Translating the Evidence on Atypical Depression Into Clinical Practice

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Although the introduction of selective serotonin reuptake inhibitors ushered in an era of relative comfort among clinicians in treating major depressive disorder (MDD), no one antidepressant is appropriate for all patients with depression. In patients with atypical symptoms, efficacy of therapeutic agents may be greatest for monoamine oxidase inhibitors (MAOIs). The first-generation MAOIs such as phenelzine and isocarboxazid were largely nonselective inhibitors of both subtypes of MAO, MAO_A and MAO_B. These medications carried with them dietary restrictions, medication restrictions, a need for titration, and a substantial side effect burden, including weight gain, cardiovascular effects (i.e., hypertension and hypotension), and sexual side effects. The second-generation MAOI selegiline is selective for MAO_B at oral doses of up to 10 mg/day. At higher doses, selegiline loses selectivity and inhibits both MAO_A and MAO_B. Because the antidepressant effects of selegiline occur with the higher doses that impact tyramine pressor effects, an ideal formulation would optimize dose while minimizing adverse effects of MAO_A inhibition in the gastrointestinal mucosa. Efforts in this direction led to formulation of the selegiline transdermal system (STS). The most common side effects are irritation at the patch site and insomnia. Drugs to be avoided with the STS include some pain medications, antidepressants, muscle relaxants, and any form of sympathomimetic amines, which include amphetamines, cold products with pseudoephedrine, phenylephrine, phenylpropanolamine, ephedrine, and stimulant-containing weight-reduction agents. Although no tyramine-restricted diet is required for the 6-mg/24-hour patch, a restricted diet is recommended for the higher-dose patches to reduce the risk of hypertensive crisis. *(J Clin Psychiatry 2007;68[suppl 3]:31–36)*

Subtyping of major depressive disorder (MDD) has seen renewed interest with the advent of pharmacogenetic and pharmacogenomic advances. Continued progress in these 2 areas may ultimately allow clinicians to select antidepressant treatments based on an individual biological basis. Although the introduction of selective serotonin reuptake inhibitors (SSRIs) began an era of relative comfort among clinicians in treating depression, it has subsequently been found that no one antidepressant is appropriate for all patients with MDD. Indeed, data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial revealed differing abilities of agents to produce benefit in different segments of a population, and one approach is not uniformly useful. Emerging treatment options may possess selective advantages for specific symptom clusters of MDD.

GENETICS AND THE ENVIRONMENT

The role of genetics in mediating risk of and resilience to MDD, as well as the interaction of environmental stressors with genes to influence the likelihood of depressive disorders, has been studied. Caspi et al.[1] suggested that a functional polymorphism in the promoter region of the gene for the serotonin transporter plays a role in susceptibility for depression. Compared with individuals with 2 long alleles in the promoter region, those with 1 or 2 short alleles had more symptoms of depression and suicidality and greater incidence of major depressive episodes in relation to stressful life events. Examining the effect of childhood maltreatment on adult depression, the researchers discovered a significant ($p < .05$) association between severe childhood maltreatment (i.e., trauma) and the risk of depression among individuals with a short allele. For example, the risk of depression for those with the 2 short alleles polymorphism was twice that of those with the 2 long alleles polymorphism. There are many polymorphisms besides this variant in the promoter region of the serotonin transporter gene that may contribute to a predisposition to depression. Continued discovery and characterization of

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This article is derived from the planning roundtable "Atypical Depression: Management Challenges and New Treatment Advances," which was held July 22, 2006, in Philadelphia, Pa., and supported by an educational grant from Bristol-Myers Squibb Company.

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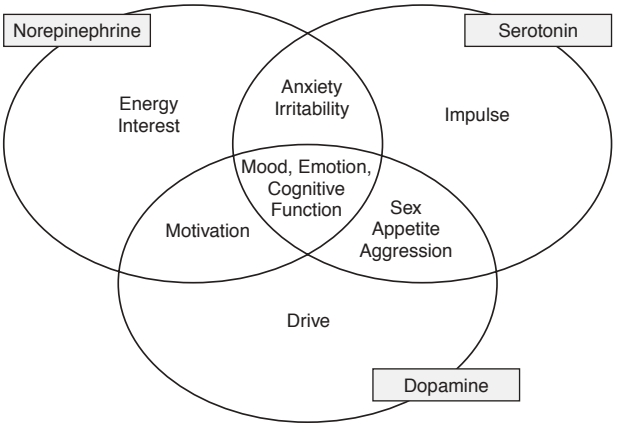
Figure 1. The Role of Neurotransmitters in Mood Disorders[a]



[a]Adapted with permission from Ressler.[3]

these variants may further expand our understanding of depression.

A reexamination[2] of data from a study of 681 patients with chronic depression either with or without a history of childhood trauma illustrates the impact of a genetic and environmental interplay component. The effects of a cognitive-behavioral analysis system of psychotherapy, the antidepressant nefazodone, or the combination were evaluated. For patients with a history of childhood trauma, psychotherapy alone produced significantly ($p = .0446$) greater improvement than medication alone, suggesting interplay between environment, genetics, and treatment response. For patients without childhood trauma, medication alone and psychotherapy alone produced similar benefits. In both groups of patients, combination treatment resulted in the greatest improvement.

TREATMENT APPROACHES TO ATYPICAL DEPRESSION

Atypical features of MDD include reverse neurovegetative signs such as oversleeping, overeating, and anergia, as well as mood reactivity and rejection sensitivity. Although not part of the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition criteria, anxiety and panic are also frequently observed.

Actions of Antidepressants

The neurotransmitters norepinephrine, serotonin, and dopamine are postulated to have overlapping symptom domains that point to their interplay in mood disorders (Figure 1).[3] Thus, there may be relationships between different neurotransmitter dysfunction and certain symptoms associated with mood disorders. However, it is overly simplistic to attribute seemingly distinct symptoms, such as energy or interest, to the lack of an associated neurotransmitter, in this case, norepinephrine, because such symptoms also relate to specific brain regions and, as such, involve other processes. Despite such interpretational difficulties, this model allows an approach toward conceptualizing treatment.

The timing for onset of action for antidepressants was once thought to take weeks but is now believed to occur much sooner in the clinical course. To examine onset of action and treatment-induced behavioral changes that precede recovery, Katz et al.[4] randomly assigned patients to receive the SSRI paroxetine, the tricyclic antidepressant (TCA) desipramine, or placebo for 6 weeks. The patients taking desipramine showed significant ($p = .023$) improvement compared with baseline at 1 and 2 weeks. Katz et al.[4] performed a modified time-to-response analysis and found that the patients taking paroxetine showed a significant ($p < .001$) reduction in hostility. Such results reflect a range of responses to antidepressant treatment and highlight the broad array of psychopharmacologic approaches in the treatment of depression.

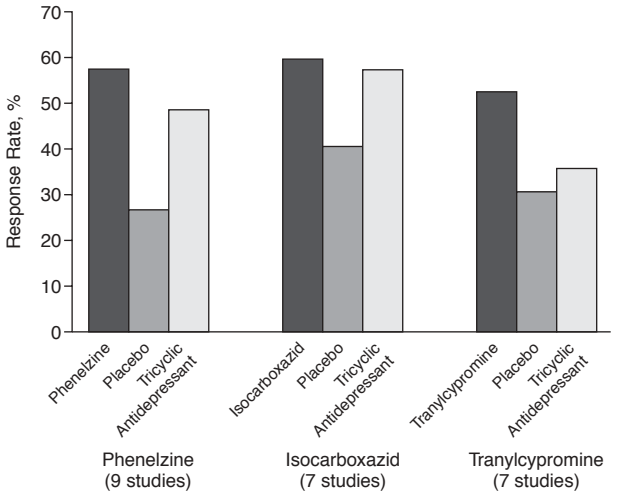
Optimizing Treatment

One of the key issues in treating patients with atypical depression is the need to identify and quantify the severity and frequency of target symptoms. These issues are often overlooked in the clinic. Symptoms that should be quantified include anergia, hypersomnia, hyperphagia, mood reactivity, rejection sensitivity, and anxiety/panic. The frequency and the severity of these symptoms should be examined routinely. It is not uncommon for patients to underrecognize improvement in target symptoms, due to the nature of their disorder. Closer examination as to frequency and severity, however, can shed light on treatment benefit or lack of benefit.

Prior to initiating treatment, clinicians should obtain a treatment history of therapies previously tried, response to therapy, the symptoms that improved with treatment versus those that worsened, side effects experienced, and whether psychotherapy was tried and what symptoms it helped and did not help. Answers to these questions are relevant to devising a treatment strategy, including whether an oral antidepressant, transdermal patch, psychotherapy, or combination of psychotherapy and pharmacotherapy is an appropriate approach.

In studies[5,6] of patients with MDD, SSRIs have provided an approximately 20% overall improvement over placebo. Post hoc analyses[7,8] reveal that the symptoms of anger, anxiety, and insomnia benefit most from SSRI treatment, while energy, drive, and pessimism have shown modest response. Although SSRIs have improved safety profiles compared with TCAs and monoamine oxidase inhibitors (MAOIs), there is a problem with persistent sexual dysfunction with long-term use. Several types of antidepressants have been studied for "atypical

Figure 2. Tricyclic Antidepressants Versus Monoamine Oxidase Inhibitors in a Meta-Analysis of 23 Outpatient Studies[a]



[a]Data from Thase et al.[12]

depression." In patients with atypical symptoms, MAOIs tend to have greater efficacy than TCAs.

If a patient with atypical symptoms of MDD has been treated for several weeks and has not responded, clinicians must first consider whether the patient's medication was optimized or whether he or she was treated with a subclinical or low therapeutic dose of medication. Too often, patients may be switched between medications without having received an adequate drug trial in terms of dosage or duration. Another consideration for suboptimal responses includes examining whether common interventions have been explored. Lastly, the use of augmentation strategies, such as modafinil, bupropion, stimulants, buspirone, atypical antipsychotics, and dopamine agonists, may be considered—although there is a paucity of data to support such interventions in atypical depression.

Adjunctive therapy. The use of adjunctive modafinil for treating the symptoms of fatigue and sleepiness in depression has been studied. In a 6-week study,[9] 136 patients were randomly assigned to treatment with modafinil or placebo along with ongoing antidepressant therapy. At baseline, fatigue and sleepiness were reported by 82% and 51% of patients, respectively. Modafinil significantly ($p < .01$) lowered sleepiness scores at week 1. Scores on fatigue severity decreased at week 1 and were significantly ($p < .05$) lower by week 2. Both effects were not significantly different from placebo at study end, suggesting the utility of modafinil may be limited to the short-term treatment of these symptoms.

The efficacy of add-on antidepressant therapy to current antidepressant therapy in patients considered to be partial responders or nonresponders has also been examined. In a 6-week, open-label study[10] of reboxetine augmentation in 61 partial or nonresponders with depression, patients were maintained on an SSRI, mirtazapine, or venlafaxine and treated with 2 mg to 8 mg of reboxetine. At study end, 54% of patients were classified as responders (Hamilton Rating Scale for Depression [HAM-D] score ≤ 50%); 46% were considered to be in remission (HAM-D ≤ 10). Although this was a small, open-label study, results suggest that reboxetine augmentation therapy may be efficacious, although larger, more rigorous augmentation studies are needed.

Monotherapy. Possible monotherapy options, in addition to the SSRIs, include the serotonin-norepinephrine reuptake inhibitors (SNRIs) (i.e., duloxetine and venlafaxine), bupropion, mirtazapine, and the MAOIs. However, there remains a paucity of data to support the use of these clinical agents in atypical depression.

The SNRIs are purported to provide faster onset, but these agents are associated with cardiovascular and autonomic side effects such as tachycardia, sweating, and increased blood pressure, and no strong data are yet available in patients with atypical depression.

The efficacy of bupropion sustained release versus placebo was reported in a post hoc analysis[11] of 910 patients with MDD who had received bupropion during randomized, double-blind trials. Principal component analysis revealed a statistically significant advantage for bupropion over placebo on measures of retardation, cognition, fatigue/lack of interest, and anxiety ($p < .01$) versus placebo.

A meta-analysis[12] of controlled studies compared MAOIs, TCAs, and placebo in outpatients with depression. This analysis of the intent-to-treat data revealed similar improvements among the MAOIs phenelzine, isocarboxazid, and tranylcypromine (Figure 2).

In a review of studies of patients with atypical symptoms randomly assigned to phenelzine,[13] the TCA imipramine, or placebo, consistently greater benefit was reported in patients taking phenelzine compared with imipramine and placebo. However, phenelzine and imipramine were equally effective in patients with typical vegetative symptoms.

The efficacy of MAOIs in bipolar depression has also been studied. Early studies reported the greater efficacy of tranylcypromine over placebo[14] and imipramine,[15,16] in patients with anergic bipolar depression. Response rates ranged from 75% to 91% for tranylcypromine, compared with 24% for placebo and 48% to 50% for imipramine. In comparative studies of patients with bipolar depression,[17,18] the MAOI moclobemide and imipramine were not significantly different in terms of efficacy, but imipramine was associated with higher rates of adverse events. Thus, the use of the MAOI in individuals with bipolar depression and anergic features may be preferred.

Taken together, data from these meta-analyses and the individual studies suggest that MAOIs may be more

effective than TCAs and placebo in the treatment of atypical unipolar and bipolar depression.

MECHANISM OF ACTION OF MAOIs

Monoamine oxidase inhibitors are associated with a variety of changes in receptors and signal transduction pathways. Monoamine oxidase causes oxidative deamination of a number of important neurotransmitters. The MAO_A isoform metabolizes norepinephrine, serotonin, tyramine, and dopamine.[19] MAO_B is more selective for phenylethylamine but also metabolizes tyramine and dopamine. Monoamine oxidase is irreversibly bound by first-generation MAOIs, and new MAO must be synthesized, which takes 14 days. Monoamine oxidase inhibitors decrease the metabolism of norepinephrine, serotonin, and dopamine, thereby increasing synaptic concentrations of these neurotransmitters. Ultimately, this cascade of events leads to changes in receptor and signal transduction functioning.

The MAOIs have different selectivity for MAO_A and MAO_B. The first-generation MAOIs such as phenelzine and isocarboxazid were largely nonselective and irreversible inhibitors of both subtypes of MAO throughout the body. These agents are associated with dietary restrictions, medication restrictions, a need for titration, and a substantial side effect burden, including weight gain, cardiovascular effects (i.e., hypertension and hypotension), and sexual side effects. The second-generation MAOIs (e.g., selegiline or clorgyline) were more selective than the first generation but still irreversibly bound MAOI isozymes. The third-generation MAOIs (e.g., moclobemide) were both selective and reversibly bound MAOIs. Although it had been hoped that the introduction of reversible MAO_A inhibitors like moclobemide would decrease the risk of food and medication interactions, they may be less effective.[20] Despite the selectivity and reversibility of newer agents, an MAOI with optimal efficacy and improved safety remained elusive. Efforts to maintain efficacy while reducing the risk for hypertensive crisis led to the introduction of a transdermally administered second-generation MAOI.

SELEGILINE TRANSDERMAL SYSTEM

Selegiline is selective for MAO_B at oral doses of up to 10 mg/day and is approved for treating Parkinson's disease. At higher doses required for antidepressant efficacy, selegiline loses selectivity and irreversibly inhibits both MAO_A and MAO_B.[21] Thus, at doses for which selegiline is efficacious as an antidepressant, patients run the risk of tyramine pressor reactions. This led to the formulation of the selegiline transdermal system (STS), a formulation that optimizes the dose as an antidepressant while minimizing effects of MAO_A inhibition on the gastrointestinal mucosa.

The STS is a patch matrix that contains 3 layers: an outer backing similar to a plastic bandage, an adhesive drug layer, and a release liner that is placed directly against the skin. The pharmacokinetic pattern of the STS shows a slower time to peak concentration and longer duration of optimal plasma levels than oral selegiline.[22] This delivery system permits delivery of higher levels of the primary medication and bypasses intestinal absorption as well as first pass metabolism in the liver.[23] The end result is higher sustained blood levels of selegiline and significantly less inhibition of MAO_A in the duodenum and liver. Therefore, STS extended-release formulation reduces the risk of tyramine ingestion–associated hypertensive crisis.

Although rigorous studies are needed, other benefits of the STS may include improved tolerability over the first-generation MAOIs,[24] less hypotension, and fewer sexual side effects.[25] No dietary restriction requirement has been imposed for the 6 mg/24 hour patch, although dietary restrictions are recommended for the 9 mg/24 hour patch and the 12 mg/24 hour patch.[22]

Five studies were submitted to the U.S. Food and Drug Administration as part of the new drug application submission; the 3 positive pivotal studies[24–27] are described below. In a 6-week, multicenter, double-blind study,[24] 177 patients with MDD participated in a 1-week, single-blind lead-in phase, and individuals were randomly assigned to receive a placebo patch or 6 mg/24 hour STS. Entry criteria included a 17-item HAM-D (HAM-D-17) score greater than 20, and efficacy measures included the HAM-D-17, the 28-item HAM-D (HAM-D-28), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions (CGI) scale. Subjects in this study were placed on a tyramine-restricted diet. A robust treatment response to the STS was observed as early as week 1 and maintained throughout the 6 weeks of the study. Significant benefits were reported across efficacy measures ($p \leq .04$). The major adverse event during the study was a rash at the site of application (36% for STS vs. 17% for placebo, $p = .006$). There were no signs of sexual dysfunction at the dose used. In fact, patients receiving the STS had improved sexual function measured by a self-report scale versus placebo ($p = .03$). There were no other significant drug-placebo differences in terms of adverse events.

A subsequent study[25] with the same design was conducted with 365 outpatients with MDD but lasted 8 weeks and had no dietary restrictions. In the intent-to-treat, last-observation-carried-forward analysis at study end, significant differences favoring the STS were seen in MADRS score ($p = .001$), HAM-D-28 score ($p = .039$), and item 3, suicidal ideation, on the HAM-D ($p = .021$).

Krishnan[26] performed a double-blind discontinuation study. Patients were openly treated with the STS at a dose of 6 mg/24 hour for 10 weeks, and individuals who met the response criteria of a HAM-D-17 score ≤ 10 were then randomly assigned to the STS (N = 159) or placebo patch

Table 1. Medications to Avoid During Selegiline Transdermal System Use[a]

Prescription Medications	Over-the-Counter Medications
Buspirone	Amphetamines
Carbamazepine	Decongestants
Cyclobenzaprine	Pseudoephedrine
Meperidine	Phenylephrine
Methadone	Phenylpropanolamine
Mirtazapine	Ephedrine
Oxcarbazepine	Diet pills or herbal
Propoxyphene	weight-loss products
Tramadol	Dextromethorphan
	St. John's wort

[a]Based on EMSAM prescribing information.[22]

Table 2. Monoamine Oxidase Inhibitors Reactions to Foods Containing Tyramine[a]

Severe	Moderate	Mild to None
Aged cheese	Red wine	Avocados
Aged and fermented meats	White wine	Bananas
Broad bean pods	Canned beer	Bouillon
Spoiled meats and fish		Chocolate
Soy sauce		Fresh cheeses
Tap beer		Fresh meats
Yeast extracts		Peanuts
		Soy milk

[a]Adapted with permission from Gardner et al.[28]

(N = 163) for 52 weeks. Although nearly half of patients in both treatment arms had discontinued by week 12 of the maintenance study, for those continuing, the STS produced a significant reduction (p = .006) in cumulative relapse versus placebo at endpoint.

PRACTICAL ISSUES IN USING THE SELEGILINE TRANSDERMAL SYSTEM

The transdermal selegiline patch is applied for 24 hours at a time and is available at 3 dosages: 6 mg (20 mg/20 cm^2), 9 mg (30 mg/30 cm^2), and 12 mg (40 mg/40 cm^2).[22] The most common side effects are irritation at the patch site (24% vs. 12% placebo), followed by insomnia (12% vs. 7% placebo).

Although the potential for tyramine-associated hypertensive crisis is reduced by the transdermal approach, this application does not prevent drug-drug interactions. Thus, when transitioning a patient from other treatments to the STS, it is recommended that there be at least a 1-week washout for most antidepressants (i.e., SSRIs, SNRIs, TCAs, and other MAOIs, including oral selegiline) and at least 5 weeks' washout for fluoxetine. The STS is commonly initiated employing the 6 mg/24 hour patch, and the dose is adjusted up on the basis of efficacy response and side effects.

Drugs to be avoided with the STS treatment are listed in Table 1. Patients should be reminded to not take any form of sympathomimetic amines, which includes amphetamines; cold products with pseudoephedrine, phenylephrine, phenylpropanolamine, or ephedrine; and stimulant-containing weight-reduction agents.[22] Clinicians should be vigilant about potential drug interactions, especially with the higher-dose patches.

Although no tyramine-restricted diet is required for the 6 mg/24 hour patch, a restricted diet is recommended for the higher-dose patches to reduce the risk for a hypertensive crisis. Many tyramine-restricted diets appear overly conservative and as such are difficult for patients to adhere to. More moderate diets have been systematically investigated and are now available to guide our patients (Table 2).[28]

CONCLUSION

Major depressive disorder is a heterogeneous syndrome. The etiopathophysiology of MDD is clearly influenced by both genetic and environmental factors. Our current treatment approaches are only partially effective in facilitating remission for our patients. One group that has been particularly challenging to treat is patients with atypical features. Older studies suggest that MAOIs were effective in mitigating such symptoms; however, they fell out of favor because of the need for dosage titration and their side effect burden. The approval of the STS adds an important new agent to our armamentarium for the treatment of depression.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Epitol, and others), cyclobenzaprine (Flexeril and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), isocarboxazid (Marplan), meperidine (Demerol and others), methadone (Dolophine, Methadose, and others), mirtazapine (Remeron and others), modafinil (Provigil), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), propoxyphene (Darvon and others), selegiline (Eldepryl, Zelapar, and others), selegiline transdermal system (EMSAM), tramadol (Ultram and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, buspirone, modafinil, selegiline (oral), hypericum perforatum, and reboxetine are not approved by the U.S. Food and Drug Administration for the treatment of depression.

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