HHS Public Access

Author manuscript

Neurobiol Dis. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Neurobiol Dis. 2019 November ; 131: 104257. doi:10.1016/j.nbd.2018.08.016.

Treatment Resistant Schizophrenia: Clinical, Biological, and Therapeutic Perspectives

Frederick C. Nucifora Jr., PHD, DO, MHS[a,*], **Edgar Woznica, MD**[a], **Brian J. Lee**[a], **Nicola Cascella, MD**[b], **Akira Sawa, MD, PHD**[a]

[a]Department of Psychiatry and Behavioral Sciences, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD, 21287, USA

[b]Sheppard Pratt Hospital, 6501 N. Charles Street, Baltimore, MD 21204

Abstract

Treatment resistant schizophrenia (TRS) refers to the significant proportion of schizophrenia patients who continue to have symptoms and poor outcomes despite treatment. While many definitions of TRS include failure of two different antipsychotics as a minimum criterion, the wide variability in inclusion criteria has challenged the consistency and reproducibility of results from studies of TRS. We begin by reviewing the clinical, neuroimaging, and neurobiological characteristics of TRS. We further review the current treatment strategies available, addressing clozapine, the first-line pharmacological agent for TRS, as well as pharmacological and nonpharmacological augmentation of clozapine including medication combinations, electroconvulsive therapy, repetitive transcranial magnetic stimulation, deep brain stimulation, and psychotherapies. We conclude by highlighting the most recent consensus for defining TRS proposed by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group, and provide our overview of future perspectives and directions that could help advance the field of TRS research, including the concept of TRS as a potential subtype of schizophrenia.

Keywords

Schizophrenia; Treatment-Resistant; Brain Imaging; Neurobiology; Genetics; Clozapine; Dopamine; Glutamate; ECT; rTMS; DBS; CBT

Introduction

Schizophrenia is a severe, lifelong mental disorder affecting around 1% of the world's population (Saha et al., 2005). The disease is characterized by positive, negative, and cognitive symptoms, and can lead to significant functional impairment. Medication

*Correspondence: nucifora@jhmi.edu, Department of Psychiatry and Behavioral Sciences, 600 N. Wolfe Street, Meyer 3-161, Baltimore, MD 21287, (Phone) 410-614-1780, (Fax) 410-9550753.

Declaration of Interest: the authors have no competing interests to declare.

treatment became available with the development of chlorpromazine in the 1950s, and antipsychotic medication development continues to this day. Unfortunately, not all patients respond to antipsychotic medications. Overall estimates suggest that one-fifth to one-half of patients have treatment resistant schizophrenia (TRS) (Elkis, 2007; Essock et al., 1996; Lieberman 1999; Lindenmayer, 2000). Around 30–60% of these patients respond to clozapine (Juul-Povlsen et al., 1985; Kuha and Miettinen, 1986; Lieberman et al., 1994; Lindström, 1988; Meltzer, 1989). While defining TRS has been a major challenge in the field and studies have used different criteria, most accept the failure of two different antipsychotics as a minimum criterion.

TRS patients have poorer outcomes when compared to other patients with severe mental illnesses. They also have worse achievement of functional milestones of everyday living, including lower marriage rates, and higher rates of residence in facilities (Iasevoli et al., 2016). Furthermore, persistent positive, negative, and cognitive symptoms lead to worsened social functioning (Burton et al., 2013; Galderisi et al., 2014) and long-term disability (Dickinson et al., 2006; Iasevoli et al., 2016; Rocca et al., 2014; Rosenheck et al., 2006; Twamley et al., 2002). Finally, TRS costs 3–11 fold more than schizophrenia patients in remission, adding an estimated $34 billion to the US medical system (Kennedy et al., 2014).

This review presents an overview of the significant findings in TRS compared to patients that respond to antipsychotic treatment, known as non-treatment resistant schizophrenia (non-TRS), focusing on the clinical profile, neuroimaging, neurobiology, treatment options, and guidelines for defining TRS, with the purpose of providing neurobiologists with an introduction to the field. This overview should help researchers formulate questions to advance the understanding and management of TRS, and how to consider TRS in the context of a heterogeneous disease such as schizophrenia. A critical question in the field of TRS research is whether TRS represents a more severe form of schizophrenia, with greater symptomatology but similar pathophysiology, or if it represents a distinct subtype of schizophrenia, with a different symptom profile and different pathophysiology compared to non-TRS patients. The purpose of this review is not to provide a definitive answer to this question, since this is a relatively new concept and much more research is needed for a conclusive answer. However, by reviewing the current literature focusing on replicated data addressing the differences between TRS and non-TRS, we seek to provide some insights into the growing idea that TRS is a subtype of the illness.

Background

To increase the understanding of TRS, investigators have sought to determine if patients with TRS differ in their clinical presentation or underlying biology compared to non-TRS.

Clinical Profile

A number of clinical characteristics have been associated with TRS, including poor premorbid social functioning, longer duration of untreated psychosis (Schennach et al 2012), earlier age of onset (Hollis, 2000; Reichert 2008), and a history of drug or alcohol abuse (Gupta et al 1996). However, these studies looked at predictors of non-response and did not directly compare TRS to non-TRS.

Systematic reviews have identified only a limited number of papers comparing the clinical characteristics of TRS to non-TRS patients (Gillespie et al., 2017; Seppälä et al., 2016), yet these papers yield important insights. Multiple studies have shown that TRS patients are more often of European descent (Meltzer et al., 1997; Teo et al., 2013) and of the paranoid subtype (Teo et al., 2013, Wimberley et al. 2016). Two studies indicated an earlier age of onset (Meltzer et al., 1997; Wimberley et al., 2016), but a third found that duration of illness may be a confounder (Teo et al., 2013). Importantly, they found that male sex is not associated with TRS (Meltzer et al., 1997; Teo et al., 2013; Wimberley et al., 2016), which is surprising since males are at greater risk of developing schizophrenia overall (Thorup et al., 2007).

In a prospective study of a Brazilian population, patients with onset of symptoms within 5 years of the study and no regular antipsychotic medication use were randomized to a first or second generation antipsychotic (not including clozapine). If patients failed two antipsychotics, they were considered treatment resistant. Using the Positive and Negative Symptom Scale (PANSS) as the main outcome measure, the authors determined that a lower baseline PANSS score was predictive of TRS (Kayo et al, 2012).

Perhaps the most extensive study to date exploring clinical characteristics of TRS was a population-based cohort study using the Danish national registry data to compare TRS patients to all other patients diagnosed with schizophrenia over a ten-year period (Wimberley et al., 2016). They found that compared to non-TRS, TRS patients are more likely to have a comorbid personality disorder, a more rural residence, more schooling, and a previous suicide attempt. Since past evidence suggests that residing in an urban area increases the risk of schizophrenia (Vassos et al., 2012), their finding that TRS is more often found in less urban areas was surprising. They interpreted their result as reflecting either geographic variability in prescribing guidelines or a difference in pathophysiology between TRS and non-TRS (Wimberley et al., 2016). Furthermore, at the time of their first schizophrenia diagnosis, TRS patients are more likely to be inpatient, to have required more psychotropic medications in the previous year, and to have spent more than 30 days in a psychiatric hospital in the previous year. While this study found potentially new insights into the clinical aspects of TRS compared to non-TRS, these results will need replication in other populations to determine if they are generalizable to TRS beyond Danish descent.

Heritability may also separate TRS from non-TRS, since studies suggest that TRS may be a more familial form of schizophrenia. A study that directly compared rates of schizophrenia in first-degree relatives of TRS to non-TRS patients showed higher morbidity risk of schizophrenia among first degree relatives than non-TRS patients and healthy controls (HC) (Joober et al., 2005). This is consistent with other studies that have identified a history of family psychosis as a predictor of TRS, but did not directly compare TRS to non-TRS. (Crespo-Facorro et al., 2013; Hassan and De Luca, 2015; Malaspina et al., 2000; Murray and Van, 1998)

There are also potential differences in cognitive functioning between TRS and non-TRS. The Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) study found that the correlation between overall cognition and positive symptoms was near zero, but several

other studies that compared the cognitive profile of TRS and non-TRS patients suggest that specific cognitive markers of TRS exist (Woodward and Meltzer, 2010). Two studies have found that TRS patients have greater impairment in verbal learning and memory (Joober et al., 2002; de Bartolomeis et al., 2013). Frydecka et al. demonstrated greater impairment in processing speed and executive functioning (Frydecka et al., 2015) even when controlling for the anticholinergic effects of medication as well as for psychopathology including negative symptoms, which are mildly correlated with cognitive functioning (Woodward and Meltzer, 2010). These two confounders may help explain some of the conflicting results in the field (Moustafa et al., 2016), and further research may confirm that TRS has a specific neurocognitive profile.

In summary, studies have identified several clinical differences between TRS and non-TRS. Unfortunately, none of these findings alone can predict TRS diagnostically. There is other clinical evidence to support TRS as a subtype of schizophrenia, such as a lack of association with male sex and urban dwelling, which may distinguish these patients from non-TRS. In addition, the heritability data suggests a genetic vulnerability for a TRS subtype. However, studies also identify differences that relate to severity. Studies exploring the clinical findings in this section as a whole and in a large sample size may help to distinguish a set of clinical parameters that could potentially predict which patients will develop TRS. This would be of great value to the field, and could help determine which patients may benefit from early intervention such as early use of clozapine.

Future research into the biology of TRS may have significant implications for the diagnosis and treatment of TRS and schizophrenia in general. Therefore, we highlight some recent studies in neuroimaging and neurobiology, which may inform our conceptualization of TRS and guide further investigation.

Neuroimaging

In addition to the clinical profile, researchers have used imaging studies to compare the brain structure and chemistry of TRS and non-TRS patients. Two recent systematic reviews (Mouchlianitis et al., 2016; Nakajima et al., 2015) reported the following replicated results. Patients with TRS, compared to non-TRS, have greater gray matter reduction, especially in frontal regions (Anderson et al., 2015; Kubera et al., 2014; Lawrie et al. 1995; Mitelman et al., 2005; Quarantelli et al., 2014); increased white matter volume (Anderson et al., 2015; Molina et al., 2008); reduced striatal dopamine (DA) synthesis (Bartlett et al., 1998; Demjaha et al., 2012); and elevated glutamate (Glu) concentration in the anterior cingulate cortex (Demjaha et al., 2014; Mouchlianitis et al., 2016). Finally, the TRS patients that respond to clozapine, when compared to non-TRS patients, have increased concentrations of glutamate and glutamine in the putamen and decreased concentrations in the dorsolateral prefrontal cortex (DLPFC) (Goldstein et al., 2015; Mouchlianitis et al., 2016). While these findings have been replicated, more research is necessary to determine if they are robust enough to create a neuroimaging profile able to distinguish between TRS and non-TRS patients, which would have great clinical utility.

Studies of patients with schizophrenia but not TRS specifically have found elevated striatal DA synthesis capacity, DA release, and baseline DA levels when compared to HC (Abi-

Dargham et al., 2000; Fusar-Poli and Meyer-Lindenberg, 2012; Howes et al., 2007; Howes et al., 2012; Laruelle et al., 1996; Nakajima et al., 2015). Importantly, increased striatal synaptic DA has been linked to antipsychotic response (Abi-Dargham et al., 2000), with 50% occupancy of the D2 dopamine receptor necessary to achieve clinical response (Abi-Dargham and Laruelle, 2005; Demjaha et al., 2012). However, studies of TRS patients found treatment resistance even after 95% occupancy of D2 receptors (Coppens et al., 1991). Demjaha et al. found higher striatal DA synthesis capacity in non-TRS patients than TRS patients and HC, and furthermore found no difference in DA synthesis capacity between TRS and HC (Demjaha et al., 2012). Kim et al. recently extended this work by studying TRS patients who had responded to clozapine, thereby removing the confounder of comparing highly symptomatic TRS patients to less symptomatic non-TRS patients (Kim et al., 2017). TRS patients responsive to clozapine again were shown to have lower DA synthesis capacity than non-TRS, suggesting that a difference in DA synthesis capacity is a trait marker of TRS (reflecting different pathophysiology) rather than a state maker (related to symptom severity). These preliminary findings indicate the possibility that schizophrenia patients who respond to antipsychotics have higher levels of striatal DA synthesis, while TRS patients may not respond due to having physiologic levels of DA, and that Glu elevation and its associated excitotoxicity may instead account, at least in part, for the schizophrenic syndrome in TRS. This hypothesis, however, requires further validation.

In summary, numerous imaging studies have compared TRS and non-TRS patients, but only a few results have been replicated. An exciting early hypothesis from the data indicates that TRS patients may have DA levels comparable to HC as well as elevated Glu, explaining in part why these patients are resistant to anti-dopaminergic medications. Furthermore, these imaging studies indicate that TRS and non-TRS may possibly arise from different pathophysiological mechanisms, reflected by differing brain changes, suggesting that TRS may represent a subtype of schizophrenia. Further research validating this may have significant clinical implications by yielding imaging profiles that could confirm or even predict TRS vs. non-TRS. However, neurobiological studies are likely necessary to clarify causal mechanisms underlying the possible pathophysiological differences between TRS and non-TRS.

Neurobiology

In addition to the clinical and imaging profiles, researchers have investigated possible neurobiological differences between TRS and non-TRS. A major issue in the field is the great variability in inclusion criteria for defining TRS patients. Clozapine treatment is a more widely applied criterion that could be used as a proxy for TRS, since it is the only medication with a Food and Drug Administration (FDA) indication for TRS, and typically patients on clozapine have not responded to at least two other antipsychotics. Therefore, genetic differences associated with clozapine treatment and response, assessed through pharmacogenetics, pharmacogenomics, and gene expression profiling, could yield valuable insights into genetic differences underlying TRS.

Pharmacogenetics—Pharmacogenetic studies of clozapine have mainly focused on the neurotransmitters systems thought to be related to clozapine’s efficacy. Single nucleotide

polymorphisms (SNPs) in the *DRD1* gene, encoding the D1 receptor; *DRD2* gene, encoding the D2 receptor; *DRD3* gene, encoding the D3 receptor; and the 5-HT receptor system (HTR2A, HTR2C, and HTR6) have been identified as potentially related to response to clozapine. However, many studies show conflicting results likely due to different definitions of clozapine responders (Leucht et al., 2013), as well as the different ethnicities of their subjects (Akamine et al., 2017; Lee et al., 2012; Lin et al., 1999, Xu et al., 2016). There are several reviews in the literature that address this topic in more detail (Arranz et al., 1998; Lett et al., 2012; Sriretnakumar et al., 2015; Zhang and Malhotra, 2013).

Pharmacogenomics—Pharmacogenomic studies provide an unbiased approach to understand the mechanisms of antipsychotic response, since they use genome-wide data instead of a candidate gene approach, and can provide insights into TRS. While schizophrenia is likely caused by a combination of genetic and environmental risk factors (Brown, 2011; Kannan et al., 2013; McGrath et al., 2013,), the genetic contribution is often caused by many common genetic variants each with a small effect size (International Schizophrenia Consortium, 2009). The largest GWAS to date (36,989 cases and 113,075 controls), identified 108 genome wide significant loci, supporting the polygenic nature of the disease (ref). In addition, rare structural variants (Mowry& Gratten, 2013) and copy number variants (CNV) have been associated with schizophrenia and clinical traits (Yeo et al., 2013; Martin et al., 2015). Different subtypes of schizophrenia may be more related to the genetic burden than to environmental interactions. Some studies suggest that TRS may be more influenced by genetic vulnerabilities and the hereditary studies described above further suggest this possibility. Studies have looked at polygenic risk scores (PRS) since they can capture the genetic load of trait-associated alleles across many loci (Euesden et al., 2015; Wray et al., 2007), using SNPs associated with a phenotype of interest from genome-wide association study (GWAS) samples and creating a sum of their phenotype-associated alleles (Levine et al., 2014; Wray et al., 2007). PRS thus gives an approximation of the genetic risk burden, with a higher PRS indicating a greater disease risk. In addition, studies have looked at rare duplications and deletions related to TRS and provide some important insights.

Several recent studies have tried to determine if a greater genetic burden equates to a greater likelihood of developing TRS. All of these studies used clozapine treatment as a proxy for TRS. Frank et al. (2015) compared patients with a history of clozapine treatment to clozapine-naive patients, using the risk alleles identified from a GWAS of schizophrenia, and showed that patients with TRS have higher PRS. They also showed by a *post hoc* analysis that a positive family history of schizophrenia was significantly associated with increased PRS in the overall sample. Ikeda et al. (2015) used PRS to compare responders to non-responders and found a significant enrichment of risk alleles in TRS patients. A study by Ruderfer et al. (2016) demonstrated that increased genetic risk variants track with clozapine treatment, using the significant genomic regions identified from the GWAS by the Schizophrenia Psychiatric Genomics Consortium (PGC) as risk loci (Psychiatric Genomics Consortium, 2014). They found that 347 antipsychotic gene targets were enriched for singleton disruptive mutations in the TRS group compared to the non-TRS. They also saw enrichment in antipsychotic efficacy genes with singleton disruptive mutations from the PhamGKB cohort. Furthermore, Martin and Mowry (2016) showed that there is an increased

burden of rare genome wide total copy number duplications in TRS and an association between fewer years of schooling and earlier age of onset with TRS. However, like the recent Danish study (Wimberley et al., 2016), they did not find a significant association between PRS and TRS in their study population. Many of the sample sizes in these studies were small, so studies with larger sample sizes are important to help determine the relevance of PRS and rare variants for TRS.

Beyond PRS and rare mutations and deletions, GWAS data related to clozapine treatment have highlighted specific alleles as genetic risk factors, again using clozapine as a proxy for TRS. The CLOZUK (Hamshere et al., 2013) study identified three new loci that meet genome-wide significance, in addition to demonstrating an overlap of about 47% in the SNPs previously reported by the PGC. In another genome-wide study, there was a significant association between clozapine response and a genetic variant in *D2DR,* which was also highlighted by the PGC GWAS (Huang et al., 2016).

Gene expression profiling—Finally, the biological differences between TRS and non-TRS can be determined at the gene expression level, using unbiased high-throughput methods such as microarray and RNA-seq. As an example, Lee et al. (2017) performed the first gene expression study of human brain data analyzing the effect of clozapine, and found specific genes and pathways regulated by clozapine compared to other antipsychotics. Not only could this data provide insights into TRS indirectly, since clozapine is used as a proxy for TRS in pharmacogenetic and pharmacogenomic studies, but further gene expression studies could directly assess TRS. Experiments such as these could identify genes and pathways that are differentially regulated in TRS, and possibly determine specific mechanisms leading to the development of TRS. This would provide strong evidence of a subtype as well as tailored therapeutic targets.

The neurobiology of schizophrenia is complicated in part due to the heterogeneity of the illness. Understanding the underlying genetics of schizophrenia and specifically TRS is critical. Overall, the studies described in this section suggest a larger or different genetic predisposition for TRS and could support the hypothesis of a specific subtype related to TRS. While there is likely a continuum of illness severity, there may be a threshold where a greater genetic burden leads to a different pathophysiology underlying the subtype of TRS. The data described in this section together with the hereditary data suggest that TRS may be a more genetic form of the illness. However, environmental influences cannot be ruled out and is an area that is under-explored in the literature.

Taken together, there is clinical, imaging, and biological evidence that TRS represents a distinct subtype of schizophrenia. Furthermore, the treatment of TRS patients is guided by different strategies compared to non-TRS patients, of which we will now give an overview.

Treatments

While understanding the clinical and biological aspects of TRS are important, finding effective treatment options is critical to patients and their wellbeing. At present, treatment

options are limited but fall into three categories: medications, brain stimulation, and psychotherapy.

Medications

Clozapine—The only medication with an FDA indication for TRS is clozapine. Clozapine has been shown to be superior to all other antipsychotics in multiple studies and meta-analyses, though a recent network meta-analysis has challenged these results (Samara et al., 2016).

The first study to show that clozapine is superior to all other antipsychotics was conducted by Kane et al. and led to FDA approval. This study (Kane et al., 1988) was a multicenter clinical trial comparing clozapine to chlorpromazine in patients who failed treatment with haloperidol. The authors showed that 30% of patients on clozapine compared to 4% on chlorpromazine had significant improvements in their symptoms. This study was important because it showed that clozapine could successfully treat TRS, since all the subjects had failed at least two antipsychotics before randomization. The study also demonstrated clozapine's superiority over the first generation or "typical" antipsychotics. Later meta-analyses have corroborated clozapine's superiority over first generation antipsychotics (Chakos et al., 2001; Siskind et al., 2016)

Two pivotal prospective effectiveness studies demonstrated clozapine's superiority among the second generation or "atypical" antipsychotics. The first trial, the Clinical Antipsychotic Trial of Intervention and Effectiveness (CATIE) phase 2 investigation, randomized patients who had failed to respond to one of the four atypical antipsychotics used in the CATIE phase 1 study (risperidone, quetiapine, ziprasidone, or olanzapine) to clozapine or one of three other medications they had not taken (risperidone, quetiapine or olanzapine) (McEvoy et al., 2006).

The study showed superior results in time to discontinuation (the primary outcome) and less discontinuation by the end of the study in patients receiving clozapine compared to quetiapine, risperidone, or olanzapine. In addition, the patients on clozapine showed significant improvement in their total PANSS scores at three months compared those on quetiapine or risperidone (but not olanzapine).

The second study, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (Lewis et al., 2006), examined patients with TRS and randomized them to clozapine or either risperidone, olanzapine, quetiapine, or amisulpride. This study showed that patients on clozapine had a significant improvement in PANSS total score at one year follow up. Patients also showed a trend towards improvement in Quality of Life scores compared to the other antipsychotics. In addition, at three months, patients on clozapine reported greater improvement in their overall mental health compared to the other atypical antipsychotics.

Meta-analyses of antipsychotic medications in the short-term treatment of non-TRS patients substantiate clozapine's superiority (Siskind et al., 2016). Leucht et al. demonstrated clozapine's superiority to 14 other antipsychotics by utilizing a Bayesian-framework,

multiple-treatments meta-analysis of randomized controlled trials (RCTs) to compare antipsychotics and placebo in the acute treatment of schizophrenia (Leucht et al., 2013). Using this method they showed that clozapine is the most efficacious antipsychotic, and the only medication approved in the United States to separate from all other antipsychotics in efficacy.

Specifically in TRS, meta-analyses of antipsychotic medications have shown clozapine's superiority over first generation antipsychotics (Chakos et al., 2001; Siskind et al., 2016). However, recent network meta-analysis (NMA) of all antipsychotics in TRS failed to find clozapine to be superior to the second generation antipsychotics (Samara et al., 2016) included in the study. The authors and an accompanying editorial (Kane and Correll, 2016) noted several reasons why clozapine may not have shown superiority in this study. One, the study relied on randomized and double-blinded control studies which may have a sampling bias towards less ill individuals. Two, they also were unable to include three large efficacy studies, including the CATIE and CUtLASS studies described above, because the clozapine arm was open label or unblinded and this did not meet the inclusion criteria of their NMA. Due to monitoring and side effects, it is difficult to blind clozapine treatment. Three, there is no standard definition of TRS, as will be discussed in the TRRIP section below, creating heterogeneity even within TRS studies. Four, there may have been attrition and reporting bias in some studies included in the NMA. Five, the average clozapine dose was lower in the NMA than in previous studies. And six, the effect of previous antipsychotic treatment for patients on clozapine cannot be ruled out.

Thus, the advantage of clozapine is its demonstrated superior efficacy among first generation antipsychotics, which includes benefit in domains other than positive symptoms such as negative symptoms, suicidality, violence, and quality of life (Meltzer et al., 2003; Glazer and Dickson, 1998). Further studies are necessary to draw firm conclusions regarding clozapine and second generation antipsychotics, possibly including more severely ill patients in the studies. Clozapine's adverse effects are also well known, most notably the rare but life-threatening risk of agranulocytosis, which has led to requisites for use (such as enrollment in a national registry and weekly blood monitoring) that have limited its utilization. Moreover, up to 30% of TRS patients do not respond to clozapine, or any other medication (Meltzer 1992; Lieberman et al., 1994). It is possible that DA antagonism is not directly related to the pathophysiology of TRS and this could explain the poor response rates. Evidence from neuroimaging suggests that Glu could be more involved in TRS, but interestingly glutamatergic agents have not shown promising results in treating TRS. This could be either because Glu is not directly related to symptoms in TRS or, as described above, the heterogeneity of schizophrenia is so diverse that response is not identified when studying schizophrenia in general. Furthermore, negative and cognitive symptoms may be a prominent feature of the illness and also do not respond well to antipsychotic medication. Experiments to understand the mechanisms beyond neuroreceptor binding are critical to understanding the mechanism of schizophrenia and TRS. Unbiased gene expression profile experiments as described in this review could help to identify novel therapeutic targets.

Clozapine Augmentation—Despite the superior efficacy of clozapine, up to 30% of patients do not respond to clozapine, and thus strategies to treat these patients have mainly

focused on augmenting clozapine with other antipsychotics or non-pharmacological modalities. Thus far, the results of adding a second pharmacological agent have been modest. The most commonly used strategy is the addition of a second antipsychotic (Porcelli et al., 2012). A meta-analysis of 14 randomized, placebo-controlled, double-blind studies of multiple typical and atypical antipsychotics found a small benefit (effect size −0.239, CI −0.45, −0.026, P=0.028) (Taylor et al., 2012). Risperidone is the most studied antipsychotic augmentation medication since some researchers hypothesized that clozapine's weak D2-antagonistic properties would be enhanced by risperidone's highpotency D2 blockade (Freudenreich and Goff, 2002; Kontaxakis et al., 2006; Porcelli et al., 2012). Results of a recent meta-analysis of five RCTs however showed no benefit for clozapine augmentation with risperidone (Porcelli et al., 2012). Moreover, the addition of a second antipsychotic also increases the risk of side effects (Englisch and Zink, 2012; Porcelli et al., 2012), and thus may not be the most promising strategy for TRS.

Augmentation with a mood stabilizer has also shown limited results. In a meta-analysis of 5 RCTs, clozapine augmented with lamotdrigine showed decreased total symptoms based on the PANSS or Brief Psychiatric Rating Scale (BPRS) (standard mean difference 0.57, CI 0.25–0.89, $p<0.001$) (Tiihonen et al., 2009). However, a later meta-analysis of the same studies noted an outlier, and after removal of this outlier (Zoccali et al., 2007) the results were no longer significant (Sommer et al., 2012). Topiramate has also been used to augment clozapine but RCTs and meta-analyses do not show strong support for this strategy (Sommer et al., 2012).

For augmentation with antidepressants, citalopram, fluoxetine, fluvoxamine, and mirtazapine have been studied in RCTs. However, only citalopram showed improvements in total symptoms and negative symptoms in one small study (Sommer et al., 2012).

Glutamatergic agents such as CX 516, D-cycloserine, D-serine, glycine, and sarcosine have also been studied, but have not shown promising results (Sommer et al., 2012). Furthermore, tetrabenazine, a vesicular monoamine transporter (VMAT-2) inhibitor, has been used as an augmenting agent but also failed to demonstrate improvement in symptoms (Remington et al., 2012).

In summary, augmenting clozapine with psychotropic medications may be advantageous because of the relative ease of clinical implementation compared to involving nonpharmacological modalities. However, results for any psychotropic medication have been modest at best. It is possible that focusing on neurotrasmitter systems is not the most promising way to address TRS. For the most part, all of the medications used to treat and augment schizophrenia are based on neuroreceptor systems such as DA, serotonin, and Glu. Experiments that determine what downstream genes and pathways are most relevant could lead to better therapeutic targets. There may be specific pathways amenable to treatment based on TRS compared to non-TRS, or positive compared to negative symptoms, and this further highlights the need for studies to determine if TRS is truly a distinct subtype of schizophrenia and how to best define this subtype.

Importantly, there is a high medication non-compliance rate in schizophrenia (Andrews et al, 2017; Cramer and Rosenheck, 1998; Haddad et al., 2014), which complicates the implementation of multiple medications. Furthermore, polypharmacy entails a greater risk of adverse effects than monotherapy, supporting the exploration of non-pharmacological augmentation strategies.

Brain Stimulation Procedures

Since the results of augmenting clozapine with other medications have been modest, researchers have also explored the utility of brain stimulation procedures such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS) in TRS patients.

Electroconvulsive Therapy—ECT has been administered to schizophrenia patients since the 1930s (Endler, 1988). Although it is now mainly indicated for refractory mood disorders, studies have continued to evaluate the effect of augmenting antipsychotic medications with ECT for TRS. A 2003 double-blinded study of TRS patients reported significant improvement in the group receiving 6 rounds of ECT augmentation of chlorpromazine, but not in the sham-ECT group (Goswami et al., 2003). A 2005 Cochrane review identified 9 trials and found greater clinical improvement after ECT compared to placebo or sham-ECT (Tharyan and Adams, 2005). Zheng et al. (2016) noted that RCTs of ECT augmentation of non-clozapine antipsychotics have yielded conflicting results, but their meta-analysis of 11 such studies indicates that ECT augmentation causes more symptomatic improvement than antipsychotic monotherapy, but also more headache and memory impairment.

In reports comparing clozapine, clozapine and ECT, or ECT alone in TRS patients, all three interventions led to improvement, with some evidence that combination of clozapine and ECT has synergistic effects (Kupchik et al., 2000; Masoudzadeh and Khalilian, 2007). A metaanalysis by Lally et al. (2016) found that 66% of patients in 5 studies responded to clozapine with ECT augmentation (with a mean of 11 treatments), with 32% reporting relapse after ECT and 14% reporting adverse effects such as memory impairment. Of these, only one study (Petrides et al., 2015) was a blinded RCT.

This study, conducted by Petrides et al. (2015), is a prospective randomized study of patients with clozapine resistance (defined as persistence of symptoms after at least 12 weeks on clozapine with an adequate blood level) with a crossover design. Over 8 weeks, 19 patients were treated with clozapine alone and 20 treated with clozapine augmented with bilateral ECT (mean of 16 treatments). Of the latter group, 50% showed response (defined as ≥40% symptom reduction based on psychosis subscores of the BPRS and the Clinical Global Impressions scale) and 60% showed a response of ≥20% symptom reduction. No patients in the former group reported response, and so all 19 were then treated with clozapine and ECT for another 8 weeks (mean of 14 treatments), leading to 47% responding. Posthoc analyses showed that the ECT group had significantly lower psychosis subscores from the third week to the end of the trial, but there were no significant differences in negative symptoms. There were no significant differences between the groups in adverse events, except for one patient in the ECT group who was removed for clinical concern for seizure activity (but not

confirmed by electroencephalogram) and two occasions when ECT was postponed due to mild confusion. However, neither group showed significant change in global cognition (assessed by Mini-Mental Status Exam) after the trial.

Thus the advantages of ECT include its extensive use in treating mood disorders, the demonstration of efficacy for clozapine-resistant patients by a blinded RCT, and the potential for synergistic effects for combining clozapine with ECT. However, it has disadvantages including demonstrated adverse effects (such as memory impairment), and unclear benefit for negative symptoms. Patients also undergo anesthesia which carries some risks, and require several treatments as well as possibly maintenance ECT to achieve lasting results.

Repetitive Transcranial Magnetic Stimulation—As the optimal techniques are being developed for rTMS to treat a wide variety of psychiatric disorders, researchers have investigated its utility in specific symptoms of TRS (Miyamoto et al., 2014). Currently, given the need to place the electromagnetic coil over a small surface area, the research has focused on which area and technique to use for specific symptoms, such as positive and negative, rather than for all symptoms.

To treat persistent auditory hallucinations (AH) that have not responded to two different antipsychotic medications, researchers have applied rTMS to the left tempoparietal cortex (leTPC) (Otani et al., 2014; Rosenquist et al., 2014). The leTPC was chosen due to a previous positron emission tomography study finding activation in this region during AH (Silbersweig et al., 1995), its central role in speech perception (Benson et al., 2001; Fiez et al., 1996; Hoffman et al., 2003; Ojemann, 1978), and its proximity to the skull allowing for the application of rTMS (Hoffman et al., 2003). Further support for applying rTMS to the leTPC came later from a functional magnetic resonance imaging study which demonstrated that rTMS directed at the leTPC decreased cerebral blood flow to other areas implicated in AH, including the primary auditory cortex, left Broca's area, and cingulate cortex (Kindler et al., 2013; Rosenquist et al., 2014). Given the activation properties of the leTPC, researchers have applied low-frequency (1Hz) TMS to achieve an inhibitory effect (Rosenquist et al., 2014).

The first sham-controlled trial found that 75% (9/12) of patients in the active phase vs. 17% (2/12) in sham phase had a 50% reduction in AH (X^2=8.22, P=0.004) (Hoffman et al., 2003). A subsequent meta-analysis of 17 randomized, double blind, sham-controlled studies found a mean weighted effect size in reducing AH of 0.44 (95%CI 0.19–0.68) (Slotema et al., 2012). Notably, when they narrowed their analysis to the 5 studies that reported outcomes at 1 month post-treatment, their results were no longer significant (effect size 0.40, 95%CI −0.23 – 1.02), suggesting that the benefit may not be durable or that patients may require maintenance rTMS, a developing concept in the field (Rachid, 2017). A more recent Cochrane Reviews meta-analysis of twenty-two studies, however, concluded that while there is some evidence that rTMS improved auditory hallucinations, the evidence was not robust (Dougall et al., 2015). They called for improved study design and standardization of protocols and outcome measures, a request they acknowledged is challenging in a developing field still at an exploratory phase. Currently, the Schizophrenia Patient Outcomes

Research Team guidelines recommend using rTMS for AH, but it does not have FDA approval (Kreyenbuhl et al., 2009).

While studies of rTMS on negative symptoms have not studied TRS patients, it is a novel therapy that may prove to be beneficial. Negative symptoms in schizophrenia have been hypothesized to result from hypoactivity in the prefrontal cortex (Wolkin et al., 1992), so researchers have used high frequency rTMS (frequencies above 1Hz, generally 10–20Hz) to provoke an excitatory effect (Rosenquist et al., 2014). The first pilot study (Cohen et al., 1999) directed high frequency (20Hz) TMS on the DLPFC, and found 12% reduction in negative symptoms as measured by the PANSS. Since then, more studies have replicated their results, and a meta-analysis of 8 studies that used high-frequency rTMS found a pooled effect size of 0.58 (95%CI 0.11 – 10.4, p=0.014) (Freitas et al., 2009). A separate, concurrent meta-analysis found a similar effect size (0.43, 95%CI 0.05–0.80) (Dlabač-de Lange et al., 2010). Since a separate study found larger effect sizes when setting the TMS to each patient's peak α frequency (between 8 and 13 Hz) (Jin et al., 2005), the researchers repeated their analysis after removing 1Hz and 20Hz studies and including only 10Hz studies, and found a larger effect size (0.63, 95%CI 0.11 – 1.15) (Dlabač-de Lange et al., 2010). However, it is important to note the Cochrane Reviews meta-analysis that found the data to be highly heterogeneous, not robust, and concluded that there is no evidence for rTMS in improving negative symptoms, highlighting the need for greater standardization (Dougall et al., 2015).

The advantages of rTMS are that it is a non-invasive procedure and has evidence for reducing persistent AH. For negative symptoms, we only have results from non-TRS patients thus far, but as there is a paucity of treatments for negative symptoms, the early results are worth following up with further research.

Deep Brain Stimulation—In addition to ECT and rTMS, researchers are exploring the role of DBS in TRS, though the results are preliminary. DBS is delivered via electrodes usually implanted in both brain hemispheres. These electrodes emit short-lasting, balanced pulses of constant frequency and defined voltage, which is thought to attenuate clinical symptoms by balancing dysfunctional networks in neuropsychiatric disorders. At present, DBS has been delivered to more than 50,000 individuals suffering from idiopathic Parkinson's disease, essential tremor, and dystonia (Deuschl et al., 2006).

In schizophrenia, researchers are considering targeting the nucleus accumbens (NAc), hippocampus, globus pallidum internal segment (GPi), mediodorsal thalamus (MD), and medial septal nucleus (MSN) to modulate behavioral and neurophysiological aberrances (Bikovsky et al., 2016; Klein et al., 2013; Ma et al., 2014; Perez et al., 2013). Thus far, only two case reports have been presented, and these have targeted the NAc (Corripio et al., 2016; Plewnia et al., 2008).

The first report came from a patient with both OCD and residual schizophrenia. The patient's symptoms of OCD and psychosocial functioning were 25–58% improved with unilateral stimulation of NAc. However, the patient's predominant negative symptoms of schizophrenia were not significantly changed by DBS. Importantly, DBS did not cause

symptoms of psychosis (Plewnia et al., 2008). The second patient showed a 62% reduction in positive symptoms and 33% improvement in negative symptoms after 4 weeks of unilateral left side stimulation (Corripio et al., 2016). The patient was then trialed on bilateral stimulation, but experienced akathisia. After switching back to unilateral stimulation, the patient experienced a relapse of negative symptoms with the positive symptoms remaining improved over baseline. As the results of only two patients receiving DBS for schizophrenia have been reported, further research is needed.

Thus, DBS has the potential to directly target brain regions intracranially, and modulate specific circuits that could be perturbed in schizophrenia, and as such could be an exciting new treatment strategy. However, this modality is relatively new to schizophrenia treatment, and so far only a few clinical studies have begun assessing its effect. While it has the potential to be effective and possibly reduce the need for medication, it is also a surgical and thus relatively invasive procedure, with the risk of associated side effects such as hardware malfunction.

Psychotherapy

Other nonpharmacological techniques play an important role in treatment, and various psychotherapies have been developed to alleviate symptoms in TRS.

Several researchers have modified cognitive behavioral therapy (CBT) principles specifically for patients with schizophrenia and have largely focused on persistent positive symptoms (Burns et al., 2014). In general, these approaches help patients to normalize their symptoms, to place their psychotic experiences on a continuum with nonpsychotic experiences, and to discuss the origins of their hallucinations (Burns et al., 2014). While multiple meta-analyses have assessed CBT's effectiveness for schizophrenia patients in general (Gould et al., 2001; Lynch et al., 2010; Pfammatter et al., 2006; Rector and Beck, 2012; Sarin et al., 2011; Wykes et al., 2008; Zimmermann et al., 2005), only one (Burns et al., 2014) has restricted itself to "medication-resistant" patients who have psychotic symptoms despite being on a stable antipsychotic regimen of at least chlorpromazine 300mg or equivalent for three months. In this meta-analysis, they included 12 RCTs and found that CBT is moderately effective for positive symptoms (effect size 0.47, 95%CI 0.27–0.67) and general symptoms (effect size 0.52, CI 0.35–0.70) (Burns et al., 2014).

Three of the 12 studies in the meta-analysis come closer to the definition of TRS used in the pharmacologic literature. Pinto et al. (1999) included 41 patients who had documented failure to respond to two previous antipsychotic trials, each at least six weeks in duration at dosages of chlorpromazine 600mg or equivalent, and were currently on clozapine. The CBT group had lower BPRS and Scale for the Assessment of Positive Symptoms (SAPS) scores (Pinto et al., 1999). Valmaggia et al. (2005) randomized 62 patients who had continued symptoms despite trials of two different antipsychotics, of which at least one was an atypical, taken at sufficient dose and length per prescription guidelines. They found CBT reduced the Auditory Hallucination Scale and disruption of life related to AH, though the results were not maintained at follow up (Valmaggia et al., 2005). Finally, Barretto et al. (2009) randomized 21 patients who were refractory to clozapine and found decreases in BPRS, PANSS total, and PANSS general psychopathology. Taken together, these studies

suggest CBT is likely helpful for TRS, though further study using stricter criteria is warranted.

Others have sought to counter the functional impairment due to schizophrenia's cognitive deficits using a therapy known as cognitive remediation (CR). CR works through either compensatory strategies to improve function despite deficits or through CR exercises that strengthen cognition (Twamley et al., 2003). We know of no CR studies that directly study TRS, though two may have captured similar populations. Silverstein found increased attention span after CR in four patients residing in state hospitals for years with chronic schizophrenia (Silverstein et al., 1998). Lindenmayer randomized 71 patients with schizophrenia or schizoaffective disorder (as well as 14 with bipolar disorder) who were in a state psychiatric hospital for lengthy, though not specified, admissions and found improvement in composite measures of overall cognitive functioning as well as psychomotor speed and verbal learning (Lindenmayer et al., 2008). These two studies suggest CR may aid TRS, but further study is also indicated.

In summary, CBT has been shown to ameliorate persistent AH and CR may improve the cognitive deficits of schizophrenia, an essential part of improving functioning. Psychotherapy techniques have the advantage of avoiding the side effects and risks of pharmacological and procedural modalities, though they are not necessarily side effect free. Unfortunately, they are time-intensive and require the patient to be engaged and able to participate in therapy.

Summary of Treatments

In summary, medications are the mainstay of treatment for TRS at this time. Clozapine is currently the only medication with FDA approval for TRS, but augmentation with additional medications is of limited benefit. Medications have the advantage of being easy to give and can be taken at home, but their effect can be limited by non-compliance, a common problem in schizophrenia treatment. Medications are non-invasive but clozapine comes with several life-threatening side effects, and augmentation of clozapine increases the risk of side effects.

Given its poor outcomes and difficulty of successful treatment, TRS warrants the exploration of advanced treatment options beyond medications. There is growing evidence supporting ECT's efficacy, including in combination with clozapine. While ECT is non-invasive, it requires anesthesia and can cause transient confusion and memory impairment. rTMS is also noninvasive, but provides more targeted stimulation of specific brain areas. Thus far it has only been studied for specific symptoms, and it shows promising early results. However, both ECT and rTMS require multiple treatments and may require repeated maintenance treatments over time. Long-term side effects of rTMS are not known at this time. DBS is a novel intracranial therapy that can target specific brain regions even more directly. It has the potential to target specific neurocircuits, but is an invasive surgical procedure, with the additional risk of hardware malfunction. Finally, psychotherapy is non-invasive and can lessen symptom burden, but is time-intensive and requires patient investment.

The advantages and disadvantages of these current treatment options (summarized in Table 2), and the results of studies investigating these treatments, underscore the importance of a

valid and precise definition of TRS especially in research. This is critical to advance the proper diagnosis and treatment of these patients as well as further development of more effective therapeutics.

Defining Treatment Resistance

Defining TRS has been a challenge for the field and until recently there was not any consensus. Most of the definitions have focused on lack of improvement in psychosis, likely because antipsychotic drugs most effectively target positive symptoms (Caspi et al., 2004). Unfortunately, the inconsistency in defining what constitutes an adequate drug trial or therapeutic response in the literature complicates the comparison and interpretation of TRS studies (Conley and Kelly, 2001; Suzuki et al., 2011). In addition, there are other diagnostic complications and confounders. For example, TRS was initially associated with frequent or chronic hospitalization, but it has since been shown that this factor alone is not an accurate predictor of therapeutic response or necessarily a reflection of a drug-refractory condition (Brenner et al., 1990; Conley and Kelly, 2001). Importantly, treatment non-adherence can mimic TRS. Furthermore, treatment non-adherence is associated with substance use, a potential co-morbid factor with TRS (Conley and Kelly, 2001; Elkis and Buckley, 2016; Lindenmayer, 2000).

To address these issues, the Treatment Response and Resistance in Psychosis (TRIPP) Working Group was formed (Howes et al., 2016). Expert researchers and clinicians from academia and the pharmaceutical industry assembled with two tasks. The first was to evaluate the current approaches to defining TRS, and the second was to develop consensus criteria and guidelines.

First, they surveyed 2,808 studies and identified 42 that met their inclusion criteria. The authors identified several important findings from these studies. They determined that 95% of the studies used different criteria to define TRS with only 50% of the studies reporting the operationalized criteria. Only 62% of the studies required that patients had not responded to at least two adequate treatment trials, and only 57% defined adequate treatment as lasting at least 6 weeks, the typical time for medication response. Furthermore, 48% of the studies did not report the dosage used, but instead stated “adequate dose.” The authors found that 72% of the studies used symptom rating scales to define TRS. Finally, 38% of the studies followed a prospective supervised treatment plan and only 5% assessed past adherence. These results highlight the need for a more rigorous and standardized definition of TRS.

Based on this review, the TRIPP consensus group developed guidelines for TRS diagnosis. They recommend using the term treatment resistant to describe patients that meet the criteria described in their recommendations. They stress using clinical specifiers with the domains “positive”, “negative”, and “cognitive”, or a combination with the term TRS to best describe the patients. They also recommend using standardized rating scales to objectively define TRS. This creates objective criteria instead of the often used but vague term, “not adequate” response.

The group then recommended creating an absolute threshold for TRS with at least moderate severity, preferably for more than one symptom in any given domain. They further specify that a change of less than 20% in symptoms (from rating scale) be used since a change of 20% is the minimum that can usually be detected. Finally, they recommend that functional impairment be incorporated into diagnostic criteria, and measured using validated scales in addition to symptomatology.

Next, the group addressed the conceptual characterization of treatment resistance. They suggest that TRS is not binary but a continuum of disease. Therefore, the degree of treatment resistance should be determined as well as temporal development of symptoms, which can influence course and mechanism of illness.

Defining adequate treatment is critical for any definition of TRS. The authors address duration, dosage, and number of antipsychotic trials as critical factors. They define a trial as at least 6 weeks at a therapeutic dose, usually a minimum of 600mg chlorpromazine or equivalent. They suggest that a patient must fail at least two treatment episodes with adequate trials of two different antipsychotics as defined in this paragraph to establish TRS.

They also address adherence, which is necessary to determine if a patient has TRS or is noncompliant and symptomatic. The recommendation is that patients take greater than or equal to 80% of their medications over a 12 week period. They suggest obtaining this data by a minimum of two of the following methods: pill counts, dispensing chart review, and patient or caregiver report. They also recommend obtaining an antipsychotic blood level at least once without advanced warning.

Finally, they discuss clozapine-resistant schizophrenia. They propose that this should be a subspecifier of TRS and termed ultra-treatment resistant schizophrenia (UTRS) due to the specific role of clozapine in treating TRS. To assess response or failure on clozapine, they recommend that the midpoint of the target dosage range be used as a minimum of an adequate trial. They suggest obtaining a clozapine level on two separate occasions separated by at least one week to establish adherence, and a level greater than or equal to 350ng/ml be obtained before UTRS is considered. Blood levels are most relevant since they best represent the pharmacokinetics of each patient. Finally, they recommend a trial of 3 months after plasma levels reach above 350mg.

These consensus guidelines and recommendations of the TRRIP Working Group (summarized in Table 3) provide an opportunity for the psychiatric community to use more objective criteria in diagnosing and treating TRS patients. Such a consensus is also important to conduct research studies that can be compared and integrated more easily to yield deeper insights into the biology and effective treatment of TRS. The use of consensus guidelines are also critical to address the issue of TRS as a subtype of schizophrenia. We cannot effectively determine if TRS is a subtype of schizophrenia if the definition of TRS is different for each study. One of the reasons to study TRS as a subtype is to reduce the heterogeneity of schizophrenia and increase the likelihood of understanding the pathophysiology, for which it is important to begin with a more homogeneous group.

Future perspectives

This review highlights several important issues related to TRS that can inform how the field moves forward.

First, it is important to determine if TRS is a subtype of schizophrenia. This is critical to the understanding of TRS, and could change how clinicians approach treatment. It is also important for research design. If TRS has a distinct pathophysiology, including non-TRS patients in TRS studies or vice versa could make it difficult to identify the underlying pathophysiology or hinder the development of novel treatments. It is possible that a medication may be successful in treating the pathophysiology underlying TRS but not reach significance if non-TRS patients with a different pathogenic mechanism are included in the study. While the data at this time are limited and require replication in large samples, there is clinical, neuroimaging and neurobiological data to suggest that TRS is a subtype. While some of the data could suggest that TRS is a more severe form of the illness, there could be a continuum of illness with a critical threshold that leads to a different pathogenic mechanism. The field of schizophrenia in general needs to determine how to address the concept of subtyping the illness as it is widely recognized to be a heterogeneous disease. If a subtype exist for TRS, its recognition would facilitate the development of personalized treatment strategies based on specific pathophysiology.

In order to advance our understanding of TRS as a potential subtype, independent studies should utilize standardized and objective criteria, which would yield data that can be compared and replicated. The lack of consensus in defining TRS is likely an important reason why many findings have not been replicated and conflict with each other. This need has been addressed by the TRRIP Working Group, and could guide future studies to improve the accurate diagnosis and effective treatment of TRS patients.

In order to achieve successful treatment of TRS, the field will likely need multiple treatment options. As we have discussed in a previous review (Nucifora et al., 2017), it is becoming clear that therapeutic strategies beyond D2 receptor antagonism is necessary for schizophrenia. Other neurotransmitter systems may be more relevant to TRS and unbiased approaches, such as pharmacogenomics and gene expression profiling, are critical to identify novel targets.

Modalities beyond pharmacological treatment hold promise and are worthy of further exploration; ECT, TMS, DBS, and psychotherapies could thus make a major impact on TRS. For example. as we improve our understanding of which brain areas and circuits are involved in schizophrenia, DBS would potentially allow us to directly target these areas and circuits as a method of rationally designed (mechanism-driven) treatment. However, this is too new and speculative at this time for the field to be overly optimistic.

Identifying biomarkers for TRS is another area worthy of study. At present, TRS is a complex diagnosis of exclusion (Table 3), but a biomarker could provide an easier and more direct way of diagnosing TRS. Also, this could allow for earlier detection and intervention, and thus modify the course and severity of illness, since we know that decreasing the duration of untreated psychosis can improve symptomatic outcomes.

While TRS research has mainly focused on positive symptoms, it is important to include negative and cognitive symptoms when defining and studying TRS. It is possible that there are further subtypes within TRS related to symptomatology, which would have implications on treatment development. In addition, it is also important to address the functionality of patients. It is critical to identify more objective measures of functionality and to advance patients from symptom distress to improving their real world functioning and achieving their life goals. TRS patients are particularly vulnerable to a poor quality of life. Improving our understanding of this subtype of schizophrenia can alleviate suffering, advanced treatment, and improve the quality of life for the many patients with TRS.

Acknowledgments:

We would like to thank Yukiko Lema for help with this manuscript.

Funding: This work was supported by grants from the National Institutes of Health (MH-094268 Silvio O. Conte Center).

Abbreviations:

AH	auditory hallucinations
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotic Trials for Interventions Effectiveness
CBT	Cognitive Behavioral Therapy
CI	confidence interval
CR	Cognitive Remediation
DA	dopamine
DBS	Deep Brain Stimulation
DLPFC	dorsolateral prefrontal cortex
ECT	Electroconvulsive Therapy
FDA	Food and Drug Administration
Glu	Glutamate
GWAS	genome-wide association study
HC	healthy controls
HR	hazard ratio
leTPC	left tempoparietal cortex
MD	mediodorsal thalamus
MR	morbidity risk

NMA	network meta-analysis
non-TRS	non-Treatment Resistant Schizophrenia
PANSS	Positive and Negative Symptom Scale
PGC	Psychiatric Genomics Consortium
PRS	polygenic risk scores
RCT	randomized controlled trial
SAPS	Scale for the Assessment of Positive Symptoms
SNP	single nucleotide polymorphism
rTMS	repetitive Transcranial Magnetic Stimulation
TRS	Treatment Resistant Schizophrenia
TRRIP	Treatment Response and Resistance in Psychosis
UTRS	ultra-treatment resistant schizophrenia

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Table 1.

Characteristics of TRS

We highlight clinical, imaging, and biological findings specific to treatment resistant schizophrenia (TRS), which suggest that it is a distinct subtype of schizophrenia.

Clinical profile	- Earlier age of onset - More severe and familial form of disease - Possibly associated with more rural residence, but not with male sex (unlike schizophrenia in general) - Potentially specific cognitive deficits (e.g.verbal learning and memory, processing speed, executive functioning) - Poorer outcomes and quality of life
Neuroimaging	- Greater gray matter reduction - Increased white matter volume - Reduced striatal dopamine synthesis compared to non-TRS, but no difference from healthy controls - Elevated glutamate concentration in anterior cingulate cortex
Neurobiology	- Pharmacogenetics implicate neurotransmitter systems (e.g. *DRD2*), but conflicting results - Unbiased approaches: allow identification of novel targets beyond neurotransmitter receptors Pharmacogenomics: clozapine treatment (proxy for TRS) associated with higher genetic risk burden (e.g. PRS) Gene expression profiling: specific genes and pathways could be differentially regulated in TRS

Table 2.
Overview of treatment strategies for TRS

We review the advantages of disadvantages of various treatment strategies for treatment resistant schizophrenia (TRS). We give general overviews of medications, brain stimulation procedures, and psychotherapeutic methods, and then discuss specific examples in these categories. ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; AH = auditory hallucinations; DBS = deep brain stimulation; CBT = cognitive-behavioral therapy; CR = cognitive remediation.

	ADVANTAGES	DISADVANTAGES
Medications	*General*: - Easy clinical implementation - Non-invasive *Clozapine*: - Up to 60% of TRS patients respond to clozapine - Most efficacious antipsychotic - Reduces suicide and violence *Clozapine augmentation with medications*: - Relatively easy (especially compared to non-pharmacologic al modalities)	*General*: - Approximately 30% of TRS patients do not respond to any medication - Limited by non-compliance *Clozapine*: - Well-known adverse effects (e.g. agranulocytosis) - Requires enrollment in national registry and regular blood monitoring *Clozapine augmentation with medications*: - Minimal benefit for TRS - Greater risk of adverse effects from polypharmacy
Brain Stimulation	*General*: - Novel treatments with the potential to address mechanisms unaffected by medications - Can augment medications *ECT*: - Extensive use for mood disorders - Evidence of efficacy for positive symptoms in TRS - Evidence of synergistic effects with clozapine - Non-invasive procedure *rTMS*: - Evidence of efficacy for persistent AH - Potentially treats negative symptoms (currently few other treatment options) - Non-invasive procedure *DBS*: - Only intracranial intervention available, can directly target specific brain areas	*General*: - Procedural, so can be invasive and/or require anesthesia - Not as established as medications, requires more study *ECT*: - Adverse effects (e.g. memory impairment) - Require multiple treatments and possible long-term maintenance - Unclear benefit for domains other than positive symptoms - Requires anesthesia *rTMS*: - Require multiple treatments and possible longterm maintenance - Long-term side effects unknown *DBS*: - Invasive surgical procedure - Risk of hardware malfunction - Relatively new in schizophrenia
Psychotherapy	*General*: - Can augment medications - Efficacy in reducing symptom burden - Non-invasive *CBT*: - Possible efficacy for overall impairment and positive symptoms (e.g. AH) in TRS *CR*: - Possible efficacy for cognitive deficits in TRS	*General*: - Time-intensive - Requires baseline capacity to participate/engage - Very few studies specifically assessing TRS *CBT*: - Requires trained staff *CR*: - Treatment techniques and validated measurements still in development

Table 3.

Consensus criteria for TRS

We summarize the consensus guidelines for treatment resistant schizophrenia (TRS) presented by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group (Howes et al., 2017).

A. Lack of consensus	
TRRIP systematic review	95% of studies used different criteria to define TRS 50% did not report operationalized criteria
B. Diagnosis of TRS	
Disease/functional status	At least moderate symptom severity Describe positive, negative, and/or cognitive symptoms Assess with standardized symptom rating scale At least moderate functional impairment Assess with validated functional scale
Treatment response	*Determination of treatment non-response* Defined as <20% symptom reduction over ≥6 weeks *Determination of treatment resistance* Defined as non-response to ≥2 adequate treatment trials Minimum: ≥2 different antipsychotics Optimum: ≥2 different antipsychotics, including ≥1 longacting injectable antipsychotic (for ≥4 months) *Determination of adequate treatment trial* Dosage: equivalent to ≥600 mg chlorpromazine daily Duration: ≥6 weeks at adequate dose *Determination of adherence* Defined as ≥80% prescribed doses taken Assess with ≥2 sources - e.g. patient/caregiver reports, case notes, pill counts, dispensing charts Monitoring: obtain antipsychotic plasma levels Minimum: ≥1 draw Optimum: ≥2 draws separated by ≥2 weeks (without notifying patient)
	C. Diagnosis of UTRS
Ultra-TRS	Meets above criteria for treatment resistance Plus non-response to adequate trial on clozapin Dosage: midpoint of target dosage range (Obtain clozapine level twice with level >350ng/mL) Duration: 3 months

Table 4.

Summary of future perspectives

We summarize our future perspectives of treatment resistant schizophrenia (TRS). We highlight the evidence that TRS is a distinct subtype of schizophrenia, and challenges of research without a consensus on defining TRS, gaps and future directions for our therapeutic arsenal, the value of biomarkers, and the need to address functionality as well as symptom care.

Perspective	Directions
TRS is a distinct subtype of schizophrenia	- Clinical, neuroimaging, and neurobiological evidence highlights specific characteristics of TRS
TRS requires more consistent definition	- Future studies will be more comparable and replicate findings will improve diagnosis and treatment
Improved/expanded therapeutic arsenal	- Biological pathways, brain regions, and cognitive deficits of TRS are still poorly understood - Pharmacological targets beyond neurotransmitter receptors are required - TRS will likely need multiple treatment options that could include non-pharmacological treatments
Biomarkers	- Can predict patients who are most likely to develop TRS - Early identification and intervention could possibly reduce symptom burden or risk of developing TRS
Moving beyond positive symptoms and symptom care	- Negative and cognitive symptoms must also be considered - TRS patients are especially vulnerable to poorer quality of life, so require more functional improvement