

Selection of an Antidepressant: Mirtazapine

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The number of antidepressants has expanded dramatically in the last decade as a result of the ability to design psychiatric medications in a rational manner. This paper provides a broad overview of these options while focusing on the most recently approved antidepressant, mirtazapine. The paper discusses the five major features that a physician needs to consider when selecting a medication for a patient: safety, tolerability, efficacy, payment, and simplicity. These five features are summarized by the mnemonic STEPS. The paper also proposes a pharmacologically based classificatory system that divides current antidepressants into eight groups based on the mechanism of action thought to underlie their antidepressant efficacy. Such a classificatory system can serve as an organizing principle for the practicing physician.

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Mirtazapine is the eighth antidepressant to be marketed in the United States in the past decade (Table 1). This explosion in antidepressant pharmacotherapy is due to the fact that drug development in psychiatry has moved from a process dependent on chance observation to one based on rational design.¹ As a result, antidepressants can be conceptually divided into pharmacologic classes based on the putative mechanism underlying their antidepressant efficacy (Table 2). This approach will be a cornerstone of this paper and can also be an organizing principle for the practicing physician who otherwise might find the rapid expansion in antidepressant options confusing.

Only a decade ago, tricyclic antidepressants (TCAs) were the only option the physician had, since virtually no one used monoamine oxidase inhibitors. TCAs for most physicians meant tertiary amine TCAs (e.g., amitriptyline, doxepin, imipramine). Secondary amine TCAs never made a substantial dent in the market, even though they were in many ways safer, better tolerated, and as effective as the older tertiary amine TCAs. Then came the serotonin selective reuptake inhibitors (SSRIs), which significantly expanded the antidepressant market. They replaced the tertiary amine TCAs as the antidepressants of first choice in the minds of many physicians, due principally to improved safety and tolerability. In rapid succession, the

three latest antidepressants have been added to the mix: venlafaxine, nefazodone, and now, mirtazapine.

The goal of this supplement is to provide background information on the preclinical pharmacology of mirtazapine and clinical trials data on its safety, tolerability, and efficacy to facilitate clinical decision making, particularly for physicians first using this drug following its release. The information contained in this supplement should help physicians decide where mirtazapine fits in their list of antidepressant options, which patients they will want initially to try on the medication, and what to expect from such a trial.

This supplement is composed of the following papers. Dr. Alan Frazer reviews the preclinical pharmacology of mirtazapine.² The safety and tolerability of mirtazapine based on clinical trials are reviewed by Dr. Craig Nelson,⁴ while mirtazapine's efficacy is reviewed by Drs. Jan Fawcett and Robert Barkin.⁵ Finally, Dr. Angelo Sambunaris and colleagues address future developments in the field of antidepressants and how mirtazapine may fit in that future.³

The individual papers in this supplement thus cover the five considerations that a physician must weigh when deciding where a medication fits in the overall armamentarium of a therapeutic area: safety, tolerability, efficacy, payment (i.e., cost effectiveness), and simplicity, which are summarized by the mnemonic STEPS (Table 3).

In this introductory paper, I will present a broad framework for conceptualizing the detailed information contained in the other papers composing this supplement.

Of course, the data on any new medication are limited to the somewhat rarefied population of patients who are eligible and agree to participate in clinical trials for drug registration. The typical inclusion and exclusion criteria that define such a population are listed in Table 4. When the medication enters clinical practice, practicing physicians are often at the edge of the existent knowledge, since they

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Table 1. New Antidepressants Marketed in the United States in the Past Decade

Generic	Trade Name	Manufacturer	Year
Fluoxetine	Prozac	Eli Lilly	1988
Bupropion	Wellbutrin	Glaxo-Wellcome	1989
Sertraline	Zoloft	Pfizer	1992
Paroxetine	Paxil	SmithKline Beecham	1993
Venlafaxine	Effexor	Wyeth-Ayerst	1994
Fluvoxamine ^a	Luvox	Solvay	1994
Nefazodone	Serzone	Bristol-Myers Squibb	1995
Mirtazapine	Remeron	Organon	1996

^aFluvoxamine is formally labeled for obsessive-compulsive disorder in the United States, although it is a serotonin selective reuptake inhibitor and labeled elsewhere in the world for use as an antidepressant.

Table 2. Classification of Antidepressants by Putative Mechanism(s) of Action Responsible for Their Antidepressant Efficacy

Serotonin and norepinephrine reuptake inhibition plus effects on multiple receptors and fast sodium channels
(e.g., amitriptyline, imipramine)

Serotonin selective reuptake inhibitors
(fluoxetine, fluvoxamine, paroxetine, sertraline)

Norepinephrine selective reuptake inhibitors
(e.g., desipramine)

Serotonin and norepinephrine reuptake inhibitors
(e.g., venlafaxine)

Serotonin (5-HT_{2A}) blockade and serotonin uptake inhibition
(e.g., nefazodone)^a

Serotonin (5-HT_{2A} and 5-HT_{2C}) and norepinephrine (α_2) receptor blockade
(e.g., mirtazapine)^a

Dopamine and norepinephrine reuptake inhibition
(e.g., bupropion)

Monoamine oxidase inhibition
(e.g., tranylcypromine, phenelzine)^b

^aBoth nefazodone and mirtazapine have additional mechanisms of action that are engaged at concentrations that occur under clinically relevant dosing guidelines. See Table 5 and text for additional actions of mirtazapine and reference 2.

^bOnly irreversible and nonselective monoamine oxidase inhibitors (MAOIs) are marketed in the United States but selective and reversible MAOIs are marketed elsewhere in the world.³

may be using the medication in specific types of patients (e.g., the medically ill) or in specific situations (e.g., in the presence of another medication) that have never been encountered before. That experience in the real world will, in large measure, determine the eventual acceptance of the medication.

As with most medications, mirtazapine has some features that will likely prove to be desirable for some patients and other features that will be undesirable for others. For the practicing physician, the issues will be what the general response to the drug is and whether there are specific patients for whom the drug is particularly helpful.

Based on its preclinical pharmacology, mirtazapine represents an interesting addition to the antidepressant armamentarium when compared with tertiary amine TCAs and SSRIs (Table 5). It both shares features and yet differs from the drugs in these two classes. Like SSRIs, it

Table 3. STEPS: Factors to Be Considered When Selecting a Medication for a Patient

Safety
Acute therapeutic index
Long-term safety
Risk of drug-drug interactions
Pharmacodynamically mediated
Pharmacokinetically mediated
Tolerability
Acute
Long-term
Efficacy
Overall response rate
Unique spectrum of activity in subpopulations
Rate of onset
Maintenance
Prophylactic
Payment (ie, cost-effectiveness)
Simplicity
Drug administration schedule
Ease of optimal dosing
Need for specific clinical or laboratory monitoring before or during treatment

Table 4. Typical Selection Criteria for Antidepressant Clinical Trials

Age 20–49 years (most patients)
No other psychiatric diagnosis
No apparent suicide risk
No psychoses
No episodes > 2 years
No active substance abuse
Medically healthy
No other medications
Safeguards against pregnancy

has a low affinity for muscarinic cholinergic receptors and α_1 -adrenergic receptors. For these reasons, mirtazapine, like SSRIs, produces minimal anticholinergic side effects and orthostatic hypotension, which are significant tolerability problems with tertiary amine TCAs. Mirtazapine, like SSRIs, venlafaxine, and nefazodone, does not inhibit fast sodium channels and thus does not slow intracardiac conduction. The inhibition of fast sodium channels is the mechanism of action responsible for the potentially fatal arrhythmias and seizures that can occur when a TCA overdose is taken.⁹ Mirtazapine, like SSRIs, venlafaxine, and nefazodone, has a wide therapeutic index and does not cause serious toxicity even when taken in a substantial overdose.⁴

While mirtazapine is similar to SSRIs and different from TCAs in the above respects, it is similar to TCAs and different from SSRIs in other respects (Table 5). SSRIs apparently have a single mechanism of action: the inhibition of the neuronal uptake pump for serotonin (5-HT).¹⁰ While they are selective in this respect, they are not selective in terms of the consequences that result from their indirect agonistic effect on the multitude of serotonin receptor subtypes in the brain. The absolute increase in serotonin availability and its duration of action at these different

Table 5. A Comparison of the Mechanisms of Action of Antidepressants Representative of Six of the Eight Classes Outlined in Table 2*

Mechanism of Action ^a	Amitriptyline	Desipramine	Sertraline	Venlafaxine	Nefazodone	Mirtazapine
Histamine-1 receptor	Yes	No	No	No	No	Yes
Acetylcholine receptor blockade	Yes	No	No	No	No	No
Norepinephrine uptake inhibition	Yes	Yes	No	Yes	No	No
5-HT _{2A} receptor blockade	Yes	No	No	No	Yes	Yes
α ₁ Norepinephrine receptor blockade	Yes	No	No	No	Yes	No
5-HT uptake inhibition	Yes	No	Yes	Yes	Yes	No
5-HT _{2C} receptor blockade	No	No	No	No	No	Yes
5-HT ₃ receptor blockade	No	No	No	No	No	Yes
α ₂ Norepinephrine receptor blockade	No	No	No	No	No	Yes

*Bupropion and monoamine oxidase inhibitors are not shown. The latter are not shown because they do not directly share any mechanism of action with any other class of antidepressants, although they affect dopamine, norepinephrine, and serotonin neurotransmission via their efforts on monoamine oxidase. Bupropion is not shown because its mechanism of action remains unclear. Its most potent action is the inhibition of dopamine and norepinephrine uptake, but it is so weak at affecting these sites *in vitro* as to raise questions as to whether these actions are clinically relevant.^{6,7}

^aThis table is divided into a binary system for simplicity using the following logic. The presumptive mechanism of action for the drug and class it represents is outlined in Table 2. The presumption is based on the preclinical pharmacology of the drug and the fact that it reaches sufficient concentration *in vivo* to affect this site of action given its *in vitro* potency. A "yes" is also designated in two other situations. First, a "yes" is given if the drug affects a site more potently than its presumptive antidepressant site of action. For example, amitriptyline is more potent at blocking the histamine and muscarinic acetylcholine receptor than inhibiting the norepinephrine uptake pump.

Second, a "yes" is given if the drug's *in vitro* potency, even though weaker than its primary mechanism mediating efficacy, is within one order of magnitude of affecting a site of action believed to be capable of mediating antidepressant activity. For example, amitriptyline's *in vitro* potency for affecting the 5-HT_{2A} receptor, the α₁ norepinephrine receptor, and the serotonin uptake pump is within an order of magnitude of its *in vitro* potency for affecting the norepinephrine uptake pump, its most potent effect on a site of action believed to be capable of mediating antidepressant response. The rationale for this approach is the pharmacologic rule of thumb that there must be more than an order of magnitude difference in *in vitro* potency to confidently state that one can achieve concentrations capable of affecting one site substantially without affecting the other. The above approach thus uses each drug as its own reference point for which of these sites of action it is likely to affect under clinically relevant dosing conditions. It thus has heuristic value in understanding and anticipating the clinical pharmacology of the drugs and conceptualizing their clinical use. The *in vitro* data for all drugs except mirtazapine were taken from references 6 and 7. The effect of the drugs, except mirtazapine, on the 5-HT_{2C} and 5-HT₃ receptors was from personal communication with Elliott Richelson, M.D. Since *in vitro* effects of mirtazapine were not measured in those studies, its data, including its effects on 5-HT_{2C} and 5-HT₃ receptors, were taken from reference 8.

serotonin receptor subtypes appear to be responsible for both the beneficial and adverse effects that can occur with SSRI treatment. The down-regulation of postsynaptic 5-HT_{2A} receptors and presynaptic 5-HT_{1D} receptors is believed to be responsible for their antidepressant efficacy, since such down-regulation occurs in a time course similar to that needed to experience an antidepressant effect.² In contrast, the stimulation of other serotonin receptor subtypes most likely accounts for the adverse effects associated with SSRIs as a class: gastrointestinal disturbance (e.g., nausea, diarrhea) due to increased serotonin stimulation of 5-HT₃ receptors and nervousness/restlessness due to increased serotonin stimulation of 5-HT_{2C} and 5-HT_{2A} receptor subtypes.¹¹⁻¹³ These theories are supported by the fact that the coadministration of drugs such as cisapride, a 5-HT₃ receptor antagonist, and trazodone, a 5-HT_{2A} receptor antagonist, can diminish these adverse effects of SSRIs in patients who are susceptible to them. This is an example of rational polypharmacy.^{14,15}

In contrast to SSRIs, mirtazapine does not inhibit the neuronal uptake pump for serotonin and thus does not indirectly stimulate these receptors. Instead, it is a direct antagonist of 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ receptors.² The blockade of 5-HT_{2A} receptors is another way to decrease pharmacologically the functional overactivity of this receptor that appears to be involved in the pathophysiology of at least some forms of major depressive disorder. The blockade of the 5-HT_{2C} receptor is consistent with the re-

lief of anxiety symptoms that was observed in the antidepressant clinical trials of mirtazapine.⁵ The blockade of the 5-HT₃ receptor not only is consistent with the low rate of nausea seen in the clinical trials of mirtazapine but also suggests that this drug could be used to diminish nausea due to excessive stimulation of this serotonin receptor subtype.⁴

In contrast to SSRIs, mirtazapine has direct effects on two central neurotransmitter systems that have been implicated in the pathophysiology of major depression: norepinephrine and serotonin.² Thus, it is a dual acting drug like venlafaxine.³ However, the mechanisms of action of these two drugs on these systems are different (Table 5). Venlafaxine works on both systems by inhibiting the uptake pump for both neurotransmitters. In contrast, mirtazapine affects the systems via specific receptor blockade: 5-HT_{2A}, 5-HT_{2C}, and α₂-adrenergic receptor blockade. This matter is discussed in detail by Dr. Frazer in his paper in this supplement.²

The fact that mirtazapine has different mechanisms of action from other antidepressants raises the possibility that it may have a different clinical spectrum of antidepressant activity, including efficacy in patients whose depressive episodes are not effectively treated by these other medications. Unfortunately, this matter remains speculative, as there are no data from well-designed studies testing this possibility. Whether such appropriately designed studies will be done in the future to test this possibility is

Table 6. Summary of the Pharmacokinetic Profile of Mirtazapine

Absolute bioavailability: 50% after single dose and at steady state
Dose-plasma drug level linearity from 15–80 mg/day
No autoinduction or autoinhibition of metabolism
Half-life: 20–40 hours
Peak plasma drug level (C_{max}) within 2 hours
No meal effect (i.e., fasted vs fed)
Half-life and area under the plasma drug level vs time curve (AUC) is greater in young males vs young females and elderly females and males. However, the difference is not sufficient to warrant different doses for these groups.
Metabolism is not principally dependent on CYP2D6 or CYP2C19
8-Hydroxylation preferred by (+)- enantiomer, quaternary glucuronidation by (-)- enantiomer
Renal impairment, moderate to severe, results in a 30% to 50% reduction in clearance and a 40% prolongation of half-life
Hepatic impairment results in a 33% reduction in clearance and approximately a 40% prolongation in half-life

unclear, but they certainly would be useful to the practicing physician.

Mirtazapine shares with tertiary amine TCAs the potent blockade of the histamine receptor.² SSRIs do not block this receptor. This mechanism of action is responsible for the sedative effect of tertiary amine TCAs and mirtazapine and the lack of direct sedative effects of SSRIs.⁴ This effect may be beneficial or adverse depending on when it occurs, its severity, and its duration.

Both mirtazapine and tertiary amine TCAs can be administered once a day at bedtime. Thus, physicians can use the sedative effect to the patients' benefit if they have insomnia. Since the sedative properties are due to direct competitive histamine receptor blockade, this effect is immediate and reversible. By administering these medications once a day at bedtime, the physician can also diminish the daytime somnolence produced by the blockade of this receptor. Nonetheless, mirtazapine and tertiary amine TCAs have sufficiently long half-lives that this effect can persist into the next day. This effect is dose dependent, so a dose adjustment may either increase or decrease its magnitude and duration.

As seen in Table 5, mirtazapine has several features in common with tertiary amine TCAs but several clinically important differences. There is an overlap in some of the mechanisms of action presumed to underlie the antidepressant efficacy of these drugs, specifically the blockade of 5-HT_{2A} and α_2 -adrenergic receptors.² Given this pharmacologic overlap, the question arises as to whether mirtazapine and tertiary amine TCAs also have a significant overlap in terms of antidepressant efficacy. Fortunately, that matter has been studied in a double-blind controlled manner.

The study was a follow-up protocol to a conventional double-blind, random-assignment study of the comparative efficacy of mirtazapine, amitriptyline, and placebo.¹⁶ At the end of this 6-week study, patients who had not been effectively treated with either placebo or amitriptyline

Table 7. Major Biotransformation Pathways Based on Urinary Excretion Profile in Man

Biotransformation Pathway	Relative Percentage	Cytochrome P450 Enzymes Mediating Specific Pathways ^a
Demethylation	25	CYP3A3/4
Hydroxylation	40	CYP2D6/CYP1A2
N (2) Oxidation	10	CYP3A3/4
N (2) Glucuronidation	25	Not applicable ^b

^aThis determination is based on in vitro studies using human hepatic microsomal preparations.⁶
^bGlucuronidation is phase II metabolism and not mediated by P450 enzymes.

were treated double-blind with mirtazapine, and conversely, patients who were not effectively treated with mirtazapine were treated double-blind with amitriptyline. The blind also was not broken in terms of the initial random-assignment treatment. The crossover treatment for nonresponders continued for 8 weeks.

Mirtazapine was as effective in treating patients who had not responded to placebo treatment for 6 weeks as it was in patients who had not responded to the 1-week placebo washout phase before the first phase of the study. However, mirtazapine was almost as effective in patients who had not responded to amitriptyline in the first phase of the study. These results suggest that mirtazapine is effective in patients whose depressive episodes have not been successfully treated with amitriptyline. In contrast, amitriptyline was less effective in patients who had not responded to initial treatment with mirtazapine. The fact that mirtazapine was better tolerated in amitriptyline-nonresponsive patients than amitriptyline was in patients nonresponsive to mirtazapine is also noteworthy. The reason for these findings is not understood at this time, and they deserve further follow-up. Regardless of the reason, these findings indicate to the practicing physician that mirtazapine is an option for patients who fail to respond to a tertiary amine TCA like amitriptyline, regardless of whether failure was due to lack of efficacy or tolerability problems.

Mirtazapine shares several pharmacokinetic benefits with the SSRIs. One is that treatment can be started at an effective dose immediately rather than having to start at a lower dose and titrate up, as is typically necessary with TCAs. Like TCAs and SSRIs, mirtazapine has desirable pharmacokinetic characteristics including a sufficiently long half-life to permit once-a-day dosing (Table 6).

The metabolism of mirtazapine is mediated by several cytochrome P450 enzymes including CYP1A2, CYP2D6, and CYP3A3/4 (Table 7). Since each of these P450 enzymes has a similar affinity for mirtazapine, the biotransformation is not principally dependent on any single P450 enzyme. This means that mirtazapine is less susceptible to a pharmacokinetic drug-drug interaction when coprescribed with a medication that is capable of inducing or

Table 8. In Vitro Inhibition of Specific Human Cytochrome P450 Enzymes by Mirtazapine in Relation to Specific Positive Controls for Specific P450 Enzyme Inhibition*

P450 Enzyme	Substrate Tested	Positive Control	Positive Control (Ki, μM)	Mirtazapine (Ki, μM)
CYP1A2	EROD	Fluvoxamine	0.18 ± 0.02	159 ± 23
CYP2D6	Bufuralol	Fluoxetine	4.08 ± 0.48	41 ± 4
CYP3A3/4	Testosterone	Ketoconazole	0.15 ± 0.03	209 ± 54

*Based on in vitro studies using human hepatic microsomal preparations from pooled liver samples from seven different individuals.¹⁷

*Concentrations of mirtazapine tested: 200 and 500 μM for CYP1A2; 25 and 200 μM for CYP2D6 and CYP3A3/4.

inhibiting P450 enzymes than drugs that are principally dependent on a single P450 enzyme for their elimination.

This issue is particularly relevant when a physician switches a patient from fluoxetine to a new antidepressant, since fluoxetine and its active metabolite, norfluoxetine, inhibit several P450 enzymes to varying degrees. Their half-lives are sufficiently long that their inhibition of these P450 enzymes persists for an extended interval (i.e., weeks to months depending on dose) after the switch has been made.¹⁰ Hence, fluoxetine can affect the tolerability of another drug by altering its clearance for a prolonged period after fluoxetine has been discontinued. The multiple pathways for the elimination of mirtazapine reduce the likelihood of a clinically meaningful interaction. Nonetheless, this possibility is being formally studied to provide physicians with better information about how to start mirtazapine when switching from fluoxetine.

Based on in vitro studies,¹⁷ mirtazapine is not a potent inhibitor of the following P450 enzymes: CYP1A2, CYP2D6, and CYP3A (Table 8). In vitro modeling based on the kinetic inhibition constant for mirtazapine for these various P450 enzymes coupled with knowledge of the plasma levels of mirtazapine achieved on therapeutic doses and the plasma:liver partition coefficient suggests that mirtazapine is unlikely to produce clinically relevant inhibition of these P450 enzymes. In contrast, the following SSRIs produce clinically meaningful inhibition of the following P450 enzymes at their usually effective doses: fluvoxamine, CYP1A2, CYP2C19, and CYP3A3/4; fluoxetine, CYP2D6, CYP2C19, and CYP2C9/10; and paroxetine, CYP2D6(10).

This issue is important because antidepressants are frequently used in combination with other medications.¹⁰ SSRIs such as fluoxetine can appreciably alter biotransformation and clearance of concomitantly prescribed drugs and thus cause a variety of pharmacokinetically mediated drug-drug interactions. The consequences range from loss of efficacy to tolerability problems to toxicity depending on the nature of the coprescribed drug (e.g., its therapeutic index) and the magnitude of the P450 enzyme inhibition produced, which is a dose (i.e., concentration) -dependent phenomenon.¹⁰ While mirtazapine appears to have a minimal risk of causing pharmacokinetic mediated drug-drug

interactions, the in vitro modeling predictions still require in vivo studies for confirmation. Such studies are ongoing.

While mirtazapine appears to have a low risk of causing pharmacokinetically mediated drug-drug interactions, it can cause pharmacodynamically mediated drug-drug interactions based on its effects on specific neural mechanisms of action. For example, mirtazapine can potentiate the effects of alcohol and sedative-hypnotic drugs such as diazepam, just like any other potent antihistaminic drug (Data on file, Organon). Patients should be warned of this interaction, particularly in situations where they need to be mentally alert.

In summary, mirtazapine is a welcome addition to the armamentarium of antidepressant options. That is particularly true since it has a different pharmacologic profile from other antidepressants. Physicians have fallen into the pattern of switching from one SSRI to another when the first one fails. There is no substantial body of literature to support this practice. Neither is there convincing evidence that different SSRIs have a different spectrum of antidepressant efficacy or a different tolerability profile.¹⁰ In fact, the available data support substantial overlap among the various members of this class. Antidepressants such as mirtazapine, venlafaxine, and nefazodone thus represent potentially more reasonable alternatives for the patient who has a depressive episode that is not responsive to the SSRI of first choice. Ideally, research should be done to test which of these drugs is best in such conditions, but it remains to be seen whether that will happen. Until there are empirical data on which to make such decisions, physicians will have to use their knowledge of the pharmacology of the drugs and their personal experience to guide such treatment decisions. With experience, physicians will also learn when to use mirtazapine or one of the other new non-SSRI antidepressants as the drug of first choice for specific types of patients.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), desipramine (Norpramin and others), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor)

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