Asian Outpatients with Schizophrenia: A Double-Blind Randomized Comparison of Quality of Life and Clinical Outcomes for Patients treated with Olanzapine or Haloperidol

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To examine the quality of life (QoL) and clinical outcomes for Asian schizophrenic outpatients treated with olanzapine or haloperidol. Patients were randomized to 24-weeks' treatment with either olanzapine (n = 144) or haloperidol (n = 132) in a double-blind, prospective, multi-country study. The QLS and WHO-BREF were assessed for QoL; the PANSS, BPRS and CGI scales for clinical status; the BAS, AIMS and SAS scales for physical dysfunction. Regardless of antipsychotic, QoL improved significantly at 8 weeks and maintained this improvement at 24 weeks. Compared with haloperidol, olanzapine treatment was associated with significantly better QoL in the WHO-BREF physical and social relationship domains, better improvements in extrapyramidal symptoms in BAS and SAS scores, as well as lower incidence of adverse events. Patients taking haloperidol were more likely to be co-prescribed anticholinergics. The comparatively superior side-effect profile and tolerability of olanzapine may have contributed to enhance domain-specific QoL for these Asian outpatients.

Keywords: *Antipsychotic, Asia, Haloperidol, Olanzapine, Quality of life, Schizophrenia*

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Schizophrenia is a psychotic disorder with several symptom domains that coalesce to form a potentially debilitating syndrome. Patients with schizophrenia develop a range of symptoms, including auditory hallucinations, anhedonia, and delusions. These symptoms may remit or lessen over time, or remain unresponsive to treatment, depending on a wide range of factors such as compliance to treatment and presence of side effects, many of which are poorly understood. Psychotic symptoms may also be accompanied by more insidious deficits such as cognitive impairment and social and occupational dysfunction. Recent reports estimate that only a third of patients experience complete symptomatic and social recovery[1].

Atypical antipsychotics appear to have at least equal, if not superior efficacy to conventional antipsychotics, with a lower incidence of adverse events (AE), and have become the first-line treatment option for schizophrenia and related disorders[2-4]. A recent review of pharmacoeconomic studies concluded that the higher acquisition cost of atypical medications such as olanzapine (compared with conventional agents like haloperidol) may be offset by reduced associated medical costs such as hospitalization and out-patient services[5]. This is unsurprising considering medication costs may account for less than 5% of the total direct costs of managing this disease[6]. A recent meta-analysis examining the efficacy of second-generation antipsychotics concluded that some of these agents, including olanzapine, are significantly more efficacious than their first generation counterparts[7]. This is supported by a recent observational study comparing the effectiveness of antipsychotics[8].

Haloperidol is an effective conventional antipsychotic, but is also associated with adverse events such as extra pyramidal symptoms (EPS), tardive dyskinesia (TD), and prolactin elevation[9-12]. Despite this, it is still widely prescribed in Asia, in preference to newer atypical drugs such as olanzapine. As the immediate (purchase) cost of haloperidol is much cheaper than atypical agents, authorities, physicians, patients, and their caregivers need to be able to weigh the comparative benefits of atypical agents against higher initial financial outlay.

For persistent illnesses such as schizophrenia, which can have a chronic, unremitting course, health-related QoL is crucial to the success of treatment and reintegration of patients into the community. Both objective and subjective instruments are available to assess QoL. The Quality of Life Scale (QLS) has been designed specifically to address the deficit symptoms associated with schizophrenia[13]. The QLS is based on a semi-structured interview relating to the four weeks prior to assessment, during which patient responses are used to rate 21 individual items on a scale of 0 to 6 (with lower scores reflecting greater impairment). The QLS comprises four domains: Intrapsychic Foundations examines motivation, purpose, and emotional interaction; Interpersonal Relations evaluates social functioning; Instrumental Role deals with work activity and job satisfaction; and Common Objectives and Activities uses possession of everyday objects as an index of community participation[13]. All 21 items are summed to produce a total score that ranges from 0 to 126, providing an overall summary of QoL.

The generic World Health Organization Quality of Life - Brief scale (WHOQOL-BREF) is an abbreviated version of the WHOQOL-100, which was developed to facilitate assessment of subjective QoL across disease states and patient groups, allowing for different cultural contexts[14]. Twenty-six items are scored to produce four domain scores (Physical, Psychological, Social Relationships, and Environment) within a 0 to 100 range, with 100 denoting the highest achievable QoL. This questionnaire is completed by the patient, and has been validated extensively to ensure it retains cultural relevance whilst still enabling comparison across different populations[15]. Indeed, use of this instrument was recently validated in Malaysia[16]. Due to the cultural sensitivity of subjective QoL, caution must be exercised in extrapolating results derived from populations with different ethnic origins[17].

As the majority of existing studies examining QoL (both subjective and objective) are based on primarily Caucasian populations, their application to Asian populations may be limited. The present study was established to facilitate comparison of the impact of haloperidol and olanzapine treatment for schizophrenia on QoL for outpatients in Asia. This is the first randomized, double blind comparison of olanzapine and haloperidol to focus on objective and subjective QoL and clinical outcomes for this population.

Material and Method

Study design

This was a randomized, double-blind, prospective, multi-center study (F1D-SN-S010) involving outpatients in the Philippines, Pakistan, Malaysia, Thailand, and Singapore. Informed consent was obtained from all eligible patients or their legal representative prior to screening to ensure a complete understanding of the procedure and potential risks. Following the initial

screening visit, patient assessments were scheduled at Baseline (Day 0), 2, 4, 8, 16, and 24 weeks post-baseline. Prior to randomization at Baseline, antipsychotic treatment was withheld for 2 to 9 days as an antipsychotic 'wash-out' period. The present study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approval was secured from the ethical or institutional review board of each site.

Randomization and blinding

The Mont-Saint-Guibert development center in Belgium prepared both the study drugs and the randomization schedule. Drug kits were assigned a number according to a randomization list produced on-site, then these numbered kits were consecutively allocated to patients in blocks of four stratified by country. All personnel and patients involved in the present study were blinded to the treatment assigned until data analysis, at which point the data were unblinded to authorized personnel to allow analysis. Sites were unblinded only following approval of the Clinical Study Report. All study medication was identical in appearance.

Measures

Clinical status, adverse events, vital signs, and weight were monitored at randomization (Baseline) and Weeks 2, 4, 8, 16, and 24 post-baseline to ensure patient safety and response. Adverse events (AE) were spontaneously reported throughout the present study. Clinical chemistry, electrolyte, and haematology tests were conducted at the screening visit (prior to randomization), following 8 and 24 weeks of treatment, and at study completion, discontinuation, or when clinically indicated. All female patients were tested for pregnancy at the screening visit and when clinically indicated, provided consent was given for this procedure. QoL (the primary objective) was examined using the QLS[13] and WHOQOL-BREF[14] questionnaires at Baseline, Week 8 (acute phase schizophrenia), and week 24 (maintenance phase schizophrenia). Patients were evaluated at all visits using the positive and negative symptom scale (PANSS)-extracted brief psychiatric rating scale 0-6 (BPRS)[18] as the primary parameter of efficacy. In addition, the PANSS total, positive, and negative scores[19], and the clinical global impression severity 1-7 (CGI-S) score[20] were used as secondary efficacy measures at all post-screening visits. Responders to treatment were defined as those patients who demonstrated at least a 40% decrease in BPRS total score (from baseline to endpoint), or a score of less than 18 at the last observation (endpoint). To address tolerability, EPS and TD symptoms were assessed at Baseline and all post-screening visits using the Barnes Akathisia Scale (BAS)[21], Abnormal involuntary movement scale (AIMS)[22], and Simpson-Angus Scale (SAS)[23].

Dosage/Compliance

Study drugs were administered in 5 mg increments (one capsule), starting at 5mg/day. Dosage was flexible provided the total daily dose remained within the range of 5 to 20mg, however, increases in dosage were constrained by the requirement to allow a period of 7 days between successive increases, and were restricted to patients whose CGI-S score was greater than 1. No restrictions were placed on decreasing doses in response to adverse events. Patients who missed 5 consecutive days of medication were discontinued from the study as 'non-compliant'.

Concomitant medications

The use of concomitant medications with psychotropic activity was prohibited in the present study. However, anticholinergic use was allowed provided patients were diagnosed with EPS and the dose did not exceed 6 mg per day of benzotropine mesylate or biperiden (or its equivalent). Benzodiazepines/hypnotics were permitted only for sleep, provided that they were not used in combination with other drugs of this kind, and the dose did not exceed 40 mg diazepam equivalents per day.

Selection criteria

Consenting male or female Asian outpatients aged between 18 and 65 years were evaluated by a trained psychiatrist and recruited into the present study only if they complied with several selection criteria. Patients were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) diagnostic criteria for schizophrenia, and have a BPRS total score of $\geq$ 18. Female patients of childbearing potential were also required to use a medically accepted means of contraception. In addition, patients and their caregivers were required to be both reliable and in possession of a sufficient level of understanding to achieve compliance with the protocol.

Statistical analysis

A sample size of 276 patients was planned assuming an expected treatment effect (QLS total score) of 5 units favoring olanzapine, with a standard devia-

tion of 14.8 units, 80% power, and a two-sided significance level of 5%. Analyses were conducted at baseline, 8, and 24 weeks post-baseline. Baseline demographic differences between treatment groups were assessed using the Wilcoxon Rank Sum test for continuous data and Fisher Exact test for categorical differences.

The mean change from Baseline to Week 8 or Week 24 scores derived from both clinical and health outcome instruments were assessed using general linear models that corrected for investigator effects on a last observation carried forward (LOCF) basis. Within-group and between-group differences were assessed using p-values, least squares means, and 95% confidence intervals (CI) from these models.

Modal daily doses of antipsychotics were calculated for each patient, and represent the most frequent dose taken over the course of treatment. These were summarized across treatment groups to determine the mean modal dose for this patient population. The treatment groups were compared in terms of modal doses using two-sample t-tests.

Weight gain following 8 and 24 weeks of treatment was summarized with patients grouped according to body mass index (BMI) at Baseline, using the current guidelines for people of Asian extraction[24,25]. Treatment groups were compared using general linear models for each BMI group separately. In addition, the proportion of patients who gained in excess of 7% of their baseline body weight was also compared for each treatment group using a Fisher's Exact test.

The treatment groups were compared in terms of the proportion of responders, use of anticholinergics, study completion, discontinuation, and adverse events using chi-squared tests.

Results

Patient disposition and dosage

This randomized, double-blind, prospective, multi-center study involved outpatients recruited by 22 investigators from 22 centers in the Philippines (n = 120), Pakistan (n = 60), Malaysia (n = 61), Thailand (n = 57), and Singapore (n = 11). Of the 440 patients screened for enrollment into the present study, only 309 met the selection criteria and subsequently 281 were randomized to treatment. Due to violation of selection criteria (specifically, use of additional antipsychotics), a further five patients were excluded from the analysis (n = 276). Baseline demographics, functional status, and clinical status were not significantly different (data not shown, all $p > .05$) for patients randomized to treatment with either olanzapine (n = 144) or haloperidol (n = 132). On average, patients prescribed olanzapine were 32.7 $\pm$ 10 years of age (mean $\pm$ SD), weighed 56.6 $\pm$ 11 kg with a BMI of 22.1 $\pm$ 5 kg/m^2, and 51% were male. Similarly, haloperidol-treated patients, 63% of whom were male, were 31.8 $\pm$ 10 years of age, and weighed 56.2$\pm$10 kg with a BMI of 21.5 $\pm$ 4 kg/m^2.

Study completion rates were 79% for olanzapine patients (n = 113) and 71% for haloperidol patients (n = 94, $p = .164$). The reasons for discontinuation from the present study for olanzapine- and haloperidol-treated patients, respectively, were: adverse event (n = 5, n = 13); death (n = 1, n = 0); lost to follow up (n = 7, n = 10); non-compliance (n = 8, n = 6); patient moved (n = 0, n = 1); personal conflict (n = 7, n = 5); physician decision (n = 1, n = 3); protocol violation (n = 2, n = 0). The only significant difference between the two groups was discontinuation for adverse events ($p = .032$).

During the first 8 weeks of treatment, antipsychotic dosage was not significantly different (mean modal dose ($\pm$ SD) 8.6 $\pm$ 4.0 mg/day for olanzapine and 8.1 $\pm$ 4.0 mg/day for haloperidol). Both antipsychotics were most commonly prescribed at 5 mg/day, with 49% (n = 71) of olanzapine patients, and 58% (n = 77) of haloperidol patients prescribed this dose.

Over the complete course of treatment (24 weeks), olanzapine was prescribed as a mean modal dose ($\pm$ SD) of 10.2 $\pm$ 4.6 mg per day, with 10 mg per day the most common modal dose (38% of patients, n = 54). For haloperidol, the mean modal dose was 8.7 $\pm$ 4.6 mg per day, with the majority of patients (55%, n = 72) prescribed a modal dose of 5 mg daily.

Quality of life

Patients experienced substantial impairment in regard to overall QoL in the month prior to commencing treatment (Table 1). As assessed by both the QLS (Table 1) and the WHOQOL-BREF instruments (Table 2), overall and domain-specific QoL improved for all patients during the acute treatment phase, and this improvement was maintained at 24 weeks ($p < .001$). For patients treated with olanzapine, QLS total scores improved from 44 $\pm$ 19 (mean $\pm$ SD) at Baseline to 58 $\pm$ 21 at 8 weeks, and 66 $\pm$ 23 at 24 weeks ($p < .001$). Haloperidol-treated patients also experienced significant improvement in QLS total scores, from 42$\pm$18 at Baseline to 55 $\pm$ 21 at 8 weeks, and 63 $\pm$ 23 at 24 weeks ($p < .001$). Similarly, the domain-specific QoL scores in the WHOQOL-BREF indicate significant improvements for both treatment groups from baseline to acute (8 weeks, $p < .01$) and maintenance (24 weeks, $p < .001$) phases of

Table 1. Unadjusted overall and domain-specific QoL scores in the month prior to treatment (baseline), and at the acute (8 weeks) and maintenance (24 weeks) phases of treatment with either olanzapine (n = 130) or haloperidol (n = 115), as assessed by the schizophrenia-specific Quality of Life Scale (QLS)

QLS subscale	Treatment	Baseline	Week 8	Week 24
Interpersonal Relations	Olanzapine	15.32 (7.85)	20.07 (9.09)*	23.60 (9.80)*
	Haloperidol	15.05 (7.39)	19.84 (9.23)*	23.14 (9.83)*
Intrapsychic Foundations	Olanzapine	16.32 (7.67)	21.84 (7.45)*	24.01 (8.05)*
	Haloperidol	15.56 (6.69)	19.89 (7.39)*	22.43 (7.82)*
Instrumental Role	Olanzapine	5.69 (3.77)	7.75 (4.07)*	9.01 (4.25)*
	Haloperidol	5.24 (3.38)	7.02 (3.59)*	8.06 (3.83)*
Comman Objects and Activities	Olanzapine	4.38 (2.36)	5.67 (2.42)*	6.25 (2.42)*
	Haloperidol	3.89 (2.24)	5.05 (2.27)*	5.84 (2.48)*
Total	Olanzapine	43.97 (19.20)	58.22 (20.80)*	66.14 (22.99)*
	Haloperidol	41.74 (17.82)	54.48 (20.76)*	62.52 (22.09)*

Data are expressed as mean $\pm$ SD
* $p < .001$, based on within-treatment changes, adjusted for investigator effects

Table 2. Unadjusted domain-specific QoL scores prior to treatment (baseline), and at the acute (8 weeks) and maintenance (24 weeks) phases of treatment with either olanzapine (n = 129) or haloperidol (n = 113), as assessed by the World Health Organisation Quality of Life-Brief (WHOQOL-BREF) scale

WHOQOL-BREF domain	Treatment	Baseline	Week 8	Week 24
Physical	Olanzapine	48.98 (15.36)	61.96 (11.65)**	66.00 (13.92)**
	Haloperidol	50.95 (17.17)	57.43 (15.30)*	63.43 (14.88)**
Psychological	Olanzapine	42.02 (18.32)	53.55 (14.32)**	59.82 (16.74)**
	Haloperidol	42.99 (18.98)	52.51 (16.19)*	59.18 (15.52)**
Social Relationships	Olanzapine	37.02 (21.09)	48.51 (16.88)**	55.36 (16.20)**
	Haloperidol	39.97 (22.05	49.85 (19.03)*	54.72 (16.70)**
Environment	Olanzapine	44.19 (16.50)	55.06 (11.87)**	60.37 (13.26)**
	Haloperidol	43.83 (18.48)	54.18 (15.24)**	59.18 (14.43)**

Data are expressed as mean $\pm$ SD
* $p < .01$; ** $p < .001$, based on within-treatment changes, adjusted for investigator effects

treatment. Acute treatment with olanzapine improved functioning in terms of Intrapsychic Foundations significantly more than haloperidol (Fig. 1, p = .044). As shown in Fig. 2, olanzapine treatment was also associated with significantly greater improvement in WHOQOL-BREF Physical domain scores at both 8 ($p < .001$) and 24 weeks post-baseline (p = .002). WHOQOL-BREF Social Relationship scores were also significantly improved for patients with 24 weeks of olanzapine therapy (p = .037). In regards to all other QoL domains assessed, no significant treatment differences were detected.

Clinical outcomes

Prior to treatment, patients were mildly to moderately ill (Table 3). In both treatment groups, all BPRS (Table 3) and PANSS (Table 4) scores improved over time ($p < .001$). Over the complete course of therapy, olanzapine treatment was associated with significantly greater improvements in negative symptoms than haloperidol (least squares mean change from baseline [95%CI], BPRS negative scores for olanzapine vs haloperidol: -4.8 [-5.4, -4.2] vs -3.6 [-4.2, -2.9] p = .003, and PANSS negative scores -11.0 [-12.4, -9.6] vs -8.6 [-10.1, -7.1] p = .007). These differences were not statistically significant in the acute phase (BPRS negative scores -3.7 [-4.3, -3.1] vs -3.0 [-3.6, -2.3] p = .053, and PANSS negative scores -8.1 [-9.4, -6.9] vs -7.1 [-8.5, -5.7] p = .218). A similar pattern was observed for overall symptomatology, with olanzapine patients experiencing significantly greater improvements in BPRS and PANSS

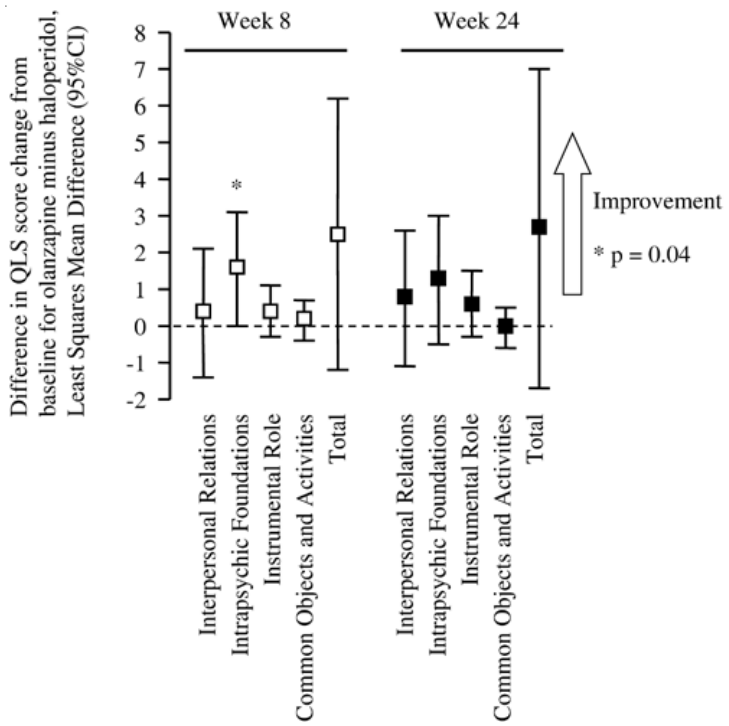

Fig. 1 Comparison of the impact of olanzapine and haloperidol treatment on quality of life scale (QLS) overall and domain-specific scores during acute (8 weeks) and maintenance (24 weeks) phases

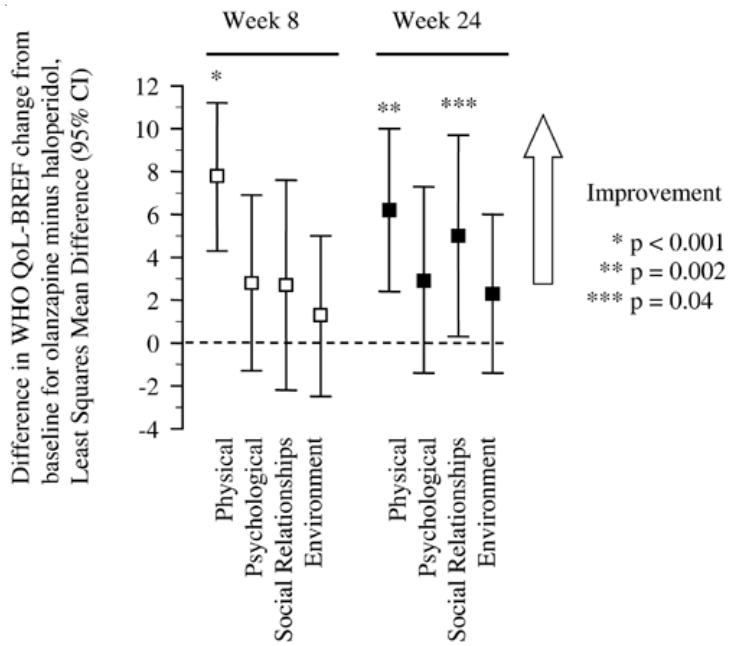

Fig. 2 Comparison of the impact of olanzapine and haloperidol treatment on WHOQOL-BREF domain-specific scores during acute (8 weeks) and maintenance (24 weeks) phases

Table 3. Change in baseline brief psychiatric rating scale (BPRS) scores following the acute (8 weeks) and maintenance (24 weeks) phases of treatment with either olanzapine or haloperidol

BPRS subscale	Timepoint	Olanzapine (n = 139)	Haloperidol (n = 123)	p-value
Positive	Baseline (mean ± SD)	12.45 (4.92)	12.39 (4.56)	-
	Change at 8 weeks (LS mean, CI)	-6.5 (-7.2, -5.7)*	-5.9 (-6.8, -5.1)*	0.287
	Change at 24 weeks (LS mean, CI)	-7.7 (-8.5, -6.8)*	-6.7 (-7.6, -5.8)*	0.082
Negative	Baseline (mean ± SD)	8.13 (3.81)	7.96 (4.05)	-
	Change at 8 weeks (LS mean, CI)	-3.7 (-4.3, -3.1)*	-3.0 (-3.6, -2.3)*	0.053
	Change at 24 weeks (LS mean, CI)	-4.8 (-5.4, -4.2)*	-3.6 (-4.2, -2.9)*	0.003
Total	Baseline (mean ± SD)	42.45 (16.58)	42.85 (17.32)	-
	Change at 8 weeks (LS mean, CI)	-22.3 (-24.7, -19.8)*	-19.3 (-22.0, -16.6)*	0.071
	Change at 24 weeks (LS mean, CI)	-26.8 (-29.5, -24.0)*	-22.4 (-25.4, -19.4)*	0.018

Abbreviations: LS = Least square; CI = Confidence interval
LS means are derived from the general linear model which adjusts the mean change for investigator effects, and are shown with 95%CIs. Baseline means are unadjusted and are shown with their associated standard deviations
* $p < .001$, within treatment effect adjusted for investigator effects

Table 4. Change in baseline positive and negative symptom scale (PANSS) scores during the acute (8 weeks) and maintenance (24 weeks) phases of treatment with either olanzapine or haloperidol

PANSS Subscale	Timepoint	Olanzapine (n = 139)[f]	Haloperidol (n = 123)	p-value
Positive	Baseline (mean ± SD)	25.35 (7.79)	25.77 (7.18)	-
	Change at 8 weeks (LS mean, CI)	-9.7 (-11.0,-8.5)*	-8.9 (-10.3,-7.6)*	0.325
	Change at 24 weeks (LS mean, CI)	-11.5 (-12.8,-10.2)*	-10.2 (-11.6,-8.7)*	0.128
Negative	Baseline (mean ± SD)	26.80 (8.01)	26.80 (8.66)	-
	Change at 8 weeks (LS mean, CI)	-8.1 (-9.4, -6.9)*	-7.1 (-8.5, -5.7)*	0.218
	Change at 24 weeks (LS mean, CI)	-11.0 (-12.4, -9.6)*	-8.6 (-10.1, -7.1)*	0.007
Total	Baseline (mean ± SD)	104.19 (28.15)	104.85 (30.20)	-
	Change at 8 weeks (LS mean, CI)	-36.0 (-40.4, -31.6)*	-31.6 (-36.3, -26.9)*	0.125
	Change at 24 weeks (LS mean, CI)	-44.6 (-49.3, -39.9)*	-36.7 (-41.8, -31.6)*	0.011

Abbreviations: LS = Least square; CI = Confidence interval
LS means are derived from the general linear model which adjusts the mean change for investigator effects, and are shown with 95%CIs. Baseline means are unadjusted and are shown with their associated standard deviations
*$p < .001$, within treatment effect adjusted for investigator effects; [f] n = 137 for negative and total PANSS

total scores at 24 weeks (BPRS total scores -26.8 [-29.5, -24.0] vs -22.4 [-25.4, -19.4] p = .018, and PANSS total scores -44.6 [-49.3, -39.9] vs -36.7 [-41.8, -31.6] p = .011), following less distinct separation of the treatment groups at 8 weeks (BPRS total scores -22.3 [-24.7, -19.8] vs -19.3 [-22.0, -16.6] p = .071, and PANSS total scores -36.0 [-40.4, -31.6] vs -31.6 [-36.3, -26.9] p = .125). Both antipsychotics showed similar efficacy in treating positive symptoms (Tables 3 and 4). CGI-S scores improved after both 8 (least squares mean change from baseline [95%CI], olanzapine vs. haloperidol: -1.2 [-1.3, -1.0] vs -1.1 [-1.3, -0.9]) and 24 weeks (-1.6 [-1.8, -1.4] vs -1.4 [-1.6, -1.2]) of treatment for all patients ($p < .001$); however, there were no statistically significant differences between treatment groups.

Similar response rates were observed in the two treatment groups. The proportion of responders for the acute phase (the first 8 weeks) was 75% (n = 104) for olanzapine, and 73% (n = 90) for haloperidol (p = .779). Eighty-four percent (n = 116) of patients in the olanzapine group met the criteria for responders following 24 weeks treatment, compared with 75% (n = 93) for haloperidol (p = .095).

Movement disorders

To address tolerability, physical dysfunction was assessed for all patients using the BAS, AIMS, and SAS scales (Table 5). Barnes Akathisia Scale total

Table 5. Baseline functional physical status and change during the acute (8 weeks) and maintenance (24 weeks) phases of treatment with either olanzapine or haloperidol, as assessed using the Barnes Akathisia Scale (BAS), abnormal involuntary movement scale (AIMS), and Simpson-Angus Scale (SAS)

Scale	Timepoint	Olanzapine (n = 139)	Haloperidol (n = 124)[f]	p-value
BAS Total	Baseline (mean ± SD)	0.98 (2.14)	1.18 (2.67)	-
	Change at 8 weeks (LS mean, CI)	-0.2 (-0.6, 0.2)	0.7 (0.3, 1.2)**	0.001
	Change at 24 weeks (LS mean, CI)	-0.2 (-0.6, 0.2)	0.5 (0.1, 0.9)***	-0.003
SAS[f] Total	Baseline (mean ± SD)	1.50 (3.46)	1.43 (2.56)	-
	Change at 8 weeks (LS mean, CI)	-0.9 (-1.5, -0.3)**	1.0 (0.3. 1.6)**	<0.001
	Change at 24 weeks (LS mean, CI)	-1.0 (-1.6, -0.5)*	0.4 (-0.2, 1.0)	<0.001
AIMS Total	Baseline (mean ± SD)	1.29 (2.90)	1.72 (4.13)	-
	Change at 8 weeks (LS mean, CI)	-0.8 (-1.3, -0.3)**	-0.1 (-0.7, 0.4)	0.053
	Change at 24 weeks (LS mean, CI)	-0.9 (-1.4, -0.3)**	-0.3 (-0.8, 0.2)	0.096

Abbreviations: LS = Least square; CI = Confidence interval
LS means are derived from the general linear model which adjusts the mean change for investigator effects, and are shown with 95%CIs. Baseline means are unadjusted and are shown with their associated standard deviations
* $p < .001$; ** $p \leq .005$; *** $p = .01$, within treatment effect adjusted for investigator effects; [f] n = 123 for SAS total

scores were reduced by olanzapine treatment at 8 ($p = .442$) and 24 weeks ($p = .252$), however, patients taking haloperidol showed significant elevations of this score at both 8 ($p = .002$) and 24 weeks ($p = .013$), indicating a worsening of akathisia compared with those patients prescribed olanzapine ($p = .001$ at 8 weeks; $p = .003$ at 24 weeks).

During the acute treatment phase, SAS scores improved with olanzapine treatment ($p = .005$), but worsened for haloperidol-treated patients ($p = .004$). By 24 weeks, patients taking olanzapine continued to show a reduction in SAS scores ($p < .001$); for haloperidol-treated patients, the mean 24-week SAS score was reduced compared with the 8-week score, but was not significantly different from the baseline score. Olanzapine treatment was associated with significantly better SAS scores than haloperidol at both 8 and 24 weeks of assessment ($p < .001$). Olanzapine therapy was associated with an improvement in the involuntary movements characteristic of TD as assessed by the AIMS (8 weeks, $p = .003$; 24 weeks $p = .001$). This was not the case for haloperidol treatment, as AIMS total scores did not change significantly for these patients. There was no statistical difference in AIMS scores between treatment groups.

Weight

Olanzapine monotherapy was associated with clinical weight gain. Following the first 8 weeks of treatment, a greater proportion of patients (26%, n = 32) experienced gain in excess of 7% of baseline weight, compared with those taking haloperidol (12%, n =13, $p = .012$). This trend was also apparent (although not statistically significant, $p = .065$) when treatment was extended for a further 16 weeks (olanzapine 44% (n = 51) vs haloperidol 32% (n = 30)).

Olanzapine- and haloperidol-treated patients with a baseline BMI classification of underweight or normal (< 23 kg/m^2) demonstrated similar weight gain with acute and maintenance antipsychotic monotherapy (Table 6). In addition, irrespective of antipsychotic therapy, obese patients, on average, did not experience clinical weight gain (i.e. > 7%). There was a differential effect of antipsychotic treatment for overweight patients (BMI of ≥ 23 to < 25 kg/m^2). For this group of patients, olanzapine monotherapy was associated with significant weight gain in both the acute and maintenance phases, whereas patients prescribed haloperidol maintained their baseline weight. The differences between treatment groups reached statistical significance for the overweight patients alone ($p < .04$).

Patient participation, adverse events, and safety

Adverse events (AE) were reported for fewer patients taking olanzapine compared with those prescribed haloperidol (42% vs 58%, $p = .011$). Dystonia was more common in patients prescribed haloperidol (olanzapine vs haloperidol: 0% vs 5%, $p = .010$), as were EPS (8% vs 24%, $p < .001$) and tremor (6% vs 14%, $p = .014$). Conversely, weight gain was more frequently associated with olanzapine treatment (9% vs 2%, $p = .006$). The proportion of patients with insomnia (5% olanzapine, 7% haloperidol) and akathisia (2% olanzapine, 5% haloperidol) was not significantly different

Table 6. The relationship between body weight change from baseline and baseline body mass index (BMI) at 8 and 24 weeks for patients prescribed either olanzapine or haloperidol

Baseline BMI, kg/m^2	Mean Weight Change, kg (95%CI)	Olanzapine	n	Haloperidol	n	p-value
Underweight < 18.5	Week 8	2.95 (1.27, 4.62)*	28	2.56 (0.69, 4.43)*	25	0.745
	Week 24	5.83 (3.32, 8.34)**	23	4.51 (1.73, 7.29)*	22	0.465
Normal ≥ 18.5 to < 23	Week 8	3.16 (2.28, 4.03)**	56	2.08 (1.17, 2.99)**	48	0.069
	Week 24	4.22 (2.93, 5.52)**	52	3.06 (1.60, 4.52)**	42	0.213
Overweight ≥ 23 to < 25	Week 8	2.92 (1.04, 4.81)*	17	-0.66 (-3.02, 1.69)	13	0.025
	Week 24	4.95 (2.02, 7.88)*	16	-0.69 (-4.50, 3.12)	11	0.033
Obese ≥25	Week 8	0.22 (-1.43, 1.87)	24	0.78 (-0.98, 2.54)	22	0.641
	Week 24	1.13 (-1.28, 3.54)	24	1.24 (-1.40, 3.88)	20	0.951

Abbreviations: CI = Confidence interval
Means are derived from the general linear model which adjusts the mean change for investigator effects, and are shown with 95%CIs
* $p < .01$; ** $p < .001$, within treatment effect adjusted for investigator effects

for either antipsychotic. Nine serious AEs were reported for patients prescribed haloperidol, and patients on olanzapine therapy reported two, one of which was a fatality unrelated to olanzapine (due to complications of hypertension).

Routine laboratory tests demonstrated that, for all electrolyte and blood parameters assessed, including liver function tests, patients were within clinically acceptable ranges throughout the study period. There were no clinically significant differences between the treatment groups.

Concomitant medications

At Baseline, a small proportion of patients in both treatment groups (< 2%) were co-prescribed anticholinergics. During the acute treatment phase, 6.9% (n = 10) of olanzapine-treated patients and 11.4% (n = 15) of patients taking haloperidol required anticholinergics. Over the entire course of treatment, the frequency of anticholinergic use rose for both olanzapine- (16.7%, n = 24) and haloperidol-treated (30.3%, n = 40) patients. However, patients taking haloperidol were more likely to be co-prescribed anticholinergics over this period (p = .010). The overall frequency of use of benzodiazepines/hypnotics was similar in the two treatment groups (59 reports of use in the olanzapine group vs 57 in the haloperidol group).

Discussion

As anticipated, antipsychotic medication was an effective and well-tolerated means of controlling the symptoms of schizophrenia in this relatively young population of Asian outpatients with mild to moderate illness severity. The 5 mg/day initial dose may not have been optimal for olanzapine, the prescription of which is recommended to reach 10 mg/day within several days of initiating treatment[26]. The lower mean modal dose in the acute phase is likely to be a reflection of the study design, as despite being able to increase the dose every 7 days, the absence of a scheduled visit at these intervals may have made such dose modifications less likely. Since the prescribed dose of olanzapine increased over the course of the present study and there were improved response rates at 24 weeks, it is possible that the initial sub-optimal dose delayed response to treatment. This has been demonstrated by other studies[27]. A similar study conducted in Europe and North America reported higher response rates for olanzapine than haloperidol following 6 weeks of therapy, however, the doses of both antipsychotics were considerably higher than those reported here (mean modal dose ± SD, 13.2 ± 5.8 mg/day for olanzapine and 11.8±5.6 mg/day for haloperidol[28]. As the dosing schedule was identical to that used in the present study, this difference may be attributable, at least in part, to the weekly cycle of assessments.

It may also be argued that the dosing regimen (5 to 20 mg, with 5 mg incremental changes) was not well suited to haloperidol either. There has been some criticism raised in literature that many perceived benefits of atypical antipsychotics are due to the excessive doses of comparator drugs used[29]. However, the mean modal dose of haloperidol prescribed throughout the present study falls well within both the guidelines in

the product information (1 to 3 mg tid, may be increased to 10 to 20 mg tid, depending on the response) and the optimal dose of 6 to 12 mg per day recommended by the American Psychiatric Association[30], as well as the local guidelines for haloperidol prescription (for example, the National Center for Mental Health in the Philippines recommends a maintenance dose of 5 to 20 mg/day[31] and the recommended maintenance dose in Malaysia is 1 to 15 mg/day[32]. Furthermore, there was high patient retention, with few patients discontinuing haloperidol treatment due to AEs attributable to high antipsychotic doses, despite EPS being reported by 24% of patients.

The primary objective of the present study was to examine QoL. Two instruments were applied: the QLS, which is disease-specific and physician-reported, and the WHOQOL-BREF scale, a widely used, multidisciplinary tool that is self-reported. Since QoL is, in part, a subjective phenomenon it is important to include patients' perceptions[6], and studies have confirmed that such self-reporting is reliable[33,34]. This is the first study to administer both tools to the same patient population, although each of these QoL instruments has been applied to patients with schizophrenia before. The significant improvement observed in QoL highlights the value of antipsychotic treatment in re-establishing normalcy via functional improvement for patients with schizophrenia. The domain-specific enhanced QoL for olanzapine-treated patients observed using the WHOQOL-BREF scale may reflect the more favorable AE profile and tolerability of olanzapine. Specifically, the greater improvement in the Physical domain scores of olanzapine-treated patients in the WHOQOL-BREF Physical domain at 8 and 24 weeks may reflect significantly lower prevalence of physical dysfunction in this group (as indicated by the greater prevalence of EPS symptoms and poorer SAS and BAS scores in the haloperidol-treated group). It may be speculated that this reduction in physical impairment underlies the significantly greater improvement in the Social relationships domain for olanzapine patients. Given that the QLS was designed to address deficit symptoms, and patients prescribed olanzapine showed significantly greater improvement in negative symptoms (and overall psychopathology), it seems surprising that the QLS did not reflect this, especially considering that current literature suggests negative symptoms are an important influence on QoL[35,36]. Indeed, a pan European comparison of olanzapine and haloperidol treatment for schizophrenia found that 6 weeks of olanzapine treatment was accompanied by highly significant improvements in QLS Total, Intrapsychic Foundations, and Interpersonal Relations scores compared with haloperidol[37]. However, the present findings are consistent with a study comparing olanzapine with placebo and haloperidol treatment for schizophrenia in North America, which failed to discriminate any significant difference on QLS domains between the two antipsychotics[38]. A recently published study[39] comparing olanzapine with haloperidol treatment for schizophrenia found that both had similar results with respect to compliance, symptoms, EPS, and overall quality of life. Patients assigned to haloperidol received prophylactic benztropine to address the risk of EPS with haloperidol treatment, and it was suggested that this accounted for the lack of difference observed between the two treatments. A direct comparison between that study and the present study is difficult, however, given the differences in study design, dosing, and population, with the patient population in the Rosenheck study, which was mostly male, older, and more severely ill.

The lack of concordance between the two instruments may reflect cultural differences in the previously untested Asian population, which may be better served by the less confrontational nature of the self-reported WHOQOL-BREF scale, rather than the physician-mediated QLS. Additionally, the present study may lack the power required to show significant differences across all measures.

Olanzapine improved both positive and negative symptoms in the present study, as has been reported in other populations [28, 37, 40]. The lack of separation between olanzapine and haloperidol for positive symptom control was consistent with similar findings from previous studies, and suggests that haloperidol and olanzapine are equally efficacious for the treatment of positive symptoms of schizophrenia in Asian outpatients. There was no significant difference between the two treatments in the control of negative symptoms at 8 weeks, which may have been related to the suboptimal starting dose of olanzapine, as discussed previously. However, by the present end of the study, there was significantly greater control of negative symptoms in the olanzapine group compared with the haloperidol group, and significantly improved total BPRS and PANSS scores in the olanzapine group. Despite this, when the overall severity of illness was assessed using the CGI-S scale, there was no statistically significant difference, which may also have contributed to the lack of observed treatment effect on QoL.

In the present study, haloperidol was associated with drug-induced akathisia and Parkinsonism,

whereas olanzapine therapy improved Parkinsonism both short- and long-term. There was also a tendency for TD symptoms to improve with olanzapine. Long-term use of haloperidol was associated with an increased use of anticholinergics, which may account for the improvement in SAS total scores between 8 and 24 weeks for patients prescribed haloperidol. Although the early prescription of anticholinergics for patients in the olanzapine group may be explained by pre-existing symptoms, increased prescription is unexpected, and appears to be unrelated to BAS, SAS, and AIMS scores. A similar prescribing practice was noted in a recent review of schizophrenia treatment for Chinese patients, with 47% of acute patients and 46% of chronic patients taking a combination of atypical antipsychotics and antiparkinson drugs[41]. Such a prescribing practice is surprising, given that olanzapine's comparatively benign EPS profile has been demonstrated in both Caucasian and Asian populations[42,43].

Patients with a baseline BMI in the overweight range treated with olanzapine gained significantly more weight than their haloperidol-treated counterparts. These results are in contrast to a study of ~1200 patients comparing olanzapine and haloperidol treatment, in which weight gain associated with olanzapine during the acute phase (6 weeks) was noted to be significantly more common among patients with a low baseline BMI[18]. At the extension phase (52 weeks) of this ~1200-patient study, patients gained significantly more weight if they were treated with olanzapine, however, this weight gain led to only one discontinuation[37]. Similarly, in the present study, no patient discontinued olanzapine treatment because of weight gain, indicating that the occurrence of comparatively greater weight gain does not lead to cessation of olanzapine treatment in the Asian outpatient population.

Combined prescription of atypical and typical agents appears to be a common practice in Asia, despite minimal evidence to support this therapy[41,44-46]. The present study supports the argument that a polypharmacy approach may be unnecessary in this population, as effective management of psychotic, neurologic, and functional symptoms can be achieved with antipsychotic monotherapy, even with restricted use of adjunct medication.

Conclusion

The present study highlights the efficacy of antipsychotic monotherapy and some of the clinical differences associated with olanzapine and haloperidol treatment. Specifically, olanzapine provided more efficacious control of positive and overall symptoms with fewer EPS adverse events, but greater weight gain compared with haloperidol. These data also prompt the speculation that the WHOQOL-BREF may be more sensitive than the QLS in Asian schizophrenia outpatient populations. Additional studies investigating the relationship between clinical and functional outcomes, and the pharmacoeconomics of antipsychotic treatment for schizophrenia in this population are required. This will allow for more accurate assessment of the long-term cost benefits of individual antipsychotic treatments.

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Abbreviations

AE	Adverse event
AIMS	Abnormal involuntary movement scale
BAS	Barnes akathisia scale
BMI	Body mass index
BPRS	Brief psychiatric rating scale
CGI-S	Clinical global impression-severity scale
CI	Confidence interval
EPS	Extrapyramidal symptoms
PANSS	Positive and negative syndrome scale
QLS	Quality of life scale
QoL	Quality of life
SAS	Simpson-Angus scale
TD	Tardive dyskinesia
WHOQOL-BREF	World Health Organization quality of life-brief scale

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การศึกษาแบบสุ่มโดยวิธีปิดเปรียบเทียบประสิทธิภาพต่อคุณภาพชีวิตในผู้ป่วยนอกโรคจิตเภทของในประเทศอาเซียนระหว่างยา โอลันซาปีนกับยาฮาโลเพอริดอล

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***วัสดุและวิธีการ**: โดยวิธีสุ่มตัวอย่างแบบปิดด้วยระยะเวลา 24 สัปดาห์ โดยมีจำนวนผู้ป่วยรักษาด้วย โอลันซาปีน 144 คน และรักษาด้วย ฮาโลเพอริดอลจำนวน 132 คน ประเมินผลการรักษา คุณภาพชีวิต ด้วย แบบวัด QLS และ WHO-BREF ประสิทธิภาพตอบสนองต่อยาทางคลินิก ด้วย PANSS, BPRS และ CGI อาการข้างเคียงประเมินด้วยแบบวัด BAS, AIMS และ SAS*

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