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MAJOR REVIEW (ORIG)

Pharmacological and Somatic Treatments for First-Episode Psychosis and Schizophrenia: Synopsis of the US Department of Veterans Affairs and US Department of Defense Clinical Practice Guidelines

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***Background*: The Departments of Veterans Affairs (VA) and Defense (DOD) provide care each year for approximately 75,000 people with first-episode psychoses or schizophrenia, but neither has formal, evidence-based guidance for treating these conditions. Recognition of this gap, together with guidance from Congress, led the Departments to develop clinical practice guidelines for first-episode psychosis and schizophrenia. This synopsis summarizes the psychopharmacological and other somatic treatment recommendations.**

***Study Design*: An interdisciplinary panel of VA and DOD mental health and primary care providers was created following methods specified by the VA/DOD Evidence-Based Practice Guideline Work Group. The panel formulated key questions that guided a comprehensive search of the intervention literature from November 2011 to December 2021, with evidence limited to findings from randomized clinical trials. Recommendations were based on evaluation of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.**

***Study Results*: The VA/DOD guideline panel developed 15 pharmacological and somatic treatment recommendations, including those on antipsychotic medication use for the treatment of first-episode psychosis and schizophrenia, use of clozapine for treatment-resistant schizophrenia, treatment of clozapine non-responders, and side effect management. There was insufficient evidence to provide recommendations for or against the use of non-antipsychotic medications or somatic treatments to treat negative or cognitive symptoms.**

***Conclusions*: The VA/DOD guideline panel developed 15 pharmacological and somatic treatment recommendations to promote optimal, evidence-based care for active service members and Veterans. However, there remain multiple treatment planning decision points for which there is a lack of data and/or effective treatments.**

Key words: veterans; service members; antipsychotic agents; treatment algorithm; treatment guidelines; systematic review; evidence-based practices.

Introduction

Over the past 60 years, there have been marked changes in the treatment of individuals with schizophrenia. The advent of multiple pharmacological and psychosocial treatments has led to the development of several

treatment guidelines or recommendations for schizophrenia designed to improve the quality of care, minimize variations in treatment, and promote the utilization of evidence-based practices.[1–4] Despite the substantial number of individuals with psychosis receiving treatment within the Department of Veterans Affairs (VA) and Department of Defense (DOD), neither health system had established formal recommendations for the treatment of people with first-episode psychoses or schizophrenia. Recognition of this gap, together with guidance from Congress,[5] led the two Departments to develop a clinical practice guideline (CPG) for these conditions.[6]

Active-duty service members have several risk factors for prodromal syndromes and first-episode psychoses related to developmental, situational, and occupational factors, including age, separation from primary support systems, and exposure to the physical and psychological stressors of training and active-duty military service. A recent report from DOD found that 3,943 active-duty service members experienced a first episode of psychosis from 2018 to 2020 and estimated that the incidence was approximately 95 per 100,000 per year.[7] In general, schizophrenia is not compatible with ongoing military service. Therefore, treatment of individuals with an established diagnosis is more likely to occur in VA after separation or discharge from active duty. Identification, evaluation, and initiation of treatment of first-episode psychoses are more critical among active-duty service members in DOD.

Based on clinical and administrative records, VA provided health care in 2021 for almost 74,000 Veterans with schizophrenia; 90.3% were men, and 9.7% were women.[6] Of these individuals, 7.5% were under age 35, 50.1% were between 35 and 64, and 42.4% were aged 65 and over. Additionally, 54.5% were White, 35.4% Black or African American, 1.3% Asian, 0.8% Native American or Alaskan Native, and 8.1% multiracial or from other or unknown races. Individuals of Hispanic ethnicity made up 9.0%. Finally, 68.4% had some degree of service-connected disability.

In fiscal year 2021, 10.2% of individuals with schizophrenia receiving treatment through VA were admitted to VA inpatient mental health units.[6] Of VA patients with schizophrenia, 10.2% were treated in programs that provided intensive case management, 5.5% were seen in day treatment programs offering intensive rehabilitation programming, and 11.1% received homeless services.[6] In addition, 3.9% were recognized and flagged as being at high risk for suicide.[6] Based on data from electronic medical records, 22.4% had a coexisting diagnosis of post-traumatic stress disorder, and 28.0% had a substance use disorder. Co-occurring medical conditions were common.[6] Nearly half (49.5%) had hypertension, 30.5% had diabetes, and 6.5% had heart failure. The average body mass index (BMI) was 29.8, indicating that a sizeable proportion were overweight or obese.[6] After controlling for age, sex, and overall medical comorbidity, the all-cause mortality rate for VA patients with schizophrenia and other psychotic disorders (including schizoaffective and bipolar disorders) was 71% greater than for VA users without mental health conditions.[8]

This paper presents a synopsis and discussion of the CPG recommendations for psychopharmacological and other somatic treatments for first-episode psychosis and schizophrenia. It includes a description of the target populations, the methods used to develop the recommendations, the fifteen recommendations for pharmacological and other somatic treatments, summaries of the evidence that supports them, and the treatment algorithm included in the CPG to complement the recommendations. The CPG's recommendations for psychosocial, rehabilitative, and recovery-oriented treatments[9] are summarized in a separate report.

This CPG is intended for use primarily by VA and DOD providers and community-based providers who care for active-duty service members or Veterans with first-episode psychosis or schizophrenia. The populations of concern include adults with first-episode psychosis or schizophrenia who are eligible for care in VA or DOD healthcare delivery systems, as well as service members and Veterans who receive care from community-based providers.

Methods

To develop CPG recommendations, the VA/DOD utilized a process outlined by the VA/DOD Evidence-Based Practice Guideline Work Group (EBPWG)[10]; the process is based on standards described for trustworthy guidelines.[11] VA and DOD leadership selected four guideline panel co-chairs, two each from VA and DOD. Leadership and co-chairs then selected a multidisciplinary panel of stakeholders with specialists from a variety of disciplines, including psychiatry, psychology, pharmacy, internal medicine, primary care, nursing, and social work. All members of the guideline project team completed conflict-of-interest disclosure forms the previous two years and verbally affirmed the disclosures throughout the project. Appendix A contains the guideline workgroup and development team members.

The guideline panel developed 20 key questions (KQs) concerning the utility of assessment tools and approaches to diagnosis and the benefits and harms of interventions for the management/treatment of first-episode psychosis and schizophrenia. In addition, the panel chose critical and important outcomes for each KQ. This synopsis focuses on findings and recommendations related to the 4 KQs related to pharmacotherapies, somatic interventions, and side effects. A systematic search of the peer-reviewed English language literature published from November 1, 2011, to December 1, 2021, was conducted to address each of these KQs. Systematic reviews (SRs)

and meta-analyses of randomized clinical trials (RCTs) were prioritized and supplemented with individual RCTs when appropriate. Inclusion criteria required that at least 85% of the study participants were diagnosed with first-episode psychosis or schizophrenia or that the study performed a subgroup analysis specifically for one of these two patient populations. The KQs, search methods, and a summary of the results can be found in the full CPG[6] at https://www.healthquality.va.gov/guidelines/MH/scz/index.asp.

The systematic review assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, and the guideline panel used GRADE to rate the strength of the recommendations.[12–14] In the GRADE system, the ultimate strength of a recommendation is based on the lowest quality of the evidence rating for any critical outcome in the body of literature reviewed for a particular recommendation. The panel also gave special consideration to instances where the harm of withholding a treatment was particularly marked. The confidence of the panel in the balance between an intervention's desirable and undesirable effects is indicated in the language of each recommendation. The phrase "we recommend (for or against)" is used when confidence is strong; "we suggest" is used when confidence is weak; and the phrase, "There is insufficient evidence to recommend for or against," is used when the panel was unable to draw inferences from the studies reviewed.

Results

The VA/DOD Clinical Practice Guideline for Management of First-Episode Psychosis and Schizophrenia[6] is available at https://www.healthquality.va.gov/guidelines/MH/scz/index.asp. **Table 1** presents the recommendations and recommendation strength for each of the psychopharmacological and other somatic treatments.

Basic Principles.

The guideline panel considered antipsychotic medications as a class rather than individual agents when evaluating the evidence for their use. This decision was based on several considerations, including similarities in estimates of their treatment effectiveness and commonalities in their mechanisms of action.[15,16] The evidence review did not find consistent differences in effectiveness between agents (other than between clozapine and others) for the overall population of individuals with schizophrenia or for subgroups characterized by patient characteristics that could support categorical recommendations for one agent over others. The most significant differences between agents are their side effect profiles and the risks for specific adverse reactions. The guideline panel recognized that there may be substantial variability in patient preferences regarding the choice of antipsychotic medications; some individuals with schizophrenia might have concerns about experiencing one or more side effects associated with a particular antipsychotic agent. Accordingly, these guidelines recommend that the choice of antipsychotic medications should be based on individualized evaluations that consider side effect profiles, potential drug-drug and drug-disease interactions, response to previous treatments, and patient preferences.

Pharmacological Treatment of First-Episode Psychosis

Recommendation: Treatment of a First Episode of Psychosis (FEP). Current evidence supports the use of antipsychotic medications (other than clozapine) as a class for the treatment of an acute episode of schizophrenia in patients with FEP (see **Table 1**). The choice of antipsychotic medication should be based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications.

The systematic review of the evidence related to the treatment of FEP yielded one SR and a meta-analysis of 17 RCTs (n = 3 156).[17] The study was designed to evaluate response rate; the authors found that 81.3% of people with FEP met a 20% reduction and 51.9% met a 50% reduction in PANSS or BPRS total score response rate criterion. Individuals experiencing FEP exhibit an increased treatment response and a greater sensitivity to adverse effects, including motor side effects.[3] A lower starting and maintenance dose of antipsychotic should be considered in individuals with FEP.[3] In addition, if a person with FEP responds to an antipsychotic medication, then evidence supports the continued use of the medication for maintenance treatment to prevent relapse and hospitalization. However, the reviewed studies did not provide information about the optimal length of treatment required to maximize responses or to minimize the rate of relapses, which precludes a treatment recommendation for the optimal length of treatment of a first episode of psychosis.[17]

The "strong for" recommendation strength is based on the Zhu et al SR and meta-analysis, which provided compelling evidence for the efficacy of antipsychotic medications as a class for the treatment of FEP,[17] and the guideline panel consensus that the benefits of antipsychotic medication strongly outweigh their potential harms and burdens. Specifically, reduction of symptoms as a primary benefit is associated with reduced patient distress and increased receptivity to psychosocial and recovery-oriented treatments. The potential harms of not providing these medications include increased risks of self-harm or harm to others, impaired work or social functioning or both, decreased quality of life, distress from untreated symptoms, and family burden, which outweighed the potential harm of adverse events, including cardiovascular, metabolic, and motor side effects.

Table 1. Recommendations and Strength of Recommendation for Pharmacological Treatments, Management of Side Effects, and Somatic Treatments

Pharmacological treatments	Recommendation strength
We recommend the use of an antipsychotic medication other than clozapine for the treatment of first-episode psychosis or an acute episode in individuals with schizophrenia who have previously responded to antipsychotic medications.[a]	Strong for
We recommend the use of an antipsychotic medication for the maintenance treatment of schizophrenia to prevent relapse and hospitalization in individuals with schizophrenia who have responded to treatment.[a]	Strong for
We suggest a trial of another antipsychotic medication for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication.[a]	Weak for
We suggest offering long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia.	Weak for
We recommend the use of clozapine for individuals with treatment-resistant schizophrenia.	Strong for
We suggest augmenting clozapine with another second-generation antipsychotic medication for individuals with treatment-resistant schizophrenia who have not experienced an adequate response to clozapine.	Weak for
There is insufficient evidence to recommend for or against augmentation with any nonantipsychotic medication for treatment of cognitive and/or negative symptoms for individuals with schizophrenia.	Neither for nor against
Management of side effects	**Recommendation strength**
We suggest using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia.	Weak for
We suggest the use of dietary interventions, exercise, individual lifestyle counseling, and/or psychoeducation for metabolic side effects of antipsychotic medication as well as the delivery of weight management services that are based on a chronic care model (eg, Enhancing Quality of Care in Psychosis) for individuals with schizophrenia.	Weak for
We suggest a trial of a vesicular monoamine transporter 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia.	Weak for
We suggest a trial of diphenhydramine for individuals with schizophrenia who are experiencing sialorrhea as a side effect of clozapine.	Weak for
There is insufficient evidence to recommend for or against any treatment for hyperprolactinemia-related side effects of antipsychotic medications in individuals with schizophrenia.	Neither for nor against
Somatic treatments	**Recommendation strength**
There is insufficient evidence to recommend for or against transcranial direct current stimulation and repetitive transcranial magnetic stimulation for individuals with schizophrenia.	Neither for nor against
There is insufficient evidence to recommend for or against electroconvulsive therapy for individuals with schizophrenia.	Neither for nor against
There is insufficient evidence to recommend for or against augmenting pharmacotherapy with acupuncture to reduce negative and positive symptoms for individuals with schizophrenia.	Neither for nor against

[a]Choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and side effect profiles of the different antipsychotic medications.

Pharmacological Treatment of Schizophrenia

Recommendation: Treatment of Acute Episodes. Antipsychotic medications (other than clozapine) as a class should be used for the treatment of an acute episode of schizophrenia in individuals with schizophrenia who have previously responded to an antipsychotic medication (see **Table 1**). The choice of antipsychotic medication should be based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications. Lower antipsychotic doses should be used in older adults with schizophrenia because of pharmacokinetic and pharmacodynamic changes, as well as potential drug-drug interactions.

The evidence base supporting the use of antipsychotic medications as a class other than clozapine includes multiple SRs and meta-analyses,[15,18–29] as well as additional RCTs[30–32] that examined the efficacy of antipsychotic medications for the treatment of acute symptomatology in participants with an acute episode of schizophrenia. The most comprehensive SR and meta-analysis included

167 double-blind RCTs and found that 51% of people treated with an antipsychotic medication had at least a minimal response to active medication versus 30% for placebo.[15]

The strong recommendation for antipsychotic medications as a class is based on several considerations. First, the rating for the quality of the evidence was based largely on the Leucht et al SR and meta-analysis, because it included almost all the studies identified for this guideline.[15] Although many of the studies included had serious flaws, analyses found that effect sizes were consistent across good, fair, and poor-quality studies, and the estimates of effects included adjustments for publication bias. Accordingly, the panel judged the overall GRADE rating for the quality of the evidence to be moderate. Second, the consensus of the guideline panel was that the benefits of antipsychotic medication strongly outweigh their potential harms and burdens. Specifically, reduction of symptoms as a primary benefit is associated with reduced patient distress and increased receptivity to psychosocial and recovery-oriented treatments. The potential harms of not providing these medications include increased risks of self-harm or harm to others, impaired work or social functioning or both, decreased quality of life, distress from untreated symptoms, and family burden. Significant harms associated with antipsychotic medication treatment include cardiovascular, metabolic, and motor side effects, sedation, and others, but these are outweighed by the benefits.

Recommendation: Maintenance Treatment. The evidence review identified an extensive array of studies, multiple SRs,[15,16,18–21,33,34] and individual RCTs,[35–37] that support the use of antipsychotic medication as a class for maintenance treatment of schizophrenia to prevent relapse and hospitalization. An SR and meta-analysis of 75 RCTs reported that antipsychotic medications were more effective than placebo for preventing relapse (24% vs 61% relapse rate; RR: 0.38) and hospitalization (7% vs 18% hospitalization rate; RR: 0.43).[16] Confidence in the evidence is strengthened by the observation that there is considerable consistency across studies regardless of their quality. Overall, it was the consensus of the guideline panel that the benefits of antipsychotic medication for maintenance treatment strongly outweigh the potential harms and burdens. Specifically, maintenance treatment is associated with decreased levels of distress and increased availability for psychosocial and rehabilitation or recovery-oriented treatments. In addition to the distress associated with increased symptoms, the potential harms of withholding these medications include increased risk of self-harm or harm to others, impaired work and social functioning, decreased quality of life, risk for engagement with the justice system, and family burden.

Recommendation: Switching Medications When Patients Do Not Respond or Tolerate Their Medication. In suggesting switching antipsychotic medications when patients do not respond or are able to tolerate a particular antipsychotic medication, the guideline panel assumed that providers have ensured that there has been an adequate treatment trial with a sufficient dose and duration and that adherence has been acceptable. In general, the studies included in the evidence that support the recommendation for the use of antipsychotic medications as a class included participants who did not experience stable, persistent responses to previous treatments.[15,16,18-32] Although the overall evidence suggests equivalent effectiveness among agents, there have been reports suggesting the superiority of one agent over another,[38] but these have generally not been replicated. Most significantly, there are no established methods for predicting what individual characteristics predict better responses to one medication over another, except for clozapine. The panel recognized that augmentation with a second agent can be an alternative to switching for individuals who do not respond to an initial medication, but observational studies suggest that augmentation is associated with increased side effects and nonadherence.[39,40] Given the observational nature of these studies, the panel did not consider them in formulating the suggestion.

Recommendation: Long-Acting Injectable (LAI) Antipsychotics. The suggestion is based on evidence from an SR demonstrating that treatment with LAI antipsychotics improves adherence in individuals with schizophrenia.[41] The SR identified 33 RCTs of oral versus LAI forms of first or second-generation antipsychotics and reported that LAIs were significantly associated with decreased rates of relapses and hospitalizations. Adherence, a critical outcome for the evidence review, was only evaluated in two RCTs. However, the available findings demonstrated significantly higher levels of adherence for individuals receiving LAIs than oral medications. The guideline panel recognized that patients who volunteer to participate in RCTs may not be representative of the population who are at the greatest risk for nonadherence, making it difficult to draw inferences from RCTs. However, we note that the SR analyzed findings from both RCTs and cohort studies and found that LAIs were associated with fewer hospitalizations than oral antipsychotics in both types of studies.

Recommendation: Clozapine for Treatment-Resistant Schizophrenia. Recent studies estimate that approximately 20–25% of people diagnosed with schizophrenia will exhibit treatment resistance.[42,43] Evidence from an SR comparing clozapine with all other antipsychotic medications in individuals who were refractory to other treatments demonstrated that improvements in total psychotic symptoms, positive symptoms, and negative symptoms were greater for clozapine than for pooled estimates for other FGAs or SGAs in clinical

trials with periods of observation up to 3 months.[44] Evidence evaluating responses over longer periods of observation suggested that the increased improvement rates persisted for positive but not negative or total symptoms.[44] Another SR that focused on pairwise comparisons of antipsychotic medications for treatment-resistant schizophrenia found no differences between clozapine and chlorpromazine, haloperidol, risperidone, olanzapine, or ziprasidone in symptomatic outcomes.[45] Nevertheless, possibly consistent with a unique role for clozapine, none of the pairwise comparisons suggested that any other medication led to greater improvements than clozapine.

The sensitivity analysis in the SR of pairwise differences may be helpful as a guide to decision-making; it suggested that estimates for the comparative effectiveness of clozapine and other antipsychotic medications did not appear to depend on the rigor of the criteria used to define treatment resistance.[45] Furthermore, the SR identified studies demonstrating that clozapine was more effective than risperidone or haloperidol for the treatment of "moderately refractory schizophrenia" and that it should be considered "for some patients who do have some response to antipsychotics, but still experience troubling symptoms."[46,47]

Recommendation: Treatment of Clozapine-Resistant Schizophrenia. Evidence from several SRs supports the suggestion that augmenting clozapine monotherapy with another second-generation antipsychotic medication may be effective in individuals with clozapine-resistant schizophrenia.[48–50] One SR found that aripiprazole or ziprasidone added to clozapine improved depressive symptoms or negative and depressive symptoms, respectively[48]; another, that aripiprazole added to clozapine improved negative symptoms and global psychopathology[49]; and another, that risperidone added to clozapine improved positive symptoms.[50] The guideline panel noted a need for careful treatment planning and shared decision-making that considers the ongoing risks and burdens of continuing clozapine for those individuals who do not respond to it and those who only exhibit partial responses. The evidence supports a suggestion to augment clozapine with another SGA, and, as discussed below, there is also evidence, albeit weak, that augmentation with ECT may be effective.[51,52] However, treatment planning should also consider the discontinuation of clozapine and the use of other medications, together with intensified rehabilitation and recovery-oriented treatments.

Recommendation: Treatment of Cognitive and Negative Symptoms with Other Agents. The guideline panel considered evidence from SRs of RCTs of oxytocin,[53] galantamine,[54] memantine,[55,56] raloxifene,[57] D-cycloserine,[58] N-acetylcysteine,[59] and a series of agents that interact with N-methyl-D-aspartate (NMDA) transmission (i.e., benzoate, CXC515, D-cycloserine, D-serine, minocycline, N-acetylcysteine, pregnenolone, L-carnosine, sarcosine, glycine)[60] for the treatment of cognitive and negative symptoms. Although some studies reported possible benefits, the panel's confidence in the quality of evidence was very low. The evidence that is currently available suggests that the benefits and harms or burdens associated with nonantipsychotic medications in the treatment of cognitive and negative symptoms appear to be balanced and are not sufficient to support recommendations for or against the use of any of these agents at this time.

In addition to the evaluation of new agents for the treatment of cognitive and negative symptoms, future studies should also evaluate the impact of reduction of anticholinergic burden on these two domains.

Management of Side Effects of Antipsychotic Medications

Recommendation: Metabolic Side Effects. The CPG includes suggestions for both pharmacological and nonpharmacological strategies for managing metabolic side effects from antipsychotic medications. The former includes augmentation with metformin, topiramate, or aripiprazole, and the latter includes dietary interventions, exercise, individual lifestyle counseling, and psychoeducation. There is also evidence from one study for the effectiveness of practice redesign following a chronic care model to support monitoring for medication-related weight gain and facilitating interventions when needed.[61]

The evidence review identified an SR and meta-analysis that considered a broad range of interventions.[62] Improvements in outcomes related to metabolic side effects, including weight loss and reduction in waist circumference, were observed with the use of metformin (29 trials), topiramate (15 trials), and aripiprazole (9 trials). The SR also reported improvements from individual lifestyle counseling (14 trials), exercise interventions (4 trials), psychoeducation (8 trials), and dietary interventions (22 trials). The estimates for effect sizes and the relative effects of the interventions varied depending on outcomes (e.g., reduction in weight, BMI, waist circumference). Although the CPG suggests augmenting current medication regimens with additional agents to manage metabolic side effects, the guideline panel recognizes that an alternative strategy, switching antipsychotic medications, may be useful. This approach is supported to some extent by findings from two RCTs identified in the SR that evaluated switching from olanzapine to quetiapine or aripiprazole; these studies reported that switching was associated with decreases in blood glucose but not in weight or BMI.[62] Overall, the consensus of the guideline panel is that the management of metabolic side effects of antipsychotic medication requires treatment planning

that considers both pharmacological (augmentation or switching) and nonpharmacological interventions.

Future studies should evaluate alternative strategies for managing metabolic side effects, including the use of glucagon-like peptide-1 agonists for this indication.

Recommendation: Tardive Dyskinesia (TD). The CPG suggests using a vesicular monoamine transporter 2 (VMAT-2) inhibitor for the treatment of TD. Evidence from an RCT suggests that the VMAT-2 inhibitor valbenazine improves Abnormal Involuntary Movement Scale (AIMS) scores and the severity of TD symptoms[63] but not global ratings of change or response rates. Although this suggestion was based specifically on the evidence of effectiveness in schizophrenia, it is consistent with findings from RCTs of VMAT-2 inhibitors (valbenazine, deutetrabenazine, and tetrabenazine) in individuals across mental health diagnoses as identified in an SR and meta-analysis of treatments for TD.[64]

Recommendation: Clozapine-Related Excess Salivation (Sialorrhea). The CPG suggests using diphenhydramine for individuals with schizophrenia experiencing sialorrhea as a side effect of clozapine. An SR and meta-analysis of 19 studies found that muscarinic antagonists and antihistamines as classes were effective.[65] However, for muscarinic-blocking agents, the positive findings could be attributed primarily to studies of propantheline, an agent that is no longer available in the US, and to a single small study with benzhexol. For antihistamines, diphenhydramine was effective and was the only agent studied with a sufficient sample size (5 RCTs, $n = 334$) to support a suggestion. Side effects include gastrointestinal issues, cognitive impairment related to its muscarinic-blocking activity, and increased sedation. The guideline panel was concerned about the cumulative anticholinergic effects of clozapine plus diphenhydramine. However, the formulation of this suggestion was guided by findings from the SR[65] which identified 4 studies that provided data on the rates of constipation when diphenhydramine was added to clozapine; it reported that the number needed to harm was 35 and that there was no statistically significant difference in rates between intervention and placebo groups. Nevertheless, it is important to recognize that clozapine has potent anticholinergic effects and that adding another muscarinic-blocking agent can increase risks. These should be addressed through psychoeducation and shared decision-making; treatment planning should include close monitoring for adverse effects and should consider a prophylactic bowel regimen.

Recommendation: Prolactin-Related Side Effects (Galactorrhea, Sexual Dysfunction, Menstrual Irregularities, Gynecomastia, and Osteoporosis). The guideline panel found insufficient evidence to recommend for or against any specific treatments for hyperprolactinemia-related side effects of antipsychotic medications. The evidence review identified two relevant RCTs.[66,67] One small study ($n = 46$) of adjunctive aripiprazole in premenopausal women found positive effects on prolactin levels, galactorrhea, and sexual dysfunction but not on normalizing menstruation.[66] The other study randomized male participants to adjunctive aripiprazole or a high dose of vitamin B6 and found reductions in prolactin levels in both groups, but it did not report on symptomatic outcomes.[67] Although the available evidence focuses on augmenting current antipsychotic medications, the panel recognizes that an alternative strategy, switching to an antipsychotic medication with a lower risk of hyperprolactinemia, may be considered. We did not evaluate the treatment of asymptomatic prolactin elevation or prolonged prolactin elevation on health outcomes in people with schizophrenia.

Somatic Treatments for Schizophrenia

Recommendation: Repeated Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS). The guideline panel found insufficient evidence to support recommendations for or against neuromodulation with rTMS or tDCS for the treatment of schizophrenia. The studies identified by the evidence synthesis reported mixed findings on the effectiveness of rTMS. An SR focused on the treatment of auditory hallucinations[68] and additional RCTs[69,70] reported no significant benefits for treating positive symptoms in individuals with schizophrenia. However, one RCT found significant improvements on the Positive and Negative Symptoms Scale total score.[71] The evidence for the benefits of the treatment of negative symptoms was also mixed. Findings from some studies,[72–74] but not others,[75–77] suggested effectiveness.

An SR and meta-analysis of tDCS versus sham treatment reported significant differences in favor of the active treatment, with effect sizes that were moderate (0.43) for negative symptoms and small (0.17) for positive symptoms.[78] Two SRs of tDCS for auditory hallucinations found opposite results,[68,78] possibly due to differences in the RCTs included in their meta-analyses.

Overall, it was the consensus of the guideline panel that the evidence related to the treatment of negative symptoms by tDCS and, possibly, by rTMS provided early signals suggesting that these treatments may be effective. Moreover, the guideline panel recognizes that research on neuromodulation is advancing rapidly and that studies that may have been informative [(79)] were published after the closing date for the evidence review. Nevertheless, it was the panel's consensus that additional research addressing issues related to patient selection, stimulus parameters, concomitant treatments, stability of responses, and the safety and effectiveness of repeated

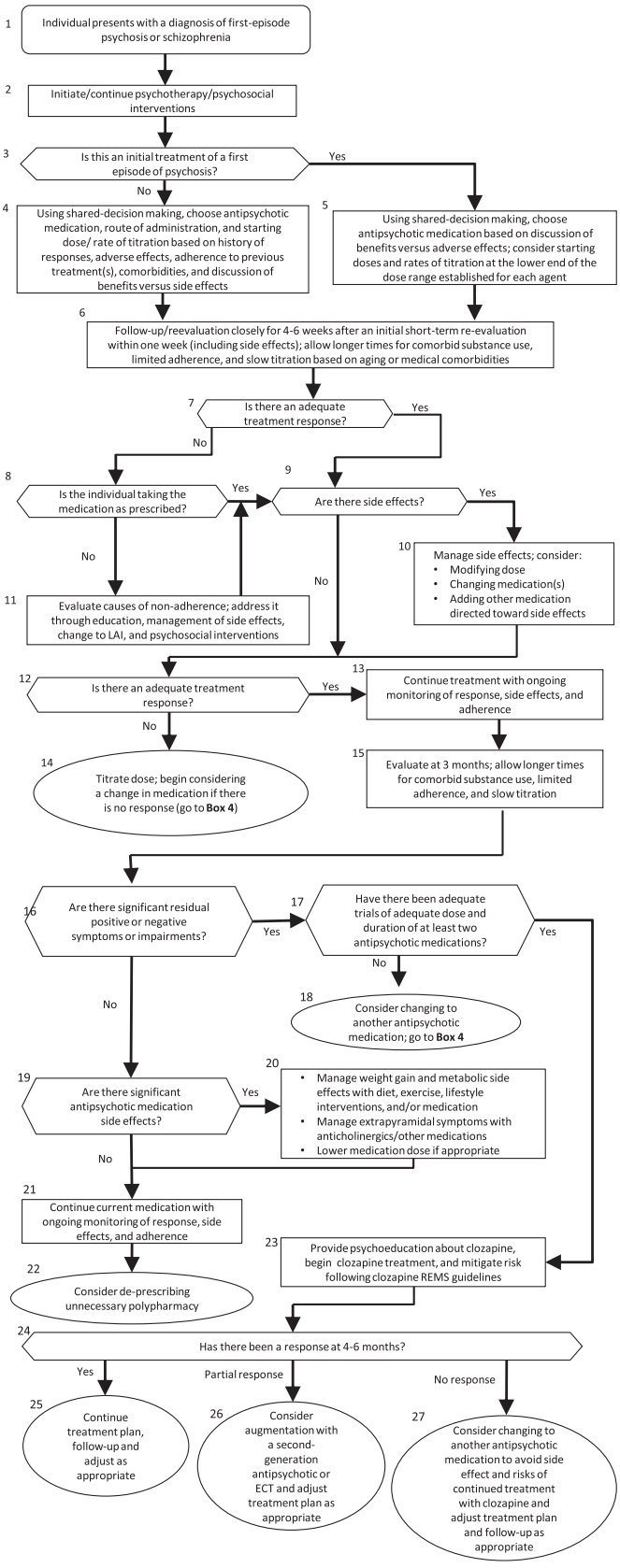

Figure 1. Algorithm for Pharmacotherapy for Treatment of Schizophrenia

treatments are necessary before it would be possible to recommend these treatments.

Recommendation: Electro-Convulsive Therapy (ECT). The guideline panel found insufficient evidence to recommend for or against the use of ECT for the treatment of schizophrenia. The evidence synthesis identified one SR and meta-analysis of ECT alone or combined with psychopharmacological interventions.[80] Findings on effectiveness were mixed. RCTs (n = 13) randomizing individuals with schizophrenia to ECT plus standard care versus standard care alone provided low-quality evidence for effectiveness for overall psychotic symptoms. However, one RCT randomizing participants to ECT versus sham ECT and one randomizing participants to ECT versus additional antipsychotic medications found no effects. The evidence synthesis identified a small-scale RCT of ECT plus clozapine versus continued treatment with clozapine alone in individuals with clozapine-resistant schizophrenia, providing low-quality evidence that the combination treatment was effective.[51,52] Although the evidence was inadequate to support a recommendation, the promising finding and limited evidence from other studies on treatments for clozapine-resistant schizophrenia led the guideline panel to include this treatment in the algorithm.

Recommendation: Acupuncture. There is insufficient evidence to recommend for or against augmenting pharmacotherapy with acupuncture to reduce negative and positive symptoms for individuals with schizophrenia. Findings from an SR of 30 RCTs (29 of them in China) suggest that acupuncture with antipsychotic medication might improve relapse rates and akathisia.[81] However, the review found that electro-acupuncture could lead to spinal fracture, the evidence was of low quality, and cultural factors likely impact the generalizability of the findings.

Algorithm for Pharmacotherapy Treatment of Schizophrenia

The CPG supplements its recommendations with an algorithm (**Figure 1**) that provides more detailed and pragmatic guidance for the ongoing decisions that must be made during treatment. While the recommendations are made strictly based on findings from RCTs, the algorithm supplements this evidence with input based on observational studies and expert consensus. For example, the algorithm, but not the recommendations, specifies timeframes for assessments after starting or changing antipsychotic medications. Further, the algorithm goes beyond the recommendations in suggesting the next steps for individuals with treatment-resistant schizophrenia who have not responded adequately to clozapine. For those who have had no response, the algorithm suggests

considering a change to another antipsychotic medication to avoid the increased risks and burdens associated with clozapine. For those who have had a partial response, it suggests considering augmentation with another second-generation antipsychotic medication or electroconvulsive therapy. In all cases, it suggests re-evaluating the overall treatment plan to consider intensifying rehabilitation and recovery-oriented programs.

Other components of the algorithm include tables that provide additional information not readily incorporated into a flow diagram. **Table 2** provides guidance about monitoring the processes and outcomes of treatment. The goal is to encourage providers to incorporate this information into measurement-based clinical care, including collecting and sharing data with patients and acting on it in the context of shared decision-making.

Table 3 offers additional guidance about the use of clozapine. The algorithm goes beyond the recommendation for clozapine for treatment-resistant schizophrenia to suggest that it should also be considered for individuals with schizophrenia or schizoaffective disorder who are at risk for suicide and, possibly, for individuals with schizophrenia with persistent aggressive behavior. The table summarizes the need for careful titration of clozapine doses, the importance of monitoring troponin or other inflammatory markers early in treatment to support recognition of myocarditis, the value of measuring blood levels of clozapine, and the need to consider bowel regimens to decrease the impact of clozapine-related gastrointestinal hypomotility especially when clozapine is prescribed along with other anticholinergic medications.

Table 2. Monitoring Treatment Processes and Outcomes

Monitoring domains to consider
Core symptoms of psychosis, schizophrenia, or both
Lab parameters (corrected QT-interval; leukocytes; neutrophils; agranulocytes; sodium; glucose; hemoglobin A1C; triglycerides; high-density and low-density cholesterol; prolactin, especially if sexual dysfunction, galactorrhea, menstrual irregularities or unexpected breast tissue changes occur; creatine phosphokinase in the case of new-onset movement disorder and as appropriate through the course of movement disorders)
Repeat laboratory measures at 3 months for clozapine and olanzapine, then annually
Repeat laboratory measures at least annually during treatment with all other antipsychotic medications
Extrapyramidal movements (cogwheel rigidity; akathisia; parkinsonism; tardive dyskinesia; acute and painful muscle tone changes)
Vitals (weight; temperature; blood pressure; heart rate changes; orthostatic hypotension; autonomic instability; unexplained fever)
Functioning (social functioning; intimacy; sexuality; parenting; workplace; education; family or other primary support group; interpersonal baseline changes)
Durable planning needs (financial; guardianship; medical, legal, or both; will)
Patient goals and preferences
Changes to life circumstances

Table 3. Clozapine Management

Provide the patient (and, where appropriate, the family) education about the benefits and risks of clozapine and ensure their understanding and consent
Confirm indications for clozapine: treatment-resistant schizophrenia; schizophrenia or schizoaffective disorder with suicidality; or, possibly, schizophrenia with persistent aggressive behavior
Evaluate symptoms and impairments with standardized assessment instruments
Consider whether the patient might have benign ethnic neutropenia
Obtain a within-range absolute neutrophil count before prescribing and dispensing
Prescribe clozapine starting at low doses with gradual titration to therapeutic doses and blood levels
Monitor absolute neutrophil counts weekly for 6 months, then once every 2 weeks for 6 months, then monthly, thereafter
Follow FDA protocols for below-threshold absolute neutrophil counts indicating neutropenia or agranulocytosis
Obtain troponin and c-reactive protein levels at baseline and monitor them weekly for at least the first month of treatment to support the early identification of myocarditis as an adverse effect
Consider prescribing bowel regimens to prevent clozapine-related gastrointestinal hypomotility and ileus, especially when the patient is also receiving other anticholinergic medications
Monitor symptoms, impairments, and side effects
Evaluate blood levels and adjust doses as appropriate to evaluate nonresponse, possible nonadherence, pharmacokinetic drug-drug or drug-smoking interactions, and to support the management of side effects

Of note, the Food and Drug Administration (FDA) has recently dropped the Clozapine Risk Evaluation and Mitigation Strategy requirements. In the future, the FDA may provide alternative guidance around the use of clozapine, which may require an update of the VA/DOD guidance on the use of clozapine.

Discussion

The VA/DOD guideline panel reviewed all relevant articles between the years of 2011-2021 on pharmacological and other somatic treatments of schizophrenia, which resulted in the development of 15 recommendations on the pharmacological treatment of schizophrenia (seven recommendations); the management of medication side effects (five recommendations), and the use of somatic treatments (three recommendations). The recommendation strength for three of the seven pharmacological treatment recommendations was "strong" and for three was "weak. The panel found that there was insufficient evidence for nonantipsychotic augmentation for the treatment of cognitive impairments or negative symptoms. The recommendations for four of the medication side effect management guidelines were "weak" with there being insufficient evidence for the guideline on the treatment of hyperprolactinemia. There was insufficient evidence for either recommendation on the use of somatic treatments for schizophrenia.

The methods to develop the VA/DOD guideline differed substantially from those used for the recent APA practice guideline.[1] Both weighed each recommendation's potential benefits and harms and then identified the confidence level in that determination, consistent with the GRADE method. While the recommendations for this guideline were based solely on evidence from RCTs (or SRs of clinical trials) published within the defined time frame, the APA guideline utilized findings from RCTs together with other forms of evidence, such as findings from observational studies and consensus opinions of experienced clinicians.

Most significantly, the two guidelines agreed in making recommendations for antipsychotic medications as a class rather than specific agents for treating acute episodes and maintenance treatment to prevent recurrences. The APA guideline suggests that patients with schizophrenia whose symptoms have improved with an antipsychotic medication should continue the same medication, while this guideline suggests a trial of another antipsychotic medication for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an initial medication. These are alternative expressions of the same principles. The two guidelines also agreed on the use of clozapine for treatment-resistant schizophrenia, LAI antipsychotics to improve adherence, and VMAT2 inhibitors to treat tardive dyskinesia.

There were some differences between the guidelines, however. The APA guideline includes recommendations or suggestions for treating antipsychotic medication-induced dystonia, Parkinsonism, and akathisia. Treatments of these side effects are addressed generically in the algorithm for this guideline but not in the recommendations; the evidence synthesis conducted to support this guideline did not identify relevant evidence within the specified time frame. In addition, the APA guideline recommends using clozapine for individuals with schizophrenia at risk for suicide and suggests its use for those at risk for aggressive behavior. These are addressed in the text and the algorithm included in this guideline but not as specific recommendations, as the evidence synthesis did not identify the information needed to develop recommendations in this area.

Recommendations included in the VA/DOD, but not in the APA guideline, address augmenting clozapine with another second-generation antipsychotic for individuals with treatment-resistant schizophrenia who did not have an adequate response to clozapine, use of pharmacological and other interventions for managing metabolic side effects of antipsychotics, and use of diphenhydramine for managing clozapine-induced sialorrhea. Despite the differences in methods and some of the recommendations, there is a high degree of agreement between the two guidelines. The similarities between the two serve as a demonstration of their concurrent validity.

Though this synopsis focuses on psychopharmacological treatment for schizophrenia, the VA/DOD guideline panel recognizes that evidence-based treatment for schizophrenia must also include psychosocial, supportive, and recovery-oriented services. The CPG separates recommendations for pharmacological and psychosocial interventions, but this is not intended to suggest that the two sets of interventions should be followed independently. To ensure that care is patient-centered, there should be coordination between them. Accordingly, the algorithm guides providers to coordinate re-evaluations of psychotherapy and rehabilitation or recovery-oriented treatments with re-evaluations of pharmacotherapy after each course of treatment. It provides guidance to consider increasing the intensity of psychosocial treatments to address increased needs when responses to medication have been inadequate and in response to increased opportunities for rehabilitation and recovery when pharmacologic treatment leads to decreases in impairments.

The major limitation associated with the methodology for developing the VA/DOD guidelines is the reliance solely on RCTs, which excludes evidence from large observational cohort studies and other sources of information. In consequence, clinical practices that are not amenable to evaluation in more formal RCTs were not evaluated and the current guidelines are silent on the utility of such practices.

In summary, the VA/DOD guideline panel developed 15 treatment recommendations for people with schizophrenia. The development of the recommendations is designed to ensure that active service members and Veterans receive optimal care for schizophrenia through the utilization of evidence-based pharmacological and somatic treatments.

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Appendix A

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