Summary: Treatment of Schizophrenia

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Introduction

The primary objectives in the treatment of schizophrenia are to reduce frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, prevent relapses, and improve functional capacity and quality of life. Treatment includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of pharmacological treatment for schizophrenia. The twenty-three antipsychotics available in our country have traditionally been classified into two major groups: 10 first-generation (conventional) agents (FGAs) and 13 second-generation (atypical) agents (SGAs), although this dichotomization can be misleading. Since the last iteration of the Florida Center for Behavioral Health Improvements and Solutions (FCBHIS) guidelines in 2019, one new antipsychotic agent (lumateperone [®Caplyta]) and a new combination (olanzapine-samidorphan [®Lybalvi]) have been introduced into clinical practice along with some new long-acting injectable formulations of existing antipsychotic agents. Basic principles of the Florida FCBHIS guidelines for the treatment of schizophrenia are summarized.

Pharmacological Treatment of Schizophrenia: What Do Antipsychotics Do?

Schizophrenia is characterized by positive (reality distortion and disorganization), negative, cognitive, and mood symptoms, with the types and severity of symptoms differing among patients and over the course of the illness. With its typical onset in early adulthood, schizophrenia tends to be a chronic illness with a relapsing and remitting course. Antipsychotic medications are the mainstay in the pharmacological treatment of schizophrenia. In addition to reducing symptoms in the acute psychotic phase of the illness, antipsychotic medications are very effective in reducing the likelihood of psychotic relapses in stable patients. Antipsychotics are most effective in ameliorating positive and disorganization symptoms, but ineffective in treating negative and cognitive symptoms. They can help but can also worsen mood symptoms (eg., neuroleptic dysphoria) and motor symptoms (eg., neuroleptic malignant syndrome). In DSM-5TR, the distinction between the different psychopathological dimensions of schizophrenia is explicitly catalogued and a simple scale for measurement of each dimension over the course of treatment (SCoRS) is provided.

Comparative Efficacy

Although it was formerly believed that FGAs are less effective than SGAs, recent trials have not confirmed this belief. Clozapine is the only antipsychotic agent that is found to be more effective than other antipsychotic agents in treating positive symptoms in otherwise refractory patients and in reducing suicidality. All other agents are found to be about equally effective, although different degrees of ease-of-use lead to minor differences in efficacy being observed in routine clinical practice. Antipsychotic medications substantially decrease likelihood of relapse in schizophrenia, without any consistent differences among agents. Since medication non-adherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates.

Safety and Tolerability

Antipsychotic medications cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in adverse-effect profiles. Compared with the FGAs, SGAs generally have a lower risk of EPS. However, due to differences in pharmacological profiles within the FGA and SGA classes, there is substantial variation within both classes in their propensity to cause EPS and metabolic adverse effects. Thus, no categorical distinction can be made between so-called FGAs and SGAs with regard to these risks. Antipsychotic medications also differ in their propensity to cause other side effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and related sexual dysfunction, and anticholinergic effects, with substantial variation within both the FGAs and the SGAs for each of these effects, without any definitive categorical separation between the two classes. Patients with schizophrenia also vary in their vulnerability to develop various adverse effects with different agents. The likelihood that a patient will develop a particular side effect thus depends on the agent selected, how that agent is used (e.g., dose, titration method, in combination with what other agents), and the patient's vulnerability.

Optimizing Individual Outcomes

Given the significant variability in drug pharmacokinetics and treatment responsivity in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. It is not currently possible to predict which antipsychotic may be optimal for a given patient. There is no best agent or best dose for all patients, although dose ranges for optimal effectiveness do appear to exist. Decisions about antipsychotic therapy therefore often entail a trial-and-error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary. To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatments in a way that is customized for the needs and vulnerabilities of the individual patient. The meticulous application of this approach can reduce the significant gap between what we know about best practices and the therapy that is actually provided for patients with schizophrenia.

The Florida Center for Behavioral Health Improvements and Solutions (FCBHIS) guidelines for the pharmacological treatment of schizophrenia were developed on the basis of our current understanding of what they do and how they compare and a clinician-friendly elaboration of key principles.

Clinical Guidance

Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia. Findings concerning efficacy for positive symptoms and disorganization suggest no consistent differences among available antipsychotics, with the exception of clozapine's superior efficacy for treatment-resistant schizophrenia. Efficacy for negative, depressive, and cognitive symptoms appears to be determined by: (i) the extent to which reduction in positive symptoms brings about improvement in these other domains and (ii) the extent to which extrapyramidal side effects (EPS) and anticholinergic effects (of the antipsychotic and of agents used to treat EPS) exacerbate them. Thus, the ability of antipsychotics to produce a potent antipsychotic effect without EPS and need for concomitant anticholinergic therapy yields multiple therapeutic benefits. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects. Choice of antipsychotic medication should be

based on individual preference, prior treatment response and side-effect experience, medical history and risk factors, and adherence history, with side-effect profile a major determinant of antipsychotic choice [Box 9].

Summary

Whereas the efficacy of these antipsychotic agents in the treatment of schizophrenia is broadly similar (with the exception of clozapine's greater efficacy in otherwise treatment-refractory patients), there are significant differences in their side-effect profiles. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of the nature of schizophrenia (multiple pathological dimensions, remitting and relapsing course), knowledge about the similarities and differences between available antipsychotic treatments, and awareness of how to use these treatments most effectively (targeted, measurement-based, individualized). Targeted use of a range of non-antipsychotic medications can be useful in reducing comorbid symptoms. Antipsychotic polypharmacy may be reasonable after dose optimization and consideration of clozapine and long-acting injectable antipsychotic agents.

Box 9. Steps to achieve optimum outcomes with currently available antipsychotics

1. Considerations in selecting the best antipsychotic for a particular patient

- Equivalent efficacy across agents
- Individual variability in response
- No good predictor of individual response to different agents
- Different agents have different side effects
- Different patients have different vulnerabilities and preferences

2. Proper antipsychotic trial sequence

- Begin with systematic 6-10 week trial of one antipsychotic with optimal dosing
- If inadequate response, follow with systematic trial of monotherapy with one or more other antipsychotics at adequate dose and duration
- If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic
- Follow with a trial of clozapine, if not tried before
- Only then consider other strategies (e.g., antipsychotic polypharmacy)

3. Good practice guidelines for ongoing antipsychotic treatment

- Measurement-based individualized care
- Repeated assessment of efficacy using reliably defined treatment targets (facilitated by use of standard rating scales)
- Careful assessment of adverse effects
- Care consistent with health monitoring protocols
- Standard protocols customized to individual vulnerabilities/needs and specific agent
- Ongoing collaboration with patient in decision-making

References

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