Pharmacological Treatment of Schizophrenia 2017-2018 Update Summary

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Introduction

The primary objectives in the treatment of schizophrenia are to reduce the frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, and improve functional capacity and quality of life. Treatment for schizophrenia includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of the pharmacological treatment for schizophrenia. The 21 antipsychotics available in the United States have traditionally been classified into two major groups: 9 first-generation (conventional) agents (FGAs) and 12 second-generation (atypical) agents (SGAs). 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. This article summarizes our current understanding of the pharmacotherapy of schizophrenia and is the basis for the ***2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults***. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of:

- The clinical and biological nature of schizophrenia in order to identify targets of treatment and define specific treatment goals;
- How available treatments compare (similarities and differences in terms of efficacy, safety/tolerability, costs, ease of use, and pharmacokinetics and pharmacodynamics); and
- How to use available treatments optimally (targeted, measurement-based, and individualized).

Nature of Schizophrenia and Definition of Treatment Targets and Treatment Goals

Schizophrenia is a chronic, remitting and relapsing illness with onset in late adolescence or early adulthood. It is characterized by multiple psychopathological dimensions (positive, negative, cognitive, mood, motor, and disorganization) each of which have distinct neurobiological underpinnings, clinical profiles, and patterns of treatment response. Each of these symptom domains contribute to functional impairment and adversely impact quality of life. Objectives of treatment therefore include maximal reduction in severity of each of these symptom domains and prevention of relapse. Since different patients exhibit varying admixtures of these symptoms, individualized tailoring of treatment is essential.

What Do Antipsychotic Medications Do?

Antipsychotic medications are the mainstay in the pharmacological treatment of schizophrenia. They are effective in treating acute psychotic relapses and reducing the likelihood of such relapses. All antipsychotics are effective in reducing positive symptoms (i.e., hallucinations, delusions, and paranoia) and disorganization, but are only minimally effective for negative and cognitive symptoms that significantly contribute to the disability associated with schizophrenia. They can

ameliorate mood and motor symptoms, but can also make them worse (e.g., neuroleptic dysphoria and neuroleptic malignant syndrome). They are associated with a range of adverse effects (e.g., motor, metabolic, and other disturbances) and differ substantially in their side-effect profiles.

How Do Antipsychotic Medications Compare?

Efficacy

With the exception of clozapine, all antipsychotic medications are about equally effective in treating positive symptoms and disorganization. Clozapine is more effective than other antipsychotics in treating positive symptoms in otherwise treatment-refractory patients and reducing suicidality in schizophrenia. The relatively minor differences in efficacy observed among the other antipsychotic agents principally relate to dosing and different degrees of ease of use. Response over the first 2-4 weeks of antipsychotic therapy is highly predictive of long-term response. The maximum effect, however, may not be achieved for several months, and trajectories of response vary considerably across patients. Responsiveness to antipsychotics also varies as a function of stage of illness, with first-episode patients responding faster and at a higher rate than those at later stages of the illness. Antipsychotics are equally ineffective in treating primary negative and cognitive symptoms while differing in their effects on secondary symptoms [when agents cause extrapyramidal side effects (EPS), they worsen secondary negative and cognitive symptoms].

Antipsychotic medications substantially decrease the likelihood of relapse in schizophrenia, without any consistent differences among agents. Since medication nonadherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates. Six agents (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, and risperidone) are available in long-acting injectable formulations requiring injections at intervals ranging from 2 weeks to 3 months.

Safety and Tolerability

Antipsychotic medications cause a range of side-effects including neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their adverse effect profiles. Compared with the FGAs, it is generally believed that the SGAs have a lower risk of EPS but a higher risk of metabolic adverse effects. 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. Increased risk of EPS has been associated with neurotoxicity, however, leading to the panel's recommendation to preferentially use SGAs rather than FGAs in the initial treatment of schizophrenia. Because of the adverse sequelae of EPS and its treatment (e.g., secondary negative symptoms, secondary depression, secondary cognitive impairment, and tardive dyskinesia), EPS must be avoided. Similarly, because of the increased mortality associated with metabolic side-effects (e.g., hyperlipidemia and diabetes mellitus), these must be minimized.

The 21 antipsychotic medications available in the United States 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, and 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. Despite exciting recent developments in pharmacogenetics, it is still not currently possible to predict which antipsychotic may be optimal for a given patient. There is also no best agent or best dose for all patients, although dose ranges for optimal effectiveness do 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.

Because of the marked inter-individual variability in both efficacy and safety/tolerability, careful measurement of both the beneficial and adverse effects in every patient during the course of antipsychotic treatment is essential. In the DSM-5 (section 3), a simple and reliable 5-point 8-item scale is available to measure response of different symptom dimensions in schizophrenia (and other psychotic disorders). The use of this scale is strongly recommended. It is easy to use and can be administered in a few minutes. Similarly, EPS, metabolic disturbances, and other side-effects should be closely monitored and appropriately addressed.

In order to make informed treatment decisions, measurement of the severity of each of the six symptom domains in the course of treatment is necessary. Since antipsychotic agents are primarily effective in the treatment of positive symptoms and disorganization, persistence of these symptoms should prompt consideration of a different antipsychotic regimen including use of clozapine or a long-acting antipsychotic agent. If positive symptoms have improved but depressive symptoms persist, use of an antidepressant should be considered. If positive symptoms improve but negative symptoms worsen, the possibility of EPS should be effectively addressed. In this manner, measurement-based pharmacological treatment enables optimal individualization of treatment in persons with schizophrenia.

To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatment 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.

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: 1) The extent to which reduction in positive symptoms brings about improvement in these other domains; and 2) The extent to which extrapyramidal side effects 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 yield 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. Systematic measurement of efficacy and adverse effects is essential and can guide optimal individualization of antipsychotic treatment.

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