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Dimensions of Outcome with Clozapine

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Various outcome measures following clozapine administration to neuroleptic-resistant schizophrenic patients are considered. The importance of a multidimensional perspective is emphasised. There was significant improvement in positive symptoms, some negative symptoms, quality of life, some types of cognitive function (e.g. semantic memory), extrapyramidal function, and tardive dyskinesia. Readmission to hospital, and family burden were markedly reduced, which achieved significant savings in the cost of treatment. Compliance with clozapine and weekly blood testing can be achieved in the majority of treatment-resistant cases. These benefits may occur independently of each other.

The assessment of response to new drug treatments for schizophrenia is ordinarily based upon three types of outcome measures. The primary measure is often psychopathology change scores, such as those derived from the Brief Psychiatric Rating Scale (BPRS: Overall & Gorham, 1962) or the Positive and Negative Syndrome Scale for Schizophrenia (PANSS; Kay *et al*, 1988). This type of outcome measure focuses on total psychopathology but also includes consideration of specific types of symptoms, e.g. positive and negative symptoms. The second type of measure is usually an overall assessment of social function and mental status before and after treatment. For this, measures such as the Clinical Global Impressions and Clinical Global Severity (CGI, CGS; Guy, 1976) are often used. Thirdly, if the treatment study is of hospitalised schizophrenic patients, it may include an assessment of ward behaviour, emphasising social function, appropriateness of behaviour, self-care, etc. The Nurses Observation Scale of In-patient Evaluation (NOSIE-30; Honigfeld & Klelt, 1965) is most frequently used for this purpose.

These three outcome measures should be sufficient to determine the efficacy of a putative antipsychotic agent, even one of a novel type, provided that the study has sufficient power, includes a comparison agent and placebo, employs random assignment, is double-blind, and, of course, uses well-trained raters. However, these three measures do not fully describe the benefits, or lack thereof, of antipsychotic medications because of the range of disabilities or disruption of normal function produced by schizophrenia in the individual patient and the burdens inflicted on his/her family and society, which go far beyond psychopathology. Even within the narrow range of outcome measures assessed by the types of rating scales noted above, e.g. psychopathology and social function, the brief time period of study and the atypical (i.e. hospital) setting of the customary four to six week in-patient study preclude, by design, assessment of the long-term impact of antipsychotic drug treatment on psychopathology and social function in the community. Moreover, such studies do not provide any measure of the effect of treatment upon the family or its societal impact.

Thus, a comprehensive assessment of outcome of treatment with antipsychotic drugs should include an assessment of additional outcome measures that affect the individual with schizophrenia, his/her family, and society. A list of many of these outcome measures is shown below:

Psychopathology
Cognitive function
Extrapyramidal symptoms (tardive dyskinesia)
Social function
Independent living
Work function
Quality of life
Readmission to hospital
Family burden
Compliance
Cost of illness and treatment
Societal.

The importance of specific consideration of each of these outcome measures is supported by the independence of many of them, as well as by the need to make risk–benefit assessments for individual measures. The latter issue is particularly important with regard to clozapine because of the 1–2% incidence of granulocytopenia or agranulocytosis associated with its use (Krupp & Barnes, 1989). The independence of multiple outcome measures in schizophrenia has been emphasised by Strauss and colleagues (Strauss & Carpenter, 1972, 1978; Strauss *et al*, 1974). These authors described outcome along four domains of functioning: work, social functioning, severity of symptoms, and duration of

time spent out of the hospital. These measures were found to have different predictors and not to be significantly correlated.

The importance of a multidimensional perspective on the outcome of clozapine treatment is also suggested by the decision of a number of public health authorities in the USA to permit continuation of trials of clozapine beyond six to twelve weeks only in those patients who show improvement in BPRS total scores. The amount of improvement specified is usually at least 20%, but sometimes it is even greater. In any event, no consideration is given to other possible types of benefit such as compliance.

This article provides a limited consideration of some of the issues and available data on this broader concept of outcome measures in schizophrenia with regard to clozapine treatment. The emphasis will be on studies of long-term clozapine treatment because many of the outcome measures listed above are meaningfully assessed only over the longer term.

Psychopathology

Clozapine was found to be more effective than haloperidol in reducing BPRS subscale ratings of positive and negative symptoms as well as total BPRS score after six weeks of in-patient treatment (Kane *et al*, 1988). This study, however, did not address the multiplicity of measures listed above. There have been several retrospective long-term studies of the outcome of clozapine treatment (e.g. Povlsen *et al*, 1985; Lindström, 1988). These have been reviewed by Safferman *et al* (1991) and are not discussed here.

In a prospective study, Meltzer *et al* (1989) reported the results of an open trial of 51 patients who had completed at least six weeks and up to 35 months (mean 10.3 (s.d. 8.1) months) of treatment with clozapine. There was a significant decrease in BPRS at six weeks, three, six, nine and 12 months, with a progressive improvement over time. Admission BPRS was 52 (s.e. 2.3) ($n = 51$) whereas the final BPRS at 12 months in 11 subjects still on clozapine was 35.6 (s.e. 3.5). Thirteen of the 51 patients (26%) had dropped out. The others had not reached the 12-month rating period.

We have now analysed data on the first 85 consecutive patients with a DSM-III-R diagnosis of schizophrenia who were treatment-resistant by the criteria of failure to respond to at least two, and in almost all cases, three or more trials of typical neuroleptic drugs. These patients included the 51 patients previously described by Meltzer *et al* (1989). Of the 85 patients, 63 (74%) were in-patients at University Hospitals of Cleveland and 22 (26%) were treated at the Cleveland Veterans Administration Hospital.

Of these 85 patients, 54 (64%) remained on clozapine at the end of 12 months. Eight patients (9%) dropped out because of adverse reactions, including one case of agranulocytosis and one of neutropenia. Lack of efficacy led to seven (8%) dropping out. Non-compliance caused 16 (19%) drop-outs. A comparison of the 54 patients who remained on clozapine for 12 months with the 31 who did not is given in Table 1. There were no significant differences in age, sex, age of onset, number of previous hospital admissions and baseline BPRS score.

Table 1
Comparison of patients completing 12-months clozapine treatment and drop-outs

Measure	Completers mean (s.d.)	Drop-outs mean (s.d.)
Age	33.9 (8.9) ($n = 54$)	36.1 (7.8) ($n = 31$)
Sex	40 M, 14 F	20 M, 11 F
Age of onset	20.5 (6.6) ($n = 43$)	21.1 (6.3) ($n = 25$)
Number of admissions	7.9 (5.3) ($n = 40$)	10.2 (8.9) ($n = 18$)
BPRS total	50.1 (11.8) ($n = 52$)	50.8 (15.6) ($n = 31$)
SADS-C positive	4.1 (2.5) ($n = 45$)	3.9 (2.4) ($n = 21$)
SADS-C negative	4.7 (3.0) ($n = 49$)	4.6 (3.9) ($n = 27$)
SADS-C disorganisation	3.4 (3.4) ($n = 48$)	3.8 (3.9) ($n = 25$)
Global assessment	31.8 (10.9) ($n = 49$)	31.7 (10.6) ($n = 28$)

The total BPRS score, BPRS positive symptoms, Schedule for Affective Disorders-Change (SADS-C; Endicott & Spitzer, 1978) negative symptoms, and disorganisation symptoms for the 54 patients who remained on clozapine for 12 months or more are given in Fig. 1. Significant improvement was noted in all four measures over the 12-month period. As all subjects must have all ratings at all time points to be included in the repeated measures, not all 54 subjects were available for these analyses. Because this was an open trial, designed, in part, to determine when clinical response occurred, and because multiple outcome measures were considered relevant, patients who showed little or no change in psychopathology were treated with clozapine beyond the conventional six-week trial period. Figure 1 shows that the major improvement in psychopathology occurred during the first six weeks.

A factor analysis of the SADS-C items which relate to psychosis found positive symptom factor (severity of delusions and hallucinations), negative symptom factor – loss of interest, depressed appearance, slowed body movement, and slowed speech; and a separate disorganisation factor, consisting of

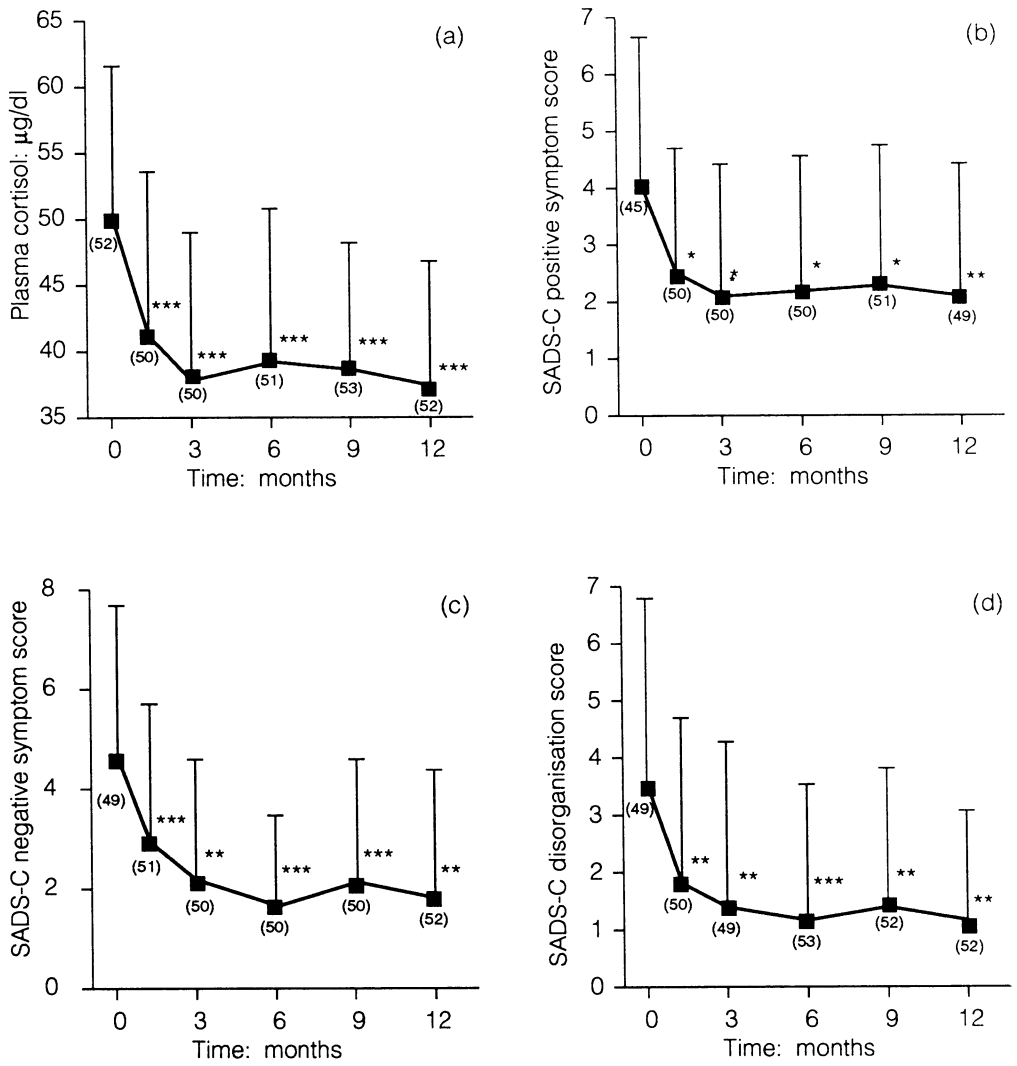

Fig. 1 (a) BPRS Total score: (b) BPRS positive symptoms; (c) SADS-C negative symptoms; and (d) SADS-C disorganisation symptoms in 54 treatment-resistant schizophrenic patients who remained on clozapine for 24 months or more. The number of patients with available data at each time period is given in parentheses. Repeated measures analysis of variance of the data for subjects with no missing time points showed significant time effects (BPRS total, $P=0.0001$; SADS-C positive, $P=0.03$; SADS-C negative, $P=0.0001$; SADS-C disorganisation, $P=0.003$). *$P<0.01$; **$P<0.001$, ***$P<0.0001$; error bars are standard deviation.

loose associations, poverty of thought content, incoherence and inappropriate affect (Thompson & Meltzer, unpublished). Improvement in the SADS disorganisation factor was particularly impressive. Although the SADS negative symptom factor includes items related to avolition and anergia only, it correlates highly with the sum of the five global ratings of the Scale for the Assessment of Negative Symptoms (SANS; Andreason 1982) rating (Thompson & Meltzer, unpublished). In a subgroup of 28 patients, for whom SANS data was available, there was a significant improvement over the 12-month period (14.4 (s.d. 5.4) v. 9.9 (s.d. 4.8), $P=0.001$).

Positive and negative symptoms on the BPRS and SADS-C were not significantly correlated at any measurement point (data not presented). Patients

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often improved in one domain without the other. The best response to clozapine by 12 months was not necessarily found in the patients who improved by six weeks.

In agreement with our previous report that response to clozapine treatment is often delayed, we examined the time in which a 20% decrease in BPRS was first recorded (Table 2). This shows that 44 of the 54 (81.5%) patients had a decrease in BPRS of 20% or more. Of these 44, less than half responded by this criterion at six weeks. Ten patients (22.7%) responded first at nine and 12 months. This provides one rationale for prolonged trials with clozapine before deciding that clozapine does not provide any advantage over typical neuroleptic drugs for a given treatment-resistant patient. Some of the patients who first responded at three and six months had the greatest percentage decrease in BPRS scores by 12 months (Meltzer *et al*, unpublished).

Table 2
Time of first response to clozapine by 20% decrease in BPRS

Time of first response: months	*n*	%	Cumulative percentage
1½	20	45.5	45.5
3	11	25.0	70.5
6	3	6.8	77.3
9	6	13.6	90.9
12	4	9.1	100.0

Of the 12 patients who had predominantly negative symptoms with only low levels of positive symptoms, six had a 50% or greater decrease in SADS-C negative symptoms during the course of 12 months treatment. This indicates that clozapine may be an effective treatment for those patients who phenomenologically resemble the type II syndrome of Crow (1980).

Cognitive function

Cognitive abnormalities are a critical element of schizophrenia. These abnormalities include deficits in attention, recently acquired memory recall, conceptual sorting, and executive function (Chapman, 1980; Seidman, 1983; Kenny & Meltzer, 1991). The effect of neuroleptic drugs on cognitive function shows that abnormalities of attention improve but that memory measures rarely improve or may worsen, perhaps because of the anticholinergic properties of some of these drugs (Perlick *et al*, 1986; Spohn & Strauss, 1989).

We examined the effects of clozapine on four types of neuropsychological measures in 25 treatment-resistant schizophrenic patients (Kenny *et al*, unpublished). The four measures were: (a) attention/short-term memory (assessed with the digit symbol and consonant trigram tests); (b) executive functions (assessed with Wisconsin card sort – categories achieved and percentage perseveration); (c) semantic memory retrieval (assessed with controlled word association and category instance generation tests) and (d) secondary free-recall memory (assessed with immediate and delayed recall tests). Significant improvement was noted in the controlled word association tests of semantic memory at six weeks and six months, and in the immediate and delayed recall test of secondary memory only at six months. Category instance generation also improved at six months only. There was no overall improvement in executive function or attention/short-term memory. However, for all tests there were some patients who improved while others showed no change or even poorer performance. These changes in cognitive function were independent of changes in psychopathology.

The sample size in this study was small. The results must be independently replicated and, if confirmed, could be of considerable importance. Firstly, improvement in semantic and secondary memory function should be of major benefit in improving work and social function. To the extent that schizophrenia is partly related to an impairment of the integration of that stored memory or previous input with current needs for the experience provided by for stored information to guide current behaviour, as proposed by Hemsley (1987) and Patterson (1987), improvements in memory should greatly improve some components of functioning. The lack of a mean overall effect of clozapine on executive function and attention despite significant improvements in psychopathology indicates that there are still very important domains of brain function in schizophrenia that are not susceptible to clozapine. It is possible that clozapine could be more effective in the non-treatment-resistant schizophrenic patient in this regard, either because the cognitive deficit is less severe or because it might be more amenable to treatment initiated at an earlier stage of the illness.

Extrapyramidal symptoms (tardive dyskinesia)

The majority, up to 95%, of patients treated with neuroleptic drugs develop some types of EPS, e.g. rigidity, tremor, dystonias, masked facies (Keepers *et al*, 1983). Van Putten & Marder (1974) suggested that Parkinsonian symptoms, especially akathisia, may be the major reason for discontinuation of neuroleptic treatment, which usually leads to relapse within a 12-month period. As reviewed by Casey (1989), studies involving over 1300 patients show that clozapine has a favourable EPS profile compared with

standard neuroleptic drugs. The incidence of tremor (6%), akathisia (6%) and rigidity (3%) has generally been reported to be much less than that with typical neuroleptic drugs (Safferman *et al*, 1991). However, two studies have reported similar rates of usually mild akathisia in clozapine- and neuroleptic-treated schizophrenics (Claghorn *et al*, 1987; Cohen *et al*, 1991). Akathisia may be difficult to distinguish from agitation arising from psychopathology. Further study of this important issue is required. It can be expected that the low incidence of EPS with clozapine will have a major impact on compliance. Of 15 patients who remained on clozapine despite no major changes in psychopathology, weekly blood drawing and miscellaneous side-effects, the major reason offered by the patients to explain their preference for clozapine over previous antipsychotic drugs was the low level of EPS compared with typical neuroleptic drugs (Meltzer *et al*, unpublished data).

Clozapine produces significantly less tardive dyskinesia (TD) than other antipsychotic drugs (Casey, 1989; Lieberman *et al*, 1989). Several cases have been reported in which abnormal involuntary movements (AIMS) developed long after clozapine was started, but these patients received other neuroleptics before clozapine. In view of the reports of tardive-like movement disorders in schizophrenic patients before the neuroleptic era, it is possible that these cases do not represent the effect of clozapine.

Clozapine has been reported not to suppress the symptoms of tardive dyskinesia (TD) in three studies (Gerlach *et al*, 1975; Gerlach & Simmelsgaard, 1978; Caine *et al*, 1979). Marked improvements in a small number of cases were reported by Shopsin *et al* (1979) and Meltzer & Luchins (1984). Lieberman *et al* (1989) reported a slight but significant decrease in AIMS scores in 30 TD patients treated with clozapine. A nearly complete remission of symptoms during the first six months was seen in 43% of the patients. No tolerance developed to the ability of clozapine to ameliorate TD. It has been suggested that clozapine may specifically remediate the biological deficit which produces TD (Lieberman *et al*, 1989).

The advantage of clozapine with regard to EPS and lack of causation of TD must be considered in evaluating risk–benefit issues with the use of this drug. It is important for compliance and also for the general sense of well-being that patients experience few EPS and are virtually free of the fear of developing or exacerbating TD.

Quality of life

Quality of life is a concept that is receiving increasing attention throughout medicine. It is particularly relevant to chronic illnesses such as schizophrenia in which the illness can transform the lives of the afflicted people and become the determining factor of how they live and work, how they relate to significant others, and what, if any, pleasurable, satisfying daily activities they can engage in. The concept of quality of life as a significant, descriptive measure for schizophrenia has been discussed in detail by Lehman (1983). The elements in Lehman's model include subjective and objective measures in the area of living situations, family, social relations, leisure activities, work, finances, personal safety and health.

The effect of clozapine on the quality of life of 38 treatment-resistant schizophrenic patients was studied by Meltzer *et al* (1990). The Quality of Life scale (QLS) developed by Heinrichs *et al* (1984) was used. This consists of four major factors: (a) intrapsychic functions (which includes items rating sense of purpose, motivation, curiosity, anhedonia, aimless activity, and empathy); (b) interpersonal relations; (c) instrumental role functioning (work, school); and (d) common objects and activities. Patients were assessed at baseline and after six months of clozapine treatment. Significant improvement was noted in the total QLS score (from 36.9 (s.d. 26.9) to 59 (s.d. 21.4)), including an increase in 59.9% in the mean score and a doubling of the median score from 28.5 to 57. There was a significant increase in all four subscales, with the greatest improvement occurring in interpersonal role function and intrapsychic function.

We have now studied 25 of these patients over a 12-month period. Baseline QLS scores increased from 36.8 (s.d. 18.7) to 72.5 (s.d. 24.1). Instrumental role function showed as much improvement as interpersonal role and intrapsychic functions. The Global Assessment Scale (GAS) score at 12 months and QLS total scores were highly correlated ($r = 0.55$, $n = 20$, $P = 0.01$). The GAS ratings for 50 of the 54 patients who remained on clozapine for 12 months or more are given in Fig. 2. There was a 36.1% improvement in global function over the 12-month period ($F = 8.88$; d.f. = 5, 36; $P = 0.0001$). BPRS and SADS-C negative symptom scores correlated with intrapsychic function scores at 12 months, indicating that the latter is a reflection of negative symptoms.

The improvement in QLS reflects highly significant clinical changes observed with clozapine treatment that are rarely, if ever, seen after switching typical neuroleptic drugs in patients who are poor responders to three or more other typical neuroleptics and in the relatively older schizophrenics studied here. The type of improvement noted here has made it possible for some chronically disabled individuals who were leading marginal social lives, in and out of hospitals,

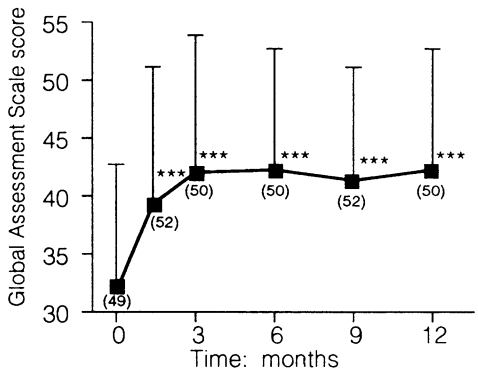

Fig. 2 Global Assessment Scale rating scores in treatment-resistant schizophrenic patients. Error bars are standard deviation. (Repeated measure ANOVA showed a significant time effect, ***$P = 0.0001$).

but usually in some type of community residence, to resume a level of functioning that would be considered within the low normal range because it includes stable interpersonal relationships, varied social activities, perhaps a limited job, and living with their families.

Readmission to hospital

Of the 85 patients started on clozapine at least 12 months before follow-up, 29 (34.1%) were admitted during the 12 months after beginning clozapine compared with 73 (85.8%) in the 12 months before clozapine, excluding the index admission ($P < 0.001$). The total number of admissions to hospital for all 85 patients decreased from 118 to 33, a 72.0% decrease. Of the 31 patients who discontinued clozapine, 13 (42%) required hospital admission. Of the 54 on clozapine for 12 months, 16 (29.6%) required admission. The total number of hospital admissions for these 54 patients fell from 71 pre-treatment to 16 after 12 months treatment. The 16 patients who needed hospital admission while on clozapine, and who remained on it during and after admission, usually recovered within two to three weeks and resumed out-patient treatment.

The low level of hospital admission was achieved with the aid of an out-patient programme that included many elements common to contemporary treatment programmes: family and patient education, various types of groups, social skills training, and vocational counselling. Controlled studies of the importance of this type of programme for achieving optimal benefit with clozapine are needed. The decreased rate of hospital readmission in the drop-outs in the 12 months after clozapine was started reflects, in part, the fact that the duration of treatment on clozapine in this group was 114.9 (s.d. 97.4) days, and that 26 of the 31 (83.9%) discontinued clozapine because of side-effects or lack of compliance rather than lack of efficacy. Lack of compliance may occur even in patients who were responding. The persistent decrease in readmission in this group may represent the persistent benefits of clozapine or psychosocial treatment, or both.

Family burden

Families of schizophrenic patients experience the burden of this illness in many ways, including: grief related to the effects of the illness on an offspring, sibling or parent; the burden of paying at least part of the direct costs of treatment; lost income in taking care of the patient; stigma; and anxiety and guilt about their role in the aetiology of the illness. This burden is particularly great in relatives of treatment-resistant schizophrenic patients. A study evaluating the effects of clozapine on this burden is being undertaken at University Hospitals of Cleveland. There are no formal results yet. However, it has been possible to observe major changes in the areas of lessened anxieties over the course of illness in the patient, greater social freedom, decreased costs of treatment and less lost income in the majority of the families of the patients in our programme (Meltzer & Davies, unpublished data).

Compliance

Despite the weekly blood drawing, compliance with clozapine in our clinic has been excellent. The incidence of non-compliance in our sample was 16 of 85 (19%). Two-thirds of this occurred within the first three months. This is much lower than the non-compliance rate in this group of patients with standard treatments. Good compliance appears to be based on the low EPS, the improvement in symptoms and education about the long-term advantages of clozapine treatment. However, a significant number of treatment-resistant patients who are candidates for clozapine treatment refuse to initiate therapy. These individuals generally have a fear of blood drawing or are sceptical about its benefits in relation to their perception of the risks of clozapine and the severity of their illness. Intensive effort in educating the patient and the family is often successful in gaining the consent of these individuals.

The greater compliance with clozapine than with typical neuroleptic drugs no doubt contributes to the low hospital admission rate, the continuing decrease in psychopathology, and improvement in quality of life.

Cost of illness and treatment

A retrospective cost–benefit analysis of clozapine was reported by Honigfeld & Patin (1990). The total cost of treatment per patient for 86 patients in the year before clozapine treatment was $80 440. In the second follow-up year after clozapine, the total cost had declined to $55 867, a $25 000 a year saving. A comparison group treated with standard drugs showed an $8000 a year decrease.

We examined the cost of treatment for 38 patients of the University Hospitals in the two years before clozapine and the two years after treatment was begun (Meltzer *et al*, unpublished). The savings with clozapine averaged $25 000 per patient, despite including the cost of clozapine, weekly monitoring of the white blood count and case management at $9000/year (Meltzer *et al*, unpublished data). This saving was mainly due to decreased hospital admission together with some decrease in ancillary costs of illness to the family. As the cost of the three components noted above has been unbundled in the USA, and is significantly less at the current time (average $6000/year), it should be noted that these savings were achieved mainly through decreased costs of recurrently admitted patients, not from discharge of long-term in-patients.

Societal

The societal impact of clozapine for treatment-resistant schizophrenia is also a relevant outcome measure. Most treatment-resistant schizophrenic patients in the United States are treated in the public sector and receive disability income. State governments generally must provide half the costs of their treatment and, because of limited availability of funding to treat the seriously mentally ill, adequate programmes are often lacking. The number of acute and chronic psychiatric beds in many areas of the USA has decreased drastically through deinstitutionalisation, so many treatment-resistant schizophrenic patients are living in nursing homes, substandard housing, in shelters, or are homeless. Many schizophrenic patients are imprisoned because of criminal activity.

If the data reported here and elsewhere on the response of treatment-resistant patients can be extrapolated to the 10–30% of schizophrenic patients who are treatment-resistant, society may expect a significant decrease in the severity of schizophrenia in about 60% of these patients. This should be accompanied by fewer readmissions to hospital which should lead to greater availability of hospital or nursing home beds to treat those patients who still need hospital admission. It is also possible that the example of the benefits to be achieved from development of more effective drugs, such as clozapine, will serve to spur investment in research on both treatments for, and the aetiology of, schizophrenia.

Conclusion

Experience with clozapine in treatment-resistant schizophrenia highlights the utility of multidimensional outcome measures and permitting sufficient trial time on clozapine for these benefits to emerge. Improvement in psychopathology should only be one outcome measure. It may be highly predictive of other benefits, but improvement in social function, decreased hospital admission, better compliance and fewer EPS may be of equal or greater importance in some patients. Moreover, these may even be independent of improvement in psychopathology.

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