The clinical pharmacology of depressive states

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Abstract

Antidepressants have good efficacy in the treatment of mood disorders, with effect sizes that have consistently been found to be greater than those of placebo. The more recent antidepressants do not have better efficacy than the compounds discovered 40 to 50 years ago, but they do have a more favorable configuration of side effects, leading to fewer dropouts. This favorable situation has made it possible to prescribe the newer antidepressants in less severe depression and in several anxiety disorders, with considerable benefit to patients. During the last decades, research into the pathophysiology of mood and anxiety disorders has provided much information on the brain circuitry, neurohormones, and neurotransmitters involved in these disorders. In parallel, biological and behavioral work on antidepressants, using animal models and new biochemical techniques, has led to a broader understanding of the mode of action of these drugs. Despite this impressive list of discoveries, much research remains to be done on the clinical, psychological, neuropsychological, physiological, and neurochemical aspects, before we can obtain a coherent description of the pathophysiological mechanisms of depression and its treatment. This will lead to a better ability to predict the quality of drug response and, therefore, to the individualization of treatment.

This review concerns the clinical pharmacology of antidepressant medication. We describe the major developments that have occurred during the last decades and list several directions for future developments. To prepare this text, we consulted clinical and fundamental publications, and reviews and meta-analyses covering many aspects of drug treatment of depressive states, such as comparative efficacy, the incidence of side effects, and dose-response curves. Despite the impressive list of discoveries, much research remains to be done on the clinical, psychological, neuropsychological, physiological, and neurochemical aspects in order to obtain a coherent view of the mechanisms of depression and its treatment.
Antidepressant drugs of the past

The area of pharmacotherapy of depression started in the 1950s, with landmark publications and discoveries that still govern the manner in which we treat depression. In 1951, the tuberculostatic drug isoniazid was synthesized, together with a series of variants, including iproniazid, the first monoamine oxidase inhibitor (MAOI). Iproniazid was first prescribed to patients suffering from tuberculosis, a condition for which it was efficacious, but induced more psychostimulation than did isoniazid. Thorough clinical observations led to the recognition of iproniazid’s antidepressant effects by Kline and colleagues, Crane and colleagues, and Scherbel and colleagues. Iproniazid was also suggested to be potentially useful in coronary disease, lupus erythematosus, and hypertension. In 1957, Kuhn described the antidepressant effect of imipramine, a tricyclic compound initially intended as an antipsychotic. Tricyclic antidepressants and MAOIs were rapidly demonstrated to be efficacious in severe depression and atypical depression, as well as in other categories of depressive disorders. However, iproniazid and other MAOIs became obsolete because of the risk of hypotension and hypertensive crisis; they are no longer marketed in many countries and rarely prescribed in countries where they remain available. Tricyclic antidepressants lead to adverse reactions, such as hypotension, prolongation of cardiac conduction, and drug-induced arrhythmia, side effects related to antagonism of the cholinergic system (dry mouth, blurred vision, constipation, urinary hesitancy, amnesia, sedation, etc), and the histaminergic system (sedation), as well as a quinidine-like effect on ion channels. Despite these adverse drug reactions and the fact that suicide attempts with MAOIs or tricyclic antidepressants generally need hospitalization, often in intensive care units, the record was definitely in favor of the use of these early antidepressants in major depression. It was generally considered that mild depression did not respond to antidepressant therapy, an opinion that has since changed considerably. Forty years ago, clinical entities such as dysthymia, seasonal affective disorder, and premenstrual dysphoria were not yet identified as such, or were known under different names, often referring to the broad category of neurosis rather than mood disorders. Panic disorder, under the label of neurosis, was treated with MAOIs by French clinicians, a few years after the discovery of these compounds. In the USA, Klein and Fink used tricyclic antidepressants in 180 inpatients and selected 14 of them retrospectively, on the basis of astute observations that led to the description of panic attacks. Other early indications for tricyclic antidepressants were enuresis in children and premature ejaculation. On the basis of clinical and basic observations, Bigger et al proposed that imipramine was a valuable antiarrhythmic medication; indeed, using dosages of up to 300 mg/day, they demonstrated that the number of ventricular extrasystoles could be considerably reduced, and that repetitive ventricular tachycardia could be suppressed. In these relatively more recent studies, nonpsychiatric patients received high doses of tricyclic antidepressants, and it was confirmed that hallucinations and delusions could be induced at these doses. Hypotheses concerning neurotransmitter changes during depression, mostly for the monoamines, but also for other neurotransmitters, led to several studies comparing the efficacy of tricyclic antidepressants as a function of monoamines and their metabolites in urine, blood, or cerebrospinal fluid. Unfortunately, in most of these studies, imipramine was considered to act mostly on noradrenaline, and clomipramine on serotonin. This was not ideal, since imipramine does have a small influence on serotonin, and, more importantly, desmethylclomipramine, the main metabolite of clomipramine, is a strong inhibitor of noradrenaline reuptake. Therefore, these early studies could
not answer the question of subtypes of depression with predominant dysfunctions in noradrenaline or serotonin.

Another peculiar consequence of the prescription of tricyclic antidepressants was the idea that several physical complaints, such as headache, peptic ulcer symptoms, arrhythmia, borderline hypotension, and prurigo, were in fact the expression of masked depression. This was based on the correct observation that these physical signs responded to tricyclic antidepressant therapy, but the conclusion was wrong: the pharmacological actions of these drugs are sufficient to explain the clinical findings, without the necessity of invoking a relationship between physical complaints and unrecognized or masked depression. For example, cardiac arrhythmia responds to tricyclic antidepressants, gastric hypersecretion is controlled by the H₂ antihistaminergic action of tricyclic antidepressants, and moderate hypertension responds to the α₂ adrenolytic action of these agents.

Tertiary amines of the tricyclics (amitriptyline, clomipramine, doxepin, imipramine, and trimipramine) are demethylated into secondary amines (desipramine, nortriptyline, and protriptyline), and these secondary amines have been marketed for many decades. They tend to be less sedating and induce fewer anticholinergic effects. Other tricyclic antidepressants and tetracyclic compounds include dothiepin, amoxapine, and maprotiline. Although we listed tricyclic antidepressants under the heading of drugs of the past, they are still prescribed today. However, the precursors of catecholamines (phenylalanine and L-tyrosine) or indolamines (5-hydroxyL-tryptophan and L-tryptophan) are no longer prescribed.

**Antidepressant drugs of the present**

There are currently between 10 and 20 different drugs marketed as antidepressants, depending on the country. The development of nontricyclic and non-MAOI antidepressants started with drugs such as fluvoxamine, mianserin, moclobemide, and tianeptine; these drugs and more recent ones, influence the monoaminergic systems in different ways, but generally with a narrower configuration of pharmacological actions than the tricyclic antidepressants.

Tricyclic antidepressants and MAOIs were called first-generation antidepressants, and selective serotonin reuptake inhibitors (SSRI) and reversible and selective inhibitors of monoamine oxidase A (RIMA) second-generation antidepressants. Third-generation antidepressants include more recent molecules, such as mirtazapine, nefazodone, milnacipran, and reboxetine. The distinction between first-, second-, and third-generation antidepressants is not absolute: for example, mirtazapine and nefazodone were recently launched onto the market; however, they resemble mianserin and trazodone, respectively, two compounds that were developed decades ago. In terms of chronology, therefore, mirtazapine and nefazodone should be considered as improved second-generation antidepressants rather than members of the third generation. The favorable therapeutic index of second- and third-generation antidepressants is reflected by lower rates of dropout, i.e., 15% with SSRI versus 20% or more with tricyclic antidepressants. This has enabled the study of the utility of the new antidepressants in many indications. Anxiety disorders became a field of active research into the efficacy of antidepressants. The goal was to find a medication that did not have the disadvantage of inducing tolerance and dependence, as was known to occur with benzodiazepines. (Thirty years ago, the reverse situation was observed, in that studies of benzodiazepines were set up
in depression, arguing that benzodiazepines had a far better therapeutic index than the tricyclic antidepressants.) In a previous review in this journal, we proposed that the indications for the newer antidepressants could be grouped under the label of antidepressant-responsive disorders (ARD).

Antidepressant drugs of the future

Taken together, the three generations of antidepressants mentioned above have the same level of clinical efficacy in the treatment of major depression, but compounds from the second and third generations share the absence of life-threatening side effects in overdose, as well as a more favorable configuration of side effects at the usual therapeutic doses, which constitutes a major advantage. Antidepressants of the fourth generation are still to come; they will also have a favorable configuration of side effects, and, more importantly, will produce a higher rate of clinical response.

Several goals seem reachable. The first concerns better efficacy in terms of the percentage of patients responding to the antidepressant. The techniques of genomics and proteomics indicate the possibility of identifying innumerable differences in gene or protein expression between sick people and controls, between patients with different clinical categories of disorders, between patients responding or not responding to treatment, and between those presenting or not presenting given side effects of the medication. Indeed, several studies on the polymorphism of the serotonin membrane transporter (5-HTT) suggest that this avenue is worth pursuing. These techniques might well lead to the conclusion that finding an antidepressant that is efficacious for almost every patient is wishful thinking, while the modulation of treatment as a function of the patient's characteristics can improve the rate of favorable response. In the future, one might sell medication in a package containing a recommendation (or a kit) to identify laboratory values that are predictive of a good response.

A second issue is that of the delay before the antidepressant effect. There are arguments in favor of the feasibility of finding a drug therapy that induces remission of depression within hours or days, rather than within 1 to 6 weeks. Indeed, spontaneous oscillations of normal mood are very fast and other biological therapies, such as sleep deprivation and electroconvulsive therapy, can achieve rapid remission; moreover, addictive psychostimulants (mostly cocaine) lead to immediate pleasure and reward. Taken together, these facts suggest that there are no inbuilt physiological limits leading to a time span of several days as a mandatory constraint for a change in mood. It might be, however, that the mechanisms that induce a rapid change in mood are not the same as those that maintain a normal mood.

The issue of an antidepressant that does not induce mania in predisposed individuals is a rather difficult one, since no efficacious antidepressant treatment is devoid of this side effect, and since the shift from depression to mania is a symptom of bipolar disorder as well as an iatrogenic change. SSRIs and bupropion have been said to induce less mania than tricyclic antidepressants, but this statement needs confirmation.

The pharmacological actions of antidepressants lead to changes in secondary messengers, in the expression of early genes, and in the synthesis of proteins, as well as changes in synaptogenesis and
neurogenesis, cerebral metabolism, glial cell activity, secretion of stress hormone, the equilibrium between neuroendocrine or neuroimmunology factors, and neuropeptide gene expression, etc. An effect common to several treatments, such as antidepressants, electroconvulsive therapy, and sleep deprivation, concerns the downregulation of corticotropin-releasing hormone mRNA in the hypothalamus and the upregulation of glucocorticoid receptor mRNA in the hippocampus, two effects that reflect a negative feedback on the activity of the hypothalamicpituitary-adrenal axis.

Clinical management of antidepressant drugs

The knowledge that has accumulated over the last 50 years now has several practical consequences. Dissemination of this information ensures that a higher percentage of the afflicted population receives adequate therapy, i.e., that clinicians avoid both the indiscriminate prescription of antidepressants and the abstention of prescription, despite clear indications. The proposals listed below cover some of the questions relative to the prescription of an antidepressant; this checklist is not exhaustive and clinicians should consult the complete text of guidelines and recommendations for further information, for example, documents by Reesal and Lam23 or Kennedy et al.24

Evaluating the indications

All subtypes of depressive disorders are indications for antidepressant therapy. Among the anxiety disorders, panic disorder, obsessive-compulsive disorder, social phobia, posttraumatic stress disorder, and generalized anxiety are indications for antidepressants, mostly SSRIs.

Deciding to prescribe

The decision to prescribe an antidepressant should rely on the evaluation of the severity of the symptoms, and the efficacy of previous psychotherapy or other medications. The decision as to whether the threshold of symptom, severity is met can vary according to the diagnosis and clinician's and the patient's wishes. Severe cases of mood or anxiety disorders should be treated with antidepressants, while the decision, to prescribe an antidepressant in moderate or even mild cases can be taken over the course of a few weeks.

Evaluating the contraindications

A review of other drugs taken by the patient enables the clinician to exclude the risk of drug-drug interactions. Inhibition of hepatic cytochrome P450 enzymes is the most cited pharmacokinetic interaction, but. not all such interactions are clinically relevant. The prescription of other medications that influence serotonin (tramadol, dextromethorphan, and sibutramine) can increase the risk of serotonergic syndrome and represents a frequent pharmacodynamic interaction. Drug-disease interactions should also be excluded; these are numerous with tricyclic antidepressants, but few with the newer antidepressants, which can be prescribed in patients suffering from many cardiovascular, respiratory, or digestive diseases. Renal or hepatic failure, physical frailty, and age above 75 are reasons to use low doses (half a tablet or less a day of any SSRI).
Choosing the first antidepressant and the dose

Tricyclic antidepressants and MAOI are outmoded and should not be prescribed as first-line treatment because their side-effect burden is too high. This opinion is not shared by all experts, notably because the new drugs are more expensive. The choice between SSRIs and the other recent antidepressants depends on the consequences of potential side effects for each patient and the desirability of inducing sedation. With SSRIs, the dosage should be one tablet a day to start with. There are no indications that two tablets a day of SSRIs are more useful than one, while they will induce more side effects. Sedative compounds, such as mirtazapine, nefazodone, or reboxetine, should be started at a low dose of one tablet a day, with a rapid increase to the usual doses within the first week of treatment.

Informing the patient

The clinician should explain which target symptoms can be expected to improve, and should discuss with the patient how to evaluate whether these goals are met. Information on the risk of side effects early in the course of treatment (anxiety, digestive symptoms, and sleep fragmentation) and later (sexual inhibition) should be provided.

Deciding to change the antidepressant

A minimum duration of 4 to 6 weeks with the same antidepressant, should be scheduled in case of depressive states and anxiety disorders, unless the side effects are so severe that the treatment must be altered. The decision to increase the dosage is often taken after 2 to 3 weeks of treatment, despite the lack of evidencebased information on the utility of doing so. Changing from one SSRI to another due to lack of efficacy can give good results in cases of depression; the question of whether this is also the case for anxiety disorders is not clear. This change can be made from one day to the next, (under surveillance for serotonergic syndrome) or after a period without antidepressant (under surveillance for antidepressant withdrawal symptoms). In case of side effects, changing to another antidepressant with a similar pharmacological mode of action entails a high risk of persistence of side effects, except for idiosyncratic conditions such as allergy. Routine drug monitoring of newer antidepressants in plasma is being studied, and has very few indications for the present. Obsessive-compulsive disorder stands apart, since improvement can occur progressively over the course of 2 to 4 months of antidepressant prescription.

Choosing the second antidepressant

Prescribing an antidepressant for treatment-resistant patients often consists in shifting from one antidepressant to another or in adding a second antidepressant with a different mode of action; this can result in a good therapeutic response. In cases of severely resistant depressive states, the addition of lithium or thyroid hormones or atypical antipsychotics constitute the next steps. The prescriptions recommended for antidepressant treatment resistance in case of anxiety disorders are less well established.
Deciding on the duration of treatment

The duration of newly initiated antidepressant treatment should be at least 6 months, preferably 1 year. This rule prevails for all indications of antidepressants. The risk of relapse is high in cases of dysthymia, panic attacks, and obsessive-compulsive disorder. In case of relapse, a prescription for 2 to 4 years can be scheduled. However, some patients might receive antidepressants for many years, when each attempt at lowering and stopping medication is followed by a relapse. Knowledge about the efficacy of long-term prescriptions is limited, and not founded on evidence-based medicine.

Adressing further questions

Here, we mention a few questions of clinical relevance.

What guides the choice of antidepressant?

There is no demonstration that any given class of antidepressants is more efficacious than another for the different categories of depression. Major depression with atypical features was considered to respond better to MAOIs than to other antidepressants. Also, there is no biological test suggesting the choice of one antidepressant over another for a given patient. It is generally recognized that patients who suffer from insomnia or who have a high degree of anxiety might benefit more from antidepressants that facilitate sleep and do not have the risk of inducing anxiety during the first days of treatment. This is sound clinical practice. However, even patients who have sleep abnormalities and who are anxious can respond favorably to an SSRI, despite the fact that these medications can decrease sleep efficiency and continuity, and carry the risk of exacerbating anxiety during the first days or weeks of treatment. The authors of this review consider that there is no indication left for tricyclic antidepressants or MAOIs as first-line therapy for any depressive or anxiety disorder. The reason for this is, aside from the known side effects of tricyclic antidepressants, the long list of physical disorders that are a contraindication to tricyclic antidepressants: heart failure, cardiac conduction disorder, hepatic insufficiency, renal insufficiency, epilepsy, Parkinson's disease, cerebrovascular disease, etc.

Are two antidepressants better than one?

The clinician can rightly ask whether there is an advantage in combining two antidepressants to multiply the targets of pharmacological actions and achieve a higher rate of efficacy. In clinical practice, the combination of two recent antidepressants is common. One such combination has been known for years, ie, to add a sedative to compensate for the stimulation due to an antidepressant; trazodone, nefazodone, mianserin, and mirtazapine can be used as sedatives, acting on sleep difficulties and anxiety in patients receiving a stimulating antidepressant. The combination of two antidepressants in other situations should be limited. In treatment-resistant patients, it is logical to combine antidepressants with different pharmacological modes of action and different clinical configurations (for example, a stimulating SSRI such as sertraline with a low or moderate dose of a sedating compound such as mirtazapine or nefazodone). There are no controlled clinical trials to confirm the benefit of combining two antidepressants.
Is there a better response at higher doses of antidepressants?

Drug-monitoring studies have indicated a linear or curvilinear relationship between efficacy and concentration of tricyclic antidepressants such as imipramine, desipramine, and nortriptyline. However, recent results from the Danish University Antidepressant Group (DUAG) have shown little difference between clomipramine doses of 25, 50, 75, 125, and 200 mg/day in severely depressed patients. With fluoxetine, 5 mg/day seems to be clinically equivalent to 20 or 40 mg/day, in terms of antidepressant effect. There are hints that venlafaxine, nefazodone, and reboxetine are more efficacious at higher doses. The explanation put forward is that the pharmacological mode of action differs as a function of the dose, a point that is difficult to prove in humans; for example, it has been said that at low doses venlafaxine acts as an SSRI, and only at higher doses does it influence the reuptake of noradrenaline. While the existence of a better response at higher doses of antidepressant is a subject of debate, there is consensus about the increased risk of side effects at higher doses. For example, dosages of 225 or 375 mg/day venlafaxine lead to 24% and 30% dropouts, respectively, in comparison to 17% for 75 mg/day and 5% for placebo. Similarly, dosages of 25 to 200 mg/day clomipramine lead to 3% to 27% dropouts, respectively. In conclusion, higher doses of antidepressants might be tried in some treatment-resistant patients, but the risk is that they might not tolerate the side effects.

Does the effect of antidepressants wear off with time?

Loss of clinical efficacy for antidepressants has been described in patients receiving tricyclic antidepressants, MAOIs, as well as recent antidepressants. This loss of efficacy could occur in up to a third of all depressed patients, for example, those having responded to fluoxetine; it often manifests itself as apathy, fatigue, as well as depression. It seems to represent a truly pharmacological and physiological problem, possibly tied to secondary changes in the dopaminergic system, although the fact that it reflects the evolution of the psychiatric disorder cannot be ruled out. Clinically, an increase in dosage can lead to remission as well as to further aggravation of symptoms. After a period with no medication, the same medication can be reintroduced, often with success. Improvement seen with placebo in clinical trials seems to have a strong tendency to disappear over time.

What is the clinical relevance of antidepressants for subsyndromal mood or anxiety disorders?

Subsyndromal or subthreshold disorders are clinical entities in which the presence of a psychiatric disorder is suggested by minor symptoms, within a continuum between normal state and an axis I diagnosis based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Although the efficacy of antidepressants has not been extensively evaluated in these conditions, there are epidemiological data showing that a subsyndromal state or the failure to achieve complete remission predicts the occurrence of a first episode or the recurrence of an axis I disorder.
References


