## Formulary Forum

# OLANZAPINE: A NEW ANTIPSYCHOTIC AGENT WITH EFFICACY IN THE MANAGEMENT OF SCHIZOPHRENIA

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**OBJECTIVE:** To review the pharmacology, pharmacokinetics, efficacy data, and adverse effects of olanzapine as a treatment for schizophrenia and to determine the advantages and disadvantages of this atypical antipsychotic agent compared with currently marketed agents.

**DATA SOURCES:** A MEDLINE computer literature search was conducted to retrieve all English-language studies and review articles involving olanzapine published as of October 1, 1996. The manufacturer of the drug, Eli Lilly and Company, provided the clinical investigator's brochure and abstracts of unpublished Phase III clinical trials.

**STUDY SELECTION:** Animal studies evaluating the pharmacology of olanzapine were evaluated, as were all open-label and double-blind studies involving the evaluation of olanzapine for the treatment of patients with schizophrenia.

**DATA EXTRACTION:** All available clinical studies were reviewed and the interpretation of data for each study was influenced by the size of the study sample, the nature of the inclusion and exclusion criteria, and the data analysis techniques used.

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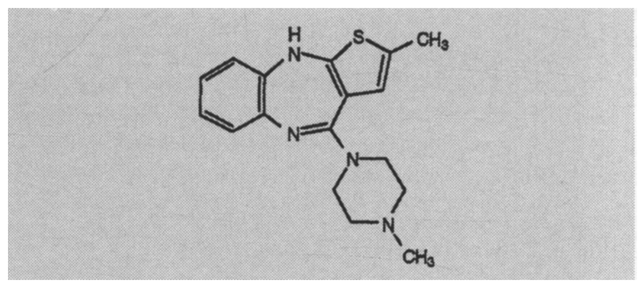

**Figure 1.** Graphic structure of olanzapine.

**DATA SYNTHESIS:** Olanzapine is a thienobenzodiazepine analog with an in vitro receptor affinity profile similar to that of clozapine. Olanzapine exhibits linear kinetics over the dosage range studied and is extensively metabolized in humans. Clinical evaluations to date have shown olanzapine to be at least as efficacious as typical antipsychotic agents in the treatment of the acute phase of schizophrenia. The drug was well tolerated, with significantly fewer extrapyramidal adverse effects than haloperidol. Current data suggest that olanzapine may be more effective than haloperidol for the treatment of negative symptoms; moreover, preliminary data suggest that fewer relapses occur over the course of treatment in patients treated with olanzapine compared with those taking haloperidol.

**CONCLUSIONS:** The exact place of olanzapine in the therapy of psychotic patients remains unclear, as more data are needed to evaluate the long-term efficacy of this agent, its impact on negative symptoms, and its potential use in patients resistant to the standard agents. Despite limitations in the current database, olanzapine is a promising treatment option for patients with schizophrenia.

**KEY WORDS:** olanzapine, schizophrenia.

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OLANZAPINE, an antipsychotic drug manufactured by Eli Lilly and Company, was approved in October 1996 for the treatment of patients with psychotic disorders. A thienobenzodiazepine analog with the chemical name of 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5] benzodiazepine, olanzapine's structure is shown in Figure 1.

The standard or typical antipsychotic agents (e.g., haloperidol, chlorpromazine, perphenazine) are effective for the treatment of patients with psychotic disorders. Since their introduction in the 1950s, these drugs have had a dramatic impact on the management of patients with schizophrenia and related psychotic disorders.[1,2] Specifically, their addition to the treatment regimen of psychotic patients allowed many of them to live outside of hospitals. Despite significant advances provided by these drugs, however, even responders to the drugs often have a residual symptomatology that interferes significantly with their social and occupational functioning.[3] Some may develop disfiguring, disabling, and potentially life-threatening adverse effects, including parkinsonian symptoms, tardive dyskinesia, and neuroleptic malignant syndrome,[4-6] while others have no appreciable clinical response to the drugs.

The Food and Drug Administration's (FDA's) approval of clozapine in 1990 as an antipsychotic medication marked the addition of an agent with superior efficacy for those with treatment-resistant schizophrenia.[7] Clozapine is generally referred to as an atypical antipsychotic because of its low propensity for causing extrapyramidal adverse effects (EPS) and raising serum prolactin concentrations. The use of clozapine has had a substantial impact on the management of patients with psychotic disorders; over 30% of patients who had been otherwise nonresponsive to or intolerant of standard therapies have had a response to the drug (in 6-wk studies). Moreover, a wide array of other benefits from the use of the drug have been described, including decrease in hospitalization and suicide, an increase in work and social abilities, and a lower risk of neuroleptic malignant syndrome and tardive dyskinesia.[8-11] Cost analyses have also shown that the use of clozapine is associated with a reduced cost of treatment, mainly because of a decrease in need for hospitalization.[12,13] However, clozapine's superior efficacy comes at a price: its use is associated with a number of adverse effects, including agranulocytosis, seizures, weight gain, sedation, sialorrhea, and enuresis.[14]

In 1994, the FDA approved the first antipsychotic agent since clozapine, risperidone. This benzisoxazole derivative is an effective antipsychotic agent that appears to have a more tolerable and less problematic adverse effect profile than the typical agents and clozapine.[15-17] Although current clinical experience shows this agent to be well tolerated (in terms of EPS) in dosages of 4–6 mg/d, it is not yet clear whether risperidone is as effective as clozapine in the management of patients whose psychotic symptomatology is resistant to standard agents.[18,19]

Research is currently directed at developing an agent that offers significant advantages over existing treatment modalities: a favorable and acceptable adverse effect profile, superior efficacy in psychotic patients (including those resistant to other agents), or the production of savings in the overall cost of therapy through decreased hospitalization rates and better occupational functioning. Initial investigations with olanzapine have revealed an overall efficacy at least as good as that of haloperidol in the treatment of acute exacerbations of schizophrenia but with potentially greater efficacy for negative signs and symptoms and considerably less likelihood of producing EPS. Preliminary longer-term data (1 y) suggest a decrease in the rate of hospitalization in olanzapine-treated patients compared with those maintained on haloperidol.[20]

## *Animal Pharmacology*

Although structurally different from clozapine, olanzapine is a thienobenzodiazepine analog that demonstrates an in vitro receptor affinity profile similar to that of clozapine.[11,21,22] This profile (particularly its effects at dopamine$_1$ [$D_1$], dopamine$_4$ [$D_4$], serotonin$_{2A}$ [5-$HT_{2A}$], and serotonin$_{2C}$ [5-$HT_{2C}$] receptors) implies that, like clozapine, olanzapine may have atypical effects (Table 1).[23-25]

Animal behavioral studies are used as screening tests for investigational drug moieties to determine which agents have the potential to produce antipsychotic effects when given to humans with psychotic disorders. Taken as a whole, data from animal behavioral studies also support the notion derived from the in vitro receptor binding profile that olanzapine may have atypical characteristics.[22,24,26-31] Table 2 provides a summary of animal pharmacology data.

Initial animal screening tests suggest that olanzapine possesses antipsychotic efficacy as a result of $D_2$ blocking activity and 5-HT antagonism. Furthermore, the animal tests suggest that olanzapine produces antipsychotic potency with minimal EPS due to specificity of activity on the firing of dopamine neurons within the A10 region of the brain. The animal behavioral and electrophysiologic stud-

**Table 1.** Affinity Constants (Ki nM) for Selected Antipsychotic Agents[23-25]

| | DOPAMINERGIC | | | SEROTONERGIC | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| DRUG | $D_1$ | $D_2$ | $D_4$ | 5-$HT_{1A}$ | 5-$HT_{2A}$ | 5-$HT_{2C}$ | $\alpha_1$ | $\alpha_2$ | $H_1$ | $M_1$ |
| Olanzapine | 31.0 ± 0.7 | 11 ± 2 | 27 ± 3 | >1000 | 4.0 ± 0.4 | 11 ± 1 | 19 ± 1 | 230 ± 40 | 7.0 ± 0.3 | 1.9 ± 0. 1 |
| Clozapine | 85 ± 7 | 125 ± 20 | 9 ± 1 | 770 ± 220 | 12 ± 3 | 8.0 ± 0.8 | 7 ± 4 | 8 ± 3 | 6 ± 2 | 1.9 ± 0.4 |
| Haloperidol | 25 ± 7 | 1.0 ± 0.004 | 5.0 ± 0.5 | 7930 ± 500 | 78 ± 22 | 3085 | 46 ± 6 | 360 ± 100 | 3630 ± 85 | 1475 ± 300 |
| Seroquel | 455 ± 105 | 160 ± 15 | | 2450 ± 500 | 220 ± 4 | 615 ± 110 | 7.0 ± 0.2 | 87 ± 4 | 11 ± 12 | 120 ± 35 |
| Risperidone | 75 ± 8 | 3.0 ± 0.1 | 7 ± 1 | 490 ± 10 | 0.6 ± 0.2 | 26 ± 5 | 2.0 ± 0.1 | 3.0 ± 0.7 | 155 ± 35 | >10 000 |
| Ritanserin | 718 ± 187 | 30 ± 23 | | | | | 35.7 ± 9.5 | 54.4 ± 15.9 | 11.8 ± 3.7 | |

5-HT = serotonin receptor; $\alpha_1$ = $\alpha_1$-adrenergic receptor; $\alpha_2$ = $\alpha_2$-adrenergic receptor; D = dopamine receptor; $H_1$ = histamine$_1$ receptor; $M_1$ = muscarinic receptor.

ies of the effects of olanzapine suggest that while at low doses it shares properties with clozapine, as its dosage is increased above the therapeutic range it may begin to more closely resemble a typical antipsychotic.

## *Pharmacokinetics*

### ABSORPTION AND DISTRIBUTION

Olanzapine is completely absorbed after oral administration. The maximum concentration ($C_{max}$) and time to reach $C_{max}$ ($t_{max}$) after single oral doses of 12 mg in six healthy male subjects were 11 ± 1 ng/mL and 4.9 ± 1.8 hours, respectively.[32] There appear to be no significant differences in kinetic parameters between the fed and fasted state. The volume of distribution of olanzapine is 1148 ± 360 L.[33]

### METABOLISM AND ELIMINATION

Olanzapine is extensively metabolized in humans. The major metabolites found in plasma are 10-*N*-glucuronide (present at steady-state at 44% of the concentration of olanzapine) and 4-*N*-desmethylolanzapine (present at steady-state at 31% of the concentration of olanzapine).[33] These metabolites lack antipsychotic activity at the concentrations that have been observed. In vitro evaluations of the human cytochrome P450 isoenzymes responsible for the formation of the three major metabolites of olanzapine have found that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in the oxidation of olanzapine.[34] CYP2D6 oxidation appears to be a minor route of metabolism; therefore, drugs that inhibit CYP2D6 are predicted to have little overall effect on the metabolism of olanzapine.

The systemic clearance of olanzapine has been estimated at 26.1 ± 12.1 L/h.[33] The plasma elimination half-life ($t_{1/2\beta}$) is 33.1 ± 10.3 hours.[32] Compared with young men, young women demonstrated an increased $t_{1/2\beta}$ (38.5 ± 6.8 vs. 29.0 ± 8.0 h) and a decreased clearance.[35,36] Moreover, elderly subjects (>65 y) are reported to have an increased $t_{1/2\beta}$ (by 53%) and $t_{max}$ (by 23%), and a lower clearance (by 8%) compared with their younger counterparts.[35,36] Despite the apparent gender- and age-related effects, the magnitude of these differences are within the normal intersubject variability and do not suggest the need for special dosing guidelines. However, individuals who have more than one factor affecting pharmacokinetics (e.g., age, gender) may exhibit differences of clinical significance.

In studies examining pharmacokinetic dose proportionality, a linear correlation between dose and AUC was found.[32] The $C_{max}$ varied proportionally and directly with the dose across the range studied (5–15 mg fasted, 15 mg fed state) (data on file, Eli Lilly and Co., Indianapolis, IN).

## *Clinical Studies*

The safety and efficacy of olanzapine has been evaluated in open-label studies and placebo-controlled, double-blind clinical trials, both with and without a haloperidol arm. Tables 3 and 4 provide a summary of these studies.

### OPEN-LABEL STUDIES

The six open-label studies (involving 122 patients diagnosed with schizophrenia or schizophreniform disorder) suggested that olanzapine possesses potent antipsychotic activity with an optimal dosage range between 2.5 and 15 mg/d. The drug was well tolerated in these studies, with hepatic transaminase elevations being the most common adverse effect (Table 3).

### DOUBLE-BLIND EVALUATIONS OF OLANZAPINE IN ACUTE EXACERBATIONS OF SCHIZOPHRENIA

Table 4 summarizes the four major double-blind, controlled studies conducted in patients (<65 y). The results of these studies have been published.[37-40]

**Table 2.** Results of Animal Behavioral Studies[22,24,26-31]

| TEST | RESULTS | INTERPRETATION |
|---|---|---|
| Conditioned avoidance | OLZ blocks conditioned avoidance in a dose-dependent fashion | this is an indicator of antipsychotic potential |
| Ability to induce catalepsy | OLZ produces catalepsy at dosages much higher than those required to inhibit conditioned avoidance | beneficial antipsychotic activity should be seen, in most patients, at doses lower than those inducing EPS |
| Apomorphine-induced climbing | OLZ is more potent than CLOZ, but less potent than HAL in blocking apomorphine-induced climbing | OLZ has a greater affinity for the $D_2$ receptor than CLOZ, but a lesser affinity than HAL |
| Blockade of 5-HTP–induced head twitching | OLZ and CLOZ both inhibit 5-HTP–induced head twitching, whereas HAL produces minimal blockade | this suggests preferential activity of both OLZ and CLOZ for serotonin receptors compared with dopamine receptors |
| Drug discrimination tests | after CLOZ administration, OLZ, but not HAL, could be substituted for CLOZ | these data suggest that OLZ shares properties with CLOZ, at least at lower doses |
| Activity in the mesolimbic A10 dopamine neurons vs. nigrostriatal A9 dopamine neurons | after repeated administration, A10 firing is decreased, while A9 firing is increased at doses much higher than those shown to be clinically effective | OLZ should be an effective antipsychotic agent with a low propensity to cause EPS |
| Corticolimbic–glutamatergic system | OLZ produces a dose-related reversal of phencyclidine-induced deficits | OLZ should share antipsychotic action similar to CLOZ, but different from typical antipsychotic agents |

5-HTP = 5-hydroxytryptophan; CLOZ = clozapine; D = dopamine; EPS = extrapyramidal adverse effects; HAL = haloperidol; OLZ = olanzapine.

Study HGAD was a 6-week, randomized, dose-ranging, placebo-controlled, multicenter study involving 335 schizophrenic patients who were randomized to receive one of four treatment arms: olanzapine low-dose (OLZ-L) [5 ± 2.5 mg/d], OLZ medium-dose (OLZ-M) [10 ± 2.5 mg/d], OLZ high-dose (OLZ-H) [15 ± 2.5 mg/d], and haloperidol (15 ± 5 mg/d).[37] Placebo was the control arm.

Study HGAP was a 6-week, fixed-dose, randomized, multicenter study involving 152 patients diagnosed with schizophrenia who were randomized to receive olanzapine 1 mg, olanzapine 10 mg, or placebo.[38]

Study E003 was a 6-week randomized, dose-ranging study involving 431 schizophrenic patients who received olanzapine 1 mg, 2.5–7.5 mg, 7.5–12.5 mg, 12.5–17.5 mg, or haloperidol 10–20 mg.[39]

Study HGAJ was a 6-week, dose-ranging study of 1996 patients that evaluated the efficacy of olanzapine 5–20 mg/d compared with haloperidol 5–20 mg/d.[40] Patients in this study were predominately diagnosed with schizophrenia (83%), although 15% had schizoaffective disorder and 2% had schizophreniform disorder.

If these studies are taken together (n = 2914), the patients enrolled were predominantly white men in their late 30s who had been ill for many years. To be enrolled in studies HGAD, HGAP, and E003, patients had to have a minimum Brief Psychiatric Rating Scale (BPRS)[41] score of 24 and a Clinical Global Impression (CGI) score of at least 4. Approximately one-half of the patients (n = 152) in the fixed-dose study (HGAP) were recruited while they were inpatients, with the length of stay ranging to 1254 days. Thus, a substantial proportion of the patients in HGAP were chronic, severely ill, and had responded poorly to, or been intolerant of, standard antipsychotic agents. In fact, 24% of them had been treated previously with clozapine.

In the HGAD dose-ranging study, OLZ-M, OLZ-H, and haloperidol were superior to placebo on rating with the to-

**Table 3.** Open-Label Studies

| STUDY | DESCRIPTION | PATIENTS (n) | DOSAGE (mg/d) | DURATION | OUTCOME |
|---|---|---|---|---|---|
| E001 (England) | open-label OLZ in schizophrenia, schizophreniform disorder | 10 | 5.0–30.0 | 4 wk optional; 2-wk extension | 6/10 pts. responded (66–87% decrease in BPRS score); 1 pt. had significant increase in LFTs leading to drug d/c |
| E004 (Sweden and Finland) | open-label OLZ in hospitalized pts. with schizophrenia or schizophreniform disorder | 9 | 5.0–15.0 | 6 wk acute; extension to 6 mo | 5 completed acute phase, 4 entered extension phase (1 opted not to continue); 2 pts. were d/c secondary to elevations in LFTs (1 during the acute phase, 1 during the extension phase); during the acute phase, the mean normalized BPRS score decreased by 20 points, the PANSS by 29.7 points; the 2 pts. who completed the extension phase sustained the positive response |
| E005 (Denmark) | open-label OLZ in hospitalized pts. with schizophrenia; to determine lowest effective dosage | 9 | 10.0–15.0 | 6 wk acute; extension to 6 mo | all 9 completed acute phase, 8 responded (mean decrease in normalized BPRS of 22.1 points); 5 completed the extension phase; 4 pts. who d/d did so for the following reasons: 3 due to pt. decision (with accompanying clinical deterioration), 1 due to deterioration of psychopathology; the 5 completers showed continued or further improvement; 2 were hospitalized secondary to worsening symptomatology; both stabilized while in the hospital on OLZ and continued the 6-mo phase |
| E006 (South Africa) | open-label, comparator: | 9 | | 6 wk acute | 4/5 treated with OLZ and 4/4 treated with HAL responded to therapy; although the mean change in BPRS score from baseline to end point was greater with HAL than with OLZ, the difference did not reach statistical significance (20.0 ± 8.8 vs. 11.6 ± 26.9) |
| | OLZ | (5) | 5.0–15.0 | | |
| | HAL | (4) | 10.0–20.0 | | |
| E010 (France) | open-label, hospitalized pts. with schizophrenia or schizophreniform disorder | 4 | 1.0–7.5 | 6 wk acute | there was a mean decrease in normalized BPRS of 18.0 points; PANSS and CGI scores showed similar improvement |
| 2001 (Japan) | open-label, hospitalized pts. with schizophrenia | 81 | 1.0–7.5 | 8 wk | 74/81 completed the trial; 7 were withdrawn: deterioration of symptoms (3), high fever (1), pt. refusal (1), escape (1), discharge (1); there was a significant decrease in total BPRS score from baseline to study end point (49 ± 11 vs. 38 ± 11); 2 serious events occurred: possible NMS (high fever, increased CPK, increased WBC), and an overdose with no clinical consequences |

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; CPK = creatine phosphokinase; d/c = discontinued; HAL = haloperidol; LFTs = liver function test results; NMS = neuroleptic malignant syndrome; OLZ = olanzapine; PANSS = Positive and Negative Symptom Scale; WBC = white blood cell count.

tal BPRS score ($p < 0.001$, $p < 0.001$, $p < 0.01$, respectively), and OLZ-H was numerically superior to haloperidol. OLZ-L and OLZ-H were statistically superior to placebo, and OLZ-H was superior to haloperidol ($p < 0.05$) for the treatment of negative symptoms as measured by the Schedule (Scale) for the Assessment of Negative Symptoms (SANS).[42] In the fixed-dose study (HGAP), olanzapine 10 mg was significantly superior to placebo in the treatment of both positive and negative psychotic symptoms, as measured by the BPRS ($p = 0.04$) and the Positive and Negative Symptom Scale (PANSS) ($p = 0.006$). Olanzapine 1.0 mg could not be distinguished from placebo. In study E003, low, medium, and high doses of olanzapine were not different from haloperidol, as measured by the BPRS, the PANSS, and the CGI. In study HGAJ, olanzapine was superior to haloperidol as measured by the overall BPRS ($p < 0.015$) and PANSS negative subscale ($p < 0.05$).[40] Furthermore, a greater proportion of the patients who were taking olanzapine (compared with those taking haloperidol) completed the acute phase of the study ($p < 0.001$).

Additionally, in study HGAJ, over one-half of the subjects displayed signs and symptoms of depression of at least moderate severity (Montgomery-Åshburg Depression Rating Scale [MADRS] ≥ 16). Both haloperidol and olanzapine were associated with baseline to end point improvement on the MADRS, but olanzapine improvement was statistically significantly superior to haloperidol.[43]

In studies HGAD and HGAP, olanzapine-treated patients (except olanzapine 1.0 mg) improved numerically on the Simpson-Angus and Barnes Akathisia scales with respect to baseline ($p \le 0.05$), whereas the haloperidol group worsened with respect to baseline ($p < 0.05$). Abnormal Involuntary Movement Scale (AIMS) scores improved slightly in all treatment groups except OLZ-L. In studies HGAJ and E003, the improvement in the olanzapine-treated patients on the Simpson-Angus, Barnes Akathisia, and AIMS scales was significantly greater in olanzapine-treated patients than in those treated with haloperidol ($p \le 0.04$).

These initial investigations are limited by a short duration (6 wk) and an inadequate washout period. Despite the limitations, however, these premarketing studies demonstrate that olanzapine is efficacious in the treatment of severe acute exacerbations of chronic schizophrenia at a dosage range of 5–20 mg/d. The decrease in the negative symptoms during olanzapine treatment, which seemed to be noted in all of the studies, is encouraging and warrants further investigation. Although EPS with olanzapine appear to be minimal even at higher dosages, in study HGAD benztropine consumption was related to the dosage of olanzapine. Further evaluation and real-world clinical experience are needed to fully assess the EPS profile of the drug.

**Table 4.** Double-Blind, Controlled Olanzapine Studies

| STUDY | DESCRIPTION | PATIENTS (n) | DOSAGE (mg/d) | DURATION | OUTCOME |
|---|---|---|---|---|---|
| HGAD (US, Canada)[37] | placebo-controlled schizophrenia | 335 | OLZ 2.5–7.5, 7.5–12.5, 12.5–17.5; HAL 10–20; placebo | 6 wk, extension to 1 y, optional double-blind indefinite extension followed by open-label extension | OLZ medium and high dose and HAL were superior to placebo on the basis of total BPRS score ($p < 0.001$, $p < 0.001$, $p < 0.01$, respectively); OLZ high dose was numerically superior to HAL; OLZ high dose was superior to HAL for negative symptoms as measured by the SANS ($p < 0.05$) |
| HGAP (US)[38] | placebo-controlled schizophrenia | 152 | OLZ 1 vs. 10 placebo | 6 wk, open-label extension | OLZ 10 mg, but not 1 mg, was superior to placebo as measured by the mean change in total BPRS score ($p = 0.004$); the incidence of EPS on OLZ 10 mg was less than that seen with placebo (8% vs. 12%) |
| E003 (Europe, South Africa, Israel, Australia)[39] | dose-ranging study, schizophrenia | 431 | OLZ 1, 2.5–7.5, 7.5–12.5, 12.5–17.5; HAL 10–20 | 6 wk, extension to 1 y, optional double-blind indefinite extension followed by open-label indefinite extension | no significant difference in OLZ groups vs. HAL as measured by the total BPRS score; OLZ high dose was superior to OLZ low dose as measured by the CGI, BPRS, and PANSS ($p \le 0.05$) |
| HGAJ (17 countries)[40] | compared with HAL in schizophrenia, schizoaffective disorder, schizophreniform disorder | 1996 | OLZ 5–20; HAL 5–20 | 6 wk, open-label | OLZ was superior to HAL on overall BPRS ($p < 0.015$), negative subscale of the PANSS ($p < 0.05$), and the MADRS total in the acute phase; transient increases in LFTs occurred in 7.9% of OLZ-treated pts. |
| HGAO (US) (data on file, Eli Lilly and Co.) | placebo-controlled study in elderly pts. with psychosis associated with dementia | 238 | OLZ 1–8 | 8 wk acute, optional open-label extension for 14 wk | OLZ did not differ statistically from placebo; only 69 of the pts. received OLZ 5 mg or more; OLZ was well tolerated with no statistically significant difference in EPS, orthostatic BP, leukopenia, or increase in LFTs compared with placebo |

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; EPS = extrapyramidal adverse effects; HAL = haloperidol; LFTs = liver function test results; MADRS = Montgomery-Åshburg Depression Rating Scale; OLZ = olanzapine; PANSS = Positive and Negative Symptom Scale; SANS = Schedule (Scale) for the Assessment of Negative Symptoms.

#### LONG-TERM EFFICACY DATA IN THE TREATMENT OF SCHIZOPHRENIA

Since schizophrenia is a relapsing disorder, the long-term efficacy of olanzapine is important. Patients who were responders during the acute phase of studies HGAD, HGAJ, and E003 were enrolled in double-blind extension studies evaluating the efficacy of olanzapine compared with placebo and haloperidol in the maintenance of clinical improvement.[20] Patients entered the extension phases of those studies at the same dosages to which they had responded during the acute trial. In a three-trial (HGAD, HGAJ, E003) meta-analysis of the data, in which need for hospitalization was used to indicate loss of response, the time of maintaining response among those treated with olanzapine was longer than those treated with either haloperidol or placebo (≥52 wk). There were no differences seen in the incidence of adverse events with olanzapine long-term compared with short-term treatment (1 y vs. 6 wk). In fact, there was a decrease in the incidence of prolactin and transaminase elevations seen in long-term treatment compared with acute therapy.[44-46] Although intriguing, further long-term prospective data on clinical symptoms and overall functioning are necessary to evaluate the efficacy of olanzapine.

#### TREATMENT-REFRACTORY PATIENTS

At present, clozapine is the only neuroleptic shown to be effective in patients refractory to typical agents.[7] Ongoing studies will assess the role of olanzapine in this population.

Currently, there is an ongoing study comparing olanzapine with chlorpromazine in treatment-refractory schizophrenic patients. This trial will enroll patients who are treatment-resistant by history, and confirm treatment resistance by a trial of haloperidol up to 60 mg/d. Nonresponders to haloperidol will enroll in a double-blind 8-week trial of olanzapine versus chlorpromazine, with an optional open-label extension for up to 2 years. The design of the acute-phase study is identical to that used to evaluate the efficacy of clozapine compared with chlorpromazine in the treatment-resistant population,[7] and should provide information on the usefulness of olanzapine in this group of patients.

### *Adverse Effects and Drug Interactions*

#### ADVERSE EFFECTS

There appear to be no absolute contraindications for treatment with olanzapine. The adverse effect profile can be seen by assessing the results from the acute double-blind studies. Table 5 lists adverse effects seen in an acute double-blind study. The most frequent adverse reactions to olanzapine were hypotension, constipation, weight gain, somnolence, agitation, and dizziness.

In study HGAD, EPS in olanzapine-treated patients occurred at a rate much lower than that associated with haloperidol 10–20 mg/d. There were no dystonic reactions reported with olanzapine, while 13% of patients treated with haloperidol experienced dystonia.[37] It is interesting to note that all olanzapine groups showed decreases in EPS ratings compared with baseline, while in the haloperidol group EPS scores increased for both akathisia and parkinsonism. Patients in all olanzapine treatment groups required significantly less benztropine than those treated with haloperidol.[37] In the fixed-dose study (HGAP), 8% of patients treated with olanzapine 10 mg/d developed EPS, while 12% of patients treated with placebo developed EPS.[38] Some of the placebo reactions were most likely due to remaining effects of previous neuroleptic treatment.

In study HGAD (the dose-ranging study conducted in the US and Canada), alanine aminotransferase (ALT) increases were noted in 12% of the patients treated with low dosages of olanzapine, in 5% of those given moderate dosages, and in 13% of those treated with high dosages of olanzapine, whereas 4% of the patients treated with either haloperidol or placebo were found to have elevations. Transaminase elevations were transient in most patients, although 6 (3%) patients treated with olanzapine were withdrawn from the dose-ranging study (HGAD) because of ALT increases. Early conservative guidelines required drug discontinuation if liver function test results were greater than twice the normal values. No patient displayed clinical signs of hepatic dysfunction, and in all cases liver function test results returned to normal after olanzapine was discontinued.[37] In the large sample study HGAJ (involving 834 patients treated with olanzapine), no patient receiving olanzapine discontinued therapy during the acute phase of the study secondary to elevated transaminase concentrations.[40]

Typical antipsychotics elevate serum prolactin concentrations, but the atypical drug clozapine does not.[14] Studies have shown that prolactin elevations in patients treated with olanzapine are transient and, at 6 weeks, are not different from those in the patients treated with placebo, and are significantly less than increases seen in patients treated with haloperidol 10–20 mg/d.[37,38] Since very few women

**Table 5.** Most Common Treatment-Emergent Adverse Events (%) in the Dose-Ranging Study HGAD[a]

| ADVERSE EVENT | OLZ 2.5–7.5 mg (n = 65) | OLZ 7.5–12.5 mg (n = 64) | OLZ 12.5–17.5 mg (n = 69) | HAL 10–20 mg (n = 69) | PLACEBO (n = 68) |
|---|---|---|---|---|---|
| Somnolence | 20.0 | 29.7 | 39.1 | 34.8 | 16.2 |
| Agitation | 16.9 | 29.7 | 26.1 | 30.4 | 23.5 |
| Asthenia | 7.7 | 9.4 | 20.3 | 21.7 | 14.7 |
| Nervousness | 16.9 | 14.1 | 20.3 | 27.5 | 19.1 |
| Dizziness | 7.7 | 9.4 | 17.4 | 7.2 | 2.9 |
| Constipation | 6.2 | 7.8 | 14.5 | 5.8 | 0.0 |
| Dry mouth | 3.1 | 4.7 | 13.0 | 4.3 | 4.4 |
| ALT increase | 12.3 | 4.7 | 13.0 | 4.3 | 4.4 |
| Akathisia | 4.6 | 6.3 | 7.2 | 15.9 | 1.5 |
| Tremor | 0.0 | 4.7 | 5.8 | 14.5 | 1.5 |

ALT = alanine transaminase; HAL = haloperidol; OLZ = olanzapine.
[a]Data taken from reference 37.

were evaluated in these studies, it is not known whether prolactin elevations will occur in women treated with olanzapine.[37]

In one of the dose-ranging studies (HGAD), there was a statistically significant positive correlation between the dosage of olanzapine and two anticholinergic adverse effects. Constipation was seen in 6%, 8%, and 14% of patients treated with olanzapine low, moderate, and high dosages, respectively, while dry mouth was seen in 3%, 5%, and 13% of patients (compared with 4% in haloperidol-treated patients). Interestingly, the relatively low rates of anticholinergic adverse effects are less than what might be expected, given olanzapine's high affinity for cholinergic receptors.[37] The reason for this is uncertain.

In study HGAD, heart rate and blood pressure showed inconsistent changes among the treatment groups, although no olanzapine treatment group demonstrated a change from baseline. Dose-dependent dizziness did not appear to correlate with measures of orthostasis.[37] In this study, significant weight gain was reported in olanzapine-treated patients, with the OLZ-M and OLZ-H groups gaining an average of approximately 3.5 kg over 6 weeks, whereas those treated with haloperidol 10–20 mg/d gained an average of 0.9 kg.[37] In the fixed-dose study (HGAP), an average weight gain of 2.2 kg over a 6-week period was reported with olanzapine 10 mg/d, compared with 0.4 kg in patients treated with placebo.[38] In the overall database, 42% of olanzapine-treated patients experienced a significant weight gain (≥7% from baseline). Long-term studies are needed to determine whether weight eventually plateaus or continues to increase with further treatment.

No cases of agranulocytosis were observed in any patient treated with olanzapine in the HGAD and HGAP studies. Of the 2500 patients in the olanzapine safety database, 26 were identified who had clinically important decreases in leukocyte or neutrophil counts during prior treatment with clozapine. None of the patients had a last leukocyte count of less than $3.0 \times 10^3/mm^3$ or a last neutrophil count of less than $2.0 \times 10^3/mm^3$, except for 1 patient with a neutrophil count of $1.5 \times 10^3/mm^3$ who began with a lower baseline neutrophil count of $1.36 \times 10^3/mm^3$ (data on file, Eli Lilly and Co.). The incidence rate of events reported as seizures or possible seizures was 0.9% (22/2500).[33] A causal relationship was not established in many cases due to confounding factors that may have contributed to the likelihood of a seizure.

#### DRUG INTERACTIONS

Subjects receiving olanzapine 12 mg/d, diazepam 10 mg/d, or biperidone 4 mg/d showed no obvious evidence of a drug interaction based on clinical observations of adverse effects (data on file, Eli Lilly and Co.). Further results from studies in which drug interactions in humans were evaluated are not yet available. The capacity of olanzapine to inhibit the enzymes of the P450 system has been evaluated in vitro.[47] Based on the results of these evaluations, typical plasma concentrations of olanzapine would not be predicted to have significant inhibition of CYP3A4, CYP2D6, CYP2C9, and CYP2C19.[47] CYP1A2 was not evaluated in this study, but another in vitro evaluation has found that CYP1A2 is involved in the formation of the *N*-desmethylolanzapine metabolite.[34] This would suggest that drugs inhibiting the CYP1A2 isoenzyme to a significant extent (e.g., fluvoxamine, ciprofloxacin) may interfere with the formation of this metabolite. Likewise, concurrent administration of olanzapine with drugs metabolized via CYP1A2 (i.e., clozapine, clomipramine, theophylline) may lead to elevated blood concentrations of one or both drugs through competitive inhibition. The clinical significance of this inhibition is unknown as the activity and toxicity of the *N*-desmethylolanzapine are unclear. Additionally, it has been found that carbamazepine causes an approximately 50% increase in the clearance of olanzapine.[33] This is believed to be because carbamazepine is a potent inducer of the CYP1A2 isoenzyme.

In evaluation of in vitro data, several factors must be kept in mind. First, in vitro results do not always predict what will happen in vivo due to limitations of the procedure, including the wide variation in the activity of the cytochrome P450 isoenzyme and the current lack of widely accepted probes for their activity in humans.[48] Second, the existence of multiple metabolic pathways for olanzapine suggest that inhibition of one route may not result in a significant overall change in clearance.[47] Third, the activity and toxicity of the metabolites are unknown at this time.

### *Geriatric and Pediatric Considerations*

Three studies of olanzapine have been completed in the elderly (>65 y), but data from only two studies are available. In a study conducted in 6 elderly women and 10 elderly men to test the pharmacokinetics and safety of olanzapine 2.5, 5, 7.5, and 10 mg/d, the $t_{1/2\beta}$ of the drug increased by a mean of 53% over what was seen in 8 subjects aged 20–41 years.[49] The increase in $t_{1/2\beta}$ was greater in men than women. No unexpected adverse events were seen, with the most common being somnolence (65% at 10 mg/d), postural hypotension, and dizziness (data on file, Eli Lilly and Co.). In the overall database of patients 65 years of age or older, 2.3% of olanzapine-treated patients experienced orthostasis compared with 6.7% of haloperidol-treated patients (data on file, Eli Lilly and Co.).

A second study[50] evaluated the efficacy of olanzapine 1–8 mg/d versus placebo in 238 elderly patients who displayed psychotic and behavioral manifestations of dementia of the Alzheimer type. Although there were no differences in efficacy between olanzapine and placebo, only 69 patients received dosages greater than 5 mg/d; therefore, olanzapine 5 mg/d may not have been a high enough dosage to produce an antipsychotic effect. Safety data showed no significant differences in liver function test results, EPS, leukopenias, or orthostasis in olanzapine versus placebo-treated patients.

Although there are no data available pertaining to the use of olanzapine in children or adolescents, a study is under way at the National Institute of Mental Health to assess the efficacy of olanzapine in the treatment of children and adolescents with schizophrenia.

### *Therapeutic Role of Olanzapine*

The place that olanzapine will occupy in the treatment of schizophrenia is yet to be determined. It is clear that olanzapine has several benefits to offer patients: it has an attractive adverse effect profile, is more effective than haloperidol for negative symptoms, and seems to be at least as effective as haloperidol for positive symptoms. Moreover, in the large dose-ranging study (HGAJ), olanzapine was shown to be superior in overall efficacy to haloperidol 5–20 mg/d. Lastly, available preliminary studies also suggest the intriguing possibility that maintenance of long-term response may be better with olanzapine than with haloperidol.[20]

Clearly, olanzapine displays a decreased incidence of EPS compared with haloperidol.[37,38] Clozapine and risperidone (at dosages <10 mg/d) have been shown to produce EPS at a lower incidence than haloperidol. Additionally, olanzapine has been compared directly with risperidone in a randomized, double-blind study sponsored by the manufacturer of olanzapine.[51] While preliminary data have been presented, they have not yet been published. There is clearly the need for systematic study of the comparative efficacy and adverse effect profile of the novel agents.

Another potential advantage of olanzapine is its minimal effects on prolactin.[37] Traditional antipsychotic agents and risperidone[52] all cause dramatic increases in prolactin concentrations. Such prolactin elevations can produce amenorrhea, galactorrhea, and gynecomastia in some patients. Clozapine is the only currently marketed antipsychotic that has not been shown to increase prolactin concentrations.[53] The advantage of olanzapine (especially in women) over typical agents, because of its minimal effects on prolactin, requires further study.

One might speculate that because of its favorable EPS profile, olanzapine may be less likely to cause tardive dyskinesia than typical agents. This condition, a potentially irreversible adverse effect of antipsychotic therapy that has been associated with all existing typical antipsychotics, occurs in approximately 15–20% of those treated with these agents.[54] A recent report of tardive dyskinesia emerging during therapy with risperidone suggests that this drug may also be associated with this troubling adverse effect, although the overall incidence is unknown.[55] Despite over 15 years of use, clozapine has rarely been reported to cause tardive dyskinesia, and in the cases reported the causality has been unclear.[56] Since prolonged exposure is usually required before tardive dyskinesia develops, it may take a number of years of postmarketing use to know whether (and how frequently) olanzapine produces this condition.

In the dose-ranging study,[40] olanzapine 12.5–17.5 mg/d was found to be more effective than haloperidol at relieving negative symptoms, although it is unclear whether this is a result of olanzapine's superior efficacy or the fact that it is less likely to produce a deficit syndrome than is haloperidol.[57] Moreover, since haloperidol causes more EPS than does olanzapine, this alone could account for the apparent relief of negative symptoms with olanzapine. Both risperidone and clozapine have been reported to have greater efficacy in the treatment of negative symptoms than typical antipsychotics, although questions arise about whether the benefits from drugs are primary or secondary (to loss of an adverse effect caused by other drugs).[58]

Based on available clinical data, olanzapine does not appear likely to produce seizures or agranulocytosis. This may offer distinct advantages over clozapine, which has been shown to have a relatively high risk of seizures, particularly at higher doses,[59,60] as well as a risk of agranulocytosis, which necessitates weekly leukocyte counts. Nonetheless, it is not yet known whether olanzapine will be as efficacious as clozapine for patients, especially treatment-resistant patients with schizophrenia.

Some concern must be raised with regard to effects of olanzapine on hepatic enzymes. Although the ALT elevations seen with olanzapine were transient, they were more common than in patients treated with haloperidol.[37] Close attention needs to be paid to these effects as additional clinical experience is gained.

Finally, olanzapine is priced considerably higher than typical antipsychotics, which are available generically (Table 6 provides a cost comparison between typical and atypical antipsychotic agents). In this age of economic concerns, the cost of olanzapine will need to be justified through cost-effectiveness analyses. Several studies with clozapine have attempted to demonstrate this,[12,13] and one study with risperidone has shown a decrease in hospitalization days after initiation of risperidone therapy.[61]

To define more clearly the place of olanzapine in the treatment of patients with schizophrenia, the following questions need to be answered: Is olanzapine efficacious and effective in patients who are refractory to standard antipsychotics or to clozapine? Are high olanzapine acquisition costs offset by an increased overall benefit? How does the EPS profile of olanzapine compare with that of risperidone and clozapine? How will the incidence of tardive dyskinesia associated with olanzapine compare with conventional antipsychotics, risperidone, and clozapine? Should olanzapine be a first-line agent and will it prevent relapse more effectively than other antipsychotics? What will be the long-term functioning of patients treated with olanzapine compared with those treated with other agents?

## *Summary*

Olanzapine is a promising new medication for the treatment of patients with schizophrenia. It has been found to be as effective as standard antipsychotic agents in the treat-

**Table 6.** Cost Comparison Between Typical and Atypical Antipsychotic Agents

| DRUG | YEARLY COST[a] ($) |
|---|---|
| Olanzapine 10 mg/d | 2365 |
| Risperidone 6 mg/d | 2450 |
| Clozapine 300 mg/d[b] | 4000 |
| Haloperidol 10 mg/d | 700 |

[a]Cost is based on average acquisition price (price may vary, based on group purchasing and negotiated prices).
[b]Cost of clozapine does not include cost of weekly monitoring of white blood cell count.

ment of acute exacerbations of schizophrenia, and has been shown to have advantages over the standard agents for the treatment of negative symptoms. The drug is well tolerated and produces significantly fewer EPS than haloperidol. Moreover, unlike standard agents, it does not cause significant elevations in prolactin concentrations. More data are needed to evaluate its long-term efficacy, its ability to treat negative symptoms, and its use in treatment-resistant patients. Moreover, the role of olanzapine as a first-line agent remains to be explored. ≏

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## EXTRACTO

**OBJETIVO:** Presentar una revisión de la literatura sobre la farmacología, farmacocinética, eficacia, y efectos secundarios de olanzapina en el tratamiento de esquizofrenia y comparar las ventajas y desventajas de este afente antisicótico atípico con otros fármacos disponibles en el mercado.

**FUENTES DE INFORMACIÓN:** Búsqueda bibliográfica en MEDLINE de artículos en inglés relacionados a olanzapina publicados hasta el 1 de octubre de 1996. La compañía farmacéutica Eli Lilly, fabricante del producto, ofreció la información preparada para investigadores clínicos y extractos de estudios clínicos Fase III.

**SELECCIÓN DE FUENTES DE INFORMACIÓN:** Se incluyeron en la revisión todos los estudios realizados en animales donde se había evaluado la farmacología de olanzapina así como todos los estudios abiertos, doble ciegos en donde se había evaluado olanzapina como tratamiento en pacientes con esquizofrenia.

**MÉTODO DE EXTRACCIÓN:** Se evaluaron todos los estudios clínicos. Para la interpretación de los datos de cada estudio se consideraron los siguientes factores: tamaño de la muestra, naturaleza de los criterios de admisión y exclusión de pacientes, y las técnicas de análisis de datos.

**SÍNTESIS:** Olanzapina es un agente análogo a tienobenzodiazepina con un perfil de afinidad de receptor in vitro similar a clozapina. Olanzapina exhibe cinética lineal en los intérvalos de dosificación estudiados. El fármaco se metaboliza extensamente en humanos. Evaluaciones clínicas han demostrado que olanzapina es tan eficaz como los agentes antisicóticos típicos en el tratamiento de la fase aguda de la esquizofrenia. El fármaco ha sido bien tolerado con significativamente menos efectos extrapiramidales que haloperidol. Estudios recientes sugieren que olanzapina puede ser más efectiva que haloperidol en el tratamiento de síntomas negativos. Datos preliminares sugieren que los pacientes que se encuentran en tratamiento con olanzapina tienen menos relapsos que los pacientes en tratamiento con haloperidol.

**CONCLUSIONES:** El papel de olanzapina en el tratamiento de pacientes sicóticos aún no está claro. Se necesitan más datos para evaluar la eficacia a largo plazo de este fármaco, su impacto en síntomas negativos, y su potencial de uso en pacientes resistentes a los fármacos tradicionales. A pesar de las limitaciones de nuestras fuentes de información, es evidente que olanzapina es una opción prometedora para pacientes con esquizofrenia.

HOMERO A MONSANTO

## RÉSUMÉ

**OBJECTIF:** Revoir la pharmacologie, la pharmacocinétique, les données d'efficacité, et les effets indésirables de l'olanzapine lors du traitement de la schizophrénie afin de comparer cet agent antipsychotique atypique aux autres agents sur le marché.

**REVUE DE LITTÉRATURE:** Une recherche informatisée dans la banque de données MEDLINE a permis de retracer toutes les études et les articles concernant l'olanzapine, publiés jusqu'en octobre 1996. Le fabricant, la compagnie Eli Lilly, a fourni les informations disponibles dans une brochure pour les chercheurs cliniques et les résumés d'études cliniques de Phase III non publiées.

**SÉLECTION DES ÉTUDES:** Les études sur des animaux évaluant la pharmacologie de l'olanzapine ont été retenues ainsi que toutes les études ouvertes ou randomisées évaluant l'olanzapine pour le traitement des patients schizophrènes.

**SÉLECTION DE L'INFORMATION:** Toutes les études cliniques ont été revues et l'interprétation des données de chaque étude a été pondérée selon la taille de l'étude, les critères d'inclusion et d'exclusion ainsi que les méthodes analytiques utilisées.

**RÉSUMÉ:** L'olanzapine est un analogue thiénobenzodiazépine qui possède une affinité in vitro pour les récepteurs identique à la clozapine. L'olanzapine possède une cinétique linéaire pour les doses étudiées et est métabolisée dans une forte proportion chez l'humain. Les données cliniques à ce jour montrent que l'olanzapine est aussi eficace que les autres antipsychotiques pour le traitement de la phase aiguë de la schizophrénie. Ce médicament est bien toléré et produit moins d'effets extrapyramidaux que l'halopéridol. Des données récentes suggèrent que l'olanzapine serait plus efficace que l'halopéridol pour le traitement des symptômes négatifs et de plus, selon des données préliminaires, les personnes traitées par l'olanzapine présenteralent moins de rechutes que celles traitées par l'halopéridol.

**CONCLUSIONS:** La place de l'olanzapine dans le traitement des patients psychotiques demeure imprécise; des données supplémentaires sont nécessaires afin d'évaluer l'efficacité à long terme de cet agent, son impact sur les symptômes négatifs, et son potentiel d'efficacité chez les patients résistants aux autres antipsychotiques. Malgré les limites de cette revue, l'olanzapine s'avère une option thérapeutique prometteuse pour les schizophrènes.

DENYSE DEMERS