

Selecting an Antidepressant by Using Mechanism of Action to Enhance Efficacy and Avoid Side Effects

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The diversity of antidepressant mechanisms available today allows clinicians to individualize treatment decisions for depressive symptoms and subtypes, as well as to avoid side effects. The mechanism of action of antidepressants allows prediction of both adverse effects and therapeutic effects. Individual antidepressants have unique psychopharmacologic profiles, and individual patients have unique clinical profiles of different symptoms and depressive subtypes. By using this knowledge, the prescriber can match drug profiles with patient profiles to select preferred agents and avoid less preferred agents. *(J Clin Psychiatry 1998;59[suppl 18]:23-29)*

Since the introduction of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) 40 years ago, 5 new classes of antidepressants have become available. Described on the basis of their varied pharmacologic mechanisms, they are selective serotonin reuptake inhibitors (SSRIs), a norepinephrine and dopamine reuptake inhibitor (bupropion), a serotonin and norepinephrine reuptake inhibitor (venlafaxine), a serotonin-2 antagonist/serotonin reuptake inhibitor (nefazodone), and an α_2 antagonist/serotonin-2 and -3 antagonist (mirtazapine)^{1,2} (Figure 1). Mirtazapine represents the most recent step in the continuing evolution of targeted specificity of action to enhance clinical efficacy and reduce undesired effects.³ The antidepressant drug evolutionary time line began with pharmacologically dirty drugs that had effects on multiple receptor systems, then further evolved to selective drugs with a single pharmacologic mechanism, and now has arrived at drugs that again offer multiple pharmacologic actions but selected to reduce undesired effects while maintaining or even enhancing clinical efficacy (Figure 2).⁴

A brief overview of antidepressant pharmacology starts with the TCAs as rather nonselectively enhancing both noradrenergic and serotonergic activity, along with having

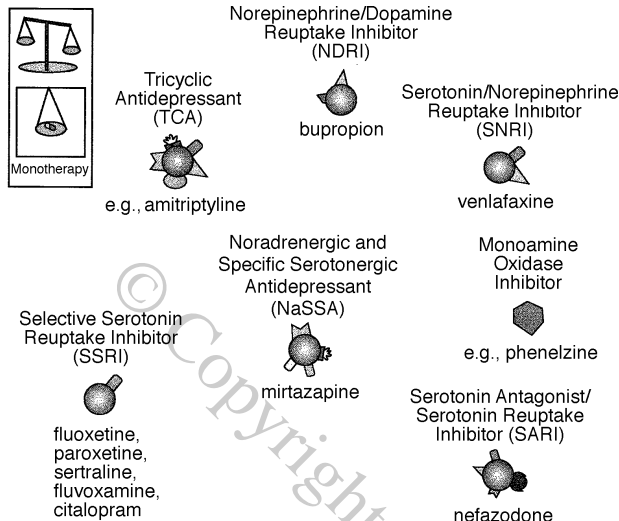
significant antagonism of histaminic, cholinergic, and adrenergic receptors.^{2,5} The pharmacologically dirty TCAs have yielded to the cleaner, more selective single-mechanism SSRIs that have greater safety in overdose and a different but usually better-tolerated adverse effect profile.⁶ While SSRIs are selective for serotonin, more serotonin is available at all presynaptic and postsynaptic receptors, leading to antidepressant efficacy but also to serotonin-mediated adverse effects.⁷ SSRIs and venlafaxine nevertheless essentially lack the adverse effects of TCAs related to blockade of cholinergic, α -adrenergic, and histaminic receptors.⁵ Nefazodone has some α -adrenergic and norepinephrine reuptake blockade, while mirtazapine is a potent histaminic receptor blocker.^{3,5,6} Venlafaxine and mirtazapine have 2 neurotransmitter mechanisms (both serotonergic and noradrenergic) rather than 1 (e.g., serotonin for SSRIs and noradrenergic/dopaminergic for bupropion), which may offer enhanced efficacy for some patients. Nefazodone and mirtazapine represent the further evolution to having purposeful additional postsynaptic serotonin antagonist effects that specifically reduce adverse effects commonly seen with general serotonin reuptake inhibitors such as SSRIs and venlafaxine.¹⁻⁷ The potential for clinically important adverse effect differences and efficacy considerations will be examined in relation to the diversity of available antidepressant drug mechanisms. These diverse pharmacologic mechanisms of action are discussed in further detail elsewhere.¹⁻⁸ What will be emphasized here is how to apply this information to antidepressant selection for various profiles of individual depressed patients. Experienced clinicians realize, however, that this approach generates guidelines for which there are many individual exceptions. Understanding pharmacologically derived guidelines may nevertheless help guide more informed prescribing decisions.

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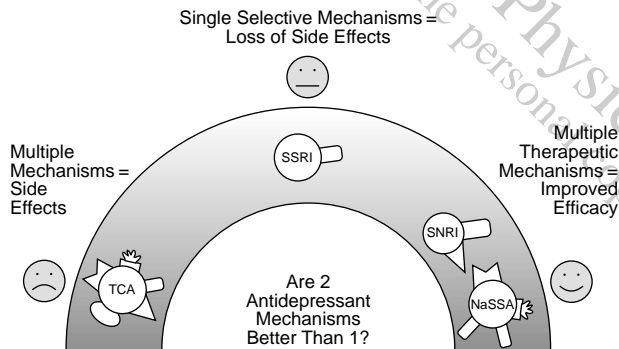
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Figure 1. The 7 Major Classes of Antidepressants*



*Adapted from reference 5, with permission.

Figure 2. Are 2 Antidepressant Mechanisms Better than 1?*



*Adapted from reference 4, with permission.

ADVERSE EFFECTS

The reasons for differences in adverse effects among antidepressants are directly related to effects on neurotransmitter receptor systems.¹⁻⁸ The continuing search for an ideal antidepressant drug involves preserving the receptor effects necessary for clinical efficacy while eliminating receptor effects responsible for adverse effects.⁹ The TCAs remain the standard of both clinical efficacy and multiple adverse effects. The pharmacology of the adverse effects of antidepressants is well understood (Tables 1 and 2).^{1-8,10} Thus, understanding the relative effects of a drug on different neurotransmitter receptors allows prediction of its more common adverse effects. The diversity of pharmacologic mechanisms among antidepressants means great diversity of expected adverse effect profiles, giving the prescriber the opportunity to select a drug to either avoid certain adverse effects (e.g., anticholinergic effects,

Table 1. Pharmacologic Mechanisms and Possible Consequences

Property	Possible Clinical Consequences
Stimulation of dopamine receptors	Agitation, aggravation of psychosis
Stimulation of norepinephrine receptors	Activation, hypertension, panic
Blockade of H ₁ histamine receptors	Sedation, weight gain
Blockade of muscarinic cholinergic receptors	Blurred near vision, dry mouth, sinus tachycardia, constipation, urinary retention, memory impairment
Blockade of α ₁ -adrenergic receptors	Dizziness, orthostatic hypotension, reflex tachycardia

Table 2. Clinically Significant Consequences of Stimulating 5-HT₂ and 5-HT₃ Receptors

5-HT ₂	Agitation
	Akathisia
	Anxiety
	Panic attacks
	Insomnia
	Sexual dysfunction
5-HT ₃	Nausea
	Gastrointestinal distress
	Diarrhea
	Headache

linergic effects, orthostatic hypotension, weight gain) or take advantage of other effects (e.g., sedation) beyond the desired antidepressant effects.

SEROTONIN, GOOD AND BAD

Many antidepressant drugs have diverse effects on serotonin receptors. The SSRIs and venlafaxine enhance serotonergic activity by reuptake inhibition.^{1,5} When the increased serotonin acts on all presynaptic and postsynaptic serotonin receptors, both desired antidepressant effects and undesired adverse effects can occur.⁷ For example, the consequences of stimulating 5-HT₂ (serotonin-2) receptors can include agitation, akathisia, anxiety, panic attacks, insomnia, and sexual dysfunction (Table 2).^{2,7,10} The consequences of stimulating 5-HT₃ receptors can include nausea, gastrointestinal distress, headache, and diarrhea (Table 2).^{2,7,10} These receptor actions may explain why patients receiving SSRIs or venlafaxine can commonly experience gastrointestinal side effects, sexual dysfunction, anxiety, and insomnia.^{2,7,10} Nefazodone, while a serotonin reuptake inhibitor, is also a potent postsynaptic 5-HT₂ blocker, which may explain why its side effect profile usually does not include significant activating effects or sexual dysfunction.^{1,2,5,8} Mirtazapine not only increases both serotonin and norepinephrine neurotransmission via α₂-adrenergic blockade, but also specifically blocks 5-HT₂ and 5-HT₃ postsynaptically.^{1-3,6,8,11} The latter 2 effects may

Table 3. Single-Mechanism Versus Dual-Action Antidepressants

Single-Action Agents	Dual-Action Agents
Mostly Norepinephrine Desipramine (TCA) Bupropion ^b Mianserin ^a	Both Norepinephrine and 5-HT Clomipramine (TCA) Venlafaxine Mirtazapine, MAOIs
Mostly 5-HT SSRIs Nefazodone	

^aMarketed in Europe.
^bMarketed in US and Canada.

well explain why mirtazapine is not generally associated with significant activating effects, sexual dysfunction, or gastrointestinal side effects.^{2,3,10}

FEWER SIDE EFFECTS WITH COMBINATION DRUG THERAPY

While combinations of antidepressant drugs are often used to treat resistant patients in an attempt to enhance clinical efficacy, addition of a second antidepressant can also be used to reduce adverse effects caused by the primary antidepressant drug.^{2,5} Trazodone, for example, is a common adjunct to SSRIs or bupropion in an attempt to treat insomnia and drug-induced activating effects.^{2,5,12} The SSRIs theoretically produce their activating effects from stimulating 5-HT₂ receptors (Table 2), while bupropion theoretically produces its activating effects by its dopaminergic and noradrenergic effects (Table 1). In doses of 50 to 100 mg/day, trazodone adds sedation, which may cancel undesired activation of SSRIs or bupropion. Although these doses are lower than those necessary for antidepressant effects of trazodone when used as a monotherapy, such low doses may nevertheless have synergistic effects with the antidepressant effects of concomitantly administered SSRIs or bupropion.^{2,5,12}

Nefazodone could offer both relief of side effects as well as enhanced efficacy when added to venlafaxine or bupropion, but dose titration to at least 300 mg/day might be necessary.¹³ As an adjunct to SSRIs, mirtazapine offers both sedation and added antidepressant effects at its initial dose of 15 mg/day.¹² Clinicians commonly add bupropion to SSRIs in an attempt to reduce SSRI-induced sexual dysfunction.² Many clinicians have abandoned the use of cyproheptadine and yohimbine due to either their adverse effects or their interference with antidepressant activity. Thus, bupropion is evolving as a preferred agent to augment SSRI-induced sexual dysfunction. While bupropion lacks serotonergic effects and thus essentially lacks the potential to cause sexual dysfunction, it increases dopamine activity, thereby providing an indirect mechanism to treat SSRI-induced sexual dysfunction, while independently providing antidepressant activity as well.^{2,5} Mirtazapine and nefazodone as adjuncts to SSRIs can also offer

Table 4. Are 2 Mechanisms Better Than 1 in Some Patients?

Onset of antidepressant effects may be more rapid
May be preferable in severe depression
May be preferable in retarded depression
May be preferable in treatment-resistant depression
May be preferable in melancholic depression
May be preferable in depressed inpatients
Dual-action clomipramine may be better than the single-action SSRIs paroxetine or citalopram
Dual-action venlafaxine or mirtazapine may be better than single-action fluoxetine
More research is needed

direct pharmacologic treatment of sexual dysfunction without the risk of interference with antidepressant effects. Observations that certain antidepressant combinations can both enhance efficacy as well as reduce side effects are mostly anecdotal,^{12,13} and although rarely documented in formal clinical trials, can be valuable tips for enhancing antidepressant tolerability as well as efficacy.

EFFICACY

An equally important but less well-established issue is whether the clinical efficacy of single neurotransmitter antidepressants is inferior to the efficacy of dual-action antidepressants (Table 3). The question has been raised whether the SSRIs went too far by removing the norepinephrine-enhancing properties of the TCAs.⁴ Clomipramine, venlafaxine, MAOIs, and mirtazapine have both serotonin and norepinephrine actions, while desipramine, bupropion, SSRIs, and nefazodone primarily act on 1 of these 2 neurotransmitters.¹⁻⁸ Clomipramine, venlafaxine, and mirtazapine all have studies supporting the idea that dual-action drugs have superior efficacy compared with single-action SSRIs,^{4,14,15} although there is also some conflicting evidence (Table 4).^{4,16,17}

Why should dual-action agents have superior efficacy? Antidepressant actions of the known antidepressants are mediated by both norepinephrine and serotonin.¹⁻⁸ Furthermore, interruption of the synthesis of either serotonin or norepinephrine has been shown to compromise the antidepressant effects of drugs whose effects are dependent on these neurotransmitters.¹⁸ The fact that clinicians treating more severely depressed patients or treatment-resistant depressions commonly combine antidepressants with independent therapeutic actions on serotonin and norepinephrine to effect a therapeutic response when single-action agents fail to work on their own supports the notion that dual-action antidepressants should have a therapeutic edge.^{2,5,12,13} More research is clearly needed comparing single-action and dual-action antidepressant drugs to answer this clinical observation.

The possibility that dual-action antidepressants have a more rapid onset of clinical effect than single-action SSRIs has similarly been suggested but not yet established

Table 5. Therapeutic Profile of SSRIs

Depression: disinhibition of the pathway to prefrontal cortex
Obsessive-compulsive disorder: disinhibition of the pathway to basal ganglia
Panic disorder: disinhibition of the pathway to limbic cortex and hippocampus
Bulimia: disinhibition of the pathway to hypothalamus

Table 6. Least Preferred Uses of SSRIs

Patients with sexual dysfunction
Patients with major relationship problems where the development of sexual dysfunction could be problematic
Patients with secondary refractoriness (i.e. loss of efficacy with long-term treatment)
Patients in whom nocturnal myoclonus is present
Patients with consistent insomnia and agitation

(Table 4). A combination of desipramine and fluoxetine has been shown to result in a more rapid down-regulation of β -adrenergic receptors compared with either drug alone, with differences observed as early as 4 days of treatment.¹⁹ In an open clinical trial, combination of these 2 antidepressants was found to have a more rapid onset of efficacy when compared to desipramine alone.²⁰ More clinical research is also required to establish firmly that dual-action antidepressants act faster than single-action agents.

MATCHING PHARMACOLOGIC PROFILES WITH CLINICAL PROFILES

Consideration of the information presented above allows suggestion of both the preferred and the least preferred uses of each of the antidepressant drugs.^{2,21} While there are often no direct head-to-head clinical trials to document the suggestions given below, knowledge of the clinical consequences of antidepressants' unique differences in mechanism may allow the prescriber to identify good and poor drug choices for an individual patient.²¹

SSRIs have well-established efficacy for major depression, obsessive-compulsive disorder, panic disorder, and bulimia (Table 5). These indications relate directly to the fact that SSRIs cause desensitization of 5-HT_{1A} receptors, leading to more serotonergic neurotransmission in the prefrontal cortex, basal ganglia, limbic cortex/hippocampus, and hypothalamus.^{2,5} The stimulation of 5-HT₂ receptors by the SSRIs leads to possible adverse effects of agitation, akathisia, anxiety, panic attacks, insomnia/myoclonic jerks, and sexual dysfunction (Table 2). SSRIs' stimulation of 5-HT₃ receptors leads to possible adverse effects of nausea, gastrointestinal distress, and diarrhea (Table 2). Thus, the least preferred uses for SSRIs could include patients with major relationship problems where development of sexual dysfunction could be problematic, patients in whom nocturnal myoclonus is present, patients with per-

Table 7. Therapeutic Uses of Bupropion

Patients with retarded depression
Patients with hypersomnia
Nonresponders to serotonergic agents
Nontolerators of serotonergic agents
Patients concerned about sexual dysfunction
Patients with cognitive slowing/pseudodementia

Table 8. Least Preferred Uses of Bupropion

Seizure disorder patients
Patients who are seizure prone or who have head injury
Patients noncompliant to multiple daily dosing
Agitated, insomniac patients

Table 9. Therapeutic Profile of Venlafaxine

At medium-to-high doses, use for melancholic, severely depressed, and hospitalized patients and for those refractory to other antidepressants
At low doses no reason to think of this drug any differently than as an SSRI
Use in retarded, hypersomnic, weight gaining, atypical depressives

sistent insomnia and agitation, patients with preexisting GI problems, and those with secondary refractoriness or loss of efficacy with long-term treatment (Table 6).

Because of its ability to boost norepinephrine and dopamine, bupropion may be preferred in patients with retarded depression, patients with hypersomnia, nonresponders to serotonergic antidepressants, nontolerators of serotonergic drugs, patients with cognitive slowing/pseudodementia, and those preferring to avoid sexual dysfunction (Table 7). Bupropion's least preferred uses could include those patients with seizure disorders or who are seizure prone, (although proconvulsant actions of bupropion appear to be reduced when administered in the new twice-a-day controlled-release formulation). Bupropion might also be less preferred for those noncompliant to twice daily dosing (for the new formulation; 3 times daily for the original formulation), and those agitated or insomniac patients (Table 8).

At low doses, venlafaxine may function more as an SSRI than as a dual serotonin and norepinephrine reuptake inhibitor, because its serotonin reuptake properties are more potent than its norepinephrine reuptake properties.⁵ Thus, at low doses it may have preferred (Table 5) and least preferred (Table 6) uses much the same as the SSRIs, with the exception that venlafaxine has generally fewer drug interactions than the SSRIs. Rather than switch to another agent or augment with a second agent when a patient has an inadequate response to venlafaxine, one can simply increase the dose and turn it into a dual-action antidepressant, almost like adding bupropion to an SSRI. The preferred profile for medium-to-high doses of venlafaxine (Table 9) may be patients who fail to respond to SSRIs,

Table 10. Least Preferred Uses of Venlafaxine

Agitated patients
 Insomniac patients
 Patients experiencing weight loss
 Patients with sexual dysfunction
 Patients with borderline or labile hypertension

Table 11. Therapeutic Uses of Nefazodone

Depression in association with
 Anxiety
 Agitation
 Sleep disturbance
 Insomnia
 Prior SSRI-induced sexual dysfunction
 Inability to tolerate SSRIs
 SSRI responders who lose their response

Table 12. Least Preferred Uses of Nefazodone

Those without cytochrome P40 2D6 isoenzyme
 Hypersomnic, regressed, retarded depressed patients
 Noncompliance with b.i.d. dosing
 Patients who have trouble following an upward titration program to arrive at optimal dosing

Table 13. Therapeutic Uses of Mirtazapine

Depression associated with
 Anxiety
 Agitation
 Insomnia
 SSRI-induced:
 Sexual dysfunction
 Nausea
 Gastrointestinal disturbance
 Agitation
 Panic
 Weight loss
 Severe depression
 For SSRI responders who have lost their response

low doses of venlafaxine, or various other antidepressants, and for melancholic, severely depressed, and hospitalized patients. Its mechanism suggests potential benefit for retarded, hypersomnic, weight gaining, atypical depressives (Table 9). The least preferred uses of venlafaxine, especially when used at high doses, might include agitated, insomniac patients, those with weight loss or sexual dysfunction, patients who have difficulty following an upward titration program toward an optimal therapeutic dose, and those with borderline or labile hypertension (Table 10). On the other hand, recent development of a once daily dosage formulation makes venlafaxine easier to use, to dose, and to tolerate, especially in anxious patients.

Nefazodone, with its 5-HT₂ blocking effects and serotonin reuptake inhibition, offers possible benefits for depression with anxiety, agitation, and sleep disturbance, for prior SSRI-induced sexual dysfunction, for inability to tolerate SSRIs, and for SSRI responders who lose their

Table 14. Least Preferred Uses of Mirtazapine

Hypersomnia
 Motor retardation
 Cognitive slowing
 Overweight

Table 15. Preferred Uses of Tricyclic Antidepressants

Well-fitting niche
 Pain
 Fibromyalgia
 Migraine
 Sedative/hypnotic
 Severe depression

Table 16. Least Preferred Uses of Tricyclic Antidepressants

Those who cannot tolerate daytime sedation, urinary retention, constipation
 Overweight patients
 Suicidal patients (TCAs toxic in overdose)
 Patients with cardiac illness
 Patients taking multiple concomitant medications (TCA drug interactions)
 Patients with dementia

Table 17. Preferred Uses of Classical Monoamine Oxidase Inhibitors

Second-line use
 Atypical depression (i.e., weight gain, hypersomnia, mood reactivity)
 Refractory patients
 Compliant patients
 Patients with associated panic attacks




























Table 18. Least Preferred Uses of Classical Monoamine Oxidase Inhibitors

Noncompliant patients
 Patients not highly motivated to monitor diet and concomitant medications
 First-line treatment for insomniac, agitated patients

response (Table 11). Nefazodone's least preferred uses could include hypersomnic, retarded depressions, non-compliance with twice daily dosing (although once daily dosing at night is a possibility once the patient has responded), and patients who have trouble following an upward titration program to arrive at an optimal dose (Table 12). For patients who have no cytochrome P450 2D6 isoenzyme, nefazodone can be metabolized to significant amounts of the anxiogenic metabolite *m*-CPP (*m*-chlorophenylpiperazine).

Mirtazapine has dual actions on both norepinephrine and serotonin via its α_2 -adrenergic blockade, coupled with postsynaptic blockade of both 5-HT₂ and 5-HT₃ receptors. Thus, the possible preferred uses would be depression associated with anxiety, agitation, insomnia, panic, weight loss, and severe depression (Table 13). It can also be a use-

Figure 3. Rather Than Choose an Antidepressant Randomly, the Prescriber Can First Profile the Patient According to the Features in the First Column*

Patient Profile	Antidepressant Drug Profile	Examples
A Panic disorder 	5-HT 	SSRIs 
Obsessive-compulsive disorder 	5-HT 	SSRIs 
Binge eating 	5-HT 	SSRIs 
B Atypical 	Activating by 5-HT or DA/NE 	SSRIs MAOIs Bupropion 
Anxious 	5-HT ₂ antagonist 	Nefazodone Mirtazapine 
Agitated 	5-HT ₂ antagonist 	Nefazodone Mirtazapine 
C Chronic pain 	5-HT ₂ antagonist/ 5-HT reuptake 	Amitriptyline Nefazodone Mirtazapine possible 
Migraine prophylaxis 	5-HT ₂ antagonist/ 5-HT reuptake 	Amitriptyline Nefazodone Mirtazapine possible 
Fibromyalgia 	5-HT ₂ antagonist/ 5-HT reuptake 	Amitriptyline Nefazodone Mirtazapine possible 

*Adapted from reference 5, with permission. By understanding pharmacologic mechanisms of action of the various antidepressants, a match can be made based upon the different drugs' profiles (middle column). Specific examples of the match are given in the third column. Abbreviations: DA = dopamine, MAOI = monoamine oxidase inhibitor, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor.

ful alternative for patients intolerant of SSRI-induced sexual dysfunction, agitation, nausea, and GI disturbance. The least preferred uses of mirtazapine may include patients with hypersomnia, psychomotor retardation, and cognitive slowing and those who are overweight (Table 14).

For comparative purposes, the most preferred and least preferred uses of tricyclic antidepressants (Tables 15 and 16) and MAO inhibitors (Tables 17 and 18) are also shown.

CONCLUSION

Both antidepressants and individual patients have unique differences, and knowledge of these differences allows more rational matching of drug and patient profiles. Rational prescribing decisions should lead to the use of different antidepressant drugs, doses, and dosing schedules among a prescriber's population of patients with depressive disorders. An observation that the vast majority of a prescriber's depressed patients are all given the same antidepressant drug would suggest a lack of individualized treatment and the missed opportunity to take advantage of the diversity of antidepressant mechanisms for the patient's benefit. Suggestions based upon the principles outlined here are summarized in Figure 3.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil), cyproheptadine (Periactin and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yoncon and others).

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