Clozapine for Treatment-Resistant Schizophrenia: National Institute of Clinical Excellence (NICE) Guidance in the Real World

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Abstract

Introduction: Clozapine, a poorly tolerated antipsychotic drug, is widely recognized as the only efficacious option in treatment-resistant psychosis. The United Kingdom (U.K.) National Institute of Clinical Excellence (NICE) guidance for its consideration defined a threshold for treatment resistance substantially more liberal than that utilized in seminal studies of efficacy. This study documented adherence to NICE guidance in a patient group likely to be enriched for treatment resistance: 150 consecutive assertive outreach and former rehabilitation inpatients. Evidence of a NICE-compliant treatment trial was adduced from case notes: treatment resistance was determined through discussion with key workers about ongoing clinical problems, including treatment-resistant patients already on clozapine. Reasons for treatment-resistant patients not receiving clozapine were documented. Levels of ongoing clinical problems were compared between treatment-resistant patients on clozapine, treatment-resistant patients not on clozapine, and non-treatment-resistant patients. **Results**: Patients' mean age was 41, with illness duration of 16 years. Twelve percent (18 patients) had not had a NICE-compliant trial of treatment, but all 3 treatment-resistant patients in this subgroup were on clozapine already. Forty-five percent of the whole group was treatment resistant: 54% of the treatment-resistant group was treated with clozapine. Of the remaining 46% (i.e., 31 treatment-resistant patients not taking clozapine), 16 refused and 15 could not be treated for medical reasons including the failure of previous trials and neutropenia. Levels of ongoing clinical problems were generally similar between clozapine-treated patients and nontreatment-resistant patients, with significantly greater problems in treatment-resistant patients not taking clozapine. However, positive symptoms remained relatively high in the clozapine group, while substance abuse was actually lower than in the other two groups, and there were no differences between any of the groups in depression and suicide risk. **Conclusions:** Tertiary referral assertive outreach and rehabilitation services include a higher proportion of treatment-resistant patients than secondary services, as appropriate. Most patients receive a NICE-compliant trial for the determination of pharmacological treatment resistance, but only just over half of the patients who need clozapine on clinical grounds are taking it. While half of these refuse, the rest encounter insuperable obstacles to treatment. In general, clozapine reduces levels of ongoing clinical problems to those of nontreatment-resistant patients. In view of the difficulties of delivering clozapine to treatment-resistant patients, the development of treatment resistance should be avoided if possible.

Key Words: Clozapine, Psychosis, Treatment Resistance, NICE

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Introduction

Clozapine is widely accepted as superior to other antipsychotic drugs in treatment-resistant schizophrenia (1-3). Its use is limited by its poor tolerability: side effects include neutropenia, weight gain, diabetes, sedation, salivation, and seizures (4).

Treatment resistance affects a significant minority of patients with schizophrenia, with estimates in the literature of 10 to 20% (5). These are patients who derive little ben-

Clinical Implications

In an ideal world, clozapine would not be necessary because treatment resistance would not be allowed to develop. In the real world, it is hoped that services may be able to prevent the onset of treatment resistance through addressing, effectively, such factors as lengthy duration of untreated psychosis, poor compliance, substance abuse, repeated relapse, disengagement and social exclusion. Our results indicate that the vast majority of patients will access a NICE-compliant trial of medication, whether treatment resistant or not, in routine clinical practice. Therefore, it behooves clinicians to evaluate whether each eligible patient under their care has made an adequate response, and to consider the use of clozapine accordingly

efit from antipsychotic drug therapy: positive and negative symptoms fail to resolve, accompanied by impairment of personal and social function, intellectual decline, depression, substance abuse and, in some patients, the need for chronic hospitalization. For such severely affected patients, even a poorly tolerated drug may afford some advantages if efficacious.

This issue was examined in a seminal study, a large randomized controlled trial of clozapine versus chlorpromazine in treatment-resistant patients (1). The operational definition of treatment resistance was rigorous, stringent and very narrow: patients entering the trial had to fulfill retrospective, cross-sectional and prospective criteria. They had to have failed to respond to 1 g chlorpromazine equivalent daily of at least three antipsychotic drugs from at least two of the classes then available (phenothiazines, thioxanthenes and butyrophenones) for at least six weeks, with no return to adequate function within the last five years. Patients had to reach multiple threshold criteria on symptomatic rating scales, and subsequently achieve a period of treatment with open haloperidol for six weeks without reducing their symptom score total by 20%, or reaching other symptom thresholds defined as indicative of response. The relatively low figure of 20% reduction in symptoms to constitute response was chosen because of the nature of the patients: it was reasoned that 20% of a large volume of symptoms was substantial, and that, in the severely ill, made for a clinically significant and worthwhile improvement.

Of the 319 patients who entered the prospective phase, 265 failed to respond to open haloperidol, and entered the double-blind phase. The results of this were unequivocal: after six weeks of clozapine treatment, approximately 30% of the patients on clozapine had made a response compared to approximately 3% of the chlorpromazine-treated group. This finding, now very well established (6), led to the reintroduction of clozapine in many countries including in the U.K. in 1990.

Furthermore, clozapine has been utilized in patients with other psychoses, which have proved resistant to treatment, however defined, with some benefit (7). This merely parallels the usage of antipsychotic treatment in general in many diagnoses, as well as schizophrenia.

The National Institute of Clinical Excellence (NICE), a U.K.-sponsored government body set up to produce clinical guidance, reported upon the drug treatment of schizophrenia in 2002 (8). Using accepted figures for lifetime risk of schizophrenia and the number of patients expected to be in treatment, the number of known patients in the U.K. was calculated. However, rather than estimate the prevalence of treatment resistance at the historical 10 to 20% level, the authors assumed a much greater prevalence of 30%. No rationale was given for this choice: the result was an estimate of 63,000 patients in the U.K. suffering from treatment-resistant schizophrenia. This very much exceeded the 13,000 patients registered with the Clozapine Patient Monitoring Service at the time. Apparently in response to this evidence of underuse of clozapine, the guidance stated that treatment resistance was now to be defined as failure to respond to two antipsychotic drugs, at least one from the atypical class, given sequentially at recommended doses for no less than eight weeks each. Clozapine was to be considered as a treatment for these patients.

This guidance was not only based on a somewhat arbitrary estimate of the prevalence of treatment resistance, but on a fundamental oversight, in that the U.K. patients for whom clozapine was to be considered were not analogous to the rigorously selected patients in the Kane study (1). It is likely that, had the liberal NICE definition of treatment resistance been utilized in that study, differences between the groups would have been very much eroded: the advantage of clozapine appears to vary directly with the severity of treatment resistance (9). Smaller differences in outcome amongst less treatment-resistant patients treated with clozapine versus other antipsychotic drugs could, therefore, have obscured the marked advantage observed for very treatment-resistant, clozapine-treated patients, to the point where the risks of clozapine could not be seen to outweigh its benefits. Even so, the only group in whom there appears to be no obvious advantage for clozapine is first-episode patients (10).

Previous work by one of us (11) indicated that most consultants in rehabilitation, where substantial numbers of treatment-resistant patients are likely to be seen, viewed NICE guidance as too liberal in respect of its threshold for

the consideration of clozapine. Noncompliance or partial compliance, substance abuse, mood disorder and chronic stressful circumstances may mimic treatment resistance, but would not be effectively addressed by clozapine. There was a preference to manage these issues if present, and even then to attempt adjunctive or further antipsychotic treatment options prior to resorting to clozapine.

The authors, therefore, set out to survey adherence to NICE guidance and its results in a rehabilitation and assertive outreach service, run on a tertiary referral basis by the lead author, Professor Ann Mortimer (AM). This service takes predominantly schizophrenia patients, alongside other patients with psychotic disorders. The illnesses of these patients are sufficiently problematic to exceed the efforts of ordinary community psychiatric services. We sought to establish the proportion of patients in rehabilitation and assertive outreach who had accessed a NICE-compliant trial for the determination of NICE-defined treatment resistance, whatever the psychotic disorder with which the patients had been diagnosed. We wished to assess the prevalence of clinical treatment resistance separately (i.e., overall adequacy or otherwise of response to treatment in terms of unresolved clinical problems according to the views of mental health professional staff most closely involved with the patients). We expected the prevalence of clinical treatment resistance to exceed even the more liberal NICE estimate of 30% of patients, given the nature of the service. Finally, we wished to establish any barriers to clozapine treatment in treatment-resistant patients for whom it was indicated, and to compare levels of unresolved clinical problems both between the treatment-resistant groups on and not on clozapine treatment, and amongst the third group of nontreatment-resistant patients.

Method

Ward and office records were used to list all patients either managed by the assertive outreach service or admitted for inpatient rehabilitation since the NICE guidance was issued in June 2002. Case notes were obtained and scrutinized for details of drug treatment. A single treatment trial was deemed adequate if the dose was at least one quarter of the British National Formulary (BNF) maximum recommended dose or more, and the antipsychotic drug was given for at least eight weeks. For audit purposes, the current and penultimate medications were considered if the current treatment had been taken for over eight weeks. If not, antipsychotic drugs were adduced to the analysis in historical order, the most recent counted before the more remote. A NICE-compliant trial consisted of two antipsychotic drugs taken sequentially (i.e., with no gap in treatment between them, at least one from the atypical class, taken in a therapeutic dose as above for at least eight weeks each).

Treatment resistance was determined by an interview with the mental health professional having most contact with the patient at the time, in most cases a community psychiatric nurse or assertive outreach team member. No patient was rated for treatment resistance during acute relapse: a small number were long-term inpatients of the rehabilitation service. The interview took place without overt reference to the adequacy or otherwise of antipsychotic treatment for NICE purposes. The professional was asked to indicate whether, in his opinion, the patient was suffering from unresolved problems in the following eight areas:

- positive symptoms
- negative symptoms
- intellectual impairment
- loss of social function
- behavioral disorder
- chronic/repeated hospitalization
- chronic depression or suicide risk
- comorbid substance abuse.

Areas were scored either present or absent after discussion. The professional was then asked to rate the overall adequacy of response to treatment as adequate or inadequate: patients deemed not to have made an adequate response overall were listed as treatment resistant. Patients currently treated with clozapine were assumed to have been considered clinically treatment resistant prior to beginning clozapine treatment. For those patients deemed treatment resistant but not currently treated with clozapine, an inquiry was made regarding any barriers to its being prescribed for the patient.

Basic demographic and clinical data were obtained from case notes, including age, sex, and duration of illness since diagnosis, *International Classification of Diseases-10th Revision (ICD-10)* diagnosis and marital status.

All results were analyzed using SPSS for Windows version 13.

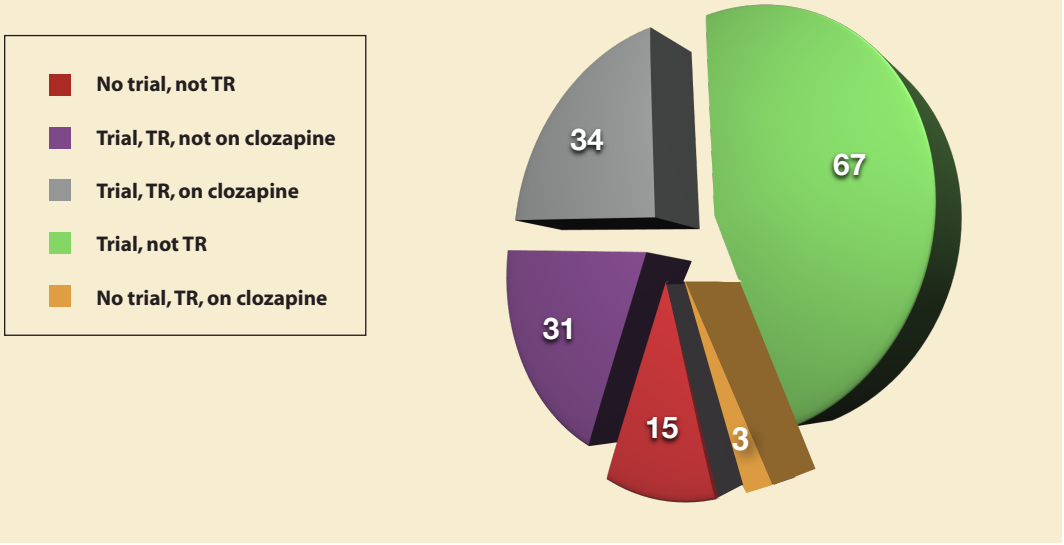
Results

A total of 150 patients were ascertained from June 2002: all notes were available, and all patients remained in contact with an appropriate professional. Therefore, the sample was complete.

The mean age of the sample was 41 years 6 months, with a wide age range (23–71, standard deviation 11 years). There were 106 men and 44 women (71% and 29%). The majority were not living with a partner: 116 were single, 19 divorced, 7 separated, 2 married, 5 cohabiting and 1 widowed. No patient had care of dependent children. *ICD-10* diagnoses were as follows: 116 had schizophrenia, 17 schizoaffective psychosis, 8 bipolar affective psychosis, 5 organic psychosis, and 4 major depression with psychotic features.

Mean duration since diagnosis was 16 years, again

Figure 1 Pie Chart of NICE Compliance in 150 Patients: Whether Medication History Comprised a Trial Following which Clozapine Could be Considered, and whether Patients were Clinically Treatment Resistant (TR)



with a wide age range (2–43, standard deviation 9 years 6 months). Regarding treatment resistance, 68 were clinically treatment resistant, and 82 were considered not treatment resistant: 45% versus 55%. The treatment-resistant patients were slightly but significantly younger than the nontreatment-resistant group, with a mean age of 38 years versus 42 years (t test, p=0.04, 95% confidence interval 0.25–7.23). This was explicable in terms of a younger age of onset, almost significantly less than the nontreatment-resistant group, 23 years and 3 months versus 25 years and 6 months (t test, p=0.06, 95% confidence interval -0.06–4.5). Duration since onset was not significantly different between the treatment-resistant and nontreatment-resistant groups.

A total of 18 patients (12%) had never had a NICE-compliant trial to determine treatment resistance in pharmacological terms. Of these, only 3 were clinically treatment resistant and all were already being treated with clozapine. Of the other 15, 13 were on no medication at the time of inclusion in the study. Most of these were perennially noncompliant, but not detainable for compulsory treatment either, and living in the community. These patients had been referred to assertive outreach service in an attempt to engage them more effectively. Only two female patients, one with a "Diogenes syndrome" and another with organic psychosis, were on no medication with the agreement of AM. Of the remaining 132 patients who had a NICE-compliant trial, 67 were not treatment resistant and 65 were treatment resistant. Of the total of 68 treatment-resistant patients (45% of the whole group), 37 (just over half) were taking clozapine, while 31 were not: 54% versus 46%. See Figures 1 and 2.

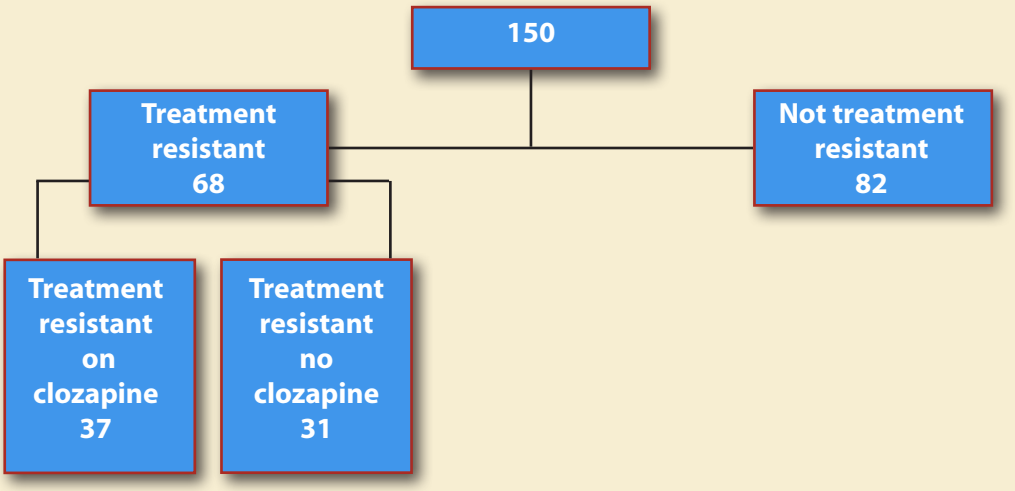
Basic demographic information on the three groups is outlined in Table 1.

Table 1 Basic Demographic and Clinical Data According to Treatment Resistance and Clozapine Treatment

Group: Number of Patients	% Male	% Diagnosed Schizophrenia or Schizoaffective	Mean Age in Years	Mean Duration of Psychosis in Years
Not treatment resistant: 82	65	85	42	17
Treatment resistant on clozapine: 37	81	92	36	15
Treatment resistant not on clozapine: 31	72	91	42	18

Regarding the reasons for treatment-resistant patients not being treated with clozapine, 16 patients, all but one being male, refused to take it despite its having been offered. In the remaining 15 patients, clozapine was effectively contraindicated: five patients had taken it previously and developed neutropenia, while five patients had failed to respond to a trial of clozapine for several months and at above "therapeutic threshold" levels. One patient developed gross sedation on 120 mg daily and another suffered exacerbations of ulcerative colitis subsequent to two attempts to treat him. The remaining three patients had Gilbert's dis-

Figure 2 Treatment Resistance and Whether on Clozapine: Numbers of Patients



ease, poorly controlled type II diabetes, and type II diabetes and gross obesity, which had led to the Clozapine Patient Monitoring Service advising not to proceed.

Levels of ongoing clinical problems are represented graphically in Figures 3 and 4. The bars represent the mean score for the group, presence or absence of the problem being scored 0 or 1 for each patient. Therefore, a bar value of 1 would indicate that every patient in the group manifested the problem.

These data were analyzed by group using the Kruskal-Wallis nonparametric analysis of variance for n samples: see Table 2. This indicated that mean scores for the treatment-resistant group not treated with clozapine were significantly greater than for the other two groups, except for substance misuse, depression and suicide risk.

Discussion

We were able to demonstrate in our sample the greater than expected proportion of patients with treatment-resistant psychosis, principally schizophrenia. Most were male: there is some evidence that estrogen benefits aspects of schizophrenia including age, severity and treatment response (12); therefore, the paucity of females was expected. Indeed the percentage of males in both treatment-resistant groups was greater than in the nontreatment-resistant group.

Figure 3 Significant Continuing Problems 1 (A score of 1.0 would indicate that every patient in that group had the problem.)

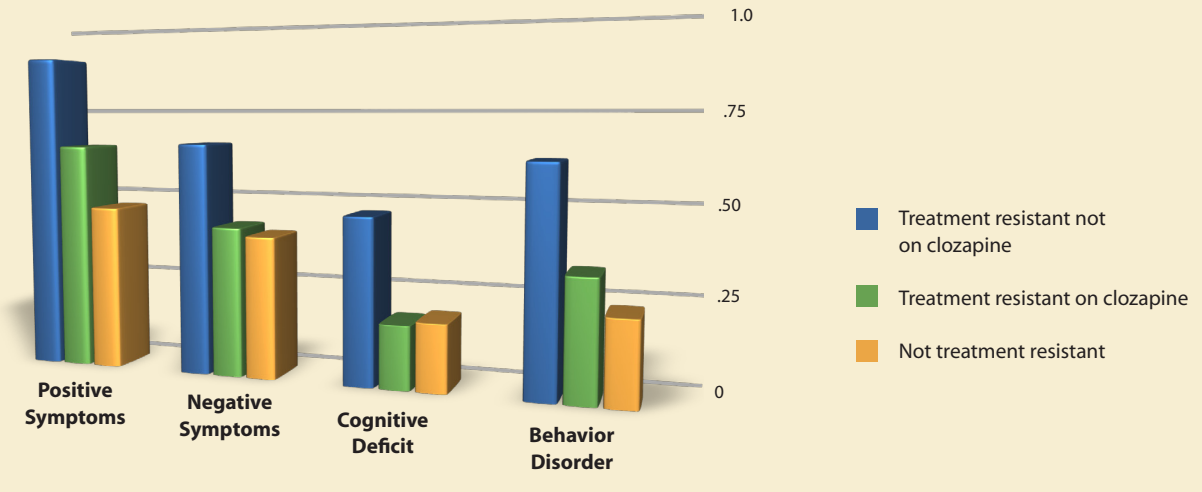


Table 2 Analysis of Variance: Levels of Residual Problems amongst Patients Not Treatment Resistant, Compared to those Treatment Resistant on Clozapine or Not on Clozapine

Test Statistics*†	Positive Symptoms	Negative Symptoms	Cognitive Deficits	Behavioral Disturbance	Substance Abuse	Social and Personal Function	Depression/ Suicide Risk	Hospitalization	Total Number of Ongoing Problem Categories
Chi-Square	15.820	8.749	12.534	13.345	5.055	15.793	.431	10.221	34.008
Df	2	2	2	2	2	2	2	2	2
Asymptotic Significance	.000	.013	.002	.001	.080	.000	.806	.006	.000

* Kruskal-Wallis test
† Grouping Variable: whether treatment resistant by whether on clozapine.

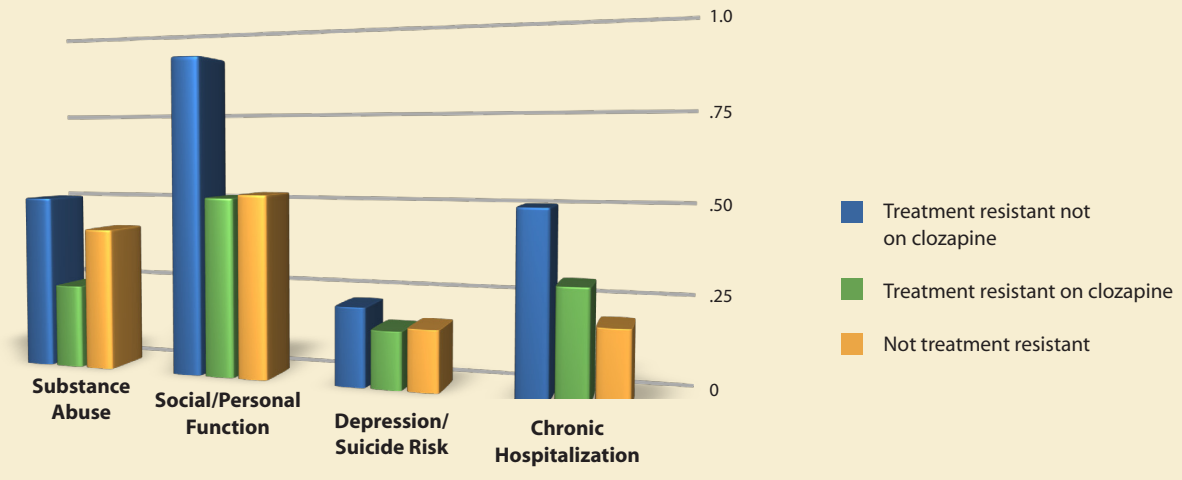
We replicated the well-established finding that earlier age of onset is associated with worse outcome, to whit, treatment resistance. Our analysis of current clinical problems across the three groups provides further evidence of the superior effectiveness of clozapine in treatment-resistant patients, since treatment-resistant patients refusing or unable to take clozapine experienced a significantly greater burden of these clinical problems. Indeed, for the most part, clozapine succeeded in reducing the level of these clinical problems to that enjoyed by the nontreatment-resistant group. This is despite our definition of treatment resistance resting upon only two trials of antipsychotic drugs and a clinical opinion, rather than the rigorous and much narrower definition of Kane et al. (1).

Our finding that only just over half of the patients deemed clinically treatment resistant were being treated was disappointing. There will always be a significant minority, approximately a quarter of the total in this study, who cannot be treated, either because it is not safe or because they have not responded. Given the drawbacks of clozapine treatment, it is important to have an "exit strategy" in patients who make no response despite several weeks or months of clozapine treatment, validated by the repeated demonstration of adequate serum levels. Options for such patients are limited: coprescription of additional antipsychotic medication is probably not effective (13).

Nonetheless, an examination of in what way the patient is failing to respond may indicate other psychotropic drugs, such as mood stabilizers or antidepressants for mood disorder, or SSRI antidepressants or low-dose amisulpride for negative symptoms. Unfortunately, ongoing positive symptomatology is the most prevalent clinical problem in our experience, and it is interesting that we observed an inferior reduction in positive symptoms on clozapine here.

Regarding clozapine refusal, there is often a sense of waiting for an opportunity to proceed when acute relapse

Figure 4 Significant Continuing Problems 2 (A score of 1.0 would indicate that every patient in that group had the problem.)



leads to compulsory detention. Treating nonconsenting patients is not easy, and is usually predicated on the presence of positive reinforcements, which can be accessed by the patient in return for their cooperation, or withdrawn if cooperation is not forthcoming. It is important to offer reinforcements on a daily basis and give patients the opportunity to redeem themselves later in the day if there is initial refusal to comply. Leave from the ward is the most useful strategy in our experience.

It remains to be seen whether the availability of Community Treatment Orders in the U.K. from November 2009 will enhance compliance with oral medications such as clozapine, as well as ensure compliance with depot medication.

Conclusions

Our results indicate that the vast majority of patients will access a NICE-compliant trial of medication, whether treatment resistant or not, in routine clinical practice. Therefore, it behooves clinicians to evaluate whether each eligible patient under their care has made an adequate response, and to consider the use of clozapine accordingly. The matter of two antipsychotic trials will only be of relevance, for the most part, in first-episode schizophrenia. Nevertheless, there is little point in deeming such a patient not treatment resistant and then failing to review this as the patient's illness course progresses. Many of the patients in this study had clearly been treatment resistant for years, yet clozapine was not considered until they entered assertive outreach or rehabilitation services. New concepts such as remission (14) may, if introduced to routine clinical practice, afford some utility in identifying nonremitting patients for whom clozapine ought to be considered, given that the vast majority will have fulfilled the psychopharmacological criteria set out in NICE. Furthermore, recent work demonstrating that the superior efficacy of atypical drugs is perhaps more illusory than real (15) raises the question of whether a trial of atypical medication should be necessary. Even so, recent meta-analyses as opposed to pragmatic trials continue to demonstrate some differences in efficacy across both conventional and atypical classes (16).

In an ideal world, clozapine would not be necessary because treatment resistance would not be allowed to develop. In the real world, it is hoped that services may be able to prevent the onset of treatment resistance through addressing, effectively, such factors as lengthy duration of untreated psychosis, poor compliance, substance abuse, repeated relapse, disengagement and social exclusion. It remains to be seen if clinicians' early intervention services are effective in preventing progression to treatment resistance during their patients' tenure, and whether the generic services offered to first-episode service "graduates" can keep up the good work (17, 18).

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