CNS SPECTRUMS

CME Review Article

Treatment Resistance and Other Complicating Factors in the Management of Schizophrenia

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Statement of Need

There is a documented gap between evidence-based practice guidelines and actual care in clinical practice for patients with schizophrenia, particularly after the first-line treatment phase. Specific gaps include underutilization of clozapine for treatment-resistant patients as well as for those with suicidal ideation.

There is evidence that providing education on evidence-based practice guidelines can improve adherence to those guidelines and likewise improve patient outcomes. To help improve outcomes for patients with schizophrenia and address these professional practice gaps, quality improvement efforts need to provide education regarding meta-guidelines for treating patients who have failed to respond to initial antipsychotic treatment.

Learning Objective

After completing this activity, participants should be better able to apply evidence-based treatment guidelines to the clinical care of patients with resistant or difficult to treat schizophrenia.

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CME REVIEW ARTICLE

Treatment resistance and other complicating factors in the management of schizophrenia

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Treatment resistance, along with its sibling partial response, remains a common phenomenon in schizophrenia, complicating the disability burden inherent in the disease. Antipsychotic medications are the mainstay of treatment, and treatment resistance has mainly been defined in terms of poor response to antipsychotic medication. At the same time, clozapine, the most effective antipsychotic, remains underutilized at the expense of exposing patients to polypharmacy. We review known causes of disability in schizophrenia, how they impact various areas of everyday functioning, and discuss potential treatment options including but not limited to pharmacological approaches aimed at maximizing treatment response and reducing treatment resistance.

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Key words: Chronic, cognition, health, refractory, schizophrenia.

Clinical Implications

- Disability rates in schizophrenia remain high, and treatment options have been narrowly defined and typically reliant on pharmacological therapies that lack efficacy.
- Disability in schizophrenia is a complex construct that requires treatment from different vantage points in addition to the current therapeutic mainstay, antipsychotic medication. These interventions include cognitive, social, and functional skills training, which have been proven effective.
- Clinicians recognize treatment resistance, but rely on polypharmacy while underutilizing clozapine, depot antipsychotics, and nonpharmacological approaches.
- Therapeutic approaches beyond antipsychotics are rarely utilized but show promise, including cognitive remediation combined with functional skills training, pharmacological cognitive enhancement, treatment of residual depression, and physical exercise interventions.
- We suggest a comprehensive approach that accounts for the multiple sources of disability in schizophrenia, including but reaching beyond more frequent use of clozapine, and may improve outcome.

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Introduction

Schizophrenia-spectrum disorders are among the world's most disabling illnesses.[1] Treatment has largely focused on pharmacological interventions aimed at controlling psychotic symptoms at the expense of other debilitating factors that also impact upon everyday functioning in important functional domains, such as independence in residence, productive activities, and social interactions–areas which are only obliquely associated with psychosis.[2,3] Consequently, treatment resistance has mostly been defined in terms of lack of response to antipsychotic medications,[4] most often clozapine.[5]

Despite wide availability of clozapine and its common worldwide use, it is typically underutilized in the U.S., as are nonpharmacological treatment approaches that may remediate areas of clinical concern other than psychosis. We suggest that successful completion of everyday activities requires the execution of a complex skill set that involves interactions not only among symptoms (positive and negative psychotic symptoms as well as depression), but also includes cognitive abilities, functional skills (the ability to perform tasks under optimal conditions), and physical health variables, whose harmonious performance within complex environment settings is required for effective everyday functioning (Figure 1), with symptoms playing a dominant, but not exclusive, role.[6] Consequently, broadly defined interventions that include these additional factors could have multifaceted

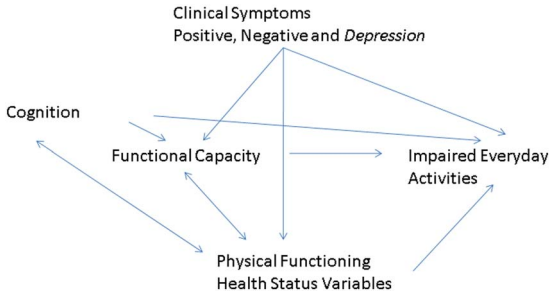

FIGURE 1. Model of Disability in Schizophrenia

benefits in obliquely related areas (cognition, physical skills) that have the potential to reduce disability, supporting the current therapeutic armamentarium.[7]

While approximately 70% of patients with schizophrenia and other psychotic disorders show a clear-cut reduction of symptoms in clinical trials and naturalistic observational studies, there is considerable variation in individual symptomatic outcome, even with adequate antipsychotic treatment, ranging from complete symptom remission to absolute refractoriness.[8] Factoring in the above mentioned additional indicators of treatment outcome, such as cognitive and functional skills, real-world performance in residential independence, productive activities, and social interactions, and even health status variables and physical impairments, treatment response becomes even more difficult to define. Moreover, recent advances in the assessment of real-world performance, rated by observers such as high-contact clinicians ("real world" achievement of milestones, social relationships), measure life skills more accurately than previously possible, improve on the validity of patient-reported outcomes for these relevant domains, and should improve objective assessment of outcomes.[9] It is critical to move beyond incomplete response of psychotic symptoms when defining treatment resistance.

The Impact of Refractory Psychotic Symptoms

While both positive and negative symptoms contribute independently to functional outcome, negative symptoms are better predictors of outcome[10,11] and are more difficult to treat.[12] However, a considerable proportion of patients will continue to experience positive symptoms, if in an attenuated form. Reduced motivation to engage in pleasurable activities, which is part of the negative symptom spectrum (including social and recreational activities, as well as failing to be motivated by traditional incentives), considerably reduces everyday functioning. Social functioning specifically is hypothesized to be most affected by negative symptoms compared to other influences, and interferes on several levels with functional outcome, such as social skills acquisition[13] and application of these skills required for daily living.[14]

Persistent psychotic symptoms and repeated relapses in partially responsive patients have the potential to lead to substantial problems, with the potential to impact on cognition and functioning. The notion that successful antipsychotic treatment can alter the natural course of schizophrenia was introduced by Wyatt,[15] who reviewed data from studies of patients who experienced extended periods of psychosis prior to their initial treatment with antipsychotic medications and compared them to patients whose first psychotic episode received medication treatment. His data suggested a disease modifying effect of antipsychotic treatment early in the course of illness. While this concept has been the subject of much research and controversy, it seems plausible that reduction of psychosis may have a beneficial effect. While there are inconsistent results regarding duration of untreated psychosis and lifelong functional outcomes, many of the inconsistent results may be due to research designs that are simply not adequate to address the question of whether lengthy periods of untreated psychosis lead to poorer outcomes, specifically in terms of very short durations of untreated psychosis examined in the study. In the studies reviewed by Wyatt, many of the patients experienced decades of untreated psychosis, while in many studies of first-episode patients, the duration of untreated psychosis is measured in weeks or months.

There are two lines of research suggesting that, after the diagnosis of a psychotic condition, the presence of psychosis, even in ambulatory patients, is associated with deterioration in functioning and alterations in brain structure. One is the longitudinal study of treatment refractory patients, who experience continued psychosis despite adequate antipsychotic treatment. The second is the longitudinal study of early-course patients across the course of multiple psychotic relapses associated with nonadherence with treatment. Both have suggested that continuous psychosis or multiple psychotic episodes have adverse consequences.

In a four-year longitudinal study of brain structure using CT scan technology, Davis *et al* compared patients who had experienced continuous psychosis despite adequate treatment for at least 5 years to similar-aged patients who were treatment responsive.[16] Those patients who experienced continuous psychosis demonstrated longitudinal ventricular enlargement that was greater in the left hemisphere than the right. Neither the treatment-responsive patients nor a sample of healthy controls demonstrated any ventricular enlargement during this time frame. In addition, a single study of the correlation between cortical changes and cognitive performance in chronic patients found that reductions in temporal and frontal lobe volumes were associated with greater cognitive decline.[17] These findings combine with studies of older patients with schizophrenia[18,19] that

have suggested that more severe psychotic symptoms predict greater cognitive and functional decline over various follow-up periods. Thus, persistent psychosis seems to be associated with progressive brain volume loss, as well as with cognitive and functional declines, and losses in critical brain regions may be the substrate for these changes.

The aforementioned studies are typically confounded by a series of issues, including institutionalization, medication status, and critical differences in age and other characteristics of the patient samples. The concept of schizophrenia as a chronically active brain process starting at or before the time of the first episode was introduced by DeLisi *et al.*[20] Reviews of the state of this research[21] reached the conclusion that brain volumes do decrease progressively starting at the time of the first episode or before. However, the data collected in a series of important studies in the Netherlands, comprehensively assessing early and mid-course patients, address this issue quite convincingly and thoroughly. Specifically, van Haren *et al* in the Netherlands have performed a series of important studies on patients with schizophrenia with 5-year follow-up methods. Their studies included a substantial number of patients identified and followed from the time of their first episode.[22] A sample of 96 patients with schizophrenia and 113 healthy controls were followed for a 5-year period.[23] During this time, patients were followed clinically and their numbers of relapses was measured, with this number ranging from 0 to 8. It was found that there was a statistically significant reduction in brain volume, specifically in left frontal and temporal regions during the observation period. Loss of frontal gray matter was also significantly associated with the number of number of relapses experienced. Interestingly, treatment with either clozapine or olanzapine attenuated those changes. This is a finding that has been replicated elsewhere, suggesting that treatments that are effective for treatment-refractory patients, clozapine specifically, also appear to have neuroprotective effects.

In the subsample of 34 first-episode patients in the study, several other additional findings emerged.[24] Volume loss in the first year of illness was associated with 5-year clinical and functional outcomes. Enlargement of the lateral ventricle predicted reduced likelihood of independence in residence at the follow-up. This is an interesting parallel to the findings of Davis *et al*,[25] who found that patients with persistent psychosis and disability also demonstrated longitudinal enlargements of the left lateral ventricle. Duration of untreated psychosis at the time of the first entry into treatment was found to be unassociated with 5-year volume changes.[26] While the Duration of Unrelated Psychosis (DUP) was related to the severity of psychosis at baseline, intervening treatment events (including development of treatment resistance and relapses) accounted for more variance in cortical atrophy over 5 years than did DUP. In terms of the clinical significance of these brain changes, van Haren *et al.*[27] demonstrated that the patients with the greatest cortical thinning over the 5-year follow-up period also had the worst 5-year outcome.

Thus, the presence of psychotic symptoms appears to be toxic to the brain and requires treatment. Further, the types of adverse consequences associated with this process are related to the other main feature of schizophrenia that is currently poorly treated: cognitive deficits.

Treatment Options

We have recently completed analysis of three large databases[27–29] containing over 600 schizophrenia patients from diverse social backgrounds. Data were collected in 4 different states (California, Florida, New York, and Georgia) and various settings (university-based, state hospital–based, community-based, and VA). We believe these data comprise a fairly comprehensive representation of symptom patterns and treatment responses in schizophrenia.

Total psychopathology and negative symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) correlated with the number of antipsychotics and mood stabilizers prescribed. Very few patients were receiving first generation antipsychotics, very few patients were receiving depot antipsychotics, and very few patients were receiving clozapine. Depression scores measured with the Beck Depression Inventory (BDI) correlated with antidepressant use.

These treatment patterns suggest that clinicians recognize treatment resistance, but there is an overreliance on polypharmacy at the expense of clozapine. Prescription of more medications, including 2 or even 3 atypical antipsychotics, and the addition of mood stabilizers was frequent. In the sample of 600 patients, only 8 patients were receiving clozapine; which was clearly underutilized, given the fact that the patients in these studies were intentionally selected to have ongoing illness and not to be recovered either clinically or functionally.

In our previous research, which was performed when it was not considered unethical to remove patients who completely failed to respond to treatment from medications, we made several discoveries about the clinical symptoms of patients with severe functional deficits and reduced clinical treatment response. When patients were removed from medications (at that date, conventional medications, usually up to 40 mg of haloperidol), there was no change in their symptoms, including no rebound, nor even increased variance in their clinical symptom scores.[30] When compared to treatment-responsive patients, the extent of response was approximately 10% of that seen in the responsive patients,[31] leading us to

speculate that treatment nonresponse was a separate syndrome from that seen in patients whose symptoms responded to antipsychotics. Treatment resistance appears to develop with nonadherence and relapse,[32] as over 90% of first-episode patients show a rapid response, with 35% of these same patients developing treatment resistance within the first 5 years of their illness.

Clozapine is superior to other antipsychotics in partial and nonresponders, unequivocally confirmed by the large-scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) trials.[33,34] In practice, as in our samples, clozapine is underprescribed; it is also generally delayed in its use among treatment-resistant patients.[35] Generous estimates for clozapine use over the past decade range from 15% to 50% of eligible patients,[36,37] with a mean duration of illness upon introduction of clozapine between 9 and 15 years, after up to 13 antipsychotic trials.[38,39] A recent VA sample indicated that only 2% of patients received clozapine, which is consistent with evidence-based guidelines, mostly at the expense of non-clozapine polypharmacy.[40] Similarly, Medicaid claims data across the U.S. for 326,119 individuals with a schizophrenia spectrum disorder showed that among 629,809 unique antipsychotic treatment episodes, 79,934 met the criteria for treatment resistance, but clozapine accounted for just 2.5% of new antipsychotic prescriptions overall and 5.5% of new prescriptions among patients with treatment-refractory illness who would be candidates for a clozapine trial.[41]

Relapse prevention, which was not investigated in our cross-sectional samples, is critically important. The risk of relapse is several times higher without medication. Nonadherence rates to oral antipsychotic medication in schizophrenia can be as high as 50%.[42,43] Long-acting antipsychotics (depot injections) are designed to improve adherence to medication, which may lead to better response due to assured delivery of the compound, but they are underutilized in our sample, corresponding to general trends.[44,45] There are apparent advantages to depot formulations: As compared to oral antipsychotics, blood levels decline much less rapidly after a missed depot injection, while avoiding certain absorption and metabolism problems of the former.[46] Symptom exacerbations happen more gradually, leaving more time for intervention and proactive stabilization. Divergent results from randomized controlled trials (RCT) regarding the effectiveness of long acting vs oral antipsychotics in schizophrenia should not dissuade from their use; the clinical population enrolled in most of these RCTs is probably not entirely reflective of clinical realities.[47–50]

One might argue that both clozapine and depot antipsychotics are useful (beyond therapeutic benefits), in that their use introduces an element of adherence. Depression was recognized and treated with antidepressants. Patients receiving antidepressants were consistently more depressed than those not receiving antidepressants. Neither electroconvulsive therapy (ECT) nor repetitive transcranial magnetic stimulation (rTMS), both of which are readily available treatment modalities, were used to augment treatment response in our samples.

In all 3 samples, negative symptoms were correlated with social outcomes, while cognitive deficits and impairments in functional capacity predicted poorer instrumental activities of daily living and poorer vocational outcomes. In these samples, rates of employment were very low, and cognitive deficits predicted a lifetime course of downward drift in vocational functioning attainment over the lifespan.[51] Meta-analyses have confirmed that cognitive deficits are minimally related to social deficits, when compared to the influence of negative symptoms or social cognition.[52]

Cognition Remediation

The recognition of cognition as both a determinant of disability in schizophrenia and, recently, a viable treatment target, has led us to propose a conceptual shift toward improving functioning as opposed to symptom control only. Cognitive remediation (CR) strategies do produce robust improvements in cognition, and, when used in conjunction with psychosocial interventions (skills training in particular), CR improves transfer of skills to real-world behavior, thus improving outcome.[53]

Recently, several pharmacological treatment strategies to improve cognition have been suggested as alternatives to CR, including adjunct treatment with already available agents (atomoxetine, D-cycloserine, modafinil), as well as novel treatment alternatives (alpha-7 nicotinic acetylcholine receptor agonists, D-cycloserine, bitopertin) aimed at direct enhancement of cognitive function.[54] The success of these pharmacological interventions has been quite limited to date, although cognitive remediation strategies appear to be quite promising interventions, and CR with pharmacological enhancement of cognition may prove useful as well.

Moreover, negative and cognitive symptoms of schizophrenia appear to be correlated, but potentially separable, domains of the illness that may shape outcome variables. They are discriminable, setting aside definitional and nosological overlaps, and may have different functional implications, creating novel research targets.[55]

Depression

Depression is common but undertreated in schizophrenia. Often overlooked, residual depressive symptoms remain prevalent in schizophrenia despite remission of

psychosis, occur in all phases of schizophrenia, and affect several domains of everyday functioning on several levels.[56,57] In any given month, approximately 35% of community-dwelling patients with schizophrenia present with at least one of the core symptoms of depression,[58] and the lifetime prevalence of depression has recently been reported to be greater than the current prevalence of negative symptoms in a very large sample of veterans with schizophrenia. Depressive symptoms may moderate the relationship between cognitive and functional skills with everyday outcome in schizophrenia.[59]

The impact of depression in individuals with schizophrenia may be motivational in nature, thus impacting hedonic capacity.[60] These patients may also be unable to volitionally retrieve their memories of previous positive experiences, leading to an increase in the inability to anticipate the pleasurable consequences of everyday actions.[28] Antidepressant treatment in schizophrenia remains under-investigated. Early clinical trials focused on adjunctive tricyclic antidepressants and selective serotonin re-uptake inhibitors (SSRIs). Adjunctive monoamine oxidase inhibitors have scarce literature support. ECT or lithium augmentations have not been specifically studied in the treatment of depression in patients with schizophrenia.[61] The one study that performed a systematic randomized and placebo controlled study did find significant benefits for depression, but not negative symptoms, with citalopram treatment.[62] Interestingly, a study we performed also found no benefits of citalopram for negative symptoms in schizophrenia patients but improved depression, suggesting that SRI antidepressants may be an effective and selective treatment for depression when carefully administered.[63]

Physical Health

The physical health status of patients with schizophrenia is extremely poor, with multiple functional implications. They have higher rates of obesity and related metabolic comorbidities than the mentally healthy[50,64–66]; dyslipidemia, insulin resistance, and hyperglycemia are all more common,[67] with correspondingly increased prevalence of cardiovascular disease, diabetes, hypertension,[68] and metabolic syndrome.[69] Health risks are amplified by low rates of medical screening, monitoring, and intervention across healthcare delivery systems.[70,71] We suggest that because of this complex adverse context, the consequential impact on physical functioning is disproportionately larger in patients with schizophrenia than in population comparisons, producing significant declines in everyday performance, while shortening lives. In support of this, we[72,73] and others[74–76] have already identified severe limitations in physical functioning among patients with schizophrenia, which, if adequately addressed, may meaningfully improve outcomes and perhaps prolong lives.

Moreover, there are clear cognitive benefits of physical exercise in healthy and diverse mentally ill populations,[77,78] reaching beyond improvements in health and physical functioning alone.[79–82] Regular physical exercise induces neurobiological, functional, and structural brain changes associated with cognition (and, by inference, functional capacity) and psychiatric symptoms. Exercise, correctly dosed and implemented, may represent an easily available, yet currently neglected, intervention that has the potential to improve physical functioning, cognition, and health, supporting and augmenting other treatment approaches. We have tested both group-based cardiovascular exercise and high-speed, weight-based circuit training to augment physical health and functioning in patients with schizophrenia. Six weeks of cardiovascular training on a treadmill improved predominantly physical health parameters (ie, body weight) and quality of life, while 8 weeks of circuit training improved depressive and psychotic symptoms, cognition, and physical performance parameters (strength, power). Larger and longer studies are needed to confirm this pattern prior to making definitive implementation suggestions. Low-impact physical exercise (such as stretching or yoga) does not appear to have particular benefits in schizophrenia.

Summary

While cross-sectional relationships between psychosis and disability, as well as their determinants, such as cognitive deficits and functional capacity, seem minimal, there is evidence from longitudinal studies that brain deficits and cognitive and functional decline arise from persistent and nonresponsive psychotic symptoms. Thus, nonresponsive psychotic symptoms have the potential to add to other influences on poor outcome, not to mention increasing risk for other adverse outcomes. Although only 1/3 of patients with treatment resistance will respond to clozapine, current data suggest that at most 10% of patients who might experience a benefit actually receive a trial of the treatment. As a result, this is a major case of underutilization of a treatment whose efficacy can be examined within a very brief time period. Risks for agranulocytosis are less than the risks of suicide, and clozapine, aside from lithium, is the only other medication proven to have a direct impact on suicidality, with a U.S. Food and Drug Administration (FDA) indication for suicide reduction.

Treatment resistance requires a serious new effort to reduce its impact. It is more common than persistent negative symptoms in otherwise responsive patients, and is as common as depression. The efficacy of clozapine is excellent in a minority of cases, and the other 2/3 of treatment-resistant patients deserve better treatments and more efforts to reduce the morbidity of their condition.

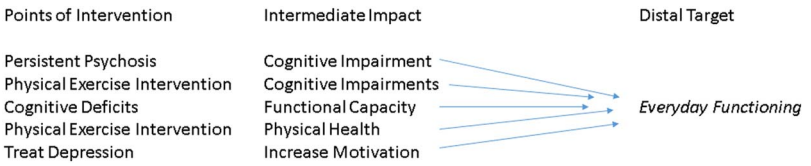

FIGURE 2. Intervention Targets

The tremendous heterogeneity of schizophrenia in various areas affecting outcome (clinical symptoms, cognition, functional capacity, physical health and performance) and the specific real-world domains affected (ie, residential, vocational, interpersonal functioning) require assessment and treatment from different vantage points,[83] aside from conscious use of psychopharmacology, especially clozapine. An increasingly complex society has increased the level of everyday functional demands on patients with schizophrenia, requiring evolving skill sets and effective deployment thereof, which needs to be accounted for when implementing comprehensive treatment plans in order to improve outcomes in relevant subdomains and globally. We have previously suggested that a multimodal approach to treatment may be indicated, moving beyond psychotic symptom control and aimed at everyday functioning (Figure 2). Cognitive remediation (CR) interventions,[84,85] as well as various psychosocial interventions and skills-based training interventions,[86] are already available, as is supported employment.[87] These interventions are optimally delivered in combination, with experimental medications (aimed at negative and cognitive symptoms) and procedures (rTMS, and even, ECT) still in experimental stages, requiring further investigation. Physical exercise programs are proven to improve physical health status and performance, and can potentially achieve positive synergistic effects with cognition and everyday functioning, if used in combination with these other approaches.

Disclosures

Dr. Harvey has served as a consultant to Abbvie, Boeheringer-Ingelheim, Forum Pharma, Forest Labs, Genentech, Lundbeck, Otsuka, Roche, Sanofi Pharma, Sunovion Pharma, and Takeda Pharma. This consultation work was on phase 2 or 3 drug development and is not related to the content of this article. Dr. Strassnig has served as a consultant to Janssen. This consultation work was on phase 3 drug development and is not related to the content of this manuscript.

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1. A 37-year-old woman with schizophrenia has failed to respond to 2 sequential adequate trials of antipsychotic monotherapy (first olanzapine, then aripiprazole). Which of the following are evidence-based but underutilized treatment strategies for a patient in this situation?

   A. Augmentation of her current monotherapy with another atypical antipsychotic
   B. Switch to clozapine
   C. A and B
   D. Neither A nor B

2. A 29-year-old man with schizophrenia has prominent symptoms of depression and is prescribed an antidepressant as adjunct to his antipsychotic medication. What is true regarding the state of research for antidepressant treatment in schizophrenia?

   A. It is well investigated and affirmed to be efficacious
   B. It is well investigated and not shown to be efficacious
   C. It is under-investigated

3. Brain imaging studies suggest that persistent psychosis may be associated with:

   A. Progressive brain volume loss
   B. Cognitive and functional decline
   C. A and B
   D. Neither A nor B

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