What do we know about treatment-resistant schizophrenia? A systematic review

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Abstract

Treatment-resistant schizophrenia (TRS) is a severe form of schizophrenia with high prevalence and human impact. Our aim was to perform a systematic review to find out the extent of published research on TRS and to determine the current knowledge of TRS. Studies were systematically collected using the databases of PubMed, Scopus and CINAHL. English language original studies and reviews on TRS with most of the sample including adults were included. The search located 449 studies. After abstract and title review, 285 studies were included regarding definitions of TRS (N=11), genetics (18), brain structure and functioning (18), cognition (8), other neurobiological studies (16), medication (158), psychotherapy and cognitive rehabilitation (12), electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) (15), prognosis (21), and other miscellaneous studies (8) on TRS. Definitions of TRS varied notably, and in most of the non-pharmacological studies the samples were small. Based on limited evidence of genetics, brain structure and functioning and cognition, TRS may present as a different disorder with different aetiology compared to non-TRS. Regarding treatments, clozapine, olanzapine, risperidone, ECT and cognitive-behavioural therapy have shown effectiveness, although the number of studies and quality of research on interventions is limited. Very little is known about risk factors, long-term course of illness and predictors of outcome in TRS, especially in naturalistic samples. Our findings suggest that TRS is a poorly defined, studied and understood condition considering its high prevalence, clinical and economic importance and poor prognosis. To create a framework of knowledge for TRS, as a basis to develop innovative studies on treatment, there is a need for a consensus on the definition of TRS. In addition, prospective long-term studies and prognostic studies are needed.

Introduction

Treatment-resistant schizophrenia (TRS) is a severe form of schizophrenia and a common condition faced by psychiatrists worldwide. One-fifth to one-third of all patients with schizophrenia is considered to be resistant to treatment (4, 140). The burden of TRS for the patients and to society is notably high (140). Patients experience unfavourable events and comorbidity associated with the disease and treatment, and unemployment and suicide risk are increased. Healthcare costs of TRS patients are 3 to 11-fold higher than schizophrenia patients in general (mainly due to high number of hospitalizations), causing 60% to 80% of the total economic burden of schizophrenia. Patients with early TRS signs and prior relapse (indicating TRS) have healthcare costs up to 2.8 times higher than patients with early response to drug treatment and no prior relapse (140). Correctly identifying and treating these patients could contribute to reduce the burden on patients themselves, the economy and society.

In the original definition of TRS (10) the patient manifests a failure to respond to three or more adequate trials of antipsychotic treatment within the last 5 years, including medication from two distinct classes with dosing at least the equivalent of 1000mg per day of chlorpromazine. In addition, there must be at least moderately severe continuous symptoms in certain psychosis symptoms (conceptual disorganization, suspiciousness, hallucinatory behaviour and unusual thought content). Lastly, there must be evidence of substantial current symptoms despite current optimized treatment to which the patient is adherent: defined as a score of greater than or equal to 45 on the Brief Psychiatric Rating Scale (BPRS) or 90 in the Positive and Negative Syndrome Scale (PANSS) (10). Different definitions of TRS will be described later in this article.

TRS may have some different biological features compared to treatment-responsive schizophrenia, for example, less dopamine synthesis abnormalities and more marked glutamatergic abnormalities (5, 7), reduced left dorsolateral prefrontal cortex (80), genetic factors (49, 54) and higher rates of minor physical anomalies (95). TRS may form a separable aetiological and diagnostic entity compared to schizophrenia in general, as epidemiological study has recently suggested (159). Despite the public health and human importance of TRS, it is a poorly studied and understood condition and the research knowledge seems scattered. To our knowledge, there are no systematic reviews summarizing scientific knowledge on several aspects of TRS, for example, aetiology, risk factors, effective treatments and prognosis.

The aim of this study was to perform a systematic review to find out the extent of published research on TRS and to determine the current knowledge of TRS.

Methods

Data collection

A computerized literature search of articles on the topic was performed in April 2015, and updated in April 2016, using electronic databases Scopus, PubMed (MEDLINE) and CINAHL (EBSCO) by information scientist, one of the authors, NH. The systematic search was implemented by using the following search strategy and algorithm to all databases: ((("ultra-resistant"[Title] OR "treatment-refractory"[Title] OR "treatment-resistant" [Title])) AND schizophrenia [Title]) AND "English"[Language]. The search was restricted to English language and there was no time restriction. We also did non-systematic manual search from the included original articles.

Study selection

Search results were evaluated by two authors (AS, EJ) based on the titles and abstracts of the articles. Additionally, the articles related to medication were re-evaluated by AS and CM. The articles included were required to meet the following criteria: original study or review (both systematic and non-systematic reviews were included) on TRS, sample including mostly adult population and English language article. The exclusion criteria were the following: conference abstract or letter or book chapter, studies focusing only on childhood-onset schizophrenia and non-English article.

Collected information

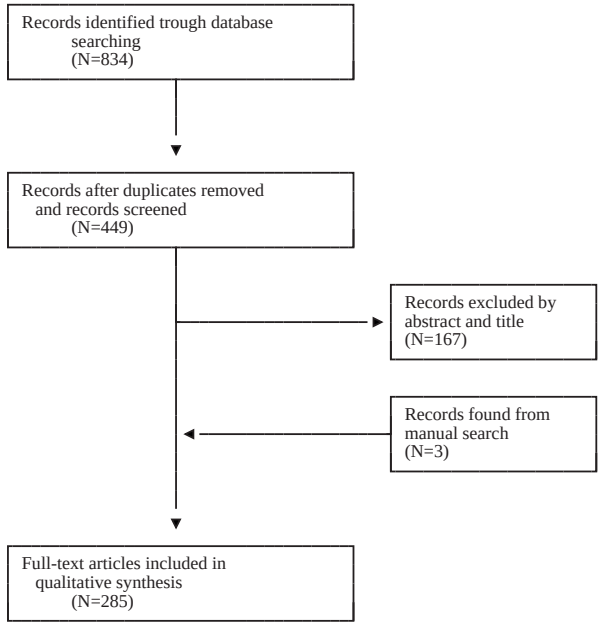
The included studies were grouped into the following categories based on their main topic: definition of TRS, genetics, brain structure and functioning, cognition, other studies on neurobiology, medication of TRS, psychotherapy and cognitive rehabilitation, electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), prognosis and other miscellaneous studies. The number of original studies and reviews in each of the categories were analysed. In addition, the main results of each study topic were collected. It should be noted that in some cases the articles were difficult to categorize into one category: if the article included several topics of TRS. For this reason, the articles by Sinclair and Adams (116) and Miyamoto et al. (109) were included in two categories (Medication of TRS and Psychotherapy and cognitive rehabilitation). Studies analysing the efficacy of medication were included into Medication of TRS, whereas studies focusing on predictors of treatment response in TRS were categorized into Prognosis.

Results

Search results

The literature search located 449 studies. All the article titles and abstracts were reviewed and three articles from the manual search were added (49, 111, 159). After this, 285 studies were included for further examination.

Figure 1. Flow chart of the selection of studies of treatment-resistant schizophrenia.



Study characteristics

The included studies were divided into ten groups based on their main topic (Table 1). A total of 11 (4%) considered definitions of TRS, 18 (6%) genetics, 18 (6%) brain structure and functioning, 8 (3%) cognition, 16 (6%) were other neurobiological studies on TRS, 158 (55%) studies considered medication in TRS, 12 (4%) psychotherapy and cognitive rehabilitation, 15 (5%) ECT and rTMS, 21 (7%) prognosis, and 8 (3%) were other miscellaneous studies on TRS.

Table 1. Number of included articles by the topic.

Topic	Total number of studies	Original articles	Reviews
Definitions of TRS	11	0	11
Genetics and TRS	18	17	1
Brain structure and functioning in TRS	18	13	5
Cognition in TRS	8	7	1
Other studies on neurobiology of TRS	16	12	4
Studies on medication in TRS	158	112	46
Psychotherapy and cognitive rehabilitation in TRS	12	7	5
Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) in TRS	15	13	2
Prognosis of TRS	21	18	3
Other, miscellaneous studies on TRS	8	6	2

What do we know about TRS?

Definition of TRS

The systematic search located 11 studies regarding the definition of treatment-resistant schizophrenia (34-44). All of these studies were reviews.

The definition of TRS varies significantly depending on the source. Selected definitions are presented in Table 2. The first and most used definition was created by Kane and colleagues in 1988 (10). The Kane definition has been modified many times since. In 2012 Suzuki et al. (24) systematically reviewed 33 studies of antipsychotic medication, updated Kane's definition and made their own proposal, described in Table 2.

The number of reviews and still lack of consensus since Kane's first definition in 1988 implicate the difficulty of creating a standardized definition of TRS. In comparison, WHO has produced, with an expert panel consensus, a definition for severe asthma (2). However, the same problem occurs regarding treatment-resistant depression, where there are no universally accepted criteria (30). Unfortunately, the varying criteria for TRS complicate scientific studies and ultimately the treatment of TRS patients.

Genetics and TRS

The systematic search located 18 studies on genetics and TRS. One of these was review (48) and 17 were original studies (45-47, 49-62).

Genes are considered to take part in the development of TRS (49, 54, 57). Despite there being a large number of genetic association studies regarding antipsychotic response, there are only few studies that have compared TRS versus non-TRS (48). Frank et al. (49) found higher polygenic risk score (based on the aggregate number of risk loci previously identified from genome-wide association studies in schizophrenia patients) among persons with a history of clozapine treatment (proxy for TRS) compared to patients with no history of clozapine treatment. Persons with history of clozapine treatment also displayed a significantly earlier age at onset and a higher frequency of insidious disease onset. These results may suggest the existence of a more severe and genetically based schizophrenia subgroup for which early intervention with clozapine could be considered.

Table 2. Selected definitions of treatment-resistant schizophrenia (TRS).

Definition	Referfence	Comment
At least three periods of treatment in the preceding five years with neuroleptic agents (from at least two chemical classes at dosages equivalent to or greater than 1000mg/day chlorpromazine for a period of six weeks), each without significant symptomatic relief **AND** No period of good functioning in the preceding five years **AND** Score of at least 45 and ≥4 in ≥2 of in the Brief Psychiatric Rating Scale (BPRS) psychotic items: conceptual disorganization, suspiciousness, hallucinatory behaviour, unusual thought content, and score of at least 4 in the Clinical Global Impression-Severity (CGI-S) **AND** No improvement after 6 weeks of treatment with haloperidol at up to 60mg or greater as measured by a reduction of at least 20% of the BPRS severity and CGI score.	Kane et al. 1988 (10)	The first definition of TRS, and one of the most narrow criteria
BPRS≥42 **AND** Non-response to ≥1 first-generation antipsychotics (FGA) at 400-600mg for 4-6 weeks, because of either insufficient effectiveness or intolerable side effects	Bitter et al. 2004 (I)	One of the most broad criteria for TRS
At least two failed adequate trials with different antipsychotics (at chlorpromazine-equivalent doses of ≥600mg/day for ≥6 consecutive weeks) that could be retrospective or preferably include prospective failure to respond to one or more antipsychotic trials **AND** Both a score of ≥4 on the Clinical Global Impression-Severity (CGI-S) and a score of ≤49 on the Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) or ≤50 on the Global Assessment of Functioning (GAF) scales	Suzuki et al. 2012 (24)	Systematic review of 33 trials

Brain structure and functioning in TRS

The systematic search located 18 articles regarding brain structure and functioning in treatment-resistant schizophrenia. Five of these articles were reviews (64, 67, 72, 73, 76) and 13 were original studies (63, 65, 66, 68-71, 74, 75, 77-80).

Nakajima et al. (73) reviewed the neuroimaging findings in TRS (and clozapine-resistant schizophrenia (CRS)). 25 studies were found, but only five studies compared TRS patients to non-TRS patients. Existing studies did not show neuroimaging correlates specifically to TRS or ultra-resistant schizophrenia (URS). Based on a more recent systematic review by Mouchlianitis et al., (72) treatment-resistant and treatment-responsive schizophrenia patients have differences in reductions of grey matter and perfusion of frontotemporal regions, and increases in white matter and basal ganglia perfusion. Clozapine treatment associated with reductions in caudate nucleus volume. Based on the available evidence, some of the neurobiological changes seen in TRS lie along a continuum with treatment-responsive schizophrenia, whereas other differences are categorical in nature and have potential to be used as biomarkers. However, further replication is needed, and for neuroimaging findings to be clinically translatable, future studies need to focus on a priori hypotheses and be adequately powered.

Non-TRS patients showed higher striatal dopamine functions than TRS patients and healthy volunteers, and there were higher glutamatergic levels in TRS in comparison with responders (65). Regarding connectivity, TRS patients showed reduced connectivity between ventral striatum and substantia nigra, and corticostriatal connectivity was more disturbed in TRS compared to non-TRS (79).

If differences in brain structure and functioning in TRS compared to non-TRS would be found it might also explain the efficacy and exact mechanism of clozapine, which is presently rather unknown. In the future, the research of the glutamatergic system could provide useful information in neuroimaging studies focused on the frontal cortical-basal ganglia-thalamic circuits. Precise definition of TRS is crucial for the future success of the research, and for the correct subtyping of study subjects into different subtypes based on the treatment response (72, 73).

Cognition in TRS

The systematic search located eight articles considering cognition in TRS. One (88) of these articles was a review and seven were original studies (81-87). Based on these, our knowledge of cognition in TRS in contrast to non-TRS is still very weak.

Frydecka et al. (83) compared cognitive performance between 53 TRS and 32 non-TRS patients. Cognitive deficits were more robust in TRS patients than in non-TRS subjects in several domains of cognition. In 19 TRS and 22 non-TRS patients, TRS patients had

poorer cognition and exhibited higher symptoms. Poorer cognitive performance correlated with more severe negative symptoms in TRS but not in non-TRS patients (82). Also non-significant results exist. There were no differences in cognitive functioning in 16 non-TRS patients, 20 TRS patients responding to clozapine monotherapy and 15 CRS patients responding to antipsychotic polypharmacy (81).

Other studies on neurobiology of TRS

The systematic search located 16 articles on other studies on neurobiology of TRS. Four of these studies were reviews (89, 90, 98, 101) and 12 were original articles (91-97, 99, 100, 102-104). The studies considered hormones, receptor functions and inflammation in TRS, for example.

Studies on medication in TRS

Antipsychotic drugs relieve symptoms and prevent relapses, but have limited efficacy particularly on negative and cognitive symptoms, and have neurological and metabolic side effects. In antipsychotic treatment, really innovative improvements, or breakthroughs in terms of new molecules or medication algorithms, have not been made during the last 20 years. Leucht et al. (13) analysed 212 suitable trials analysing the efficacy of antipsychotics in schizophrenia, and included altogether 43,049 participants. As a result, all drugs were significantly more effective than placebo. Different antipsychotics differed substantially in side effects, and small but robust differences were seen regarding efficacy.

Our systematic search located 158 individual articles on medication in TRS (references on request from the corresponding author). 46 of these were reviews and 112 were original articles. The number of double-blind randomized controlled trials (RCT), i.e. gold standard in analysing effectiveness of medication, is surprisingly low regarding TRS (14).

Clozapine has been considered as the most effective drug for patients with TRS, although new criticism for the evidence has been raised (18). The meta-analysis by Chakos et al. (3) compared the effectiveness of clozapine (CLZ) and first-generation antipsychotics (FGA) in 6 double-blind randomized controlled trials. They found a moderate overall effect in favour of clozapine. The meta-analysis by Chakos et al. (3) compared the effectiveness of CLZ and risperidone in two studies. They did not find differences in response rate. The meta-analysis by Souza et al. (23) compared the efficacy of CLZ and olanzapine in seven studies (5 efficacy trials, one safety trial

and one imaging study), and found more improvement on PANSS negative and positive subscales for the CLZ group. Based on very recent network meta-analysis by Samara et al. (18) on blinded RCT in TRS, superiority was found for olanzapine, clozapine, and risperidone compared to other antipsychotics in various efficacy outcomes in TRS, though the results were not consistent and the effect sizes were small. Though more effective than first-generation antipsychotics, rather surprisingly, there was no support for the superiority of clozapine to other second-generation antipsychotics (18).

In these meta-analyses, as in some other studies on the efficacy of antipsychotic drugs on TRS, the problem is that some samples have not been clearly defined using the operational criteria of TRS, i.e. at least part of the sample may not meet the clear definition of TRS. For example, studies may define "TRS population" just as "patients with residual positive and negative symptoms". An overly heterogeneous sample may be one reason why it has been difficult to ascertain the effectiveness of clozapine and some other antipsychotics, therefore a future focus on an operational definition of the TRS population might be one solution to change the current evidence (18).

Although these results regarding clinical work are rather confusing, Kane and Correll (9) made an important note: in the meta-analysis by Samara et al. (18), studies showing a superiority of clozapine were all open-label studies, whereas the blinded, randomized studies failed to show a difference. The fact that the studies with positive results in favour of clozapine were unblinded, mostly nonrandomized, could be interpreted in two ways the positive findings are caused by bias of treating clinicians, patients and/or raters, or, interestingly, the patients in open studies are more representative of the severely ill patients (i.e. truly TRS patients) who benefit most from clozapine, but are less likely to enrol in complex and demanding RCT. Despite somewhat confusing evidence, in clinical practice we need tested treatment algorithms for medication in TRS. At the moment, there is also evidence for clozapine from large, naturalistic register studies (17, 19). There are studies suggesting that clozapine should be offered to TRS patients earlier in their illness (19). This could potentially also lower an increased suicide rate in schizophrenia (6).

About 40% to 70% of TRS cases do not respond to clozapine. This condition is considered as clozapine-resistant schizophrenia (CRS), super-refractory schizophrenia or ultra-resistant schizophrenia (10, 109). According to a recent review (109), clozapine augmentation strategies that have at least grade B of category of evidence and have more than one trial are: 1) adding other antipsychotic drug, or 2) adding

lamotrigine (28), or 3) adding electroconvulsive therapy. There are no strategies with grade A of category of evidence. Other augmentations such as topiramate, tetrabenazine, five glutamatergic drugs, including CX516, D-cycloserine, D-serine, glycine, and sarcosine, and fluoxetine and mirtazapine have inconsistent results or negative evidence (grade D or E of category of evidence).

Despite the massive body of research on antipsychotics and many studies on TRS, to our knowledge, there are no studies on guided discontinuation of antipsychotics in TRS, nor optimal dose or dose tapering. In somatic medicine (e.g. geriatrics and oncology), medication is usually discontinued when its effects are minimal and harms are larger. Such studies or guidelines do not exist in TRS.

Psychotherapy and cognitive rehabilitation in TRS

The systematic search located 11 articles considering psychotherapy and one article on cognitive rehabilitation in TRS (111). Five of these studies were reviews (106, 108, 109, 113, 116) and seven were original articles (105, 107, 110-112, 114, 115).

Ranasinghe and Sin (113) systematically reviewed the studies on augmenting clozapine with psychosocial intervention. Research on augmenting clozapine with psychosocial interventions is scarce. Two trials of clozapine augmentation with cognitive behavioural therapy (CBT) showed as having positive effects on overall mental state. CBT adjunctive therapy is superior to the befriending control group in reducing psychotic symptoms and general psychopathology for up to 6 months at follow-up. One trial on occupational therapy, clozapine augmentation (107), suggested that the therapy significantly improved occupational performance and interpersonal relationships in 3 and 6 months follow-up.

In one randomized study, TRS patients having cognitive rehabilitation showed significantly greater improvements at 3 months in cognition, positive symptoms, functioning and insight, compared to patients participating in the occupational therapy group (111).

ECT and rTMS in TRS

The systematic search located 15 studies considering ECT (117-130) or rTMS (131) in TRS. Two of these studies were review articles (117, 126) and 13 original studies (118-125, 127-131).

There is no consensus on the role of ECT in the treatment or maintenance treatment of TRS. Chanpattana and Andrade (117) suggest that the combination of ECT and antipsychotic drugs have positive effects on some patients with TRS who did not respond to the sole treatment of medication. The treatment is more effective as a combination than separate. The long-term benefits of ECT and the specific effects and mechanisms of the treatment are still unknown.

Lally et al. (126) analysed in their very recent meta-analysis the proportion of responders to clozapine + ECT in TRS in RCT and open-label trials. There were altogether 71 people with TRS, who underwent clozapine + ECT in 4 open-label trials (N=32) and in 1 RCT (N=39). The proportion of response to clozapine + ECT was 54%. The data suggests that ECT may be an effective and safe clozapine augmentation strategy in TRS, however further research is needed before ECT can be included in standard TRS treatment algorithms (126).

There were no significant differences in cognition after combined ECT and antipsychotic therapy in TRS patients, suggesting that combined electroconvulsive therapy may not have a negative influence on the neuropsychological functioning of patients with treatment-resistant schizophrenia. The sample size of the study was 27 patients diagnosed with TRS, with 14 men and 13 women (127, 128).

In the only rTMS study, rTMS of the left temporo-parietal region (N=12) was more effective than bilateral rTMS (N=12) or placebo (N=12) in reducing auditory hallucinations in schizophrenia patients with medication-resistant auditory verbal hallucinations (131).

Prognosis of TRS

The systematic search located 21 studies regarding prognosis of TRS. Three of these studies were reviews (133, 140, 148) and 18 were original articles (132, 134-139, 141-147, 149-152). Most of these concerned treatment response as an outcome, and very little is known about other outcomes (such as occupational capacity, social remission) and long-term course of illness.

About 40% to 70% of TRS patients have an unfavourable prognosis (as measured by non-response to clozapine) (140). TRS patients are often unemployed and have an increased suicide risk compared to schizophrenia patients in general. TRS patients also have high rates of smoking (56%), alcohol abuse (51%) and substance abuse (51%) (140).

In a very recent study (132), 51% of 78 discharged (from specialized inpatient treatment for TRS) patients continued to live in the community at one-year follow-up. Severe negative symptoms, especially anhedonia/asociality, were a significant predictor of shorter post-hospital community tenure. Neurocognitive impairment and positive symptoms did not predict community outcome.

Younger age, shorter duration of illness before clozapine treatment, and fewer antipsychotic trials before the use of clozapine associated with a better response to clozapine (152). These results suggest that reducing the delay for starting clozapine may increase the effectiveness of clozapine in TRS.

Other, miscellaneous studies on TRS

The systematic search located eight articles (153-160) which did not focus specifically on any of the categories previously mentioned.

Two of these studies were original articles on risk factors of TRS compared to non-TRS. In a Danish population-based study utilizing national registers, 21% of 8044 patients fulfilled the main proxy definition of TRS during a median follow-up of 9 years. Younger age, living in a rural or less urban area, primary education level, more psychiatric hospital treatment days in the year before first schizophrenia diagnosis, inpatient at first schizophrenia diagnosis, paranoid subtype, comorbid personality disorder and previous suicide attempt were all significantly associated with TRS (159).

Yamanaka et al. (160) analysed how background and risk factors associate with TRS status (compared to non-TRS) during different phases of illness. At first-episode psychosis, lower age at onset, shorter duration of untreated psychosis, lower antipsychotic dosages and receiving ECT more often associated with TRS status. After first episode, dopamine supersensitivity psychosis (DSP), deficit syndrome, higher symptom severity and higher antipsychotic dosages associated with TRS status. Of all these factors, DSP and deficit syndrome were the strongest predictors of TRS.

Discussion

Main results

There are relatively many publications on TRS, though the number is small compared to the number of publications on schizophrenia in general (46,394 hits in April 2016 from PubMed with search algorithm schizophrenia [Title] AND "English"[Language]). However, regarding specific topics, e.g. epidemiology, prognosis, aetiology, the number of studies is surprisingly low. There are several definitions of TRS, without an internationally accepted consensus of definition. The number and quality of studies on medication and other treatments of TRS are surprisingly low. Based on the limited evidence on genetics, brain structure and functioning and cognition, TRS may present a different disorder with a different aetiology compared to non-TRS. Our findings suggest that TRS is a poorly studied and understood condition, considering its high prevalence, clinical importance and poor prognosis.

Finnish studies on TRS

In Finland, the studies on TRS have focused mostly on medication (16), especially clozapine (8, 31-33) and a combination of clozapine and another drug (25-27). Also factors relating to clozapine concentration and efficacy have been of interest, e.g. genetics (12) and smoking (20), adverse effects of clozapine (20-22, 29) and factors associated with metabolism in clozapine-treated patients (11). There is also one study on pregnancy, delivery, and socio-demographic precursors of clozapine treated schizophrenia patients (proxy for TRS) (15).

Clinical implications

Despite the number of trials, we know surprisingly little about efficacy of drugs in TRS. The major pitfalls of the studies are small sample size, heterogeneity of study samples due to lax or unclear eligibility criteria, and doubtful clinical usefulness of the term "response" (14). Despite this, in clinical practice we need to do our best for the treatment of the patients. Regarding medication, clozapine, olanzapine, and risperidone have had efficacy in various outcomes (18). The number of studies on psychosocial treatment is low. In addition, there is only one study on a promising treatment option for schizophrenia, cognitive remediation (111).

Based on naturalistic samples, markers of TRS already show at the beginning of illness (159, 160). Special focus could be paid to schizophrenia patients with a younger age at onset, more severe illness course at the beginning of the illness, the presence of personality disorder and suicidality (159), and those with psychotic relapses and deficit syndrome during the illness course (160). On the other hand, there may be a group of later TRS patients showing short duration of untreated psychosis and having smaller doses of antipsychotic medication at first episode (160). All these findings are based on just a few studies and should be considered with caution. However, based on these findings we should do our best to individually and actively treat, monitor and follow-up the patients.

Implications for future studies on TRS

In the future, first, we need a consensus of the definition of TRS. Over the years, different time periods, needs and hypotheses may have been affecting the development of the definition of TRS. In addition, the definition of TRS in trials will impact on what kind of indication the analysed drug compound will receive. In order to understand the mechanism of TRS we need well-defined groups, and if still too heterogeneous, then data-driven stratification should be considered. Since we still do not have a good understanding of TRS as a process, we are unable to find aetiology and effective treatments for TRS.

Trials should be designed with stringent and clear eligibility criteria that properly define the patient's profile. With this it would then be easier to translate the results into clinical practice and to specific populations such as TRS and clozapine-resistant schizophrenia (CRS).

Studies on epidemiology, i.e. prevalence, risk factors, course of illness in TRS, with years of follow-up are needed. Predictors of response and non-response in TRS and new treatment options for TRS should be explored. Large naturalistic and register-based samples are especially needed. Another important limitation of TRS studies is that they do not differentiate TRS with negative syndrome from TRS with positive syndrome. which are assumed to have different neurobiological basis. In the future this aspect should be considered as well.

Strengths and limitations

This is the first systematic review of all aspects of TRS. We used several electronic databases and all the abstracts were analysed by two authors, which can be considered as strengths of this study.

We did not use term clozapine in the search algorithm. To decrease the needed resources, we excluded studies focusing only on childhood schizophrenia, and we restricted our search to English language articles.

Conclusions

TRS is a poorly defined, studied and understood condition considering its clinical and economic importance and often poor prognosis. There is a need for a consensus on the definition of TRS, this being the first step towards better quality studies and better comparability and understanding of this important condition. There is also a need for longitudinal and prognostic studies and innovative treatments for TRS.

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By request from the authors

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