Clinical Guidance on the Identification and Management of Treatment-Resistant Schizophrenia

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ABSTRACT

Treatment-resistant schizophrenia (TRS) occurs in approximately 30% of individuals diagnosed with schizophrenia. The identification and management of TRS in clinical practice are inconsistent and not evidence based. No established clinically relevant criteria for defining and treating TRS exist, although guidelines have been promulgated for clozapine use among TRS patients. This report summarizes the consensus from a roundtable that focused on defining and identifying TRS, pathways to treatment resistance, current treatments, unmet needs, and disease burden. Nine clinical experts in schizophrenia and TRS participated in a closed meeting on June 23, 2017, sponsored by Lundbeck, at which published literature in key areas of TRS research was reviewed. The findings from published studies were synthesized by experts in each area and presented to the group for review and discussion. It was agreed that inadequate response to 2 different antipsychotics, each taken with adequate dose and duration, is required to establish TRS. This recommendation is consistent with guidelines for clozapine use. For each trial, objective symptom measures should be used to assess treatment response, with medication adherence ensured. Once nonresponse is established (after ≥ 12 weeks for positive symptoms [2 trials of ≥ 6 weeks]), the treatment plan should be reevaluated and alternative pharmacologic or nonpharmacologic treatments considered. With increased awareness, those involved in the care of patients with schizophrenia will be able to identify TRS earlier in its course, thus supporting more informed treatment decisions by clinicians, patients, and caregivers to reduce the overall disease burden.

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Schizophrenia is a complex, progressive, and severe mental disorder characterized by distortions in thinking, perception, emotions, language, sense of self, and behavior.[1] It is estimated that over 21 million people worldwide have schizophrenia.[1] The majority of people with this illness exhibit a prodromal period characterized by subtle changes in thoughts and perceptions, followed by the onset of psychotic symptoms.[2] Between 75% and 87% of patients with first-episode psychosis responded to the first treatment with an antipsychotic medication by 4 weeks to 1 year.[3–7] However, for patients whose illness has not clinically improved with the first antipsychotic, response rates to subsequent nonclozapine antipsychotic treatment are much lower. Studies in patients with chronic schizophrenia show that up to 30% of patients diagnosed with schizophrenia meet criteria for treatment-resistant schizophrenia (TRS), that is, failure to respond to ≥ 2 different nonclozapine antipsychotic medications.[2,8,9] Longer duration of untreated psychosis and having received multiple different antipsychotic treatments are indicators of poor prognosis.[6,10] Data suggest that response rates fall dramatically with additional psychotic relapses and serial administration of different antipsychotic treatment trials, with only 9% of patients responding to a third nonclozapine antipsychotic treatment trial in one study.[11] Furthermore, high-quality evidence for effective antipsychotic augmentation and/or combination treatments for schizophrenia is currently insufficient.[12,13]

To optimize the treatment of TRS, early identification is critical. Through early identification, the duration of inadequately controlled illness may be reduced, thereby improving long-term outcomes.[14] However, clinicians in daily practice may not readily recognize TRS as a distinct clinical entity. As a result, appropriate treatment may be delayed or not offered at all. The identification of TRS is further complicated by difficulties distinguishing it from antipsychotic nonadherence, as well as by the heterogeneous and multidimensional nature of TRS (eg, varying onset of treatment nonresponse[5,15,16] and involvement of nonresponsive positive, negative, and cognitive symptoms[17]) as well as the

Clinical Points

- Treatment-resistant schizophrenia (TRS) occurs in approximately 30% of individuals diagnosed with schizophrenia, but identification and management of TRS in clinical practice are inconsistent and not evidence based.
- To establish TRS, a patient must demonstrate inadequate response to 2 different antipsychotics, each taken with adequate dose, duration, and confirmed adherence.
- Upon recognition of TRS, the treatment plan should be reevaluated and alternative treatments considered. Recognition of TRS earlier in the course of disease will allow for more informed treatment decisions to be made by clinicians, patients, and caregivers.

lack of consensus on clinically relevant criteria for defining and treating TRS.[2,9,17,18]

This report summarizes the consensus findings of a roundtable meeting on TRS (June 23, 2017; New York, NY; sponsored by Lundbeck) that included 9 clinicians with expertise in the areas of schizophrenia and TRS. The report provides an overview of TRS and the consensus derived regarding its key domains. The goal is to increase awareness of this common phenomenon among general psychiatrists to facilitate early identification and more effective treatment of patients with TRS.

DEFINITION AND IDENTIFICATION OF TREATMENT-RESISTANT SCHIZOPHRENIA

Current treatment guidelines for schizophrenia are broadly aligned in terms of their definition of TRS (Table 1).[2,9,17,18] TRS is characterized by persistence of positive symptoms (eg, delusions, hallucinations, disorganized speech and behavior) despite adequate treatment trials with antipsychotic medications.[19] Key criteria for the definition of TRS include no significant improvement in positive symptoms after treatment with ≥ 2 different nonclozapine antipsychotic medications at adequate dose, duration, and documented adherence. Thus, the term TRS in this context refers to patients not adequately responding to first-line medication approaches. Patients not responding to clozapine or a nonpharmacologic treatment option, such as electroconvulsive therapy (ECT), represent distinct subgroups of TRS. These 2 groups can descriptively be referred to as clozapine-resistant and ECT-resistant schizophrenia.

In contrast to the relative consistency in major aspects of the definition of TRS, recommendations for what constitutes a lack of treatment response and the clinical outcomes used to assess the level of treatment response vary among the guidelines.[2,9,17,18] This issue is further complicated in patients with TRS because they are a heterogeneous patient population, likely reflecting the complexity of the clinical and neurobiological pathways leading to TRS.

Another potentially complicating issue when determining the level of treatment response is the concept of pseudoresistance, which posits that certain factors can make it appear as if a patient is not responsive to treatment when in fact the treatment response can be modified, such as through improved and/or verified antipsychotic adherence. Factors that need to be evaluated as underlying causes of pseudoresistance include medication nonadherence, pharmacokinetic issues (eg, poor drug absorption or brain penetration, drug-drug interactions, changes in metabolism or body volume) that lead to inadequate therapeutic drug levels, and specific patient characteristics (eg, substance use disorders, other medical conditions) that may exacerbate symptoms or modify treatment response.

PATHWAYS TO TREATMENT-RESISTANT SCHIZOPHRENIA

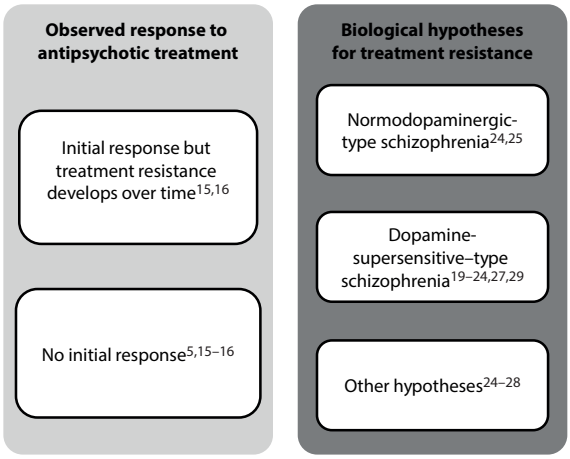
Current data suggest that there are probably multiple clinical pathways and different potential neurobiological mechanisms involved in the pathophysiology of TRS (Figure 1).[5,15,16,20–29] For example, heterogeneity has been observed in the onset of treatment nonresponse. Approximately 30% of individuals diagnosed with schizophrenia exhibit a partial response or no response to initial treatment,[8] whereas 10%–60% of individuals exhibiting an initial response to

Table 1. Guidelines for Defining Treatment-Resistant Schizophrenia

Guidelines	Prior AP Treatment Failure	Treatment Duration	Failure Criteria
APA (2004)[9]	≥ 2 Failures ≥ 1 Second-generation AP	≥ 6 wk	Little or no symptomatic response to a trial of adequate duration and dose (therapeutic range)
NICE (2014)[2]	≥ 2 Sequential failures ≥ 1 Nonclozapine second-generation AP	4–6 wk	Illness has not responded adequately despite established adherence to AP medication, prescribed at an adequate dose and for the correct duration
WFSBP (2012)[18]	≥ 2 Failures ≥ 2 Different chemical classes ≥ 1 Atypical AP	2–8 wk	No significant improvement in the psychopathology and/or target symptoms; ensured treatment adherence
TRRIP[a] (2017)[17]	≥ 2 Different APs ≥ 1 Prior treatment with long-acting injectable AP (≥ 4 mo)	≥ 6 wk (at therapeutic dose)	At least moderate disease severity and < 20% symptom reduction during a prospective trial or observation of ≥ 6 weeks; at least moderate functional impairment based on a validated scale; adherence (≥ 80% of prescribed doses) confirmed using trough serum AP levels

[a]Based on recommendations for optimum requirements.
Abbreviations: AP = antipsychotic, APA = American Psychiatric Association, NICE = National Institute for Health and Care Excellence, TRRIP = Treatment Response and Resistance in Psychosis, WFSBP = World Federation of Societies of Biological Psychiatry.

Figure 1. Clinical and Neurobiological Pathways to Treatment-Resistant Schizophrenia



antipsychotic treatment develop treatment resistance over time[5,15,16] and after multiple relapses.[30]

There are also multiple hypotheses concerning the underlying neurobiological mechanisms of TRS that account for the 2 main clinical paths to TRS (initial resistance vs resistance that emerges over time). One hypothesis posits that supersensitivity of dopamine D_2 (DRD2) receptors to dopamine contributes to the pathophysiology and development of TRS in some individuals.[20–24] This supersensitivity may be due to an increase in the number of receptors or an increase in receptor affinity for dopamine.[29] Antipsychotic medications mitigate psychosis by blocking DRD2 receptors. However, prolonged blockade of postsynaptic dopamine receptors may lead to dopamine supersensitivity, resulting in increased psychotic symptoms (breakthrough psychosis) and motor side effects such as abnormal involuntary movements (eg, tardive dyskinesia) in treated patients.[20–22] Supersensitivity may also lead to increasingly higher antipsychotic doses being used in an attempt to control breakthrough psychosis. Supporting the supersensitivity hypothesis, increases in DRD2 receptor levels have been observed in individuals with schizophrenia after prolonged antipsychotic treatment.[23,24] However, clinical support for a causal role of dopamine supersensitivity psychosis in TRS is currently lacking.[29,31]

An alternative theory for TRS, the "normodopaminergic" hypothesis, is based on evidence indicating that not all individuals with schizophrenia have characteristics of a hyperdopaminergic system.[25,26] In one positron emission tomography study, patients with TRS had lower dopamine synthesis capacity than treatment-responsive patients but a similar capacity to healthy volunteers.[26] In these patients with TRS and normal dopaminergic function, other neurotransmitter systems are proposed to contribute to the symptoms of schizophrenia. For example, changes in the glutamatergic system have been postulated to play a role in the etiology and development of TRS.[24–28] Supporting this hypothesis, anterior cingulate glutamate metabolite concentrations were found to be elevated in patients with TRS relative to healthy volunteers but not in treatment responders, suggesting a role for changes in the glutamatergic system in patients with TRS.[28] Another potential pathway to TRS is the emerging notion of *N*-methyl-D-aspartate (NMDA) antibody psychosis,[32] which can be diagnosed with a positive antibody titer to the NR1 subunit of the NMDA receptor.

BURDEN OF TREATMENT-RESISTANT SCHIZOPHRENIA

As summarized in Table 2, TRS is associated with a substantial burden for patients, treatment teams, and families/caregivers.[33–37] Patients with TRS have more severe positive and negative symptoms, greater functional limitations, and higher health care costs compared with antipsychotic treatment responders.[33] In one study, total health care costs were twice as high for patients with TRS compared with antipsychotic treatment responders after 8 weeks of treatment.[35] The persistent negative or cognitive symptoms and poor social functioning characteristics of TRS have been associated with self-stigma.[38,39] Additionally, the perception of psychosis-related violence and dangerousness can result in stigma[40] and potentially discrimination, self-harm, long-term hospitalization, and incarceration. These patient-centered aspects of TRS also require attention.

With respect to the burden of TRS on treatment teams, treatment for patients with TRS is too often associated with pessimism on the part of all concerned. Furthermore, specialized treatment units for TRS are generally lacking, which often results in patients with TRS being treated in a less sophisticated environment by health care providers with little or no training or education in the appropriate treatment of patients with TRS.[41,42] The burden of TRS on families/caregivers grows as disease chronicity increases over time, as measured by decreases in family cohesion and flexibility (ie, quality and expression of leadership and organization) and by increases in indirect costs (eg, lost work time, stress-related illness).[37]

Direct health care costs tend to be higher in patients with TRS than in the general population of patients with schizophrenia, with estimates of excess annual costs per patient (adjusted to 2016 US $) ranging from $9,550 to $35,281 across 3 studies.[43–45] One systematic review of studies of the burden of TRS reported that total health

Table 2. Burden of Treatment-Resistant Schizophrenia

Patient	Treatment Team	Family/Caregiver
• More severe positive and negative symptoms[33] • Worse neurocognitive functioning[34] • Higher health care costs[35] • Lower employment rates • Lower quality of life • Lower levels of community functioning[33]	• Pessimism • Therapeutic nihilism • Lack of intellectual curiosity • No specialized treatment teams	• Substantial amounts of time and income devoted to patient care–related activities[36] • Negative impact on the family/dissolution of the family[37]

resource utilization cost estimates were 3 to 11 times greater than the costs for non-TRS.[46] The wide range of estimated excess costs for TRS across different analyses is likely related to differences in study populations, treatment durations, definitions of TRS used, and variations in the completeness of the cost data.

Another analysis found that if 20% of the veterans with TRS initiated clozapine treatment, the mean 1-year cost savings to the Veterans Health Administration (VHA) would be $22,444 per veteran with TRS.[47] Furthermore, 95% of model simulations from this analysis estimated a savings of at least $290 million if all VHA patients with TRS not on clozapine were to initiate clozapine treatment.[47]

There are no published studies from the United States describing productivity losses in patients with TRS. However, unemployment rates may serve as a proxy for lost productivity. Two studies of individuals with schizophrenia in the United States reported high rates of unemployment (> 70%).[48,49] Given that schizophrenia symptoms and cognitive function are predictors of work outcomes[50] and antipsychotic treatment has been associated with cognitive improvement,[51] it seems likely that patients with TRS may have higher unemployment rates than patients who respond to antipsychotic treatment. In a cohort of patients with TRS from Italy, the unemployment rate was 64.7%.[52] Although unemployment data across countries are likely to be region specific, these overall data reflect the potentially high level of lost productivity due to TRS.

The economic burden of schizophrenia on society can also be observed with data from Social Security Disability Insurance (SSDI) and Supplemental Security Income (SSI) beneficiaries. Persons diagnosed with schizophrenia account for approximately 5% and 7% of beneficiaries, respectively.[53,54] The high proportion of beneficiaries with schizophrenia is markedly disproportionate to the relative prevalence of schizophrenia in the overall population (< 1%) and further reflects the low rates of employment among this population. In 2015, total annual costs associated with schizophrenia and other psychotic disorders were approximately $443 million and $248 million for SSDI and SSI, respectively.[53,54] Despite the substantial economic burden of TRS, an online review of federal funding by the National Institutes of Health indicated that funding for TRS research is approximately 7 times lower than funding for treatment-resistant major depressive disorder and approximately 563 times lower than funding for other dimensions of schizophrenia. More effective and earlier treatment of patients with TRS could potentially lessen the economic burden associated with this condition (eg, lower health care costs and increased rates of employment).

CURRENT TREATMENT AND UNMET NEEDS IN TREATMENT-RESISTANT SCHIZOPHRENIA

Current Treatment Strategies

Several strategies are widely used in clinical practice to manage patients with TRS (eg, increasing the antipsychotic trial duration, using higher doses of nonclozapine antipsychotics, switching to other nonclozapine antipsychotics, employing polypharmacy [which includes augmentation with nonclozapine antipsychotics or mood stabilizers]).[12] Across 4 studies,[55–58] the use of antipsychotic doses above recommended maximums was reported in 10.1%–36.2% of patients before they received clozapine. Furthermore, across several studies, the percentage of patients receiving antipsychotic polypharmacy ranged from 15.9% to 60.5% before they received clozapine.[56–59]

However, there is limited clinical benefit to using nonclozapine management strategies to address inadequate treatment response to antipsychotics. Agid and colleagues[60] reported that 77% (23/30) of individuals treated with at least 2 different antipsychotics (olanzapine, risperidone, or quetiapine) did not respond after 25 to 28 weeks of treatment. Additionally, only 15.5% (11/71) of individuals treated with higher dose ranges of antipsychotic therapy (olanzapine 22.5–30 mg or risperidone 6.5–10 mg) and 16.7% (10/60) of individuals switched to a different antipsychotic therapy responded to treatment.[61] Furthermore, another study[3] demonstrated that switching to another nonclozapine treatment after nonresponse to an initial nonclozapine antipsychotic treatment resulted in a treatment response in only 16.7% of individuals experiencing a first psychotic episode. These data are consistent with those of another study[4] that reported that treatment response and remission rates progressively decreased when switching between nonclozapine antipsychotics. Recently published meta-analyses[12,13] have shown that there is limited high-quality evidence to support antipsychotic augmentation strategies.

Taken together, these data suggest that increased trial duration,[60] using high-dose nonclozapine antipsychotics,[55–58,61] switching to other nonclozapine antipsychotics,[3] or employing polypharmacy (including augmentation with nonclozapine antipsychotics[12,13])[56–59] may unnecessarily delay the initiation of clozapine treatment or future effective treatments for TRS and hinder clinical response in patients who do not respond to antipsychotic therapy. Retrospective studies conducted outside the United States similarly reveal considerable hesitancy and delay in initiating patients on clozapine.[58,62–64] In a Canadian study[62] of outpatients (n = 467), approximately two-thirds (68%) were treated with ≥ 3 different antipsychotics before clozapine initiation; the median length of therapy before starting clozapine was 8.9 years for male patients and 7.7 years for female patients. Reports from the United Kingdom and Australia revealed that, on average, 3.5 to 5.5 antipsychotics were used before initiating clozapine treatment and an average of 4.0 to 9.7 years passed from diagnosis to start of clozapine.[58,63,64] Delays in the initiation of clozapine treatment have been associated with reductions in the percentage of symptomatic improvement in individuals with TRS, as measured by Brief Psychiatric Rating Scale total and psychosis scores.[14]

In patients with suboptimal response to previous antipsychotic treatment, clozapine and olanzapine were found

to be superior to haloperidol for improvement in Positive and Negative Syndrome Scale (PANSS) total and negative symptom scores.[65] In an observational study of Medicaid beneficiaries with schizophrenia, treatment with clozapine instead of antipsychotic polypharmacy was associated with reduced disease-specific emergency department use and reduced disease-specific and all-cause health care costs.[66]

Since clozapine is currently the only indicated and evidence-based treatment for TRS, but also has a number of potentially severe adverse effects,[67] the decision to use clozapine is influenced by weighing the burden of psychosis and suicidality versus the risk of weight gain, diabetes, and other adverse effects. Furthermore, the decision to initiate clozapine should be undertaken on an individual basis, in close collaboration with patients, and closely associated with early recognition of TRS because there is evidence that earlier use of clozapine is associated with better response.[68]

Efficacy of Current Treatments

There is evidence suggesting that up to 75% of individuals with a first episode of psychosis[3,60,61] and 40% of individuals with TRS[69] who did not respond to nonclozapine antipsychotics might respond to clozapine. A recent 3-phase switching study[70] found that some first-episode schizophrenia patients who do achieve cross-sectional remission after a 4-week open-label trial with an initial nonclozapine antipsychotic (amisulpride; phase 1) continued to remit after a 6-week double-blind trial of either continued treatment with amisulpride or a switch to olanzapine (phase 2). However, those patients who had not experienced cross-sectional remission after a total of 10 weeks of nonclozapine treatment had a subsequent cross-sectional remission rate after another 12 weeks of open treatment with clozapine (phase 3) of 18% among patients in the intention-to-treat group and 28% among patients who completed the clozapine trial.[70] Furthermore, the results from a network meta-analysis of randomized controlled trials comparing the efficacy of clozapine with that of other second-generation antipsychotics are inconsistent.[71] The mixed results from meta-analyses regarding the superiority of clozapine compared with other second-generation antipsychotics are likely due to meta-analytic–, patient-, and treatment-related factors, as well as problems in some cases with trial design and implementation.[72] In particular, some studies included treatment-intolerant patients as well as treatment-resistant patients, and there is considerable variation in the way treatment resistance is defined and evaluated among studies.[17] In a systematic review,[73] short-term and long-term clozapine use was reported to be superior to other antipsychotics in reducing positive psychotic symptoms, but only short-term clozapine use (not long-term use) was superior to other antipsychotics for negative symptoms in patients with treatment-refractory schizophrenia. The lack of superiority of clozapine with longer-term treatment could be due to insufficient statistical power.[72] Supporting a benefit for clozapine in the long term, naturalistic studies show reduced mortality over 7 to 11 years of treatment and reduced hospital readmission rates over an average of 5.7 years of treatment in patients receiving clozapine.[74,75] More recently, a systematic review of meta-analyses that included a quality assessment of previously published meta-analyses found that no pharmacologic combination treatment (including 5 combinations with clozapine) had sufficiently consistent efficacy to recommend the combination therapy over antipsychotic monotherapy.[12] There are those who would argue that there are insufficient data from blinded, well-controlled studies to determine which antipsychotic is most efficacious for the treatment of patients with TRS.

Nonpharmacologic adjunctive treatment (eg, cognitive behavioral therapy for psychosis [CBTp], hallucination-focused integrative therapy [HIT], repetitive transcranial magnetic stimulation [rTMS], ECT) to antipsychotic treatment may be effective for managing symptoms in individuals with TRS.[76–81] A meta-analysis of studies using CBTp in individuals with schizophrenia reported a modest beneficial effect on positive symptoms (mean weight effect size, 0.37).[76] A meta-analysis of the use of CBTp in individuals with medication-resistant psychosis reported effect sizes (Hedges *g*) of 0.47 and 0.41 for positive symptoms and 0.52 and 0.40 for general symptoms at posttreatment and follow-up, respectively.[77] In patients with persistent (> 10 years), drug-refractory auditory hallucinations, HIT resulted in significant improvements versus control patients (provided routine care) on distress scores and total burden measured with the Psychotic Symptom Rating Scales—Auditory Hallucination Rating Scale and on positive symptoms measured with the PANSS.[81] In a review[78] of studies that used rTMS as a means of neuromodulation, moderate reductions in the severity of auditory-verbal hallucinations were reported in individuals whose auditory-verbal hallucinations were medication resistant. In a meta-analysis[79] of randomized controlled trials, ECT as an adjunct to nonclozapine antipsychotic monotherapy was reported to be superior to antipsychotic monotherapy. Furthermore, in a prospective study[80] of individuals with TRS who were also nonresponders to clozapine, ECT augmentation resulted in 50% of study participants (10/20) achieving a response (defined as ≥ 40% improvement in psychotic symptoms, a Clinical Global Impressions–Severity rating < 3, and a Clinical Global Impressions–Improvement rating ≤ 2) compared with 0% of participants (n = 19) receiving clozapine without ECT augmentation. Taken together, these data suggest adjunctive nonpharmacologic therapy may be beneficial in individuals with TRS. There is evidence from meta-analyses supporting the addition of CBTp to an antipsychotic for various degrees of treatment-resistant symptoms.[76,77] However, the relative sparsity of data available for other therapies (in part due to their underutilization) limits the certainty with which conclusions can be drawn regarding their overall clinical utility.

Unmet Treatment Needs

It is important to recognize that while many individuals with TRS exhibit a positive response to clozapine, there is

Table 3. Guidance on the Identification and Management of TRS: Consensus Points

Domain	Consensus Points
Definition and identification	• Early recognition of TRS and management of psychotic symptoms are critical, as a prolonged duration of untreated psychosis is associated with negative outcomes. ◦ It is important to address the preconception that some individuals will not respond to any medication. Instead, it should be reinforced that the proper medication may not have been administered. • The recommended definition of TRS is failure to respond on any 2 AP medications, each at an adequate dose (ie, equivalent to ≥ 600 mg of chlorpromazine/d) and treatment duration. • Objective symptom measurements should be used to assess treatment response and medication adherence. ◦ Adherence should be evaluated by multiple objective means (eg, blood or urine levels, pill counts, supervised medication intake, use of depot administration agents). ◦ Examine and exclude potential contributing factors for inadequate treatment response (eg, substance abuse disorders, neurocognitive disorders).
Pathways to resistance	• TRS is not a homogeneous subgroup within the schizophrenia spectrum; different clinical and neurobiological pathways may be involved in the condition. • The pathophysiology of TRS is not yet well understood. There are still gaps in the knowledge of the underlying neurobiological pathways; currently, evidence suggests a role for both dopaminergic and nondopaminergic pathways.
Burden	• The burden of TRS on patients, family/caregivers, payers, and society is substantial across a range of human, societal, and economic domains. • The effective management of TRS may have a positive impact on the overall burden associated with the condition. • The stigma associated with schizophrenia, and most likely TRS, may be mitigated by the early identification of TRS and effective treatment of psychotic symptoms.
Current treatment	• Reevaluate the treatment plan after nonresponse to 2 AP drugs (after a minimum treatment of 12 weeks for positive symptoms [2 trials of ≥ 6 weeks]) and consider alternative pharmacologic treatments, including clozapine. ◦ In certain circumstances (eg, risk of suicide), a treatment duration of 2 weeks may be sufficient before considering additional clinical measures, including the use of clozapine. Adjunctive treatment with nonpharmacologic interventions (eg, CBTp, ECT, rTMS) should be considered. • Treatment choices should be a shared decision-making process among the treatment team, the patient, and the family/caregivers. • High-dose AP, hospitalizations, and evidence of ineffective polypharmacy should be considered as potential markers for patients with TRS.

Abbreviations: AP = antipsychotic, CBTp = cognitive behavioral therapy for psychosis, ECT = electroconvulsive therapy, rTMS = repetitive transcranial magnetic stimulation, TRS = treatment-resistant schizophrenia.

a subset of individuals who are clozapine resistant.[3,60,61] It has been proposed that individuals with TRS should be categorized according to this dichotomy in treatment response (clozapine responders vs clozapine nonresponders).[19,82] A wide range of values has been reported for the prevalence of clozapine-resistant schizophrenia, or "ultra TRS," but a recent meta-analysis[69] found that as many as 60% of patients failed to respond to clozapine across short- and long-term studies. Moreover, mixed results have been obtained for the use of pharmacologic[12] adjunctive treatments, while results have been generally positive for nonpharmacologic adjunctive treatments including ECT[79] in non-TRS and TRS[83] patients as well as for 9 months of CBT in patients who are resistant to clozapine, although results were not sustained at 21 months.[84] As a clinically defined subgroup that may have unique biological characteristics, further studies of patients not responding to ECT are warranted.

A percentage of individuals with TRS refuse clozapine treatment. In one study, 9 of 23 patients (39%) who failed to respond to 2 antipsychotic trials refused to receive clozapine in a subsequent trial.[60] In another study, 35% (20/57) of patients (no previous trials with clozapine) admitted to an acute ward for schizophrenia or schizoaffective disorder stated that they would refuse clozapine.[85] The defining features of these populations of individuals with TRS (nonclozapine antipsychotic treatment resistant vs clozapine treatment resistant) need to be further elucidated. In addition, it will be important to further understand how to optimize clozapine treatment, as there is limited evidence regarding adequate clozapine doses and adequate plasma clozapine levels required for a clozapine trial. It is possible that in some of the cases of clozapine resistance, treatment was not optimized.

CONSENSUS SUMMARY

Definition and Identification of Treatment-Resistant Schizophrenia

The early recognition of TRS and management of its associated psychotic symptoms are critical because a prolonged duration of persistent and ineffectively treated psychosis is associated with negative outcomes.[14] It is important to overcome the therapeutic nihilism that sometimes leads to sustained, ineffective treatment.[86] Rather, it should be considered that the appropriate treatment has not yet been provided to the patient, including currently available long-acting injectable medications in the case of nonadherence. Identifying the underlying reason that patients are treatment resistant may be difficult because of the heterogeneous and multidimensional nature of the factors that may contribute to its etiology. Additionally, there may be other contributing factors, such as access and continuity of comprehensive care. There is clearly a need for more training of clinicians to facilitate the earlier identification and appropriate management of TRS. In some regions and settings, the establishment of specialty units

or clinics could help to improve the care of such patients. In a study examining a comprehensive, multidisciplinary, team-based treatment approach for first-episode psychosis in the United States, it was reported that comprehensive care for first-episode psychosis improved both functional and clinical outcomes.[87] Clozapine clinics have been established at a number of psychiatric facilities around the world, and although no formal studies of outcomes in comparison to usual care have been reported, it is likely that treatment by clinicians with special expertise has a variety of advantages. It has been suggested that clozapine clinics expand clozapine accessibility, enhance physician competency with clozapine, and provide better training for residents and other trainees.[88]

The consensus definition of TRS is the failure of ≥2 different antipsychotic medication trials at adequate dose and duration of ≥6 weeks, with objective assessments of adherence (Tables 1 and 3). This recommendation is consistent with the recently published guidelines of the Treatment Response and Resistance in Psychosis Working Group.[17] Before and after antipsychotic trials, objective symptom measurement and medication adherence tools (eg, blood or urine levels, pill counts, supervised medication intake, use of long-acting injectable formulations) should be used to verify the presence of TRS.

Pathways to Treatment Resistance in Treatment-Resistant Schizophrenia

Evidence suggests that there is no single pathway, biological phenotype, or clinical phenotype that accounts for all cases of TRS. Multiple neurobiological mechanisms are likely to occur across patients with TRS. Although gaps in understanding of the causes and evolution of TRS exist, current evidence suggests both dopaminergic and nondopaminergic mechanisms may account for the pathophysiology of TRS.[20–29] There is also a need to clarify the role of pseudoresistance in TRS. The development of algorithms/flow diagrams may help to provide direction to clinicians on the potential factors that may contribute to nonresponse, including the role of nonadherence.

Areas of future research that will help to further clarify the pathophysiology of TRS and reliably identify it include the use of genotyping and other biomarkers (eg, neuroimaging) and further examination of the role of oxidative stress and inflammation. The development of an algorithm based on a simple assessment tool, which evaluates treatment response, focuses on positive symptoms, and accounts for sources of pseudoresistance, would also be useful in accelerating the identification of patients with TRS. However, a detailed description of such an assessment tool is beyond the scope of the current report. The authors plan on presenting a proposal in a future publication.

Burden of Treatment-Resistant Schizophrenia

There are substantial personal, societal, and economic burdens associated with TRS (Tables 2 and 3). Based on an online review of federal funding, TRS research funding is substantially lower than that provided for other psychiatric disorders (ie, bipolar disorder, major depressive disorder, and other domains in schizophrenia). The disease burden associated with TRS may be substantially reduced by early identification and effective treatment.

Current Treatment and Unmet Needs in Treatment-Resistant Schizophrenia

Consensus treatment guidelines for TRS recommend that patients be reevaluated at 12 weeks after a first episode of psychosis (after 2 antipsychotic trials of ≥6 weeks in duration at an adequate dose [ie, ≥600 mg chlorpromazine equivalents/d]; Table 3). However, in some circumstances (eg, high risk of suicide), a treatment duration of 2 weeks may be sufficient before considering if additional clinical intervention is needed. The use of alternative pharmacotherapies, including clozapine, or nonpharmacologic adjunctive treatments (eg, CBTp, ECT, rTMS, HIT) should be considered if treatment response is not optimal. It is also important to emphasize that treatment choices should be a shared decision-making process among the treatment team, the patient, and the patient's family/caregivers.

CONCLUSIONS

The early identification of patients with TRS is critical for optimizing treatment because early recognition may help reduce the duration of persistent psychosis and improve long-term treatment outcomes. By increasing awareness and disseminating criteria for identifying TRS, those involved in the care of patients with schizophrenia will be able to identify TRS earlier in its course and make more informed treatment decisions. Considering the available evidence, it is anticipated that more timely and effective intervention for patients with TRS will result in improved long-term outcomes, reduced disease burden, and lower overall health care costs.

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