Prior Antipsychotic Prescribing in Patients Currently Receiving Clozapine: A Case Note Review

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Background: Clozapine is indicated for the treatment of resistant schizophrenia, which is usually defined as failure to respond to adequate trials of 2 antipsychotics. It is thought that only clozapine is likely to be effective in such cases and that other drugs are ineffective. We sought to discover prior patterns of antipsychotic prescribing in schizophrenic patients eventually prescribed clozapine.

Method: Prescribing histories were obtained from prescription charts and case notes for all inpatients prescribed clozapine in 4 hospitals in southeast London during April 2001.

Results: 120 patients were identified, of whom 112 had been diagnosed with schizophrenia or schizoaffective disorder and whose data were analyzed. The mean duration of illness was 15.1 years. Subjects had experienced a mean of 9.2 (range, 2–35) episodes of antipsychotic prescription before clozapine was first used, with 5.7 (range, 0–25) episodes constituting adequate trials (drug used at therapeutic dose for 6 weeks). The mean number of different antipsychotics used was 5.5 (range, 1–13), with a mean of 4.0 (range, 0–12) given an adequate trial. Ninety percent of patients (N = 101) had received an atypical antipsychotic before first use of clozapine, and 65% (N = 73) had previously received antipsychotic polypharmacy. The mean maximum theoretical delay in using clozapine was 5.0 years (range, 0–11.1 years). Longer delay was significantly ($p < .05$) associated with being aged over 30 years at the time of the study, being diagnosed with psychotic illness before the introduction of clozapine, and completing adequate trials of 2 different antipsychotics before the introduction of clozapine or risperidone.

Conclusion: Clozapine treatment was quite likely delayed for longer than is clinically desirable. This delay may have important effects on quality of life, clinical outcome, and health resource utilization.

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In the United Kingdom and many other countries, clozapine is licensed for use in resistant schizophrenia, that is, schizophrenia in which patients are unresponsive to, or intolerant of, conventional antipsychotics.[1] *Nonresponsiveness* is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least 2 marketed antipsychotics prescribed for adequate durations. *Intolerance* is defined as the impossibility of achieving adequate benefit with conventional drugs because of severe intolerable neurologic adverse effects.

Clozapine's labeling is now somewhat anachronistic, since there are many atypical antipsychotics that might be used when there is neurologic intolerance to older conventional drugs. However, clozapine remains the only drug with proven efficacy in the treatment of schizophrenia not responding to other antipsychotics,[2] and so its use after the failure of 2 antipsychotics given at therapeutic doses for adequate duration is justified and widely recommended.[3]

It might be argued that, given the unique efficacy of clozapine in refractory schizophrenia, it should be prescribed immediately after the failure of a second antipsychotic. We could find no published studies that have examined whether practice mirrors this view. In the present study, we retrospectively examined the prescribing histories of patients treated with clozapine in 4 south London, United Kingdom, hospitals.

METHOD

The study included hospitalized patients from inpatient units at the Maudsley, Bethlem, Greenwich, and Bexley hospitals. Ethical committee approval was obtained. Pa-

tients receiving clozapine were identified from the pharmacy computer systems. Information was then garnered from prescription charts and patient case notes. For all hospitals in the study, case notes contained handwritten, contemporaneous descriptions of progress and treatments, typed discharge summaries, correspondence, pathology and toxicology reports, original inpatient and discharge prescription charts, and carbon copies of outpatient prescriptions. All prescriptions included drug name, dose, dosing frequency, and intended duration of treatment or quantity to be dispensed. Inpatients' charts also included start date, end date, time of administration, and whether the drug was administered.

Patients' diagnoses were taken from handwritten notes or discharge summaries. The most recent diagnosis was recorded. Racial origin was also obtained from notes or discharge summaries. Duration of illness was calculated as the time of first diagnosis of psychotic illness (during the time of first admission to hospital) to the time of data collection.

Prior prescribing was categorized as follows. (1) The number of episodes of antipsychotic use before first use of clozapine (the number of times any antipsychotic was prescribed [and administered, for inpatients] as a regular prescription for any duration longer than 24 hours, at any dose) was calculated. "Double counting" was used: the use of the same drug at different times was recorded as multiple episodes, as long as these episodes were separated by at least 6 weeks without treatment or by the intervening use of a different antipsychotic prescribed (regularly) for at least 24 hours. (2) The number of antipsychotics used before the first use of clozapine (the number of different drugs prescribed regularly [and administered, for inpatients] for any duration longer than 24 hours, at any dose) was calculated, with no double counting of drugs. (3) The number of "adequate trial" episodes before first use of clozapine (the number of times an antipsychotic was prescribed [and administered, for inpatients] at a recognized therapeutic dose[4] continuously for at least 6 weeks) was calculated. Adequate use of the same drug at different times was recorded as multiple episodes, as described above. Prescription charts, discharge prescriptions, and copies of outpatient prescriptions were scrutinized to assure continuous prescribing. (4) The number of adequate trials of different antipsychotics before first use of clozapine (the number of different antipsychotics prescribed [and administered, for inpatients] at a recognized therapeutic dose continuously for at least 6 weeks) was calculated, with no double counting of drugs. Prescription charts were utilized, as described above. (5) The number of episodes of prescribing of different (nonclozapine) atypical antipsychotics before first use of clozapine (any dose, any duration longer than 24 hours; no double counting of drugs) was calculated. Atypicals were defined as amisulpride, olanzapine, quetiapine, remoxipride, risperidone, sertindole, sulpiride, ziprasidone, and zotepine.

Table 1. Prescribing Histories of 112 Patients Receiving Clozapine

Variable	Mean	Median	Range
No. of episodes of antipsychotic use	9.2	7	2–35
No. of antipsychotics used	5.5	5	1–13
No. of episodes of adequate trial	5.7	5	0–25
No. of antipsychotics given adequate trial	4.0	3	0–12
No. of atypical antipsychotics used	1.5	1	0–5

In all cases, the number of prescribing episodes and drugs prescribed before first use of clozapine was calculated. Also recorded was prior coprescription of antipsychotics (antipsychotic polypharmacy), defined as the continuous prescription of 2 or more antipsychotics to be taken regularly (not "as necessary") for at least 6 weeks.

The main outcome measure was the maximum theoretical delay in clozapine use, defined as the time from the end of the sixth week of continuous treatment with a second antipsychotic given at a recognized therapeutic dose (i.e., the time at which a patient might first be defined as resistant to treatment) to the first use of clozapine, but excluding the period before January 1990, when clozapine was not available. For example, a patient completing a second 6-week trial of a second therapeutic antipsychotic in January 1986 but starting clozapine in January 1991 would be ascribed a theoretical delay of 1 year (the period between 1986 and 1990 being excluded).

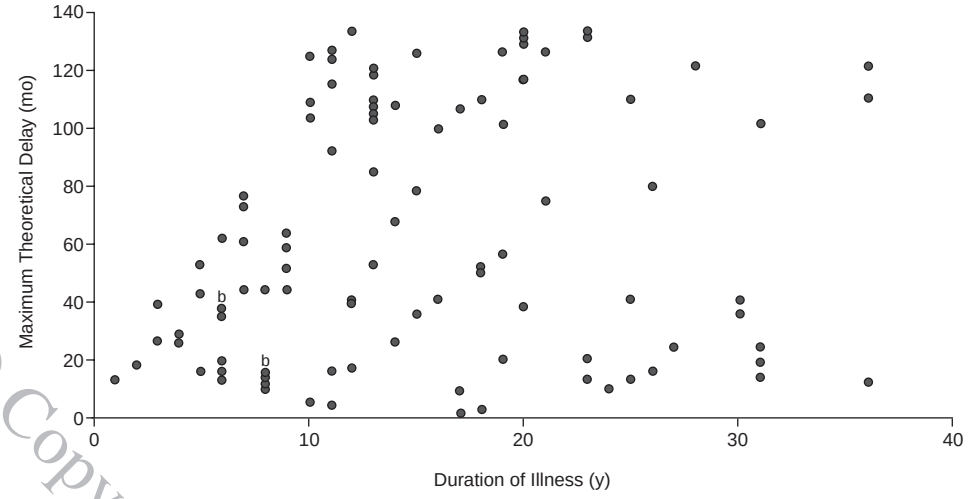
In analyses of factors associated with theoretical delay, mean values were compared using an unpaired, 2-sided Student t test, after assuring normal distribution of data. The association between duration of illness and theoretical delay was analyzed by scatterplot and Pearson correlation coefficient.

RESULTS

Prescribing histories were obtained for 120 patients. Eight of these patients had diagnoses other than schizophrenia or schizoaffective disorder (bipolar disorder [N = 3], delusional disorder [N = 2], borderline personality disorder [N = 2], and depression [N = 1]). Data for these patients were excluded from further analyses. Of the remaining 112 patients, 106 (95%) were diagnosed with schizophrenia, and 6 (5%), with schizoaffective disorder. Eighty-six subjects (77%) were male.

Mean age of subjects was 35.7 years (range, 19–80 years). Sixty-eight subjects (61%) were white; 31 (28%), black African or Afro-Caribbean; 7 (6%), mixed race; and 6 (5%), Asian. Mean duration of illness was 15.1 years, (median = 13.0 years; range, 1–37 years). Mean duration of clozapine use was 2.4 years (median = 1.2 years; range, 0–10.3 years). Prescribing histories are summarized in Table 1.

Figure 1. Duration of Illness Versus Theoretical Delay (N = 100)[a]



[a]r = 0.155, p = .24.
[b]Represents 2 patients.

One hundred one subjects (90%) had received an atypical antipsychotic at some time before receiving clozapine; 97 (87%) had received depot medication. Seventy-three subjects (65%) had been previously coprescribed 2 or more regular antipsychotics for more than 6 weeks. Of the 112-subject cohort, 49 (44%) had been switched directly from depot medication (with or without coprescribed oral typical drugs) to clozapine, and 41 (37%), directly from an oral atypical medication (with or without coprescribed oral typical drugs). Of the remainder, 11 subjects (10%) were switched directly from an oral typical drug (prescribed as the sole antipsychotic), and 1 (1%), from a combination of depot and atypical drugs. Ten subjects (9%) were receiving no treatment in the month (oral medication) or 3 months (depot medication) before starting clozapine.

One hundred subjects (89%) had received 2 adequate trials of different antipsychotics (12 subjects [11%] had never received 2 such trials). The mean maximum theoretical delay in these 100 patients was 5.0 years (range, 0–11.1 years).

Mean maximum theoretical delay in starting clozapine was longer in the following subject groups (N = 100, as noted above): patients aged over 30 years at the time of analysis (mean delay = 5.4 years vs. 3.7 years for subjects 30 years of age or younger; p = .036), patients diagnosed with schizophrenia/schizoaffective disorder before the introduction of clozapine (mean delay = 5.8 years vs. 3.6 years for those diagnosed after introduction; p = .003), patients completing a second adequate trial of a second antipsychotic before the introduction of clozapine (mean delay = 6.5 years vs. 4.6 years for those completing both trials after introduction; p = .032), and patients completing a second adequate trial of a second antipsychotic before the introduction of risperidone in December 1992 (mean delay = 5.9 years vs. 4.2 years for those completing trials after introduction; p = .021).

Mean theoretical delay was not significantly associated with differences in gender (mean delay: men, 4.8 years; women, 5.8 years; p = .30); race (mean delay: white, 4.6 years; nonwhite, 5.4 years; p = .37); or duration of illness (Pearson correlation coefficient = 0.155, p = .24; Figure 1).

DISCUSSION

The main findings of this retrospective analysis were that the use of clozapine was delayed, on average, for up to 5 years; that patients received more than 5 antipsychotics, on average, before being prescribed clozapine; and that two thirds of patients had previously been subjected to antipsychotic polypharmacy. The delay in using clozapine was significantly longer in subjects older than 30 years, in those diagnosed before the introduction of clozapine, and in those potentially meeting treatment resistance criteria before the introduction of clozapine or risperidone.

The data presented here do not show unequivocally that clozapine treatment is unnecessarily or inappropriately delayed, because it is possible that subjects in this study developed resistance during treatment with a sequence of antipsychotics and that clozapine was used as soon as treatment resistance emerged and was identified. However, this possibility seems unlikely, and it is very probable that clozapine was used later than was clinically desirable in this cohort of patients. Evidence

for this proposition includes the high rates of antipsychotic coprescription before use of clozapine (indicating prior poor response from single drug treatment), the high number of episodes of antipsychotic use and of different drugs used (perhaps more likely to be a result of sequential poor response than of sequential poor tolerability), and the extensive difference between mean duration of illness (15.1 years) and duration of clozapine use (2.4 years).

The concepts of primary and developing treatment resistance are important factors in inferring meaning from our results. Several studies have shown that inconsistent or intermittent treatment with antipsychotics leads to a poorer outcome,[5,6] perhaps indicating that resistance to treatment may develop as a result. It is not possible to determine for patients in this study whether prior antipsychotic treatment was continuous at all times; prescribing may have been continuous for many, but compliance could not be assured for patients who were discharged from inpatient care at some point. It is probable that many patients in our cohort received intermittent treatment, especially when one considers that the number of episodes of antipsychotic use was almost double the number of antipsychotics used. It is likely, therefore, that a proportion of patients developed treatment resistance through the intermittent use of antipsychotics or repeated relapse. This proportion is, however, unlikely to be a majority; an investigation by Meltzer et al.[7] found that in a group of treatment-resistant patients, more than half (56%) had never responded to any antipsychotic, with the remainder developing treatment resistance during the course of their illness.

The significantly different delays in using clozapine in certain subgroups of patients are intriguing. It seems that patients progressed to the use of clozapine more quickly if they were younger, had a more recent diagnosis of schizophrenia/schizoaffective disorder, or had met criteria for treatment resistance after the introduction of clozapine or risperidone. The overall impression is that clozapine is more readily prescribed for younger patients who have more recently become treatment resistant. Clozapine seems to have been used less readily in older patients with a longer history of poor response. This finding rather goes against expectations; it might have been logically assumed that clozapine would be quickly prescribed, once introduced, to patients with long-standing treatment resistance. The opposite seems to be true in this cohort. Also of note is that the introduction of risperidone seemed not to increase theoretical delay in using clozapine; in fact, mean delay was reduced after the introduction of risperidone, probably because of the factors outlined above. There were too few data to compare treatment delay in patients potentially meeting treatment resistance criteria after the introduction of other atypicals (e.g., olanzapine in October 1996).

If clozapine treatment is indeed unnecessarily delayed, as our data suggest, then what are the reasons? For many subjects in this cohort, reasons for the delay were recorded in case notes. Although not systematically evaluated, it seemed that patient reluctance was common—many patients apparently refused to undergo blood testing or to consider oral medication. While this is understandable, it is noteworthy that patients stabilized on clozapine treatment seem to readily accept blood testing and have very positive views of treatment.[8] Also, patients who initially refuse treatment, perhaps because of severe psychotic symptoms, can, under extreme circumstances, be treated against their will and may readily accept treatment when their mental state improves.[9] In some cases, fears were expressed over the consequences of noncompliance with an oral medication. Many psychiatrists who treat mentally disordered offenders withhold clozapine from patients who they believe may benefit from it because of concerns over their inability to supervise consumption when the patient leaves the hospital.[10] Low baseline white blood cell counts also delayed treatment in some patients, probably because prescribers feared inducing agranulocytosis. Although there are no objective data to support this perceived association, patients with a low baseline white blood cell count may be more likely to develop neutropenia.[11] This may lead to many additional blood samples being required and raise anxieties about the physical health of the patient. Other recorded reasons included prior doubts over diagnosis (reluctance to prescribe outside the labeled indications) and earlier refusal to prescribe clozapine in units from which patients were transferred. Other possible reasons include prescriber or patient fears about hematologic toxicity or other adverse effects, budget limitations, lack of experience in prescribing clozapine, and doubts over the special or unique efficacy of clozapine in refractory schizophrenia.

In fact, unfounded high expectations of other atypical antipsychotics may be an important cause of delay in the use of clozapine. Many atypicals have been promoted on the basis that they are more effective than typical drugs, and some clinical trials[12–14] support this view. However, a systematic analysis[2] found that data suggesting efficacy for other atypicals in true treatment resistance were equivocal and in some contrast to the more cogent data supporting the use of clozapine. In the present study, 90% of subjects had previously received 1 or more atypical antipsychotics.

Eleven percent of patients had not received an adequate trial of 2 antipsychotics before being prescribed clozapine. These patients did not, then, fulfill criteria for treatment resistance, but may have been treatment intolerant (although this seems unlikely, given the range of benign atypicals now available). Another explanation is that of poor understanding by the prescriber of what constitutes adequate dose and duration of treatment.

The majority of patients in this study experienced treatment with several different antipsychotics, often in combination, before being prescribed clozapine. Switching between typical antipsychotics is unlikely to be effective in acute relapse.[15] On the other hand, clozapine is effective in early treatment resistance[16] and in first-episode refractory schizophrenia[17] and is more effective than haloperidol even in moderate treatment resistance.[18] It is probable, therefore, that patients in this study had, for whatever reason, treatment with a potentially effective drug withheld while successive ineffective treatments were evaluated. Delaying treatment with clozapine may affect resource utilization, since clozapine appears to be more cost-effective than typical drugs.[19] It should also be noted that this delay is suggested, by the results of our study, to have occurred in a selective cohort: those who eventually were prescribed clozapine. There may, of course, be extensive use of sequentially ineffective drugs in patients who have not yet been prescribed clozapine. This possibility remains unevaluated.

In conclusion, patients in this study were likely to have received multiple antipsychotics, often in combination and including atypical antipsychotics, before starting clozapine. There was a substantial delay in beginning clozapine treatment, which was unlikely to have been the result in all cases of treatment resistance developing as illness progressed. Clozapine treatment was quite likely delayed for longer than is clinically desirable in many patients in this study, particularly older patients and those diagnosed before clozapine's introduction, and this delay may have had an important impact on patients' quality of life, clinical outcome, and resource utilization. Future studies should evaluate reasons for delaying clozapine treatment.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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