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Review Article

Combination Therapy for Treatment Resistant Schizophrenia

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Abstract

The pharmacological management of treatment resistant schizophrenia provides clinicians with a broad range of clinical challenges. Antipsychotic combinations involve pharmacokinetic and pharmacodynamic interactions with physical side effects. Consideration of the effect of long-term progress and physical consequence of medications are central to therapy selection. Clozapine is the gold standard for treatment resistant schizophrenia in spite of the various side effects, but clozapine may fail or be refused by patients. Clinicians are left with very little choices in such circumstances and combination of antipsychotics is considered as one option. Olanzapine-amisulpiride combination may be a choice in pre-clozapine clinical situations and in cases where clozapine fails.

Keywords: resistant schizophrenia, combination, clozapine, olanzapine, amisulpiride

Abbreviations: SCZ- schizophrenia

Schizophrenia (SCZ) is a chronic relapsing and remitting disorder with a lifetime prevalence of 4 per 1000 persons.[1]Positive symptoms include delusions and hallucinations. Negative symptoms are characterised by deficits in normal behaviour, which are categorised into five domains: blunted affect, alogia, social withdrawal, anhedonia, and avolition. In clinical practice, when monotherapy fails multiple augmentation strategies – such as another antipsychotic, mood-stabilisers, benzodiazepines, lithium, electroconvulsive therapy, and repetitive trans-cranial magnetic stimulation – have been used to improve the clinical state of these patients, but evidence relating to the use of these interventions is lacking.[2]None of the regulatory bodies has openly endorsed polytherapy with antipsychotics.

The introduction of chlorpromazine in the 1950s revolutionised psychiatry, and the coming of slow-release, slow-acting forms (depot medication) contributed to the closure of asylums and paved the way to community psychiatry. Second-generation antipsychotics ameliorated the situation for a number of psychotic patients, but some remained resistant to all forms of psychopharmacology. In 1958, clozapine was formulated and marketed commercially in 1972.[3] The arrival of clozapine facilitated the rescue of some schizophrenia sufferers for a short time, but the drug disappeared from the scene because of initial untoward incidents.[4,5] The observation that clozapine has the potential to control the motor symptoms of tardive dyskinesia and to treat the psychotic symptoms of patients already diagnosed with tardive dyskinesia, led to its reintroduction, but with restrictions.[6,7,8] Clozapine is recommended for use only after a trial of two other antipsychotics. Combining depot antipsychotics with oral drugs of a different class has been the practice ever since the introduction of depot medications, and this practice has come to have general clinical acceptance.

Treatment resistance

Historically, it was observed that a specific group of chlorpromazine users remained symptomatic. They were considered to be refractory to phenothiazines. The availability of clozapine led to a better definition of treatment resistance. 'Response to treatment' means a reduction in the severity of symptoms, while 'remission' implies an absence of symptoms for a considerable period. 'Recovery' signifies absence of the disease for a long period.[9]'Treatment resistant schizophrenia' (TRS) is the term used for persistence of psychotic symptoms despite a certain number of adequate treatments. Since the introduction of first-generation antipsychotics, clinicians have been cognizant of TRS and operational definitions have been used such as those developed by Kane et al.[10] Sometimes, treatment has been based on algorithms such as the Texas Medication Algorithm Project (TMAP).

According to the most common definition of TRS, if patients present with persistent, moderate to severe, positive disorganization or negative symptoms together with poor social and work function over a prolonged period of time after at least 2 adequate trials of neuroleptic drugs, they may meet the criteria of having TRS.[11] A common agreement is that adequate drug treatment requires a duration of 4 to 10 weeks, a dosage equivalent to 1000 mg/d of chlorpromazine, and trials of 2 to 3 different classes of antipsychotic drugs.[12] The current treatment guidelines recommend 2 or more treatment trials of atypical antipsychotics at adequate dosages. Adequate response to treatment has been defined as at least a 20% reduction in symptoms as measured by rating scales. Typical antipsychotics can also be used for 4 to 6 weeks to screen for TRS.

Resistance to treatment and poor outcome are different from genuine TRS. Resistance to treatment may be defined as a state in which the patient has access to medication, but the effectiveness of the treatment is suboptimal. TRS may be conceptualised as a state in which medication has reached target receptors but does not seem to be effective. Chronicity has often been misconstrued with treatment-resistance. Schizophrenia is a chronic disorder that progresses to various levels of clinical deterioration without sustained remission or full recovery. Poor-outcome SCZ applies to 50% of patients, and TRS comprises a subset of such patients. In these, cognitive impairment, negative symptoms and mood symptoms are independent of positive symptoms, resulting in poor-outcome SCZ.

It is generally accepted that 30% of SCZ sufferers have TRS. Many people with SCZ do not achieve a satisfactory treatment response to their initial antipsychotic drug treatment. They may manifest a poor response to therapy because of intolerance to medication, poor adherence and inappropriate dosing, as well as true resistance of their illness to antipsychotic drug therapy. Assessing treatment resistance is a priority in the management of TRS. [13] TRS has to be closely evaluated before a comprehensive management plan is developed (Table 1). From a multidimensional point of view, TRS is dependent on manifold factors, such as longer duration, several episodes, gender, early onset, poor pre-morbid personality, family history, substance misuse, presence of soft neurological signs and a long untreated period.[14] Genes are thought to be involved in the development of TRS; reliable genetic prediction of which patients will be TRS would have serious clinical implications. Structural neuroimaging techniques have revealed that TRS patients do not differ importantly than those responsive SCZ in terms of brain abnormalities.[15]

When clozapine fails or rejected

Clozapine may be the preferred drug for TRS – effectively the gold standard – but its side effects put off many patients to the extent that some of them refuse clozapine therapy. It is a unique atypical antipsychotic and there is robust evidence supporting its use in people with TRS. Though clozapine often represents the best hope for recovery, it is associated with severe and enduring adverse reactions that may delay its prescription and increase morbidity and mortality. The major side effects are a) agranulocytosis; b) metabolic side effects; c) myocarditis; d) seizures; e) severe constipation with gastrointestinal complications such as intestinal obstruction, bowel perforation, paralytics ileus and toxic megacolon; and f) sialorrhea. These side effects hinder the popular use of clozapine in TRS. It is a life-saving drug, but without extra care it may itself shorten the life span. Side effects are more common with higher doses. It has been estimated that between 10 and 60% of patients resistant or intolerant with other antipsychotic drugs respond to clozapine.

The side effects mentioned above are inevitably an impediment to its common use. When standard doses (300mg to 5oomg) do not produce the desired effects or patients develop unwanted effects, combining clozapine with other antipsychotics is a common practice for TRS. To mention a few antipsychotics, amisulpride and aripiprazole are atypical antipsychotics ordinarily used in combination with clozapine. The anti-salivatory effect of amisulpride and the alerting effect of aripiprazole are added advantages of such a combination, and these drugs are fairly weight neutral – in contrast to clozapine. Clozapine, representing a second generation of so-called atypical antipsychotic drugs, has shown positive effects in desperate cases of TRS. Furthermore, two epidemiological studies have shown that clozapine has the lowest mortality rate among antipsychotics.

Nevertheless, even supported by the literature as the best-known antipsychotic in terms of efficacy and rates of response, a sizeable number of patients remain resistant to clozapine therapy and continue as symptomatic and dysfunctional. It has been estimated that 40–70% of patients on clozapine may not respond satisfactorily to it.[16] When patients do not respond to clozapine, they are categorised as super-refractory, but the very concept of super-refractory state is debatable. They do not differ from the refractory cases in terms of demographical factors but have high score of positive symptoms. It may be simply explainable that the aetiological mechanism of the illness of such patients may be different from the clozapine responders and that makes them unresponsive to clozapine. There are no operational definitions for super-refractory schizophrenia. According to the schizophrenia algorithm of the International Psychopharmacology Algorithm Project (www.jpap.org), persistence of psychotic symptoms after a trial with adequate doses of clozapine(300-900mg/day) for at least six months is designated as super-refractory cases. [17]

Many predictors of clozapine response have been suggested without any firm ground. These include severe clinical symptoms, higher levels of functioning before the onset of schizophrenia, low levels of homovanillic acid and 5-hydroxyindoleacetic acid in cerebrospinal fluid, reduced metabolism in the prefrontal cortex, reduced volume of the caudate, and the improvement of P50 gating at the 500-ms prepulse interval. [18] However, none of these factors is consistent or specific as a predictor of clozapine response. More genetic and brain imaging studies are warranted with such patients. In these cases, augmenting strategies are necessary, and some have been in use: typical and atypical antipsychotics, mood stabilizers, antidepressants and electroconvulsive therapy. Some studies have favoured ECT, but no definitive conclusion has been drawn. So also, half of clozapine patients discontinue taking the medication on their own accord. In a retrospectively studied sample of patients who discontinued clozapine, the majority terminated the treatment as a result of their own decision or because of non-compliance with medical procedures such as blood sampling.[19]

There are currently no evidence-based pharmacotherapies for the TRS patients who do not respond to clozapine [20,21] or those

who terminate clozapine therapy due to adversative reactions. [22] In the nutshell, clinicians should be prepared to try different alternative treatment options for TRS and super-refractory cases. Thus, combination therapy may become a choice as pre-clozapine therapy or post-clozapine therapy. Clozapine is not a drug that could normally be imposed on patients, but it has to be earned by the patient.

Combination therapy

The range of antipsychotic medications available is wide, with variable effectiveness, and there are also differing profiles for typical and atypical agents, adding to a confusing array of terminologies and dilemmas regarding what the best drug for service users is.[23] Combination therapy involves the addition of a second antipsychotic to the therapy regimen. It is different from adjunctive therapy, in which a second agent is employed to reverse an emergent side effect or to obtain a complementary clinical effect. Augmentation involves the use of a non-antipsychotic along with the antipsychotic already in use. Combination therapy and augmentation therapy are sometimes used interchangeably. In general, 'combination' refers to the use of more than one type of disease-specific treatment to treat a particular illness.

A change from one antipsychotic to another in same class seldom produces any additional benefit, whereas switching to an antipsychotic with a different mechanism of action has proved to produce a more impressive response rate. Combination becomes desirable when the drug already in use produces some favourable effect, but that is not sufficient to control the symptoms. It is imperative to distinguish between partial response and no response when considering a change in medication. Past antipsychotic drug response, adverse effect profile differences, concomitant medical disorders and concurrent drug therapy are factors to be considered when choosing between switching and combination or augmentation approaches. A switch is indicated when there is no response to the drug and combination therapy; augmentation is recommended for partial response. Another antipsychotic combination may become necessary as an option for TRS patients who cannot be treated with clozapine for various reasons. It is common practice in such situations to add a second antipsychotic, in combination with the original one.

Clinical team do not have to be disheartened or disillusioned when clozapine therapy fails due to non-response or clozapine intolerance, and also when augmentation and combination therapies do not bring about the desired outcome. Switching back to atypical drugs once again may turn out to be effective in some cases and clozapine is not to be considered as the last resort. A multicentre open label 18-week trial evaluated a switch to olanzapine in 48 clozapine resistant or intolerant patients. [24] Switching to olanzapine 5-25 mg per day resulted in a mean drop in total scores on the Positive and Negative Syndrome Scale (PANNS) and Brief Psychiatric Rating Scale (BPRS) of 17.7 (14.2%) and 9.8 points (20.2%) respectively.

Cautions

Monotherapy is the most desirable form of treatment for SCZ. There is no good objective evidence to support dual antipsychotic therapy except in combination with clozapine. The evidence base supporting such combinations consists mostly of small open-label studies and case series.[25] Combination therapy should be considered only when several attempts at monotherapy, including one atypical antipsychotic, fail. It is assumed that two different treatments together may have a different mechanism of action and therapeutic response from that of either drug alone. Studies have been conducted to determine whether treatment with antipsychotic combinations is effective for SCZ and whether such treatment is safe for the same illness. The results of trial studies are based on very low or low-quality results, and research that provides high-quality evidence is needed before firm conclusions may be drawn. The results so far show that there may be some clinical benefit in combination therapy in that more people receiving a combination of antipsychotics showed an improvement in symptoms. For other important outcomes – such as relapse, hospitalisation, adverse events and discontinuing treatment – no clear differences between the two treatment options were observed. Currently, most evidence regarding the use of antipsychotic combinations comes from short-term trials; the assessment of long-term efficacy and safety is limited. There is some very low-quality evidence that a combination of antipsychotics may improve the clinical response.

There are published case reports of serious side effects, such as a higher prevalence of extrapyramidal symptoms (EPS), metabolic side effects, paralytic ileus, grand mal seizures and prolonged QTc in association with a combination of antipsychotics.[26]Combining three antipsychotics may be extremely dangerous; studies have revealed that such a procedure substantially increases mortality.[27]A negative case control study exists.[28] It should be usual practice to document the rationale for combined antipsychotic use in individual cases in clinical records, along with a clear account of benefits and disadvantages, including side effects.

Newer combinations and augmentation strategies are supported only by case reports and open trial data. Along with advantages, a number of potential concerns regarding antipsychotic combinations have been identified (Table 2) and specific clinical cautions have to be implemented in combination therapy (Table 3). Yet, fixed combinations of drugs are common in medicine and at one time were common in psychiatry. An example is small doses of an antipsychotic in combination with an antidepressant for treating major depression; this lost popularity because of side effects. Also, SNRI-NaSSA combination therapy (e.g. California Rocket Fuel) is prevalently used for treatment-resistant depression.

Olanzapine–Amisulpride combination

In spite of the objections put forward against combination therapy, there are isolated case studies favouring the olanzapine–amisulpride combination. Zink et al. (2004) performed a retrospective study, aiming at the systematic evaluation of patients on combined olanzapine and amisulpride. The open study designed as a retrospective chart review of Zink et al. concludes that the olanzapine–amisulpride combination for TRS is encouraging, but requires further evaluation in prospective and randomised studies.[29]They point out that a reduction of the daily dose of both drugs helped to minimise the side effects of these drugs – such as weight gain and EPS – resulting in better compliance. They did not notice any additional side effects or undesirable drug interactions.

Within the heterogeneous group of atypical antipsychotics, the thienobenzodiazepine derivative olanzapine has a receptor profile that is quite similar to that of clozapine, indicated by having a greater affinity for serotonergic 5-HT_{2A} receptors than for dopaminergic D_2 receptors. The positive and negative symptoms of schizophrenic psychoses usually respond well to this drug. In contrast to clozapine, olanzapine does not induce major agranulocytosis but may, in a significant number of cases, lead to troublesome side effects including significant weight gain, type ii diabetes, sedation, anticholinergic effects and transient increases in liver enzymes. Assertive weight management from the start of treatment is recommended. Weight should be monitored and also waist circumference measurements made. In addition, blood lipids should be assessed routinely. A suggested schedule for these investigations would be at 3, 6, and 12-month intervals, and biannually thereafter.[30]The pharmacology of antipsychotics is not the only factor that determines their effect on weight. Olanzapine has also been shown to elevate prolactin significantly in some patients.[31] As indicated earlier, Olanzapine can succeed in some cases even where clozapine fails.[24]

Amisulpride is an atypical antipsychotic of the benzamide class. It blocks D2 and D3 receptors (presynaptic in low doses, postsynaptic in higher). Unlike other atypical or typical **antipsychotics, it has low affinity for serotonin,** •-adrenergic, histaminergic, muscarinic and sigma receptors including D1, D4 and D5 receptors. It can lead to dose-related EPS that are significantly less than those of typical antipsychotics such as haloperidol and comparable to risperidone.[32]It is recognised that amisulpride is only sparingly metabolised by liver enzymes, and thus it is not known to participate in many drug interactions.[33] Amisulpride may elevate prolactin, which may cause sexual dysfunction, osteoporosis, amenorrhoea, gynaecomastia or galactorrhoea. It is a weight-neutral compound and may ameliorate negative symptoms.[34] Both olanzapine and amisulpiride are not associated with QTc prolongation.

One advantage of the combination of these drugs is that when olanzapine and amisulpride are combined, they may be given at a lower dose, which will spare the patients from the main unwanted side effects of the individual drugs: the over-sedation and weight gain of olanzapine; and the hyperprolactinemia of amisulpride, resulting in sexual side effects of a particularly undesirable extent. Our limited studies have found that this combination was well tolerated by TRS patients and its efficaciousness was similar to that of clozapine, but without any major side effects. Patients have been fully compliant. The combination of these drugs is managed by slowly introducing them one at a time and has been transformative in many cases. More studies of the olanzapine–amisulpride combination are needed in order to report on such outcomes as relapse, remission, social functioning, service utilisation, cost-effectiveness, satisfaction with care, and quality of life.

Table 1. Assessing Treatment Resistance

Re-evaluate current antipsychotic treatment
Has an adequate trial been given?
Suboptimal dose and non-adherence can lead to pseudo-resistance-poor adherence is unwaveringly associated with adverse effects, poor insight, and a poor therapeutic alliance.
Consider exceeding BNF limits-recommended only in specialist centres
Review the differential diagnosis eg schizo-affective disorder or bipolar affective disorder-Bipolar Disorder can present with first rank symptoms in the initial stages, it could take up to 10 years to establish a diagnosis of BD.
Asses for psychotic symptoms
Re-evaluate personal history and psychological pressures
Investigate co-morbid psychiatric symptoms eg substance misuse or alcohol dependency, depression, obsessive compulsive disorder and panic attacks
Investigate organic factors-temporal lobe epilepsy, endocrinopathies
Check blood levels if facilities available
Longer duration
Multiple episodes
Male gender
Onset of illness at an earlier age
Poor pre-morbid functioning
Length of untreated psychosis
Family history of schizophrenia
Soft neurological signs-lateral and third ventricular enlargement and low catecholamine level in CSF
Suicidal tendencies
Aggression
Asses adverse effects of psychiatric and other medications that may mimic worsening of positive and negative symptoms
Complete physical and neurological examination
and specialist consultation, as appropriate
Rule out the desire to to be ill

Table 2. Advantages and disadvantages

Advantages:
Discontinuation symptoms due to the withdrawal of the first antipsychotic could be avoided
Patients unresponsive to the initial antipsychotic may achieve clinical response when the second agent is introduced
Patient does not have to cope with another waiting period for the

substituted drug to produce full results
The benefits of the first drug are preserved in addition to the favourable effects of the added drug
Switching involves tapering off the initial drug, wash out period and delay in the onset of the second drug
Switching of antipsychotic drug requires additional supervision and care in the transitional period and could be delayed due to discontinuation symptoms; the addition of a second antipsychotic drug solves these problems
Disadvantages:
The possibility of unnecessarily high doses
An increased acute and/or chronic side-effect burden
Adverse pharmacodynamic and pharmacokinetic interactions
Difficulties in determining cause and effect of multiple treatments
Potential increased mortality,
Higher costs
Poorly documented risks and benefits of this practice
Reduced compliance

Table 3 Physical cautions with combination

History of cardiac disorder
(eg, MI, arrythmias, abnormal ECG)
Hepatic impairment
Renal impairment
Obesity (high BMI)
Heavy smoking
High alcohol intake
Substance misuse
Hyperlipidaemia
Above age 70
ECG, Haematological investigations.
Side effect rating scales
Physical effects
Record justification for combination

Summary

Combination therapies are the second choice when monotherapy fails. Clozapine is the first choice in severe cases of TRS, but there are super-refractory cases of TRS where clozapine fails. At least in isolated cases, the combination of olanzapine and amisulpride (Ami-olan combination) is worth considering for TRS patients who are reluctant to go on to clozapine therapy or in instances when clozapine failed, or patents dropped out. Combination therapies are normally avoided, but clinicians' helplessness and patients' despair justifies such measures in hard-to-treat cases of TRS. Only time will tell whether this combination will become an important part of clinical practice in future or will be ruled out as just another dual antipsychotic therapy.

The aetiology of SCZ remains obscure. The symptoms of different psychotic disorders are not clearly demarcated and there are no physiological parameters on which to make a firm diagnosis. In such a situation, the treatment of TRS has to be tailored on an individual basis. Even though it is normally well calculated, it may be somewhat hit and miss. Finding the right combination of antipsychotics or augmenting agents when the clinician is stranded and torn between monotherapy and polypharmacy is a gargantuan task. Clinical judgement along with patient preference must take over when treatment algorithms fall short. Given the data on polytherapy with antipsychotics that is available, it is hard to make any firm recommendation regarding its efficacy and safety of its use. Clinicians should be reminded that they should try monotherapy in adequate dosages before considering combinations.

For the management of TRS, comprehensive treatment strategies that integrate pharmacological, psychological, and psychosocial approaches are highly relevant and for that to happen, TRS should be clearly recognised. NICE offers very little guidance on clozapine resistant cases of SCZ. Combination of antipsychotics is not a panacea or a permanent solution for TRS. More investigation of schizophrenic illness is the only way forward. In comparison with other medical conditions (eg,HIV), research into it is making little progress. As it stands now, deconstructing clozapine's unique pharmacology may offer 'light at the end of the tunnel' for patients who are clozapine intolerant or non-responders.

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Competing Interests

None declared

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