

Treatment Resistant Schizophrenia

General Principles

“Treatment resistant” schizophrenia (TRS) is defined by an inadequate response to a succession of treatments” (Taylor and Duncan-McConnell, 2000). An inadequate response need not be restricted to the persistence of positive symptoms, but this is the most common definition. It can be applied even if a patient has not had a trial of ECT. The concept of treatment resistance should not be confused with: “chronic schizophrenia” as chronicity and “resistance” are different concepts. Chronic patients can respond to standard treatments and treatment resistance may be as high as 15% even in first episode patients (McGorry et al., 2003). The prevalence of TRS is estimated to be 30-50% of patients with the diagnosis of schizophrenia but some authors have reported even higher rates (Meltzer and Kostakoglu, 2001)

Two forms of treatment resistant schizophrenia are: 1) Kraepelinean schizophrenia which refers to patients with severe, persistent cognitive deterioration; and 2) “negative” or “deficit” schizophrenia: schizophrenia patients with prominent and persistent primary negative symptoms, including very flat affect.

Operational Criteria of ATRS: TRS is present if the patient fulfills the following 3 criteria which are modified from those of Kane et al (1988) to be useful in everyday clinical practice:

- 1) No period of good functioning in previous 5 years; 2) prior non-response to at least 2 antipsychotic drugs of two different chemical classes for at least 4-6 weeks each at doses ≥ 400 mg equivalents of chlorpromazine or 5 mg/day risperidone; 3) moderate to severe psychopathology, especially positive symptoms: conceptual disorganization, suspiciousness, delusions or hallucinatory behavior.
- 2) In keeping with our view that TRS refers to more than persistent positive symptoms, we recommend considering patients to have TRS if they exhibit any of the following after two trials of 4-6 weeks duration each, with two different antipsychotics at adequate doses : persistent psychotic symptoms, recurrent mood symptoms, repeated suicide attempts or suicidal ideation, uncontrolled aggressive behavior, moderate- severe negative symptoms or moderate-severe cognitive impairment

Treatment approaches to TRS

A meta-analysis of 12 randomized controlled trials of atypical antipsychotic drugs found that clozapine was the treatment of choice for TRS. (Chakos et al: 2001). However, Moncrieff (2003) has concluded that meta-analyses of the clozapine literature may have overestimated the advantage of clozapine over typical antipsychotic drugs. The systematic review of Taylor and Duncan- McDonnell (2000) analyzed 14 randomized controlled trials of atypicals in the treatment of ATRS as well as retrospective analyses, case reports and switching studies and reached the same conclusion (A). Two meta-analyses showed

evidence that CBT is effective in patients with persistent psychotic symptoms (Gould et al., 2001;Pilling et al., 2002)

Variables which interfere in clozapine treatment

Recently Schulte (2003) reviewed studies of drug monitoring and time of response in clozapine treatment. They concluded that the duration of trial of clozapine should be a minimum of 8 weeks up to 6 months, the dose range should be 300-900 mg/day and plasma levels should be at least 350-450 µg/L

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