# Treatment resistance in schizophrenia

Thomas RE Barnes
Serdar Dursun

**Abstract**
In a substantial proportion of people with schizophrenia the illness shows a poor response to antipsychotic medication. Failure to achieve remission even after the first episode is limited to relatively few cases, and more commonly patients become progressively unresponsive to medication. There are no reliable predictors of treatment-resistant schizophrenia (TRS), and the condition defies delineation in terms of symptom profile or neurobiological features. Indeed, it remains to be determined whether TRS should be considered as a distinct subtype of schizophrenia or viewed simply as the more severe end of the illness spectrum, characterized by refractory symptoms and poor integration into the community. Despite recent advances in pharmacotherapy, and new data on the clinical effectiveness of clozapine, the clinical care and management of people with TRS continue to present a major clinical challenge. In this article, we present a concise clinical review of TRS, with discussion of the different and evolving definitions, the clinical assessment, and the evidence for pharmacological and non-pharmacological strategies.

**Keywords** clozapine; cognitive behavioural therapy; first-generation antipsychotic; medication adherence; polypharmacy; second-generation antipsychotic; treatment-resistant schizophrenia

In up to a third of people with schizophrenia, the illness shows a poor response to first-generation antipsychotics (FGAs).[1] While a relatively small proportion will fail to achieve remission even after the first episode, more commonly patients become progressively more unresponsive to medication.[2] For example, Wiersma et al.[3] studied a cohort of patients over successive psychotic episodes, and found that following relapse around 1 in 6 did not did not remit from the episode, and experienced persistent psychotic symptoms.

Despite recent advances in pharmacotherapy, treatment-resistant schizophrenia (TRS) is likely to remain a major clinical challenge. There are no reliable predictors of poor response to medication, and TRS defies delineation in terms of characteristic symptom profile. It remains to be determined whether TRS should be viewed simply as the more severe end of the illness spectrum, characterized by refractory symptoms and poor integration into the community, or as a distinct subtype of schizophrenia. In this regard, some neurobiological correlates of treatment resistance have been identified, including progressive and/or static cortical atrophy detected by neuro-imaging,[4,5] and neurochemical findings relating to dysfunction of the dopaminergic, serotonergic, and glutamatergic brain pathways.[6]

## Definitions

Traditionally, the notion of poor response to antipsychotic medication has been rather ill defined, tending to be framed in terms of continuing positive symptoms and frequent or long-term hospitalization.[7] For many years, the diagnostic criteria used for TRS were inconsistent, as may be noted across the trials in the 1970s comparing standard and high or mega doses of antipsychotic medication. However, in a landmark trial comparing clozapine and chlorpromazine in TRS, Kane et al.[8] applied strict inclusion criteria that clearly defined the study sample and provided the first explicit definition of treatment resistance (Table 1). The criteria addressed poor social and occupational function as well as a lack of past treatment response and persistence of symptoms.

Subsequently, demonstration of the efficacy of clozapine in TRS, and the development of other pharmacological and non-pharmacological treatments that may be of benefit, has raised expectations of potential therapeutic response in a broader group of patients with poor or inadequate response.[11] This is reflected in the use of less restrictive definitions of TRS, such as those produced by Conley and Kelly[9] or the National Institute for Clinical Excellence[10] (Table 1). Clinically, the broader notion of 'incomplete recovery' may be useful, as it acknowledges the presence of disability in functional and psychosocial aspects that is persistent despite adequate treatment, referring to psychotherapeutic and psychosocial interventions as well as antipsychotic medication.[12] Further, unlike the rather negative label of 'treatment resistance', the term 'incomplete recovery' also recognizes the potential for a better therapeutic outcome.

## Clinical evaluation of treatment-resistant schizophrenia (Table 2)

A range of symptom domains may contribute to poor community function, including persistent positive symptoms, prominent negative symptoms, co-morbid depression, neurocognitive deficits, social cognition deficits, disturbed behaviour, and medication side effects, including extrapyramidal symptoms. The profile of such elements will vary markedly between individuals with TRS, and will largely determine the treatment targets and intervention strategies for different patients. For this group of patients, treatment goals should be slanted towards social reintegration, focusing on symptoms or behaviour that have proved to be disruptive

***Thomas RE Barnes*** *MD FRCPsych DSc is Professor of Clinical Psychiatry at Imperial College, London, UK. He has a longstanding research interest in the psychopharmacology of schizophrenia and for 15 years ran a tertiary-referral clinical service for people with treatment-resistant schizophrenia. Conflicts of interest. Conflicts of interest: acted as a consultant/advisory board member for the pharmaceutical industry on occasion.*

***Serdar Dursun*** *MD PhD FRCPC is Professor of Psychiatry in the Department of Psychiatry, University of Alberta, Edmonton, Canada; Director, Centre for Psychiatric Assessment and Therapeutics, Mental Health Programme, Capital Health, Edmonton; and Admitting Psychiatrist, Grey Nuns Community Hospital, Edmonton. Competing interests: Consultant/advisory board member and Lecturer for the pharmaceutical industry on occasion.*

 

## Definitions of treatment-resistant schizophrenia

**Kane et al. (1988)[8]**

- Persistent positive symptoms
- Current presence of at least moderately severe illness (BPRS >45, CGI >4)
- Persistence of illness: no stable period of good social/occupational functioning in past 5 years
- Drug-refractory condition: three periods of treatment in preceding 5 years with first-generation antipsychotics in doses greater than 1000 mg chlorpromazine equivalents/day, for 6 weeks without significant improvement

**Conley and Kelly (2001)[9]**

- Drug-refractory condition: at least two previous antipsychotic drug trials of 4–6 weeks' duration at 400–600 mg/day (chlorpromazine equivalents, mg/day) with no clinical improvement
- Persistence of illness: more than 5 years with no period of social or occupational functioning
- Persistent psychotic symptoms (BPRS 18 >45, CGI >4)

**National Institute of Clinical Excellence (2002)[10]**

- Lack of a satisfactory clinical improvement despite the sequential use of the recommended doses for 6–8 weeks of at least two antipsychotic drugs, at least one of which should be a second-generation antipsychotic

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression scale.

**Table 1**

or poorly tolerated in the community, or deficits that otherwise impair social functioning.

The psychopharmacological history of the patient should be scrutinized to determine response to past trials of antipsychotic medication, particularly those that were adequate in terms of dose, duration, and adherence. Given that poor adherence to medication can be a major factor influencing recovery, information on the therapeutic response to periods of treatment with long-acting antipsychotic injections is particularly useful. Unlike oral medication, covert non-adherence is not possible with such treatment and, if the receipt of injections has been well documented, response can be judged in the context of guaranteed medication delivery.

Aside from such medication issues, consideration should be given to other factors that can have a deleterious impact on illness outcome, such as psychosocial stressors, physical co-morbidity, and concurrent substance use. Thus, a range of clinical investigations should be considered in the initial assessment of TRS, including routine haematological and biochemical laboratory investigations, and drug screen (urine or possibly hair analysis).[13] If not already carried out, a brain scan (ideally magnetic resonance imaging) and neuropsychological testing may well be warranted. Suspicion of any organic cause should prompt appropriate investigation and referral.

## Key aspects of clinical assessment of treatment-resistant schizophrenia

- Review the psychiatric diagnosis
- Review investigations such as CT brain scan, EEG, urine drug screen
- Review past treatment and response
- Review persistent symptoms to be targeted:
  - Co-morbid depression/anxiety symptoms
  - Disabling/distressing symptoms
  - Behavioural disturbance
- Consider treatment adherence issues
- Consider adverse impact of co-morbid substance use

CT, computed tomography; EEG,, electroencephalography.

**Table 2**

## Pharmacological strategies for treatment-resistance schizophrenia (Table 3)

If a patient has failed to respond despite adequate trials of antipsychotic medication, one option is to switch to another antipsychotic, choosing an appropriate FGA or second-generation antipsychotic (SGA). The evidence base for such a strategy is limited. There is a lack of well controlled studies, and they tend to have methodological problems, such as inadequate definition of TRS or the inclusion of treatment-intolerant patients. The findings do not provide much cause for optimism: only a small proportion of previously unresponsive patients are likely to show a clinically relevant improvement.[14,15] Similarly, none of the clinical trials comparing standard and high doses of antipsychotic medication for TRS has shown a significant advantage for the latter (see below). There is also a range of possibilities for augmenting a FGA or SGA, including another antipsychotic (see below),

## Pharmacological strategies used for treatment-resistant schizophrenia

**Antipsychotic medication**

- Ensure adequate trials of both first- and second-generation antipsychotics (other than clozapine) in terms of dose, duration, and adherence
- If receiving high-dose treatment, consider drug dose reduction
- High-dose antipsychotics
- Combined antipsychotics
- Clozapine
- Clozapine augmentation

**Adjunctive treatment**

- Lithium
- Carbamazepine
- Sodium valproate
- Antidepressant
- Benzodiazepine
- Lamotrigine

**Table 3**