Clinical Study Report

Drug substance:	Quetiapine fumarate
Study code:	D1441L00002
Date:	04 April 2006

Efficacy and Tolerability of Olanzapine, Quetiapine and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52 Week Comparison

Study dates:	First subject enrolled: 15 March 2002 Last subject enrolled: 22 February 2005
Phase of development:	Therapeutic use (IV)
International Co-ordinating Investigator:	Jeffrey A. Lieberman, MD Psychiatrist-in-Chief, New York Presbyterian Hospital & Columbia University Medical Center 1051 Riverside Drive - Unit #4 New York, New York 10032
Sponsor's Responsible Medical Officer:	Martin Brecher, MD

This study was performed in compliance with Good Clinical Practice.

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Drug substance(s):	quetiapine fumarate	**SYNOPSIS**	
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Date:	06 April 2006		

Efficacy and Tolerability of Olanzapine, Quetiapine and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52 Week Comparison

International co-ordinating investigator

Jeffrey A. Lieberman, MD

Study centre(s)

This study was conducted in 24 centers in the USA, and 2 centers in Canada.

Publications

Marx C. Comparison of atypicals in first-episode psychosis (CAFE): A randomized, 52-week comparison of olanzapine, quetiapine, and risperidone. Oral report presented at the *World Congress of Biological Psychiatry*. 2005 June 28-July 3; Vienna, Austria.
Lieberman J, McEvoy JP, Perkins D, Hamer R. Comparison of atypicals in first-episode psychosis: a randomized, 52-week comparison of olanzapine, quetiapine, and risperidone. Eur Neuropsychopharmacol. 2005;15(Suppl 3):S525. Erratum in: *Eur Neuropsychopharmacol*. 2005;15(Suppl 3):S526.
McEvoy JP, Lieberman JA, Perkins D, Hamer RM. Comparison of Atypicals in First-Episode Psychosis (CAFE): A Randomized, 52-Week Comparison of Olanzapine, Quetiapine, and Risperidone. Poster presented at the *US Psychiatric and Mental Health Congress*. 2005 November 7-10; Las Vegas, Nevada, USA.
Keefe R, Gu H, Perkins D, McEvoy J, Hamer R, Lieberman J. A Comparison of the Effects of Olanzapine, Quetiapine, and Risperidone on Neurocognitive Function in First-Episode Psychosis. *Neuropsychopharmacology*. 2005;30(Suppl 1):S192.
McEvoy JP, Lieberman JA, Perkins D, Hamer RM. Comparison of Atypicals in First-Episode Psychosis (CAFE): A Randomized, 52-Week Comparison of Olanzapine, Quetiapine, and Risperidone. *Neuropsychopharmacology*. 2005;30(Suppl 1):S201.
Keefe RSE, Gu H, Perkins D, Hamer RM, Lieberman JA. The effects of olanzapine, quetiapine, and risperidone on neurocognitive function in first-episode psychosis: A double-blind, 52-week comparison. *Schizophr Res*. 2006;81(Suppl 1):S54.
McEvoy JP, Lieberman JA, Perkins D, Hamer RM. Comparison of olanzapine, quetiapine, and risperidone in first-episode psychosis: A randomized, 52-week trial. *Schizophr Res*. 2006;81(Suppl 1):S22.

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Keefe R, Gu H, Perkins D, McEvoy J, Hamer R, Lieberman J. A Comparison of the Effects of Olanzapine, Quetiapine, and Risperidone on Neurocognitive Function in First-Episode *Psychosis. Eur Psychiatry*. 2006:21(Suppl 1).

Study dates		**Phase of development**
First subject enrolled	15 March 2002	Therapeutic use (IV)
Last subject completed	22 February 2005	

Objectives

Primary objective

To evaluate the effectiveness of olanzapine, quetiapine, and risperidone in the treatment of the first episode of psychosis. The primary outcome variable to evaluate effectiveness is "all cause pharmacologic treatment discontinuation," as reflected by the proportion of patients that discontinue from the study prior to 52 weeks of treatment.

Secondary objective

To evaluate the effectiveness of olanzapine, quetiapine, and risperidone in the treatment of the first episode of psychosis by comparing the time to "all-cause pharmacologic treatment discontinuation."

To examine the efficacy of olanzapine, quetiapine, and risperidone in treating symptoms of schizophrenia, as follows:

- Effects on total symptoms, and on positive, negative, mood, insight into illness (ITAQ) and substance use symptoms at 12, 24 and 52 weeks (or LOCF) of treatment, as measured by change from baseline in PANSS total score, positive and negative sub-scales, the Calgary Depression Rating Scale, and substance use (AUS/DUS).
- Effects on neurocognition (attention, memory, executive function, social cognition) at 12 and 52 weeks (or LOCF), as measured by change from baseline
- The proportion of individuals that are remitted (defined as no item on the PANSS > 3 and CGI rated "mildly ill" or less).
- Time to illness remission.
- Proportion of subjects that end study participation due to lack of efficacy prior to 52 weeks of treatment.
- Quality of life (QOL) and service utilization outcomes at 12, 24 and 52 weeks (or LOCF).

To compare the tolerability of olanzapine, quetiapine, and risperidone in first episode patients as indicated by:

0 Risk of akathisia (Barnes global score >2), Parkinsonian symptoms (Simpson Angus total score > 3), and clinically significant EPS (indicated by treatment with benztropine, lorazepam or propranolol for treatment of medication side effects at any time prior to the evaluation time point) at 12, 24 and 52 weeks (or LOCF) of treatment.

1 Proportion of subjects that end study participation due to intolerance prior to 52 weeks of treatment.

2 Proportion of subjects that have a clinically significant increase in weight (increase in BMI of 3 or more points) and proportion of subjects that are obese (BMI > 30) at 12, 24, and 52 weeks of treatment.

3 Mean change in fasting cholesterol, triglycerides, HgA1c and glucose at 12, 24 and 52 weeks (or LOCF) of treatment.

4 Mean change in prolactin, estrogen or testosterone level and proportion of subjects with sexual adverse effects at 12 and 52 weeks (or LOCF) of treatment.

5 Change (baseline to highest value) of: akathisia (Barnes Akathisia Scale), Parkinsonism (Simpson-Angus Rating Scale), weight gain and frequency of adverse events at 12, 24 and 52 weeks (or LOCF) of treatment.

6 Overall adherence to treatment at 12, 24 and 52 weeks (or LOCF). Adherence is defined on a 4-point likert scale, rated after a structured clinical interview (please see Source Document for details, adherence is rated as: 1=always/almost always, 76-100% of the time; 2=Usually, 51-75% of the time; 3=Sometimes, 26- 50% of the time; 4=Never/Almost never, 0-25% of the time).

Study design

This was a 52-week, randomized, double-blind, flexible-dose, multicenter study comparing the efficacy and tolerability of olanzapine, quetiapine and risperidone in the treatment of first episode psychosis.

Target subject population and sample size

First-episode patients with DSM-IV diagnoses of schizophrenia, schizophreniform, or schizoaffective disorder. 132 patients per treatment arm to ensure an overall statistical power of 80% with an overall statistical significance level of a=0.05 and a non-inferiority margin of 0.2. To preserve power and statistical significance each comparison (quetiapine vs risperidone, and quetiapine vs olanzapine) was powered at 90% with a statistical significance of a=0.025.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

- Quetiapine, 100mg capsules, BID (AstraZeneca lots: 6083C, 7536F)
- Risperdone: 0.5mg tablets, BID (Janssen lots: 91P1062E, 93P0034, 3LG453)
- Olanzapine: 2.5 mg tablets, BID (Eli Lilly lots: 5AG24M, 6AF59M, 7EC95M

Any previous antipsychotic therapy was tapered and discontinued during the first 2 weeks of double-blind treatment. On days 1 and 2, each patient received one capsule daily in the evening of olanzapine (2.5 mg), quetiapine (100 mg), or risperidone (0.5 mg). At the

treating physician's discretion, this dose could be increased by one capsule every other day,up to a maximum of four capsules BID.

Duration of treatment

52 Weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics
Criteria for evaluation were defined as part of objectives in the clinical protocol See objectives section above. In addition, the Symptom Onset in Schizophrenia (SOS) Scale, and the Structured Clinical Interview for DSMIV disorders were assessed at baseline.

Safety

Safety assessment included: serious adverse events, spontaneously reported adverse events, elicited adverse events of special interest (daytime drowsiness, weight gain, increased sleep hours, insomnia, menstrual irregularities, sex drive, akinesia, dry mouth, akathisia, sexual arousal, sexual orgasim, orthostatic faintness, constipation, sialorrhea, skin rash, gynecomastia, urinary hesitancy, incontinence/nocturia, and galactorrhea), hematology and chemistry findings, vital signs, Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movements Scale (AIMS).

Statistical methods

Statistical analyses tested for non-inferiority of quetiapine versus risperidone, and quetiapine versus olanzapine in all-cause treatment discontinuation rates up to 52 weeks (primary outcome measure). This was tested using Blackwelder's non-inferiority normal approximation with a pre-specified 20% non-inferiority margin, and using a significance level of 0.025 for each of the 2 pair-wise comparisons. Efficacy measures were tested using a mixed random coefficients model with fixed effects for treatment, baseline, center, and with random effects for the intercept and log(time). All analyses were performed on the MITT population.

Subject population

Treatment groups were well balanced with respect to demographic and baseline characteristics (see table S1). Only 9 (2.4%) patients were ill for greater than 60 months before study enrolment, and only 16 (5.4%) of patients were taking antipsychotics for more than 16 weeks before enrolment.
There was little difference between treatment groups in assessments at baseline. The mean (SD) scores in the study scales were: PANSS Total, 73.8 (15.8); PANSS Positive, 18.6 (5.1); PANSS Negative, 19.6 (6.2); CGI-Severity, 4.3 (0.8); CDRS total, 13.0 (4.2); Heinrich-Carpenter Vocational Subscale, 8.9 (7.); and Heinrich-Carpenter Social Subscale, 20.9 (10.3); and ITAQ total, 14.4 (5.9).

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Table S1 Subject population and disposition

		Quetiapine		Risperidone		Olanzapine		Total	
Population									
N randomised (N planned)		134	(132)	133	(132)	133	(132)	400	(396)
Demographic characteristics									
Sex n (%)	Male	92	(68.7)	99	(74.4)	101	(75.9)	292	(73.0)
	Female	42	(31.3)	34	(25.6)	32	(24.1)	108	(27.0)
Age (years)	Mean (SD)	25.0	(6.1)	23.9	(5.5)	24.7	(5.8)	24.5	(5.8)
Race n (%)	Caucasian	66	(49.3)	78	(58.7)	61	(45.9)	205	(51.3)
	Black	60	(44.8)	51	(38.4)	61	(45.9)	172	(43.0)
	Other	8	(6.0)	4	(3.0)	11	(8.3)	23	(5.8)
Baseline characteristics									
Age of Onset (years)	Mean (SD)	23.9	(5.7)	23.0	(5.7)	23.4	(5.3)	23.5	(5.6)
	Range	15 to 43		12 to 44		16 to 41		12 to 44	
Drug Naïve n (%)		36	(26.9)	28	(21.1)	32	(24.2)	96	(24.1)
Inpatient n (%)		29	(21.6)	26	(19.7)	29	(21.8)	84	(21.1)
Duration of Illness (Months)	Mean (SD)	15.1	(20.0)	12.7	(17.9)	11.0	(12.9)	12.9	(17.3)
	Range	1 to 166		0 to 124		0 to 62		0 to 166	
Disposition									
N analysed for safety[a]		134		133		133		400	
N analysed for efficacy (ITT)		134		133		133		400	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing

ITT=Intention to treat; N=Number; l

Efficacy and pharmacokinetic results

Overall, 70.3% of patients discontinued. Based on the pre-specified 20% margin for clinically significant inferiority, quetiapine proved non-inferior to olanzapine or risperidone on this primary outcome measure (Table S2). The median times to all-cause discontinuation for olanzapine (28 weeks), quetiapine (25 weeks), and risperidone (25 weeks) did not differ significantly. When specific reasons for discontinuation were

examined, patients receiving olanzapine had fewer administrative discontinuations (3.8%) than those receiving quetiapine (10.5%) or risperidone (9.8%), but there were no other notable differences across the treatment groups. The most frequent reason for discontinuation in the study population was patient decision despite the recommendations of the treating clinician to continue treatment (41.5%).

Table S2 Reasons for Discontinuation

Reason	Number (%) of subjects who discontinued							
	Quetiapine (N=134)		Risperidone (N=133)		Olanzapine (N=133)		Total (n=400)	
Subjects who Completed [N(%)]	39	(29.1)	38	(28.6)	42	(31.6)	119	(29.7)
All-Cause Discontinuation [a] [N(%)]	95	(70.9)	95	(71.4)	91	(68.4)	281	(70.3)
Administrative Discontinuation [b] [N(%)]	14	(10.5)	13	(9.8)	5	(3.8%)	32	(8.0)
Clinical Discontinuation: Inadequate Therapeutic Effect [N(%)]	16	(11.9)	12	(9.0)	15	(11.3)	43	(10.8)
Clinical Discontinuation: Unacceptable Side Effects [N(%)]	13	(9.7)	13	(9.8)	14	(10.5)	40	(10.0)
Clinical Discontinuation: Patient Decision [N(%)]	52	(38.8)	57	(42.9)	57	(42.9)	166	(41.5)

[a] No statistically significant difference by Blackwelder non-inferiority test.
[b] Discontinuation due to an independent external event (eg, moving with family to another state)

Patients dose over the trial were summarized as the modal dose. The mean (SD) modal doses in mg were: quetiapine, 506 (215); risperidone, 2.37 (0.98); and olanzapine 11.65 (5.32).

All treatment groups showed improvements in symptoms. There were no significant differences across the treatment groups in the PANSS total scores. At 12 weeks, mean change from baseline in PANSS Positive subscale scores showed greater reductions for olanzapine (-5.2 [SE=0.36]) and risperidone (-5.1 [SE=0.36]) than for quetiapine (-4.0 [SE=0.35]; quetiapine versus olanzapine, p=0.017; quetiapine versus risperidone, p=0.031), but this significant difference persisted only with olanzapine at week 52 (olanzapine, -5.3 [SE=0.51] versus quetiapine, -7.1 [SE=0.51]; p=0.013). On all other measures (PANSS Negative and General subscales, CGI-S, CDRS, H-C QLS Social and Vocational Subscales), the three treatment groups did not differ significantly.

Sixty-four percent of olanzapine-treated patients, 58% of quetiapine-treated patients, and 65% of risperidone-treated patients met pre-determined treatment-responder criteria (<=3 for all PANSS items and <=3 for the CGI Severity item) at some point during the study. The rates of response were not significantly different between the treatment groups.

Safety results

Similar numbers of SAEs occurred between treatment arms, with fewer in the olanzapine arm. A total of 18 SAEs occurred in the quetiapine (7), risperidone (7), and olanzapine (4). treatment groups. These included two suicide attempts and one alleged homicide in

the olanzapine group, two completed suicides and one case of suicidal ideation in the quetiapine group, and one suicide attempt in the risperidone group.

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]					
	Quetiapine (N=134)		Risperidone (N=133)		Olanzapine (N=133)	
Any adverse events (Spontaneously reported)	98	(73.1)	90	(67.7)	88	(66.2)
Serious adverse events	7	(5.2)	7	(5.3)	4	(3.0)
Serious adverse events leading to death	2	(1.5)	0	(0)	0	(0)
Serious adverse events not leading to death	5	(3.7)	7	(5.3)	4	(3.0)
Discontinuations of study treatment due to adverse events	13	(9.7)	13	(9.8)	14	(10.5)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Spontaneously reported adverse events were similar across treatment groups, with slightly more in the quetiapine arm (Table S3).

Elicited adverse events that clinicians scored as moderate or severe at some time during the trial are summarized as follows: The most frequent elicited adverse events in the olanzapine treatment group were daytime drowsiness (53%), weight gain (51%), and insomnia (38%). The most frequent elicited adverse events in the quetiapine group were daytime drowsiness (58%), increased sleep hours (42%), and weight gain (40%). The most frequent elicited adverse events in the risperidone group were daytime drowsiness (50%), menstrual irregularities in women (47%), and weight gain (41%). Dry mouth was more common in quetiapine-treated patients than in olanzapine- or risperidone-treated patients. Sialorrhea was more common in risperidone-treated patients than in olanzapine- or quetiapine-treated patients. Gynecomastia was more common in risperidone-treated patients than in quetiapine-treated patients. Hypersomnia was more common in quetiapine-treated patients than in risperidone-treated patients.

Over the course of the trial, only 16% of patients had any SAS item rated >1 (mild), only 7% had a rating >2 (mild) on the BARS global severity item, and only 1% had a score >2 (mild) on the AIMS global severity item. There were no significant differences across the treatment groups. The proportion of patients receiving concomitant medications (i.e., medications to treat a side effect or comorbid medical illness) for parkinsonism or akathisia was lower in the quetiapine-treated group (4%) when compared with those treated with olanzapine (11%; quetiapine versus olanzapine, p=0.021) or risperidone (8%; quetiapine versus risperidone, p=0.131).

Olanzapine was associated with the greatest increases in body weight and related measures. At week 12, the olanzapine-treated group had more weight gain, a higher increase in BMI, and a higher proportion of patients with a BMI increase of at least 1 unit compared with the quetiapine and risperidone groups (p<=0.01). These differences

between olanzapine and quetiapine or risperidone were also observed at week 52 (p<=0.02), but did not reach significance for the proportion of patients with a BMI increase of at least 1 unit in the risperidone group (p=0.063). Furthermore, 80% of olanzapine-treated patients had gained >=7% of their baseline weight, compared with 50% and 58% of quetiapine- and risperidone-treated patients, respectively, at week 52 (observed cases). Risperidone was associated with greater increases in weight and BMI in women than was quetiapine.
Risperidone was associated with the least elevations in fasting triglycerides and cholesterol and the smallest reduction in HDL cholesterol, while Risperidone produced greater increases in prolactin than olanzapine and quetiapine at weeks 12 and 52.