Evaluation and management of treatment-resistant schizophrenia

AUTHORS: John Kane, MD, Jose M Rubio, MD, Taishiro Kishimoto, MD, Christoph U Correll, MD
SECTION EDITOR: Stephen Marder, MD
DEPUTY EDITOR: Michael Friedman, MD

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INTRODUCTION

Antipsychotic medication is first-line treatment for schizophrenia. Most patients show substantial improvement in psychotic symptoms in response to antipsychotics; however, for many, improvement is insufficient to meet stringent criteria for remission, and a substantial proportion experience residual treatment-resistant symptoms.

Patients who do not respond adequately to antipsychotics should be reevaluated to rule out or address causes other than nonresponsiveness to medication (ie, pseudoresistance). Current medication and psychosocial interventions should be optimized. Treatment strategies for patients who remain incompletely responsive to antipsychotic medications include changes to antipsychotic doses and drugs, use of clozapine (in eligible patients), and drug augmentation.

This topic addresses the evaluation and management of treatment-resistant schizophrenia. The epidemiology, pathogenesis, clinical manifestations, course, assessment, diagnosis and treatment of schizophrenia are reviewed separately, as are the presentation and treatment of anxiety and depression co-occurring with schizophrenia and guidelines for prescribing clozapine. (See "Schizophrenia in adults: Epidemiology and pathogenesis" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis" and "Schizophrenia in adults: Maintenance therapy and side effect management" and "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication" and "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course,

assessment and diagnosis" and "Anxiety in schizophrenia" and "Depression in schizophrenia" and "Schizophrenia in adults: Guidelines for prescribing clozapine".)

DEFINITION

Epidemiologic studies of treatment-resistant schizophrenia and practice guidelines on its treatment are based on varying definitions of treatment-resistant schizophrenia, limiting the utility of the results [1]. In response, in 2017 an international panel of experts, the Treatment Response and Resistance in Psychosis (TRRIP) Working Group, published consensus-based criteria (minimal and optimal) for the diagnosis of treatment-resistant schizophrenia. Their work included specifications for the collection of clinical data needed to establish the diagnosis [2].

- **Minimal TRRIP criteria for treatment-resistant schizophrenia** – Based on cross-sectional clinical assessment supplemented by collateral sources of information (eg, medical record documentation, caregiver's report).
  - Diagnosis – DSM-5 diagnosis of schizophrenia.
  - Symptom severity – At least moderate symptom severity (>3 in psychotic symptom items) as rated using a standardized scale (eg, Positive and Negative Syndrome Scale [PANSS] or Brief Psychiatric Rating Scale [BPRS]).
  - Functional impairment – At least moderate impairment measured using a validated scale (eg, Social and Occupational Functioning Assessment Scale).
  - Prior treatment – At least two trials of ≥6 weeks at a therapeutic dose (equivalent to ≥600 mg chlorpromazine) with adherence ≥80 percent of prescribed doses.
- **Optimal TRRIP criteria for treatment-resistant schizophrenia** – The minimal criteria (above) with the addition of:
  - Prospective evaluation of symptom severity using a standardized scale (eg, PANSS or BPRS) confirming <20 percent symptom reduction over six weeks of treatment.
  - One of the two antipsychotic trials should be a long-acting injectable antipsychotic. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)
  - Antipsychotic adherence should be confirmed by ≥2 antipsychotic plasma levels.

PREVALENCE

A sizeable proportion of patients with schizophrenia do not respond sufficiently to antipsychotics [3]; however, the absence of consensus criteria for defining treatment-resistant schizophrenia prior to 2017 limited efforts to determine the prevalence of the condition. Estimates based on varying definitions have ranged from 66.3 to 83.4 percent:

- In a 2017 meta-analysis of placebo-controlled studies in patients with acute exacerbation of schizophrenia, 49 percent of patients experienced little or no response (>20 percent of symptom improvement) with one trial of antipsychotic medication [3].
- In a multiple-phase trial in individuals with a first psychotic episode, only 16.6 percent of individuals who had failed the first antipsychotic trial met response criteria (ie, Clinical Global Impressions Scale >2 [much improved]) with a second antipsychotic trial [4].
- In a prospective, observational study of 341 patients with schizophrenia or schizoaffective disorder treated with an antipsychotic medication in Belgium, 71 percent did not achieve severity and duration criteria for remission [5].
- A cohort study that followed individuals with a first episode of schizophrenia for the first 10 years after diagnosis found that 23 percent met treatment-resistance criteria, of whom 84 percent were so from treatment onset [6].
- In a cohort of first episode cohort of patients with schizophrenia followed for five years, 33.7 percent met treatment-resistance criteria, of whom 70 percent were treatment resistant from illness onset [7].

“Ultra-resistance” (ie, schizophrenia patients resistant to both non-clozapine antipsychotics and clozapine) was estimated at 12 to 20 percent of treated patients in a systematic review and meta-analysis of 21 clinical trials with 25 treatment comparisons. A pooled response rate to clozapine of 40 percent was found among schizophrenia patients who had previously demonstrated resistance to non-clozapine antipsychotics [8].

EVALUATION

Our clinical approach to diagnosing treatment-resistant schizophrenia is based on the Treatment Response and Resistance in Psychosis Working Group criteria. The sections that follow provide more detailed information and supporting evidence for each step.

Overview — Epidemiologic data suggest that the diagnosis of treatment-resistant schizophrenia may often be overlooked [9,10], and when made, it is often years after the criteria were met [9]. For this reason, it is important that clinicians are proactive in the evaluation and management of residual symptoms despite ongoing treatment.

The treatment of choice for treatment-resistant schizophrenia is clozapine, which has superior efficacy in this population compared with other antipsychotics [8,11-13]. However, because clozapine can cause significant adverse effects, there are a number of steps that should be taken prior to a clozapine trial:

- Assess for other causes of residual schizophrenia symptoms (ie, pseudoresistance) (see 'Assess for pseudoresistance' below)
- Optimizing nonpharmacologic treatment (see 'Adequacy of nonpharmacologic treatment' below)
- Optimizing current antipsychotic drug treatment (see 'Adequacy of antipsychotic trials' below)

If these steps do not lead to symptom remission, and the patient has had at least two antipsychotic trials of six weeks or more at maximally tolerated doses while monitoring for treatment adherence, we would then proceed to a clozapine trial. (See 'Clozapine' below.)

Assess for pseudoresistance — When a patient with schizophrenia appears to be resistant to standard antipsychotic treatment, he or she should be evaluated for causes of pseudoresistance or treatment nonresponse due to reasons other than medication nonresponse. Findings of other factors causing or contributing to the persistence of symptoms can prompt changes to the patient's clinical management other than antipsychotic drug treatment.

Reevaluation of the primary diagnosis — Reevaluation of the primary diagnosis is indicated in patients who are not responsive to antipsychotic treatment. The differential diagnosis and diagnostic evaluation of patients presenting with schizophrenia-like symptoms is discussed separately. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Diagnosis'.)

Co-occurring conditions — Co-occurring mental disorders, substance use disorders, and medical conditions contribute to the illness burden of patients with schizophrenia; if untreated, these conditions can impede effective treatment of schizophrenia. Medical and psychiatric evaluations should include assessment for co-occurring conditions, followed by treatment.

- Mental disorders – The identification and management of mental disorders most commonly co-occurring with schizophrenia are discussed separately. (See "Anxiety in schizophrenia" and "Depression in schizophrenia" and "Management of obsessive-compulsive disorder in adults".)

- Substance use disorders – The identification and management of substance use disorders co-occurring with schizophrenia are discussed separately. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

- Medical conditions – A patient with nonresponsive schizophrenia should receive a history and physical exam for factors contributing to their clinical status. As one prominent example, obesity is common in chronically ill patients with schizophrenia. Such patients should be evaluated for sleep apnea and, if present, receive treatment. (See "Clinical presentation and diagnosis of obstructive sleep apnea in adults".)

Antipsychotic drug side effects — Side effects, such as akathisia, parkinsonism (including akinesia), sedation, and insomnia, need to be assessed and treated, as they can mimic ongoing agitation or negative symptoms, and can lead to functional disability as well as possibly a greater tendency for ongoing psychopathology and relapse. In such cases, a dose reduction may result in improvement. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

Since efficacy can be affected by other prescribed medications or over the counter agents, a thorough evaluation of potential drug-drug interactions should also be performed [14]. As examples:

- Carbamazepine reduces the levels of all antipsychotics that are metabolized by the liver with the exceptions of:

  - Amisulpride, which is excreted renally
  - Paliperidone, which does not undergo first pass metabolism

- Levels of olanzapine and clozapine can be reduced in patients who start smoking, which stimulates the cytochrome P450 1A2 enzyme that is involved in the antipsychotics' metabolism.

- Levels of aripiprazole and risperidone, which are metabolized by the cytochrome P450 2D6 enzyme, can be elevated by co-treatment with fluoxetine and paroxetine that are metabolized by the same enzyme system.

Medication nonadherence — Nonadherence to antipsychotic drugs is often overlooked by patients and clinicians, yet it is a common reason for pseudoresistance. As an example, a 2018 study found that 35 percent of individuals provisionally diagnosed with treatment-resistant schizophrenia had a subtherapeutic antipsychotic plasma level [15].

Nonadherence should be considered a potential reason for nonresponse until proven otherwise. Options for evaluating the role of nonadherence include:

- Normalize nonadherence as a common consequence of having to take drugs daily and ask the patient about missed or lower-than-prescribed doses in a nonjudgmental way.
- Arrange for supervised medication intake, which may be easier to observe if the antipsychotic is given as an orally dissolving or liquid formulation.
- Check a blood level of the antipsychotic drug. An absent level or a low level despite relatively high doses indicate nonadherence (or unusual metabolism).
- Provide the patient with at trial of a long-acting injectable (LAI) antipsychotic.

  LAI antipsychotics should not be reserved only for established nonadherence but should be used in most patients with schizophrenia needing antipsychotic medication. Epidemiologic studies suggest that LAI antipsychotics have 20 to 30 percent greater efficacy for reducing hospitalization and mortality compared with their daily oral counterparts, most likely because of assured adherence [16-18]. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

Technology-assisted strategies may have a role in facilitating treatment adherence with antipsychotic drugs if acceptable to the patient in shared decision-making. Aripiprazole was approved by the Food and Drug Administration of the United States as the first “digital medicine” [19]. This drug contains a biodegradable chip that signals to a torso-worn patch when it has been swallowed, and patients can decide whether to share this information with the clinician and others [20]. Additionally, some online platforms and applications remind patients to take their prescribed drugs [21]. The use of such technologies to improve treatment adherence is only emerging; clinical trials are needed to determine whether they improve adherence and clinical outcomes [22].

Adequacy of antipsychotic trials — Prior to designating a schizophrenia patient as treatment resistant, prior antipsychotic trials should be evaluated for their adequacy. Was it continued for at least six weeks at the maximally tolerated dose within the medication’s recommended range?

(See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Treatment-resistant schizophrenia'.)

Additional strategies for optimizing antipsychotic pharmacotherapy for schizophrenia (table 1) include:

- Antipsychotic dose escalation above recommended dose
- Switching to a different non-clozapine antipsychotic

Clinical trials of these strategies have failed to find consistent, convincing evidence of efficacy. Most of the trials have been limited by small sample sizes, and inconsistent or absent criteria for prior antipsychotic treatment or degree of response. The role of medication adherence was rarely formally assessed. Most trials were of short duration, leaving the long-term maintenance effect of the strategies unclear.

- Antipsychotic dose escalation – An antipsychotic trial should be conducted at the highest tolerated dose within the maximum recommended dose range prior to concluding that the clinical response to the medication was inadequate.

  Dose escalation beyond recommended maximum antipsychotic doses have not been supported by clinical trials:

  - A 2015 meta-analysis of five randomized clinical trials compared dose escalation beyond recommended ranges versus treatment continuation with doses in the recommended range in a pooled total of 348 patients with schizophrenia. No differences were observed in Positive and Negative Syndrome Scale (PANSS)/Brief Psychiatric Rating Scale score change between groups [23].

  - A 2018 Cochrane review of 10 randomized controlled trials with 675 schizophrenia patients did not find a clear differences between dose increase and dose maintenance in the rate of clinically relevant responses (risk ratio = 1.09, 95% CI 0.86-1.40), PANSS total score change (standardized mean difference = -1.44, 95% CI -6.85 to 3.97), or study discontinuation due to adverse effects (risk ratio = 1.63, 95% CI 0.52-5.07) [24]. We do not generally recommend dose increases of antipsychotics above doses recommended by the manufacturer [25].

- Switching antipsychotics – There is little empirical support for the efficacy of switching from one non-clozapine antipsychotic to another after an inadequate clinical response to an antipsychotic trial.

A retrospective data analysis of 244 patients with first-episode schizophrenia found that only 16.6 percent of individuals who changed antipsychotics after failing to respond to the first drug responded to the switch [4].

- Comparing approaches – A randomized clinical trial comparing dose escalation versus switching antipsychotics in patients with schizophrenia after an antipsychotic trial resulting in nonresponse did not find a difference between groups [26].

Adequacy of nonpharmacologic treatment — The patient's nonpharmacologic treatment should be evaluated and optimized prior to diagnosing treatment resistance.

- **Triggers and stressors** – Triggers for worsening symptoms of schizophrenia, as well as stressors and factors interfering with effective treatment, need to be identified and addressed as much as possible. In this context, the strengths of the individual and the potential impact of the support system need to be evaluated and utilized to help overcome treatment refractoriness to the extent possible.

- **Psychosocial interventions** – Although psychosocial interventions given alone are not sufficiently effective in schizophrenia, providing them as an adjunct to antipsychotic medication has been found to improve patient outcomes. Cognitive-behavioral therapy (CBT) directly focuses on symptom control; the other interventions can reduce symptoms indirectly in treatment-resistant patients by reducing patient or family stress, improving adherence, or providing outreach that helps patients remain in the community; skills training can improve functioning. Patients with treatment-resistant schizophrenia and the following indications should be provided a trial of the associated intervention:

  - **Cognitive-behavioral therapy** – In patients who experience persistent delusions or hallucinations despite adequate trials of antipsychotic medication [27]. (See "Schizophrenia in adults: Psychosocial management", section on 'Cognitive-behavioral therapy'.)

    Multiple meta-analyses of clinical trials of adjunctive CBT for patients with schizophrenia found mixed evidence of efficacy in patients with an incomplete response to antipsychotics. In our clinical experience, despite the mixed findings, CBT can be helpful and lacks side effects. CBT should be provided for individuals with treatment-resistant schizophrenia when available.

    - A 2018 meta-analysis of 60 randomized clinical trials with 5992 patients with schizophrenia found no convincing evidence for the superiority of CBT versus usual

care for relapse, mental state, quality of life, social function, or satisfaction with care [28].

- A 2015 meta-analysis of 35 randomized trials with 2312 patients with schizophrenia found no benefits of CBT for negative symptoms compared with control conditions [29].

- A 2014 meta-analysis of 34 clinical trials of CBT for psychosis with 4791 patients with schizophrenia found small effect sizes favoring CBT over control for the reduction of overall symptoms (Hedges' g = -0.33, 95% CI -0.47 to -0.19) [30].

- **Family psychoeducational interventions** – In patients who have had a recent psychotic relapse and have significant ongoing contact with family members [31]. (See "Schizophrenia in adults: Psychosocial management", section on 'Family-based Interventions'.)

- **Social skills training** – In patients who have deficits in skills needed for everyday activities [32]. (See "Schizophrenia in adults: Psychosocial management", section on 'Social skills training'.)

- **Assertive community treatment –** In patients with a recent history of repeated hospitalization or homelessness [33]. (See "Assertive community treatment for patients with severe mental illness".)

- **Crisis intervention –** In patients with an acute psychosocial stressor who are in emotional crisis, leading to symptom exacerbation [34].

DIAGNOSIS

If the patient's clinical response remains inadequate despite addressing these factors, and Treatment Response and Resistance in Psychosis Working Group criteria are met, treatment-resistant schizophrenia should be diagnosed. (See 'Definition' above.)

MANAGEMENT

Management of patients with treatment-resistant schizophrenia includes the determination of clozapine eligibility, treatment with clozapine (preferably) or an alternative, and for patients who continue to respond inadequately, trials of other interventions with lesser evidence supporting efficacy.

Clozapine

Eligibility — To be eligible for a clozapine trial, a patient with treatment-resistant schizophrenia (see 'Definition' above) should additionally meet the following criteria:

- Absolute neutrophil count ≥1500 cells/microliter
- Determination by the physician as well as the patient and family if possible that the benefits of clozapine outweighing the risks
- Ability to adhere to treatment monitoring
- Patient/family agreement

Guidelines for prescribing clozapine are reviewed in detail separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Although some have advocated reducing the number of antipsychotic trials required by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group definition from two to one before clozapine is used [35,36], we believe this recommendation is premature given the limitations of the supporting data and the risks of agranulocytosis and other serious side effects with clozapine [37]. Studies suggest some advantages to using clozapine in individuals with only a partial response to non-clozapine antipsychotics (as opposed to the “less than minimal response” recommended by the TRRIP criteria) [38].

Efficacy — Randomized trials have shown that clozapine has greater efficacy compared with other antipsychotics in treating patients with schizophrenia who have responded poorly to prior antipsychotic trials. These findings have been summarized in head-to-head and network meta-analyses [8,12,13], as well as in comparative effectiveness studies [39].

A meta-analysis comparing the efficacy of clozapine with first or second generation antipsychotics in 25 trials including 2364 patients found that patients treated with clozapine experienced greater clinical improvement in total symptoms (standard mean difference [SMD] = -0.29, 95% CI -0.49 to -0.09) [8]. When only long-term trials were included in the analysis, greater improvement was seen (SMD = -0.39, 95% CI -0.61 to -0.17). This clinical advantage was observed in long-term studies for positive symptoms (SMD = -0.27, 95% CI -0.47 to -0.08) and negative symptoms (SMD = -0.25, 95% CI -0.40 to -0.10).

As an example, a randomized trial compared treatment with clozapine (up to 900 mg daily) with chlorpromazine (up to 1800 mg daily) in 268 patients with schizophrenia who had failed to respond to at least three different first-generation antipsychotics [11]. After a six-week treatment period, a greater proportion of clozapine-treated patients experienced a clinically significant response compared with patients in the chlorpromazine-treated group (30 versus 4

percent). A clinically significant response was defined a priori based on scores from the Brief Psychiatric Rating Scale and the Clinical Global Impressions scale.

A 2016 network meta-analysis comparing clozapine with first- or second-generation antipsychotics in 40 randomized trials with 5172 patients with treatment-resistant schizophrenia found mixed results [12]. Methodologic issues in the included trials, for example, the potential exclusion of the most severely treatment-resistant patients, and use of relatively low clozapine doses in some trials, preclude drawing firm conclusions from the study [40].

Analysis of prospectively collected data from a national cohort of individuals diagnosed with schizophrenia in Sweden demonstrated consistently greater effectiveness of clozapine compared with oral olanzapine, the most frequently prescribed drug. Patients receiving clozapine had a lower risk of hospitalization compared with patients prescribed olanzapine (hazard ratio = 0.58, 95% CI 0.53-0.63) [39].

Administration — Guidelines for prescribing clozapine, including medical contraindications, pharmacology, dosing, monitoring, and adverse effects are described separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Discontinuation — If tolerated and without adverse consequences, a clozapine trial should be given for at least 24 weeks in patients with treatment-resistant schizophrenia, as studies have found clinical improvement can continue for this duration [8,41]. Additionally, adequate clozapine exposure should be measured by therapeutic drug monitoring confirming that plasma levels are above 350 ng/dl. (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Just as shared decision-making should if possible precede the start of clozapine, the decision to discontinue clozapine due to lack of efficacy should be discussed with the patient and family. Some of clozapine's benefits involve patient satisfaction, increased well-being, and functionality that are not always as obvious to clinicians as they might be to patients and family members. The benefits of clozapine should be sufficiently clear to justify continuation of the drug but should not be limited to symptoms of psychosis.

Alternatives for patients ineligible for or refusing clozapine — A significant proportion of patients with treatment-resistant schizophrenia have contraindications to clozapine or refuse the medication. Because the evidence of efficacy of alternative treatments is limited, we suggest that, prior to their use, patients are carefully reviewed to ensure that:

- The patient meets TRRIP criteria for treatment-resistant schizophrenia. (See 'Definition' above.)

- The adequacy of the patient's prior antipsychotic trials has been evaluated and, if inadequate, that optimized antipsychotic treatment was insufficiently effective. (See 'Adequacy of antipsychotic trials' above.)

- The treatment team, patient, and family have determined that clozapine is not a viable treatment.

Several alternatives to clozapine have been tested in randomized clinical trials of patients with treatment-resistant schizophrenia, but most of the findings are mixed and are from trials with methodologic limitations. Nonetheless, these treatments are used by patients who have responded inadequately to prior treatments and have a clinical status and health-related quality of life that is sufficiently poor that the patient, family, and treatment team have decided that the treatments are justified despite the very limited evidence of efficacy.

- Electroconvulsive therapy (ECT)
- Lamotrigine, topiramate, minocycline
- Repetitive transcranial magnetic stimulation (rTMS)

For patients with treatment-resistant schizophrenia for whom clozapine is not an option, we suggest antipsychotic augmentation of antipsychotic treatment with ECT rather than medication or rTMS (see 'Electroconvulsive therapy' below). This recommendation is based on the indirect though robust evidence of efficacy for ECT augmenting clozapine in treatment-resistant schizophrenia (see 'Treatment of clozapine-resistant schizophrenia' below) rather than on the sparse data comparing it with antipsychotic monotherapy. (See 'Electroconvulsive therapy' below.)

For patients who do not respond to an eight-week trial of ECT augmentation (delivered two to three times per week), we suggest treatment with lamotrigine (also an eight-week trial that if unsuccessful should be followed by trials of topiramate and minocycline), followed by a trial of rTMS. This ordering is based on the consistency of the evidence supporting each intervention. This "hierarchy" of recommendations is based on indirect evidence, as there are no data comparing these treatments head-to-head. (See 'Electroconvulsive therapy' below and 'Medication strategies' below and 'Repetitive transcranial magnetic stimulation (rTMS)' below.)

Electroconvulsive therapy — A 2016 meta-analysis of 11 randomized clinical trials with 818 participants with schizophrenia trials compared ECT augmenting a non-clozapine antipsychotic with a non-clozapine antipsychotic alone [42]. ECT was superior to control for total symptom improvement (SMD = -0.67, 95% CI -0.95 to -0.39), and study defined response (risk ratio = 1.48, 95% CI 1.24-1.77), with a number needed to treat (NNT) between four and nine [42]. The most

frequent side effects of ECT were headache, with a number needed to harm (NNH) of six, and memory impairment, with an NNH of three.

Other trials have tested ECT augmentation of antipsychotic drugs in antipsychotic-resistant patients without regard to whether the patient was receiving clozapine or another antipsychotic drug. A meta-analysis of 18 randomized clinical trials (17 conducted in China) with 1394 schizophrenia patients for whom clozapine resistance had not been systematically confirmed found that ECT augmentation of antipsychotic treatment was superior to antipsychotic medication treatment alone on several outcomes including:

- Endpoint assessment (67.7 versus 41.4 percent, risk ratio = 1.66, 95% CI 1.38-1.99; NNT = 4)
- Study-defined response at post-ECT assessment (53.6 versus 25.4 percent, risk ratio = 1.94, 95% CI 1.59-2.36; number needed to treat [NNT] = 3)
- Remission at post-ECT assessment (13.3 versus 3.7 percent, risk ratio = 3.28, 95% CI 1.80-5.99; NNT = 13)
- Endpoint assessment (23.6 versus 13.3 percent, risk ratio = 1.80, 95% CI 1.39-2.35; NNT = 14) [43]

Patient-reported memory impairment (24.2 versus 0 percent; NNH = 4) and headache (14.5 versus 1.6 percent; NNH = 8) occurred more frequently with patients receiving adjunctive ECT.

Medication strategies — Augmentation of a non-clozapine antipsychotic with other medications has not shown convincing evidence of efficacy in clinical trials. A meta-analysis of 381 randomized clinical trials published in 2017 identified 42 antipsychotic augmentation strategies that were initially found to be superior to placebo: for total psychopathology (14), for positive symptoms (6) and for negative symptoms (4), with effect sizes that ranged from small (0.2) to large (0.8 to 1.3) [44].

Despite statistically significant results for some outcomes, the findings and methodologic limitations of these trials leads us to conclude that none of the 42 augmentation strategies are supported by sufficient evidence of efficacy from meta-analysis to recommend its use. Limitations included small samples, lack of replication in a large single trial, absence of testing in samples of patients with well-defined treatment-resistant schizophrenia, heterogeneity of results, and publication bias. An inverse relationship was found between the quality of the meta-analyzed clinical trials and the effect size of any advantage [44].

Medications with the best balance between effect size versus the risk of bias were:

- Lamotrigine (typical dose: 100 to 200 mg/day) – Three randomized trials found adjunctive lamotrigine to be superior to placebo in reducing symptoms of antipsychotic-treated schizophrenia (standard mean difference= -0.73 95% CI -1.26 to -0.20).

- Minocycline (typical dose 100 to 200 mg/day) – A meta-analysis of eight randomized trials compared adjunctive minocycline with placebo in 581 patients with antipsychotic-treated schizophrenia [45]. Patients treated with minocycline experienced reduced symptoms compared with placebo (SMD = -0.59 95% CI -0.15 to 0.03).

- Topiramate (typical dose 100 to 400 mg/day) – A meta-analysis of 13 randomized trials with 651 antipsychotic treated patients with schizophrenia compared topiramate augmentation with placebo augmentation or antipsychotic monotherapy. Topiramate outperformed the comparator on reduction in symptoms (SMD = -0.58, 95% CI -0.82 to -0.35).

Repetitive transcranial magnetic stimulation (rTMS) — Mixed results have been found in short-term clinical trials of rTMS in schizophrenia; there is an absence of long-term evidence.

- A 2018 meta-analysis of 22 randomized clinical randomized trials with 827 schizophrenia patients found rTMS applied to the frontal cortex reduced negative symptoms in patients with schizophrenia already being treated with antipsychotic drugs compared with antipsychotic treatment alone with an effect size = 0.64 (95% CI 0.32-0.96) [46]. Trials including younger patients found larger effect sizes compared with trials including older patients.

- A 2015 Cochrane systematic review and meta-analysis found no difference in overall symptoms comparing temporoparietal rTMS plus standard treatment with standard treatment alone [47]. More recently, a clinical trial found no difference in auditory hallucinations when temporoparietal rTMS was compared with placebo treatment in individuals with antipsychotic-resistant hallucinations [48].

- An updated meta-analysis investigated the effect of transcranial direct current stimulation (tDCS), a neuromodulatory intervention that uses direct current, and of rTMS, as adjunctive treatments in schizophrenia [49].

    - In seven randomized clinical trials in 105 patients with schizophrenia, compared with sham, tDCS reduced negative symptoms (Hedge's g = -0.63), with a nonsignificant trend toward reducing positive and overall symptoms. Efficacy for positive but not negative symptoms was linearly associated with cumulative tDCS stimulation.

- In 30 randomized trials of rTMS in 768 patients with schizophrenia, compared with sham, rTMS reduced hallucinations (Hedge's g = -0.51) and negative symptoms (Hedge's g = -0.49) but was associated with a modest nonsignificant trend toward worsening of some positive symptoms (Hedge's g = 0.28).

Side effects of rTMS include pain at the site of stimulation, muscle twitching during treatment sessions, posttreatment headache and toothache, and, rarely, seizures. Patients with a seizure disorder should not receive rTMS.

Treatment of clozapine-resistant schizophrenia — We define clozapine resistance as the failure to show adequate improvement after a 24-week trial of clozapine [8,41]. Between 50 and 60 percent of patients with treatment-resistant schizophrenia fail to meet response criteria to clozapine after such a trial [13,41]. These patients are often referred to as "ultra-treatment," but the term "clozapine-resistant" is preferred to avoid confusion with patients who respond to ECT augmentation of clozapine, or with ECT-resistant patients.

For clozapine-resistant patients with schizophrenia, we favor ECT augmentation of clozapine rather than medication augmentation [44,50]. Clinical trials of the medications below have very limited evidence of efficacy and multiple methodologic limitations, and therefore should be used only if ECT augmentation is not viable.

Augmentation with electroconvulsive therapy (ECT) — Only one trial has tested ECT augmentation of clozapine in schizophrenia patients with confirmed clozapine resistance, finding ECT augmentation to reduce schizophrenia symptoms compared with continuing clozapine treatment alone [51]. The single-blind, eight-week trial randomly assigned 39 patients with clozapine-resistant schizophrenia to continue clozapine or to receive bilateral ECT (two to three sessions/week) along with continuing clozapine. Patients treated with ECT and clozapine were more likely to meet criteria for clinical response (≥40 percent reduction in psychosis) compared with patients receiving clozapine alone (50 versus 0 percent). The control group demonstrated a similar response to ECT upon crossing over to receive ECT after the randomized phase was completed. Two patients required the postponement of an ECT session because of mild confusion.

Augmentation with medication

- **Non-clozapine antipsychotic** – The addition of a non-clozapine antipsychotic to clozapine for individuals with residual symptoms despite clozapine treatment is controversial. A meta-analysis of two randomized trials with a total of 626 patients found a benefit to clozapine augmentation with a first-generation antipsychotic (SMD = -0.52, 95% CI -0.90 to -0.14), and a second-generation antipsychotic (SMD = -0.52, 95% CI -0.93 to -0.11)

compared with clozapine monotherapy, although these differences were not significant when only high quality studies were analyzed [52]. Also, in an overview of meta-analyses of combination treatments, none of the meta-analyses of pharmacologic augmentation of clozapine yielded superior results to control [44].

Augmentation with aripiprazole has been studied more extensively than other antipsychotics because of the unique pharmacodynamic characteristics of the second-generation antipsychotics. Analysis of data from a national registry of health care data in Finland found that individuals who were treated with clozapine (the most efficacious monotherapy in the study) were 14 percent less likely to be hospitalized for psychosis during periods when they were also prescribed aripiprazole (hazard ratio = 0.86; 95% CI 0.79-0.94) [53]. The effect of the combination was more pronounced in first-episode patients (hazard ratio = 0.78; 95% CI 0.63-0.96).

- **Other medications** – The combination of other drugs with clozapine has been consistently ineffective in meta-analyses of randomized clinical trials, and for this reason their use is generally not recommended [44]. Weak evidence provides some support for augmentation with first- or second-generation antipsychotics, and certain antidepressants (fluoxetine, duloxetine, citalopram) for persistent negative symptoms. Still weaker evidence supports clozapine augmentation with mood-stabilizers, anticonvulsants, pro-glutamatergic agents [54], rTMS, or tDCS [50].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- While most patients show significant improvement in psychotic symptoms in response to antipsychotic drugs, a substantial proportion experience residual treatment-resistant symptoms. (See 'Prevalence' above.)
- To facilitate greater accuracy and reliability in the diagnosis of treatment-resistant schizophrenia, we favor the use of the minimal consensus-based criteria developed the Treatment Response and Resistance in Psychosis (TRRIP) Working Group (see 'Definition' above):

- Symptom severity – At least moderate symptom severity (>3 in psychotic symptom items) as rated using a standardized scale (eg, Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale).

- Functional impairment – At least moderate impairment measured using a validated scale (eg, Social and Occupational Functioning Assessment Scale).

- Prior treatment – At least two trials of ≥6 weeks at a therapeutic dose (equivalent to ≥600 mg chlorpromazine) with adherence ≥80 percent of prescribed doses.

Optimal TRRIP criteria further call for one of the two antipsychotic trials to be for a long-acting injectable antipsychotic (see "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication") and for antipsychotic adherence to be established longitudinally with ≥2 plasma levels.

- Prior to making a diagnosis of treatment-resistant schizophrenia, the clinician should rule out or address causes of pseudoresistance, including (see 'Assess for pseudoresistance' above):

  - Misdiagnosis of primary disorder
  - Co-occurring mental or substance-use disorders, or medical conditions
  - Antipsychotic drug side effects
  - Medication nonadherence
  - Drug-drug interactions

- The patient's antipsychotic drug treatment (table 1) and nonpharmacologic treatment should be evaluated and optimized (see 'Adequacy of nonpharmacologic treatment' above):

- For patients with treatment-resistant schizophrenia as defined by the TRRIP criteria who meet the clozapine eligibility criteria below, we recommend first-line treatment with clozapine rather than other medications (**Grade 1A**). (See 'Clozapine' above and "Schizophrenia in adults: Guidelines for prescribing clozapine".)

  - Absolute neutrophil count ≥1500 cells/microliter

  - Determination by physician as well as the patient and family if possible that the benefits of clozapine outweigh the risks

  - Ability to adhere to treatment monitoring

- For patients with treatment-resistant schizophrenia who are not eligible for (or refuse) clozapine, we favor augmentation of a non-clozapine antipsychotic with electroconvulsive therapy (ECT) rather than medication or repetitive transcranial magnetic stimulation. If ECT is not effective, we would treat with lamotrigine. Minocycline or topiramate are reasonable alternatives. (See 'Alternatives for patients ineligible for or refusing clozapine' above.)

- For clozapine-resistant patients with schizophrenia, we favor ECT augmentation of clozapine rather than medication; however, no approach has shown convincing evidence of efficacy. (See 'Treatment of clozapine-resistant schizophrenia' above.)

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