his or her status as responder or nonresponder in any pattern across the study period. We further compared overall response between the 2 groups, which was fulfilled if a patient met response criteria at least once at any of the 4 assessment time points. Note that a conservative approach has been adopted to deal with missing values in the sense that missing values were taken to be failure to respond.

Remission was defined as (1) a score of ≤ 3 (i.e., mild) on each item of the BPRS psychotic subscale (suspiciousness, hallucinations, unusual thought content, and conceptual disorganization), (2) a CGI severity rating of mild or less, and (3) a CGI global improvement rating of at least minimally improved.

Analyses of 8-week follow-up period (Part 2). Only those who completed Part 1 (the fixed-dose part of the trial) were included in the analysis of Part 2. The number of subjects available for the analysis of Part 2 was 94, with 47 each in the 200-mg and 400-mg treatment groups. Efficacy measures were computed according to treatment group in the same way as above, to describe the naturalistic dose escalation according to initial treatment dose and investigate whether the initial treatment dose of quetiapine (200 mg vs. 400 mg) had an impact on medication dose and outcome at 12 weeks.

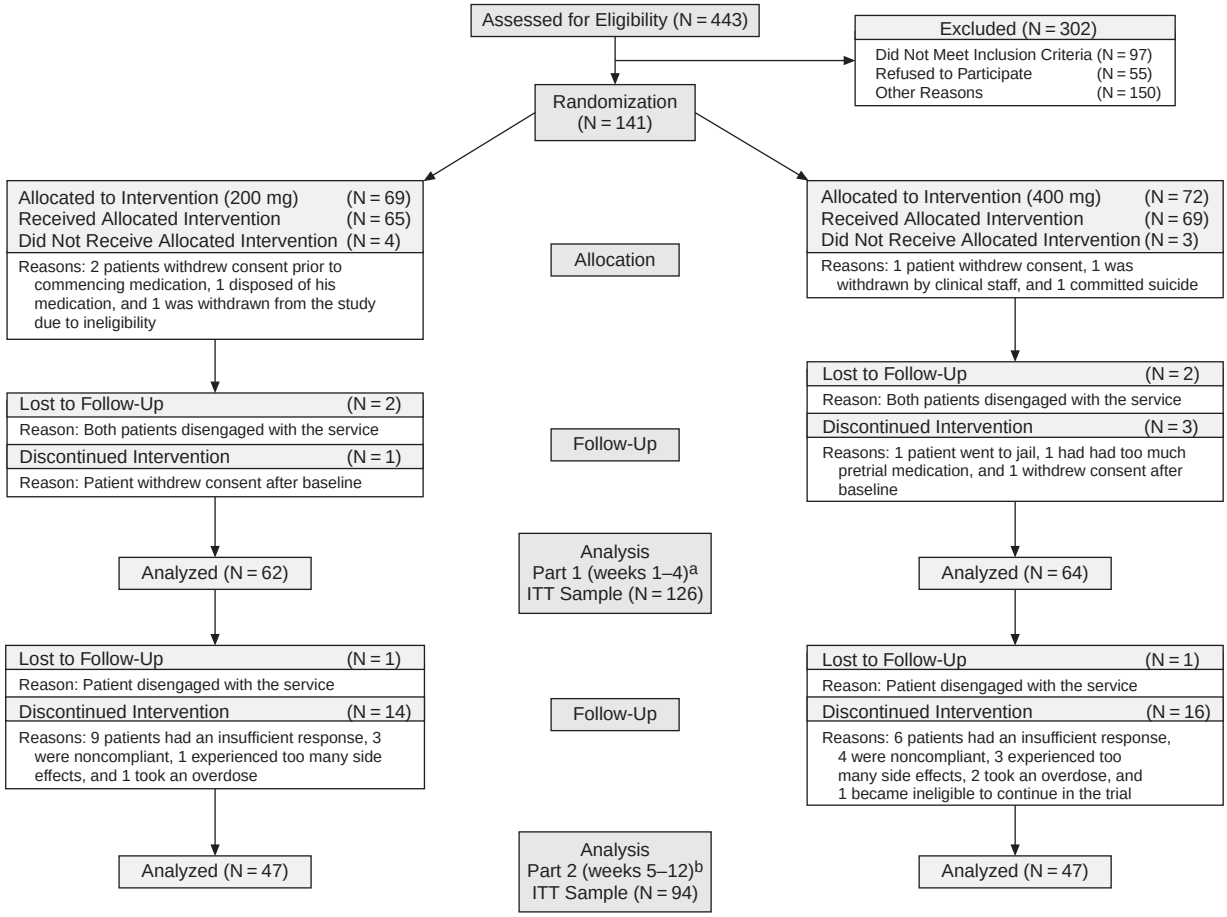
Secondary outcome analysis—tolerability. Tolerability was assessed using the UKU. In order to have a single measure of side effect for each UKU item, the mean rating over the 4-week trial period was computed for each UKU item. For cases with missing values, the mean rating was based on the nonmissing ratings only. With this

Table 1. Demographic and Baseline Characteristics of the Quetiapine 200-mg vs. 400-mg Comparison Groups in Part 1 of the Study

Characteristic by Group	Mean	Median	SD	Minimum	Maximum	Valid N
Age, y						
200 mg	19.7	20.0	2.6	15	24	62
400 mg	19.0	18.0	2.9	15	24	64
Duration of untreated psychosis, mo						
200 mg	7.6	3.0	13.6	0	72	59
400 mg	7.4	3.0	10.9	0	48	62
Percent male	Percent					
200 mg	71.0					62
400 mg	64.1					64
Percent with family history of schizophrenia						
200 mg	24.2					62
400 mg	18.8					64
Percent antipsychotic naive						
200 mg	32.3					62
400 mg	34.4					62
Percent with nonaffective psychosis diagnosis						
200 mg	75.8					62
400 mg	75.0					64
Percent with substance use diagnosis						
200 mg	40.3					62
400 mg	42.2					64
BPRS total score	Mean					
200 mg	67.0	66.5	9.8	50	92	62
400 mg	62.5	61.0	10.2	39	87	62
BPRS psychotic score						
200 mg	17.6	17.0	3.0	11	25	62
400 mg	16.2	16.0	3.3	9	25	62
SANS total score						
200 mg	39.0	40.0	16.1	11	70	62
400 mg	35.9	36.0	15.9	10	76	63
SANS affective flattening or blunting score						
200 mg	12.6	12.0	6.5	2	27	62
400 mg	12.7	13.0	6.3	0	26	63
SANS alogia score						
200 mg	7.0	7.0	3.8	0	14	62
400 mg	5.9	6.0	3.8	0	16	63
SANS avolition-apathy score						
200 mg	6.8	7.0	2.8	0	12	62
400 mg	6.1	6.0	2.9	0	13	63
SANS anhedonia-asociality score						
200 mg	8.5	8.5	3.6	2	16	62
400 mg	8.0	8.0	4.2	0	17	63
SANS attention score						
200 mg	4.1	4.0	2.8	0	8	62
400 mg	3.1	3.0	2.4	0	8	63
YMRS total score						
200 mg	11.6	10.0	7.2	2	28	61
400 mg	9.8	9.0	6.3	0	25	63
GAF score						
200 mg	44.7	42.0	10.8	20	75	62
400 mg	48.9	50.0	12.0	20	78	62
SOFAS score						
200 mg	47.0	46.5	11.6	25	80	62
400 mg	49.9	50.0	10.4	31	80	62
CGI-Severity of Illness score						
200 mg	5.2	5.0	0.8	3	7	62
400 mg	4.9	5.0	0.7	4	7	62
CDSS total score						
200 mg	8.8	9.0	4.5	0	17	62
400 mg	8.9	10.0	4.3	0	20	62
UKU total score						
200 mg	9.4	9.0	5.2	0	25	62
400 mg	12.3	10.0	8.2	1	54	63
UKU psychic total score						
200 mg	7.5	7.0	4.2	0	19	62
400 mg	8.3	8.0	4.0	0	22	63
UKU neurologic total score						
200 mg	0.5	0.0	1.1	0	5	62
400 mg	0.8	0.0	1.5	0	8	63
UKU autonomic total score						
200 mg	1.0	0.0	1.6	0	6	62
400 mg	2.0	1.0	3.0	0	17	63

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CGI = Clinical Global Impressions, GAF = Global Assessment of Functioning, SANS = Scale for the Assessment of Negative Symptoms, SOFAS = Social and Occupational Functioning Assessment Scale, UKU = Udvalg for Kliniske Undersogelser side effects rating scale, YMRS = Young Mania Rating Scale.

Figure 1. CONSORT Flowchart of Single-Center Study of Quetiapine 200-mg vs. 400-mg Dosing in Drug-Naive First-Episode Psychosis Patients



[a]Part 1 is a double-blind, controlled, 4-week, fixed-dose study comparing 200 mg/day vs. 400 mg/day of quetiapine.
[b]Part 2 is a single-blind (rater), open-label, flexible-dose study.
Abbreviations: CONSORT = Consolidated Standards of Reporting Trials, ITT = intent to treat.

procedure, of the 126 subjects included in the ITT analysis, 116 have nonmissing mean ratings for each UKU item. Note that each UKU item is rated on a 4-point scale of increasing severity ranging from 0 (no or doubtful) to 3 (severe). So it is of interest to compute the percentages of subjects that reported a mean severity rating for each UKU item. A mean rating ≥ 0 means that a particular side effect has appeared at least once across the trial; a mean rating ≥ 0.5 means that a particular side effect appeared either several times or with moderate to marked severity. We further computed the frequency at each time point and investigated whether side effects changed between baseline and week 4 and 12, respectively, according to treatment group, as well as for all participants.

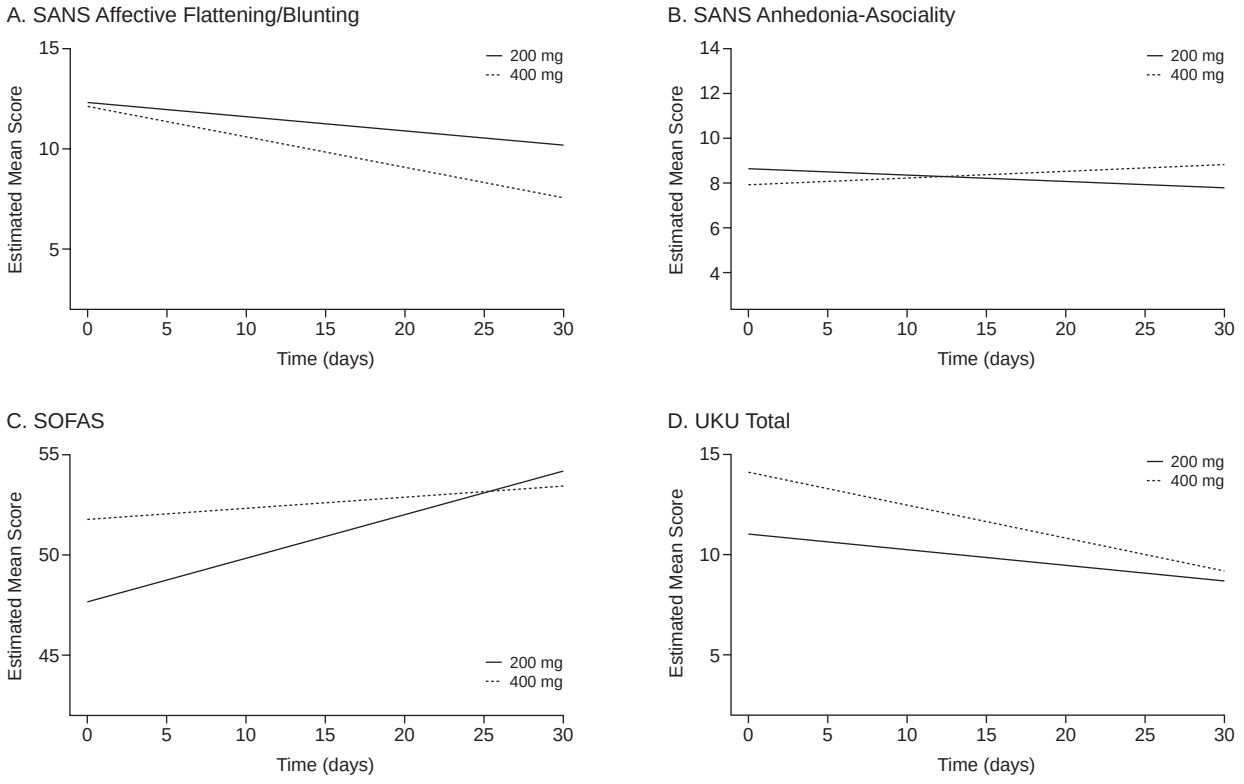
Safety measures. We calculated descriptive statistics for vital signs, weight, and blood examination results at baseline, week 4, and week 12 for the group as a whole, as well as according to treatment group.

RESULTS

Symptomatic Outcome and Overall Tolerability (Part 1)

The linear mixed-effects modeling indicates that efficacy between the 2 treatment groups was similar for most outcome measures except for 3 measures that were significant at the .05 level and 2 further measures that were at trend level (p value just above .05). These 5 measures are SANS anhedonia-asociality subscale (p = .011), SOFAS (p = .020), GAF (p = .070), SANS affective flattening or blunting subscale (p = .051), and UKU total (p = .056). Figure 2 presents the plots of the estimated time trends for these measures over the initial 4-week period, suggesting that the 200-mg group improved more for the SANS anhedonia-asociality subscale, whereas the 400-mg group showed a slight deterioration. SOFAS and GAF, as measures of social and global functioning,

Figure 2. Linear Mixed-Effects Model Analysis of Time Trends for Selected Rating Scales by 200-mg and 400-mg Quetiapine Intervention Groups in Part 1 of the Study



Abbreviations: SANS = Scale for the Assessment of Negative Symptoms, SOFAS = Social and Occupational Functioning Assessment Scale, UKU = Udvalg for Kliniske Undersogelser side effects rating scale.

respectively, also improved significantly more in the 200-mg group than in the 400-mg group. However, both measures started at a lower level in the 200-mg group, meaning that they may have had more room to improve. Furthermore, the 200-mg group tended to show less overall side effects as measured with the UKU side effect scale. Incorporating as covariates gender, age, duration of untreated psychosis, diagnostic grouping (affective vs. nonaffective), baseline illicit substance use in the past 3 months (yes/no), cumulative pretrial antipsychotic dose (chlorpromazine equivalent), and MARS total score did not change these results irrespective of whether the covariates were considered individually or altogether. Finally, even though the 400-mg group appeared to show more improvement (a steeper line) for the SANS affective flattening or blunting subscale, this finding was not significant after adjusting for all covariates.

Table 2 shows the mean outcome scores for behavioral and tolerability measures at baseline and week 4. ANCOVA has been applied to compare the 2 treatment groups in terms of the change in scores between week 4 and baseline, with baseline scores as covariates. A significant difference between the 2 groups is found on 1 measure only, namely the SANS anhedonia-asociality subscale (mean = –0.7 [SD = 3.2], p = .032), and confirms the results of the mixed-model analysis indicating that the 200-mg group shows a decrease in social withdrawal, whereas the 400-mg group shows a worsening (mean = 1.1 [SD = 3.3]). Incorporating the same covariates as described above in our ANCOVA model does not change any of the results reported above irrespective of whether the covariates are considered individually or altogether.

Symptomatic and Functional Outcome (Part 2)

Linear mixed-effects modeling was used again to analyze the time trends between baseline and week 12. Our analysis includes only 3 outcome measures, namely the GAF, SOFAS, and CGI-Severity of Illness score, as these were the only measures that had extra assessments at weeks 6, 8, and 10 between week 4 and week 12. The results indicate that there is no significant difference between the 2 treatment groups in terms of time trends from baseline to week 12. Furthermore, ANCOVA was applied to compare the 2 treatment groups in terms of change in score on the outcome measures between baseline and week 12. The baseline score was used as a covariate to account for baseline symptomatology. A significant difference between the 2 groups was found on the

Table 2. Symptomatology According to Rating Scale Scores Between Baseline and Week 4 in Part 1 of the Study

	200-mg Quetiapine Group (N = 46)		400-mg Quetiapine Group (N = 45)	
Rating Scale	Mean	SD	Mean	SD
BPRS total				
Baseline	66.7	9.4	59.4	8.2
Week 4	51.2	11.0	47.1	12.1
BPRS psychotic				
Baseline	17.6	3.0	15.2	2.7
Week 4	11.9	3.7	10.6	3.2
SANS total				
Baseline	39.2	16.9	32.6	13.9
Week 4	31.1	17.2	26.1	14.0
SANS affective flattening or blunting				
Baseline	13.0	6.8	11.8	5.7
Week 4	10.5	6.7	7.7	5.7
SANS alogia				
Baseline	6.9	3.9	5.4	3.6
Week 4	4.7	3.6	3.0	3.0
SANS avolition-apathy				
Baseline	6.7	2.9	5.3	2.7
Week 4	5.5	3.0	4.7	2.8
SANS anhedonia-asociality				
Baseline	8.3	3.5	7.3	3.9
Week 4	7.6	3.7	8.4	4.0
SANS attention				
Baseline	4.3	2.8	2.9	2.2
Week 4	2.8	2.4	2.4	2.2
YMRS total				
Baseline	10.9	6.8	8.8	6.3
Week 4	8.9	7.1	6.4	7.4
GAF				
Baseline	45.1	10.8	51.0	11.3
Week 4	52.9	13.9	55.3	10.7
SOFAS				
Baseline	46.6	11.9	51.9	9.9
Week 4	53.8	13.2	53.7	10.3
CGI-Severity of Illness				
Baseline	5.2	0.9	4.8	0.6
Week 4	4.1	1.0	3.7	0.8
CDSS total				
Baseline	8.8	4.6	8.3	4.0
Week 4	5.5	3.5	5.8	4.2
UKU total				
Baseline	9.6	5.2	12.2	8.7
Week 4	7.8	5.3	9.0	7.1
UKU psychic total				
Baseline	7.6	4.1	8.3	4.1
Week 4	5.8	4.3	5.8	4.2
UKU neurologic total				
Baseline	0.6	1.2	0.7	1.2
Week 4	0.2	0.6	0.6	1.4
UKU autonomic total				
Baseline	1.1	1.7	2.0	3.2
Week 4	1.4	1.5	1.7	1.9

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CGI = Clinical Global Impressions, GAF = Global Assessment of Functioning, SANS = Scale for the Assessment of Negative Symptoms, SOFAS = Social and Occupational Functioning Assessment Scale, UKU = Udvalg for Kliniske Undersogelser side effects rating scale, YMRS = Young Mania Rating Scale.

CGI-Severity of Illness scale (p = .026). The ANCOVA results indicate that the 400-mg group showed a slightly bigger decrease on the CGI severity scale (mean = –1.8 [SD = 1.1]) compared to the 200-mg group (mean = –1.5 [SD = 1.0]). However, the rate difference was small (with a CGI change-score difference of 0.3). On the other hand, a higher percentage of subjects in the 200-mg group remained on quetiapine (90.2% vs. 77.5%) in comparison with the 400-mg group, although this finding did not reach the level of significance (Fisher exact test, p = .14). Analysis incorporating the covariates mentioned above did not change the results irrespective of whether the covariates were considered individually or altogether.

Response and Remission Rates (Part 1)

Table 3 gives the response and remission rates for the 2 groups at each time point during the first 4 weeks. The part labeled "Overall" gives the percentage of subjects who met criteria for response or remission at least once in any of the 4 weeks. It can be seen that the 200-mg treatment group had consistently higher percentages of responders all through the 4 weeks as well as overall. However, none of the p values are significant at the .05 level, although some are quite small. Looking at remission, the opposite picture emerges—the 400-mg treatment group seemed to be doing better at week 4 (p = .08). However, again none of the p values are significant.

Response and Remission Rates (Part 2)

Response and remission rates between the 2 groups did not differ significantly (Table 4); however, numerically, a higher proportion of patients treated in the 400-mg group met response criteria (57.6% vs. 46.2%, p = .33) and remission criteria (31.9% vs. 23.4%, p = .36). Note that since Part 2 was not a fixed-dose trial and the clinicians were allowed to change medication and dosage as they saw fit, it would be unreasonable to regard those with missing values as nonresponders or as not being in remission. So the results presented in Table 4 are based on only those cases that have valid values at week 12.

Overall Dropout Rates and Reasons for Dropout (Part 1)

The overall dropout rates of the 2 treatment groups were very similar (24.2% for the 200-mg group vs. 26.6% for the 400-mg group) and were not significantly different (χ^2 test, p = .76). Table 5 additionally describes the reasons for dropout in each case. However, the number of subjects per cell is too small to reach the level of statistical significance (Fisher exact test, p = .82). The data may be suggestive that a higher proportion of patients in the 200-mg treatment group dropped out due to insufficient response (60% vs. 35%), whereas a higher proportion in the 400-mg treatment group dropped out due to too many side effects (18% vs. 7%).

Dose Escalation and Average Maintenance Dose of Quetiapine (Part 2)

Linear mixed-effects modeling was applied to compare the 2 treatment groups in terms of the time trends of daily dosage during Part 2 of the trial. All subjects (N = 94) who completed Part 1 were included in the

Table 3. Response and Remission Rates by Week in Part 1 of the Study According to Quetiapine Treatment Group

	Week 1		Week 2		Week 3		Week 4		Overall	
Response or Remission	%	p Value	%	p Value	%	p Value	%	p Value	%	p Value
Response										
200-mg group (N = 62)	27.4	.06	35.5	.09	33.9	.37	32.3	.27	61.3	.10
400-mg group (N = 64)	14.1		21.9		26.6		23.4		46.9	
Remission										
200-mg group (N = 62)	4.8	.97	6.5	.37	8.1	.41	8.1	.08	14.5	.20
400-mg group (N = 64)	4.7		10.9		12.5		18.8		23.4	

Table 4. Response and Remission Rates in Part 2 of the Study by Quetiapine Treatment Group

	Response		Remission	
Treatment Group	%	p Value	%	p Value
200 mg (N = 62)	46.2	.33	23.4	.36
400 mg (N = 64)	57.6		31.9	

Table 5. Reasons for Dropping Out During Part 1 of the Study by Quetiapine Treatment Group and by Total Sample

Reason for Dropping Out	200-mg Group	400-mg Group	Total Sample
Overdose			
Count	1	2	3
Percent within group	6.7	11.8	9.4
Insufficient response			
Count	9	6	15
Percent within group	60.0	35.3	46.9
Subject ineligible to continue the trial			
Count	0	1	1
Percent within group	0.0	5.9	3.1
Subject lost to follow-up			
Count	1	1	2
Percent within group	6.7	5.9	6.3
Subject noncompliant			
Count	3	4	7
Percent within group	20.0	23.5	21.9
Too many side effects			
Count	1	3	4
Percent within group	6.7	17.6	12.5
Total			
Count	15	17	32
Percent within group	100.0	100.0	100.0

mixed-effects modeling analysis. The 200-mg group had a faster rate of increase in prescribed daily dosage. However, the difference in rate did not reach significance (p = .19). The mean daily dose of antipsychotic medication at week 12 did not differ significantly between the 200-mg and 400-mg groups (242.3 mg [SD = 97.7 mg] vs. 299.5 mg [SD = 215.9 mg], respectively, p = .13). When 1 outlier in the 400-mg group who received 1500 mg/day of quetiapine (a protocol violation) was excluded from the analysis, the mean dosage of the 400-mg group dropped to 269.5 mg/day (SD = 101.0 mg). A higher percentage of subjects in the 200-mg group remained on quetiapine treatment (90.5% vs. 78.0%). However, the difference did not reach significance (Fisher exact test, p = .14).

Table 6. Number of Days in Hospital According to Quetiapine Treatment Group

Treatment Group	Mean	Median	SD	Minimum	Maximum	Valid N
200 mg	17.4	11.5	17.8	1	84	20
400 mg	9.6	8.0	7.8	3	26	7

Hospital Admission Rate and Number of Days in Hospital

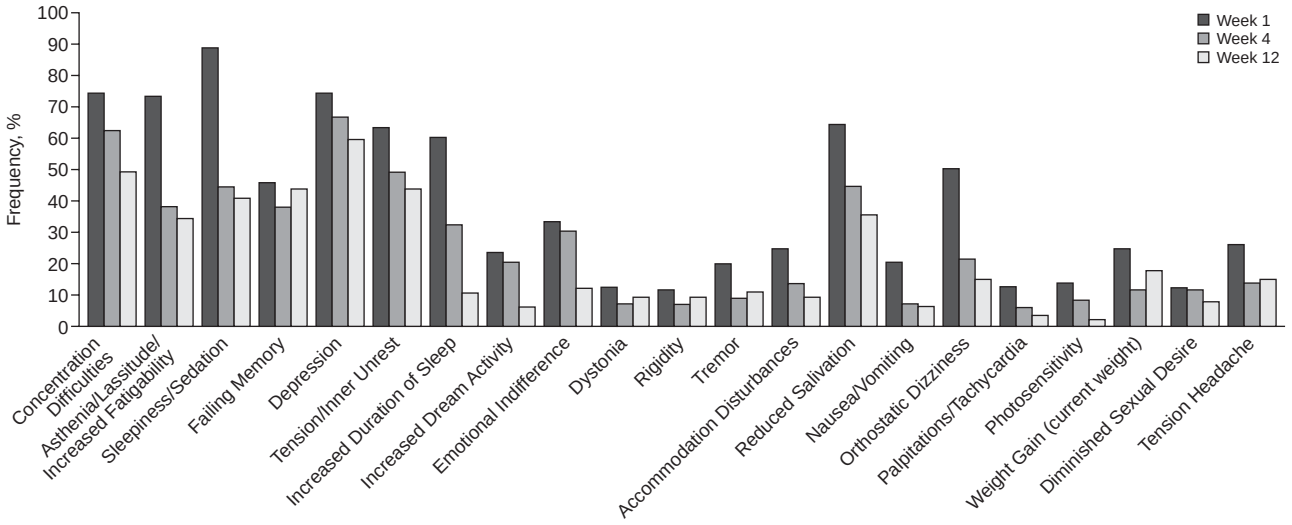
The raw data of the whole sample indicate that the 200-mg group had a higher hospital admission rate (50.5% in the 200-mg group vs. 26.6% in the 400-mg group; χ^2 test, p = .005). However, the proportion of subjects in the 200-mg group recruited while admitted to hospital was much larger than the proportion in the 400-mg group (Table 6). If we compare the admission rate of only those who were recruited as outpatients and were admitted thereafter, the difference in admission rate between the 2 treatment groups is markedly smaller (21.3% for the 200-mg group vs. 17.2% for the 400-mg group) and the χ^2 test p value is .56. Post hoc analysis of the subgroup that had hospital admissions during the 12-week trial suggests that, for those who had been admitted to hospital, the 200-mg group had a higher mean number of days in hospital (17.4 vs. 9.6). However, the difference does not reach statistical significance (t test, p = .26), in particular after excluding 1 extreme outlier (p = .57).

Tolerability (Parts 1 and 2)

Figure 3 shows all UKU items that were reported more frequently than 10%. Overall, one can see that side effects were reported most frequently at week 1. The frequency of reported side effects dropped dramatically across the trial. At week 12, predominantly psychological UKU items (sedation, concentration difficulties, memory problems, depression, asthenia) were still reported relatively frequently (up to 40%), whereas most of the other reported side effects dropped to less than 10%, except for reduced salivation, tension headache, tremor, orthostatic dizziness, emotional indifference, and weight gain, which were just above 10%.

Nine of 10 drug-naive first-episode patients reported some sedation after 1 week of treatment, but the difference between the groups did not reach significance.

Figure 3. Frequency of Reported UKU Side-Effect Items Across the Trial[a]



[a]The total N varies according to the time point: N = 90 for weeks 1 and 4, and N = 69 for week 12.
Abbreviation: UKU = Udvalg for Kliniske Undersogelser side effects rating scale.

Table 7. Udvalg for Kliniske Undersogelser (UKU) Side Effect Items Significantly Differing Between Quetiapine Treatment Groups

	Mean Rating, Baseline to Week 4						Mean Rating, Baseline to Week 12					
	Mean Rating > 0[a]			Mean Rating > 0.5[b]			Mean Rating > 0[a]			Mean Rating > 0.5[b]		
UKU Item by Group	%	N	p Value	%	N	p Value	%	N	p Value	%	N	p Value
1.6 Tension/inner unrest												
200 mg	88.7	53	.081	67.9	53	.316	92.1	38	.054	76.3	38	.075
400 mg	75.0	52		57.7	52		74.2	31		54.8	31	
1.7 Increased duration sleep												
200 mg	73.6	53	1	45.3	53	.698	79.0	38	.76	36.8	38	.055
400 mg	75.0	52		50.0	52		83.9	31		61.3	31	
1.8 Reduced duration sleep												
200 mg	47.2	53	.001	18.9	53	.072	55.3	38	.001	21.1	38	.035
400 mg	15.4	52		5.8	52		12.9	31		3.2	31	
2.5 Tremor												
200 mg	24.5	53	.098	11.3	53	.05	29.0	38	.307	13.2	38	.217
400 mg	40.4	52		26.9	52		43.3	30		26.7	30	
3.3 Reduced salivation												
200 mg	67.9	53	.035	49.1	53	.028	73.7	38	.002	55.3	38	.019
400 mg	86.5	52		71.2	52		100	30		83.3	30	
4.5 Weight gain												
200 mg	35.9	53	.079	11.3	53	.741	42.1	38	.09	13.2	38	1
400 mg	53.9	52		7.7	52		64.5	31		12.9	31	

[a]A mean rating of ≥ 0 means that a particular side effect has appeared at least once across the trial.
[b]A mean rating of ≥ 0.5 means that a particular side effect appeared either several times or with moderate to marked severity.

However, numerically, one half of the 200-mg group versus two thirds of the 400-mg group reported moderate to marked sedation in the initial 4 weeks of treatment. Orthostatic dizziness was also reported quite commonly, with 60% in the 200-mg group and 70% in the 400-mg group reporting some dizziness, and 14% in the 200-mg group versus 22% in the 400-mg group reporting moderate to marked dizziness. Once again, the difference between the groups did not reach statistical significance. Less frequent but still important was the finding that some patients experienced paresthesias (5.3% in the 200-mg group and 18.6% in the 400-mg group), with the rate difference also not reaching statistical significance.

A clear dose response characteristic was found for 5 items (Table 7). The rate difference of reported side effects between the 2 treatment groups was relevant for changes in sleep pattern, with more patients reporting reduced sleep in the 200-mg group and more patients reporting increased sleep in the 400-mg group. Unexpected was the finding that more than twice as many patients

Table 8. Weight Changes Across the Trial (at week 4 and week 12) by Quetiapine Dosage Group and by Total Subjects

Weight-Change Variable	Mean	Median	SD	Minimum	Maximum	Valid N	p Value for t Test
Week 4 weight minus baseline weight, kg							
200-mg group	2.3	1.0	3.1	–3	9	27	.90
400-mg group	2.4	3.0	2.5	–3	9	33	
All subjects	2.4	2.0	2.8	–3	9	60	
Week 12 weight minus baseline weight, kg							
200-mg group	2.3	1.0	3.5	–3	10	15	.94
400-mg group	2.2	2.0	3.9	–4	8	18	
All subjects	2.2	2.0	3.7	–4	10	33	

receiving 400 mg than 200 mg reported moderate tremor within the first 4 weeks (mean rating of > 0.5 in 26.9% vs. 11.3%, respectively, p = .05). Reduced salivation was another commonly reported side effect with an average rate difference between the groups of about 20%, with more patients reporting a dry mouth in the 400-mg group compared to the 200-mg group across the whole trial period. Again, the latter suggests a clear dose dependency for this side effect and is in line with recently published data.[27] Particularly important for this young population is the finding that 14% in the 200-mg group and 19% in the 400-mg group reported some sexual side effects, with 7% versus 14%, respectively, describing moderate to marked sexual side effects. Again, the rate difference between the groups was not significant. Twice as many first-episode patients reported tension headache in the 400-mg group compared to the 200-mg group, although the rate differences between the 2 treatment groups did not reach statistical significance.

Finally, more patients reported weight gain in the 400-mg group than in the 200-mg group. However, there was no difference in absolute weight change measured in kg between baseline and week 4 or 12, respectively (Table 8). The mean weight gain was 2.0 to 2.5 kg and happened mainly within the first 4 weeks of treatment, without reaching statistical significance between the 2 treatment groups. Interestingly, the range of weight gain was quite large, with some patients losing up to 4 kg and others putting on up to 10 kg in weight (the variance is most likely the reason why no statistically significant result for mean weight change could be demonstrated between the treatment groups).

DISCUSSION

We recruited 141 drug-naive first-episode psychosis patients into a controlled, randomized, double-blind, single-center treatment study of either 200 mg or 400 mg of quetiapine for a period of 4 weeks (Part 1). Around 75% of patients completed Part 1, and the final intent-to-treat sample was 126 patients. The 200-mg group showed less social withdrawal (lower SANS anhedonia scores) and slightly better social and global functioning, as well as fewer general and extrapyramidal side effects. The 200-mg dose group had a higher initial response rate compared to the 400-mg dose group. However, it seems that the 400-mg dose group showed a trend for higher remission rates toward the end of the randomized trial period. Sedation, altered sleep, concentration difficulties, asthenia, depression, and orthostatic dizziness were the most commonly reported side effects in drug-naive first-episode psychosis patients, without a statistically significant difference between treatment groups. Most of the initially reported side effects diminished or disappeared within 4 weeks. An unexpected finding was that of a dose dependency of some of the side effects—e.g., twice as many drug-naive first-episode patients reported some tremor in the 400-mg group compared to the 200-mg group, and nearly 50% more reported reduced salivation.

The completers of Part 1 of the study entered a single-blind, flexible-dose study of 8 weeks' duration (Part 2; 94 patients). In the second part of the study, only 7 additional patients dropped out of the 200-mg group, whereas 14 more patients dropped out of the 400-mg group. About 1 in 4 patients had remitted by week 12 (23.4% for the 200-mg group and 31.9% for the 400-mg group, with χ^2 test p = .36). The mean dose for the 2 groups at week 12 was not significantly different. The mean maintenance dose of quetiapine at 3 months was 268 mg/day and was lower than that in previous first-episode psychosis studies.[4,8] There are several potential explanations. First, our sample consisted of a relatively young group of drug-naive first-episode psychosis patients. About half of them did not meet criteria for schizophrenia but rather for other types of psychosis, such as schizophreniform psychosis, major depression with psychotic features, or psychosis not otherwise specified. Illness severity and illness course are therefore primary mitigating factors. Second, a large proportion of patients were outpatients, and it is quite likely that these patients would require lower doses than inpatients, who may receive quetiapine not only as an antipsychotic, but also for sedation. Third, while not statistically significant, a higher percentage of patients met response and remission criteria on the 400-mg dose of quetiapine, and this subgroup also had shorter hospital stays, suggesting that the higher dose might have been slightly more effective than the lower dose, in particular in the inpatient setting. Conversely, however, the 200-mg group showed greater tolerability (also without reaching statistical significance). Taken together, both findings indicate that dosing has to be carefully considered in drug-naive first-episode psychosis patients, with rapid dose escalation potentially resulting in reduced treatment adherence due to tolerability issues, and with insufficient dosing resulting in poor treatment response due to lack of efficacy. We

believe that our results reflect that ORYGEN psychiatrists, as specialists in the field of optimal treatment of early psychosis, tried to find the optimal balance between efficacy and tolerability. Furthermore, some previous studies allowed only doses higher than 300 mg, and dose recommendations were based on chronic schizophrenia (potentially biasing dosing toward higher doses), whereas our study allowed flexible dose adaptation as clinically indicated. Interestingly, clinicians did not increase to higher doses during Part 2 of the study despite the fact that they had the opportunity to do so. We were surprised that only a very few patients ended up on high doses despite the option for clinicians to increase the dose as clinically indicated after week 4. In fact, the mean dose of 268 mg/day suggests that clinicians decided to reduce the dose in the majority of first-episode psychosis patients who were initially treated with 400 mg/day rather than increase it. The latter supports our decision to compare 200 mg versus 400 mg in Part 1, indicating that we chose an appropriate dose range.

The admission rate of patients recruited as outpatients was similar in both groups, and the number of days in hospital was not statistically different between the groups, in particular after removing 1 extreme outlier (which explained the relatively large difference between median and mean in terms of number of days in hospital). It is unclear whether higher doses are necessary in the inpatient setting. In particular, our finding that more patients in the 200-mg group reported tension is suggestive that 200 mg may be too low in an inpatient setting or that, besides using higher doses of quetiapine, the initial addition of benzodiazepines should also be considered for the acute phase to prevent unnecessary dose escalation of quetiapine.

A limitation of our study is that the total number of participants and completers may have been too small to detect small differences in efficacy and tolerability between the groups. Our current sample size enabled us to demonstrate that 5 UKU items (tension, sleep pattern, salivation, tremor, weight) differed between the 2 treatment groups. However, for these 5 items, the rate difference between the groups was relatively small, and the majority of patients no longer experienced side effects at week 12. The raw data for other UKU items pointed in the same direction, with the 400-mg group showing more side effects than the 200-mg group but without reaching the level of significance. It may be that the study was underpowered to demonstrate slight differences between the 2 quetiapine treatment groups for the other UKU items. The clinical relevance of such small differences is questionable. However, on an individual basis, the monitoring of side effects is of major importance to prevent early drug discontinuation.

In conclusion, our study suggests that quetiapine fumarate is a safe and well-tolerated antipsychotic medication at an initial target dose of 250 mg/day to 300 mg/day in drug-naive first-episode psychosis patients. Dose titration should be cautious, and side effects should be monitored carefully. If clinically indicated, further dose escalation in drug-naive first-episode psychosis patients should be slow and side effects should be addressed to reduce the risk of noncompliance. The proposed target dose is about 50% of doses employed in more recent studies of multiepisode patients.[28–31] The latter confirms that the landmark study of McEvoy et al.[10] demonstrating that drug-naive first-episode patients need about 50% less typical neuroleptic than multiepisode schizophrenia patients is also true for the atypical antipsychotic quetiapine. Our finding is of particular importance, considering contemporary clinical practice that increasingly appears to involve escalating the quetiapine dose very quickly to 600 to 800 mg, without allowing adequate time at lower doses (e.g., 2–3 weeks at 300 mg) prior to further dose escalation. We believe that our study provides some evidence that the dosing strategy in drug-naive first-episode patients is different from that for multiepisode patients and that rapid dose escalation may result in increasing noncompliance due to tolerability issues early in the treatment course. We therefore recommend that in drug-naive first-episode psychosis patients an initial target dose of 250 to 300 mg should be maintained for 2 weeks and that clinicians should further increase the dose only if patients do not show a clinically meaningful response after this time. Future studies may consider genetic variation (e.g., cytochrome P450 3A4) to better explain and eventually predict the large variations in dosing and side effects associated with quetiapine fumarate.

Drug names: diazepam (Valium and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), temazepam (Restoril and others), zolpidem (Ambien and others), zopiclone (Lunesta).

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