

Is olanzapine clinically effective? A naturalistic outcome survey in two hospital settings

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AIM • To determine the clinical effectiveness of olanzapine in two hospital settings.

DESIGN • Prospective naturalistic systematic clinical evaluation.

SUBJECTS AND SETTING • All patients with a clinical diagnosis of schizophrenia who were prescribed olanzapine over a one-year period, at the Lothian Primary Care NHS Trust (LPCT) and the State Hospital (SH), Carstairs (a high security facility), were given a standardised assessment using five clinical measures. The same measures were repeated after six months in those patients still taking olanzapine.

OUTCOME MEASURES • Linear rating scales with anchor points were used for the standardised assessment. The five scales measured outcome in clinical

global impression, positive and negative psychotic symptoms, drug-related side effects and quality of life.

RESULTS • 58 of 116 patients (50%) at LPCT were still taking olanzapine at six months (mean dose 15mg). These patients had a statistically significant reduction in all ratings at six months. 28 patients (24%) had a 40% or greater reduction in positive symptoms. 37 of 48 patients (77%) at the SH were still prescribed olanzapine at six months with a mean dose of 17.3mg. 4 (of the 5) ratings indicated significant improvement. 21 (44%) of the SH patients showed a 40% or greater reduction in positive symptoms.

CONCLUSIONS • Olanzapine appears to be clinically effective in both general adult and high security psychiatric settings. Routine monitoring of outcomes in psychiatric settings is feasible and can be usefully employed to assess the impact of new treatments.

New antipsychotic drugs have been modelled on clozapine to have greater blockade at 5HT₂ receptors than traditional drugs, with the expectation of equal or greater efficacy and reduced extrapyramidal symptoms. Olanzapine (Zyprexa) is an antipsychotic agent with proven efficacy in treating the positive symptoms of schizophrenia, with fewer extrapyramidal adverse effects than haloperidol.¹ Individual trials

have suggested that it may be superior to haloperidol in the alleviation of negative symptoms, improving quality of life and in treatment resistance, but this has not been confirmed in the Cochrane review.¹ Demonstrating efficacy in randomised controlled trials is however not the same as showing effectiveness in routine clinical practice. Ever mounting financial pressures on the National Health Service mean that effectiveness should be routinely and regularly demonstrated. Lothian drug evaluation panel (advisers to the area drug and therapeutics committee) requested that olanzap-

ine is monitored and a monitoring system was developed which involved auditing the effects of olanzapine on several clinical indices in two hospital settings.

METHOD

Subjects All patients with a clinical diagnosis of schizophrenia who were prescribed olanzapine were prospectively recruited into the study. The Lothian Primary Care NHS Trust (LPCT) study ran from January 1998 to December 1998; six-month follow-up assessments ran to July 1999. The

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TABLE 1: LOTHIAN PRIMARY CARE NHS TRUST AND STATE HOSPITAL PATIENT DEMOGRAPHICS

Demographic details	LPCT (n=116)	SH (n=48)
Patient cohort	Mixed primary and secondary care settings	Detained inpatients
Gender (male:female)	67:49	46:2
Mean age	35.9 (sd=16.1)	34.8 (sd=10.9)
Most frequent reason for initiating treatment with olanzapine	Avoidance of intolerable side effects 55 patients (47%)	Refractory schizophrenia, 33 patients (69%)
Mean starting dose	9.0mg (sd=4.0)	15.7mg (sd=4.9)
Mean dose at 6 months	15.0mg (sd=5.1)	17.3mg (sd=4.7)
Number of drop outs	52 patients (45%)	4 patients (8%)
Most common reason for treatment discontinuation	Non-compliance, 18 patients (15%)	Lack of efficacy, 3 patients (6%)

State Hospital patients were recruited between May 1998 and April 1999, with follow-up to October 1999. One-hundred-and-sixteen and 48 patients respectively were enrolled (see Table 1 for demographics).

Measures Demographic and clinical information (including one or more of five pre-specified reasons for initiating olanzapine) was documented by the prescribing clinician. A standardised assessment form devised for this study was completed. Five linear analogue scales with referenced anchor points were used. Scales comprised the Clinical Global Impression (CGI) scale (score range 0 to 7), as well as an estimate of the positive and negative symptoms of schizophrenia, drug-related adverse effects and impaired quality of life (score range 0 to 4). For all assessments the score increases with severity of symptoms. Where possible, the same clinicians reassessed the patients still taking olanzapine at six months.

The CGI scale was adapted for the second assessment in LPCT patients, to reflect improvement "entirely attributable to drug treatment" (Clinical Global Improvement score), as an internal reliability check.

Reliability Two psychiatrists (MT and RS) independently interviewed 10 randomly chosen individuals from the LPCT study group with whom they were previously unacquainted. Subjects were interviewed by both doctors on the same day. Weighted kappa scores were 0.60 for CGI, 0.44 for positive symptoms, 0.39 for negative symptoms, 0.69 for drug-related side effects, and 0.75 for quality of life impairment.

Statistics Scores at baseline and six months were compared with the non-parametric Wilcoxon matched-pairs signed-ranks test, but mean scores are presented here for ease of comprehension. Clinical response was defined as a 40 per cent or greater reduction in positive symptoms, using the criteria from the Cochrane review,¹ calculated as the difference in positive symptom ratings at time 1 and time 2 divided by the severity at time 1. Response rates were calculated on an "intention to treat" basis.

RESULTS

Lothian Primary Care NHS Trust study Sixty-seven males and 49 females were included in the LPCT cohort, age range 14–94 years; mean age 35.9 (sd=16.1) years.

Criteria for patient selection as indicated by clinician (n=116) The clinical indicators were intolerable side effects from traditional antipsychotics (55 patients; 47 per cent), minimisation of side effects from outset of treatment a priority (38 patients; 33 per cent), marked negative symptoms (19 patients; 16 per cent), refractory schizophrenia (32 patients; 28 per cent), and other (32 patients; 28 per cent). More than one of

these criteria were noted in 48 patients (41 per cent).

Dose The mean daily starting dose (n=116) was 9mg (sd=4.0), with a range of 2.5–25mg. The mean daily dose at six months (n=58) was 15mg (sd=5.1), with a dose range of 5–30mg.

Co-prescribing of other antipsychotics At baseline (n=116), 31 patients (27 per cent) were receiving concurrent treatment with one other antipsychotic agent, six (5 per cent) were receiving two others and one patient (1 per cent) three other antipsychotic agents in addition to olanzapine. At six months (n=58), 10 patients (17 per cent) were receiving one other antipsychotic and one patient (2 per cent) was receiving two others.

Drop outs Fifty-two (45 per cent) of the 116 patients discontinued treatment within six months for the following reasons: lack of efficacy (15 patients; 13 per cent), side effects (nine patients; 8 per cent), non-compliance (18 patients; 15 per cent), withdrew consent (one patient; 1 per cent), other reasons (nine patients; 8 per cent). Six patients (5 per cent) were lost to follow up.

Baseline assessments (n=116) The mean CGI score at baseline was 5.0 (sd=1.2) indicating that the average patient was "markedly ill". The other ratings were: positive symptoms, mean score 2.3 (2=moderate severity), sd=1.2; negative symptoms, mean score 1.6 (1=mild, 2=moderate severity), sd=1.1; drug-induced side effects, mean score 2.0 (mild), sd=1.5; impairment in quality of life, mean score 3.2 (3=moderate, 4=severe), sd=0.8.

Clinical Global Improvement attributed entirely to treatment with olanzapine over six months (n=58) Clinical Global Improvement is shown in Table 2. Forty-eight patients (83 per cent) were scored as minimally improved, much improved or very much improved. The mean CGI score was 2.2 (2=much improved, 3=minimally improved), sd=1.1.

Comparison of baseline and follow-up assessments (n=58) Improvement was found in all assessments (all $P < 0.0001$ on Wilcoxon matched-pairs signed-ranks test). The comparative mean scores are shown in Table 3. Only 28 of 116 patients (24 per cent), had a 40 per cent or more reduction in positive symptoms at six months. Of these 28 patients, 25 were also rated as having at least some improvement in terms of CGI suggesting good internal reliability. Nineteen of the 32 patients prescribed olanzapine for treatment resistance were still taking the drug at six months and eight of them (25 per cent) had responded.

TABLE 2: CLINICAL GLOBAL IMPROVEMENT OVER SIX MONTHS IN LOTHIAN PRIMARY CARE NHS TRUST PATIENTS (N=58)

Clinical Global Improvement score	Number of patients
0=not assessed	2
1=very much improved	12
2=much improved	24
3=minimally improved	12
4=no change	7
5=minimally worse	0
6= much worse	1
7=very much worse	0

TABLE 3: BASELINE AND FOLLOW-UP ASSESSMENTS IN LOTHIAN PRIMARY CARE NHS TRUST PATIENTS (N=58)

Assessment details	Mean score at baseline	Mean score at 6 months
Severity of positive symptoms	2.26	1.16
Severity of negative symptoms	1.58	1.19
Severity of drug induced side effects	1.97	0.83
Impairment in quality of life	3.22	2.09

The State Hospital study Forty-six men and two women were included in the State Hospital cohort, age range 19–58 years, mean age 34.8 (sd=10.9) years.

Criteria for patient selection as indicated by clinician (n=48) Intolerable side effects from traditional antipsychotics (18 patients; 38 per cent), minimisation of side effects from outset a priority (8 patients; 17 per cent), marked negative symptoms (6 patients; 13 per cent), refractory schizophrenia (33 patients; 69 per cent), other (1 patient; 2 per cent), more than one of these criteria (18 patients; 37 per cent).

Dose The mean daily starting dose (n=48) was 15.7mg (sd=4.9); dose range 5–20mg. The mean daily dose at six months (n=37) was 17.3mg (sd=4.7); dose range 10–30mg.

Co-prescribing of other antipsychotics At baseline (n=48), 13 patients (27 per cent) were receiving concurrent treatment with one other antipsychotic agent and one patient (2 per cent) was receiving two other antipsychotic agents in addition to olanzapine. At six months (n=37), eight patients (22 per cent) were receiving one other antipsychotic and one patient (3 per cent) was receiving two others.

Drop outs Four (8 per cent) of the 48 patients discontinued treatment within six months for the following reasons: lack of efficacy (three patients; 6 per cent), non-compliance (one patient; 2 per cent). Seven patients (15 per cent) were lost to follow up.

Baseline assessments (n=48) The CGI mean score was 5.1 (markedly ill), sd=1.7; positive

TABLE 4: CLINICAL GLOBAL IMPRESSION AT BASELINE AND SIX MONTHS IN STATE HOSPITAL PATIENTS (N=37)

Clinical Global Impression score	Number of patients at baseline	Number of patients at 6 months
0=Not assessed	1	0
1=Normal, not at all ill	0	1
2=Borderline, mentally ill	0	5
3=Mildly ill	4	8
4=Moderately ill	9	10
5=Markedly ill	9	7
6=Severely ill	2	4
7=Among the most extremely ill	12	2

TABLE 5: BASELINE AND FOLLOW-UP ASSESSMENTS IN STATE HOSPITAL PATIENTS (N=37)

Assessment details	Mean score at baseline	Mean score at 6 months
Severity of positive symptoms	2.50	1.50
Severity of negative symptoms	1.80	1.50
Severity of drug induced side effects	1.90	0.80
Impairment in quality of life	3.00	2.10

symptoms, mean score 2.5 (moderate to marked severity), $sd=1.1$; negative symptoms, mean score 1.8 (mild to moderate), $sd=1.2$; drug-induced side effects, mean score 1.8 (minimal to mild), $sd=1.4$; impairment in quality of life, mean score 3.1 (moderate to severe), $sd=1.2$.

Severity of illness at baseline and six months (n=37) CGI at baseline and six months is shown in Table 4. A mean score of 5.1 (markedly ill) at baseline fell to a mean score of 4.0 (moderately ill) at six months. This was found to be statistically significant ($P<0.001$).

Comparison of baseline and follow-up assessments (n=37) The comparative mean scores are shown in Table 5. Improvements in all assessments were found. This was statistically significant in the assessments for positive symptoms, severity of drug-induced side effects and improvement in quality of life ($P 0.0001$) but not for negative symptoms. Twenty-one (44 per cent) SH patients had a 40 per cent or greater reduction in positive symptoms. Twenty-four (73 per cent) SH patients prescribed olanzapine for treatment resistance were still on the drug after six months and 14 (42 per cent) of them had responded.

DISCUSSION

Main findings Of the patients in the general adult psychiatry setting, approximately half were still prescribed olanzapine at six months follow up. All clinical ratings were significantly reduced in these patients as a group, and approximately a quarter of

them had a good clinical response as defined by a 40 per cent or greater reduction in positive symptoms. Even among the "treatment resistant" patients, a quarter showed a clinically significant response at six months.

The results were similar in the State Hospital setting, despite the fact that most of these patients were judged to be treatment resistant. This may be attributable to better compliance with medication than before incarceration. It is notable that drop out rates were only 8 per cent among patients in the State Hospital compared with 45 per cent in LPCT and 36–61 per cent reported in Cochrane.¹

Strengths and limitations of this report A naturalistic design was adopted for this study. Data were collected prospectively on a consecutively recruited sample of patients with a clinical diagnosis of schizophrenia. Symptom severity was measured with a simple compound scale based on

standardised psychiatric rating scales with proven reliability. Importantly, all schizophrenic patients were included regardless of any additional diagnoses or problems. The findings, therefore, complement those reported from randomised controlled trials

where the necessary use of inclusion and exclusion criteria mean the results might not be applicable to all patients, especially those who are involuntarily detained or with substance abuse co-morbidity.

We must, of course, acknowledge several limitations of the study. We did not have the resources to conduct standardised psychiatric interviews in all subjects and we cannot, therefore, be sure that they meet diagnostic criteria for schizophrenia, although the subjects are likely to be representative of patients given a clinical diagnosis of the same. Similarly, we did not employ strict criteria for the definition of treatment resistance and this could explain our apparently high levels of response in such notoriously difficult to treat patients. The lack of a control group means that benefits noted cannot be definitely attributable to olanzapine rather than other potentially therapeutic factors. While we demonstrated that the scale we used had satisfactory inter-rater reliability at one point in time, we cannot be sure that all the raters used in the study would have agreed with each other to an acceptable extent, or that our measure of change in severity of symptoms is a valid measure of clinical response. However, an additional measure of CGI improvement in the LPCT patients was strongly associated with clinical response and our kappa values of 0.4–0.75 are similar to the typical values of 0.5 for most of the components of the physical examination in general medical practice.² In studies such as this, one has to balance what is desirable with what is practical, and the use of potentially different raters for particular patients is analogous to clinical situations where one doctor has to assess the effect of a drug prescribed by another. The use of some outcome rating is at least likely to provide more reliable information than that which is entirely based on components of a typical mental state examination in routine psychiatric practice, which may be even less reliable than a typical physical examination.³

Other related studies Some naturalistic outcome data are available for clozapine and risperidone, comparatively little for olanzapine, and none we are aware of for other new antipsychotic drugs. Procyshyn and Zerjav⁴ reported that eight of 30 Canadian inpatients had a clinically significant reduction "in at least one target symptom" on a mean dose of 19.8mg of olanzapine over up to 120 days. Ho *et al*⁵ found statistically significant reductions on ratings of positive psychotic symptoms, total symptoms, a global assessment and some measures of quality of life in 13 of 21 inpatients in Iowa who remained on olanzapine and were followed up at six months (mean dose 30.8mg daily on follow up).

Taylor *et al*⁶ reported that 16 patients (44 per cent) had at least a 20 per cent fall in scores on the Brief Psychiatric Rating Scale (BPRS) over a six-week inpatient stay. They found no such improvement in 12 treatment resistant patients, but the drug dosage was not specified in that report. Mountjoy

Summary

CLINICAL IMPLICATIONS

- Olanzapine is likely to be clinically effective in general and high security psychiatric settings
- The fact that we have obtained similar results in two prospectively and consecutively recruited groups of patients with schizophrenia, suggests that our results are likely to be generalisable to most psychiatric settings
- Routine monitoring of clinical effectiveness is feasible in psychiatry

LIMITATIONS

- The lack of a control group means that we cannot be certain that the benefits described are attributable to olanzapine
- The apparent reduction in the severity of negative symptoms could be attributable to a reduction in extrapyramidal side effects, ie, secondary negative symptoms
- Treatment resistance was determined by the individual clinician initiating treatment

*et al*⁷ in a naturalistic British study, found that 11 of 23 treatment resistant patients responded to high-dose olanzapine. Dursun *et al*⁸ found that eight of 16 patients who had failed to respond to at least three antipsychotic drugs from at least two different chemical classes had a 20 per cent decrease in scores on the BPRS after 16 weeks outpatient treatment in Nova Scotia where the mean follow up dose was 21.8mg daily.

The results of our study are consistent with the published literature. Our study appears to be the largest evaluation of the effects of olanzapine in treatment resistant patients in everyday clinical practice, but the findings must be interpreted cautiously for the reasons already stated. There is, as yet, no convincing evidence from randomised controlled trials that olanzapine is efficacious in treatment resistance.¹ It should also be noted that there are no previous demonstrations of significant improvements in negative symptoms in these effectiveness studies, and it may be that the apparent benefits observed (and which have been reported in some trials) are attributable to a reduction in extrapyra-

midal side effects and, therefore, fewer secondary rather than primary negative symptoms.

The only previous clinical effectiveness study in a State Hospital setting that we are aware of is that conducted by Chengappa *et al*⁹ in Pennsylvania, although State Hospitals in the two nations can differ markedly. They reported that "ward privileges" (which amounted to some freedom in determining one's use of time) increased, while the duration of hospital stay and number of readmissions fell, over a two-year period of treatment with risperidone.

Implications The importance of this study is, therefore, two-fold. There are few clinical effectiveness studies of olanzapine in the worldwide literature, only one of which is from outside North America, and no previous studies that we are aware of on the effectiveness of olanzapine in a secure psychiatric setting. We have demonstrated the clinical effectiveness of olanzapine in a "markedly ill" group of patients with a clinical diagnosis of schizophrenia who are likely to be representative of such patients at least in British psychiatric settings. Second-

ly, we have demonstrated the practical feasibility of routinely measuring patient outcomes in two psychiatric settings. Such an approach could be easily adopted for routine monitoring of the effects of newly available drugs, and could conceivably be adapted for studies of outcomes of other treatment approaches.

Locally based assessments are compatible with national benchmarking and are arguably essential if clinicians are to adapt the results from randomised controlled trials to their own clinical practice. The information generated would be able to inform the development of local treatment guidelines. Clinical effectiveness, naturalistic outcome or audit studies cannot replace randomised controlled trials, but nor are they obviated by them. They are complementary and both are necessary.

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