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# Factors which can make Patients Difficult to Treat

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Despite considerable advances in the treatment of schizophrenia, there remains a sizeable subgroup of individuals with this illness who are considered difficult to treat. There are a number of factors which may contribute to this phenomenon and given increasing pressure to reduce health care expenditures, the challenge of managing this patient population is becoming increasingly pressing.

For the purposes of this discussion we would identify five major factors which can make patients difficult to treat. First, refractoriness to treatment, meaning that available medications and other treatment methods are not effective in alleviating the target signs and symptoms. These symptoms may be positive, negative, disorganised or involve violent and aggressive or suicidal behaviour. Second, the problem of adverse effects which may limit or preclude the administration of effective treatment. A whole range of such adverse reactions can come into play in this context. Third, noncompliance with treatment, which can vary in time course and degree and is often covert. Fourth, the problem of comorbid conditions. At present substance abuse is probably the most frequent and challenging comorbid condition, however, depression, anxiety disorders, obsessive–compulsive disorder and personality disorders can also occur in patients with schizophrenia and complicate treatment response. Fifth, there is another category of treatment 'resistance' or treatment 'failure' occurring in the maintenance phase of treatment, specifically those patients who relapse despite seemingly adequate antipsychotic medication prophylaxis.

What follows is a more detailed discussion of these factors, their clinical relevance and the kinds of symptoms that might be involved.

## Refractoriness to treatment

Numerous double-blind, placebo-controlled trials have been conducted documenting the significant impact of antipsychotic drug treatment. In early trials conducted in the 1960s (Cole *et al*, 1966) approximately 70% of patients derived marked benefit from antipsychotic medication. A variety of attempts were made over the years to identify predictors of drug response and though numerous factors have been suggested, no predictor has been shown to be powerful enough to identify patients for whom a trial of antipsychotic medication would not be indicated.

Several more recent studies suggest that the proportion of patients engaged in clinical trials who are not deriving marked benefit from medication is considerably higher (averaging 50%) (Van Putten *et al*, 1990; Levinson *et al*, 1990; Rifkin *et* al, 1991; McEvoy *et al*, 1991; Kinon *et al*, 1993). Questions arise as to what might account for this apparent change. This change may be more apparent then real in that the nature of the patients included in modern-day clinical trials might be quite different. First, there have been substantial changes in the nosology over the past 30 years and schizophrenia is more narrowly defined and diagnosed in many countries than it was previously. Second, the criteria by which patients are hospitalised (and therefore available for in-patient clinical trials) have also changed. Those patients who are more responsive to medication are more likely to be managed on an out-patient basis. (The potential role of substance abuse in diminishing drug responsiveness will be discussed subsequently.)

It is difficult to determine the prevalence of poor treatment response. One strategy for examining this issue is applying eligibility criteria for clozapine treatment to specific populations. Epidemiological assessments of this issue have been reported by three groups of investigators. Terkelsen & Grosser (1990) utilised three large scale surveys of patients in the N.Y. State hospital system conducted between 1987 and 1988. The criteria for clozapine eligibility were somewhat more stringent than the current U.S. FDA labelling indications for clozapine.

These authors reported that 18% of in-patients and 24% of out-patients would have been considered sufficiently treatment refractory to be eligible for clozapine. (Unfortunately no assessment was made of the adequacy of prior medication

trials.) Juarez-Reyes (1995) studied a stratified random cluster sample of 293 patients served by a country and state hospital system in 1991. When patients who had failed on at least two drugs, for at least four weeks in doses of at least 600 mg chlorpromazine equivalents as well as patients with tardive dyskinesia were included, 43% of the patients met the treatment refractory criteria.

Essock *et al* (1996) screened the entire population ($n = 1300$) in the Connecticut state hospital system and found that 60% met the FDA approved indications (. . . "severely ill schizophrenic patients who fail to show acceptable response to adequate courses of standard antipsychotic drug treatment"). These authors extrapolated their data to estimate that on any given day in US county and state hospital approximately 40 000 patients would meet those eligibility criteria for clozapine.

The kinds of symptoms that these patients have are not different in any identifiable way from those patients who have responded better to conventional treatment. Studies determining the prevalence of treatment refractoriness have generally utilised continued presence of moderate or severe psychotic signs and symptoms to identify eligible patients. If one examines baseline Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) scores among patients participating in double-blind controlled trials of clozapine, this provides some indication of the range and severity of psychopathology seen in eligible patients.

Kane *et al* (1988) studied 267 patients with a mean age of 36 who had been ill on average 16 years. Eighty per cent were male, 65% Caucasian, 23% Afro-American, and 10% Hispanic. Patients had been previously hospitalised an average of nine times (median seven) and the duration of the current hospitalisation averaged 216 weeks (median 104). Fifty per cent of patients were classified as undifferentiated subtype (DSM–III) and 34% paranoid. The mean BPRS score at baseline was 61 (s.d. 11) and the mean score on the cluster for the four psychotic items (hallucinations, unusual thought content, conceptual disorganisation and suspiciousness) was 19 (s.d. 4).

Breier *et al* (1994) studied out-patients with schizophrenia who had histories of only partial response to conventional neuroleptics and had not responded to a prospective six-week trial of fluphenazine. Thirty-nine patients completed a double-blind, random assignment 10 week comparison of clozapine and haloperidol. The average age was 34, 72% were male and patients had been ill on average for 14 years. In this sample of refractory patients, the mean BPRS total score was 38 and the mean sum of the four positive symptom items (conceptual disorganisation, hallucinations, unusual thought content and suspiciousness) was 12. The mean total score on the Scale for the Assessment of Negative Symptoms was 45. Of these 39 patients, 11 (28%) met the authors' criteria for 'deficit' schizophrenia.

Kane *et al* (1995) have reported preliminary data from a 29 week double-blind, random assignment comparison of clozapine and haloperidol in poor or partially responding schizophrenic out-patients. These patients were on average 40 years of age, had been ill for 19 years, and had an average of 10 prior hospitalisations. Their mean BPRS score at baseline was 44.

Overall, the initial or residual positive symptoms do not predict or characterise treatment refractory patients though the presence of primary negative symptoms is associated with poorer treatment response and poorer long-term outcome (Lieberman *et al*, 1991). Other variables which do show some correlation with poor neuroleptic response include abnormalities on brain imaging and poor premorbid social adjustment, rather than specific symptoms or symptom patterns.

Other aspects of psychopathology which make patients difficult to treat can include antisocial and violent behaviour. Remington *et al* (1993) reviewed the circumstances under which patients received 'high dose' antipsychotic drug treatment and found that such individuals had significantly higher scores on the BPRS factor "hostile-suspiciousness" and the Nurses Observation Scale for In-patient Evaluation (Honigfeld *et al*, 1966) factor "irritability" as compared with those patients who received regular doses. These dosage comparisons were made on the basis of total neuroleptic dose administered in the first 24 hours so the dosage decision was not influenced by neuroleptic responsiveness since it would be difficult to establish such a judgement in the first 24 hours. In addition, the majority of patients in the high dose group were bipolar manic depressives, suggesting the importance of manic agitation, irritability and potential violent behaviour in considering the problem of neuroleptic treatment refractoriness. It is important to emphasise that available data do not support any advantage for high or very high dose treatment in this context, however, many clinicians apparently still employ this startegy in an attempt to produce a more rapid treatment response or to avoid difficult patient management problems.

Negative or deficit symptoms continue to be difficult to treat although not with the same degree

of acuity or urgency as experienced by clinicians facing violent behaviour or florid psychosis. At the same time, however, negative symptoms contribute enormously to psychosocial and vocational disability. Although negative symptoms evident in the context of an acute exacerbation of positive symptoms may benefit significantly from antipsychotic drug treatment, residual negative or deficit symptoms are those that persist and do not generally improve over time or with drug treatment. The extent to which new, novel or atypical drugs are truly superior in this context has not been adequately established. In relatively short-term trials with clozapine (Kane *et al*, 1988) and risperidone (Marder & Meibach, 1994), superiority was demonstrated in comparison to chlorpromazine or haloperidol; however, there is reason to believe that some of these differences may have been attributable to differences in drug-induced parkinsonism (Kane *et al*, 1994). In one study which specifically examined the effect of clozapine on carefully defined deficit symptoms, no significant impact was observed (Breier *et al*, 1994).

## Adverse effects

A substantial proportion of patients treated with antipsychotic drugs develop intolerable adverse effects. These can be acute (e.g. akathisia) or chronic (e.g. tardive dyskinesia or tardive dystonia). It is difficult to estimate the number of patients for whom taking medication becomes intolerable because of these adverse effects, but it is certainly not uncommon. Tardive dyskinesia is seen in approximately 20% of chronically-treated patients (Jeste & Caligiuri, 1993) and develops in approximately 5% of patients per year of cumulative neuroleptic exposure (Kane *et al*, 1995). Although the majority of these cases are mild and may not be progressive, the emergence of abnormal involuntary movements certainly requires a new benefit-to-risk assessment. In addition, a subgroup of patients do develop a condition which can be severe and disabling.

There are some patients who are extremely sensitive to the Parkinsonian side-effects of antipsychotic drugs. In some such cases, this sensitivity precludes providing an adequate dose of the antipsychotic in order to control the acute psychosis. This is more dramatically apparent in patients with idiopathic Parkinson's disease who develop psychosis on dopamine agonists. The addition of an antipsychotic drug can produce severe worsening in the underlying Parkinson's disease. Clozapine has been shown to be uniquely helpful in this context, in very low doses (Safferman *et al*, 1994). Assessing the full impact of adverse effects on making patients "difficult to treat" is not easy, but certainly high rates of noncompliance in medication-taking are due in no small part to a variety of adverse effects.

## Noncompliance

One of the most frequent reasons for readmission to hospital among patients with schizophrenia is noncompliance. It is often easy for patients to mislead themselves regarding vulnerability to relapse because they may stop taking medication for a few days or weeks and see no ill effects and then assume that the risk of relapse has been exaggerated. In reality among patients in stable remission most relapses will not occur for several months. Many factors contribute to noncompliance, ranging from the adverse effects previously discussed, to lack of adequate information, poor psychosocial supports, demoralisation, etc. Long-acting injectable drugs can be very helpful in reducing rates of noncompliance and also providing the clinician clear evidence of whether or not noncompliance has occurred (i.e. missing an injection). Some patients and clinicians, however, are reluctant to use depot medications, therefore, many patients who could benefit are not receiving them. Rates of noncompliance are difficult to determine, but even in controlled trials where patients are selected to some extent based on good compliance as many as 30% become noncompliant within one year (Kane, 1985). Therefore, overcoming this difficulty represents an enormous clinical and public health challenge.

## Comorbid conditions

Substance abuse has become an enormous problem in the treatment of schizophrenia during the past two decades. There are a number of theories as to what leads to substance abuse in this context, but the reality is that it frequently makes patients difficult to treat. Nearly half of the psychiatric patients seen in emergency rooms or on in-patient psychiatric wards have experienced substance abuse disorders at some time in their lives (Galanter *et al*, 1988). An epidemiological study (Regier *et al*, 1990) found that the lifetime prevalence of any substance abuse in patients with schizophrenia was 47% and that prevalence of cocaine abuse in this population was 17%. A more recent study (Shaner *et al*, 1993) found a 56% rate of substance abuse in patients

with schizophrenia and a 27% rate of cocaine abuse.

Substance abuse can worsen the symptoms that patients have and can contribute to poor long-term outcome. Since patients often are not fully honest about the type and frequency of such activity, it is difficult at times to appreciate the role that substance abuse can be playing in creating a number of clinical difficulties. Schizophrenic patients with comorbid substance abuse are vulnerable to homelessness and poor compliance with treatment programmes (Drake *et al*, 1991). It is also clear that cocaine, amphetamine and other agents are capable of leading to an increase in aggressive and antisocial behaviour as well as increasing psychotic signs and symptoms (Yesavage *et al*, 1993). Many patients with comorbid substance abuse engage in criminal activity and ultimately their involvement in the criminal justice system also contributes to the difficulties in providing optimum treatment.

Other comorbid syndromes also receiving increasing attention in patients with schizophrenia include: depression, obsessive–compulsive disorder, and panic disorder. These syndromes may complicate the diagnostic and treatment process. Few controlled trials have been conducted providing guidelines for the management of these patients with the exception of post-psychotic depressive episodes (Siris *et al*, 1987).

## Maintenance failures

Another category of patients who might be considered treatment refractory (or partially so) are those individuals who relapse despite adequate maintenance treatment. There is an extensive series of long-term maintenance trials in schizophrenia, many of which have utilised depot antipsychotic medications. Therefore, relapses occurring in these trials cannot be attributed to noncompliance in medication-taking or inadequate dosing of prophylactic medication. The mechanism accounting for this treatment failure or breakthrough has not been elucidated, but it would appear that those patients are relapsing despite adequate dopamine $D_2$ receptor blockade. Therefore, some other pathophysiological mechanism must be coming into play. There is no evidence that these patients have any specific psychopathological, demographic or treatment history characteristics that would enable clinicians to predict their vulnerability to relapse beforehand. Nor do we have any systematic data from clinical trials providing guidelines as to how these patients should be managed.

## Conclusion

This is a brief summary of those symptoms and problems which can make some patients with schizophrenia particularly difficult to treat. Clinicians are all too aware of how frequently these challenges present themselves and how few systematically collected data are available to provide guidance in treatment planning.

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