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NEW ANTIDEPRESSANTS

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INTRODUCTION

During the 35 years of their existence, many new antidepressants have been introduced into clinical practice. From the late 1950s until 1980, the two major classes of these drugs included so-called tricyclics and the monoamine oxidase (MAO) inhibitors. Several additional types of drugs designated variously as "heterocyclic" or "second-generation" antidepressants appeared during the 1980s. Despite the large number of compounds from which to choose, available antidepressants have not been entirely satisfying to clinicians. First, response was somewhat unpredictable, with only about 60% of patients obtaining a satisfactory outcome. Second, most drugs were somewhat unpleasant to take; a variety of unwanted effects was caused by the nonspecificity of their pharmacological actions. Third, beneficial effects, when obtained, were often slow to appear. Fourth, many of these drugs were dangerously toxic if taken in overdoses. Such drawbacks were sufficient to impel a continuing search for new drugs with some advantage in one or the other of these areas.

SELECTIVE SEROTONIN UPTAKE INHIBITORS

Nonselective inhibition of serotonin uptake is a characteristic of many tricyclic antidepressants, such as amitriptyline. Norepinephrine uptake was also inhibited. Increased but incomplete selectivity for serotonin was achieved by drugs such as clomipramine and zimelidine.

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A major problem with previous antidepressants has been the lack of specificity of their pharmacological actions. Tricyclics, for instance, have antimuscarinic, antihistamine, and α adrenergic blocking actions that account for their many unwanted actions without an appreciable contribution to their therapeutic effects. The major thrust among these new drugs has been to narrow the range of pharmacologic actions, presumably focussing on those that may be therapeutic.

Fluoxetine

This drug was the first truly specific serotonin uptake blocker. It contains the propylamine side chain found in most tricyclics (Figure 1). Fluoxetine has no effect on the uptake of other aminergic transmitters, nor does it possess much affinity for any adrenoreceptors, histamine, muscarinic, $GABA_B$ or 5HT receptors. Inhibition of serotonin uptake in rat brain synaptosomes occurs at a concentration less than 200 times that which produced inhibition of norepinephrine uptake. In man, a dose of 30 mg/day produces 67% uptake inhibition by the seventh day (1).

Fluoxetine is unusual in that both the parent drug and the active metabolite, norfluoxetine, have plasma half-lives measured in days, and both interfere with P-450 drug-metabolizing enzymes, prolonging the half-life of many other drugs (2). Thus far, these attributes have not been a deterrent to its clinical use (Table 1). A number of tricyclic antidepressants may show increased plasma concentrations in the presence of fluoxetine. Thus, some caution may be required when either changing patients from a tricyclic to fluoxetine, or vice versa.

An even more important interaction to be avoided is the use of fluoxetine in the presence of a monoamine oxidase (MAO) inhibitor. Because the MAO inhibitor increases serotonin concentrations by interfering with its catabolism, and fluoxetine increases its availability at the synapse by interfering with uptake, excessive serotonergic activity results. The clinical syndrome, the so-called serotonin syndrome, is serious and sometimes fatal. Patients may develop hyperthermia, rigidity, myoclonus, rapid changes in vital signs, and alterations of mental status. Cyproheptadine, a serotonin antagonist, has been tried in treatment. Because of the long half-lives of both MAO inhibitors and fluoxetine, the latter drug should not be started until MAO inhibitors have been discontinued for at least 14 days; the recommended interval for the reverse switch is 5 weeks.

Although fluoxetine has never been convincingly established as more effective than other antidepressants, its different side-effect profile has been more clinically acceptable (3). Usual daily doses range between 20 and 80 mg but some patients may require as little as 10 mg. Unlike the tricyclics, which evoke unwanted autonomic, anticholinergic, and sedative side effects,

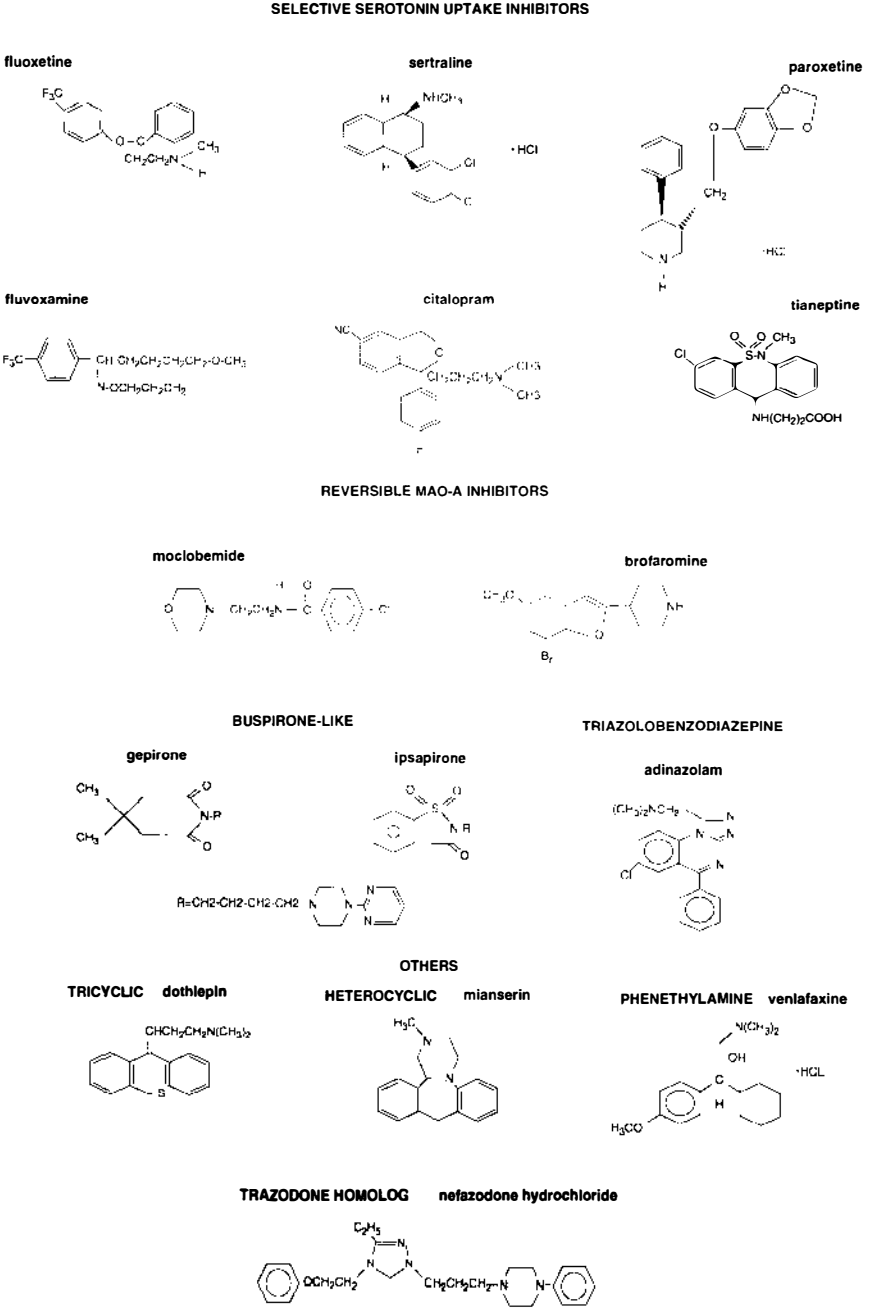

Figure 1 Structural formulae of various types of new antidepressants. It is notable that even within a single class, defined pharmacologically, the structures vary considerably.

Table 1 Pharmacokinetic parameters of selective serotonin uptake inhibitors

	Oral absorption %	Volume of distribution L/Kg	Plasma protein-binding %	Active metabolite	Plasma T ½	Therapeutic range
Fluoxetine hydrochloride	95	20–42	80–95	norfluoxetine	42–72 h 7–15 days	not identified
Sertraline hydrochloride	slow	20	98	N-desmethyl	22–35 h	not identified
Paroxetine hydrochloride	100	31–28	95	none	24 h (mean)	not identified
Fluvoxamine maleate	90	5.1	77	none	15 h (mean)	not identified

the most frequent side effects of fluoxetine have been nausea and anxiety. This single advantage propelled it rapidly to become the most widely prescribed antidepressant.

An anecdotal report that patients treated with fluoxetine developed increased suicidal thoughts has created much controversy. No adequate pharmacological explanation suffices to account for such a complication. At present, the consensus is that suicidal thoughts are part of the clinical spectrum of depression and that they are no more common with fluoxetine than with other antidepressants or placebo. As yet, the drug seems to be a considerably smaller risk for use as a suicidal weapon than many other antidepressants. Overdoses have resulted in death but seldom when fluoxetine was the only drug taken.

Sertraline

The second specific serotonin uptake inhibitor to reach the market is structurally different, being a 1-amino-tetrahydronapthalene (Figure 1). Sertraline inhibits serotonin uptake strongly but only weakly inhibits uptake of norepinephrine and dopamine. It is more potent and more specific in serotonin uptake inhibition than fluoxetine or chlorimipramine. Essentially it has no other pharmacologic effects than inhibition of serotonin uptake.

Unlike fluoxetine, which undergoes little first-pass metabolism, sertraline is extensively metabolized. An N-demethylated metabolite is formed that has only about 10% of the activity of the parent drug. The plasma half-life of sertraline is much shorter than that of fluoxetine, being in the range of 22 to 35 hours, similar to that of most other antidepressants. Other pharmacokinetic parameters are shown in Table 1. The drug induces the P-450 drug-metabolizing enzymes, but no significant interactions have been reported due to this action (4). As with fluoxetine, as well as other specific serotonin uptake inhibitors, a major interaction can occur when sertraline is given concurrently with MAO inhibitors. However, the shorter half-life of sertraline does not require a long interval between stopping sertraline and starting the MAO inhibitors.

The efficacy of sertraline for depression has been proven in a number of controlled comparisons with placebo, amitriptyline, and other antidepressants. Usually both active drugs have been superior to placebo, with no differences between them. The usual dose of sertraline has been 50 mg with weekly increments to as much as 200 mg/day, depending on response. Side effects of dizziness, dry mouth, nausea, diarrhea, tremors, insomnia, and male sexual dysfunction have been frequent, contrasting with sedation and anticholinergic side effects from amitriptyline. The frequency and intensity of side effects as well as the rate of dropouts due to side effects was similar between sertraline and amitriptyline (5, 6). The few cases of overdoses already reported have all survived without adverse sequelae.

Paroxetine

This specific serotonin uptake inhibitor is a phenylpiperidine derivative (Figure 1). The potency of paroxetine is 2 to 3 orders of magnitude greater for inhibition of serotonin uptake than for norepinephrine or dopamine. Its selectivity for serotonin is greater than that of fluoxetine, sertraline, and fluvoxamine. The drug has no affinity for the various serotonin receptors; its affinity for muscarinic receptors was 15 times less than that of amitriptyline (7). The pharmacokinetic parameters are shown in Table 1. A similar interaction should occur between MAO inhibitors and paroxetine as with other serotonin uptake inhibitors.

The only current indication for paroxetine is depression. Double-blind, parallel-group studies have compared its efficacy with that of placebo, imipramine, amitriptyline, dothiepin, and mianserin (8, 9). Usual doses have been 20 to 30 mg/day given once. Efficacy has been relatively similar among comparisons with other antidepressants, but has been maintained as long as 4 years. Paroxetine produced fewer anticholinergic and sedative side effects than comparative drugs, with fewer patients withdrawing from treatment because of them. Nausea and somnolence were the major symptoms from paroxetine. Overdoses of this drug have been relatively benign.

Fluvoxamine

This 2-aminoethyl oxime arylketone represents still another chemical structure among this diverse group of drugs (Figure 1). Fluvoxamine increases concentrations of serotonin at the synapse by blocking uptake, binding with high affinity to the serotonin uptake site. It has very low affinity for the receptors of other neurotransmitters. Its pharmacokinetic properties are shown in Table 1. The drug has no active metabolites and the plasma half-life, while highly variable, is relatively short. Its major indication is depression. The usual starting dose is 100 mg/day, with increments as required up to 300 mg/day. As with other serotonin uptake inhibitors, the drug should not be used in conjunction with MAO inhibitors. Clinical studies indicate that it is as effective in depression overall as imipramine but with the usual differences in the profile of side effects (10). Nausea, headache, and insomnia are the most frequent side effects. The drug has been marketed in Europe where it is widely used for treatment of major depressive disorders. Fluvoxamine has been relatively safe in overdoses; no deaths have occurred when it has been the only drug present.

Citalopram

This selective serotonin uptake inhibitor has the dimethylaminopropyl side-chain so characteristic of tricyclics (Figure 1). Although it blocks uptake of

serotonin it has only a low affinity for a range of receptors. Longterm administration up-regulates α-1 adrenoreceptors and down-regulates β-2 adrenoreceptors in rat brain; unlike many other antidepressants, it does not down-regulate the β-adrenoreceptor-coupled adenylate cyclase system. An elimination half-life of about 33 hours permits once daily dosing. The major metabolite is only weakly active (11). Most controlled clinical evaluations have shown the drug to be equally effective to other antidepressants. The side effect profile somewhat resembles that of other drugs in this class. This drug, too, seems to be relatively safe in overdoses.

Others

Tianeptine is a dibenzothiazepine derivative with a selective action of inhibiting serotonin uptake. It represents still another of the great variety of chemical structures of the members of this class of drugs. Clinical studies indicate some degree of antidepressant action (12).

General Comments

A major justification for the introduction of new antidepressants is that they offer more alternatives to clinicians should older drugs fail. Thus, even though they may not be more efficacious overall than earlier drugs, they may be effective in some patients who do not respond to the earlier drugs. This assertion is probably true, although it must apply to only a relatively small number of patients. Tolerance for side effects is somewhat idiosyncratic; patients differ in determining what bothers them. Often one trades one set of side effects for another, although in the case of fluoxetine, the trade seems to be acceptable. Trying to document a more rapid clinical response is extremely difficult and has not been established for any new antidepressant. Finally, safety in overdose is a major consideration for a treatment of patients who are likely to be suicidal. This advantage is still incompletely determined for drugs of this class, but thus far it seems to be genuine.

In addition to the indication of the specific serotonin uptake inhibitors for treatment of depression, they are currently under investigation as appetite suppressants and for the treatment of obsessive-compulsive disorder. Fluoxetine, in doses of 60 and 20 mg/day, has been shown to be superior to placebo for patients with bulimia nervosa (13). Sporadic reports have suggested other possible indications but none has been fully explored.

SELECTIVE, REVERSIBLE MAO INHIBITORS

Most available MAO inhibitors are nonselective, that is, they inhibit both MAO-A and MAO-B. MAO-A is the enzyme responsible for the metabolism of tyramine, an indirect sympathomimetic amine. Blockade of MAO-A allows

the accumulation of tyramine and the production of acute hypertensive crises, one of the most serious adverse effects of nonselective MAO inhibitors. Although one would expect that a selective MAO-B inhibitor might prevent this interaction, most such drugs, such as deprenyl (seligiline), become nonselective at doses close to those required therapeutically. Further, deprenyl preferentially affects the metabolism of dopamine, accounting for its utility as an anti-Parkinson drug.

It is the long duration of MAO-A inhibition that causes problems. A short-acting MAO-A inhibitor allows recovery of enzyme activity in a few hours rather than the 2–3 weeks required by the "irreversible" MAO inhibitors. This difference, which mitigates the possibility of a severe hypertensive interaction, is the major potential advantage of reversible inhibitors.

Moclobemide

This benzamide derivative, different in chemical structure from existing MAO inhibitors, selectively inhibits the deamination of serotonin, norepinephrine, and dopamine. When compared with placebo and amitriptyline, moclobemide was as effective as amitriptyline, with both drugs being superior to placebo. On the other hand, it was superior to amitriptyline in having fewer side effects (14). Thus far, acute hypertensive episodes are unknown with this drug. It is effective in a variety of depressive subtypes.

Bromfaromine

This drug is also a potent, reversible and specific inhibitor of MAO-A. In addition, it also modestly inhibits the uptake of serotonin at clinical doses (15). Clinical trials have demonstrated its efficacy as an antidepressant, but it is not as far along in its development as moclobemide.

General Comments

MAO inhibitors have never been popular antidepressants, largely because of the fear of severe hypertensive crises following ingestion of tyramine-containing foods or sympathomimetic medications. During the past decade, these fears have been alleviated by the known precautions to prevent such interactions. The failings of tricyclic and heterocyclic antidepressants have also led clinicians to consider the use of MAO inhibitors more often. Whether the single advantage of the new reversible MAO-A inhibitors will reinforce this trend remains to be seen.

BENZODIAZEPINES

Classical benzodiazepines have generally been thought to play only an adjunctive role in the treatment of depression. Triazolobenzodiazepines are

thought to possess special qualities that make them more useful as antidepressants. The role of the first of these drugs, alprazolam, has been controversial (16). A related compound, adinazolam, has been found to sensitize hippocampal neurons to serotonin following chronic administration (17). Thus, a potential rationale exists for trying this drug for treatment of depression.

Three parallel groups of 22 patients each were treated with adinazolam, diazepam, and amitriptyline for four weeks. Patients were selected not only on the basis of clinical manifestations but also by having either a positive dexamethasone suppression test or an abnormal contingent negative variation. Amitriptyline was superior, but adinazolam was in between that drug and diazepam in efficacy (18). As might have been expected, the benzodiazepines produced fewer anticholinergic side effects than amitriptyline.

Acceptance of benzodiazepines as antidepressants has been grudging. First, no known pharmacological action of these drugs provides a rationale for their use in treating depression; few differences have been observed among members of this class. Second, the doses used for treating depression, which may vary from 30 to 80 mg/day of diazepam equivalents, are likely to produce physical dependence and withdrawal syndromes on discontinuation.

Benzodiazepines can be construed as gabamimetic compounds. A compound more closely linked to GABA, fengabine, has been tried as an antidepressant. In several comparisons with various tricyclics, it proved overall to be equally efficacious and better tolerated (19).

PARTIAL AGONISTS TO THE $5HT_{1A}$ RECEPTOR

The introduction of buspirone as a novel anxiolytic has raised many possibilities for new approaches to the treatment of anxiety and depression. It is now believed that buspirone acts as a partial agonist at the $5HT_{1A}$ serotonin receptor. Actually, it is hypothesized that the drug will act as an antagonist in the presence of too much serotonin and as an agonist when serotonin is deficient, essentially stabilizing serotoninergic activity (20). Some of these actions might be pertinent to an antidepressant effect and some of the congeners of buspirone are being tested clinically for antidepressant action.

Gepirone

This drug, like buspirone and ipsapirone, is a pyrimidynyl piperazine derivative (Figure 1). It too acts as a partial agonist at $5HT_{1A}$ receptors. Studies of its utility in both anxiety and depression have shown evidence of efficacy in controlled trials. Among numerous metabolites, only one, the 1-pyrimidynyl piperazine, is active. Early clinical trials suggest that the drug has antidepressant activity (21).

Ipsapirone

This drug differs somewhat from the others in this series in that its elimination half-life is extremely short, 1–2 hours (22). It shows the usual side effects of drugs of this type, sweating, fatigue, poor concentration, tremor, and nausea. Its efficacy for treating depression is under study.

General Comments

The efficacy of buspirone as an anxiolytic has been questioned. Its mode of action is still somewhat uncertain. Perhaps this class of drugs has been miscast and should have been promoted as antidepressants. If they turn out to be effective antidepressants, they will provide additional impetus for elucidating the role of serotonin in the pathogenesis of the disorder.

HETEROCYCLICS

Mianserin

Although mianserin was introduced into practice in 1976, it has not yet appeared on the U.S. market. It has a four-ring structure and a mode of action different from most available drugs. It blocks α-2 adrenoreceptors presynaptically, α-1-receptors postsynpatically, and antagonizes $5HT_2$, $5HT_{1C}$ receptors and H_1 receptors. Compared with most tricyclic antidepressants, it has weak antimuscarinic activity (23). These actions make it a drug with highly sedative actions but weak anticholinergic side effects. It has been shown in double-blind placebo-controlled trials to be superior to placebo, but the differences have not been impressive. This apparently less-than-desirable efficacy (largely in mildly or moderately depressed patients) as well as reports of agranulocytosis and aplastic anemia from the drug no doubt accounts for its restricted popularity.

Others

Oxaprotiline and other active metabolites of maprotiline are under investigation. It seems unlikely that they will possess material advantages over the parent drug.

General Comments

The so-called heterocyclics, such as amoxapine, maprotiline, trazodone, and others introduced as antidepressants during the 1980s, have been disappointing. Not only do they show no special advantages over tricyclics but they may actually have more adverse consequences. However, as one can deduce from the nomenclature, this is a diverse group.

TRICYCLICS

Dothiopen, which has an isosteric substitution on a sulfur-atom for an oxygen-atom in the structure of doxepin, is marketed elsewhere in the world. It is not markedly different from doxepin, which is doubtless why it has not been promoted in the USA (24). Lofepramine is another tricyclic currently under investigation. It remains to be seen if it has any significant differences from available tricyclics.

NONSELECTIVE AMINERGIC NEUROTRANSMITTER UPTAKE INHIBITORS

Venlafaxine

This phenethylamine inhibits uptake of serotonin, norepinephrine, and, to a lesser extent, dopamine (Figure 1). It has no affinity for brain muscarinic cholinergic, histaminergic, or adrenergic receptors. Unique among the antidepressants, following a single dose venlafaxine produces a prolonged desensitization of β-adrenergic receptors. Its major metabolite is O-desmethylvenlafaxine, which is pharmacologically similar to venlafaxine. Six controlled trials have shown effectiveness equivalent to reference treatment. Side effects include: nausea, dizziness, insomnia, and dry mouth---effects similar to other serotonin uptake-inhibiting drugs.

On the basis of currently known pharmacological actions, venlafaxine should not be remarkably different from traditional antidepressants. However, its narrower spectrum of actions may provide some advantage regarding side effects.

SEROTONIN UPTAKE INHIBITOR AND $5HT_2$ RECEPTOR ANTAGONIST

Nefazodone

Nefazodone is a chemical analog of trazodone—both are members of the phenylpiperazine class of antidepressants. Nefazodone is a serotonin antagonist, which blocks $5HT_2$ receptors, as well as inhibiting neuronal uptake of serotonin. It has minimal activity as histamine, acetylcholine, and α-adrenergic receptors. Metabolites include hydroxynefazodone, which is thought to be similar to nefazodone in its actions, and metachloro-phenylpiperazine—a more complex metabolite. Efficacy studies are currently being evaluated (25).

Trazodone itself has been a somewhat controversial antidepressant, with many clinicians now using it as a short-acting hypnotic for depressed patients

rather than as a first-line antidepressant. Whether homologs of this series will prove to be more acceptable is doubtful.

CONCLUSIONS

Many new antidepressants are in various stages of development. Most offer different chemical structures and modes of action as compared with the standard antidepressants. Some seem to have possible advantages in having more tolerable side effects or in being less likely to be lethal when taken in overdose. Unfortunately, none has been shown overall to be more effective than the drugs already available. That so many diverse pharmacologic mechanisms may be able to alleviate depression is still a puzzle. For that reason, the search goes on.

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