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TREATMENT-RESISTANT SCHIZOPHRENIA: CHALLENGES AND IMPLICATIONS FOR CLINICAL PRACTICE

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SUMMARY

Despite pharmacological advances in the treatment of schizophrenia, significant number of patients continue to be treatment-resistant. Poor control of symptoms could be related to low concentration of antipsychotics because of non-adherence or pharmacokinetic issues. However, there is growing evidence that "true" treatment-resistance might be associated with biological changes, i.e. alterations in dopaminergic and glutaminergic systems, genetics, neurodegeneration and neuroinflamation.

Clozapine is recommended as first-line treatment for treatment-resistant schizophrenia (TRS) in all guidelines. Clozapine-ECT combination is effective in majority of those patients, at least in short-term. However, more than half of patients with TRS have resistance or intolerance to clozapine, and more interventions are needed. Different combination and augmentation strategies may offer some advantage, but evidence is limited. Given the severity and complexity of TRS, there is an urgent need for better treatment. Treatment strategies beyond dopamine, such as glutamate-modelling agents, nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal treatment, are under investigation.

Key words: *treatment-resistant schizophrenia (TRS) – antipsychotics - clozapine*

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INTRODUCTION

Before the advent of antipsychotics (APs), majority of patients with schizophrenia were placed in asylum for the rest of their lives. Since the introduction of chlorpromazine in 1952, APs have changed dramatically the prognosis of those patients. However, despite effective treatment, roughly 30% of patients are considered treatment-resistant (Teo et al. 2013). Some studies reported even higher percentage of treatment resistance such as 42% (Hassan & De Luca 2015). Those patients have high rates of smoking (56%), alcohol abuse (51%), substance abuse (51%), suicide ideation (44%) and poor quality of life (Kennedy et al. 2014). Annual costs for patients with treatment resistant schizophrenia (TRS) are 3-11-fold higher compared to patients with schizophrenia in general (Kennedy et al. 2014), and they often have long hospitalizations (Hasan et al. 2012). Treatment resistance represents the greatest unmet need in schizophrenia care (Nakajima et al. 2015).

There is no universally accepted definition of what is TRS (Molina et al. 2012, Sinclair & Adams 2014). Various criteria have been used. The first scientifically validated definition was that of Kane, 1998 (Molina et al. 2012). It defines treatment with different classes of APs at equal doses of 1000 mg/day of chlorpromazine for at least 3 periods of 6 weeks in the last 5 years without significant clinical improvement (Kane et al. 1998). Given that the highest approved dose of new generation APs, such as risperidone, olanzapine, aripiprazole and ziprasidone are below the equivalence of such high dose of chlorpromazine (Woods 2003), less strict criteria about the dosage of APs are widely accepted (Molina et al. 2012). According to most guidelines which are in use today, TRS is defined as lack of significant improvement to ≥ 2 antipsychotic trials at therapeutic doses (at least one with atypical antipsychotic), lasting ≥ 6 weeks (Lehman et al. 2004; Canadian Psychiatric Association 2005, Hasan et al. 2012). Treatment resistance can be further defined narrowly in terms of persistent positive symptoms poorly responsive to antipsychotic medication or broadly, to include persistent negative or cognitive symptoms and other kinds of disabilities. Some studies recognized two groups of patients with TRS: those who responded to clozapine, and those with clozapine-resistant or ultra-treatment resistant schizophrenia.

Revealing individual factors associated with treatment resistance may help in treatment decisions. We propose the model of 5 „C"s: Correct diagnosis, Comorbid conditions, Compliance, Concentration of APs, Continuous psychosocial stressors:

- Correct diagnosis of TRS is important, in order to rule out pseudoresistance. Namely, severe personality disorders, mania or depressive disorders with psychotic features are sometimes difficult to distinguish from schizophrenia (Dold & Leucht 2014). Other brain diseases can mimic the presentation of schizophrenia, such as anti-NMDAR encephalitis. The most frequent psychiatric symptoms of autoimmune encephalitis are delusions, manic mood and aggression (Kayser et al. 2013), which could be easily diagnosed as schizophrenia. While isolated psychotic symptoms are rare (Kayser et al. 2013), most patients also have memory difficulties, headache, confusion, seizures, symptoms of autonomic instability, movement disorder, or decrease in consciousness level, which, in turn, might be confused with

adverse events of APs. Psychotic symptoms with atypical presentation require additional diagnostic procedures, such as both serum and cerebrospinal fluid antibody testing (Höftberger 2015), lumbar puncture, EEG, and MR. Anti-NMDAR encephalitis occurs more frequently in women, and is associated with ovarian teratoma (Kayser et al. 2013).

- Comorbidities such as substance abuse, affective disorders, and obsessive-compulsive disorder or personality disorders should be considered, as they also contribute to treatment resistance (Dold & Leucht 2014). While anxiety symptoms might be secondary to caffeine or alcohol abuse (Canadian Psychiatric Association 2005), negative symptoms could be confused with depression, and irritability may indicate mania (Canadian Psychiatric Association 2005). Side effects of APs can also mask treatment response. For example, akathisia can be misinterpreted as psychotic agitation, while extrapyramidal symptoms (EPS) may resemble negative symptoms (Dold & Leucht 2014).
- Compliance with antipsychotic regimen is essential for improvement. Noncompliance is common in patients with schizophrenia. Although the rate of noncompliance among patients with TRS was not systemically investigated, it can be considered a major reason for non-response to antipsychotic medication (Dold & Leucht 2014). Reduced adherence to pharmacological treatment was associated with substance use, higher levels of hostility, and impaired insight (Czobor et al. 2015). Patients who resist treatment should be distinguished from those who are truly treatment-resistant. Addressing compliance to treatment and optimizing current treatment regimens, including the introduction with long-acting injectable antipsychotics, may enhance clinical outcomes (Jakovljević 2014).
- Concentration of APs was subtherapeutic in one-third of patients identified to have TRS (McCutcheon et al. 2015). Among patients with TRS who were given clozapine, more than quarter of them had clozapine levels below efficacy threshold (Rajkumar et al. 2013). Low levels of APs could be due to poor adherence, low dose, or pharmacokinetic issues. Although there is no convincing evidence for a strict relationship between drug concentrations and response, measurements of plasma levels may be useful in cases of inefficacy, or occurrence of severe adverse effects, even at low doses (Dold & Leucht 2014).
- Continuous psychosocial stressors, including poverty, poor housing, and inadequate social support may influence treatment outcomes. Patients with schizophrenia were reported to have pathological response to psychosocial stress task, in terms of sensitized dopaminergic response (Mizrahi et al. 2012). In assessing TRS, factors such as poor social environment and support, should be addressed (Hasan et al. 2012). Furthermore, treatment resistance was related to cumulative lifetime adversities (Hassan & De Luca 2015).

Treatment resistance might also be associated with biological changes, i.e. alterations in dopaminergic and glutaminergic systems, genetics, neurodegeneration and neuroinflammation.

Involvement of dopaminergic system

Striatal dopamine synthesis capacity in TRS was lower compared to patients in remission, and there were no differences between patients with TRS and healthy control (Demjaha et al. 2012). The lack of elevation in presynaptic striatal dopamine synthesis capacity in patients with treatment-resistant illness could provide an explanation for the ineffectiveness of antipsychotic treatment in this group (Demjaha et al. 2012). Since this study was cross-sectional (Demjaha et al. 2012), it is unknown whether dopamine synthesis capacity was initially not elevated, or it was the effect of drugs. However both treatment-resistant and remitted group were matched for antipsychotic dosage. Those patients were not receiving clozapine (Demjaha et al. 2012). Post-mortem study found a higher density of dopaminergic synapses in caudate nucleus in patients with good treatment response in schizophrenia, compared to those with TRS (Roberts et al. 2009). Schizophrenic patients with high dopamine release were more responsive to antipsychotic drugs than those patients who had dopamine levels lower than or comparable to that of healthy volunteers (Abi-Dargham et al. 2000). The larger number of dopaminergic synapses in treatment responsive patients may account for the higher levels of striatal dopamine in treatment responsive patients (Nakajima et al. 2015). These data indicate that patients meeting criteria for TRS may have a form (or forms) of the illness that are mediated beyond dopamine neurotransmission (Nakajima et al. 2015).

Dopamine supersensitivity psychosis (DSP)

Long-term antipsychotic treatment may lead to dopamine D2 receptor upregulation (Iyo et al. 2013), which, in turn, might result in both DSP and tardive dyskinesia. In animal models, dopamine supersensitivity occurs during long-term treatment with haloperidol, but not aripiprazol (Tadakoro et al. 2012). In DSP, tolerance develops to antipsychotic effects, in terms of worsening of psychosis in spite of regular treatment, or immediate occurrence/worsening of psychotic symptoms after decrease of drug dose. DSP was reported in more than half of patients with TRS (Suzuki et al. 2015). Risperidone long-acting injection improved symptoms in patients with both TRS and DSP, who were previously treated with high dose of oral APs (about 1000 mg of chlorpromazine equivalent) (Kimura et al. 2014). Interestingly, the consequent improvement was greater in patients with TRS who had DSP, compared to

those who did not have DSP (Kimura et al. 2014). Those findings add evidence to assumption that DSP occurs in a significant proportion of TRS, and that decreasing the level of dopamine D2 receptor blockade might alleviate symptoms of TRS. In turn, there would be no point in using high doses of APs in those patients

Involvement of glutaminergic system

Dopamine system does not exist in isolation, and the interaction between glutamate and dopamine has been widely documented (Nakajima et al. 2015). The glutamate hypothesis represents one of a number of alternative models of TRS, while acknowledging the limitations of dopaminergic theory in TRS (Nakajima et al. 2015). Patients with TRS had elevated anterior cingulate cortex (ACC) glutamate levels, compared to healthy volunteers in a small study (Demjaha et al. 2014). Furthermore, higher glutamate levels were reported in the ACC of first-episode patients who still had psychotic symptoms after at least 1 course of antipsychotic medication compared to those whose symptoms remitted (Egerton et al. 2012). In contrast to those studies, first-episode patients had increased total glutamate + glutamine (Glx) levels scaled to creatine in the dorsolateral prefrontal cortex (DLPFC), compared to patients with TRS resistant to clozapine (Goldstein et al. 2015). In the same study, the group with TRS taking clozapine had higher Glx levels in the putamen than the first-line responders or TRS resistant to clozapine (Goldstein et al. 2015). Those findings suggest that both nonresponders and treatment-resistant patients to APs have a range of abnormalities in glutaminergic system in different parts of the brain. Glutamate system might be a novel target for the treatment of TRS.

Genetic risk

While numerous studies have investigated different aspects of genetics of schizophrenia, only a few have focused on TRS. Among them, some studies regarded clozapine treatment as a proxy for antipsychotic treatment resistance (Zhang et al. 2013; Frank et al. 2015). Increased genetic loading for schizophrenia is also a risk factor for TRS (Frank et al. 2015). Genetic risk was assessed by measuring the polygenic risk score (Frank et al. 2015).

Among a set of 74 candidate genes suggested by the CATIE study, only the brain-derived neurotrophic factor gene (BDNF) was associated with antipsychotic treatment resistance. Among three single nucleotide polymorphisms, Val/Val genotype was less frequently represented in patients who received clozapine, compared to both Met/Val and Met/Met genotypes (Zhang et al. 2013). In another study, Met carriers of BDNF Val66Met polymorphism more frequently had poor response to olanzapine, compared to Val/Val genotype in patients with schizophrenia (Nikolac et al. 2014). However, testing 384 candidate gene loci related to the neurobiology of schizophrenia did not indicate any robust association with TRS (Teo et al. 2012). Finally, a post-mortem analysis reported that epigenetics, in terms of restricting the expression of genes, might also play a role in TRS (Chase et al. 2013).

Neurodegeneration

In spite of numerous imaging studies in schizophrenia, only a few structural and functional neuroimaging studies have investigated TRS (Nakajima et al. 2015). This is because the majority of investigations have focused on at risk mental state and first-episode schizophrenia, rather than on TRS (Nakajima et al. 2015). In a cross-sectional study, grey matter volumes were significantly smaller in patients with TRS, compared with both controls and responders to first-line treatment. In addition, patients resistant to clozapine showed significantly larger ventricular CSF volumes compared with controls and responders to first-line treatment. This grey matter loss was the most extensive in superior temporal gyrus (Anderson et al. 2015). In another study, patents with TRS had a widespread reduction in cortical thickness in frontal, parietal, temporal and occipital regions bilaterally (Zugman et al. 2013). Patients with TRS also had decreased thickness in the left dorsolateral prefrontal cortex (DLPFC), which was proposed as a putative marker for treatment resistance (Zugman et al. 2013). Compared to healthy controls, replicated findings to date include hypometabolism in the PFC hypermetabolism in the basal ganglia and structural anomalies in the corpus callosum of patients with TRS (for review, please see Nakajima et al. 2015).

Neuroinflammation

Due to emerging evidence regarding the important role of the blood-brain barrier, combined testing of serum and cerebrospinal fluid is likely to be more appropriate to answer this question than pure serum analyses (Steiner et al. 2015). Recently, determination of different antineuronal antibodies in TRS have been suggested (Steiner et al. 2015).

Poor premorbid social functioning, an insidious disease onset and an early age-at-onset (Frank et al. 2015), as well as longer duration of illness (Teo et al. 2013, Chanpattana & Sackeim 2010) were associated with poor treatment response. While TRS may be obvious early in treatment (within 6 months), in most cases it emerges later, following a series of episodes. It was reported that 14.4% patients who initially responded to treatment, met nonresponse criteria after relapse (Emsley et al. 2012). Furthermore, after each relapse, 1 in 6 subjects did not remit from the last psychotic episode (Wiersma et al. 1998). In this study continuous psychotic or negative symptoms gradually increased from 27% after first to 47% after forth episode respectively (Wiersma et al. 1998). Treatment resistance appears to be related to the stage of schizophrenia. Those findings might suggest DSP or neurodegeneration.

Treatment of TRS

Although resistant to treatment, patients with TRS need treatment. Target symptoms should be identified, in terms of persistent positive or negative symptoms, cognitive dysfunction with severe impairment, bizarre behaviour, affective symptoms, aggression/violence and suicidal behaviour, deficits in vocational and social functioning and a poor quality of life (Hasan et al. 2012). None less, clinicians should continue to be hopeful of positive change, and not view such patients nihilistically. No patient should be regarded as a 'lost cause', even though symptoms are unremitting (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines 2005).

Clozapine

Clozapine is currently the only antipsychotic which has indication for TRS. It is recommended as first-line treatment for TRS in all guidelines. More than 15 years ago, a randomised trial John Kane and colleagues investigated the effects of clozapine compared with chlorpromazine in patients with TRS (Kane et al. 1998). Benefits of clozapine relative to other APs in TRS have been confirmed in other studies and meta-analyses (Hasan et al. 2012). Even today, based on the current and still growing evidence, clozapine remains the gold standard (Dold & Leucht 2014) and first-line treatment in patients with TRS (Hasan et al. 2012). Clozapine was particularly effective against aggression and violence in patients with TRS (Frogley et al. 2012). Due to its unique antisuicidal properties, it was estimated that if all suitable patients with TRS received clozapine therapy, approximately 53 suicides could be avoided in the UK each year (Duggan et al. 2003).

However, despite advantages of clozapine, TRS remains one of the most important clinical challenges in the pharmacological management of schizophrenia (Dold & Leucht 2014). Clozapine is not a panacea for TRS.

Up to 70% of patients with TRS will have an inadequate response to clozapine and more interventions are needed. On the other hand, clozapine has poorer tolerability compared to other APs. It has common (sedation, constipation, sialorrhea, weight gain, metabolic syndrome, synus-tachycardia), as well as uncommon, but serious (agranulocytosis, seizures, myocarditis, ketoacidosis) adverse events (Lundblad et al. 2015). From those reasons, some patients discontinue clozapine even before it has reached target plasma concentration. Despite recommendations in clinical guidelines, and probably due to safety concerns, clozapine remains underutilized in patients with TRS (Warnez & Alessi-Severini 2014), and its use is often substantially delayed (Howes et al. 2012). Further important limitations of clozapine in comparison to other APs arise from the necessity of slow dose titration and weekly blood counts within the first 18 weeks of treatment (and subsequently every month) (Dold & Leucht 2014). There is also considerable variability among individuals in clozapine blood levels. For example, patients on clozapine doses from 100 to 650 mg/day, had 30-fold interindividual variability among its serum levels (Rajkumar et al. 2013). According to guidelines, dose range of 100–900 mg and a threshold clozapine level of 350 ng/ml is recommended (Suzuki et al. 2011, Hasan et al. 2012). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines recommend mean dosage of 400 mg/day clozapine and highlighted that some patients might respond to doses as low as 100–200 mg/day, whereas others may need doses of up to 900 mg/day (Hasan et al. 2012). Therefore, individual adjustment of clozapine dose is important, due to the high inter-individual variability in plasma levels (Rajkumar et al. 2013). Given the induction of clozapine metabolism by nicotine, cigarette smokers may require higher doses of clozapine, while abrupt cessation of smoking could lead to clozapine intoxication (Sagud et al. 2009). In addition, due to pharmacokinetic and pharmacodynamics properties of clozapine, twice daily rather than once daily dosing of clozapine is recommended (Procyshyn et al. 2014). The duration of an adequate trial with clozapine is considered to be 4 to 6 months (Canadian Psychiatric Association 2005).

Combination or augmentation of clozapine

In spite of general principle of "monotherapy before polytherapy" (Canadian Psychiatric Association 2005), some patients will benefit with combination or augmentation treatment. The options for patients with TRS resistant or intolerant to clozapine are limited (Hasan et al. 2012). The best evidence of efficacy was reported for ECT (Petrides et al. 2015). Augmentation of clozapine with ECT was effective in half of TRS patients, which is the highest response rate reported with any type of clozapine augmentation (Petrides et al. 2015). In recent review, 37.5-100% patients with the combination of clozapine and ECT improved in short-term (Grover et al. 2015). Given the clear benefits of clozapine in patients with TRS, a trial of clozapine will generally be indicated before treatment with ECT (Lehman et al. 2004). However, clozapine-ECT combination should be considered in patients with treatment-resistant schizophrenia who do not respond to clozapine (Grover et al. 2015).

A combination of clozapine and a second generation antipsychotic (SGA) should be considered for patients whose symptoms have not responded adequately to clozapine alone. From a pharmacological point of view, it seems auspicious to combine antipsychotic agents with low antidopaminergic properties such as clozapine with APs that are characterised by a particularly strong affinity to dopamine D2 receptors, such as amisulpride, sulpiride, haloperidol or risperidone (Dold & Leucht 2014). The combination of clozapine with risperidone (Hasan et al. 2012) or sulpiride (SIGN 2013) may offer some advantage. Combination of clozapine with aripiprazole can reduce antipsychotic-induced metabolic adverse effects.

Many drugs (APs, antidepressants, mood stabilizers and other agents) have been evaluated as CLZ add-on therapies without demonstrating convincing efficacy in TRS (Muscatello et al. 2014). A trial of clozapine augmentation with lamotrigine may be considered for those whose with an insufficient response to clozapine alone (SIGN 2013). Creative, instead of more dogmatic approach to treatment guidelines could advance everyday clinical practice (Jakovljević 2014).

APs other than clozapine

Uncertainty still exists which antipsychotic should be given when clozapine treatment is not tolerated or not effective (Dold & Leucht 2014). Switch to another SGA, preferentially olanzapine or risperidone, is recommended in case of intolerance/inefficacy of clozapine (Hasan et al. 2012). When switching drugs in TRS, gradual tapering is recommended, due to prevention of both destabilization of illness because of rapid withdrawal of previous drug, and adverse events due to rapid increase of the dose of new drug (SIGN 2013). The use of long-acting injectable APs can sometimes be a possibility to rule out non-adherence (Dold & Leucht 2014). Recent search of the Cochrane Schizophrenia Group's comprehensive Trials Register revealed that combinations of APs other than clozapine are underresearched (Sinclair & Adams 2014). While polypharmacy is prevalent in clinical practice, there are, however, only four studies investigating combinations of non-clozapine APs in TRS (total of 297 participants) (Sinclair & Adams 2014). However, in clinical practice, patients with TRS are very often treated with complicated regimens, usually with several APs in high doses, plus other medications, with limited benefit and many side effects. (Matei et al. 2014). In these cases, APs simply do not work (Matei et al. 2014). In the absence of a therapeutic response, clinicians may be tempted to increase the dose or add new medications (sometimes a second or third antipsychotic drug) (Matei et al. 2014). Palliative measures, such as sedation and sleep improvement, have been suggested in those patients with ultra-TRS, instead of high-dose polypharmacy which had no effect, but had a heavy burden of adverse effects (Matei et al. 2014). Long duration of illness or absence of affective symptoms were associated with poor response to combination of ECT and flupentixole in patients with TRS (Chanpattana & Sackeim 2010).

High doses of APs

Prescription of APs above the maximum licensed dose is frequent in clinical practice (Howes et al. 2012). While there is little convincing evidence that such off-label prescription has any therapeutic advantage, there is clear evidence for a greater side-effect burden and the need for appropriate safety monitoring (College report CR190 2014). In addition, high doses of APs may eventually result in DSP. Prescribing higher than maximum dosages of APs should be considered in patients with unusually low plasma levels during treatment with usual doses of APs. Drug plasma levels could be insufficient because of incomplete absorption and/or rapid metabolism, or there could be poor penetration across the blood–brain barrier. In those patients, poor response is due to insufficient dopamine D2 receptor blockade. While dopamine D2 receptor blockade is necessary, it may not be sufficient in the case of TRS. It can be speculated that prescription of high doses of APs to a subgroup patients with TRS who already have optimal plasma levels (which correspond to percentage of dopamine D2 occupancy) may alleviate psychotic symptoms by binding to receptors other than D2 receptors. Treatment with high doses may carefully be tried only after evidence-based strategies for TRS are exhausted (SIGN, 2013).

Other treatment

Other compounds (acetylcholinesterase inhibitors and β-blockers) have been investigated as augmentation of APs without demonstrating convincing efficacy in treating TRS. In general, there is no sufficient evidence to advise the general use of pharmacological augmentation strategies in treatment-resistant schizophrenia (Dold & Leucht 2014). However, nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, diclofenac, naproxen sodium or acetylsalicylic acid have the potential to improve psychopathology (for review, please see Hasan et al. 2012).

Interventions in TRS include not only pharmacological interventions but also psychological interventions. The most commonly evaluated psychotherapeutic treatments are cognitive behavioural therapy (CBT) (Sinclair & Adams, 2014). The review of 16 published articles from 12 randomized controlled trials found that CBT was associated with robust improvements in the positive symptoms of psychotic disorders (Burns et al. 2014). Optimal management requires the integration of medical and psychosocial interventions (Canadian Psychiatric Association 2005).

Also, evidence for augmenting APs with antidepressants seems lacking as no individual drug had more than one study and these trials included only 244 participants in total (Sinclair & Adams 2014). The authors concluded that the great majority of trials in this area were grossly underpowered to find any clinically important outcome (Sinclair & Adams 2014).

Recent study reported that transdermal estradiol was effective as adjunctive therapy for premenopausal women with TRS, particularly for positive symptoms (Kulkarni et al. 2015). However, potential side effects, particularly those associated with long-term treatment, should also be taken into account. Based on involvement of glutamate system in TRS, glutamate pathways are promising sites for intervention. Different glutamate-modelling agents (glycine, D-serine, D-cycloserine, ampakine) did not show consistent evidence of

efficacy, as add on treatment to APs, in TRS. Preliminary conclusions regarding favourable effects of clozapine augmentation with glutamate antagonists (lamotrigine, topiramate and memantine) are based on a small number of trials. Notably the memantine trial showed impressive effect sizes. It is supposed to be effective due to upregulation of NMDA receptors, which, in turn, are dysfunctional in schizophrenia (for review, please see Veerman et al. 2014). Therefore additional studies in larger samples are needed.

Conclusion

In spite of 60 years of psychopharmacology, TRS remains an enormous challenge. The aetiology of TRS appears to be heterogeneous, complex and under investigated. Schizophrenia is a continuum. Probably there is no simple explanation of why some patients completely recover after single episode, whilst others have progressive outcome with severe deterioration. More well-designed trials are required to establish true efficacy and safety of current regimens, including CLZ augmentation strategies. Given the severity and complexity TRS, there is an urgent need for better treatment. Different treatment strategies beyond dopamine are being investigated, such as immunotherapy, glutaminergic agents and hormonal treatment. So far, careful use of clozapine remains the first-line treatment. In those who are resistant or intolerable to clozapine, there are several pharmacological options, with weak or moderate evidence of efficacy. According to current knowledge and wide-spread clinical practice, TRS is difficult to treat. However, there is a room for optimism. Firstly, schizophrenia has highly variable presentation and course, and patients with TRS are very heterogeneous group. Secondly, given the ever-increasing influx of new data, new treatment for TRS will likely emerge. Thirdly, prevention of TRS is probably the best treatment, at least in some patients. We hypothesize that early intervention, identification of psychosocial stressors, measures to improve adherence, maintenance treatment with the lowest effective dose of APs and monitoring of early signs of relapse, might help prevent treatment-resistance. Individual treatment in each patent with TRS is strongly advised in all guidelines and expert opinions.

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