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Review of recent clinical studies with olanzapine

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Olanzapine is a novel antipsychotic agent displaying a unique and pleotrophic pharmacology, which distinguishes it from other existing treatments. Clinical investigations employing olanzapine have demonstrated a number of potential therapeutic advantages in reference not only to placebo but also to contemporary drug standards in the management of psychosis. This paper reviews data on the pharmacokinetics, efficacy and safety of olanzapine, its benefits for quality of life, and economic aspects to assist clinicians in determining where they can usefully employ it.

PHARMACOKINETIC STUDIES

Olanzapine is well absorbed following oral administration without any effect of food. Peak plasma concentrations are achieved within five hours of dosing, which is advantageous in a drug prescribed for acute behavioural control. Because the mean plasma half-life of the parent compound is 31 hours (range: 21–54 hours), once-daily dosing is recommended, which should contribute to better compliance than with drugs given more frequently. There is a linear relationship between a dose and the resultant plasma concentration, which should simplify dosage titration if required during treatment. Clearance is not significantly affected by age, gender, or race, which permits standard dosing in these respective subsets. Unlike current antipsychotic agents, all of which carry a risk for drug–drug interactions, olanzapine has a weak affinity for any of the principal hepatic cytochromes, and this in turn predicts a low risk for pharmacokinetic drug interactions. Indeed, *in vivo* drug interaction studies demonstrate no influence of olanzapine on drugs metabolised through the cytochrome P450 systems, including imipramine, diazepam, theophylline, warfarin, and selective serotonin reuptake inhibitors. However, co-administration of fluvoxamine, which potently inhibits cytochrome 1A2, may lead to a small increase in steady-state plasma levels of olanzapine. Co-administration of carbamazepine and olanzapine resulted in a modest increase in olanzapine clearance, due to hepatic enzyme induction by carbamazepine.

Considering all of the variables, including race, age, gender and drug interactions, within schizophrenia there typically appears to be little reason to deviate from the recommended starting dose of 10 mg daily.

IMAGING STUDIES

Building on single-dose *in vitro* and *ex vitro* receptor binding studies, Pilowsky and coworkers compared the dopamine receptor affinity of olanzapine with that of clozapine, haloperidol, and risperidone, using single photon emission computed tomography (SPECT), in clinically responsive patients with schizophrenia who had been on drug therapy for six weeks (Pilowsky *et al*, 1996). Both olanzapine and clozapine demonstrated low D_2 striatal receptor affinity, while haloperidol and risperidone responders exhibited significantly greater D_2 occupancy. Based on these observations, the investigators concluded that the higher degree of striatal binding exhibited by both haloperidol and risperidone would predict a higher clinical risk for associated extrapyramidal events than either clozapine or olanzapine, within those clinically effective dosages.

CLINICAL STUDIES

Olanzapine *v.* haloperidol and/or placebo

Four pivotal clinical studies of olanzapaine were conducted in patients with schizophrenia and related conditions. The first study compared olanzapine (10 and 1 mg) with placebo (Beasley *et al*, 1996*a*); the second compared olanzapine (5, 10, or 15 ± 2.5 mg) with haloperidol (10–20 mg) and placebo (Beasley *et al*, 1996*b*; Tollefson & Sanger, 1997); the third compared olanzapine (5, 10, 15, or 20 mg) with haloperidol (5, 10, 15, or 20 mg) and olanzapine (1 mg) (Beasley *et al*, 1997*a*); and the fourth, a 17-nation dose-ranging trial involving almost 2000 patients, compared olanzapine (range: 5–20 mg) with haloperidol (range: 5–20 mg) (Tollefson *et al*, 1997*b*). Prophylactic anticholinergic agents were not permitted in any of the studies but could be administered if a patient developed extrapyramidal side-effects (EPS).

Efficacy

In studies 1 and 2, olanzapine ($\geqslant 10$ mg) was significantly better than placebo in treating general psychopathology, as measured by the Brief Psychiatric Rating Scale (BPRS; Woerner *et al*, 1988). Numerical differences suggesting the increased efficacy of olanzapine at 5, 10, 15, or 20 mg compared with 1 mg of olanzapine were observed in study 3. When drug effects on positive symptoms were assessed, both olanzapine and haloperidol were statistically found to be superior to placebo. Olanzapine was comparable to haloperidol in

studies 2 and 3 and in study 4 tended ($P<10$) to be superior to haloperidol on positive symptoms.

Negative symptoms

Novel antipsychotic agents should exhibit a broad spectrum of efficacy, including effectiveness against the negative symptoms. In the olanzapine trials, negative symptoms were evaluated by the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1986) in studies 1, 3, and 4 and by the Scale for the Assessment of Negative Symptoms of schizophrenia (SANS; Andreasen, 1982) in study 2. Figure 1 summarises the negative symptom change from baseline to end-point within each study. Statistically significant differences were observed favouring olanzapine (10 mg) over placebo in study 1, olanzapine (15 ± 2.5 mg) over both placebo and haloperidol (10–20 mg) in study 2, and olanzapine (5–20 mg) over haloperidol (5–20 mg) in study 4. A trend favouring olanzapine (5–20 mg) over haloperidol (5–20 mg) was also seen in study 3, but the differences did not reach statistical significance.

In study 2, three fixed doses of olanzapine (5, 10, or 15 ± 2.5 mg) were compared with both placebo and haloperidol (10–20 mg) (Beasley *et al*, 1996*b*; Tollefson & Sanger, 1997). Use of statistical analysis of covariance (path analysis) permitted isolation of the relative contributions to negative symptom improvement on the SANS by indirect or secondary factors (i.e. positive symptoms, depressive symptoms, EPS). The remaining advantage of olanzapine relative to placebo (>50%) and haloperidol (>80%) in treating negative symptoms

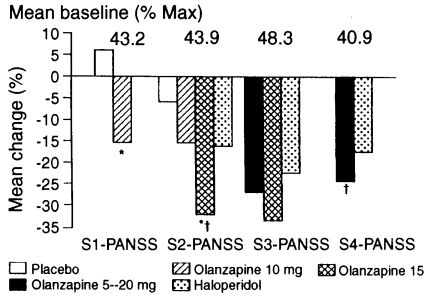

Fig. 1 Negative symptom scales – studies 1–4, acute phase mean change (%), LOCF (Beasley *et al*, 1997*b*). *$P\leqslant0.010$ *v.* placebo; †$P\leqslant0.050$ *v.* haloperidol: LOCF, last observation carried forward; S, study; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms. (Reproduced by kind permission of Physicians Postgraduate Press.)

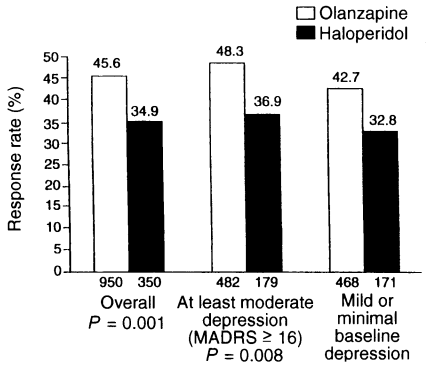

Fig. 2 Montgomery–Åsberg Depression Rating Scale acute response rate.

probably represents a direct treatment effect on primary negative features. The differences in direct effects were statistically significant for both comparisons and favoured olanzapine. In contrast, the limited benefit of haloperidol regarding negative symptoms resulted almost exclusively from improvement in positive symptoms when compared with placebo. This secondary impact on negative symptoms was actually adversely offset by an increase in haloperidol-associated EPS.

It is particularly noteworthy that olanzapine was significantly more effective against negative symptoms than the active comparator haloperidol, and that 84% of this treatment advantage, which was a statistically significant difference, resulted from a direct negative-symptom effect.

Comorbid mood symptoms

Secondary depression, which is common in schizophrenia, is predictive of a poorer prognosis, including greater difficulty reintegrating into society and a higher risk of suicide. Patients in study 4 were evaluated prospectively for depressive signs and symptoms with the Montgomery–Åsberg Depression Rating Scale (MADRS) (Tollefson *et al*, 1997*c*). Across the entire study population, there was a statistically significant baseline to end-point improvement in MADRS total score favouring olanzapine over haloperidol. Superior treatment effects were evident on each of the 10 individual MADRS items. About 55% of the study patients had a baseline MADRS score $\geqslant16$, which was defined *a priori* as at least moderate depression. In this more severely depressed group, the improvement in MADRS total score was again significantly greater among those treated with olanzapine. Furthermore, among all patients, including those who were at least moderately depressed, a 50% or greater improvement from baseline MADRS score occurred significantly more often among those who were treated with olanzapine (Fig. 2). When path analysis was again used to isolate the relative contributions to positive symptom improvement, negative symptom improvement, and EPS, more than half (57%) of the greater improvement in depressive symptoms and signs observed with olanzapine relative to haloperidol appeared to be the result of a direct antidepressant effect. This effect alone was statistically significant, favouring olanzapine over haloperidol. It has already been suggested in the literature (Harrow *et al*, 1994) that neuroleptic drugs may actually induce dysphoria, and indeed, a significantly greater number of haloperidol-treated patients experienced a 50% or greater worsening of mood (MADRS total score) from baseline. As a

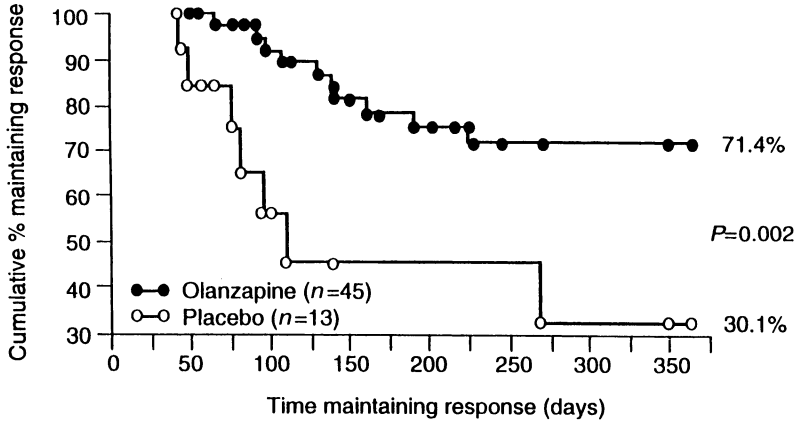

Fig. 3 Olanzapine *v.* placebo. Time for which psychopathological symptoms were maintained at a sufficiently low level to avoid the need for hospitalisation (Beasley, 1997*b*). (Reproduced by kind permission of Physicians Postgraduate Press.)

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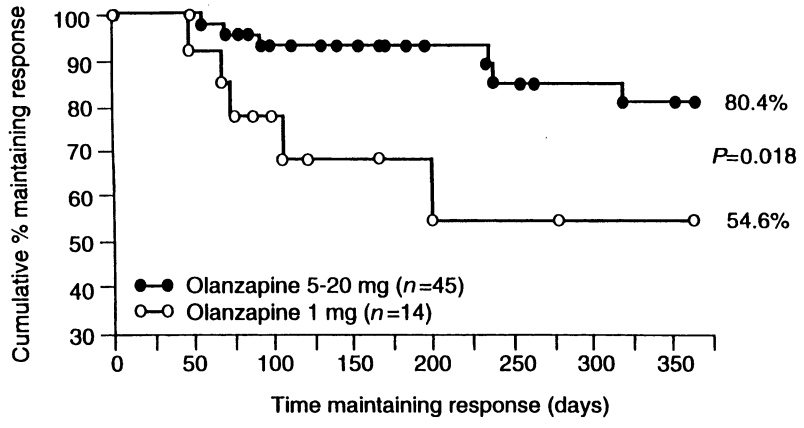

Fig. 4 Olanzapine: 5–20 mg *v.* 1 mg. Time for which psychopathological symptoms were maintained at a sufficiently low level to avoid the need for hospitalisation (Beasley *et al*, 1997*b*). (Reproduced by kind permission of Physicians Postgraduate Press.)

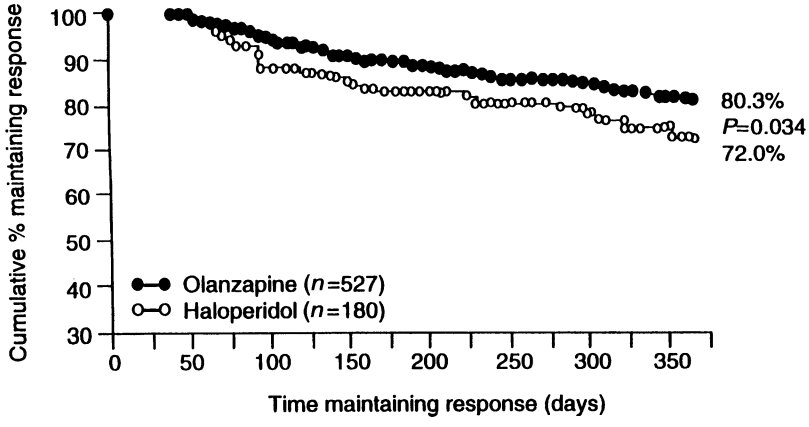

Fig. 5 Olanzapine *v.* haloperidol. Time for which psychopathological symptoms were maintained at a sufficiently low level to avoid the need for hospitalisation (Beasley *et al*, 1997*b*). (Reproduced by kind permission of Physicians Postgraduate Press.)

further proof that the advantages of olanzapine were not due to deterioration in mood associated with haloperidol, we eliminated all patients who experienced a treatment-associated mood worsening of 50% or more. When this data set was re-analysed, the improvement in MADRS score still favoured treatment with olanzapine.

Maintenance therapy

Olanzapine has been shown to be an effective long-term maintenance option in schizophrenia in three long-term double-blind responder trials. Over the course of one year (study 2), 71.4% of olanzapine-treated patients *v.* 30.1% of placebo-treated patients maintained their clinical response and did not need to return to a psychiatric hospital (Fig. 3) (Dellva *et al*, 1997). This difference was statistically significant. Therapeutic doses of olanzapine (5–20 mg) were also found to be significantly more effective than a 1 mg dose of olanzapine in maintaining clinical response in the study 3 extension (Fig. 4). It was especially noteworthy that a meta-analysis of studies 2, 3, and 4 demonstrated that olanzapine (5–20 mg) was also statistically significantly more effective than the conventional drug, haloperidol (5–20 mg), in maintaining acute clinical response (Fig. 5).

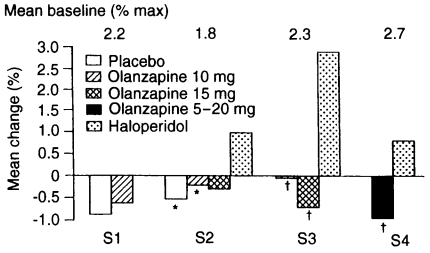

Fig. 6 Acute extrapyramidal side-effects: Simpson–Angus Scale mean change (LOCF). *$P \leq 0.050$ *v.* haloperidol; †$P \leq 0.001$ *v.* haloperidol; LOCF, last observation carried forward (Nemeroff, 1997). (Reproduced by kind permission of Physicians Postgraduate Press.)

Adverse events

The occurrence of adverse events in the placebo-controlled trials was comparable for the two treatments, illustrating the overall tolerability of olanzapine. Overall, fewer olanzapine-treated patients discontinued treatment due to adverse events than placebo-treated patients (Beasley *et al*, 1996*a*,*b*). Olanzapine-treated patients experienced significantly more somnolence, dizziness, weight gain, and akathisia, while placebo-treated patients exhibited more frequent paranoid reaction, anorexia, flu syndrome, delusions, and weight loss. Interestingly, none of the traditional anticholinergic events were seen significantly more often with olanzapine than with placebo.

In active-controlled trials, fewer olanzapine-treated patients discontinued treatment due to adverse events than did haloperidol-treated patients. Rates of discontinuation because of adverse events, including akathisia, anxiety, sleep disorder, and extrapyramidal syndrome, were statistically significantly greater in haloperidol-treated patients than in olanzapine-treated patients.

Extrapyramidal side-effects

In the two placebo-controlled pivotal clinical studies (studies 1 and 2), patients randomised to placebo showed baseline-to-end-point improvement in EPS as measured by the Simpson–Angus scale. Interestingly, all four pivotal studies showed improvements in EPS from baseline among patients treated with olanzapine. Analysis of the multiple, fixed-dose arms (studies 2 and 3) did not reveal a dose-dependent increase in EPS events. In contrast, in the three pivotal studies that included haloperidol (studies 2, 3, and 4), patients treated with this conventional agent showed an expected baseline-to-end-point worsening in EPS, despite significantly greater use of anticholinergic therapy than in the olanzapine cohort. Furthermore, the differences in the categorical emergence of EPS between olanzapine and haloperidol were statistically significant (Fig. 6). Similar acute results were observed for akathisia ratings as measured by the Barnes Akathisia

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Scale (Barnes, 1989). During the double-blind maintenance portions of studies 2, 3 and 4, olanzapine was also associated with a significantly lower incidence of new treatment-associated tardive dyskinesia as measured by the Abnormal Involuntary Movement Scale (Tollefson *et al*, 1997*a*).

Quality of life and health economic benefit

Aside from safety and efficacy issues, the quality of life associated with an antipsychotic medication and the economic differences between agents are increasingly important considerations. In the three pivotal studies that included haloperidol (studies 2, 3, and 4), the overall improvement in patients' quality of life during the one-year treatment period was significantly greater with olanzapine, as measured by the Heinrich Carpenter Scale (Heinrichs *et al*, 1984). Prior to entry, the distribution of gainfully employed patients was comparable between the two study groups. However, by the end of both the acute and continuation phases, a significantly greater number of olanzapine-treated patients were reintegrated into the work force (Fig. 7). While the pharmaceutical cost of olanzapine exceeds that of haloperidol, the total direct cost of illness, including both in-patient and out-patient medical expenses, was significantly lower among patients treated with olanzapine. The net savings per olanzapine-treated patient over the one-year study period was US$2174.

Suicidality

Across the four pivotal studies, there were fewer suicide attempts among patients treated with olanzapine than among those treated with either placebo or haloperidol. In the large comparative study of olanzapine *v.* haloperidol, analysis of MADRS item 10 ('suicidal ideation') showed essentially no change from baseline to end-point for haloperidol. In contrast, the olanzapine cohort showed a significant improvement at end-point.

Prolactin data

Novel antipsychotic agents appear to have relatively low D_2 receptor affinity, including the tuberoinfundibular system, which would predict a lessened impact on the secretion of prolactin. In study 2, male subjects (to control for menstrually-related variance) were evaluated for the differential effect of treatment on plasma prolactin. As expected, placebo was not found to be associated with a significant increase in prolactin, whereas haloperidol was associated with an acute and sustained prolactin elevation that was still evident after six weeks of treatment. While olanzapine produced a modest elevation of serum prolactin, that appeared to be dose-dependent at week 2, by week 4 and through week 6, prolactin levels with all three olanzapine dosages (5, 10, or 15 mg) were comparable to placebo and significantly less than haloperidol (Fig. 8). No dose-dependent effect was evident at end-point. Thus, olanzapine appeared to have only a transient effect on serum prolactin.

First-episode patients

Newer agents are often initially reserved for patients who have been refractory to conventional therapy. However, people newly diagnosed as having schizophrenia may be even more suitable candidates for such treatments. In study 4, a subset of first-episode patients (59 treated with olanzapine and 24 with haloperidol) was compared in *post hoc* analysis. Within this subset, a significantly higher percentage (65%) of the first-episode cohort treated with olanzapine responded to therapy, as defined by at least a 40% improvement in the BPRS, than those treated with haloperidol (30%). Moreover, this 65% response rate among first-episode olanzapine patients exceeded the 45% rate among multiple-episode responders to olanzapine. In contrast, the response rate to haloperidol (approximately 1/3) was nearly identical in both the first- and multi-episode groups (Fig. 9). There were also significantly fewer discontinuations because of adverse events with olanzapine than with haloperidol among first-episode patients. The EPS advantage of olanzapine relative to

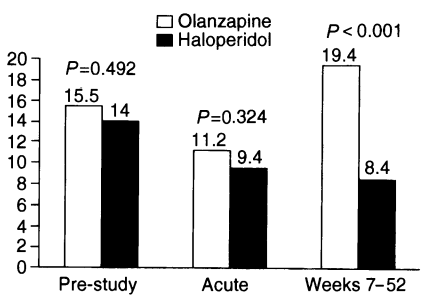

Fig. 7 Percentage of patients engaged in work (full-time and part-time).

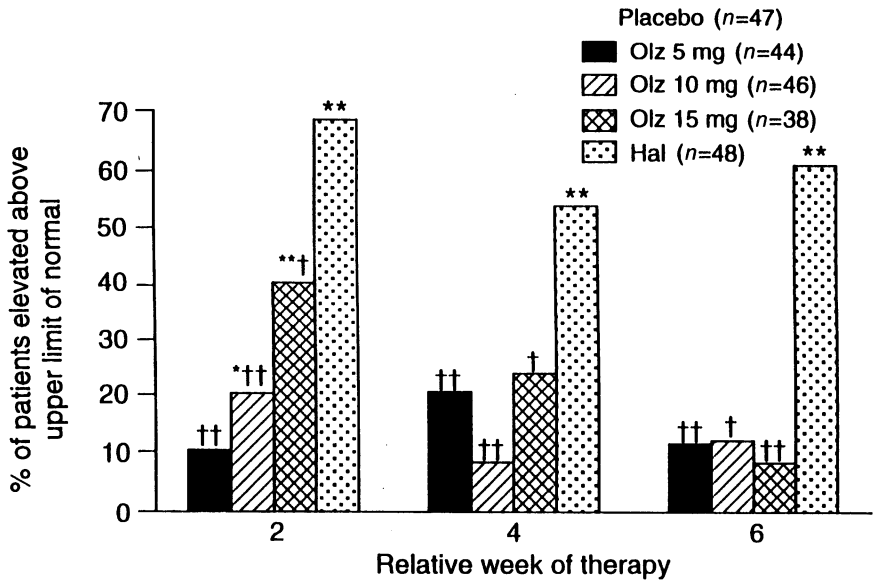

Fig. 8 Treatment-emergent categorical increases in prolactin (males). *$P \leqslant 0.05$ *v.* placebo; **$P < 0.001$ *v.* placebo; †$P \leqslant 0.05$ *v.* haloperidol; ††$P < 0.001$ *v.* haloperidol: Olz, olanzapine; Hal, haloperidol.

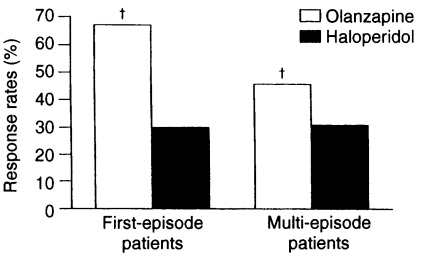

Fig. 9 A comparison of acute response rates in first- and multi-episode schizophrenic patients (≥40% improvement on BPRS from baseline). †$P \leqslant 0.003$ olanzapine *v.* haloperidol.

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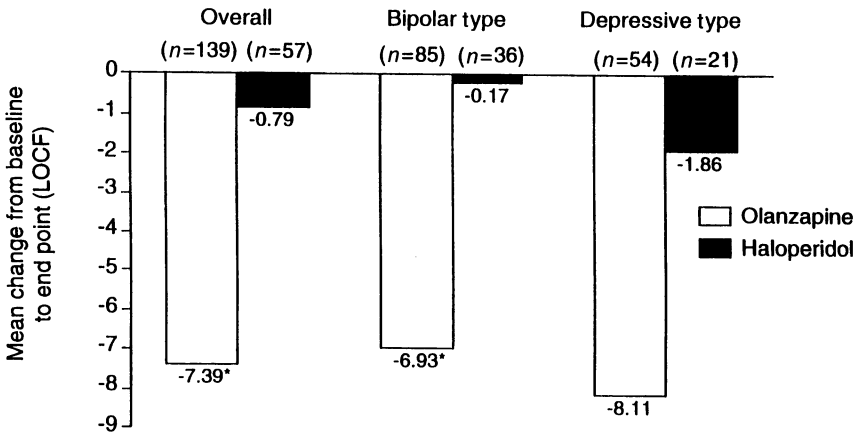

Fig. 10 Acute baseline to end-point MADRS total score improvement among schizoaffective patients; *$P \leqslant 0.01$: LOCF, last observation carried forward (Glazer, 1997). (Reproduced by kind permission of Physicians Postgraduate Press.)

haloperidol was even more evident than that seen for the multi-episode group.

Patients with schizoaffective disorder

In study 4 comparing olanzapine with haloperidol, a sample of 288 schizoaffective patients were evaluated *post hoc*. (The sample included both bipolar and depressive types.) Improvement, defined by change in either the MADRS total score (Fig. 10) or BPRS total score, was significantly greater for those treated with olanzapine than for those treated with haloperidol. In addition to greater improvement in depressive symptoms (MADRS), those treated with olanzapine also showed greater improvement on a subset of mania-related items (BPRS).

Olanzapine *v.* risperidone

The final results from a large multi-centre study comparing olanzapine with risperidone were recently reported (Tran *et al*, 1997). An eight-week acute treatment phase was followed by a 20-week continuation phase. Dosing with olanzapine began at 15 mg daily and ranged from 10 to 20 mg daily, while dosing with risperidone started at 2 mg daily and ranged from 4 to 12 mg daily. After six months of treatment, the percentage of patients with improvement of at least 40% on the PANSS was significantly higher with olanzapine than with risperidone.

Furthermore, 87.9% of olanzapine-treated responders maintained their symptomatic improvement ($\geqslant$20% PANSS) during the maintenance phase, compared to 67.7% of risperidone-treated responders, a difference that was statistically significant in favour of olanzapine (Fig. 11). Significantly greater improvement in patients' negative symptoms scores (SANS) characterised olanzapine. The categorical incidence of EPS was significantly greater among risperidone-treated patients, despite the fact that anticholinergic agents were used significantly more often by this group. Similarly, persistent elevation of serum prolactin was evident at 28 weeks with risperidone but not with olanzapine. Sexual dysfunction was also a significantly more common adverse event among risperidone patients (both male and female). Both treatments were associated with weight gain; however, weight gain was somewhat higher among olanzapine-treated patients.

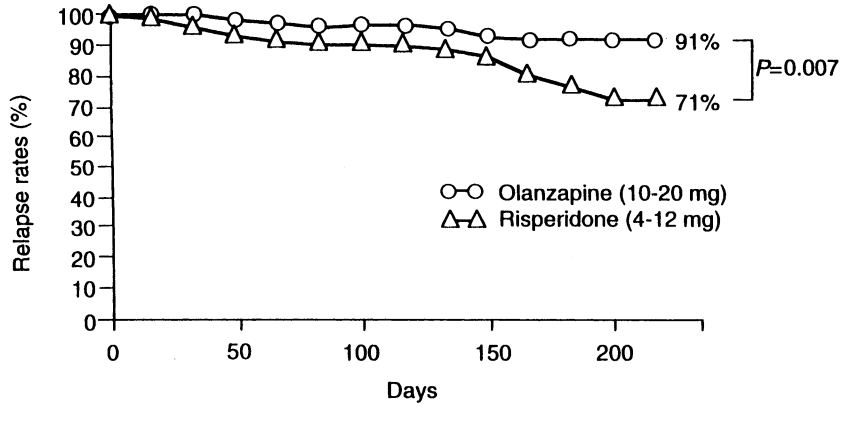

Fig. 11 Maintenance of response to treatment of acute condition with olanzapine and risperidone. (Response defined as $\geqslant$20% improvement on PANSS at week 8; relapse defined as $\geqslant$20% deterioration on PANSS plus $\geqslant$3 deterioration on CGI after 8 weeks (Tran *et al*, 1997).) (Reproduced by kind permission of Williams & Wilkins.)

Olanzapine in clozapine-resistant patients

Patients with schizophrenia who were unresponsive to, and/or intolerant of, clozapine recently participated in an open-label trial of olanzapine (5–25 mg daily) for 18 weeks (Tollefson, 1997*c*). About 90% of the patients had become resistant to clozapine and about 17% had experienced adverse events, including leucopenia or frank agranulocytosis, which necessitated discontinuation of clozapine. After six weeks on olanzapine, approximately one-third of the sample achieved a decrease of 20% on their PANSS total score. About half of the sample achieved at least some clinical improvement on their Clinical Global Impression and Patient Global Impression scales (Guy, 1976). Approximately 10% were rated much improved. With respect to EPS, the highest EPS score at any time during the open-label period was still lower than the EPS rating at baseline. Among patients with clozapine-related leucopenia or agranulocytosis, no haematological cross-reactivity was observed while on olanzapine.

CONCLUSIONS

Throughout a series of controlled clinical trials in over 3600 patients, the novel antipsychotic agent olanzapine has demonstrated a broad range of efficacy (for positive, negative, and depressive symptoms), improved response and maintenance rates, and a safety profile comparable to placebo and superior to that of standard therapeutic drugs. Furthermore, olanzapine has been shown to improve the quality of life significantly, enhance employment capacity, and reduce the overall direct costs of illness. Taken together, these data provide a strong impetus to consider novel therapeutics, such as olanzapine, as the

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first-line choice for treatment of schizophrenia at any point in the life course of the disease.

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