*Original Article*

# Efficacy and Safety of Olanzapine versus Haloperidol in the Treatment of Taiwanese Schizophrenia Patients

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**Objective:** Olanzapine is a novel atypical antipsychotic agent that became available in 1998 in Taiwan. To investigate the safety and efficacy profile of olanzapine in Taiwanese patients with schizophrenia, a prospective multi-center trial was conducted. **Methods:** In this 14-week, randomized, double-blinded study, 54 schizophrenic patients in Taiwan were given olanzapine (N=26; mean modal dose 14.2 mg/day) or haloperidol (N=28; mean modal dose 13.4 mg/day). **Results:** Olanzapine was significantly superior to haloperidol in improving baseline to endpoint mean scores (p=.021) on the Positive Scale of the Positive and Negative Symptom Scale (PANSS) and the Abnormal Involuntary Movement Scale (AIMS) (p=.011). There were no statistically significant differences between olanzapine and haloperidol on the other rating scales of efficacy and extrapyramidal symptoms (EPS). The response rate (a decrease of 40% on BPRS total score) was 54.2% with olanzapine compared to 28.6% with haloperidol. Olanzapine-treated patients had significantly lower incidences of treatment-emergent EPS, agitation, and amblyopia ($p < .050$) than haloperidol-treated patients, while haloperidol-treated patients experienced significantly less weight gain (p=.002). **Conclusion:** Olanzapine is an effective and well tolerated agent for the treatment of Taiwanese patients with schizophrenia. The increased body weight under olanzapine treatment deserves clinical attention.

**Key words: schizophrenia, olanzapine, haloperidol**
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## Introduction

Typical (conventional) antipsychotic agents such as haloperidol have shown some degree of efficacy in reducing either the severity or relapse of schizophrenia; however, these conventional therapies have their limitations. Nearly one-half of patients with schizophrenia who had been treated with typical antipsychotic agents showed poor or

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no response[1]. Furthermore, treatment using typical antipsychotics has often been associated with troublesome side effects which not only cause patient suffering, but also contribute to nearly 50% patient noncompliance with medication[2]. The most commonly observed side effects are extrapyramidal symptoms (EPS)[3] and hyperprolactinemia-related symptoms[4].

Conventional antipsychotics-associated side effects have raised the need for novel antipsychotics, which can exhibit broader efficacy, lower incidence of extrapyramidal symptoms, and minimal perturbation of prolactin levels. The prototype of an atypical antipsychotic, clozapine, seems to meet these requirements[5]. However, the application of clozapine is limited due to its potentially lethal side effect, agranulocytosis. Additionally, Asian patients on clozapine seem to be more likely to experience anti-cholinergic and other side effects than do Caucasians[6-8].

Olanzapine is a novel antipsychotic with low affinity for the α2-adrenergic receptor; it has shown a greater affinity for the 5-$HT_2$ receptor than the D2 receptor. Multinational clinical trials comparing olanzapine with conventional neuroleptic agents and placebos have found evidence for improved efficacy in Caucasian psychotic patients [9-10]. In order to investigate the safety and efficacy profile of olanzapine in Taiwanese schizophrenic patients, we conducted a randomized double-blind olanzapine vs. haloperidol, multicenter trial in Taiwan from 1997 to 1998.

## Methods

### Patient Population

Patients were Taiwanese between the ages of 18 to 65 years who signed written informed consent documents after the details of the study had been fully explained. Patients met the criteria set down in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) for schizophrenia, schizophreniform, or schizoaffective disorders. Patients must have had clinically significant psychotic symptoms (positive and/or negative) and had either 1) a baseline BPRS (Brief Psychiatric Rating Scale) total score, extracted from the PANSS (0 to 6 rating scale), of at least 18 and were not currently being treated with any neuroleptic drug, or 2) were not demonstrating optimal clinical response to his/her current neuroleptic treatment or were judged intolerant of his/her current neuroleptic medication(s) (except for haloperidol). In this[not sure what you are referring to here?? the second??] case, the patient entered the study without having a minimum extracted BPRS score. Patients were enrolled by 4 investigative sites in Taiwan: National Taiwan University Hospital, Taoyuan Psychiatric Center, Taipei City Psychiatric Center, and Veterans General Hospital-Taipei.

### Study Design

This was a randomized, double-blind study consisting of two study periods. Study Period I included a 2- to 9-day washout period during which screening tests, patient history, and psychiatric and physical examinations were performed (Visits 1 and 2). Patients who did not meet the criteria for enrollment (see "Exclusion Criteria" below) were disqualified from the study at Visit 2. Baseline scores on psychiatric rating scales were established at Visit 2, prior to receiving the study drugs. Study Period II was the 14-week double-blind therapy period beginning with randomization at Visit 2 and continuing through Visit 10. Qualified patients from Study Period I were randomized (1:1 ratio) at Visit 2 to either olanzapine (5, 10, 15, or

20 mg/day) or haloperidol (5, 10, 15, or 20 mg/day), beginning at 5 mg/day. Patients were assessed weekly from Visits 2 to 8 and then every 4 weeks from Visits 8 to 10. Active study medication was given once a day in the evening. The dose could be increased or decreased in increments or decrements of 5 mg/day, but not more frequently than 7 days following the last dose increase. Patients who could not tolerate the minimum daily dose of 5 mg were discontinued from the study. Dosing decreases and medication discontinuation due to safety concerns were allowed at any time at the discretion of the investigator.

## Exclusion Criteria

Any of the following reasons were basis for exclusion of a patient from the study: (1) pregnancy or lactation; (2) serious, unstable physical illness such that hospitalization for the disease was anticipated within 3 months or death was anticipated within 3 years; (3) uncorrected hypothyroidism or hyperthyroidism; (4) myasthenia gravis; (5) narrow-angle glaucoma; (6) chronic urinary retention and/or clinically significant prostatic hypertrophy; (7) one or more seizures without a clear and resolved etiology; (8) leukopenia or history of leukopenia without a clear and resolved etiology; (9) current jaundice and/or elevation of total bilirubin, alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), gamma-glutamyl transferase (GGT), or alkaline phosphatase to any level that exceeded three times the upper limit of the laboratory normal range; (10) positive hepatitis surface antigen (HbsAg) or positive IgM fraction of the hepatitis core antibody (anti-HBc (IgM)); (11) history of severe allergies or multiple adverse drug reactions; (12) DSM-IV substance (alcohol or other drug) abuse or dependence within the past 3 months; (13) judgement by clinicians to be a serious suicide risk; or (14) participation in a clinical trial of another investigational drug within 1 month (30 days) prior to study entry (Visit 1).

Restricted concomitant medication therapy was as follows: (1) drugs with primarily central nervous system activity; (2) an injectable depot neuroleptic within less than one of the patient's dosing intervals between depot neuroleptic injections prior to study entry; (3) lithium, anticonvulsants, benzodiazepines (except as allowed by the protocol), antidepressants (except fluoxetine), psychostimulants, reversible monoamine oxidase inhibitors, reserpine, guanethidine, or guanadrel within 1 week prior to Visit 2 (the start of active treatment); (4) nonreversible monoamine oxidase inhibitors within 2 weeks prior to Visit 2; (5) fluoxetine within 4 weeks prior to Visit 2; (6) remoxipride within 6 months (180 days) prior to Visit 2; (7) olanzapine; or (8) clozapine within 4 weeks prior to Visit 2.

## Efficacy and Safety Assessments

The efficacy of olanzapine and haloperidol was assessed using the PANSS-extracted BPRS [11], the PANSS total, positive, and negative scores[12], the Clinical Global Impression (CGI)-Severity scale[13], and the Montgomery-Asberg Depression Rating Scale (MADRS)[14]. Treatment responders were defined a priori as patients who achieved ≥40% reduction in BPRS total score from the baseline.

Safety evaluations for extrapyramidal symptoms (EPS) included the AIMS[13], Simpson-Angus Scale (SAS)[15], and Barnes Akathisia Scale (BAS)[16]. Vital signs (blood pressure, pulse, weight, and temperature) were measured at each visit. Clinical laboratory testing (clinical chemistry, electrolyte group, hematology, and urinalysis) was performed at Visits 1 and 2, at any time a patient completed or discontinued the stu-

dy, or when clinically indicated. Clinical chemistry was also performed biweekly (Visits 4, 6, and 8) during the first 6 weeks of double-blind therapy and monthly for the remainder of the study. Blood samples to measure plasma prolactin concentrations were taken at the baseline and Visit 8. Blood and urine specimens were collected and sent to the central laboratory for analysis.

### Statistical Methods

Continuous numbers were compared with t-test, and categorical numbers were compared with Fisher's exact test. Differences were considered to be statistically significant for p values greater than or equal to 0.05.

## Results

Patients had a mean age of 35.8±9.0 years, and 51.9% were male. The severity of illness and demographics among treatment groups were comparable at the baseline. The mean modal dosages of olanzapine and haloperidol were 14.2 mg/day and 13.4 mg/day, respectively. The median modal dosage of both drugs was 15 mg/day. The most frequently used concomitant medication was lorazepam, taken by 63% of patients (57.7% of olanzapine-treated vs. 67.9% of haloperidol-treated patients). There was a statistically significant difference ($p < 0.001$, Fisher's exact test) in the use of anticholinergic agents (biperiden hydrochloride, benztropine mesylate, trihexyphenidyl hydrochloride, and biperiden) between the olanzapine (23.1%) and haloperidol (89.3%) groups.

A total of 72 patients entered Study Period I. Of these, 54 (26 olanzapine, 28 haloperidol) were randomized in Study Period II. Sixteen of the olanzapine-treated patients (61.5%) compared to 14 of the haloperidol-treated patients (50.0%) completed the double-blind phase (Table 1). Ten olanzapine-treated patients discontinued the study, with one discontinuing as a result of an adverse event (gastrointestinal hemorrhage) and two for lack of efficacy. By comparison, 14 haloperidol-treated patients discontinued the study, with one discontinuing as a result of an adverse event (extrapyramidal symptoms) and five for lack of efficacy. Table 2 summarizes the mean changes of efficacy and tolerability from baseline to endpoint.

A significantly larger mean increase in weight from baseline to endpoint ($F=11.20$, $df=1$, $p=0.002$) was observed with olanzapine (4.71 kg) compared to haloperidol (0.51 kg) during Study Period II. The percentages of patients who gained 7% or more of their baseline body weight were 50.0% with olanzapine treatment and 11.1% with haloperidol treatment. The ranges of weight change were 0 to 11.2 kg with olanzapine and -11.2 to 9 kg with haloperidol. There were no other statistically significant differences in vital signs.

There was a statistically significant difference between treatment groups in the laboratory analysis for mean change from baseline to endpoint of plasma prolactin concentrations ($p < 0.001$, based on the Wilcoxon Rank Sums Test). There was a decrease in the mean change from baseline to endpoint of plasma prolactin concentrations (% upper limit of normal reference range [URL]) with olanzapine (n=20) (mean change -4.34% ±143.18% URL), and an increase with haloperidol (n=23) (mean change 173.62% ±156.88% URL). The baseline plasma prolactin concentrations were 100.35%±162.30% URL for the olanzapine group and 60.36%±46.55% URL for the haloperidol group. Furthermore, 78.9% (15/19) of at-risk haloperidol-treated patients (patients whose prolactin levels were within a normal

**Table 1. Patient disposition by visit**

| Reason for discontinuation | Treatment group | Visit 3 n (%) | Visit 4 n (%) | Visit 5 n (%) | Visit 8 n (%) | Visit 9 n (%) | Visit 10 n (%) | Total n (%) |
|---|---|---|---|---|---|---|---|---|
| Reporting interval complete | Olanzapine | 0 | 0 | 0 | 0 | 0 | 16 (61.5) | |
| | Haloperidol | 0 | 0 | 0 | 0 | 0 | 14 (50) | |
| Satisfactory response | Olanzapine | 0 | 0 | 0 | 0 | 1 (3.8) | 0 | 1 (1.85) |
| | Haloperidol | 0 | 0 | 0 | 1 (3.6) | 0 | 0 | 1 (1.85) |
| Adverse event | Olanzapine | 1 (3.8) | 0 | 0 | 0 | 0 | 0 | 1 (1.85) |
| | Haloperidol | 0 | 1 (3.6) | 0 | 0 | 0 | 0 | 1 (1.85) |
| Lost to follow-up | Olanzapine | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Haloperidol | 0 | 0 | 0 | 0 | 1 (3.6) | 0 | 1 (1.85) |
| Criteria not met / compliance | Olanzapine | 1 (3.8) | 0 | 0 | 0 | 0 | 0 | 1 (1.85) |
| | Haloperidol | 0 | 0 | 0 | 0 | 1 (3.6) | 0 | 1 (1.85) |
| Patient decision | Olanzapine | 1 (3.8) | 0 | 0 | 1 (3.8) | 0 | 0 | 2 (3.7) |
| | Haloperidol | 0 | 1 (3.6) | 0 | 0 | 1 (3.6) | 0 | 2 (3.7) |
| Physician decision | Olanzapine | 1 (3.8) | 0 | 1 (3.8) | 0 | 0 | 1 (3.8) | 3 (5.6) |
| | Haloperidol | 0 | 0 | 0 | 1 (3.6) | 2 (7.1) | 0 | 3 (5.6) |
| Lack of efficacy | Olanzapine | 0 | 0 | 0 | 1 (3.8) | 1 (3.8) | 0 | 2 (3.7) |
| | Haloperidol | 1 (3.6) | 0 | 0 | 0 | 4 (14.3) | 0 | 5 (9.3) |

range) compared to 20.0% (3/15) of at-risk olanzapine-treated patients ($p < 0.001$, Fisher's exact test) had a prolactin level exceeding one time the upper reference limit (100% URL).

While there were no statistically significant differences in the mean change from baseline to endpoint in hepatic enzymes between the two treatment groups, olanzapine-treated patients had slight elevations in AST/SGOT and ALT/SGPT while haloperidol-treated patients had decreases in AST/SGOT and ALT/SGPT. Both olanzapine and haloperidol treatment groups had slight elevations in alkaline phosphatase, and some decreases in GGT.

## Discussion

In this study, judged by the PANSS positive scale, patients treated with olanzapine showed significantly greater improvement than did patients treated with haloperidol. However, no similar effect could be observed when patients were evaluated using the PANSS negative scale, although olanzapine was numerically superior to haloperidol on this scale. Olanzapine has been shown to decrease negative symptoms to a greater extent than has haloperidol[10]. Previous studies have suggested that atypical antipsychotics, such as

**Table 2. Mean change from baseline to endpoint in efficacy rating scales**

| Rating scale | Therapy | N | Baseline (mean ± SD) | Change to endpoint (mean ± SD) | p-value [a] |
|---|---|---|---|---|---|
| BPRS total | Olanzapine | 24 | 26.96 ± 9.58 | -11.13 ± 8.73 | 0.078 |
| | Haloperidol | 28 | 25.96 ± 10.99 | -5.64 ± 12.40 | |
| PANSS total | Olanzapine | 24 | 79.29 ± 16.27 | -17.38 ± 16.16 | 0.162 |
| | Haloperidol | 28 | 79.86 ± 22.33 | -9.75 ± 22.60 | |
| PANSS positive | Olanzapine | 24 | 23.50 ± 6.32 | -6.92 ± 5.66 | 0.021 |
| | Haloperidol | 28 | 21.79 ± 6.22 | -2.32 ± 7.05 | |
| PANSS negative | Olanzapine | 24 | 18.38 ± 8.57 | -3.67 ± 5.37 | 0.525 |
| | Haloperidol | 28 | 20.57 ± 10.16 | -2.86 ± 6.67 | |
| MADRS | Olanzapine | 24 | 8.83 ± 9.02 | -5.17 ± 7.99 | 0.801 |
| | Haloperidol | 28 | 8.21 ± 7.26 | -3.43 ± 7.60 | |
| CGI-Severity | Olanzapine | 24 | 5.00 ± 0.93 | -1.13 ± 0.95 | 0.976 |
| | Haloperidol | 28 | 5.14 ± 0 .80 | -1.11 ± 1.23 | |

Abbreviations: Brief Psychiatric Rating Scale (BPRS; extracted from PANSS, 0-6 scale); Positive and Negative Syndrome Scale (PANSS); Montgomery-Asberg Depression Rating Scale (MADRS); Clinical Global Impression (CGI).
[a] The last observation was carried forward; t-test was used to compare continuous numbers. The difference is considered statistically significant if the p value is greater than or equal to 0.05.

clozapine, have better effects on negative symptoms[17]. However, other studies have indicated that improvements in negative symptoms are far fewer than those in positive, depressive, or extrapyramidal symptoms[18].

Significant weight gain of olanzapine-treated patients seen in this study has also been observed in previous studies[10,19]. One might suspect that a patient could gain quite a lot of weight if he/she were continually treated with olanzapine. All recently released antipsychotics appear to share the adverse effect of body weight gain. Both clozapine[20] and risperidone[21] cause more weight gain in patients than do haloperidol and other typical antipsychotics.

The mean prolactin level doubled from baseline to endpoint in the haloperidol-treated group; however, it decreased in the olanzapine-treated group. It has been noted that almost all typical neuroleptics raise the serum prolactin level by removal of the action of dopamine on D2 receptors in pituitary lactotropes[?]. Hyperprolactinemia can result in several clinical sequelae (e.g., galactorrhea, amenorrhea, irregular menses, anovulation, impotence, azoospermia, gynecomastia, and inhibition of pregnancy). Therefore, either dose reduction (which may result in inadequate therapy), or even discontinuation of treatment must often be considered[22].

In this study, olanzapine-treated patients had

**Table 3. Treatment-emergent adverse events[a] with a frequency ≥ 10% in either treatment group**

| Adverse event | Olanzapine (N=26) n (%) | Haloperidol (N=28) n (%) | Total (N=54) n (%) | p-value [b] |
|---|---|---|---|---|
| Extrapyramidal symptoms | 1 (3.8) | 8 (28.6) | 9 (16.7) | 0.025 |
| Hypertonia | 1 (3.8) | 7 (25.0) | 8 (14.8) | 0.052 |
| Dizziness | 3 (11.5) | 4 (14.3) | 7 (13.0) | 1.00 |
| Agitation | 0 | 6 (21.4) | 6 (11.1) | 0.024 |
| Amblyopia | 0 | 6 (21.4) | 6 (11.1) | 0.024 |
| Tremor | 1 (3.8) | 5 (17.9) | 6 (11.1) | 0.194 |
| Abdominal pain | 3 (11.5) | 2 (7.1) | 5 (9.3) | 0.663 |
| Akathisia | 0 | 5 (17.9) | 5 (9.3) | 0.052 |
| Constipation | 1 (3.8) | 4 (14.3) | 5 (9.3) | 0.353 |
| Headache | 2 (7.7) | 3 (10.7) | 5 (9.3) | 1.00 |
| Pain | 3 (11.5) | 2 (7.1) | 5 (9.3) | 0.663 |
| Chest pain | 1 (3.8) | 3 (10.7) | 4 (7.4) | 0.612 |
| Diarrhea | 3 (11.5) | 1 (3.6) | 4 (7.4) | 0.342 |
| Rhinitis | 1 (3.8) | 3 (10.7) | 4 (7.4) | 0.612 |

[a] Any event that worsened from the baseline or first appeared during the treatment period.
[b] Frequencies were analyzed using Fisher's exact test.

**Table 4. Mean change from baseline to endpoint in extrapyramidal symptom rating scales**

| Rating scale | Therapy | N | Baseline (mean ± SD) | Change to endpoint (mean ± SD) | p-value [a] |
|---|---|---|---|---|---|
| SAS | Olanzapine | 24 | 1.42 ± 2.80 | 0.08 ± 1.38 | 0.872 |
| | Haloperidol | 28 | 1.89 ± 3.00 | 0.14 ± 3.62 | |
| AIMS | Olanzapine | 24 | 0.67 ± 1.58 | -0.42 ± 1.18 | 0.011 |
| | Haloperidol | 28 | 0.14 ± 0.52 | 0.64 ± 1.81 | |
| BAS | Olanzapine | 24 | 0.63 ± 2.10 | -0.25 ± 2.44 | 0.314 |
| | Haloperidol | 28 | 0.82 ± 1.81 | 0.39 ± 1.37 | |

Abbreviations: Simpson-Angus Scale (SAS); Abnormal Involuntary Movement Scale; (AIMS); Barnes Akathisia Scale (BAS).
[a] The last observation was carried forward; t-test was used to compare continuous numbers. The difference is considered statistically significant if the p value is greater than or equal to 0.05.

a lower incidence of treatment-emergent EPS than did haloperidol-treated patients. The actual difference in the incidence of EPS between the two treatment groups may have been greater, since olanzapine-treated patients received far less anticholinergic medication than did haloperidol-treated patients. These data have confirmed the finding that olanzapine-treated patients have a low incidence of EPS, which was suggested in an animal study assessing behavioral pharmacological data [23] and was observed during controlled clinical trials[24]. However, since daily doses of olanzapine at 30 mg or higher could lead to more than 80% D2 receptor occupancy, systematic clinical trials may be necessary to evaluate EPS and prolactin elevations at doses higher than 20 mg/day.

Olanzapine-treated patients had fewer extrapyramidal adverse events, a lower incidence of tardive dyskinesia, and a lower dropout rate over the course of the study. The only frequent undesirable adverse event observed was weight gain which may be related to a lower pretreatment body mass.

## Clinical Implication

1. The advent of new antipsychotic agents with more-favorable safety profiles has provided an important treatment option for patients with schizophrenia.

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