Pharmacotherapy of Depression: The American Current Status

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(Received for publication on September 12, 1990)

Abstract. This paper is a brief review which deals with research findings, clinical issues, and strategies in the pharmacotherapy of clinical depression. The author introduces antidepressants which are currently available in the United States. They include heterocyclic antidepressants (tricyclic antidepressants and second-generation antidepressants), monoamine oxidase inhibitors, lithium, carbamazepine, and others. Under the description of each drug category, therapeutic and side effects are briefly discussed in the context of psychiatric practice in America. Then, the author gives a bird’s eye view of American pharmacotherapy of using antidepressants in acute, maintenance, and prophylactic treatments of depression. (Keio J Med 39 (4): 237–241, December 1990)

Key words: antidepressants, MAOIs, lithium, carbamazepine

Introduction

This paper is a brief review which deals with research findings, clinical issues, and strategies in pharmacotherapy of clinical depression. It covers antidepressants used in the United States, acute treatment of depression, maintenance treatment of depression, and prophylactic treatment of depression.

This paper is not intended as an in-depth review of the field. But it is a quick introduction of current American status in the clinical practice of pharmacological treatment of depression.

Available Antidepressants in the U.S.

On the U.S. market, there are four categories of chemicals which have antidepressant or mood-stabilizing effects:

Heterocyclic Antidepressants

Table 1 is a list of tricyclic antidepressants (TCAs) and second-generation antidepressants. Adapted from most updated literature,1–3 the list includes all currently available American heterocyclic antidepressants with putative action sites in the central neurotransmission. The TCAs are so designated due to their central structural formula, which has three rings or closed-chain structures. Having been introduced to the American market in the past decade, the second-generation antidepressants have monocyclic (bupropion), bicyclic (fluoxetine), tricyclic (amoxapine, clomipramine), and tetracyclic (maprotiline) rings in the central nucleus of the chemical structures.

The term “heterocyclic antidepressants” is often called “cyclic antidepressants” for simplification by many authors in American psychiatric literature. The term...
“TCA-like antidepressants” is also used for heterocyclic antidepressants to distinguish from monoamine oxidase inhibitor (MAOI) antidepressants, which also have 1 or 2 rings in each chemical structure.

The heterocyclic antidepressants can benefit 65–80% of depressed patients, but placebo can improve about only 20–40% of the control group. The half-lives of these agents are fairly long (20–160 hours), thus single daily dosage at bedtime is generally indicated. (The exceptions are fluoxetine and bupropion. The latter is recommended in divided doses whereas the former is to be administered in the morning.) Absorptions of heterocyclic antidepressants are fairly well. It takes 5 to 20 days to achieve a steady state level of the agents. There are up to 36-fold differences in plasma levels among patients who have received the same dose. These differences seem to be largely genetically determined.

The typical side effects of heterocyclic antidepressants include sedation, dry mouth, constipation, urinary retention, dizziness, orthostatic hypotension, weight gain, blurred vision, nausea, vomiting, tachycardia, palpitation of the heart, heart block, peculiar taste, etc. Not rarely, drug-induced sexual dysfunctions are also reported in both male and female patients. Besides fluoxetine and bupropion, most heterocyclic antidepressants are implicated with patients’ weight gain. Because of this characteristic, fluoxetine has enjoyed unprecedented popularity in publications for American lay public press.

Monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase inhibitor (MAOI) antidepressants marketed in the U.S. include phenelzine, isocarboxazid, and tranylcypromine. The chemical distinction between hydrazine (phenelzine and isocarboxazid) and non-hydrazine (tranylcypromine) MAOIs do not bear much clinical significance. Most psychiatrists in the U.S. reserve MAOIs as second-line drugs in the pharmacotherapy of depression if (1) a couple of heterocyclic antidepressants do not work, (2) the depressed patients cannot tolerate the heterocyclic side effects, or (3) electroconvulsive therapy (ECT) is inappropriate or refused. MAOIs are often thought to be the drugs of choice for “atypical” depressed patients who overeat and/or oversleep. MAOIs have been underprescribed by American psychiatrists due to undue overemphasis on side effects in the literature. Recent clinical studies in treating phobia and post-traumatic stress syndrome have caused resurgence of interest in MAOIs, most by discovering the old wisdom in the literature about MAOIs. The knowledge of antidepressant effect and at least 80% reduction of the platelet MAO enzymatic activity has advanced the clinical practice to obtain optimal therapeutic MAOI dosage level.

The greatest concern for MAOI-mediated patients is the dietary and drug restrictions during MAOI therapy. The interaction of MAOIs with tyramine-containing foods and beverages as well as certain drugs, may cause hypertensive crisis with some or all of the following symptoms: headache, palpitation of the heart, stiffness in the neck, nausea, vomiting, sweating, dilated pupils, and photophobia. Foods, beverages and drugs to be avoided are listed in Tables 2 and 3.

Lithium

Lithium carbonate was introduced into the U.S. in the early 1970s. It has been officially accepted by the American Psychiatric Association as treatments of choice in acute mania and prophylactic maintenance therapy beyond the supposed end of the current manic episode to prevent future manic or depressive recurrences. Researchers at New York State Psychiatric Institute started to explore lithium prophylaxis of depression when lithium was available as an investigational drug. Later, investigators at the University of Montreal and Yale independently discovered the lithium augmentation effect of depression among patients who have already received
TCAs. The augmentation effect of depression can be achieved in a couple of days when lithium reaches the serum level of 0.4–0.6 mEq/l instead of typical recommended therapeutic ranges of 0.5–1.5 mEq/l.

The initial side effects are nausea, stomach cramps, being thirsty, muscle weakness, tremors of the hands, weight, etc. These side effects are usually transient but some of them may persist during the course of lithium therapy. Although the official recommended laboratory workups are many, regular blood tests for serum lithium levels as well as initial tests for creatinine, blood urea nitrogen, and thyroid profiles are done by a majority of practicing psychiatrists in the U.S.

**Carbamazepine and other antiepileptic agents**

The introduction of carbamazepine in psychiatric use is a Japanese contribution. Takezaki and Hanaoka first in 1971 discovered the usefulness of carbamazepine in affective disorders. Then, Okuma and associates in 1973 first reported in English that carbamazepine has antimanic and prophylactic effects on bipolar disorder. Ten years later, the psychiatric use of carbamazepine started to kindle the researchers’ interest at the National Institute of Mental Health (NIMH) and comparative controlled studies of carbamazepine efficacy were published.

Carbamazepine is also shown to be especially beneficial in treating acute episodes or preventing the relapses of “rapid cycling patients” who are the bipolar disorder patients having four or more episodes of illnesses per year. In a recent review of literature, Post and associates concluded that rapid cyclers often show inadequate response to lithium carbonate and vulnerable to antidepressant-induced switches of cycle acceleration. Kukopulos and co-workers also suggested that the use of antidepressants on the rapid cyclers contributes the non-response rate in mood stabilization when lithium carbonate is used. Although the clinical indication of carbamazepine for antimanic or antidepressant effect has never been formally included in the PDR, it is rather widely used in the U.S., especially if any patients who are refractory or intolerable to the lithium side effects, such as diarrhea, tremors of the hands, and facial acnes.

Usually, the carbamazepine antidepressant effects are achieved with 600-1600 mg/day at serum levels of 8–12 ng/ml. The side effects of carbamazepine are relatively mild and tolerable. But, physicians are always alert to look of patients’ fever, sore throat, and subcutaneous bleedings, to obtain complete blood counts once a week in the first month, then once every two weeks in the next several months, and thereafter once a month as long as the patient continues to receive carbamazepine.

Beside using carbamazepine, American psychiatrists are assessing the antidepressant effects of sodium valproate, which was first introduced for psychiatric treatment in Europe in 1966. It is expected that in the future more clinical data on sodium valproate or other new antiepileptic agents (clonazepam, for example) will be added in the literature.

**Managements of Clinical Depression**

To characterize the American psychopharmacological practice, I would like to describe each phase of pharmacotherapy according to the needs of patients’ clinical courses: acute treatment, maintenance treatment and prophylactic treatment.

The description here is intended to be a birds eye view of the state of arts in the American clinical psychopharmacology. To keep the length and the scope of this paper, the detailed supportive research data in basic neuroscience and the particulars of specific medications are omitted here. The readers who are interested in more in-depth discussions of the issues should refer to the literature cited in the text of this paper.

**Acute treatment of depression**

Under the pressure for cost-containment in medical care resources by the American government and the third party payers, the indication of admitting a non-suicidal depressive patient to inpatient service becomes stricter every day. The American psychiatrists would be amazed at the report of the patients’ lengthy stay of 1 to 2 months in the Japanese psychiatric hospital.

The earlier research excitement attempting to differentiate two types of norepinephrine or serotonin depression, do not give any clinical validity. It also does not mean much clinically to dichotomize heterocyclic antidepressants by separating norepinephrine and serotonin reuptake blockers as shown in Table 1, since there is no discernible clinical characteristics of depression to justify the choice of one heterocyclic over another in terms of clinical efficacy. However, the medication neurotransmitter profiles can help the patient to predict what kind of side effects that patient will experience, although the data cannot help psychiatrists predict the treatment responses.

Heterocyclic antidepressants are the mainstay of treating depression in both outpatient and inpatient settings. Thus, assessing the clinical response, interpreting the side effects of heterocyclics and compromising the patients’ tolerance of side effects are daily routines in the clinic where acute depressive patients are attending.

ECT has a high recovery rate and is used for quick and effective treatment for severe depression. But this effective therapy has been unduly stigmatized by the
public and American civil libertarians. MAOIs are indicated for those who are refractory to heterocyclic(s) and who have clinical features of or history of panic attacks. Depressed patients with mood-congruent psychotic features need a combination of a heterocyclic and a low dose of a neuroleptic agent. It is logical to prescribe amoxapine which has both antidepressive and anti-psychotic properties for the treatment of psychotic depression.

Maintenance treatment of depression

Post at NIMH has long hypothesized that antidepressant agents can suppress depressive symptoms without immediately correcting the underlying biological process of the depression. Thus, if the antidepressant, such as imipramine, is stopped before the whole episode of depression is over, the patient may have the risk of running the unfinished course of the depressive process. This concept has dictated the concept of maintenance treatment of depression, which means administering the antidepressant continuously after acute depressive symptoms have disappeared.

A collaborative project of NIHM in 1986 provided the first study-derived guidelines on the length of continued therapy, to prevent either the premature withdrawal of the drug and subsequent relapse or unnecessarily prolonged treatment. The findings of the results indicate that withdrawal of maintenance therapy is safe only after the patient has been free of significant symptoms for 16–20 weeks. During the medication withdrawal, the physician should focus on mild as well as severe symptoms in the decision to terminate maintenance therapy.

Prophylactic treatment of depression

Depression is notorious for the tendency to recur in its natural course. Angst and coworkers in Switzerland demonstrated that depressive cycle length decreased from about 3 years after the first episode, to 2 years after the second, and to 1 1/2 years after the third. They also found that there is a 70% risk probability of developing 2 or more depressive episodes in the subsequent 5 years after a patient has had two major depressive episodes within 5 years.

That lithium remains the mainstay for prophylactic treatment for most patients with bipolar disorders and 10 to 15 percent of patients with unipolar disorders, has been officially approved by the American Psychiatric Association in 1975 and NIMH in 1985. The theoretical and practical aspects dealing with the issues of lithium maintenance have been recently detailed in a monograph.

The NIMH Conference Report in 1985 concluded that either a heterocyclic antidepressant or lithium is effective in the prophylaxis of recurrent mood disorders. The heterocyclic antidepressant is more effectively, easily, and popularly used than lithium in preventing depression. Thus, the heterocyclic antidepressant is mostly used for prophylactic treatment of depression. Mostly, American psychiatrists prescribe at a time only one antidepressant rather than polypharmacy which may be popular in Japan.

Concluding Remarks

In a recent NIMH community survey on epidemiologic catchment areas, major depression is found to be a major psychiatric problem in the general population, especially for the female. In the U.S., depression is often called the common cold in psychiatry. Nishizono of Fukuoka University in 1989 also suggests that the Japanese have moved from Morita nervousness and hysteria (before World War II), and from the Era of Anxiety (after World War II) to the Era of Depression. Thus, the needs to advance pharmacotherapy as the effective treatment method for depression are apparently urgent in both the East and the West. Exchanges in psychiatric knowledge can stimulate the progress on improving psychiatric care for the depressive sufferers.

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