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Innovative Antidepressant Newcomers: Suitability in Primary Care

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Author's Note

Clinical depression is highly prevalent in the general population and in primary care settings. Although clinicians presently have a broad array of pharmacological agents for the treatment of depression, including selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, overall response rates and remission rates with these pharmacological agents remain relatively modest. In this edition of Primary Care Reports, *we present an overview of several newer antidepressants, three of which are presently marketed in the United States (i.e., transdermal selegiline, trazodone extended-release, vilazodone) as well as one antidepressant that is due to arrive to market in 2012 (i.e., agomelatine). Although each of these antidepressants has a unique aspect and is, or will be, indicated by the Food and Drug Administration (FDA) for the treatment of major depression, they are not in our opinion equally favorable for utilization in the primary care setting. In this article, we will provide an overview of each antidepressant as well as a conservative opinion about each antidepressant's suitability for the primary care setting. Given this preamble, we invite the reader to draw his/her own conclusions about each antidepressant before reading our summary at the end of each section — i.e., is this antidepressant drug feasible for use in your practice?*

Introduction

Depression is surprisingly prevalent and can be challenging to treat, as indicated by the findings of a large prospective trial of sequenced depression treatments in a naturalistic sample of patients, the STAR*D study (Sequenced Treatment Alternatives to Relieve Depression). Because of this clinical challenge, a number of new and innovative antidepressant medications are emerging for the treatment of various mood and anxiety disorders (*see Table 1*). Although the ultimate impact of these medications in general clinical settings remains unknown, they represent novel current or future treatment options for primary care clinicians. In this issue of *Primary Care Reports*, we review three of these antidepressant freshmen as well as an antidepressant that will soon arrive to the U.S. market, and examine each in the context of its suitability in primary care. For each antidepressant medication, we will conclude the descriptive material by offering an informal rating of its suitability in the primary care setting, keeping in mind that all new medications will be accompanied by a cost offset.

For this review, we elected to define novel antidepressants as either: (1) truly unique in terms of their means of medication delivery (e.g., transdermal) or (2) unique with regard to their antidepressant action (i.e., despite its recent

Executive Summary

The treatment of depression is one of the most common problems facing primary care physicians. The appropriate choice of antidepressant medications becomes more complex with the introduction of new pharmacologic agents. Patients are bombarded in the media by pharma's claims — often perhaps scaring patients through the FDA's mandate that requires the disclosure of side effects, which for these drugs may be more dangerous than the disease itself.

- Depression is highly prevalent in the general population at about 21%.
- The STAR*D trial, which more closely represents the population being treated in practices, found that two-thirds of participants did not experience remission with an initial drug trial for depresssion.
- Transdermal selegiline irreversibly inhibits monoamine oxidase and has an absence of food restrictions at the lowest dose.
- Extended-release trazodone can be administed once daily but can prolong the QT interval.
- Vilazodone has a unique mechanism of action with no sexual dysfunction and minimal weight gain.

entry into the antidepressant market, we excluded desvenlavaxine [Pristique™] because it is a member of an established class of antidepressants, the serotonin-norepinephrine re-uptake inhibitors). Also, note that subsections for each antidepressant may vary in length (e.g., pharmacology, overdose profile), which is a reflection of the varying available information on the antidepressant under discussion.

The Prevalence of Depression in the United States

According to the findings of the National Comorbidity Survey Replication study, an investigation of the prevalence of various psychiatric disorders in the community, the lifetime prevalence of any mood disorder in the general population is about 21% (i.e., one in five).[1] As for the lifetime prevalence rates of the individual subtypes of depression, major depression is most frequent at 17%, followed by bipolar disorders at 4%, and dysthymia at 3%. These findings indicate that depression is highly prevalent in the community.

With regard to the prevalence of depression in primary care settings, Linzer and colleagues examined rates of mood disorders among 1000 patients who were being seen at one of four primary care clinics. In this large sample of outpatients, 26% of respondents reported current depression.[2] As for rates between the genders, 31% of women and 19% of men met the criteria for any mood disorder, indicating that mood disorders are likely to be a common clinical complaint in the primary care setting. Findings from these studies reinforce the impression that depression is highly prevalent, regardless of setting.

The STAR*D Trial

For years, clinicians have noted that the antidepressant response rates and remission rates reported in Phase 3 pharmaceutical trials are somewhat better than those observed in clinical practice. The most likely explanation for this is the nature of the inclusion/exclusion criteria undertaken in these trials. For example, often these samples exclude potential participants who have coexisting medical or psychiatric disorders, suicidal ideation, alcohol/drug problems, and/or chronic depression.[3] In addition, potential candidates may be excluded if they are taking certain types of medication. This exclusionary process ultimately results in an atypical sample, with subsequent clinical results being difficult to generalize to

Table 1: New and Upcoming Antidepressants to the U.S. Market

Antidepressant	FDA Status	FDA Indication
Transdermal selegiline patch (Emsam™)	Approved 2006	Major depression
Trazodone extended-release (Oleptro™)	Approved 2010	Major depression
Vilazodone (Viibryd™)	Approved 2011	Major depression
Agomelatine (Valdoxan™)	Anticipated 2012	Probably major depression

Note: FDA = Food and Drug Administration

typical clinical populations. As summarized by Gaynes, "…the available 'evidence' from clinical trials involves a largely 'pure,' uncomplicated population of depressed patients…."[3]

In an effort to examine the effects of depression treatments in *typical* clinical populations, the National Institute of Mental Health sponsored a multi-step treatment study titled, "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D). This study was historically unique in that it was the largest and longest prospective study of depression treatment ever undertaken in the United States. A total of 2876 patients were recruited from 14 centers and initially enrolled in the study. These participants were accessed from 18 primary care clinics as well as 23 psychiatric clinics (i.e., the sample was mixed with both primary care and psychiatric outpatients).[3] Exclusion criteria were fairly minimal and included bipolar disorder, psychosis, obsessive-compulsive disorder, eating disorder, and a past history of seizures. To illustrate the broad nature of this study population, only 22.2% of participants in the STAR*D study would have met study-entry criteria for typical Phase 3 trials for depression.[4] Enrollment in STAR*D began in the year 2000, and the eventual cost of the study was $35 million over a 6-year period.[5]

As suggested by the name of the study, participants were subjected to sequential treatment options or levels for depression, both pharmacological (monotherapy and augmentation strategies) and psychological (i.e., cognitive-behavioral therapy), if a treatment failed. There were four general levels, but at each level with the exception of the first, there was the possibility of several intervention options. At the first level, all participants underwent a trial with citalopram.

In the aftermath of the study, investigators examined cumulative remission rates, which represent the overall remission rates for the entire sample at a given level of treatment. At level 1, there was a remission rate of 33%.[6] At levels 2, 3, and 4, the cumulative remission rates were 57%, 63%, and 67%, respectively.[6] Note that the last percentage represents the overall remission rate for the entire sample, which for many participants entailed exposure to several levels of treatment. Overall, two-thirds of participants experienced remission.

As expected, there were a number of epidemiological and clinical scenarios that predicted lower response rates to depression treatment. These included minority status, lower socioeconomic status, poor premorbid functioning, comorbid Axis I psychiatric disorders, and anxious and/or melancholic features.[7] In addition, researchers found that both alcohol and drug use resulted in significantly reduced rates of remission[8] as well as depression accompanied by somatic symptomatology.[9] Finally, among responders (i.e., those who evidenced improvement but not full remission) but not remitters, several symptom domains were persistent. The most common were insomnia (94.6%), sad mood (70.6%), and decreased concentration (69.6%).[10]

What can we conclude about the STAR*D findings? Unlike the remission rates reported in Phase 3 clinical trials with an exposure to one drug (i.e., 35%-40%), remission rates at the first level in STAR*D were somewhat lower (33%).[6] In addition, persistence in treatment undertakings resulted in a cumulative remission rate of two-thirds. However, one could re-interpret the STAR*D data and conclude that with an initial drug trial for depression, two-thirds of participants do not experience remission. Likewise, after extensive levels of various interventions, one-third of the participants remain ineffectively treated.

Overall, STAR*D findings support the clinical impression that depression is extremely challenging to treat, and that clinician and patient perseverance is required. It is this very treatment-resistance that underscores the limitations of our currently available antidepressants. This theme, in turn, is behind the search for better and more novel antidepressant medications. In the following pages, we will discuss four antidepressants that are new-to-market or on the horizon. One represents a familiar pharmacological strategy whereas three represent novel pharmacological strategies. Only further clinical evaluation will determine if these antidepressant additions will improve current remission rates for depression.

Transdermal Selegiline (Emsam™)

Background

Transdermal selegilene (Emsam™) is an irreversible monoamine oxidase inhibitor (MAOI) that has been uniquely formulated into a transdermal technology.[11] It is the first antidepressant in the United States to be administered through a transdermal delivery system.[12] This antidepressant was approved by the FDA in 2006 for the treatment of major depression.[11]

To tease out the nuances of transdermal selegiline, pre-existing MAOIs, such as phenelzine (Nardil™), are all oral formulations that inhibit both monoamine oxidase A (found in the brain, gastrointestinal tract, and liver) and monoamine oxidase B (found predominantly in the brain). This broad level of monoamine oxidase inhibition impedes the catabolism of dopamine, norepinephrine, and serotonin in both the peripheral and central nervous systems. The extended preservation of these monoamines is believed to be the explanation for the antidepressant effects of these pharmacologically unusual medications. However, traditional MAOIs are well known for their potential to cause hypertensive crises when ingested with particular drugs (e.g., sympathomimetics, psychostimulants) and foods containing high-pressor amines (i.e., "the tyramine reaction").

By bypassing absorption in the gastrointestinal tract, transdermal selegiline at the lowest dose (i.e., 6 mg/24 hour) minimally inhibits monamine oxidase A (MAO-A) in the digestive tract and liver. This unique pharmacological aspect eliminates the need

for food restrictions at the lowest dose of the transdermal patch (i.e., 6 mg/24 hours), which is also the target treatment dose recommended by the manufacturer. In addition to this unique bypass effect, animal studies suggest a differential inhibition of MAO-A by selegiline, with higher inhibition in the brain, but only 30%-40% inhibition in the gastrointestinal tract, again accounting for a reduced risk of food interactions.[13] Importantly, this disproportionate effect appears to wane at higher doses.

Pharmacology

Following absorption, transdermal selegiline is approximately 90% plasma-protein bound and readily crosses the blood-brain barrier.[11] This antidepressant is ultimately metabolized to desmethylselegiline and methamphetamine, both of which are further metabolized to amphetamine.[14] The mean half-lives of transdermal selegiline and its two major metabolites are between 18 and 25 hours, with steady state levels attained in about 5 days.[14]

Sample Studies

In a double-blind, placebo-controlled trial, Bodkin and Amsterdam examined 177 adult psychiatric outpatients with major depressive disorder; the active treatment group was receiving 20 mg per day of transdermal selegiline (note the high dose in this study).[15] After 6 weeks, participants taking transdermal selegiline evidenced greater improvement on all study measures for depression compared with participants on placebo.

Amsterdam also reported the results of a treatment trial with transdermal selegiline in 365 patients from 16 different study sites.[16] The trial was double-blind and placebo-controlled, and all participants suffered from major depression. Again, a number of study measures for depression evidenced the superiority of transdermal selegiline over placebo.

Finally, Feiger and colleagues enrolled 265 patients with major depression into a double-blind, placebo-controlled trial of transdermal selegiline.[17] In doses varying from 6-12 mg/24 hours, there was empirical evidence of short-term efficacy (8 weeks).

Dosing

Transdermal selegiline is supplied in 6 mg, 9 mg, and 12 mg/24 hour transdermal patches.[11] Dosages are initiated at 6 mg/24 hours, which is the recommended target dose. The dose can be increased, if clinically indicated, at intervals of no less than 2 weeks, to 9 mg and 12 mg/24 hours. The maximum dosage is 12 mg/24 hours.

Typical Side Effects

According to available studies, transdermal selegiline is generally well tolerated, with local reactions at the application site being the most commonly reported adverse phenomena. Most of these cutaneous reactions are of mild-to-moderate severity.[11,18] Transdermal selegiline also may cause postural hypotension, particularly in the elderly, as well as mild weight loss.[11] Transdermal selegiline should be discontinued at least 10 days prior to elective surgery.[11] Transdermal selegiline may induce suicidal ideation, precipitate serotonin syndrome in combination with other serotonergic-enhancing medications, and/or induce mania/hypomania.

Adjustments for Hepatic/Renal Disease

No dosage adjustments are required for transdermal selegiline in mild-to-moderate hepatic insufficiency or in renal disease.[11]

Overdose Profile

Although overdose with transdermal selegiline has not been well studied, overdose with traditional MAOI agents is typically associated with central nervous system and cardiovascular toxicity.[14] The intensity of symptoms tends to relate to the extent of the overdose. There is no specific antidote for overdose and medical treatment is supportive in nature.[14]

Unique Features

Transdermal selegiline is less cumbersome than traditional MAOIs because the transdermal delivery system eliminates the potential risk of food interactions at the 6 mg/24 hour dose.

Suitability in Primary Care

Although transdermal selegiline is an interesting and novel approach to the treatment of major depression, there are numerous and less complicated pharmacological alternatives to undertake in primary care settings. Importantly, the risk of a hypertensive crisis with offending medications remains at all doses and continues with specified foods at moderate-to-high doses. In our opinion, the consideration of this type of pharmacological intervention likely indicates that the patient is fairly complicated from a psychiatric perspective, if not pharmacologically refractory. Because of its potential risk profile, transdermal selegiline is likely to be relegated to psychiatrically complex patients, with trials being undertaken mostly by psychiatrists. Not surprisingly, during a 12-month period ending in March 2007, transdermal selegiline accounted for fewer than 0.1% of all antidepressant prescriptions.[19] (*See Table 2 for a summary of transdermal selegiline.*)

Table 2: Synopsis of Transdermal Selegiline

- **Mechanism of action: Irreversible inhibition of monoamine oxidase**
- **Unique feature: Absence of food restrictions at the lowest dose (6 mg/24 hour)**
- **Potential risks: Drug interactions (all doses) as well as food interactions at higher doses (9 mg and 12 mg/24 hour)**
- **Recommendation for primary care: Avoid**

Primary care recommendation for transdermal selegiline: *Avoid.*

Trazodone Extended-Release (Oleptro™)

Background

Trazodone, which was initially approved by the FDA in 1981 for the treatment of major depression, was approved in 2010 as an extended-release formulation.[11] Although regular-release trazodone is administered in divided daily doses, trazodone extended-release is administered as a single dose at bedtime.[11] Like regular-release trazodone, the explicit antidepressant mechanism of trazodone extended-release remains unknown, but the drug singularly affects serotonin. In this role, trazodone appears to inhibit the reuptake of serotonin, and function both as a serotonin antagonist at low dose and a serotonin agonist at high dose (i.e., it has a unique mechanism of action among the antidepressants).[11]

Pharmacology

Trazodone has a biphasic elimination pattern, with the first phase being 3 to 6 hours and the second phase being 5 to 9 hours.[11] However, there appears to be wide inter-individual variation in clearance.

Sample Studies

In a randomized, double-blind, placebo-controlled, 8-week study by Sheehan and colleagues,[20] trazodone extended-release evidenced significant separation from placebo as early as the first week of exposure — a clinical separation that was maintained at the end of the study. According to investigators, the new formulation of trazodone was well tolerated, although adverse effects, such as somnolence and fatigue, were approximately twice as common in the active treatment group compared to placebo (30% and 15%, respectively, in the treated cohort).

Dosing

Trazodone extended-release is available in 150 mg and 300 mg tablets, and both formulations are scored. The typical starting dose is 150 mg at bedtime, with dosage increases of 75 mg every three days to a maximum of 375 mg per day, as clinically indicated.

Typical Side Effects

According to the package insert for trazodone extended-release,[21] the most common side effects are somnolence/sedation (46%), headache (33%), dry mouth (25%), and dizziness (25%). In addition to the typical antidepressant warnings related to suicidal ideation, serotonin syndrome, and the possible induction of mania/hypomania, trazodone extended-release may prolong the QT interval (the prescriber is advised to be aware of co-administering trazodone with other medications that may prolong the QT interval, as this may result in Torsades de Pointes and sudden death). Because of the preceding risk, trazodone extended-release should be avoided during the initial recovery phase from a myocardial infarction.[21] The drug also may cause orthostatic hypotension and priapism (rare), and has the potential for causing abnormal bleeding (related to its serotonergic effects on platelets), although no cases of the latter adverse effect have been reported.[21] At the time of discontinuation, trazodone extended-release should be weaned to avoid any withdrawal symptoms.

Adjustments for Hepatic/Renal Disease

In the presence of either hepatic[11] or renal disease,[21] the manufacturer recommends cautious dosing.

Overdose Profile

Overdose of regular-release trazodone has been associated with respiratory arrest, seizures, and changes on the electrocardiogram.[21] Treatment of overdose consists of supportive care.[21]

Unique Features

The new trazodone extended-release improves the tolerability of an historic antidepressant by enabling once-per-day administration and reducing daytime sedation.

Suitability in Primary Care

Given the continuing risk of daytime sedation and potential cardiac consequences of trazodone extended-release (particularly in elderly populations), coupled with the availability of a number of well-tolerated alternative antidepressants, this medication is likely to be relegated to specific patients who are refractory to usual antidepressant therapies (e.g., selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors). These resistant individuals are probably best treated by a psychiatrist. (*See Table 3 for a summary of trazodone extended-release.*)

Primary care recommendation for trazodone extended-release: *Very selective use (antidepressant-refractory younger patients without cardiac disease).*

Vilazodone (Viibryd™)

Background

Vilazodone was developed in Germany, where it was licensed in 2001.[22] According to the manufacturer, vilazodone has two distinct

Table 3: Synopsis of Trazodone Extended-Release

- **Mechanism of action: Serotonin reuptake inhibition, serotonin antagonism at low dose and serotonin agonism at high dose**
- **Unique feature: Compare with its forerunner, trazodone regular-release, once per day dosing at bedtime**
- **Potential risks: Daytime sedation and the risk of QT prolongation, particularly with QT-prolonging co-administered drugs**
- **Recommendation for primary care: Very selective use, in younger patients without cardiac disease and not on co-administered drugs that might prolong the QT interval**

actions: (1) serotonin reuptake inhibition (akin to a selective serotonin reuptake inhibitor) and (2) partial 5HT1a agonism. This latter feature is characteristic of the azapirones, a pharmacological class of drugs that includes buspirone (Buspar™). Vilazodone was approved by the FDA in 2011 for the treatment of major depression[23] and is being marketed in the United States by Clinical Data.[24]

Pharmacology

Although vilazodone's pharmacological activity is attributed to the parent drug, the compound has a hydroxylated metabolite.[22] Food increases the bioavailability of vilazodone.[25] Following absorption, the drug is predominantly metabolized through hepatic cytochrome 3A4 of the P450 isoenzyme system. The half-life of vilazodone is approximately 25 hours, enabling once-per-day dosing.[25]

Sample Studies

Using a randomized, double-blind, placebo-controlled trial, Rickels and colleagues examined vilazodone in a sample of 410 participants.[26] In this 8-week study, the mean changes from baseline on two study measures for depression were significantly greater than placebo. A second 8-week study mirrored the preceding findings.[25] Treatment-emergent adverse events in the Rickels et al study included diarrhea (24%), nausea (19%), and headache (13%).[26]

Dosing

Vilazodone is supplied in 10 mg, 20 mg, and 40 mg tablets. The manufacturer suggests initiating the dose at 10 mg per day for 7 days, then increasing the dose to 20 mg per day for 7 days, and then to 40 mg per day, thereafter, which is the recommended dose.[25]

Typical Side Effects

The most common side effects of vilazodone appear to be diarrhea, nausea, and somnolence. Most adverse events, as noted in the study by Rickels et al,[26] are of mild-to-moderate intensity. To date, vilazodone has not been associated with any changes in the electrocardiogram. In addition, the drug appears to be weight-neutral.[25] As with other antidepressants, vilazodone has warnings related to suicidal ideation, serotonin syndrome, and the induction of mania/hypomania. Because of its serotonergic profile, the drug may cause abnormal bleeding, particularly when co-administered with nonsteroidal anti-inflammatory drugs.[25] Vilazodone has not been evaluated in patients with seizure disorders. At the time of discontinuation, vilazodone should be weaned to avoid a withdrawal syndrome.

Adjustments for Hepatic/Renal Disease

In the presence of liver disease, cautious dosing is advised.[11] No dosage adjustments are indicated in the presence of renal disease.[11,25]

Overdose Profile

There is little available information about the consequences of overdose with vilazodone. To date, there have been five reported overdoses and all individuals have recovered.[25] The treatment of vilazodone overdose consists of supportive care.[25]

Unique Features

Vilazodone represents a unique class of antidepressants, is well tolerated, has minimal sexual side effects, and appears to be weight neutral.

Suitability for Primary Care

If broader exposure in general populations demonstrates good efficacy and cost is reasonable, this antidepressant may be very viable in the primary care setting. Specifically, if vilazodone is as efficacious as selective serotonin reuptake inhibitors and has the additional advantages of being weight neutral with minimal sexual dysfunction, it may capture a significant portion of the antidepressant market. In addition, vilazodone does not appear to have any limitations with regard to cardiac syndromes. (*See Table 4 for a summary of vilazodone.*)

Primary care recommendation for vilazodone: *if clinically validated and cost competitive, consider use after this medication has had broader population exposure.*

Table 4: Synopsis of Vilazodone

- **Mechanism of action: Selective serotonin reuptake inhibition, 5HT1a partial agonist**
- **Unique feature: Unique pharmacological action, with no sexual dysfunction and minimal weight gain**
- **Potential risks: Given the cost of a new product, will vilazodone be competitive with the current antidepressant stalwarts?**
- **Recommendation for primary care: If cost competitive, consider after broader population exposure and confirmation of unique features**

Agomelatine (Valdoxan™, Thymanax™)

Background

Agomelatine, which is expected to be available in the United States in 2012, is a unique antidepressant that exhibits MT1 and MT2 receptor-site agonism and 5HT2c antagonism.[27] The former function is believed to re-synchronize circadian rhythms (i.e., it is a melatonergic antidepressant).[27] The latter function blocks the disinhibition of norepinephrine and dopamine, enhancing their release (i.e., therefore, agomelatine is a noradrenergic/dopaminergic antidepressant).[28] Agomelatine is a structural analogue of melatonin[29] and was developed by the European pharmaceutical company, Servier Laboratories Ltd.[30] The drug was first approved for clinical use in the European Union in 2009.[30] Servier sold the rights to market agomelatine

in the United States to Novartis.[30]

Pharmacology

Agomelatine is well absorbed orally, with greater bioavailability in women compared with men.[27] Food intake does not appear to alter the absorption or bioavailability of agomelatine.[27] The drug is 95% plasma-protein bound and is metabolized predominantly by hepatic cytochrome 1A2 of the P450 isoenzyme system (90%).[27] Because of this metabolic route, several drugs (e.g., fluvoxamine, estrogens, propranolol) may inhibit the metabolism of agomelatine through their potentials to inhibit cytochrome 1A2, resulting in an increase in agomelatine levels. The elimination of agomelatine is rapid, with a plasma half-life between 1 and 2 hours.[27]

Sample Studies

Agomelatine has been examined in several clinical studies. For example, in a 6-week, randomized, double-blind study, Lemoine and colleagues reported beneficial effects of agomelatine from the first week of treatment, with even better responses among participants than the comparator antidepressant, venlafaxine extended-release.[31] The efficacy of agomelatine was further demonstrated in 6-week and 8-week studies, both double-blind and placebo-controlled.[32,33] Agomelatine has also demonstrated efficacy in a maintenance trial.[34] An unusual strategy for a new-to-market antidepressant, agomelatine has been empirically compared with a number of other competitive antidepressants, including venlafaxine,[31] paroxetine,[33] and fluoxetine,[35] with either comparable or better clinical results. Additional studies[36,37] and the results of a pooled study[38] also attest to the antidepressant efficacy of agomelatine. With regard to psychiatric symptoms other than those encountered in major depression, agomelatine has also been effective in the treatment of anxiety symptoms[39,40] as well as seasonal affective disorder.[41]

Dosing

Agomelatine is manufactured as a 25 mg tablet,[27] and the initial dosage is 25 mg at bedtime. The manufacturers indicate that if there is no symptom response, the dose should be increased to 50 mg at bedtime (two 25 mg tablets).

Typical Side Effects

Side effects with agomelatine are generally mild and transient, and occur within the first two weeks of treatment. Nausea and dizziness are most commonly reported and occur in 1%-10% of patients,[27] although agomelatine may also cause somnolence, insomnia, migraine headaches, anxiety, constipation or diarrhea, fatigue, back pain, and hyperhidrosis, also in 1%-10% of patients.

Despite the preceding possible side effect of insomnia, agomelatine paradoxically appears to improve overall sleep quality without daytime sedation.[42] In support of this impression, according to Kupfer, agomelatine resulted in sleep electroencephalographic changes that were consistent with desirable improvements in sleep architecture.[43] In addition, Salva and colleagues reported improved sleep continuity and quality with agomelatine.[44] Lemoine and colleagues found that, compared with venlafaxine, agomelatine resulted in faster sleep onset, better sleep quality, and fewer awakenings.[31] The overall effect of agomelatine with regard to sleep appears to be a re-synchronization of Circadian rhythms.

Agomelatine has little consequence on sexual functioning, an adverse effect that is commonly encountered with the use of selective serotonin reuptake inhibitors. In support of this finding, studies indicate that agomelatine was significantly less likely to cause sexual dysfunction in comparison with either paroxetine[45] or venlafaxine extended-release.[46] The comparison study with venlafaxine extended-release is particularly provocative, as serotonin norepinephrine reuptake inhibitors demonstrate fairly good profiles with regard to sexual functioning.

Unlike the majority of antidepressants, particularly serotonergic agents such as selective serotonin reuptake inhibitors and venlafaxine, agomelatine is not associated with a discontinuation syndrome. This finding was confirmed in a 12-week study highlighted by abrupt cessation of the drug[47] as well as a 24-week study.[34]

With regard to potential limitations, according to the manufacturer, agomelatine may cause an increase in serum hepatic transaminases.[27] The prevalence of this side effect is 1.1%.[27] In clinical studies, elevations of these hepatic transaminases have been as high as three times the upper limit of the normal range.[27] With the discontinuation of agomelatine, hepatic transaminases have returned to normal. At the present time, the manufacturer is recommending baseline liver function tests with follow-up testing at 6, 12, and 24 weeks.[27]

Like other antidepressants, the induction of suicide and/or hypomania/mania is a potential risk.[27] However, because agomelatine does not enhance serotonin, there is no apparent risk of serotonin syndrome or abnormal bleeding due to serotonergic effects on platelets.

Adjustments for Hepatic/Renal Disease

Agomelatine is contraindicated in the presence of hepatic impairment, but requires no dosage adjustment in renal impairment.[27]

Overdose Profile

Being a new antidepressant, there is limited information on the safety of agomelatine in overdose.[27] However, available reports suggest that agomelatine overdoses are characterized by somnolence, fatigue, agitation, anxiety, tension, dizziness, and/or malaise.[27] According to the product information summary, one individual overdosed on 2450 mg of agomelatine and spontaneously recovered without medical incident.[27] As with the preceding antidepressants, the treatment of agomelatine overdose consists of supportive care.[27]

Suitability for Primary Care

If the present impressions of agomelatine are confirmed with broader clinical experience, this antidepressant will be a unique addition that is well tolerated, performs equally well if not better than selective serotonin reuptake inhibitors and serotonin norepinephrine

Table 5: Synopsis of Agomelatine

- Mechanism of action: MT1/MT2 effects with 5HT2c antagonism (blocks inhibition effects of this receptor with a subsequent release of norepinephrine and dopamine)
- Unique features: Unique pharmacological action, re-synchronizes sleep patterns, minimal sexual dysfunction, weight neutral, no discontinuation syndrome, as effective if not more so than current antidepressant stalwarts
- Potential risks: Hepatic enzyme elevation, required periodic laboratory testing, unknown overdose risk
- Recommendation for primary care: Consider for general use if the above claims are supported in broader population samples and overall cost is not prohibitive

reuptake inhibitors, has minimal sexual dysfunction, is weight neutral, and has no discontinuation syndrome. The only clinical limitations are the contraindication in liver disease and the required liver function tests, the latter of which adds additional inconvenience for the patient as well as cost to the treatment. As with all new antidepressants, the drug's overall safety profile in overdose will need to be further assessed. If the overdose profile indicates a broad margin of safety, agomelatine may be a very suitable antidepressant candidate in the primary care setting. (*See Table 5 for a summary of agomelatine.*)

Primary care recommendation for agomelatine: *A potentially excellent antidepressant in the primary care setting, pending further assessment of overdose and hepatic risks, and cost determination.*

Conclusions

A number of antidepressant newcomers have arrived to the United States, or are about to arrive, to aid clinicians in the treatment of depression. As always, each antidepressant has to be evaluated in terms of its risk–benefit ratio as well as cost profile. Each of the four antidepressants that we have presented has a varying risk–benefit ratio. For example, transdermal selegiline remains a risk-laden proposition due to potential drug interactions, despite a lessened risk of food interactions at the 6 mg/24 hour dose. Trazodone extended-release is likely to be a better tolerated antidepressant than its forerunner, trazodone regular-release, but the risk of daytime sedation is ever-present and the clinician needs to be mindful of co-administering medications that prolong the QT interval. Vilazodone has the potential effectiveness of a selective serotonin reuptake inhibitor, without weight gain or sexual dysfunction, but will the potential cost of this newcomer unseat established antidepressants? Finally, agomelatine appears to be the most robust newcomer, boasting a unique pharmacological profile characterized by the absence of a discontinuation syndrome, improved sleep patterns, weight neutrality, and minimal sexual dysfunction. Yet, accompanying laboratory studies and cost of the medication may curtail acceptability. As in all pharmacological considerations, the decision to prescribe will be multifold, depending on risk/benefit ratio, cost, experience of the clinician, availability of psychiatric support, patient complexity, etc. However, these newcomers appear to be the advent of a new era—one that is characterized by creative psychopharmacology and by antidepressants with unique styles of action.

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CME Questions

1. Selegiline transdermal (Emsam™) is a MAOI that is uniquely characterized by:
   a. the absence of drug interactions at the dose of 6mg/24 hour.
   b. the absence of food interactions at the dose of 6mg/24 hour.
   c. the absence of both drug and food interactions at the dose of 6 mg/24 hour.
   d. the absence of both drug and food interactions at all available doses.

2. Trazodone extended-release (Oleptro™):
   a. is administered several times per day in equal amounts.
   b. is administered once per day, in the morning.
   c. is administered once per day, in the evening.
   d. is administered several times per day, with the majority of the dosage in the evening.

3. Vilazodone's (Viibryd™) proposed mechanism of action is:
   a. selective serotonin reuptake inhibition and 5HT1a agonism.
   b. serotonin norepinephrine reuptake inhibition and 5HT2c antagonism.
   c. 5HT pre-synaptic receptor activity with 5HT1d agonism.
   d. pre-synaptic and post-synaptic receptor site activity.

4. Vilazodone (Viibryd™) side effects may include all of the following except:
   a. diarrhea.
   b. nausea.
   c. weight gain.
   d. somnolence.

5. Vilazodone (Viibryd™):
   a. usually decreases libido.
   b. has minimal sexual dysfunction.
   c. usually delays orgasm.
   d. usually causes erectile dysfunction.

6. Agomelatine (Valdoxan™) is a:
   a. MT1/MT2 antidepressant with 5HT1a agonism.
   b. 5HT1a, 5HT2c antidepressant.
   c. MT1/MT2 antidepressant with 5HT2c antagonism.
   d. 5HT1a agonist with 5HT2c antagonist.

7. In terms of neurotransmitter effects, agomelatine (Valdoxan™) results in:
   a. an increase in serotonin.
   b. an increase in dopamine.
   c. an increase in GABA.
   d. a decrease in serotonin.

8. Agomelatine (Valdoxan™) is characterized by all of the following except:
   a. minimal sexual dysfunction.
   b. a discontinuation syndrome.
   c. weight neutrality.
   d. re-synchronization of sleep patterns.

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