Use of Antiepileptic Drugs in Schizophrenia
A Review of Efficacy and Tolerability

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Summary

During the last 20 years, research has indicated that antiepileptic drugs such as carbamazepine, valproic acid (sodium valproate) and clonazepam have therapeutic effects in disorders other than epilepsy. These agents are beneficial in patients with manic and depressive disorders, and have a mood-stabilising effect in schizophrenic and schizoaffective disorders that present with comorbid affective symptoms, such as excitation and aggression. Furthermore, a prophylactic effect on the recurrence of mood disorders is also observed.

Many schizophrenic and schizoaffective patients do not respond or only partially respond to antipsychotics. Antiepileptic drugs may have an important clinical role as adjuncts to antipsychotics in the treatment of these patients. Carbamazepine has been studied most extensively, and therapeutic effect has been reported in many studies. Valproic acid has also been shown to have a similar effect.

The response of a patient to different mood-stabilising drugs, such as lithium, carbamazepine, valproic acid or clonazepam, is not necessarily the same. Therefore, a clinical strategy of rotating trials in a sequential fashion may be useful for the treatment of nonresponders or partial responders to antipsychotics. An appropriate strategy may include starting treatment with lithium or carbamazepine followed by valproic acid and then clonazepam. If no individual agent is effective, a combination of 2 or 3 agents may be useful.
The treatment of first choice for schizophrenic and related disorders is pharmacotherapy with antipsychotic drugs. However, many patients do not respond completely or adequately to this treatment. Particularly, negative symptoms (such as thought disorder, withdrawal and autism) tend to improve to a lesser extent than positive symptoms (such as hallucinations and delusions). Furthermore, psychomotor excitement and aggression are sometimes difficult to control with conventional antipsychotic treatment.

Therefore, extensive investigations of adjunctive drugs for coadministration with antipsychotics and alternatives to antipsychotics have been performed. Anticonvulsants have recently emerged as an important adjunctive to antipsychotics for some patients with schizophrenia.

It is well established that the use of antiepileptic drugs in patients with epilepsy usually leads not only to the control of seizures but also to an improvement in concomitant psychotic symptoms and personality disorders. In the early 1940s, several researchers reported beneficial effects of phenytoin in patients with nonepileptic psychoses, such as schizophrenia and other psychomotor excitement. Subsequently, Lambert reported an antimanic effect of valpromide (dipropylacetamide), an amide of valproic acid (sodium valproate).

It was noticed early on that carbamazepine, which had been developed as an anticonvulsant for partial and generalised seizures, had a beneficial effect on the psychiatric symptoms of patients with epilepsy. Dalby carried out a study on the antiepileptic and psychotropic effects of carbamazepine for the treatment of psychomotor (complex partial) epilepsy. He found that the improvement in mood was independent of improvement in the seizure disorder.

On the basis of these observations, psychiatrists began to use antiepileptic drugs for the treatment of psychiatric disorders. Several antiepileptic drugs, including carbamazepine, valproic acid, acetazolamide and clonazepam, have been found to be effective treatments for emotional and mood disturbances of various aetiology.

1. Rationale for the Use of Antiepileptic Agents in Schizophrenia

The main subject of this review is the use of antiepileptic drugs in schizophrenia. However, a brief description of the effect of antiepileptic drugs on mood disorders will also be given. This is because the symptoms of schizophrenia, such as hallucinations and delusions, are not influenced significantly by antiepileptics, while affective disturbances such as excitation and aggression are improved. Thus, antiepileptic drugs seem to have a common effect on mood in both mood and schizophrenic disorders.

1.1 Carbamazepine

In the early 1970s, carbamazepine was found to be an effective treatment for mania. Systematic investigations of carbamazepine in patients in the manic phase of bipolar affective disorder were initiated in Japan using a noncomparative trial design. Takezaki and Hanaoka administered carbamazepine to 20 patients, while Okuma and colleagues assessed the drug in 90 patients. It was demonstrated that carbamazepine has antimanic effects in patients with bipolar disorder and has a prophylactic effect by preventing the recurrence of the disorder.

The antimanic effect was subsequently confirmed in double-blind studies comparing carbamazepine with chlorpromazine, and using a placebo-controlled crossover trial design. Okuma and colleagues confirmed the prophylactic effect of carbamazepine in a double-blind, placebo-controlled study.

The antimanic and prophylactic effects of carbamazepine in bipolar disorder have been confirmed by many researchers throughout the world in noncomparative and controlled studies. Double-blind, parallel-group trials have shown that carbamazepine has antimanic and prophylactic effects in bipolar affective disorder comparable to those of lithium.