Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology

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Objective: Research and clinical translation in schizophrenia is limited by inconsistent definitions of treatment resistance and response. To address this issue, the authors evaluated current approaches and then developed consensus criteria and guidelines.

Method: A systematic review of randomized antipsychotic clinical trials in treatment-resistant schizophrenia was performed, and definitions of treatment resistance were extracted. Subsequently, consensus operationalized criteria were developed through 1) a multiphase, mixed methods approach, 2) identification of key criteria via an online survey, and 3) meetings to achieve consensus.

Results: Of 2,808 studies identified, 42 met inclusion criteria. Of these, 21 studies (50%) did not provide operationalized criteria. In the remaining studies, criteria varied considerably, particularly regarding symptom severity, prior treatment duration, and antipsychotic dosage thresholds; only two studies (5%) utilized the same criteria. The consensus group identified minimum and optimal criteria, employing the following principles: 1) current symptoms of a minimum duration and severity determined by a standardized rating scale; 2) moderate or worse functional impairment; 3) prior treatment consisting of at least two different antipsychotic trials, each for a minimum duration and dosage; 4) systematic monitoring of adherence and meeting of minimum adherence criteria; 5) ideally at least one prospective treatment trial; and 6) criteria that clearly separate responsive from treatment-resistant patients.

Conclusions: There is considerable variation in current approaches to defining treatment resistance in schizophrenia. The authors present consensus guidelines that operationalize criteria for determining and reporting treatment resistance, adequate treatment, and treatment response, providing a benchmark for research and clinical translation.

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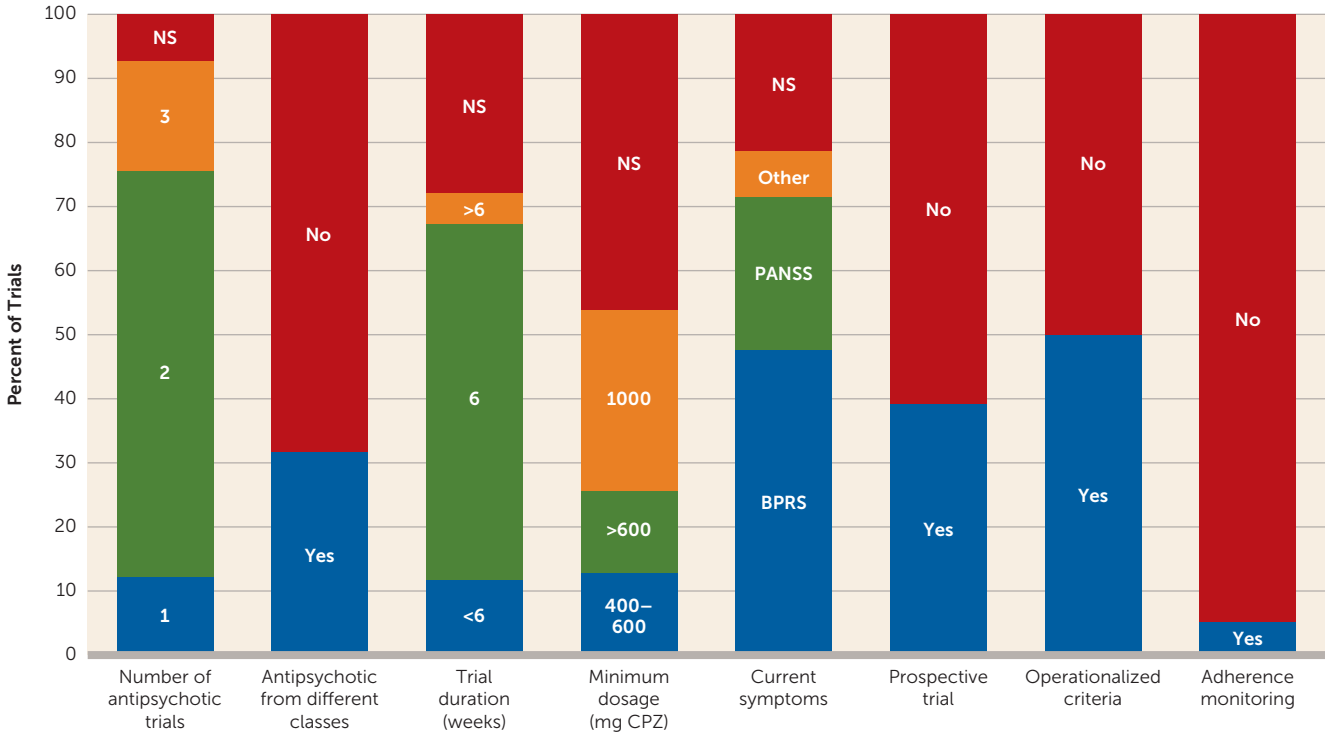
Schizophrenia is a severe mental disorder characterized by positive, negative, and cognitive symptoms (1). The treatment of schizophrenia was revolutionized by the introduction of chlorpromazine in the 1950s (2). However, it rapidly became clear that some patients showed little if any clinical response to treatment with multiple different antipsychotic drugs, with the sole exception of clozapine (3). In 1988, clozapine was shown to be effective where other antipsychotic drugs had failed (4), crystallizing the concept that in a proportion of patients, schizophrenia is resistant to most antipsychotics.

A considerable amount of research has been devoted to treatment resistance and its management, and the findings have formed a key component of treatment guidelines around the world (5–8). However, studies have used a variety of different approaches to defining treatment resistance, such that patients included in one study could be excluded from another, as illustrated in Figure 1 (9).

See related feature: **Clinical Guidance** *(Table of Contents)*

FIGURE 1. Summary of Criteria Used in Clinical Trials of Treatment-Resistant Schizophrenia[a]



[a] CPZ=chlorpromazine equivalents; BPRS=Brief Psychiatric Rating Scale; NS=not specified; PANSS=Positive and Negative Syndrome Scale. See Table S1 in the online data supplement for further details of the studies.

Consequently, comparing studies may be akin to comparing apples to oranges. This is a major hindrance to the field, making the interpretation of meta-analyses difficult and potentially contributing to failures to replicate findings. For example, a recent network meta-analysis concluded that clozapine was no more efficacious than other second-generation antipsychotics for treatment-resistant schizophrenia (10), in contrast to findings from an earlier meta-analysis, by the same group, in which studies that focused only on treatment-resistant patients were excluded (11).

Direct comparisons with the same intervention are also affected. For example, Bitter et al. (12) found olanzapine to be efficacious, while Buchanan et al. (13) found no benefit for it. Heterogeneity of study designs and populations, including less restrictive definitions of resistance (see Figure 1), may contribute to these inconsistencies (14).

This lack of uniformity in the definition of treatment resistance also has an impact on clinical guidelines that seek to distill the evidence from studies. Not surprisingly, given the variation in criteria used in the studies, treatment guidelines use vague definitions that are open to a wide range of interpretations (Table 1), potentially leading to inconsistent clinical management and treatment delays (15, 16).

In view of this situation, the Treatment Response and Resistance in Psychosis (TRRIP) working group was formed to establish consensus criteria to standardize the definition of treatment resistance. The aim was to develop criteria to aid study design and facilitate comparison of results from different studies. These recommendations are not intended to restrict research from using other criteria. However, with a consensus benchmark, it will be possible to specify how studies using other criteria differ from the consensus criteria and to investigate how this might influence results.

GENERAL REQUIREMENTS FOR TREATMENT RESISTANCE

Several factors were considered in developing the criteria. First, the criteria must encompass a core definition of treatment resistance that captures the worldwide understanding of the concept. Second, the criteria must be applicable across a range of study designs, from longitudinal clinical trials to experimental medicine studies to cross-sectional mechanistic investigations. Third, the criteria must identify a group of patients who are clearly distinct from those whose illness is not treatment resistant. Finally, the criteria must be practical, so that they can be used in a wide range of settings but still be rigorous.

Three key elements define the concept of treatment-resistant schizophrenia: 1) a confirmed diagnosis of schizophrenia based on validated criteria, 2) adequate pharmacological treatment, and 3) persistence of significant symptoms despite adequate treatment. We recognize that the optimal approach to determining lack of treatment response would be to identify patients at their first psychotic episode and prospectively assess their response to sequential adequate treatment trials. However, this is unlikely to be practical for the majority of studies, and it would be infeasible for identifying the many patients who develop resistance after years

TABLE 1. Recommendations in International Guidelines for When to Consider a Patient's Schizophrenia Treatment Resistant[a]

	Requirements of Previous Treatment					
Guideline	Minimum Number of Failed Antipsychotic Trials	Specified Antipsychotic	Adequate Treatment Episode Duration	Dosage	Severity of Illness	Other
APA (6)	2	"At least one of which is a second-generation antipsychotic"	≥6 weeks	Therapeutic range	"A clinically inadequate response" "and for patients with persistent suicidal ideation or behavior that has not responded to other treatments"	
RANZCP (23)	2	Recommends both first and second trial to be of an atypical antipsychotic	6–8 weeks	Specific dosages specified	"Poor response"	"If poor … adherence, or persistent suicide risk, positively offer trial of clozapine"
BAP (24)	2	"One of the trials should be of an antipsychotic with an established, favourable efficacy profile in comparison with other antipsychotics"	"Adequate"	"Adequate"	"Schizophrenic illness has shown a poor response to, or intolerance of the neurological side effects of [previous treatment]"	"Poor … adherence and … substance use should be excluded as causes of the … poor response to antipsychotic"
IPAP	2	"An atypical or, if not available, a trial of haloperidol, chlorpromazine or other typical antipsychotic"	4–6 weeks	"Adequate"	"Psychosis or moderate-to-severe tardive dyskinesia or tardive dystonia after adjusting dose"	
Maudsley (25)	2	Consider use of either first- or second-generation antipsychotic	2–3 weeks for trial of first antipsychotic in first-episode psychosis; 6-week trial for a subsequent antipsychotic before clozapine	At least minimum effective dose, then titrated to response	Not specified	
MOHS (26)	2	No	Adequate	Adequate	"Illness has not responded adequately to treatment"	Two trials should be given "sequentially"
NICE (5)	2	"One of the drugs should be a non-clozapine second-generation antipsychotic"	Not specified	Adequate	"Illness has not responded adequately to treatment"	Two trials should be given "sequentially"
WFSBP (7)	2	"One of which should be an atypical antipsychotic"	6–8 weeks	Recommended dosage	No improvement at all or only insufficient improvement in the target symptoms	Adherence should be ensured, if necessary by checking drug concentrations

[a] APA=American Psychiatric Association; BAP=British Association for Psychopharmacology; IPAP=International Psychopharmacology Algorithm Project (www.ipap.org); MOHS=Ministry of Health Singapore; NICE=National Institute for Health and Care Excellence; RANZCP=Royal Australian and New Zealand College of Psychiatrists; WFSBP=World Federation of Societies of Biological Psychiatry.

of treatment. In view of this fact, the criteria also need to allow for cross-sectional identification of treatment resistance.

However, the risk of false positives is likely to be greater with the cross-sectional identification of treatment resistance than with prospective determination. This is because cross-sectional identification requires the retrospective determination of response and adequacy of treatment and is dependent on potentially less reliable sources of information, such as case notes and patient or informant report data. While with any approach there is a risk of false positives, it is important to have criteria that are sufficiently rigorous to capture the construct, yet also practical enough to be used in studies. Hence, we present two sets of criteria: minimum criteria and optimum criteria. The optimum criteria are to be used where possible, particularly in clinical trials and hypothesis testing, where the false positive rate should be low. The minimum criteria might be used for initial studies and hypothesis generation, where there are practical limitations on study design and some false positives can be accepted.

METHOD

An iterative approach was adopted to develop criteria for treatment resistance in schizophrenia. Initially, a systematic review of definitions of treatment-resistant schizophrenia used in clinical trials was conducted. A literature search of PubMed, PsycINFO, and Embase from January 1980 to January 2016 was undertaken using the search string "(randomized or random or randomly) and (resistant or refractory or clozapine) and (schizophrenia)." Titles and abstracts were reviewed to initially determine eligibility. The reference lists of all relevant articles were also searched, as were the reference lists of relevant review articles, to further identify potential studies. Studies were included if they were randomized controlled trials of a pharmacological intervention in adults with treatment-resistant schizophrenia. Studies were excluded if they were naturalistic studies, studies purely of biomarkers such as neuroimaging measures, studies of adjuvant treatments or nonpharmacological interventions, or studies of childhood-onset or late-onset schizophrenia.

The data extracted were the prerequisites for previous antipsychotic treatment (requirements of different antipsychotics, minimum treatment duration, dosage), the specified severity of symptoms, and whether there was a stipulation for treatment resistance to be prospectively demonstrated. Additionally, whether or not criteria were operationalized was recorded. To be considered as operationalized, the study had to report criteria that met the following characteristics: 1) the use of a validated rating scale to determine symptom severity; 2) a specification of minimum symptom duration; and 3) a definition of adequate treatment that specified minimum dosage, duration, and number of previous antipsychotics.

Subsequently, a working group—consisting of expert researchers and clinicians, scientists from the pharmaceutical industry, and other specialists with experience and expertise in the area of schizophrenia—was identified by the cochairs of the TRRIP working group (O.H., J.M.K., C.U.C.). This was augmented by attendees at TRRIP meetings held at international conferences in the field. Members of the final working group included researchers who had published recently in the field and researchers who attended the inaugural TRRIP meeting at the Schizophrenia International Research Society biennial meeting in 2014. The working group mapped out the key criteria and operationalized them.

Second, members of the TRRIP working group were contacted and invited to take part in an online survey to identify key areas of agreement and disagreement. The survey was developed by the TRRIP cochairs and modified with input from TRRIP work group members. In its final version (see the data supplement that accompanies the online edition of this article), the survey was conducted using SurveyMonkey (www.surveymonkey.com). Forty-eight researchers and clinicians were invited by e-mail to take part in the survey. Over the 30-day collection period, 29 responses (60%), covering 13 countries, were received; three responses (10%) were incomplete. (See the data supplement for a summary of the responses to individual items.) These responses were synthesized and refined during subsequent discussions among the whole group to derive the consensus recommendations for both minimum and optimum criteria.

Third, the working group met to consider and revise criteria for which there was a lack of consensus. The revised criteria were circulated to the TRRIP working group members and presented as part of an open workshop at an international meeting in the field for further discussion, input, and refinement. Finally, consensus was reached regarding this publication through review by all authors.

TRRIP Meetings

Criteria were discussed at the Schizophrenia International Research Society biennial meetings (2014 and 2016), the American College of Neuropsychopharmacology Annual Meeting (2014), and the International Congress on Schizophrenia Research (2015), where the open workshop also occurred.

RESULTS

Systematic Review

A total of 2,808 studies were identified, of which 42 met selection criteria and were included in the review (see Figure 1). Operationalized criteria were reported in 21 studies (50%). Only two of the 42 studies used identical criteria to define treatment resistance, and these were from the same research group. In all, 26 studies (62%) required that patients had not responded to at least two adequate treatment trials; there was no specification regarding class of antipsychotic in 29 studies (69%); 24 studies (57%) defined an adequate treatment episode as lasting at least 6 weeks; and only 22 studies (52%) specified dosage in terms of chlorpromazine equivalents, while the remainder used terms such as

"adequate" without reporting a dosage. Twenty studies (48%) rated current symptoms using the Brief Psychiatric Rating Scale (BPRS) (17), and 10 (24%) used the Positive and Negative Syndrome Scale (PANSS) (18). Sixteen studies (38%) employed a prospective phase of supervised treatment as part of the inclusion process. Two of the studies (5%) described assessment of past adherence, but neither described the methods employed.

Consensus Recommendations

The consensus criteria are summarized in Table 2 and discussed below. See the online data supplement for further discussion of the basis for these recommendations.

1. Terminology. It is recommended that the term "treatment-resistant schizophrenia" be used to describe cases of schizophrenia meeting the criteria outlined below and that use of this term be restricted to patients meeting these criteria. The consistent use of this term will facilitate communication and the identification of relevant literature. In the future, if treatments other than antidopaminergic antipsychotics become established for schizophrenia, it may be necessary to add treatment specifiers, such as dopamine-blocking treatment-resistant schizophrenia.

2. Clinical subspecifiers. The initial trials demonstrating the superiority of clozapine for treatment resistance were undertaken in patients with a high degree of positive symptoms, and in clinical practice this remains the archetypal patient with treatment-resistant illness, driven also by the fact that current effective treatments for schizophrenia remain limited to positive symptoms. However, an increasing amount of research has investigated groups of patients who, while termed "treatment resistant," may differ significantly from one another in their symptom profile. As a result, there is a need for clarity as to patients' clinical profile. A patient's illness may meet criteria based on overall symptoms or based on specific subdomains of positive, negative, or cognitive symptoms. It may not be appropriate to compare groups of patients in whom the illness is predominantly resistant to treatment in one domain with groups whose illness is predominantly resistant in another domain. In view of this, two recommendations are made: first, that the symptom domains used to define resistance be made explicit, and second, that the domain be specified using the subspecifiers "positive," "negative," or "cognitive" (the latter contingent on developing reliable criteria). Where the patient group is defined as meeting a given threshold of positive symptoms, this is specified as "treatment-resistant schizophrenia–positive symptom domain," and similarly "treatment-resistant schizophrenia–negative symptom domain" and "treatment-resistant schizophrenia–cognitive symptom domain" for the other categories. Where more than one domain is involved, this may be specified—for example, as "treatment-resistant schizophrenia–positive and negative symptom domains."

3. Symptom thresholds.

3.1. Rating scales. As can be seen from our summary of clinical guidelines for treatment resistance (Table 1), the current clinical guidelines for symptom response use terms such as "not adequate" that are poorly operationalized. Furthermore, the reliability of these definitions for treatment resistance has not been established. In view of this situation, a clinical or case note diagnosis of treatment resistance based on clinical guidelines cannot be recommended. Instead, it is recommended that a standardized, validated symptom rating scale, such as the PANSS (18), the BPRS (17), the Scale for the Assessment of Negative Symptoms (SANS) (27), or the Scale for the Assessment of Positive Symptoms (SAPS) (28), be used to measure current overall, positive, and negative symptom severity.

3.2. Absolute thresholds. There are two components to the symptomatic assessment of treatment resistance. The first is the absolute threshold of current symptom severity. It is conceivable, although in practice unlikely, that a patient has never had more than mild symptoms but has not shown a response to a series of treatments. While the patient's symptoms are treatment resistant, there are clinical and methodological risks associated with including such a patient in studies. First, mild severity on rating scales is at the borderline with uncertain symptoms. Given that interrater reliability for rating scales is 0.85–0.9, even when carefully applied (29), the measurement error means that there is the risk of including patients with uncertain symptoms. Second, the clinical risk-benefit balance in patients with mild symptoms is very different from that in patients with more severe symptoms, where the severity of the condition provides much stronger support for experimental interventions. In view of this, it is recommended that the minimum threshold for current symptoms should be at least moderate severity, as defined on a standardized rating scale.

By the same token, it is conceivable that a patient could have a rating of moderate severity on just one symptom item and no other ratings. Given measurement error, there is the risk that this patient's illness is subthreshold. Thus, it is recommended that the threshold of at least moderate severity is attained for more than one symptom in the given domain, or, if there is only one symptom, it should be at least severe. These criteria are minimum thresholds that are designed to ensure that patients are clearly currently unwell to a degree that would warrant intervention. These severity threshold criteria are intended to apply to each domain. Thus, for example, a study of resistant positive symptoms would require at least two positive symptoms of moderate or greater severity or at least one symptom with at least a severe rating, and a study of negative symptoms would require at least two negative symptoms at moderate or greater severity or at least one symptom with at least a severe rating. A study of both resistant negative and resistant positive symptoms would need to meet these criteria in each domain. Of course, a study may recruit patients who are much more severely ill. We do not mean to preclude research focusing on patients who are

TABLE 2. Consensus Criteria for Assessment and Definition of Treatment-Resistant Schizophrenia[a]

Domain and Subdomain	Minimum Requirement	Optimum Requirement
Current symptoms		
Assessment	Interview using standardized rating scale (e.g., PANSS, BPRS, SANS, SAPS)	Prospective evaluation of treatment using a standardized rating scale
Severity	At least moderate severity	At least moderate severity and <20% symptom reduction during a prospective trial or observation of ≥6 weeks
Duration	≥12 weeks	≥12 weeks; specify duration of treatment resistance
Subjective distress	Not required	Not required
Functioning	At least moderate functional impairment measured using a validated scale (e.g., SOFAS)	At least moderate functional impairment, measured using a validated scale (e.g., SOFAS)
Adequate treatment		
Assessment of past response	Information to be gathered from patient/carer reports, staff and case notes, pill counts, and dispensing charts	Information to be gathered from patient/carer reports, staff and case notes, pill counts, and dispensing charts
Duration	≥6 weeks at a therapeutic dosage; record minimum and mean (SD) duration for each treatment episode	≥6 weeks at a therapeutic dosage; record minimum and mean (SD) duration for each treatment episode
Dosage	Equivalent to ≥600 mg of chlorpromazine per day.[b] Record minimum and mean (SD) dosage for each drug.	Equivalent to ≥600 mg of chlorpromazine per day.[b] Record minimum and mean (SD) dosage for each drug.
Number of antipsychotics	≥2 past adequate treatment episodes with different antipsychotic drugs. Specify median number of failed antipsychotic trials.	≥2 past treatment episodes with different antipsychotic drugs and at least one utilizing a long-acting injectable antipsychotic (for at least 4 months). Specify median number of failed antipsychotic trials.
Current adherence	≥80% of prescribed doses taken. Adherence should be assessed using at least two sources (pill counts, dispensing chart reviews, and patient/carer report). Antipsychotic plasma levels monitored on at least one occasion. Specify methods used to establish adherence.	Same as the minimum criteria, with the addition of trough antipsychotic serum levels measured on at least two occasions separated by at least 2 weeks (without prior notification of patient)
Symptom domain	Positive, negative, cognitive	Same as for minimum criteria
Time course	Early onset (within 1 year of treatment onset), medium-term onset (1–5 years after treatment onset), late onset (>5 years after treatment onset)	Same as for minimum criteria
Ultra–treatment resistant: clozapine	Meets the above criteria for treatment resistance plus failure to respond to adequate clozapine treatment[c]	Same as for minimum criteria

[a] BPRS=Brief Psychiatric Rating Scale; PANSS=Positive and Negative Syndrome Scale; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SOFAS=Social and Occupational Functioning Scale. All patients should have a diagnosis of schizophrenia made using established criteria and a clinical review to establish that their symptoms are not primarily due to comorbidity or substance misuse.
[b] Based on established conversion criteria (e.g., 19–22).
[c] See section 5.5.

not included in these definitions, but we recommend that the criteria used are given relative to these criteria so that their differentiating characteristics are clear and reported. This will facilitate future comparisons across studies.

It should be relatively straightforward to apply the minimum criteria discussed above to positive and negative symptom domains where validated scales exist. However, there is no cognitive symptom domain in the most widely used clinical rating scales (e.g., PANSS, BPRS, SANS, SAPS), and few if any items cover cognitive symptoms in these rating scales. Therefore, it is not currently possible to recommend threshold criteria for cognitive symptoms. However, a number of current initiatives, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and others (30, 31), aim to develop and validate reliable cognitive batteries for the assessment of cognitive symptoms in schizophrenia. These will enable the establishment of criteria for treatment resistance in the cognitive domain in the future. It should also be noted that factor analyses of rating scales have identified other domains, which may be of interest in specific studies. We recommend that where these are used, they be specified in the same manner as the domains listed here.

3.3. Symptom change. The second component of symptomatic assessment is the determination of response to treatment relative to a baseline. Ideally, this should be performed prospectively for two treatment episodes with different antipsychotic drugs. While this will not always be practical, it is recommended that there be at least one prospective evaluation of treatment efficacy. If this is not possible, then this should be clearly specified and a retrospective assessment of response to treatment obtained as a minimum.

A change of 20% is the minimum that can be routinely detected clinically (32). Therefore, a reduction of less than 20% will correspond to a clinically insignificant reduction in symptoms. It could be argued that larger reductions may still not be clinically meaningful. However, given that an improvement of ≥20% has been used to identify treatment responders (33), requiring a reduction of <20% ensures that the treatment-resistant group does not overlap with treatment responders. Therefore, it is recommended that at the end of the prospective evaluation, the absolute symptom severity rating criteria described above should still be met, and that symptom reduction should be <20% both for the total rating and the specific domain of interest before such a patient is included in a prospective treatment trial of treatment-resistant schizophrenia. In the event that a patient shows an improvement of ≥20% during the prospective observation period, then the patient should be re-evaluated and, if absolute criteria for treatment-resistance are still met, be observed for another prospective evaluation period. Only patients who during the prospective observation improve by <20% and still fulfill absolute severity thresholds for treatment resistance should be categorized as having treatment-resistant illness and included in prospective studies. In contrast, precise quantitative assessment is unlikely to be feasible for retrospective evaluation (which is exactly why we recommend prospective evaluation of treatment resistance). Therefore, for past treatment episodes, we recommend that patients should be rated as less than "minimally improved" on the overall change in the Clinical Global Impression–Schizophrenia Scale (34). It is recommended that multiple sources of information, including patient and caregiver reports, case notes, and staff report, be used to evaluate past response. Nevertheless, because measurement error is likely to be larger in the retrospective evaluation of response to past treatment, in order to be conservative, it is recommended that where there is missing information or doubt, investigators err on the side of caution and exclude subjects or prospectively evaluate nonresponse in at least this subgroup. A further important requirement is that investigators ensure that rating scales are adjusted to a baseline of zero. For example, a score change from 90 to 60 in the 30-item PANSS, in which each item is scored 1–7, represents a 50.0% reduction rather than 33.3%. Using a nonzero score for absent symptoms with the PANSS will lead to underestimation of treatment effects when percentage change in symptoms is calculated (35).

3.4. Functional impact. It is of course conceivable that a subject has symptoms at threshold severity but that these symptoms have little functional impact (36, 37). Thus, in addition to symptom severity, it is recommended that functional impairment be measured using a recognized, validated measure and that this be reported. Scales that only index functioning, such as the Role Functioning Scale (38) and the Social and Occupational Functioning Scale (SOFAS) (39), are preferred over scales that include symptom assessment as part of the measure, as symptom severity can strongly influence ratings. To be consistent with required symptom thresholds, we propose that functional impairment be of moderate (e.g., a score <60 on the SOFAS) or greater severity.

Distress caused by symptoms is also an important factor to consider. However, because of the lack of insight associated with schizophrenia (40), some patients may not report distress. Furthermore, distress is subjective and difficult to operationalize. It is therefore recommended that subjective distress not be a requirement (although measuring and recording it is desirable to capture patient-centered outcomes).

It should be recognized that symptoms and function may fluctuate as part of the natural history of the disorder and that there is an element of measurement error in the assessment of symptoms (1, 29). Therefore, it is necessary to establish that symptoms have persisted over a reasonable period of time to be clear that a patient's illness is truly treatment resistant. It is recommended that the *minimum* duration of symptoms be 12 weeks, during which time symptoms and functional impairment must be of at least moderate severity, and that the minimum duration be clearly identified.

4. Characterizing treatment resistance.

4.1. Degree. Treatment resistance is mostly treated as a binary variable as a study entry or treatment decision criterion in research and clinical practice. This is often necessary for research purposes and when making clinical decisions. Clinically, however, a continuum is apparent (41). Hence, carefully characterizing patients will aid finer-grained assessments of biological mechanisms or treatment effects in well-defined subgroups of patients with treatment-resistant illness. Thus, it is recommended that symptom and functional measures be reported in as much detail as possible. As a minimum, this should include positive and negative symptom ratings using a validated instrument such as the BPRS, the PANSS, or the SAPS and SANS, and a measure of functional impairment using a validated measure such as the Role Functioning Scale or the SOFAS (18, 27, 28, 39, 42, 43). These measures should also be used to characterize change after an intervention, as treatment may affect certain symptom domains more than others. This characterization will facilitate research into the continuum of treatment resistance and enable better comparison between studies as well as an estimation of the room for improvement at an individual level.

4.2. Temporal development. In some patients, treatment resistance is present from illness onset, while in others, the illness shows an initial response to treatment and resistance develops subsequently (44–48). From a theoretical perspective, both the mechanisms underlying resistance and the therapeutic implications may be different in these two situations; for example, clozapine does not show clear superiority over other antipsychotic drugs in first-episode patients who do not have treatment-resistant illness (49, 50). While the importance of this is not clear, to facilitate research into these issues, it is recommended that it be specified whether patients have had treatment-resistant illness from within the

first year of treatment (early-onset treatment resistance) or developed it 1 to 5 years after onset of treatment (medium-term-onset treatment resistance) or more than 5 years after onset of treatment (late-onset treatment resistance). Ideally, the duration of treatment resistance should also be ascertained and reported. Other factors posited to be relevant to the pathophysiology of resistance, such as development of resistance following relapse and substance misuse, should be recorded where possible (51). It is important to note that duration of treatment resistance relates to treatment onset and not illness onset; otherwise it could be confounded by duration of untreated psychosis.

5. Defining adequate treatment.

5.1. Duration. It could always be argued that a patient may respond if treatment is given for a little longer, which, taken to the extreme, leads to the requirement that a patient would need to take a given treatment for life to be certain they will not respond. However, few nonresponders within the first 6 weeks go on to respond later, and clinical trials for licensing, which form a large portion of the evidence base, generally last 4–6 weeks (52). Clearly there is the need to balance the risk of false positives with practical considerations. Thus it is recommended that each antipsychotic treatment episode should have lasted *at least* 6 weeks, at a therapeutic dosage (see section 5.2), to be deemed "adequate." Thus, given the minimum number of different antipsychotic treatment episodes (see section 5.3), the minimum duration of treatment required is 12 weeks. As outlined below (section 5.5), to rule out "pseudo-resistance" due to inadequate treatment adherence, the optimal definition of treatment resistance would include at least one failed trial with a long-acting injectable antipsychotic, given for at least 6 weeks after it has achieved steady state (generally at least 4 months from commencing treatment) (53, 54).

5.2. Dosage. For a treatment episode to be deemed therapeutic, the *minimum* dosage of prescribed oral or injectable antipsychotic should be the target dosage—or the midpoint of the target range—for the acute treatment of schizophrenia given in the manufacturer's summary of product characteristics. If this is not clear or practical, it is recommended that a total daily dose equivalent to 600 mg of chlorpromazine (determined using established conversion ratios such as those provided in articles regarding dose conversion [e.g., 19–22]) be used as the minimum. Where there is a range of possibilities, it is recommended that clinicians err on the side of a higher minimum daily dose. If a medication trial must be aborted because of intolerability before reaching the criteria of an adequate dosage for at least 6 weeks, it should not be counted as a failed adequate treatment trial.

5.3. Number of past treatment episodes. Failure of at least two adequate treatment episodes with different antipsychotic drugs, each meeting the above criteria, is required to establish treatment resistance. In some clinical guidelines it is recommended that these trials include different types of antipsychotics (such as first- and second-generation drugs) (Table 1). However, given the overlap in side effects, efficacy, and receptor profiles among currently available non-clozapine antipsychotics, the consensus was that the current data do not delineate distinct categories of non-clozapine antipsychotics (11, 55). There was some disagreement about this conclusion among the working group members, as olanzapine, risperidone, and amisulpride show consistent, although small, advantages in meta-analyses of efficacy (56). However, consensus was reached that, when considering this from a practical perspective as well, specifying particular drugs would limit generalizability, not least because a given drug may not be readily available in some settings (for example, amisulpride in the United States). In view of this, a requirement to use particular categories or drugs (apart from clozapine) is not currently recommended. Of course, particular drugs may be stipulated in a given study when there is a specific reason to focus on patients who have not responded to a certain drug or group of drugs. In practice, many patients will have tried a large number of different drugs (16). In view of this, the total number of failed adequate antipsychotic treatment trials, the drugs, and their dosage and route of administration should be ascertained and reported where possible. As mentioned above, a trial with a long-acting injectable antipsychotic would be optimal to establish treatment resistance not confounded by treatment nonadherence.

In terms of both duration and number of treatment trials, it is necessary to optimize treatment promptly, yet also to minimize the risk of prematurely discarding potentially effective treatments. Arguments can be made for extending treatment trials, given that a proportion of patients appear to show a delayed response (57); conversely, it can also be argued that treatment with a second non-clozapine antipsychotic after initial treatment failure is not warranted, given that response rates seem to be below 20% (44). The proposed criterion of at least two trials lasting a minimum of 6 weeks aims to strike a balance between these two opposing views.

5.4. Clozapine-resistant schizophrenia. For clarity, and because of the specific role of clozapine in the treatment of resistant schizophrenia (58–62), failure to respond to clozapine is to be used as a subspecifier of treatment-resistant illness—"clozapine-resistant schizophrenia." In addition to using the midpoint of the dosage range as a minimum requirement for an adequate trial, and the adherence requirements described below (section 5.5), it is recommended that trough serum levels of clozapine be measured on at least two occasions separated by at least 1 week at a stable dosage of clozapine. This is important not only to establish adherence but also because of the link between serum levels of clozapine and response (63–67). Clozapine levels ≥350 ng/mL (68) constitute an optimum threshold requirement for establishing nonresponse to clozapine treatment. It is strongly recommended that serum levels be used, not least because of the major effect of smoking and gender on clozapine's pharmacokinetics, but when obtaining blood samples is not feasible, a minimum dosage of 500 mg/day is

recommended, unless tolerability issues restrict the dosage range. This dosage is in the middle of the approved range for clozapine, and it was only at dosages over 400 mg/day that clozapine proved superior to other antipsychotics in a meta-analysis of head-to-head comparisons (69).

The duration of an adequate trial of clozapine remains to be definitively determined (70). Studies have variously recommended trial durations ranging from 4 to 12 months (71–73). Others, however, have suggested that the time course of response to clozapine is not significantly different from that for non-clozapine antipsychotics (74–76), and the perception of a delayed response may be due primarily to the time taken to reach a therapeutic level (77). Because of the lack of clarity as to how to proceed after a failed clozapine trial, and the clinical effort required to establish treatment with clozapine, we recommend that clozapine therapy be tried for a duration of at least 3 months after attainment of therapeutic plasma levels.

5.5. Adherence. Because of difficulties with adhering to dosing schedules, lack of illness insight, side effect burden, cognitive impairment, and other factors, nonadherence is a significant problem in the treatment of schizophrenia and is often underrecognized (78–81). Nonadherence may be the single largest source of unrecognized error in studies of treatment resistance (78). Consequently, it is important to make strenuous efforts to determine adherence and to apply criteria to exclude poorly adherent subjects, who can represent false positive "pseudo-resistant" cases. While 100% adherence is rare even in clinical trial settings (82, 83), it is necessary to be close to this figure; otherwise, the study will be of nonadherence rather than of treatment resistance.

As a minimum, it is recommended that patients have taken ≥80% of prescribed doses at the prescribed dosage over the required ≥12-week treatment period during which the criteria for treatment resistance have persisted. This adherence level should be determined by as many sources as feasible, including a minimum of two of the following: pill counts, dispensing chart review, and patient/caregiver report. Sources should be specified, but patient report alone is unlikely to be sufficient (42). In addition, given that there may still be covert nonadherence, antipsychotic blood levels should be determined in all patients taking oral medication on at least one occasion (and optimally on at least two occasions, separated by at least 2 weeks). Because anticipation of blood testing could encourage an unrepresentative period of increased adherence beforehand, tests should be conducted without advance notice. Where guidelines (such as the Maudsley Prescribing Guidelines [25]) indicate a minimum plasma level associated with response, this should be used as a minimum criterion. However, where there is a lack of consensus as to what is a therapeutic plasma level, a minimum level will need to be set based on what can be expected in people regularly taking the drug at a therapeutic dosage (84). Nevertheless, unless blood level monitoring is frequent, covert nonadherence is still possible. Thus, where possible, or as a pragmatic and likely superior alternative to documenting adequate antipsychotic blood levels on at least one occasion, it is recommended that one of the failed treatment episodes involve a long-acting injectable antipsychotic or, alternatively, that adherence in one treatment episode have been monitored via direct observation or with technological assistance that signals actual ingestion (85).

6. Defining adequate treatment responders. Cross-sectional and mechanistic studies will often require a comparator group of participants who have shown a good response to treatment. For consistency, the same clinical rating scales should be used to identify this group as those used to identify the treatment-resistant group. In addition, the criteria need to ensure that there is a clear distinction between groups. This precondition requires that the criteria make allowance for measurement error and have a clear separation of thresholds in order to avoid the inclusion of participants rated in a borderline zone who are potentially eligible for both groups, depending on the rater or the day that they are rated. Thus, it is recommended that for an absolute symptom threshold, responders show no more than mild symptom severity across the symptom items in the domain(s) of interest, and that they have shown this over at least 12 weeks. Where possible, it is recommended that response be ascertained prospectively over at least 6 weeks and defined as at least a 20% improvement in symptom scores for the domain of interest as well as meeting the absolute thresholds. Furthermore, there may be circumstances—for example, studies in first-episode patients—where this threshold may be of insufficient stringency. In these circumstances, investigators may choose even more rigorous stability criteria to define adequate treatment response, such as having achieved remission, consisting of no more than mild positive and negative symptoms for ≥6 months (8) or no symptoms at all. In addition to the symptom severity threshold, current functional impairment should not be more than mild (e.g., a score >60 on the SOFAS) in all circumstances. Table 3 presents a summary of the criteria.

DISCUSSION

Our review of the criteria currently used to define treatment resistance in clinical trials identified significant limitations in published studies. Notably, 50% of studies did not use fully operationalized criteria, rendering it impossible to accurately replicate these studies. Furthermore, there was wide variation in the criteria used, with 95% of studies using different criteria, complicating comparisons across studies. Finally, in many studies, key aspects of determining treatment resistance were not specified. For example, assessment of prior antipsychotic adherence was not specified in 95% of studies. These findings indicate a need for criteria that can be used as a benchmark for future studies.

We developed criteria to address this need. Across a wide range of areas, there was a relatively clear consensus in the working group as to how best to define treatment-resistant

schizophrenia. The consensus criteria are summarized in Table 2. The criteria we suggest show agreement in a number of domains with those used in the majority of studies in the literature, in particular the requirements for at least two failed treatment trials, each of a minimum of 6 weeks, and the use of standardized rating scales (see Table S1 in the online data supplement). However, our recommendations differ from approaches used by most studies in the literature in several key domains. In particular, our recommendations have clear criteria for ensuring adequate adherence and for the inclusion of functional impairment. Furthermore, our recommendations include specifiers to characterize the sample, and they cover reporting standards to aid comparisons across studies. Finally, we recommend a lower minimum antipsychotic dosage than many early studies required, reflecting the recognition in the field that very high dosages generally increase the risk of side effects without additional therapeutic benefit.

The universal adoption of these consensus criteria would facilitate literature searches and meta-analyses as well as help to improve the design of studies. The implementation of operationalized criteria should improve the quality and reproducibility of research in the area of treatment-resistant schizophrenia, both in the neurobiological and treatment domains, akin to what has been achieved by operationalizing criteria for treatment remission in schizophrenia (8). The next step is to utilize the criteria in different research settings to evaluate their ease of use and reliability, both within and between raters. We encourage interested researchers to help with this effort by forming a TRRIP Trial Network. It should be noted that these criteria are not intended to govern clinical practice in the sense that clozapine should only be prescribed to patients fulfilling research criteria for treatment-resistant schizophrenia. Thus, this is not a treatment guideline, and the various clinical scenarios that may prompt clinicians to use different treatments for patients with schizophrenia are not addressed here.

Strengths and Limitations

The recommendations presented here were developed through an iterative process and in consultation with expert researchers and clinicians from across the world. As such, they extend previous recommendations (e.g., 86, 87) to reflect a wide body of opinion, and they have been refined to be applicable to a variety of settings. Nevertheless, a limitation is that they may not reflect practice or opinion in all locations. We have attempted to consult widely to mitigate this issue, and we sought to produce criteria that are sufficiently representative as to be useful to the field. Furthermore, we have attempted to produce practical criteria that can be easily implemented while also addressing the limitations of previous approaches.

Although not all invited experts responded to the online survey, they all participated in discussions and the development of the consensus criteria. Moreover, while the survey identified some areas where there were small majorities (see the online data supplement), subsequent discussions clarified and refined the criteria to enable agreement, and all participants subscribe to the final criteria presented here.

TABLE 3. Criteria for Establishing a Group of Patients With Adequate Treatment Response[a]

Measure	Criterion
Symptom severity	Symptoms rated at no more than mild severity
Duration	Response sustained for a minimum of 12 weeks
Functioning	Impairment rated as mild or better on a standardized scale (e.g., SOFAS)

[a] SOFAS=Social and Occupational Functioning Scale.

Although in clinical care and in treatment guidelines, antipsychotic treatment combined with psychosocial strategies is advocated for the optimal care of people with schizophrenia, we did not specify a minimum level of "adequate" psychosocial interventions as a prerequisite before treatment resistance could be identified. This decision was not based on an underestimate of the importance of psychosocial treatments but rather on the current lack of operationalized criteria for determining adequate psychosocial treatment (88). We anticipate revising this aspect once initiatives to develop criteria have reported data that will allow for a standardized approach.

An important conceptual issue is that the recommendations are based on clinical criteria only. The clinical endpoint may involve multiple pathophysiological pathways, which may have different treatment implications. While clinical criteria are the current state of the art, we anticipate that ultimately the classification will be revised and informed by the underlying biology and mechanisms as evidence on them emerges (89–91).

A further potential issue is that there is likely a continuum of treatment response and that dichotomous categories such as "adequate treatment response" and "treatment resistance" are crude and reductionist. The endorsement of some (established) rating scales or some "cutoffs" to achieve this, from a list of many other potentially useful options, may be considered as a compromise. While we acknowledge this, clinicians and patients have to make choices about whether to continue with a given treatment, and research studies require randomized treatment assignments. In this context, the categorization we propose aims to prioritize specificity over sensitivity and should help facilitate both clinical care and research decisions.

The criteria recommended here reflect a consensus on the balance between practical considerations, the risk of false positives, and the potential to translate findings derived from studies into clinical practice. It is acknowledged that alternative cutoffs may be more appropriate in specific studies, but we recommend that these criteria be specified in reference to the benchmarks outlined here, so that it is clear how they differ.

Finally, we have codified the concept that treatment resistance may develop at different stages of the illness or be present from illness onset. Clinically, it is clear that there are some patients who initially experience a good response to antipsychotic treatment and treatment resistance later develops, while others have little or no response from treatment onset (44–48). This is of considerable potential clinical and mechanistic importance. However, despite this widespread clinical observation, there is relatively little research evidence on this issue (44–48). Our categorization does introduce boundary issues, particularly between early and late treatment resistance, where it may be argued that there is likely to be little difference between a patient who develops treatment resistance after 4 years of treatment and one who develops it after 5 years of treatment. However, practical considerations required a cutoff that would be easy to apply and that reflected widespread clinical and research definitions of the early course of schizophrenia, which include the first 5 years following illness onset (92, 93). It is intended that the criteria will stimulate research into whether there are differences between patients who develop treatment resistance early, late, or from illness onset, and that it will clarify the reporting of studies.

CONCLUSIONS AND FUTURE DIRECTIONS

Treatment-resistant schizophrenia is a major clinical problem, and clinical guidelines throughout the world recommend specific treatments for affected individuals (5–7). A wide variety of criteria have been applied in research studies. As a consequence, clinical guidelines based on these studies use imprecise or inconsistent definitions that are likely to include patients with very different clinical characteristics from those of the patients included in the clinical trials on which the guidelines are based. Furthermore, the variation in criteria limits comparison of studies, complicates the interpretation of findings, and may contribute to the failure to replicate findings (12, 13).

We have developed operationalized criteria to address this issue based on a process of wide consultation and refinement, involving expert researchers and clinicians, scientists from the pharmaceutical industry, and other specialists who are active in the field. It is intended that these criteria provide benchmarks to aid study design and reporting as well as research on the neurobiology of more homogeneously defined subgroups and the development of novel treatment strategies. We acknowledge that some criteria may not be appropriate for certain questions or studies. It is not intended that these criteria prevent studies using alternative criteria, but where researchers use alternative criteria, we strongly recommend that the differences be indicated (and justified) against the benchmarks presented in Table 2.

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