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Review

Evolution of The Concept of Treatment-Resistant Schizophrenia

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Abstract: Therapy-resistant schizophrenia and its subtype, ultra-resistant schizophrenia, remain one of the most serious socially significant psychiatric disorders. The lack of unified diagnostic criteria complicates the interpretation of research data in this area and reduces the effectiveness of therapy in real clinical practice. The development of standardised approaches and in-depth study of resistance mechanisms remain priority tasks of modern psychiatry. The analysis of the literature shows that ideas about therapy-resistant schizophrenia have changed significantly over the last decades. This narrative review considers the criteria for treatment-resistant schizophrenia from the first criteria proposed by Kane et al. to the current ones, including TRRIP, which take into account the duration of therapy, the dose of the drug, the form of its administration, and the patient's compliance. Special attention is paid to the criteria for ultra-resistant schizophrenia in the absence of therapeutic response to clozapine. Currently, there are significant differences in the definition of therapy-resistant schizophrenia, which underline the need to unify its diagnostic criteria.

Keywords: *treatment-resistant schizophrenia; ultra-resistant schizophrenia; clozapine; criteria; methods for overcoming resistance, pharmacotherapy of schizophrenia.*

1. INTRODUCTION

Schizophrenia is a chronic mental disorder characterized by a combination of positive, negative, and cognitive symptoms that significantly affect the patient's life [1]. Despite significant progress in the field of pharmacotherapy and psychosocial interventions, about 20–30% of patients experience insufficient therapeutic efficacy of standard treatment methods, which leads to the development of the phenomenon of treatment-resistant schizophrenia (TRS) [2, 3]. This phenomenon is associated with a decline in the quality of life of patients [4], a high frequency of relapses, and significant economic costs of treatment [5–7]. Despite the widespread use of the term, there is still no consensus on its definition and diagnostic criteria.

The aim of the study is to conduct an analysis of existing approaches to the definition and criteria for establishing therapeutic resistance in schizophrenia.

2. MATERIALS AND METHODS

The search for articles published before 01.04.2025 was conducted in the PubMed, eLIBRARY.RU, Google Scholar databases, using the keywords: "types of therapeutic resistance", "therapeutically resistant schizophrenia", "clozapine resistant schizophrenia", "treatment resistant schizophrenia". The analysis included full-text articles in English and Russian, containing the results of randomized and non-randomized clinical trials, meta-analyses, systematic and narrative reviews. Initially,

4209 publications were found, 44 publications that most accurately met the objectives of this article were analyzed.

3. RESULTS

3.1 Historical aspect

TRS became the subject of intensive study at the end of the 20th century, when it became obvious that a significant percentage of patients did not achieve remission even with adequate therapy. One of the first and most significant approaches to defining resistance were the criteria proposed by Kane et al. in 1988 [8]. In their study, they defined resistance as the absence of significant improvement after at least two courses of antipsychotic therapy lasting at least 6 weeks each, provided that adequate doses of drugs were used. These diagnostic features became the basis for subsequent studies and clinical guidelines.

This concept was developed as part of a study of clozapine, the first antipsychotic to prove its effectiveness in patients with TRS [9, 10]. TRS criteria according to Kane et al. included the following key elements: no improvement in positive symptoms (delusions, hallucinations) after two courses of therapy, use of antipsychotics in adequate doses (equivalent to 400–600 mg chlorpromazine per day), and a duration of at least 6 weeks for each course of therapy. Despite their importance, these TRS criteria have a number of limitations. Firstly, they are overly focused on positive symptoms. The criteria were oriented towards reducing positive symptoms (delusions, hallucinations), ignoring negative symptoms (apathy, emotional impoverishment) and cognitive impairment, which play a key role in the functional outcomes of patients [11–14]. Secondly, there are problems with the definition of "adequate therapy": although adequate doses of antipsychotics were assumed, the concept of "adequacy" remained subjective and dependent on the clinical context in subsequent studies [15]. Thirdly, pseudo-resistance, namely poor compliance, diagnostic errors, and the presence of comorbid disorders that could lead to overdiagnosis of resistance, were not taken into account [16]. In addition, the Kane criteria were developed in the era of typical antipsychotics, and their applicability to atypical antipsychotics with different mechanisms of action remains questionable [17–19]. Finally, although Kane clearly distinguished between treatment-resistant and non-resistant cases, in real clinical practice this distinction is not always so clear, since different degrees of response to antipsychotic therapy are possible [20].

Thus, historical approaches to defining treatment resistance in schizophrenia laid the foundation for modern criteria, but their limitations highlight the need for a more comprehensive and individualized approach.

3.2 Modern approaches

Along with the growing interest in the issue of developing and overcoming resistance in schizophrenia, the ambiguity of interpretations of this term in various studies has increasingly attracted attention. In 2017, the international Treatment Response and Resistance in Psychosis working group (TRRIP) drew attention to this problem [15]. The researchers found that in most clinical trials, the definitions of TRS were not clear enough. They also emphasized that in almost all the analyzed studies, the criteria for medication adherence were formulated incorrectly. Having analyzed the differences in the understanding of TRS presented in the leading guidelines for the treatment of schizophrenia of that period, they presented their vision.

Table 1. Abbreviated criteria for treatment-resistant schizophrenia adopted by the Treatment-Resistant Psychosis Guidelines Working Group (TRRIP)

Minimum criteria	Optimum criteria
Symptoms persist for more than 12 weeks, with the patient's condition interfering with his or her daily life and reducing the patient's level of functioning.	Accuracy is higher when analyzing individual symptom groups and when validated psychiatric scales are used.
The ineffectiveness of the previous treatment was confirmed.	The most reliable method of assessment is a comprehensive approach that includes analysis of the tablet intake log.
Treatment should continue for at least 6 weeks using two antipsychotics from different groups in sufficient dosage (equivalent to 600 mg chlorpromazine per day).	The criterion will be considered more reliable if the patient additionally underwent a 6-week course of a long-acting antipsychotic.
Monitor medication adherence using pill counts, review of medication cards, and patient or caregiver reports, confirming that the patient is taking at least 80% of prescribed medications. Plasma levels of antipsychotic medications are monitored at least once. [21, 22]	Additionally, serum trough levels of antipsychotic drugs should be measured at least twice at intervals of at least two weeks (without prior notification to the patient).

The TRRIP criteria cover current symptoms and their dynamics, as well as the adequacy of treatment. For each of these aspects, minimal and optimal requirements are defined, where the optimal ones imply a more complete assessment of symptoms and clear confirmation of the patient's compliance with the medication regimen. Below is an abbreviated version of the TRRS criteria formed by the international steering group: (Table 1).

In our study we compared the currently relevant leading clinical guidelines for consistency in resistance criteria. (Table 2).

Table 2. Criteria for treatment-resistant schizophrenia adopted in different countries

	Number of courses of antipsychotics	Type of antipsychotic	Course duration	Dose	Severity of symptoms	Compliance testing	Consideration of functional outcomes	Citation
APA[1] (2021)	2	Different groups, one of which is in a prolonged form	6 weeks	Equivalent to 600 mg of chlorpromazine	Medium severity according to a scale (e.g., PANSS[9], BPRS[10], etc.)	Confirmation of intake of at least 80% (counting tablet dosage forms, keeping a dispensing log, interviewing carers). Measurement of blood AP[11] concentrations	Moderate functional impairment according to a scale (e.g., SOFAS[12])	[23]

BAP[2] (2020)	2	The use of prolonged dosage forms is recommended	«Adequate»	«Adequate»	Less than 20% reduction in total BPRS/PANSS score	Measurement of blood AP concentration	Reducing «target symptoms» that cause distress	[24]
NICE[3] (2014)	2	One of the APs is second-generation, different from clozapine	Not specified	«Adequate»	«Persistent positive, negative, affective and cognitive symptoms, inappropriate behaviour »	« Adequate adherence to treatment »	«Poor psychosocial and social functioning»	[25]
WFSBP[4] (2012)	2	Different groups, one of which is second-generation	2-8 weeks	«Recommended »	«Persistent positive or negative symptoms, severe cognitive impairment, inappropriate behaviour, affective symptoms»	Measurement of blood AP concentration if necessary	«Decreased professional and social functioning, poor quality of life»	[26]
RANZP[5] (2016)	2	«First or second generation »	From 6 weeks	Equivalent to 300 mg of chlorpromazine	«Persistent positive symptoms »	Use of prolonged dosage forms for patients at risk of low compliance	Not specified	[27]
VA/DoD[6] (2024)	2	«Different »	From 6 weeks	«Target dose corresponding to the effective doses specified in the FDA[13]-approved instructions »	«At least moderate symptoms»	Not specified	Not specified	[28]

CPA[7] (2017)	2	«Different »	From 6 weeks	«At the average or maximum dose of the therapeutic range allowed»	«2 or more positive symptoms of at least moderate severity, or one positive symptom of severe or more severe severity». Less than 20% reduction in total PANSS score	Documented adherence (counting tablet dosage forms, keeping a log of drug dispensing) or measurement of blood concentrations of APs	«Although the spectrum of symptoms that should be included in the definition of treatment resistance continues to be debated, positive symptoms are central»	[29]
RSP[8] (2024)	2	Different chemical classes (at least one of the antipsychotics should be second generation)	6 - 8 weeks	« In recommended therapeutic dosages »	«No reduction in psychopathological symptomatology and/or other key symptoms»	Including, if possible, determination of drug concentrations in blood plasma	Not specified	[30]

Note: 1- The American Psychiatric Association, 2- British Association for Psychopharmacology, 3- National Institute for Clinical Excellence, 4- World Federation of Societies of Biological Psychiatry, 5- Royal Australian and New Zealand College of Psychiatrists, 6- The Department of Veterans Affairs and the Department of Defense guidelines, 7- Canadian Psychiatric Association, 8- Russian Society of Psychiatrists, 9- Positive and Negative Syndrome Scale, 10- Brief Psychiatric Rating Scale, 11- antipsychotic, 12- Social and Occupational Functioning Assessment Scale, 13- Food and Drug Administration

3.3 Ultra-resistant schizophrenia

In the early 2000s, the first publications appeared indicating that some patients did not demonstrate a meaningful response even to clozapine [31-33]. Already then, researchers pointed that the main limitations of ultra-resistant schizophrenia (URS) studies were the heterogeneity of clozapine resistance criteria, the lack of unified therapeutic doses, and the uncertain duration of treatment [34, 35]. Most guidelines published between 2002 and 2016 agree on one thing: two ineffective courses of therapy are sufficient to consider the disease as resistant to treatment [36].

Later, the scientific community made attempts to unify approaches and clearly distinguish the concepts of resistance and ultra-resistance. Criteria for URS have been proposed for the treatment of patients who do not respond to clozapine or other potential therapeutic strategies (e.g., high doses, combinations of antipsychotics, electroconvulsive therapy) [37-40].

Table 3. Guidelines Affinity Score (GAS) [Campana et al. (2021)]

Conformity criterion	**Points**
Compliance with the time requirement (clozapine use continued for at least 8 weeks prior to study inclusion);	1 point
Achieving the maximum tolerated dose of clozapine before assessing its effectiveness;	1 point
Determination of the concentration of clozapine in blood plasma with a threshold of not less than 350 ng/ml before the start of the study;	2 points
Use of a clinical scale to assess lack of efficacy of clozapine therapy;	1 point
Define inadequate response as a PANSS total score of at least 58 or BPRS total score of at least 32;	2 points
Maximum score.	5 points

These rates are reflected in international clinical guidelines for the treatment of schizophrenia [26, 41, 42]. However, as with the definition of TRS, there was again inconsistency and imprecision in the understanding of the concept, which hampered the interpretation and reproducibility of the results, reduced the reliability of meta-analytic findings, and limited the possibility of their practical application.

The TRRIP Working Group defined a category of «ultra-treatment resistance»— failure to respond to clozapine treatment despite meeting TRRS criteria. Despite the clinical importance of this subgroup, it has received little attention in research. Ultra-treatment resistance represents a distinct category from classical TRRS and requires a more specific definition.

In 2021, Campana et al. conducted a systematic review [43] covering 71 studies involving 2731 patients who were prescribed clozapine in combination with various augmentation agents. This was the first and largest meta-analysis aimed at characterizing patients with URS. The review assessed the different definitions of URS used in the studies and compared them with national and international schizophrenia treatment guidelines for consistency. In general, all guidelines define URS as the absence of a tolerable response to clozapine plasma concentrations above 350 ng/mL and a treatment duration of at least 8–12 weeks after reaching the therapeutic level. However, significant differences were also identified. For example, most of the clinical guidelines selected by the researchers indicate a minimum use of clozapine of 8 weeks, while the TRRIP and Canadian guidelines suggest a minimum of 12 weeks. The recommended dosage of clozapine also varies across protocols, ranging from 100 to 900 mg/day.

In the study by Campana et al. (2021), a "Guideline Compliance Assessment" was developed, representing the most comprehensive URS criteria for analyzing the included studies. Each study was assigned a score based on several parameters (Table 3).

Thus, the results of this study provide the most comprehensive understanding of URS to date and provide an important tool for evaluating patients with URS that can be used both in further research and in actual clinical practice.

4. DISCUSSION

A literature review showed that approaches to defining TRS have evolved significantly over the past decades. Historically, the most significant are the criteria proposed by Kane et al., which formed the basis for subsequent studies. Modern recommendations, in particular the TRRIP criteria, offer a more comprehensive and standardized approach that takes into account not only the duration of therapy and the

dosage of drugs used, but also objective indicators of compliance with the treatment regimen.

We analyzed current international and national guidelines for consistency in the criteria for establishing TRS.

During the study, it became obvious that most guidelines are updated extremely rarely. For example, NICE (National Institute for Clinical Excellence) [25] last revised its guidelines in 2014, WFSBP (World Federation of Societies of Biological Psychiatry) [26] in 2012, RANZP (Royal Australian and New Zealand College of Psychiatrists) [27] in 2016, CPA (Canadian Psychiatric Association) in 2017 [29]. Only a few organizations have released updates in the last 3–4 years: APA (The American Psychiatric Association) – 2021 [23], BAP (British Association for Psychopharmacology) – 2020 [24], VA/DoD (The Department of Veterans Affairs and the Department of Defense guidelines) – 2024 [28], RSP (Russian Society of Psychiatrists) -2024 [30]. This leads to the risk of using outdated criteria in modern clinical practice.

Based on the review of guidelines, certain similarities in criteria can be identified, but there are also significant differences (Table 4).

Table 4. Comparison of criteria for establishing therapeutic resistance

Common features	**Different features**
Number of courses of antipsychotic therapy required: All guidelines require at least two courses of antipsychotics.	Functional outcomes: Not considered in all guidelines. Only the APA guidelines suggest quantifying the severity of impairment.
Duration of treatment: Most guidelines agree on the need for therapy for 6–8 weeks to assess response.	Leading symptoms: the scientific community still focuses more on positive symptoms, although in the group of patients with TRS, it is the negative symptoms that more often cause distress or disability.
Type of drugs: in most cases, it is necessary to use antipsychotics of different classes, with the obligatory inclusion of a second-generation antipsychotic. The use of a prolonged-action antipsychotic is also often recommended.	Compliance monitoring methods: the range of methods used ranges from simple patient surveys to mandatory determination of plasma concentrations of antipsychotics.
Compliance testing: Objective verification of adherence to treatment, including measurement of blood drug levels, is often recommended.	Level of detail in resistance criteria: for example, the 2021 APA criteria, which most fully reflect the TRRIP criteria, propose standardizing the TRRIP features using generally accepted scales. Thus, the TRRIP threshold is defined more unambiguously. At the same time, other guidelines often use more general formulations.
	Antipsychotic Dose: Two guidelines use the TRRIP-recommended "chlorpromazine equivalent," but with different numerical values. Other guidelines do not regulate drug doses, referring to the drug labels without including this criterion.

Thus, we came to the conclusion that it is necessary to update the existing guidelines using unified and relevant criteria.

Particular attention is paid to the phenomenon of ultra-resistant schizophrenia — a subgroup of patients who do not respond to clozapine. Accumulated data indicate that in a significant proportion of patients, even the use of clozapine does not provide a significant reduction in psychotic symptoms.

Moreover, in some cases, resistance to therapy is combined with severe cognitive and negative impairments that are not amenable to correction.

In this regard, a subgroup of patients with URS was identified — a condition in which standard therapeutic approaches, including treatment with clozapine, are insufficiently effective or do not lead to clinically significant improvement at all. The identification of URS as a separate phenotype of schizophrenia is associated with the need to develop specific therapeutic strategies that go beyond traditional antipsychotic therapy. Thus, according to the international research program [44]. In case of resistance to clozapine, it should be augmented with other antipsychotics, antidepressants, mood stabilizers or electroconvulsive therapy (ECT), and new treatment approaches should be developed, including immunological approaches, neurostimulation and psychotherapeutic methods. According to the results of the meta-analysis by Yeh TC et al. (2023) [45], the addition of mirtazapine, memantine to clozapine and ECT were the most effective augmentation options for URS. The study by Zubov DS et al. (2020) [46] indicates that the combination of ECT and psychopharmacotherapy contributes to a more pronounced clinical improvement in patients with URS. However, according to the conclusion of Oleneva EV et al. (2021) [47], the long course of the disease and the predominance of paranoid symptoms reduce the effectiveness of ECT in URS. An analysis of the literature [48] indicates the feasibility of using modern antipsychotics, primarily third-generation ones, which, despite the limited research, have demonstrated high efficiency in reducing psychopathological symptoms both in monotherapy and in combination with clozapine. Augmentation with antidepressants, mood stabilizers, and glutamatergic drugs is also considered as a possible strategy for overcoming resistance, but convincing evidence of its effectiveness is still lacking [48]. A review of meta-analyses [49] showed that combination strategies improve general symptoms of schizophrenia compared to monotherapy, but the low quality of studies reduces the reliability of recommendations in favor of such therapy. Further studies have shown a significant difference between the group of patients with URS and TRS also in the context of cognitive dysfunction [50], which, together with the variety of approaches to therapy, requires more serious costs for treatment and social support [13]. Given the high degree of disability in this group of patients, the study of the mechanisms of URS and the development of new approaches to treatment are one of the priority tasks of modern psychiatry.

5. CONCLUSION

The clinical situation when a patient with schizophrenia does not respond to standard treatment methods remains one of the biggest problems in psychiatry, which requires more and more new research on this topic. Treatment-resistant and ultra-resistant forms of schizophrenia remain among the most complex and socially significant diseases. In this article, we touched upon the problems of heterogeneity of approaches to defining the concepts of TRS and URS, gave an idea of the historical aspects and existing diagnostic criteria. Despite the existence of various diagnostic criteria, there is still no universal application, which complicates clinical use and reduces the comparability of research results. The creation of unified, clearly formulated diagnostic approaches to TRS and URS is a necessary step to improve the effectiveness of therapy, develop

personalized intervention strategies and reduce the burden of the disease for patients and the health care system as a whole.

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