Therapy-Resistant Schizophrenia
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It is well known that up to 30% of patients with schizophrenia do not respond to treatment with antipsychotic drugs that are usually effective, in at least in improving positive symptoms. Treatment-resistant schizophrenia (TRS) represents an even greater burden for affected patients, their significant others and society. This volume of *Advances in Biological Psychiatry* is dedicated to a comprehensive analysis of TRS, with reviews of the concept, assessment, neurobiology and treatment.

TRS is to be distinguished from poor-outcome schizophrenia. Long-term (15–25 years) multicenter epidemiological studies promoted by the World Health Organization showed that 50% of patients with psychosis have a poor outcome [1]. A meta-analysis of the literature encompassing a century of schizophrenia treatment – biological, surgical and psychopharmacological – showed that patients with favorable outcome represent only 40% of cases [2]. TRS as defined in this volume represents only a subset of poor-outcome schizophrenia, i.e. those with persistent moderate-to-severe positive symptoms. Poor outcome can even occur in schizophrenic patients with good control of psychotic symptoms because of the functional effects of cognitive impairment, negative symptoms and mood symptoms that are independent of positive symptoms.

The discovery of chlorpromazine in the 1950s led to the first effective treatment for positive symptoms in the majority of patients with schizophrenia, even those who had been psychotic for decades. This allowed massive discharges from public and private mental hospitals, enabling patients to begin community residence and treatment. However, a group of patients continued to have persistent delusions or hallucinations, or both, despite treatment with chlorpromazine and related drugs. These patients are correctly referred to as being treatment resistant to the so-called typical antipsychotic drugs (sometimes referred to as first-generation drugs) [3]. With the exception of clozapine, none of the newer antipsychotic drugs (i.e. the atypical antipsychotic drugs, such as risperidone and olanzapine) used at conventional doses are able to treat the majority of such patients, although some do respond, suggesting heterogeneity in this class of patients.

As pointed out by Lindenmayer in this issue, TRS can have a devastating effect on individuals and families, representing a significant public health problem.
Despite the persistence of positive symptoms (which by definition means TRS), clinicians often fail to make the appropriate diagnosis and clinical decision, which would be to suggest clozapine treatment, the only drug that is approved for TRS. There are, of course, many other treatments which have been used and are occasionally successful. More research is needed to provide additional treatments for TRS, as clozapine has a number of serious side effects and is ineffective in about one third of TRS cases. The proper assessment and management of TRS is fully discussed in the chapters by Lindenmayer & Khan and Lambert in this volume.

A number of factors have been suggested to lead to TRS. These include the duration of untreated psychosis, as reviewed by Bobo and Meltzer, but the evidence for its relevance is much weaker than many have thought. Genetic factors are considered by De Luca et al., while brain structural and functional abnormalities, as described by Borgio et al. in this issue, are also important in the pathophysiology of TRS and may be genetic in origin. TRS is not due to cognitive impairment, as this is found with equal severity in TRS and nonTRS. This is detailed in the chapter by Woodward and Meltzer.

The landmark study of Kane et al. [4] showed that clozapine was superior to chlorpromazine, a typical antipsychotic drug, in patients with TRS as defined here, not simply a waste basket on 'poor response'. The validity of this study has been confirmed worldwide, but despite this, the use of clozapine is much less than it should be. Only 5% of patients with schizophrenia in the USA receive clozapine, which has also been indicated to reduce the risk of suicide [5, 6]. China and Finland are two countries in which clozapine is used widely. As pointed out by Meltzer in this issue, clozapine is still considered to be the most effective of all antipsychotic drugs, despite the introduction of many new classes of antipsychotics and considerable advances in the treatment of TRS. The limited use is due to an exaggerated fear of the risk of agranulocytosis, as well as very real side effects such as tachycardia, sialorrhea, seizures, myocarditis, weight gain, type II diabetes and OCD symptoms.

Partial responders to clozapine remain a challenge for the treatment of TRS. The addition of other antipsychotic drugs is usually ineffective, whereas ECT is often helpful. The chapters in this volume by Remington, Champattana, Jandl and Kaschka, and Souza et al. provide full discussions of pharmacological, as well as non-pharmacological, strategies to provide supplemental treatments for clozapine in TRS patients.

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