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Cognition, functioning and quality of life in schizophrenia treatment: Results of a one-year randomized controlled trial of olanzapine and quetiapine

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Abstract

Background: Cognitive deficits are recognized as a critical determinant of functional outcomes in schizophrenia; and second generation antipsychotic drugs have been touted for their potential to enhance cognitive functioning and community tenure.
Objectives: The study examined the relative merits of olanzapine and quetiapine in improving cognitive deficits and enhancing psychosocial functioning in a sample of community dwelling adults previously treated with first generation antipsychotic drugs for schizophrenia.
Methods: In a prospective, rater-blinded study, 86 participants were randomized to receive either olanzapine or quetiapine, and assessed at baseline and after 3, 6, 9 and 12 months. Outcome measures included, besides symptoms and side effects rating scales, the subjective scale to investigate cognition in schizophrenia (SSTICS), a computer-assisted cognitive test battery (COGLAB), the sickness impact profile (SIP), the global assessment of functioning (GAF) scale, and the drug attitude inventory (DAI).
Results: Both olanzapine and quetiapine were equally effective in improving symptom severity and decreasing the neurological side effects. Quetiapine was significantly better tolerated ($p=0.002$), improved self-rated cognitive dysfunction ($p=0.002$) and subjects' performance on selected neurocognitive tasks ($p=0.01$). Olanzapine use was associated with greater symptom stability, fewer drop outs ($p=0.01$) and frequent metabolic aberrations ($p=0.001$). The accrued benefits of drug therapy, however, were not reflected as significant gains in daily functioning and quality of life.
Conclusions: Quetiapine is noted to have specific cognition enhancing properties in schizophrenia that warrants further exploration. The observed clinical and cognitive benefits associated with quetiapine may likely be attributable to its loose binding to, and fast dissociation from the dopamine receptors. Olanzapine has proved to be a reliable antipsychotic drug with a greater liability to cause metabolic abnormalities.

Keywords: Schizophrenia; Cognition; Outcomes; Olanzapine; Quetiapine; Quality of life

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1. Introduction

Cognitive deficits have been recognized as an important dimension of schizophrenia syndrome, and are increasingly considered as crucial determinants of functional outcomes (Heinrichs and Zakzanis, 1998; Hofer et al., 2005). This has given rise to concepts such as neuro-protection and cognitive enhancement, forming new frontiers in schizophrenia research and creating new challenges for antipsychotic drug development (Stip et al., 2005; Jarskog and Lieberman, 2006; Marder, 2006). Recent animal studies have suggested possible neuro-protective benefits associated with various second generation antipsychotic drugs (Lang et al., 2004; Yulug et al., 2006). These observations coupled with continuing clinical demands for better treatments prompted the study of the cognition-enhancing potential of second generation antipsychotic drugs in the treatment of schizophrenia. Results from the preliminary studies have been encouraging but inconsistent, prompting further research (Sax et al., 1998; Kasper and Muller-Spahn, 2000; Velligan et al., 2003; Harvey, 2006; Lindenmayer et al., 2007).

Improving cognitive deficits in schizophrenia is, of course, the means to reach an end, i.e., to achieve better community functioning. The range of potential functional outcomes includes improved self care and daily routine, independent living, employment and social reintegration. There have been several reports to date, linking cognitive deficits to some of these indices of instrumental functioning though many of them are cross-sectional studies on chronically ill populations saddled with multiple confounding issues such as comorbid physical and psychiatric disorders, cumulative effects of psychotropic medications, substance abuse and effects of institutionalization (Chwastiak et al., 2006). Considering this complex profile of the clinical population, it is arguable if the novel antipsychotic drugs can improve not only the cognitive deficits but also the quality of community tenure.

It is equally unclear if improvement in cognitive deficits leads to an improvement in patient reported outcomes (PRO) such as self esteem, subjective well being and quality of life of the individual. There have been numerous studies that were eager to establish the benefits of second generation antipsychotic drugs in terms of improvement in quality of life, but the quality of life measures used in many of the studies failed to distinguish between the subjective aspects of quality of life and the composite indices derived from activities of daily living (Awad and Voruganti, 2004a,b; Keefe et al., 2006). Clinical observations indicate that marginal improvement in cognitive deficits and over-zealous attempts to return to competitive employment could lead to difficulties with coping, increased subjective distress and lowered quality of life. Such scenarios account for the frequent finding of poor correlations found between patients' self appraisals and raters' objective assessments of psychosocial functioning and quality of life. Reconciling the disparities between patient reported outcomes (PRO) and scores derived from objective, standardized instruments, thus, continues to remain a challenge in the field of outcome evaluation (Awad and Voruganti, 2007).

Some of the important short-comings of the studies in this field included small sample sizes, relatively short duration of the trials, varied test batteries employed, lack of focus on patients' self reports, and a failure to examine the impact of cognitive deficits on psychosocial functioning and quality of life (Green et al., 2000; Harvey and McClure, 2006). The present study sought to examine the therapeutic potential of the second generation antipsychotic drugs in terms of improving cognitive deficits, instrumental functioning and quality of life.

2. Methods

The study was designed as a 12 month, prospective, rater-blinded, randomized, controlled trial aimed at comparing the relative merits of olanzapine and quetiapine in improving cognitive deficits and psychosocial functioning in schizophrenia. Since improvement in psychosocial functioning and quality of life may require a longer period of treatment to manifest, the study was designed as a one-year naturalistic trial. Due to logistic reasons, the comparators were limited to two of the atypical antipsychotic drugs (olanzapine and quetiapine) popular at the time of the study conception. The study was conducted as a multi-site trial within a defined geographical area, coordinated by a single team of investigators and evaluators, to minimize the short-comings of traditional multi-centre clinical trials. The protocol was approved by the local ethics board, and the study was registered under the clinical trials registry (ClinicalTrials.gov identifier NCT00182442).

3. Subjects

The study participants included subjects with an established diagnosis of schizophrenia (DSM-IV) confirmed through the administration of structured clinical interview schedule for DSM-IV (SCID). The entry criteria included people of either sex, between 18 and 65 years age, who were treated with first generation

antipsychotic drugs and were in need of a switch to a second generation antipsychotic drug due to unresolved symptoms or distressing side effects. People with developmental disorders, epilepsy or acquired brain injury and significant substance abuse comorbidity were excluded. Also, people who were not competent to consent for the study were not considered. After obtaining a written informed consent, participants underwent a comprehensive physical examination and routine investigations to rule out significant physical disorders. Subjects were recruited from five communities that represented key socio-demographic characteristics including urban vs. rural, culturally homogeneous vs. multi-cultural, recently diagnosed vs. chronically mentally ill, and those living in catchment areas of a teaching institution as well as community hospitals. The range of antipsychotic medications and their dosage at enrolment were as following: chlorpromazine (400–800 mg daily), clopenthixol (100–200 mg/2 weeks), flupenthixol (40–100 mg/2 weeks), fluphenazine (25–100 mg/week), haloperidol (5–20 mg/day), loxapine (25–80 mg/day), perphenazine (8–32 mg/day), piportil (100–200 mg/4 weeks) and trifluperazine (15–60 mg/day). Since the study was conceived as a naturalistic clinical trial, subjects who were on concomitant medications (SSRIs, divalproex sodium, lithium and benzodiazepines) for ancillary symptoms (anxiety and depression etc.) were also considered for randomization. Concomitant medications and co-interventions were recorded, and considered during analysis.

4. Evaluation methods

The focus of the study was to evaluate non-traditional, effectiveness measures involving cognitive performance, psychosocial functioning and quality of life, specifically the subjective or patient reported outcomes (PRO). The dimensions of evaluation included measurement of psychotic symptoms, side effects (extra-pyramidal side effects, akathisia, and abnormal involuntary movements), subjective tolerability of antipsychotic drugs, self-reported cognitive dysfunction, objectively measured cognitive deficits, psychosocial functioning and quality of life. The list of rating scales used is summarized in Table 1, and details of the neurocognitive test battery are provided below.

COGLAB is multi-paradigmatic cognitive test battery developed for computer-assisted neurocognitive assessment. The original version of the software included a selection of 6 tests aimed at assessing "information processing" deficits in pre-attentional, attentional, psychomotor and conceptual domains of cognitive functioning in schizophrenia (Spaulding et al., 1981). The following is a summary of the tests employed in this study, and the scoring parameters used in the analysis.

4.1. Mueller–Lyer visual illusion task

This test examines the individual's proneness to illusion. An arrow figure is presented on the screen and the subject is asked to adjust its length until the two halves are equal in size. The percentage of accuracy achieved over three trials is the index of measurement.

4.2. Size estimation task

In this test of visual-spatial abilities, a square graphic figure is presented on the screen as a standard, followed 5 s later by two duplicate figures of different sizes. The subject is instructed to indicate by pushing the buttons which of the two is closer in size to the original standard. Ten trials are administered, with the relative sizes and positions varying from trial to trial, and the index of measurement is the mean number of over- or under-estimates.

4.3. Asarnow's (vigilance and span of apprehension) test

It is a combination of a continuous performance test (CPT) and a span of apprehension or scanning paradigm, aimed at measuring vigilance and false alarms during vigilance. The subject is instructed to watch the screen for a specified target digit and to press a button when it appears, ignoring all other digits. Total number of accurate "hits" represents the score.

4.4. Visual backward masking (iconic memory) test

The test was designed to assess analysis processes that operate early in the visual information processing system. Pairs of digits are presented on the screen for 16 ms, followed by, at various intervals, two X's of equal duration. There are 30 stimulus presentations, 10 each at longer intervals (long mask), shorter intervals (short mask) or no mask. Number of correctly identified digits in the three categories is scored by the computer.

4.5. Wisconsin card sorting test (WCST)

In this test, the subject discerns through trial and error three sorting parameters (colour, number and shape), guided by the feedback of "right" or "wrong" prompts

Table 1
Summary of evaluation methods

Domain of assessment/test/ scale	Brief description, interpretation and clinical significance
I. Symptoms	
Positive and negative syndromes scale [PANSS]	30 item interviewer administered scale; scores range between 30 and 210, and a higher score is indicative of a greater severity of illness (Kay et al., 1987).
II. Side effects	
1. Simpson–Angus Scale [SAS]	10 item scale; scores range between 0 and 40; higher scores indicate greater severity of extra-pyramidal side effects (Simpson and Angus, 1970).
2. Barnes akathisia scale [BAS]	Interviewer-administered scale to quantify akathisia; score ranges between 0–13 (Barnes, 1989).
3. Abnormal involuntary movements scale [AIMS]	Interviewer-administered scale to quantify dyskinesia; score ranges between 0 and 40 (Guy, 1976).
4. UKU side effects rating scale, self report version [UKU-SR]	45 item, self-administered scale to quantify common side effects, scores range between 0 and 180 (Lingjaerde et al., 1987; Lindstrom et al., 2001).
5. Drug attitude inventory [DAI]	10 item self-administered scale; Score ranges between −10 to +10; higher score indicates improved tolerability (Awad, 1993).
6. Body weight, image and self esteem [BWISE] scale	12 item self-administered scale; Score ranges between 12–36; higher score indicates better self image and esteem (Awad and Voruganti, 2004b).
III. Cognitive impairment	
1. Subjective scale to investigate cognition in schizophrenia [SSTICS]	21 item, self-administered scale to quantify self-rated cognitive dysfunction; scores range between 0 and 84, higher score indicates greater cognitive deficits (Stip et al., 2003).
2. Cognitive laboratory or COGLAB	Computer-assisted, self-administered cognitive test battery consisting of 6 subtests; requires about 20–30 min for administration (Spaulding et al., 1981; Voruganti et al., 1997).
IV. Functional outcomes	
1. Sickness impact profile [SIP]	Score ranges between 0–83; higher score indicates superior functioning (Bergner et al., 1981; Awad et al., 1997).
2. Global assessment of functioning [GAF]	Single item, global rating by interviewer; score ranges between 0–90; higher score indicates superior function (Endicott et al., 1976; APA, 1994).
V. Physical health indices	
1. Fasting blood glucose	<5.6 mmol/l represents euglycemia; ≥5.6 mmol/l suggests dysglycemia.
2. Weight	Weight gain recorded in kilograms
VI. Other global outcomes	
Personal Evaluation of Transitions in Treatment [PETiT]	Compliance subscale has 6 items; scores range between 6 and 18, higher scores indicate better treatment adherence (Voruganti and Awad, 2002)

for each card sorted. The relevant sorting parameter changes after every five correct card attempts, and the subject must apprehend the change and modulate his/her strategy accordingly. The card sorting task in COGLAB yields three scores. One is the number of errors required to finish the test, the other is the number of errors attributable to perseverative sorting by a parameter that is no longer the correct one, and finally the total score of correct sorts accomplished.

5. Study procedures

Consented patients were assessed at baseline, clinically monitored at monthly intervals or as often as necessary, and the evaluation battery was administered at 1, 3, 6, 9 and 12 month points during follow-up. Switch to the newer medications was achieved through an "overlap" strategy of gradual tapering of the previous drug and a gradual increase of the new medication. Optimizing the study drugs in terms of dosing, pace of increase and use of adjunctive medications was left to the discretion of the treating clinicians. Outcome evaluations were carried out by the research personnel blinded to the medication regime, and cognitive testing was performed with the help of a computer, eliminating the scope for bias. Treatment adherence was ensured with blister packs, self-reporting, pill counts and collateral information from informants. Supportive psychotherapy, case management, family intervention, occupational therapy and vocational rehabilitation measures were provided as indicated by individual's needs and were recorded for every patient. Rescue medications included benzodiazepines (lorazepam or clonazepam for anxiety and agitation or sleeping difficulties); and adjunctive antipsychotic medications or anti-Parkinsonian medications were added, if felt necessary by the physician, and were recorded for every patient.

6. Data analysis

A fully evaluable patient was defined as a patient who has a completed a baseline and end of the study assessment

and, at least, 3 months of follow-up. Descriptive statistics were computed for the patient characteristics: age, gender, marital status, education, residential status and duration of illness. Similarity of groups was ascertained using Student's *t*-test for independent groups. Data was summarized in tables using means, standard deviations, sample size, measures and percentages (for categorical variables). Also, for categorical measures the chi-square test of significance was used.

Scores from the rating scales were entered into a database and statistical analysis was carried out with SPSS v15. Pre- and 12 month post-intervention scores were compared to examine differences with tests of within subjects effects [Greenhouse–Geisser] and tests of between subjects contrasts [repeated measures analysis of variance] using test scores and drug category as factors. Multivariate tests employed included Pillai's trace, assuming sphericity [Mauchly's test]; and non-parametric tests of significance included chi-square and Fisher's exact test (where applicable). Levels of significance set as $p<0.05$ for primary outcomes (cognitive test scores) and $p<0.01$ for secondary outcomes (functional and tolerability measures).

7. Results

One participant dropped out within the first week after the enrolment due to an unanticipated geographical move. The remaining 85 participants completed the study, with a 98% adherence to the assessment schedule. The socio-demographic, clinical and treatment characteristics of the treatment groups are summarized in Table 2. The study groups were similar and comparable in terms of their clinical and demographic profiles. Also, there were no significant differences between groups at the baseline in terms of neurocognitive performance, drug therapy and the co-interventions received.

Table 2
Sample description at baseline

	Olanzapine ($n=42$)	Quetiapine ($n=43$)	Significance
Age (in years)	41.33 (13.61)	38.72 (14.37)	$F=1.58$, $df=83$, $p=0.2$
Sex (Male:Female)	35 (83%): 7 (17%)	28 (65%): 15 (35%)	$\chi^2=2.78$, $df=1$, $p=0.03$
Marital status (Married: Single/separated)	8 (19%): 34 (81%)	8 (18%): 35 (82%)	$\chi^2=1.05$, $df=3$, $p=0.7$
Education (years in school)	11.83 (2.15)	12.2 (2.34)	$F=0.067$, $df=83$, $p=0.7$
Occupation (Employed: Unemployed)	1:41	1:42	$\chi^2=0.34$, $df=3$, $p=0.8$
Residential status (Independent: Shared living)	16 (38%): 26 (62%)	21 (49%): 22 (41%)	$\chi^2=1.85$, $df=3$, $p=0.6$
Duration of illness (years)	15.33 (11.31)	14.16 (11.76)	$F=0.32$, $df=83$, $p=0.5$
Dose (mg) (mean±SD)	17.2 (2.5)	612.8 (122.6)	Not applicable

The changes in scores on the symptoms, side effects and tolerability ratings are summarized in Table 3. The magnitude of improvement was similar with both the medications, and there were no statistically significant differences between the two groups on the mean PANSS total scores or the conventional subscales. Subjects in the quetiapine group, however, showed greater improvement on the cognitive cluster derived from selected items of the PANSS. Quetiapine recipients also showed greater improvement in their mean DAI scores and the compliance subscale, suggestive of its better subjective tolerability and acceptability (see Table 3).

Subjects in the olanzapine group achieved greater symptom stability over the 12 month follow-up period, while quetiapine recipients remained vulnerable to experience "break through" symptoms during the study period. Greater number of subjects in the olanzapine group (40 out of 42) remained symptom-free or symptomatically stable for greater number of weeks over the study period, while a minority of subjects in the quetiapine group (7 out of 43) experienced episodic exacerbation of symptoms (operationally defined as a mean increase of $\geq$10% of PANSS score), requiring frequent optimization of drug dose or the use of adjunctive medications. These brief intermittent psychotic episodes (BIPS) were noted to occur in the context of stressful life events (e.g. change of accommodation or work-related stress), lasted less than a week, and warranted a temporary increase of the assigned antipsychotic (e.g. increase of quetiapine by 100 mg.) or the addition of an adjunctive medication (e.g. clonazepam or lorazepam) for periods ranging between 2–4 weeks. Subjects who were relatively older, chronically ill and previously treated with high dose, high potency antipsychotic drugs, often in the form of long acting depot injections, were especially more vulnerable to experience such break through symptoms, during the switch to quetiapine. The BIPS were not always captured by the periodically administered rating scales, but were recorded during routine follow-up visits.

The differences between the drugs in terms of self-reported cognitive dysfunction, computer-assisted cognitive tests, and measures of psychosocial functioning are summarized in Table 4. These results indicate that quetiapine brought about greater improvement in self-rated cognitive dysfunction (SSTICS mean scores) and selected cognitive function tests (backward masking,

Table 3
Clinical outcomes — changes in symptoms and side effects at 12 months

Scales/indices	Olanzapine (n=42)		Quetiapine (n=43)		Analysis of variance F, df and significance
	Baseline	12 months	Baseline	12 months	
1. PANSS					
a. Total	82.1 (15.8)	48.5 (9.9)	79.1 (16.8)	49.4 (12.0)	F=1.67 (df=1,79), p=0.28
b. Positive symptom subscale	25.3 (5.88)	15.5 (4.58)	19.5 (5.97)	11.14 (4.3)	F=0.001 (df=1,79), p=0.97
c. Negative symptom subscale	19.3 (5.67)	10.9 (3.15)	23.24 (5.4)	14.8 (6.03)	F=1.037 (df=1,79), p=0.31
d. General psychopathology subscale	37.5 (7.20)	22.3 (4.99)	36.39 (8.6)	23.78 (6.2)	F=1.772 (df=1,79), p=0.18
e. Cognitive cluster [a]	22.8 (6.32)	18.4 (5.41)	23.27 (5.7)	15.64 (4.9)	F=11.28 (df=1,79), p=0.02 *
2. UKU-SR	32.4 (15.6)	21.9 (10.7)	30.7 (10.1)	16.14 (8.8)	F=2.674 (df=1,79), p=0.1
3. SAS	2.37 (4.01)	0.37 (1.21)	2.12 (3.89)	0.26 (1.24)	F=0.035 (df=1,79), p=0.85
4. AIMS	0.95 (1.46)	0.92 (1.50)	0.63 (1.31)	0.75 (1.06)	F=0.024 (df=1,75), p=0.62
5. BAS	2.82 (2.81)	0.05 (0.32)	2.00 (2.33)	0.13 (0.47)	F=2.239 (df=1,79), p=0.13
6. DAI	3.45 (3.78)	3.70 (1.50)	3.19 (4.76)	6.26 (1.22)	F=10.69 (df=1,79), p=0.002 *
7. PETiT (compliance subscale)	14.4 (2.59)	14.7 (3.1)	14.5 (2.83)	16.34 (1.79)	F=3.622 (df=1,67), p=0.06
8. BWISE	11.13 (3.1)	10.95 (3.0)	10.63 (2.9)	15.68 (3.1)	F=52.73 (df=1,79), p=0.001 *
9. Weight gain (kg)	–	7.24 (2.43)	–	2.84 (1.72)	F=5.679 (df=1,79), p=0.02 *
10. Number of Dysglycemics [b]	1	13	3	4	χ^2=30.71 (df=1,80), p=0.001 *

[a] Cumulative total of 5 items — difficulty in abstract thinking, disorientation, conceptual disorganization, stereotyped thinking and poor judgment (Kay et al., 1987).
[b] Dysglycemia is defined as fasting plasma glucose (FPG) of ≥5.6 mmol/l (The expert committee on the diagnosis and classification of diabetes mellitus, 2003).
* Statistically significant.

Asarnow's and Wisconsin card sorting tests), compared to olanzapine. Psychosocial functioning improved significantly among subjects in both the groups, though there were no significant differences between the two drugs in terms of the improvement noted on the GAF and SIP mean scores at the end of 12 months. On the other hand, 4 subjects (out of 43) treated with quetiapine went to obtain competitive employment while only one subject (out of 42) from the olanzapine group was working towards the end of 12 month follow-up.

Table 4
Functional outcomes: changes in cognitive deficits and psychosocial functions after 12 months of treatment

Tests/scales	Olanzapine (n=42)		Quetiapine (n=43)		Analysis of variance F, df and significance
	Baseline	12 months	Baseline	12 months	
I. Cognitive functions					
1. Subjective scale to investigate cognition in schizophrenia (SSTICS)	35.4 (19.4)	30.2 (18.2)	34.0 (13.2)	19.4 (12.4)	F=10.54 (df=1,71), p=0.002 *
2. COGLAB					
a. Muller–Lyer's Visual task [a]	65.3 (10.7)	71.3 (10.6)	60.7 (10.8)	67.2 (10.5)	F=1.36 (df=1,81), p=0.56
b. Size estimation task [b]	4.40 (1.75)	2.88 (1.15)	4.19 (1.53)	2.39 (0.62)	F=0.84 (df=1,81), p=0.36
c. Backward masking task [c]	16.00 (3.5)	21.0 (4.82)	18.19 (3.5)	26.17 (5.4)	F=10.81 (df=1,81), p=0.01*
d. Asarnow's task [d]	9.69 (1.19)	13.16 (2.3)	10.12 (1.5)	15.39 (2.4)	F=12.73 (df=1,81), p=0.01*
e. Wisconsin card sorting test [e]					
i. Total score	57.9 (11.4)	63.0 (11.6)	55.9 (12.1)	65.4 (12.6)	F=34.74 (df=1,80), p=0.001*
ii. Perseverative errors	20.83 (4.6)	17.19 (3.7)	21.85 (4.7)	12.12 (3.5)	F=65.74 (df=1,81), p=0.001*
iii. Random errors	24.00 (6.1)	17.42 (4.2)	24.85 (6.1)	11.39 (3.9)	F=35.4 (df=1,81), p=0.001*
II. Psychosocial functioning					
1. Sickness impact profile (SIP)	57.4 (17.0)	65.7 (13.7)	54.7 (13.2)	64.8 (14.6)	F=0.431 (df=1,78), p=0.51
2. Global assessment of functioning (GAF) scale	43.77 (8.8)	64.72 (7.8)	42.9 (9.70)	66.1 (8.05)	F=0.881 (df=1,79), p=0.35

[a] Percentage of accuracy achieved.
[b] Mean number of over- or under-estimates.
[c] Total number of accurate "hits" scored.
[d] Total number of accurate "hits" scored.
[e] Total number of correct responses, number of perseverative errors and random errors are indices under consideration.
* Statistically significant.

Correlations between symptom, neurocognitive and functioning variables were calculated for the entire sample, controlling for age, duration of illness and baseline neurocognitive scores. Results indicated that symptom severity, with the exception of cognitive cluster scores, was largely uncorrelated with the test and performance variables. Cognitive cluster scores derived from the PANSS revealed modest correlation with the subjective cognitive dysfunction on SSTICS ($r=0.31, p=0.05$) and level of functioning on GAF ($r=-0.32$, $p=0.05$) and SIP ($r=0.29$, $p=0.05$). Among the neurocognitive test variables, performance on the WCST (total score) showed moderate correlations with the GAF ($r=0.42$, $p=0.05$) and SIP ($r=-0.39$, $p=0.05$) scores. More robust correlations were found between the subjective measure of cognitive dysfunction (SSTICS) and other outcome measures, as following: with the SIP ($r=0.77$, $p=0.001$), WCST ($r=-0.68$, $p=0.05$), span of apprehension test ($r=-0.51$, $p=0.05$), backward masking task ($r=-0.49$, $p=0.05$) and GAF scores ($r=-0.41$, $p=0.05$).

Other notable findings include the excess weight gain and impaired glucose tolerance associated with olanzapine, which was reflected in clinical observations (weight records and fasting glucose values) as well as the mean ratings on the Body Weight, Image and Self Esteem (BWISE) evaluation scale. Weight gain was negatively correlated with BWISE scores ($r=0.84$, $p=0.001$) and functional outcomes on SIP ($r=0.72$, $p=0.05$) at 12 months.

8. Discussion

Switching patients from first generation to the second generation antipsychotic drugs (olanzapine or quetiapine) was unequivocally successful for this group of subjects, in terms of clinically and statistically significant improvements in symptom severity, burden of side effects, tolerability and psychosocial functioning. The two drugs seem to have some distinctive profiles however; olanzapine offered greater symptom stability and longer remissions, while quetiapine was better tolerated and led to a greater improvement in cognitive functions, especially on subjective measures. These findings have significant clinical and heuristic implications. The following themes merit further discussion — i. the relative merits of atypical antipsychotic drugs, with regard to their cognition-enhancing effects, ii. the distinctive pharmacodynamic profiles of quetiapine and olanzapine, and iii. the inconsistent link between cognition, functioning and quality of life.

The cognition enhancing effects of the second generation antipsychotic drugs, when considered as a group, remain modest and inconsistent despite various large scale studies (Keefe et al., 2007). It has also become apparent that not all "atypicals are created equal", and some antipsychotics may bring about a distinct improvement in cognitive functions more than the other. Among the newer atypical drugs, preliminary data indicate that quetiapine may possess specific cognition enhancing effects (Fleming et al., 2001; Good et al., 2002; Purdon et al., 2001; Velligan et al., 2003). Though quetiapine's potential to enhance cognitive deficits in schizophrenia has been documented in previous studies, our study provides the robust evidence yet to substantiate this claim. Cumulative observations from this as well as the other studies suggest that cognition-enhancing effect of quetiapine is especially more evident when it is used among younger, neuroleptic-naïve patients with first episode of psychosis (Voruganti et al., 2002). These observations also suggest that the improved cognitive performance associated with quetiapine use is not merely an improvement in cognitive blunting attributable to the prior neuroleptic use but indeed a true enhancement of cognitive functions (Woodward et al., 2007).

One of the interesting themes arising out of the study is the observed clinical performance of quetiapine, and a likely pharmacodynamic explanation for its distinctive properties (Horacek et al., 2006). The triad of cognitive improvement, superior tolerability and a tenuous control of psychotic symptoms observed with quetiapine could be attributable to its loose binding and rapid dissociation at the dopamine D_2 receptor sites (Seeman and Tallerico, 1998; Kapur et al., 2000). The low affinity of the drug to the dopamine D_2 receptors may have conferred on it a lower cognitive blunting effect and superior tolerability, while its antipsychotic action remains more subtle and easily reversible. These empirical findings offer fresh insight into implications of the fast dissociation hypothesis (Kapur and Seeman, 2001), and help to establish a correlation between pharmacodynamic events and clinical responses, similar to the relationship between D_2 receptor occupancy and the emergence of extrapyramidal side effects (Kapur et al., 1995).

The dual properties of therapeutic reliability and a higher incidence of metabolic complications associated with the olanzapine use have been noted in earlier studies as well (Lieberman et al., 2005). Though the drug was perceived by the study subjects as tolerable and effective during the early months, its overall acceptability waned towards the end of the 12 month study period due to the distressing consequences of weight gain.

The study was only partially successful in supporting the commonly presumed link between improved cognitive performance, superior community functioning and

enhanced quality of life, the outcomes desired in the long term treatment of schizophrenia. (Voruganti et al., 1997; Salkever et al., 2006). While such cascade of benefits is clinically intuitive and theoretically logical, there is no definitive clinical evidence to substantiate this complex interrelationship. The modest improvement in cognitive functions noted with quetiapine in the present study did not translate into measurable improvement on instrumental functioning or quality of life measures, though a significantly greater number of subjects in the quetiapine group were employed towards the end of the study.

The lack of a consistent and predictable relationship between improvement in symptoms, side effects, cognitive performance and instrumental functioning noted in this study as well as in other studies, has remained a methodological challenge for clinicians and researchers alike. It is unclear at the present time if this lack of consistency is related to problems with the validity of the measures, a poor definition of the underlying constructs, or the effect of other confounding variables that are yet to be identified (Green et al., 2004; Buchanan et al., 2005). It could also be the case that the beneficial effects of medications alone are not enough to significantly improve distal outcomes such as instrumental functioning and quality of life. Novel antipsychotic drugs are likely to improve cognitive potential in schizophrenia, which requires additional psychosocial rehabilitation efforts to complement their effects and bring about a measurable change in instrumental functioning and productivity.

The present study also raises a number of broader questions related to the cognitive deficits associated with schizophrenia. Are there specific cognitive functions that are more crucial than the others towards improving community functioning? Is there a threshold for improved cognitive performance to manifest itself as clinically noticeable improvement in functioning? Is the duration of accrued benefits and clinical stability an essential element of meaningful improvement in productivity? Does an improvement in cognitive functions need to be supplemented with adequate psychosocial interventions, in order to maximize the benefits of antipsychotic drug therapy? And, finally, does an improved instrumental functioning lead to an enhanced subjective quality of life? Needless to say, cognitive deficits represent the next frontier to explore in schizophrenia treatment and research.

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Contributors

The following is a list of contributions by individual authors towards the study:

L.P. Voruganti — Study design, data collection, analysis, preparation of manuscript and administration

A.G. Awad — Data collection, preparation of manuscript and administration

G. Parker — Data collection and compilation

C. Forrest — Study design, set-up and administration

Y. Usmani — Data compilation, computerization and data management

M.L.D. Fernando — Subject enrollment and ongoing clinical support

S. Senthilal — Subject enrollment and ongoing clinical support.

Conflict of interest

None of the authors have a conflict of interest.

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