Development of New Antidepressants

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A large number of novel antidepressants acting on a variety of neurotransmitter receptors are currently undergoing clinical evaluation. Most agents have a dual mechanism of action on two or more neurotransmitter receptors, including two serotonin receptors, two noradrenergic receptors, or a combination of serotonin and noradrenergic mechanisms. The most recently approved agent, mirtazapine, is an example of this approach of simultaneously targeting both the serotonergic and noradrenergic systems. Specifically, mirtazapine's α_2 antagonism disinhibits both serotonin and norepinephrine neurotransmission while its serotonin-2 and serotonin-3 antagonist properties reduce the side effects normally associated with nonselective serotonin receptor activation by serotonin selective reuptake inhibitors (SSRIs). This approach of "designer polypharmacy" applies principles of rational pharmacologic combinations to enhance efficacy and improve tolerability of the new and emerging antidepressants.
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Depression is a chronic illness that affects people of all ages. The lifetime risk of major depressive disorder in community samples varies from 10% to 25% for women and 5% to 12% for men.[1] Although there are many effective antidepressant agents available today, the current armamentarium of treatments is often inadequate, with unsatisfactory results in about one third of all subjects treated.[2] This gives impetus for research to provide new therapies. There are also other forces driving the development of new antidepressants. It is no longer merely a search for better safety, tolerability, and efficacy. The development of new antidepressant drugs is being influenced profoundly by health care reforms in the United States and throughout the world.

Thus, the novel antidepressant agent of the future must be shown to be not only safe and effective, but cost effective as well. Studies of depression are highlighting the direct health care costs of treating a particular disease state and evaluating the costs to society of not treating a particular illness. For example, depression is underrecognized and undertreated, with perhaps only one third to one half of sufferers receiving any treatment at all. Would additional treatment of the underserved lead only to increases in direct treatment costs, or would it cause a net decrease in costs to society due to the reduction of costs associated with the burden of inadequately treated illness?

One recent pharmacoeconomic study placed the cost of depression in the United States at a staggering $43.7 billion a year.[3] A similar study indicated that the annual cost of depression in the United Kingdom was 222 million pounds sterling ($355 million).[4] Although these two studies used different methodologies to calculate the cost of depression, they both concluded that depression is a tremendous economic burden to society as well as to patients and their families. In this age of health care cost containment, it is clear that corporate America, society, and the government have economic interests in purchasing cost-effective health care services. Thus, antidepressants of the future must demonstrate that their costs are returned with dividends to society. Otherwise, these antidepressants may end up being approved by regulatory agencies as safe and effective treatments for depression but not widely used by managed care or government-sponsored health care groups.

Here we review antidepressants in development, presenting the available data that suggest the safety and efficacy of these compounds in major depressive disorder. In 1985, the Pharmaceutical Research and Manufacturers of America listed 16 compounds in development for the treatment of affective disorders, although by 1997 many of

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Table 1. Serotonin Selective Reuptake Inhibitors Recently in Development (Not Marketed in the U.S.)

Agents	Status/Comments
Paroxetine SR[a]	Oral sustained release formulation
Citalopram[a]	Phase III U.S. (approved in Europe)
Cericlamine	Uncertain
Femoxetine	Uncertain
Cyanodothiepin	Uncertain
Litoxetine	Uncertain
Zimeldine	Discontinued/toxicity
Viqualine	Discontinued/nausea
Alaproclate	Discontinued
Ifoxetine	Discontinued
Tiflucarbine	Discontinued

[a]Most promising for U.S. marketing.

these compounds had already been dropped from development (see Table 1). There are numerous other compounds currently in development worldwide (see Tables 2–5). Mirtazapine is the latest compound to be approved in the United States and will therefore be discussed in somewhat more detail here. Many of the compounds listed in Tables 1 through 5 are reviewed in the sections that follow. Whether any of these agents will ultimately be approved and be clinically successful will increasingly depend upon the ability of novel features of antidepressants to command a premium in terms of cost effectiveness in actual clinical use. As such, cost-effectiveness studies of antidepressants are generally lacking, particularly for drugs that are still early in development. Therefore, we will emphasize the safety and efficacy issues of novel putative antidepressant agents. We hope that studies of the cost effectiveness of antidepressants will become an early part of the clinical testing of such agents in the future.

SEROTONERGIC AGENTS

Of the various classes of antidepressants that are currently available, there are a multitude that have a common mechanism of action; that is, they influence the neurotransmission of serotonin (5-hydroxytryptamine [5-HT]). In addition to the serotonin selective reuptake inhibitors (SSRIs), there are compounds that have more than one action on the serotonin system as well as some that have one serotonergic mechanism plus one mechanism on another neurotransmitter system. Several of the various compounds in development as antidepressants that influence serotonergic neurotransmission are reviewed below.

Serotonin Selective Reuptake Inhibitors (SSRIs)

SSRIs have a high ratio of 5-HT uptake inhibition compared to noradrenaline (norepinephrine [NE]) uptake inhibition.[5] This contrasts them with classical tricyclic antidepressants (TCAs), which inhibit both 5-HT and NE uptake. Furthermore, SSRIs may *up*-regulate β_1-adrenergic receptors after chronic treatment, a finding different from classical antidepressants, which mostly *down*-regulate central β_1-adrenergic receptors.[6,7] Thus, SSRIs interact with the noradrenergic system in a manner that is far different from that of classical TCAs. Both, however, inhibit 5-HT reuptake and down-regulate 5-HT_{2A} receptors.[2,8]

SSRIs have been available since the early 1980s.[9] The first drug of this type—zimeldine—was marketed in 1982, but due to its serious hypersensitivity side effects (fever, myalgia, malaise, increased transaminases, and occasionally the development of a Guillain-Barre syndrome), it was withdrawn in 1983.[10] Other compounds from this class that have been withdrawn or failed to enter the market include alaproclate, ifoxetine, tiflucarbine, indalpine (agranulocytosis), and viqualine (nausea).

The first compound of the SSRI class that was introduced and remained on the market in Europe was fluvoxamine (1983). In the United States, it was fluoxetine (1988)[11,12] Since then, various SSRIs, such as sertraline and paroxetine, have entered the market. Many others are still under development, such as citalopram (approved in Europe but not yet in the United States), cericlamine, femoxetine, cyanodothiepin, and litoxetine. Although launched as breakthrough drugs due to their favorable side effect profiles compared to the classical antidepressants that preceded them, SSRIs are considered by some to be better characterized as modest, though welcome, advances in the treatment of depression.[13] That is, SSRIs appear to be no faster in onset nor any more robust in the treatment of depression than TCAs. In fact, some investigators, particularly in Europe, believe that in the subpopulation of melancholic depressed patients, especially inpatients, SSRIs may even be inferior to other antidepressants.[14–16]

One drawback of the SSRIs is their potent inhibition of the liver cytochrome P450 isoenzymes 2D6 and in some cases 3A3/4. This may be the basis of numerous interactions with psychotropic compounds such as neuroleptics, β-adrenergic-blocking drugs, and TCAs, as well as many other drugs metabolized via these isoenzymes, including terfenidine, astemizole, certain benzodiazepines, erythromycin, ketoconazole, and others.[17] Another bothersome drawback of the SSRIs is their frequent association with sexual dysfunction, which can interfere with long-term compliance.

The majority of antidepressant clinical trials of SSRIs have been conducted with outpatients suffering from major depression of a moderate intensity. Perhaps the greatest number of trials have been conducted with fluoxetine. Various doses have been tested in dose-ranging studies—5 mg, 10 mg, 20 mg, 40 mg, and 60 mg/day[18,19]—with no clear dose-response relationship. This lack of a definitive dose-response curve is a typical finding with antidepressant trials in general and with SSRIs in particular. For example, approximately 55% to 65% of all patients were responders in the entire dose range of fluoxetine tested. Response to fluoxetine cannot be related to plasma levels of fluoxetine.[20] If patients treated for 3 weeks do not

respond to 20 mg/day of fluoxetine, a dose increase to 60 mg/day is no more effective than continuous treatment at 20 mg/day.[21]

Since fluoxetine, sertraline, and paroxetine have been reviewed repeatedly, data from such studies will not be reviewed extensively here.[22] In a meta-analysis of 63 randomized, controlled trials comparing a variety of SSRIs with TCAs, the overall efficacy of both classes of drugs was comparable.[23] The total dropout rate in both groups was also comparable (32% to 33%); however, slightly more patients dropped out due to adverse events during therapy with TCAs (18.8%) compared with SSRIs (15.4%). The SSRIs are definitely less toxic in overdose compared with the TCAs.[24] In general, SSRIs also seem to be better tolerated than TCAs, although their main drawback is the high incidence of gastrointestinal side effects, especially nausea. Furthermore, complaints about sexual dysfunction seem to occur all too frequently.

In a primary care setting, these compounds seem to be ideal for the general practitioner to prescribe. The concern of primary care providers in treating depression with a TCA seems to have all but disappeared with the release of the SSRIs and their improved safety and tolerability profiles. The continuing problem is that the diagnosis of depression is still unrecognized in many cases, and only a small fraction of patients needing treatment with antidepressants are treated adequately.[25,26]

Citalopram. Citalopram, an SSRI on the market in several European countries, is the most selective SSRI currently available but is not widely known in the United States, as it is still in development.[27] In controlled trials versus an active drug, the efficacy of citalopram seems to be equal to the tetracyclic compound mianserin or to amitriptyline and various other TCAs. However, published reports are somewhat incomplete, patient numbers are low, and placebo controls are often lacking.[28,29] Firm conclusions from these trials, therefore, cannot be drawn. Well-designed, placebo-controlled trials are currently in progress in the United States.

One published study of 149 elderly depressed patients with or without concomitant dementia reports that citalopram (10-30 mg/day) reduced the mean Hamilton Rating Scale for Depression (HAM-D) score from 22 at baseline to 12 after 6 weeks of treatment, which was significantly better than the reduction in mean HAM-D score for patients taking placebo (22 to 16).[30] Patients suffering from poststroke depression also seem to be responsive to citalopram treatment. In a double-blind, placebo-controlled, 6-week trial in 66 patients, citalopram (10–40 mg/day) reduced scores on the HAM-D significantly over placebo.[31]

In a recent trial using a relapse design, citalopram showed efficacy during long-term treatment. However, there were methodological weaknesses to this study, such as the absence of a prospective definition of the primary endpoint.[32]

Table 2. Serotonergic Agents Recently in Development (Not Marketed in the U.S.)

Mechanism[a]	Agent	Status/Comments
5-HT + NE reuptake blockade	Venlafaxine SR	Oral sustained release formulation
	Milnacipran	
5-HT_2 antagonist + 5-HT reuptake blockade	Nefazodone	New Indications
	YM-992	Phase I
5-HT reuptake enhancer	Tianeptine	Phase II
5-HT + DA reuptake blockade	Minaprine	Phase II
	Bazinaprine	Uncertain
Pure 5-HT_2 antagonists	Ritanserin	Discontinued for depression
		Phase II for other indications
	Amesergide	Discontinued
5-HT_2/5-HT1A antagonists	BMS 181, 10.1	Discontinued
	Adatanserin	Uncertain
	FG 5893	Uncertain
	BIMT-17	Phase II
Other 5-HT	KW-6055	Uncertain
	PMD145	Uncertain
	SP-186	Uncertain

[a]5-HT = 5-hydroxytryptamine (serotonin), NE = norepinephrine, DA = dopamine.

To date, additional placebo-controlled studies on the efficacy and safety of citalopram as well as comparisons with other SSRIs are not yet published. Clear data on dose-response relationships and plasma are still missing, and the exact place of citalopram within the class of SSRIs is open to further discussion.

Dual Mechanisms (Serotonin Plus)

Drugs with a second mechanism besides the inhibition of serotonin reuptake are being developed as well[2,33–35] (Table 2). The extent to which a second mechanism is responsible for the efficacy of these drugs is still unknown. Claims of superiority over other compounds, such as an earlier onset of action, should be generally regarded as premature or methodologically weak.

Venlafaxine is a mixed uptake inhibitor. In addition to inhibiting the reuptake of serotonin, it also inhibits the reuptake of norepinephrine and, to a lesser extent, dopamine.[2,36] In a recent double-blind trial in hospitalized patients suffering from major depression with melancholia, the efficacy and safety of venlafaxine (200 mg/day) and fluoxetine (40 mg/day) were compared during 6 weeks of treatment.[37] Sixty-seven patients qualified for the intent-to-treat analysis. Although it was unclear whether the primary endpoints were defined in advance, significantly more patients responded to venlafaxine than to fluoxetine, using a decrease of 50% or more on the Montgomery-Asberg Depression Rating Scale (MADRS) (76% vs 47%) or on the HAM-D (76% vs 41%) or a Clinical Global Impression (CGI) improvement of 1 or 2 (76% vs 47%) as the responder definition.

This result supports the general conception by some investigators mentioned above that SSRIs are not the agents of first choice in severe depression. The SSRIs' lack of a

rapid onset of effect, lack of a robust effect, and possible inferior efficacy to TCAs in severe depression cause some clinicians to seek a better compound and to propose venlafaxine as such an agent.

In a placebo-controlled study of sufficient power in 312 depressed outpatients receiving three different doses, venlafaxine proved to be effective and safe.[38] In a 1-year study of 149 patients (completers), venlafaxine appeared to be well tolerated and safe.[39]

Adjustment to lower doses of venlafaxine in patients with renal impairment is recommended if creatinine clearance reaches values below 30 mL/min.[40] The compound forms a metabolite of almost equal activity, higher plasma concentrations, and longer half-life compared with the parent compound.[41]

Finally, claims or suggestions that venlafaxine has an early onset of action are not supported by studies using methodology acceptable to regulatory agencies throughout the world. Notably, some analyses of venlafaxine's onset of antidepressant action have been conducted post hoc and are therefore of limited value.

Milnacipran also has a dual mechanism, namely inhibition of both serotonin and norepinephrine reuptake,[42] similar to venlafaxine. Its preliminary efficacy was demonstrated in a double-blind, placebo-controlled pilot study in 58 hospitalized patients.[43] In a small, placebo-controlled, 5-week study in 58 inpatients, milnacipran was statistically superior to placebo from Week 2 onwards.[44] In a larger, double-blind, controlled trial, two different doses of milnacipran (25 mg b.i.d. and 50 mg b.i.d.) were compared with 75 mg amitriptyline b.i.d. in a total of 144 depressed inpatients during 4 weeks.[45] Early dropouts in the first 2 weeks of treatment (13) were not included in the statistical analysis. During the first 2 weeks, amitriptyline was significantly superior to both doses of milnacipran. At the endpoint of the study, the decrease in HAM-D scores was comparable in the amitriptyline group and the highest-dose group of milnacipran. Dropouts due to adverse events were comparable in all three groups. The absence of placebo, the relatively small patient numbers per group, and the omission of an appropriate intent-to-treat analysis of all subjects, rather than just those who did not drop out by week 2, all combine to make it difficult to assess whether milnacipran will ultimately prove to be a good antidepressant.

A third antidepressant that inhibits both serotonin and norepinephrine uptake is duloxetine. Although some data suggest preliminary evidence of efficacy in major depressive disorder, too little is yet published on this compound to determine its safety and efficacy profile. It has also been reported to have been dropped from further clinical development in depression.

Nefazodone is an antidepressant with potent antagonist properties at serotonin-2 receptors and weaker serotonin reuptake blocking properties.[2,35] Nefazodone in two dose ranges (50–250 mg/day and 100–500 mg/day) was compared to imipramine (50–250 mg/day) and placebo in a 6-week, double-blind, comparison trial.[46] One hundred eighty outpatients suffering from major depression were randomized to one of the four arms. One hundred fifteen patients (64%) completed the trial. The high-dose group of nefazodone (endpoint mean, 460 mg/day) and the patients taking imipramine had a significantly greater reduction on the HAM-D compared with placebo. In total, 57% of patients taking high-dose nefazodone responded, 49% of those taking imipramine, 35% of patients taking low-dose nefazodone (endpoint mean, 214 mg/day), and 31% of patients in the placebo group.

A significantly larger percentage of patients reported adverse events in the high-dose nefazodone group than in the placebo group: orthostatic symptoms (14%), constipation (27%), dry mouth (30%), blurred vision (14%), and visual disorder (16%). Although the side effect profile was clearly better than that of imipramine, direct comparisons with SSRIs are lacking. It may be that nefazodone causes less sexual dysfunction than SSRIs, but this must await direct head-to-head comparisons prior to being established. Preliminary findings are indeed encouraging.[47]

Tianeptine is a compound on the market in Europe that acts via a paradoxical mechanism of action. It inhibits adenylate cyclase stimulation induced by 5-HT in the same way fluoxetine does, but it also stimulates serotonin uptake.[48] Tianeptine has been tested in double-blind trials versus amitriptyline in a variety of patients suffering from depression, dysthymia, anxiety, or alcoholism.[49–51] At endpoint, both drugs were equal in efficacy. Several open trials have given hints of tianeptine's efficacy in depression and melancholia.[52,53] Long-term treatment (up to 6 months) appears to be safe.[54] Because these trials were either not statistically powered or lacked a placebo control, and they were conducted in patients suffering from various states of depression, a clear answer as to whether this drug is effective in major depression cannot yet be given.

Minaprine is another compound with a dual mechanism of action. It facilitates both serotonergic and dopaminergic neurotransmission through an unknown mechanism.[55] Minaprine in two fixed doses (100 mg b.i.d. or t.i.d.) was compared with imipramine (50 mg t.i.d.) in a double-blind trial.[56] At 6 weeks of treatment, the number of responders on imipramine was 42%, on low-dose minaprine 50%, and on high-dose minaprine 33%. The same pattern of inverse dose response was suggested by the reduction of scores on the HAM-D, where low-dose minaprine and imipramine reduced the score more than high-dose minaprine did, although the differences did not reach statistical significance. This was probably due to the fact that the study seemed to be underpowered (36–38 patients in each treatment group). However, in an earlier placebo-controlled trial, minaprine at 300 mg/day did not show efficacy at lower doses.[57] Minaprine 100 mg b.i.d. and 200 mg q.d.

Table 3. Serotonin 1A Agonists Recently in Development (Not Marketed in the U.S.)

Agent	Status/Comments
Transdermal buspirone[a]	New Formulation
Gepirone	Licensed; Phase II
Tandospirone	Discontinued U.S.; Phase III Japan
Ipsapirone	Discontinued
CP93-393[a] (sunepitron)	Phase II; May also be α_2 antagonist
Zalospirone	Phase II
Flesinoxan	Phase III
Metanopirone	Phase II

[a]Most promising for U.S. marketing.

compared to amitriptiline 25–50 mg t.i.d. in a double-blind trial of 6 weeks duration in 144 outpatients suffering from major depression decreased the HAM-D from 23 to 11 in each of the treatment arms.[58] The same results have been shown in a study with fewer patients.[59] Although these data suggest that low-dose minaprine might be an effective antidepressant, the absence of methodologically sound, placebo-controlled trials and the small number of patients treated in each arm does not allow a firm conclusion.

A drug similar to minaprine is bazinaprine. Its spectrum of activity is comparable to minaprine, but definitive clinical trials are not yet complete.

5-HT_{1A} Agonists

Drugs with selective affinity for the serotonin 1A (5-HT_{1A}) subtype include buspirone, gepirone, tandospirone, ipsapirone, CP93-393 (sunepitron), zalospirone, and flesinoxan (Table 3). These compounds seem to be effective in both anxiety as well as in depression.[60–64] Down-regulation of 5-HT_{1A} receptors is possible with SSRIs as well as with the 5-HT_{1A} ligands,[2,8,65] which may explain why both classes of agents are apparently effective antidepressants.

For example, in a 4-week, fixed-dose study of ipsapirone, 7.5 mg t.i.d., compared with placebo in 34 patients suffering from neurotic depression, HAM-D scores from Week 1 onwards decreased significantly more in the ipsapirone group than in the placebo group.[66] Data from placebo-controlled trials in depression and melancholia seem to indicate that various other 5-HT_{1A} ligands indeed possess antidepressant efficacy.[64,67–70] However, development of ipsapirone stopped in 1996. The development of metanopirone stopped in 1994. To date, the only results of treatment with flesinoxan that have been published are the results of an open trial in a small number of refractory depressed patients.[71] However, the preclinical profile of flesinoxan also indicates that the drug might indeed be a putative antidepressant.[72]

To summarize, there is evidence suggesting 5-HT_{1A} ligands are effective and safe in major depression. Various double-blind trials are currently underway using controlled release formulations of these drugs, such as a transdermal formulation of buspirone. The place of the 5-HT_{1A} ligands compared to SSRIs and to TCAs will be evaluable in the near future.

5-HT_{2A} Antagonists

In depressed states, up-regulation (increased density) of 5-HT_{2A} receptors has been reported (Table 2).[73,74] Ritanserin, a selective 5-$HT_{2A/2C}$ antagonist has been called a powerful "thymosthenic" agent and has been reported to restore normal sleep patterns from the sleep disturbances (increase of slow wave sleep) seen in dysthymic patients.[75] These findings could not be reproduced in patients suffering from major depression.[76] The clinical meaning of restoring slow wave sleep in dysthymic patients remains open for speculation.

In a small, double-blind study, ritanserin was compared with amitriptyline in depressed patients suffering from headache.[77] Both drugs seem to be equally potent in reducing depressive symptomatology and headache. However, the small numbers and the absence of placebo in this trial of a patient group that is traditionally known to be highly sensitive to placebo effects does not allow any firm conclusions to be made from this study. Data on the efficacy and safety of ritanserin in dysthymia have been published, but data on major depression or melancholia are lacking.[78] Therefore, it cannot yet be conclusively stated that this compound is an antidepressant. In fact, clinical development studies for this compound are no longer focusing on depression; a full clinical development program in cocaine and alcohol abuse is ongoing.[79,80]

Other 5-HT Mechanisms

In addition to ligands with selective affinity for only one receptor, there are drugs under development with mixed affinities for various serotonergic receptors, such as 5-HT_{1A} agonism combined with 5-HT_2 antagonism (adatanserin, FG 5893, BIMT-17) (Table 2). Clinical data on the efficacy and safety of these compounds as antidepressants are not yet available.

Another way to increase serotonin availability in the brain is through the administration of serotonin precursors. Various compounds have been identified that increase brain concentrations of serotonin and sometimes concentrations of norepinephrine or dopamine. Some compounds are only known by their code names, such as KW-6055, PMD-145, and SP-186. Tramadol and triptosine have been under development since the 1980s for the treatment of depression, but data on clinical trials have not been published to date.

THE REVERSIBLE INHIBITORS OF MONOAMINE OXIDASE A (RIMAs)

Irreversible and nonspecific inhibitors of monoamine oxidase were the first modern antidepressants introduced

Table 4. Antidepressants Acting on Various Neurotransmitter Systems Recently in Development (Not Marketed in the U.S.)

Mechanism	Agent	Comments
RIMA[a]	Moclobemide	Discontinued in U.S. Marketed in Europe
	Brofaromine	Discontinued
	Cimoxatone	Uncertain
	RS-8359	Uncertain
	Befloxatone[b]	Phase II
	Toloxatone	Uncertain
Other	Acetyl-L-Carnitine	Phase II
	S-Adenosyl-methionine	Phase II
	DHEA (dehydroepiandrosterone)	Phase II
	Inositol	Phase II

[a]RIMA = Reversible inhibitor of monoamine oxidase A.
[b]Most promising for U.S. marketing.

in the 1950s.[81] However, after initial success, these drugs have become second-line drugs relative to the TCAs and SSRIs, due to the poorer tolerability of monoamine oxidase inhibitors (MAOIs) compared with other available classes of antidepressants.[82] That is, in order to avoid potentially dangerous elevations of blood pressure, patients taking MAOIs must keep a restricted diet of low tyramine and avoid numerous other drugs to prevent drug interactions. Even patients who keep these dietary and drug restrictions (and thus avoid dangerous hypertensive episodes) may still experience other unacceptable side effects, such as orthostatic hypotension, sexual dysfunction, and insomnia. These all contributed to the decline of MAOI use in the 1970s.

The discovery that monoamine oxidase exists in two isoenzymes, MAO-A and MAO-B, led to the development of more selective inhibitors.[83–85] Furthermore, new MAO-A inhibitors such as moclobemide, brofaromine, cimoxatone, RS-8359, befloxatone, and toloxatone are all reversible (Table 4).

Novel RIMAs do not interact with dietary tyramine, although caution must still be used to avoid interactions with SSRIs or venlafaxine in order to prevent the potentially fatal "serotonin syndrome." This syndrome includes such initial symptoms as tremor, hypertonicity, myoclonus, and autonomic dysfunction, which can then progress to hallucinations, hyperthermia, and finally death. Caution is also needed when RIMAs are used in combination with over-the-counter agents such as cimetidine or nasal decongestants as well as with meperidine.[86,87] Although evidence has been published in support of brofaromine's efficacy and safety in depression, including resistant forms, the development of this drug has been discontinued.[88–90]

To date, most clinical data on RIMAs has been published on moclobemide.[91,92] Moclobemide has been tested in various placebo-controlled trials. Its efficacy in the dose range 300–600 mg/day seems to be no different than fluoxetine's (20–40 mg/day), and its overall side effect profile was comparable, although more patients on moclobemide complained about sleep problems, due to its activating effect.[93] The same results were obtained in a comparison with fluvoxamine.[94]

In a large, placebo-controlled trial, 490 patients suffering from major depression were treated with imipramine (up to 200 mg/day) and moclobemide (100–600 mg/day) in a flexible-dose design.[95] Approximately 30% dropped out. The efficacy analysis showed that both active arms decreased the HAM-D in a comparable way and significantly more than did placebo. However, a specification of the population analyzed (completers, intent-to-treat analysis) was not given.

In 129 inpatients suffering from severe depression ("endogenous depression"), moclobemide (300–600 mg/day) decreased scores on the HAM-D by the same amount as clomipramine (100–200 mg/day) did.[96]

Various controlled trials have indicated that RIMAs might be effective and safe in social phobia and panic disorder, in addition to depression.[97–99]

The various concerns associated with the use of MAOIs may be overcome by the availability of RIMAs. As to whether these compounds will be efficacious in treating major depressive disorder or even various subtypes of depression or treatment-resistant cases remains to be seen. The MAOI diet may become a thing of the past if these compounds gain acceptance and begin to replace the traditional MAOIs. Only time and more clinical trial data will address these issues. As moclobemide has been dropped from further development in the United States, befloxatone may be the most likely RIMA to enter the U.S. market.

NORADRENERGIC AGENTS

Although there is a wealth of information that implicates monoamine dysfunction in the etiology of depressive illness, there is still disagreement as to what role, if any, norepinephrine plays in depression. Norepinephrine, 5-HT, and dopamine have each been studied, and research suggests that there is likely no single abnormality, nor any simple biochemical abnormality that can account for the syndrome of major depressive disorder.

Thus, pharmacologic mechanisms targeting the noradrenergic system are also rational possibilities for new antidepressants (Table 5). This thinking includes several different strategies: selective inhibitors of norepinephrine reuptake, agonists and antagonists of adrenergic receptor subtypes, and modulators of adrenergic second messenger systems.

Noradrenergic Selective Reuptake Inhibitors

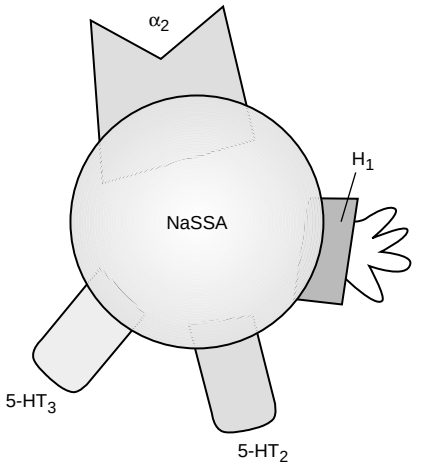
No truly selective inhibitor of noradrenergic reuptake has advanced very far into clinical trials in the United States. The norepinephrine selective agent reboxetine is currently in clinical testing and approved in the U.K. The marketed agents bupropion, maprotiline, and desipramine

Table 5. Noradrenergic Agents Recently in Development (Not Marketed in the U.S.)*

Mechanism	Agent	Comments
NE reuptake inhibition	Org 4428	Discontinued
	155U88	Phase I
	Reboxetine	Phase III; approved in UK
Pure α_2 antagonist	Idazoxan	Discontinued
	Fluparoxan	Discontinued
α_2 Antagonist plus	Mirtazapine[a]	Aug 1996 US approval
	A-75200	Discontinued
Second messenger	Rolipram	Phase II
β Agonist	Flebuterol	Uncertain
	SR 46349	Phase I
	SR 57227	Phase I
	SR-58611	Phase I
α_1 Agonist	SDZ-NVI-085	Uncertain
Adrenergic transmitter releaser	Pipoxazole	Uncertain
NE/DA reuptake inhibition	Bupropion SR[a]	Oral sustained release formulation

*Abbreviations: NE = norepinephrine, DA=dopamine.
[a]Most recent antidepressants approved in the U.S.

Figure 1. Noradrenergic and Specific Serotonergic Antidepressant*



*Adapted from reference 2, with permission. Mirtazapine (Remeron) is designated as a noradrenergic and specific serotonergic antidepressant (NaSSA). This designation derives from its unique pharmacology. Thus, α_2 antagonism accounts for both its pro-adrenergic properties (Figure 2) and its pro-serotonergic properties (Figures 3 and 5). Additionally, serotonin 2 (5-HT_2) and serotonin 3 (5-HT_3) receptors are blocked, with the net actions of the enhanced 5-HT release being more specifically directed to other serotonin receptors, particularly 5-HT_{1A} receptors (see Figures 3 and 5). An additional property is antihistaminergic actions (H_1).

all have some noradrenergic selectivity,[2] but they also have additional pharmacologic mechanisms. Org 4428, a selective noradrenergic reuptake inhibitor, has recently been discontinued from clinical trials. Another agent, 155U88, has dopamine and norepinephrine reuptake blocking properties and is yet to be tested in man.

Targeting Adrenergic Receptor Subtypes

Adrenoceptors are divided into three main classifications: α_1, α_2, and β. There are also additional subtypes of each, including β_1, β_2, and β_3 receptor subtypes, as well as others. Presynaptic α_2 receptors act as autoreceptors, thereby diminishing the outflow of norepinephrine from noradrenergic synapses. Thus, if an agonist binds to the presynaptic α_2 receptor, norepinephrine outflow is blocked. However, if an antagonist binds to the presynaptic α_2 receptor, norepinephrine outflow is enhanced. Thus, one approach to enhancing norepinephrine action at noradrenergic synapses is to block presynaptic α_2 receptors. The "turning on" of norepinephrine release by α_2 blockade is also known as "disinhibition."

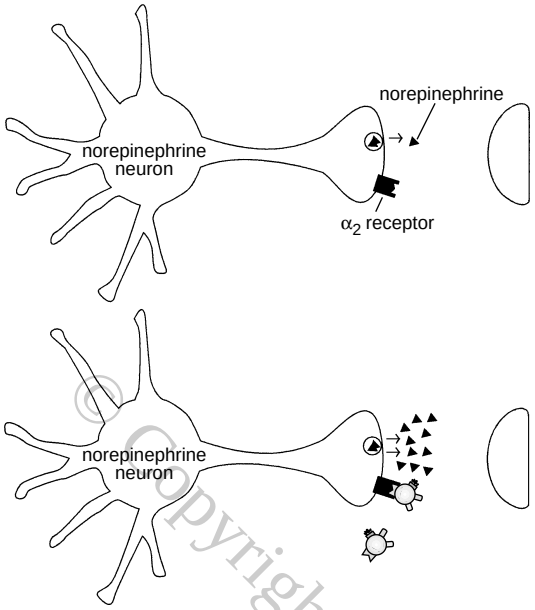
Selective agents in this class have been tested, but none has been shown to have a profile with sufficient safety and efficacy to continue in clinical testing. Those compounds with an α_2-adrenergic antagonist mechanism that remain in clinical development or practice have an additional neurotransmitter mechanism as well. The first of these is mianserin, an α_2 antagonist with 5-HT_{2A} antagonist properties, which is already marketed in Europe but not in the United States for the treatment of depression.

A related compound is an analog of mianserin, 6-azamianserin, also known as Org 3770 or mirtazapine. Mirtazapine has recently been approved for marketing in various European countries and in the United States. Mirtazapine has a unique pharmacologic profile amongst the antidepressants currently approved for marketing in the United States. Mirtazapine is a presynaptic α_2-adrenergic antagonist at noradrenergic neuronal autoreceptors and at serotonergic (5-HT) neuronal heteroreceptors, and it has low affinity for presynaptic α_1 adrenoreceptors located on 5-HT neurons.[100] This relatively selective blockade of α_2 adrenoreceptors is postulated to effectively increase central noradrenergic and serotonergic activity. In addition, mirtazapine is a potent postsynaptic 5-HT_2 and 5-HT_3 antagonist, with no significant affinity for the 5-HT_{1A} or 5-HT_{1B} receptors.[100–102] Thus, it is one of the very few known antidepressants that acts by pharmacologic mechanisms other than neurotransmitter reuptake blockade.

One way to designate the pharmacologic actions of mirtazapine is as a noradrenergic and specific serotonergic antidepressant (see Figure 1). The predominant antidepressant action of mirtazapine may well be a result of its α_2-adrenergic antagonist properties. This has implications not only for noradrenergic functioning, but also for serotonergic receptor functioning (see Figures 2–5). That is, blocking α_2 receptors on noradrenergic neurons disinhibits the noradrenergic neuron, thus causing norepinephrine release. This action occurs because the α_2 receptors normally function as autoreceptors (Figure 2, top). When they are blocked by mirtazapine, they no longer shut off NE release; thus NE release is enhanced (Figure 2, bottom).

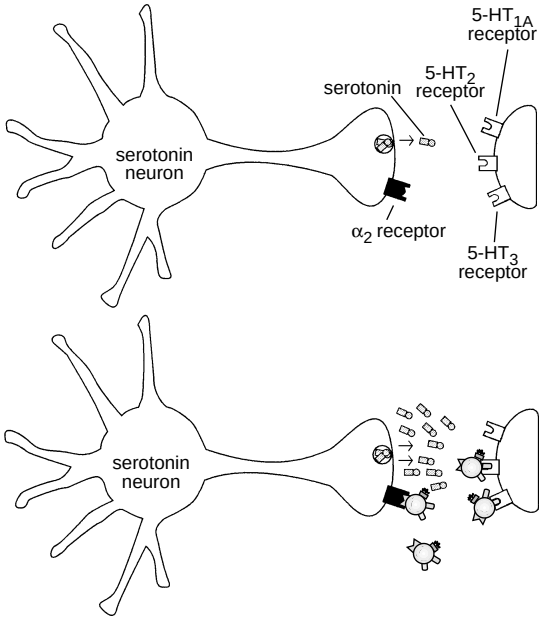
Interestingly, there are also α_2 receptors on serotonin nerve terminals, called terminal heteroreceptors (Figure 3, top). The release of 5-HT is inhibited when norepineph-

Figure 2. Norepinephrine Release and Disinhibition*



*Adapted from reference 2, with permission. Norepinephrine release is regulated by α_2 receptors on axon terminals (top). Normally, norepinephrine acts as an agonist when its levels build up, shutting off its own release (negative feedback). However, if α_2 receptors are blocked by mirtazapine, norepinephrine can no longer shut off its own release, and synaptic levels of norepinephrine are increased (bottom). This is also known as disinhibition.

Figure 3. 5-HT Release Inhibition and Mirtazapine Block of α_2 Receptors*



*Adapted from reference 2, with permission. Serotonin neurons have α_2 receptors on their axon terminals (top), just like the norepinephrine neurons shown in Figure 2. This is so norepinephrine input from neighboring norepinephrine axons can inhibit 5-HT release (top). However, if mirtazapine blocks these α_2 receptors, norepinephrine can no longer inhibit 5-HT release, and synaptic concentrations of 5-HT are enhanced (bottom). Even though 5-HT levels are enhanced, 5-HT actions are directed to the 5-HT$_{1A}$ postsynaptic receptor, because mirtazapine simultaneously blocks 5-HT$_2$ and 5-HT$_3$ receptors. This may account for lower sexual dysfunction and lower gastrointestinal side effects of mirtazapine. It is this emphasis of 5-HT itself on the remaining 5-HT$_{1A}$ receptors that can be considered "specific serotonergic."

rine binds to the α_2 receptors located on the 5-HT neurons. Thus, when mirtazapine blocks the α_2 terminal hetero-receptors on 5-HT neurons, 5-HT release is enhanced by disinhibition of the 5-HT neuron (Figure 3, bottom).

A second mechanism relates to the fact that NE controls the firing rate of 5-HT neurons (Figure 4). Specifically, NE *increases* the firing rate of 5-HT neurons when it binds to the α_2 adrenoreceptors located on 5-HT neuronal cell bodies and dendrites (Figure 5).

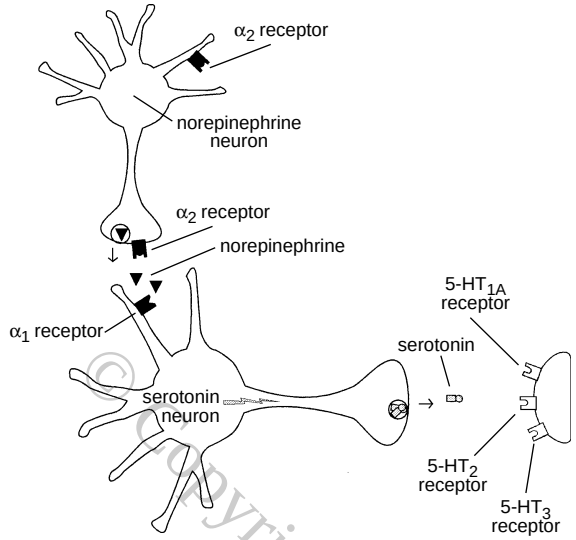
Therefore, mirtazapine increases the release of NE and 5-HT from the neurons by two mechanisms. The high affinity of mirtazapine for the presynaptic α_2 receptors on NE and 5-HT axon terminals prevents NE from binding to these receptors and inhibiting the release of NE and 5-HT (Figures 2 and 3). Mirtazapine is thus said to "disinhibit" both NE and 5-HT neurons.

On the other hand, the low affinity of mirtazapine for α_1 receptors on the 5-HT neuronal cell body and dendrites allows NE to bind to this receptor and thereby increases the firing rate of the 5-HT neuron (Figures 4 and 5). These mechanisms are postulated to increase both noradrenergic and serotonergic activity in the central nervous system.

Note, however, that the net effects of mirtazapine increasing synaptic 5-HT at 5-HT postsynaptic receptors is unlike the net effects of SSRIs increasing synaptic 5-HT at 5-HT postsynaptic receptors. Whereas SSRIs increase 5-HT at every available 5-HT receptor subtype, mirtazapine's other properties cause 5-HT actions at 5-HT$_2$ and 5-HT$_3$ receptors to be blocked (Figures 3 and 5). This should cause a preferential agonist action at the remaining 5-HT receptor subtypes, especially at 5-HT$_{1A}$ receptors (Figures 3 and 5). Mirtazapine's blockade of 5-HT$_2$ and 5-HT$_3$ receptors is postulated to explain the absence of the serotonergic side effects associated with nonselective 5-HT receptor activation by SSRIs. This may also contribute to the anxiolytic and sleep-enhancing properties of mirtazapine.[101] In addition, this should make mirtazapine cause less sexual dysfunction than the SSRIs (like nefazodone, which also blocks 5-HT$_2$ receptors and produces less sexual dysfunction). Mirtazapine should also cause less nausea and gastrointestinal complaints mediated by 5-HT$_3$ receptor stimulation, acting like the pure 5-HT$_3$ antagonists such as ondansetron.

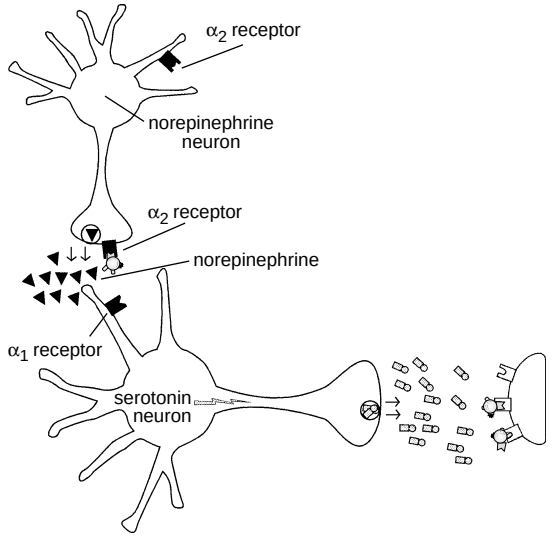
Finally, the antihistaminergic properties of mirtazapine probably do not contribute to its therapeutic efficacy as an antidepressant, but they may mediate the properties of weight gain and sedation. Sedation may be helpful for patients with insomnia associated with depression. Mirtazapine's antihistaminergic properties may account for the

Figure 4. Serotonin Release Caused by Norepinephrine Stimulation*



*Adapted from reference 2, with permission. Norepinephrine neurons innervate serotonin neurons. The connection between them is an α_1 receptor on the serotonin neuron. It is an excitatory connection, so that norepinephrine stimulation of this receptor will cause the postsynaptic 5-HT neuron to release serotonin (see also Figure 5).

Figure 5. The Action of 5-HT on Postsynaptic 5-HT$_{1A}$ Receptors by Mirtazapine*



*Adapted from reference 2, with permission. When mirtazapine blocks α_2 receptors on norepinephrine neurons, it causes norepinephrine release, just as depicted earlier in Figure 2. When that norepinephrine release occurs at the connection between a norepinephrine neuron and a 5-HT neuron, this also causes the release of 5-HT. This is because norepinephrine release onto 5-HT neurons stimulates a postsynaptic α_1 receptor, which in turn causes increased neuronal firing and release of 5-HT. Note, however, that 5-HT release does not affect all postsynaptic 5-HT receptors. Just as demonstrated in Figure 3, mirtazapine simultaneously blocks 5-HT$_2$ and 5-HT$_3$ receptors, leaving a more specific action of 5-HT on postsynaptic 5-HT$_{1A}$ receptors.

somewhat surprising lack of activating properties ordinarily associated with pure α_2-adrenergic antagonism and NE release.

In a 6-week, double-blind, placebo-controlled trial, Claghorn and Lesem found mirtazapine to be more effective than placebo in treating the symptoms of major depression in an adult outpatient group.[103] In this study, drug versus placebo differences were evident at Week 1 utilizing an analysis of the number of patients who attained at least a 50% reduction in HAM-D scores. By Weeks 2 and 3, two to three times as many patients treated with mirtazapine as placebo-treated patients met the 50% drop in HAM-D criteria, although this finding was lost by the occurrence of dropouts in the placebo group at Weeks 4, 5, and 6. Lack of efficacy accounted for twice as many placebo patients dropping out of the trial as mirtazapine-treated patients. The most significant adverse event was somnolence, which was reported by 28 patients in the mirtazapine group versus 2 patients in the placebo group.

In a study of sleep in six healthy volunteers, mirtazapine not only augmented sleep but also deepened sleep as shown by an increase in stage 3 sleep and a concurrent reduction in stage 1 sleep.[104] There was also a decrease in sleep latency, a reduction in nighttime awakenings, and an increase in the latency between sleep onset and the first rapid eye movement (REM) sleep epoch. These changes suggest that the compound may ameliorate the sleep disturbances in depression. Mirtazapine at a dose of 15 mg/day had a similar effect on anxiety and insomnia when compared with 10 mg/day diazepam in female patients undergoing gynecological surgery.[105] Mirtazapine's propensity to ameliorate sleep disturbance in depressed patients was evaluated in a meta-analysis of HAM-D Factor VI, which consists of Item 4 (difficulty falling asleep), Item 5 (restless or disturbed sleep during the night), and Item 6 (early morning awakening). Mirtazapine was significantly ($p < .05$) more effective than placebo in reducing sleep disturbance at all six weekly visits in short-term U.S. clinical trials (Data on file, Organon).

In this light, one can see that an antidepressant effect is desirable, but that the additional effects on sleep and anxiety are also beneficial to some patients. It will remain to be seen whether these clinical attributes hold up in larger clinical use. Several other studies have been published that document the efficacy and safety of mirtazapine as an antidepressant[103,106–109] (see Kasper[110] for a meta-analysis of European studies).

Another approach to the noradrenergic mechanism for the treatment of depression is to combine α_2 receptor antagonism with norepinephrine reuptake blockade. One such compound is A-75200, which was recently studied, but will apparently not progress further in clinical development. A-75200 is a racemic mixture. One enantiomer (RR) is an antagonist at the α_2-adrenergic receptor, while the other enantiomer (SS) is an inhibitor of norepinephrine uptake. Since this compound has a dual mechanism of ac-

tion, it is hypothesized to be capable of producing a faster onset of antidepressant action.

In one early study of A-75200, 91 patients (60 male and 31 female) meeting the DSM-III-R criteria for major depressive disorder were randomized to 8 weeks' treatment with A-75200, 60-140 mg/day, versus placebo.[111] At endpoint evaluation using the primary efficacy variable of the HAM-D, A-75200 failed to show a significant change from baseline when compared with placebo (32.6% versus 24.9%, respectively). An analysis of core depression items revealed a decrease that began at Week 1 and continued to Week 8 and was statistically significant when compared with placebo (38% versus 15.2%, $p < .02$). Adverse events included headache, myalgia, dizziness, and insomnia, with only insomnia occurring significantly more often in A-75200 than in placebo. The overall tolerability of A-75200 is thus quite good. There were no other differences noted on review of laboratory or physical examination data.[112] Future research requires trials at higher doses, but development of this compound has ceased.

Adrenergic Second Messenger Modulators

The second messenger "dysbalance" hypothesis of affective disorders suggests that the functional imbalance of the two major intraneuronal signal-amplification systems leads to affective disorders. These two systems are the adenylate cyclase and the phospholipase-C systems. This hypothesis proposes that a hypofunction of cyclic-3',5' monophosphate-mediated effector cell responses along with an absolute or relative dominance of the inositol-phosphate/diacylglycerol-mediated response will result in depression.[113–115]

Rolipram. One compound undergoing development as an antidepressant using this second messenger dysbalance hypothesis is rolipram (Table 5). Its proposed mechanism of action is via stimulation of noradrenergic neurotransmission both presynaptically and postsynaptically. Presynaptically, rolipram stimulates neurotransmission by increasing norepinephrine synthesis and release. Postsynaptically, it inhibits cyclic adenosine monophosphate decomposition, thus enhancing second-messenger concentration through inhibition of phosphodiesterase enzyme.[116,117] Rolipram displays no anticholinergic effects, no inhibition of MAO, and no reuptake blockade of serotonin, norepinephrine, or dopamine.

Several clinical trials of rolipram have been undertaken in Europe. Although these trials were relatively small and in all but one a placebo arm was not used, we will present the highlights of each trial in a brief review. In a 4-week, double-blind, active-controlled (imipramine) trial of 74 patients (38 rolipram vs 36 imipramine) with a diagnosis of major depressive disorder, rolipram 1 mg t.i.d. showed no statistically significant difference to imipramine 50 mg t.i.d. on the HAM-D at any evaluation point. No difference was shown on the CGI, with 88% of the rolipram patients and 80% of the imipramine patients showing improvement at endpoint. Frequent adverse events for rolipram included sweating, hypotension, anorexia, and headache, whereas imipramine-treated patients more frequently reported tremor and constipation.[118]

In a 4-week, randomized, double-blind, active-controlled (imipramine) trial carried out on 64 Austrian inpatients with major depressive disorder, imipramine proved to have a more favorable outcome than rolipram on the HAM-D. No difference was detected on the CGI. Adverse events included sweating and nausea for rolipram and dry mouth for imipramine-treated patients. No other differences were noted.[119]

Another small trial comparing rolipram to nortriptyline showed nortriptyline to be superior on the HAM-D and CGI, although rolipram was better tolerated. The conclusion from this trial was that both agents work as antidepressants, but rolipram 0.5 mg t.i.d. is probably too low a dose.[120]

A dose-finding trial of rolipram, 0.25 mg, 0.5 mg, and 1.0 mg t.i.d., showed no advantage at doses over 0.5 mg t.i.d.[121] Finally, two small trials of 39 and 50 patients respectively were carried out in the United Kingdom. The first trial showed no advantage over placebo on the HAM-D, MADRS, and CGI,[122] and the second trial revealed that amitriptyline had a rate of recovery greater than rolipram. In fact, twice as many patients taking rolipram dropped out due to lack of efficacy than those taking amitriptyline.[123]

Thus, although the data on rolipram appear a bit confusing, several trials show it to be as effective as TCAs. A demonstration of a specific advantage over previous therapy makes a new antidepressant acceptable and even desirable to clinicians and patients. With no demonstration of a specific advantage, rolipram needs to be studied in larger, multicenter trials comparing it to an active drug and placebo in order to make a more proper comparison of the safety, tolerability, and efficacy of rolipram.

Other Noradrenergic Mechanisms

There are numerous other compounds in development with various mechanisms of action tied into the adrenergic system. These include flebuterol (β agonist), SR-58611A (β_3 agonist), SDZ-NVI-085 (α_1 agonist), and pipoxazole (adrenergic transmitter releaser) (Table 5). Although there are numerous compounds listed here, it is still too early to obtain an overall impression of their safety, tolerability, and efficacy, because publication of trial data by sponsors is limited.

OTHER NEUROTRANSMITTER MECHANISMS

Acetyl-L-carnitine has a chemical structure similar to acetylcholine (Table 4). It stimulates the muscarinic cholinergic neurons in the same way acetylcholine does.[124] In

open trials this compound decreased depression scores in elderly demented patients. In a placebo-controlled trial, 60 senile patients with dysthymic disturbances according to DSM-III were treated over 60 days.[125] Acetyl-L-carnitine decreased the HAM-D significantly more (from 22 to 11) than placebo did (from 21 to 20).

S-adenosyl-methionine (SAM) is a methyl group donor in the biosynthesis of phospholipids. The role of this mechanism or related mechanisms in the treatment of depression remains speculative. This compound has been tested in depression since the 1970s.[126] Several small uncontrolled and placebo-controlled trials suggest that SAM might be useful in depression.[127,128] However, methodologically sound trials including sufficient patients and comparing SAM with placebo and active reference compounds have not been published yet.

CONCLUSION

As research continues to reveal the neurophysiologic mechanisms of psychiatric illness at cellular and molecular levels, more treatments will become available. Antidepressants in development are being defined from various classes with different mechanisms of action. The serotonergic agents dominate the field (e.g., there are more than 10 5-HT_{1A} agonists in various stages of development). Of the seven α_2 adrenoceptor antagonists recently in development, at least four have been discontinued. The point to remember here is that the field is in a constant state of transition. One may attempt to keep track of developments on a case-by-case basis. This may prove to be impossible due to the number of agents in development. It may be far easier to try to focus on an entire class of agents and the data on efficacy and tolerability as development proceeds.

Due to these developments, the section of most reviews on future treatments now called "other treatments" will continue to diversify and expand. There are already numerous preclinical publications regarding work in progress with compounds that do not fall into any of the previously mentioned categories. These compounds are being tested in animal models of psychiatric illness in hopes of identifying new potential treatments and providing a better understanding of the nature of these illnesses.

PROFILE OF THE IDEAL ANTIDEPRESSANT

Given the recent entry of numerous new antidepressants into clinical practice, researchers are becoming increasingly aware that all the new antidepressants so far discovered have failed to surpass the plateau of efficacy exhibited by the classical antidepressant agents (TCAs and MAOIs). Since the newer antidepressants have generally improved side effect profiles, there is increasing pressure to identify a new antidepressant that exhibits enhanced efficacy. Here we will mention various problems in developing an ideal antidepressant and leave it up to the reader to decide how much of this is feasible and how much has been driven by marketing forces, clinical forces, regulatory forces, or economics.

The first item on this wish list is a *rapid onset of efficacy*. Data have shown that following the ingestion of an antidepressant, a synaptic effect occurs within hours, but the antidepressant effect is often not seen for several weeks. The expected delay in efficacy for any antidepressant is between 10 days to 3 weeks at therapeutic doses. The ability to shorten the lag time between initiation of treatment and response would be very desirable. A decrease in suffering and a decreased risk of suicide for patients and financial benefits to society from decreased length of hospitalizations are just a few of the reasons why everyone pursues this "Holy Grail" of antidepressant psychopharmacology.

Data have been presented on venlafaxine that suggest that it may indeed have a rapid onset of action.[129] This was proposed on the basis of results from two placebo-controlled trials that employed rapid escalation of doses to 200 mg/day or more. In the first study,[129] which was conducted in severely depressed patients with melancholia, venlafaxine was shown to have a statistically significant advantage over placebo on the MADRS after 4 days of treatment and on the HAM-D after 1 week of treatment. A second study[129] conducted in outpatients with major depression indicated that there was a statistically significant difference from placebo at Week 1, and this difference was sustained throughout the study. In addition, the highest dose of venlafaxine (375 mg/day) reached statistical significance on all parameters (HAM-D, MADRS, and CGI-severity).

Why then did venlafaxine not obtain approval in the United States for rapid onset of effect in its labeling? The simplest answer is that there is no set standard for measuring rapid onset of action. Should response be measured as a drop on the HAM-D of 50% or to a level of less than 10 points, or should some new definition be used for such an action?

Another aspect of an ideal antidepressant would be *greater efficacy* than previous antidepressants. There are numerous problems with this requirement, as there is no agreed definition of what greater efficacy means. Is it a higher percentage than the 67% response rate of all known antidepressants when tested in a traditional clinical trial population? Is it efficacy greater than comparator agents when tested in patients who fail to respond to one or more prior antidepressant treatments? Is it efficacy greater than comparator agents in patients who have the most complex treatment situations (i.e., psychotic patients, bipolar patients, post-ECT maintenance patients, depressed patients with a second Axis I psychiatric disorder, depressed patients with a major medical disorder)? Such patients are virtually never included in clinical testing of a putative

novel antidepressant until after registration of the drug. Should this change?

An increasingly critical aspect of an ideal antidepressant is its being *cost effective*. Does this mean increased productivity at work, enhanced quality of personal life, or reduced overall health care expenditures when the new agent is used compared to a less expensive agent? Outcome studies are the current emphasis of cost-conscious managed care organizations, yet we do not have a good methodology for what to measure nor for how to apply cost accounting to such measurements. It is imperative to ask oneself: "Why would one chose to use the newest and latest compound if there is no direct indication that it is superior to the older and less expensive treatments that have preceded it?"

The answer may lie in the profile of an ideal antidepressant as a more effective medication, with rapid onset of effect, better tolerability, and ease of dosing that is cost effective compared to less expensive antidepressants.

Drug names: amitriptyline (Elavil and others), astemizole (Hismanal), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), desipramine (Norpramin), erythromycin, fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil), ketoconazole (Nizoral), maprotiline (Ludiomil), meperidine (Demerol and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), terfenadine (Seldane), venlafaxine (Effexor).

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