There is no general agreement about what is treatment resistance. For the present discussion it is taken as a patient diagnosed to be suffering from schizophrenia by an experienced psychiatrist after careful workout, who has failed to achieve significant symptom reduction or regain adequate social or occupational functioning after two different courses of first line antipsychotic treatment. The antipsychotic drugs must be given in adequate doses and each for at least 4-6 weeks. Treatment resistance occurs in about 20% of cases. If there is no improvement after measures are taken to deal with treatment resistance, the patient is considered treatment refractory. This is fortunately rare.

Factors that contribute to treatment resistance are (1) male sex, (2) early onset (3) prolonged duration of untreated psychosis (4) chronic patients (5) hebephrenic schizophrenia, a type of schizophrenia characterised by disorganisation of thoughts, (6) history of obstetric complications (7) history of prenatal and perinatal problems.

Probable neurobiological correlates are

(1) cortical atrophy and cerebellar atrophy. This is confirmed by neuroimaging studies.1,2
(2) low activities of MAO-A (Monoamine oxidase A) and COMT (Catechol-O-methyltransferase)3.

This is confirmed by genetic studies. Patients who respond poorly to antipsychotic drugs are six times more likely to have genotypes for low activities of MAO-A and COMT. It is postulated that these patients have a poor ability to metabolise dopamine.

The following guide may be used by clinicians to deal with treatment resistance:

**Review the diagnosis.** There are many conditions that can mimic schizophrenia. Is the syndrome one of delirium or dementia? Does the patient suffer from a symptomatic psychosis due to a general medical condition? This includes a long list of differential diagnoses such as nutritional deficiencies (nicotinamide or cyanocobalamin), endocrine disorders (Addison’s disease, Cushing’s syndrome, thyroid disorders), metabolic diseases (Wilson’s disease, porphyrias), infectious diseases (syphilis), diseases of the brain (epilepsy or hydrocephalus), substances of abuse (cocaïne, amphetamine) or toxic substances (arsenic, mercury). Some therapeutic agents may also be responsible (steroids, sibutramine, bromocriptine etc).

A full investigation including blood test, brain scan and screening for drugs of abuse must be carried out.

**Determine the adequacy of treatment doses and duration.** Each drug has an optimal dose. Patients must receive an optimal dose of the administered drug for 4-6 weeks. If a patient is going to respond, usually some improvement will be seen in the first 2 weeks, and a good effect will be seen in 4-6 weeks. 70% of the total improvement in one year is seen during this period. If there is no response during this period, the drug will probably be ineffective. It is a common problem with non-specialists handling such patients that an inadequate dose of drugs has been given.5,6,7

**Substances from lifestyle habits**—tobacco and caffeine.8,9,10,11
The point prevalence of tobacco smoking is 71% in male schizophrenics and 44% among female schizophrenics. Polycyclic hydrocarbons in cigarettes induce hepatic cytochrome P450 enzymes that metabolise haloperidol, olanzapine and clozapine, resulting in lower serum levels. Smokers therefore require a 50% increase in doses of these medications.
Schizophrenics consume more caffeine from beverages than the average person.

In North America, the amount is 500 versus 200 mg per day. Caffeine acts on adenosine receptors in the central nervous system to enhance dopamine neurotransmission. There is some evidence that caffeine increases positive symptoms and hostility in schizophrenics. Patients may also purposely increase their caffeine intake to alleviate their negative symptoms. Therefore caffeine intake should be reduced or controlled in the treatment of schizophrenic patients.

**Substances of Abuse.** In North America 50% of schizophrenics are drug abusers.

Drugs like cocaine, cannabis and methamphetamine can induce and maintain schizophrenic symptoms, giving a picture of treatment resistance. Chronic excessive use of alcohol is also a problem. Drug abusers are less compliant to treatment regimes.12-14

**Prescribed drugs** Omeprazole, rifampicin, ritonavir, carbamazepine and phenytoin induce CYP1A2 activity and patients require a 50% higher dose of olanzapine and clozapine. Rifampicin, carbamazepine and phenytoin induce CYP3A. Quetiapine needs to be increased 5 fold, risperidone and aripiprazole 2 fold and ziprasidone by 50% when co-administered with these drugs. Oxcarbazepine, topiramate and St. John’s Wort are also enzyme inducers.15,16

Drugs like selective serotonin reuptake inhibitors inhibit cytochrome P450 enzymes.

When these drugs are withdrawn, there is increased activity of the enzymes with enhanced degradation of antipsychotic drugs. This may result in emergence of psychotic symptoms that have been under control.17

**Genetic polymorphism.** Certain population groups have a greater incidence of duplication in the CYP2D6 genes. This enzyme is important in the elimination of haloperidol, zuclophenixol, risperidone, thioridazine and perphenazine. Patients with a double dose of the gene are rapid metabolisers of the drugs concerned. This occurs in 3% of white northern Europeans, 10% of white southern Europeans, 16% of Saudi Arabsians and 29% of Ethiopians. Such patients are more prone to relapses and multiple hospitalisation. Hence blood level monitoring and genotyping may be necessary when dealing with this group of patients.18-21

**Pharmacological Strategies in dealing with treatment resistance.** If a patient has not responded to a first generation antipsychotic drug, a trial of another first generation drug would not be useful. A first line atypical drug should be started. About 50% of patients respond well. Should this fail, the option is to go on to another first line atypical drug, or to start clozapine. The choice to take will depend on the actual clinical situation and the patient’s preference. For example, if weight gain is a problem with olanzapine, then risperidone may be used instead. If there is significant extrapyramidal symptoms, quetiapine may be an alternative. Patients may not wish to have clozapine due to the need to have frequent blood tests.

Clozapine is the gold standard for treatment of resistant schizophrenia. It is particularly useful in cases with persistent auditory hallucination, suicidal risk, tardive dyskinesia and hostility. An adequate serum level of more than 250 ng/ml must be ensured, especially in cases that do not seem to respond adequately. Monitoring for agranulocytosis, lipid disturbance, seizure and other side effects is required.22,23

Pharmacological augmentation Antipsychotic drugs are dopamine receptor blockers. Drugs that act on a different receptor system may be tried in augmentation therapy. Lamotrigine affects glutamate neurotransmission and has been used with some success in treatment of resistant schizophrenia. It may be used with first or second generation antipsychotic drugs. The control of positive symptoms is improved with the addition of Lamotrigine.24,25

Valproate acts on GABA receptors and indirectly modulates dopamine activity in the brain. The addition of valproate had been found to reduce agitation and hostility in schizophrenic patients.26,27

The omega-3 polyunsaturated fatty acid EPA is found to have some short term benefits in cases with residual symptoms. The dose is 2-3 gm daily.28,29

Non-pharmacological strategies. Counselling, psychological support, education, removal of psychological stress and social rehabilitation are always important measures in treating schizophrenic patients. This is more so in cases of resistant schizophrenia. A specific cognitive behaviour technique has been developed for use in schizophrenic patients with positive results.30

Electroconvulsive therapy has been used in cases of resistant schizophrenia, Benefits are observed in some cases although systematic study of its application in resistant schizophrenia is lacking.31

Repetitive transcranial magnetic stimulation involves daily application of a magnetic field to the temporoparietal region for 10-14 days. Each session lasts 20 minutes. Patients do not require sedation or hospitalisation. It is found to reduce symptoms in patients with treatment resistant auditory hallucination. Further evaluation of this procedure is required.32

Adapted from: H.A.Nasrallah and R.F.White

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**References**


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