



Current Pharmacotherapy Strategies and Considerations for the Cognitive Dysfunction Associated with Schizophrenia: A Mini Review

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Abstract

Cognitive dysfunction associated with schizophrenia is a core symptom that is strongly related to functional levels. In fact, cognitive dysfunction in patients with schizophrenia is due to a combination of the cognitive impairment induced by schizophrenia itself and that induced by the medications that psychiatrists prescribe. It is difficult to differentiate between the two sources, and at present, no medications have a large effect size in terms of improving the cognitive dysfunction induced by the disease itself. Therefore psychiatrists should strive to minimize drug-induced cognitive dysfunction when prescribing medications. In view of the cognitive dysfunction that patients with schizophrenia experience, it is important for psychiatrists who prescribe psychotropic agents to decrease chlorpromazine-equivalent doses and to dose each atypical antipsychotic as a monotherapy. The psychiatrist should avoid the chronic administration of the anticholinergic agents and benzodiazepines. In addition, adherence is important for preventing relapses, which can decrease cognitive function. In patients with schizophrenia, it is important to balance pharmacotherapy with the consideration of factors that contribute to cognitive dysfunction. The development of medications that can effectively treat the cognitive dysfunction caused by the disease itself is eagerly anticipated.

Keywords

Schizophrenia, Cognitive function, Pharmacotherapy, adherence, atypical antipsychotic

Introduction

The estimated prevalence of cognitive dysfunction in schizophrenia patients is 75% to 85%. Cognitive dysfunction is considered a core feature of the disease because it significantly affects patients' social and occupational functioning [1,2]. A meta-analysis of clinical trials investigating the effectiveness of antipsychotics on cognitive function in schizophrenia found that second-generation antipsychotics (SGAs) are slightly more effective than first-generation antipsychotics (FGAs), and each drug exerts a different effect on cognitive function [3]. However, recent studies have indicated that antipsychotics are limited in how much they can improve patients' cognitive function [4,5]. The cognitive dysfunction in schizophrenia consists of both disease-related impairment and antipsychotic drug-induced impairment, and it is difficult to distinguish between these two etiologies. Drug-induced cognitive

impairment is caused by the psychoactive drugs that psychiatrists prescribe. Currently, the disease-related cognitive impairment is considered difficult to treat, whereas drug-induced cognitive impairment may be treatable or preventable.

This paper reviews pharmacological strategies that can help psychiatrists when treating schizophrenia patients with cognitive dysfunction.

Antipsychotic Polypharmacy and Cognitive Function

Antipsychotic polypharmacy is associated with reduced adherence, increased cost and a greater frequency of side effects [6-8]. Many patients with schizophrenia received antipsychotic polypharmacy. Polypharmacy has been found to adversely affect extrapyramidal symptoms, metabolic syndromes and oversedation in addition to cognitive functions [9,10]. We previously reported that even combined drug therapy that used atypical antipsychotics with reduced likelihoods of inducing adverse reactions had adverse effects on cognitive function [10]. A study investigating the effectiveness of switching from antipsychotic polypharmacy to monotherapy showed that the patients who switched to monotherapy showed greater improvement on measure of attention and processing speed compared with who continued with polypharmacy [11].

In addition, the dopamine supersensitivity reaction in schizophrenia is somewhat similar to the dopamine supersensitivity that is induced by antipsychotic drugs. The probability that antipsychotic drugs induced dopamine supersensitivity can lead to cognitive difficulties is shown by the fact that D2 receptors, selectively genetically elevated in the striatum, reduced cognitive performance in animals [12]. Attention and memory problems in schizophrenia may directly result from dopamine overstimulation and are worsened by the lowered self-confidence that ensue from them.

These results indicate that monotherapy is less detrimental to cognitive function than antipsychotic polypharmacy.

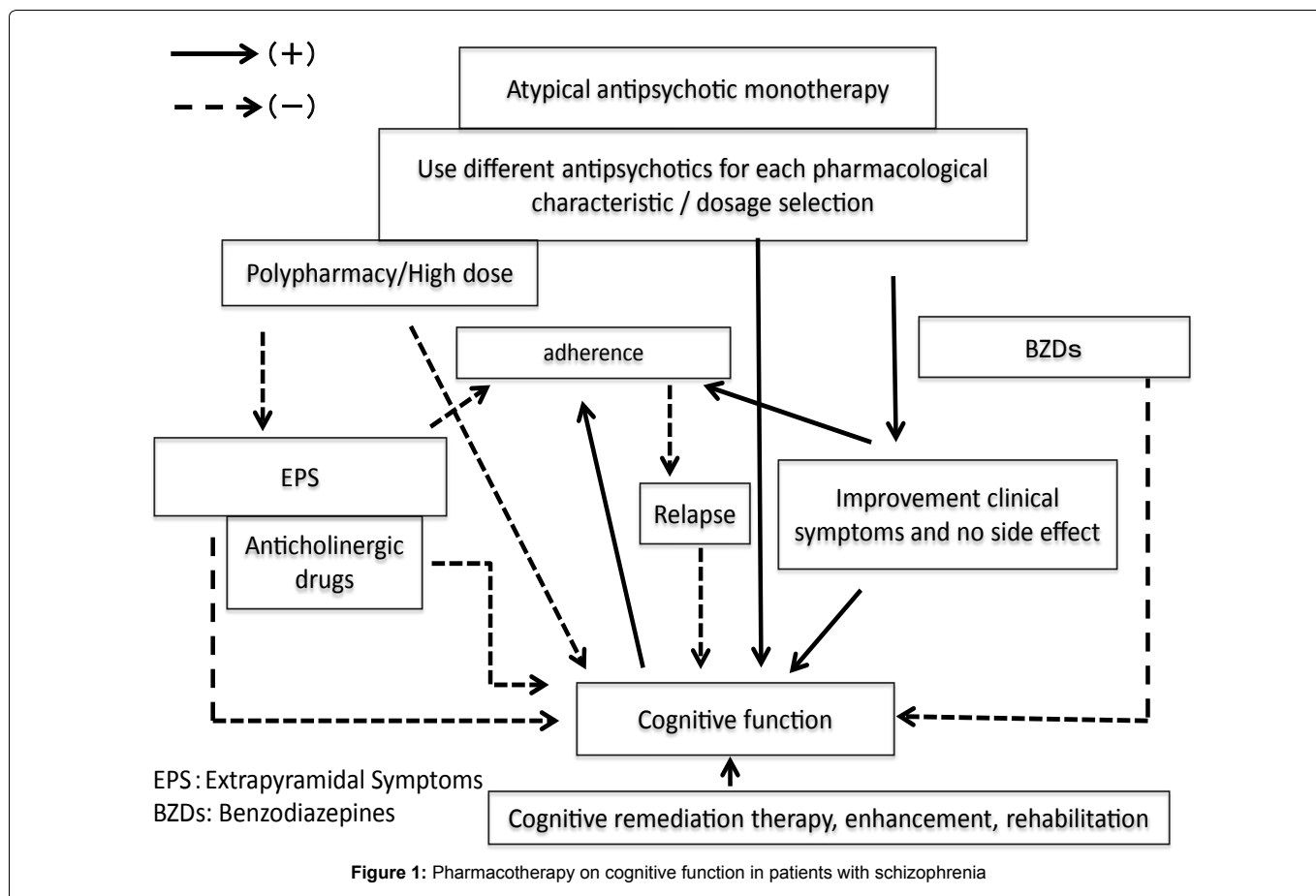
Antipsychotic Dose and Cognitive Function

Several studies have reported that consuming large amounts of antipsychotics has harmful effects on cognitive function, suggesting that the amount of drugs consumed is positively correlated with the degree of possible harm to cognitive function. In fact, a study investigating

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the relationship between cognitive dysfunction and the occupancy rate of dopamine D2 receptors, estimated by the concentration of antipsychotics, showed that the a D2 receptor occupancy rate of 77% or higher may be related to cognitive impairment [13]. Recent studies have suggested that the effects of antipsychotics on cognitive function may vary depending on the dose of each drug [10,14,15]. We previously reported that risperidone and olanzapine doses were adversely correlated with cognitive function in patients with chronic schizophrenia, but the dose of aripiprazole monotherapy did not show the same relationship [16]. Takeuchi et al. reported that reduced doses of risperidone and olanzapine led to improvements in cognitive function. These results suggest that although the dose of antipsychotics relates to cognitive function, the pharmacological profile may be different for each antipsychotic in monotherapy [17].

Anticholinergic Drugs and Cognitive Function

Anticholinergic drugs are commonly used to treat extrapyramidal symptoms in patients with schizophrenia. However, the long-term use of anticholinergic drugs for schizophrenic patients leads to impairments in attention, memory, learning ability, and executive function. Mori et al. reported that reducing or discontinuing anticholinergic drugs led to improvements in immediate memory and verbal working memory in patients who were concurrently taking FGAs or risperidone [18]. Furthermore, Ogino et al. reported that the gradual discontinuation of biperiden in chronic schizophrenia patients who were concurrently treated with SGA monotherapy lead to improvements in motor function, attention, processing speed, and verbal fluency [19]. Therefore, treatment strategies should include selecting drugs that have a lower risk of inducing extrapyramidal symptoms, avoiding polypharmacy, and avoiding the use of anticholinergic drugs.

Benzodiazepines and Cognitive Function

In schizophrenia treatment, benzodiazepines (BZDs) are usually prescribed for agitation, anxiety, insomnia, catatonia, panic attacks, and extrapyramidal symptoms either as a monotherapy or as an adjunct to antipsychotic drugs [20-22]. However, BZDs can

cause various adverse effects, such as sedation, ataxia, behavioral disinhibition, dependence, abuse, and withdrawal symptoms upon cessation [23]. In addition, the long-term use of BZDs has been shown to cause impairments in a variety of cognitive functions, including attention, verbal learning, memory, processing speed, and visuospatial ability [24-26]. A meta-analysis of the effects of benzodiazepines tapering on cognitive function in schizophrenia found that tapering led to improvement in verbal memory and working memory [27]. The results of a secondary analysis examining the differences between the complete discontinuation and incomplete discontinuation groups suggested that improvements in working memory could be achieved even with the incomplete discontinuation of daytime benzodiazepines.

Adherence and Cognitive Function

It has been repeatedly noted that schizophrenia patients have poor treatment adherence [28-30]. Poor treatment adherence is the most predictive factor for the relapse of schizophrenia. Disease relapse results in further deteriorations of cognitive function. Therefore, the prevention of relapse is an important pharmacological strategy.

Summary

This review summarizes the current state of research on the effects of pharmacotherapy on cognitive function in patients with schizophrenia (Figure 1). Although atypical antipsychotics were expected to be effective for improving cognitive function, the effect size was moderate, and atypical antipsychotics can even be harmful depending on their dose and prescription pattern. Based on the current evidence, psychiatrists should minimize the occurrence of drug-induced cognitive dysfunction. To achieve this goal, antipsychotic monotherapy with careful dosing consideration is important. Regarding concurrently prescribed drugs, anticholinergics and benzodiazepines should be administered with care. In addition, relapse prevention is important because cognitive function deteriorates after each relapse. Finally, the most important factor predicting relapse is treatment adherence. Pharmacotherapy should

consider these points. In the future, it is expected that a new drug that specifically targets cognitive impairment will be developed and will contribute to the functional outcomes of patients with schizophrenia.

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