The Interface

AGOMELATINE:
A Novel Antidepressant

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Depression is highly prevalent in community and primary care samples. According to the findings of the Sequential Treatment Alternatives to Relieve Depression study, after multiple clinical interventions, approximately one-third of patients never fully experienced remission from depression. This somber finding invites consideration of novel antidepressant options, which may in the near future include agomelatine. Agomelatine is a melatonergic agonist and a $5HT_{2c}$ antagonist (i.e., it has a unique mechanism of action). The melatonergic function appears to improve sleep patterns, whereas the serotonergic antagonism results in the release of norepinephrine and dopamine. Given the current information, the overall side-effect profile of agomelatine appears relatively mild. For example, agomelatine has no discontinuation syndrome, exhibits infrequent sexual dysfunction, and is generally weight neutral. The drug appears to be relatively safe in overdose. On a cautionary note, however, one percent of patients experience elevated hepatic transaminases while on treatment. Overall, agomelatine may be a unique pharmacological addition in the clinical war on depression in both psychiatric and primary care settings—if further evaluation in clinical trials supports reasonable risk.

KEY WORDS

Agomelatine, antidepressant, depression

INTRODUCTION

Depression is highly prevalent in community as well as primary care samples. For example, according to the findings of the National Comorbidity Survey Replication study, which examined the prevalence of various Axis I disorders in the general population, the lifetime prevalence of any type of depression is 21 percent, or one in five persons.[1] In a landmark study of the prevalence of depression in primary care settings, Spitzer et al[2] reported rates for current dysthymia, major depression, and any mood disorder of eight, 12, and 26 percent, respectively. In a more recent study of mood disorders in a German primary care population, Wittchen et al[3] found that 6 percent of patients suffered from current major depression, with 1.6 percent of these individuals meeting criteria for comorbid generalized anxiety disorder. The preceding findings indicate that a significant minority of individuals in the community and in primary care settings struggle with depression at some point in their lifetimes.

Despite the numerous and diverse array of available pharmacological treatments, the effective resolution of depression remains challenging. To underscore this impression, we will briefly review the landmark study, Sequenced Treatment Alternatives to Relieve Depression

(STAR*D). We will then introduce agomelatine, a novel antidepressant that may be approaching entry into the United States antidepressant market.

STAR*D OVERVIEW

Clinicians have long noted that the response and remission rates reported in pharmaceutical trials are oftentimes higher than corresponding rates experienced in clinical practice. This difference is most likely explained by the exclusionary criteria encountered in most, if not all, pharmaceutical trials. Various exclusions in these research protocols result in a relatively pure population of severely depressed individuals with little comorbidity (e.g., few, if any, studies allow for serious medical problems, alcohol/substance use disorders, or comorbid psychiatric conditions). In an effort to examine treatments for depression in more naturalistic populations, the National Institute of Mental Health undertook a longitudinal study to determine sequential depression-treatment outcomes in a relatively unrestricted clinical population—the STAR*D study.

The STAR*D study was initiated in the year 2000.[4] In the recruitment phase, investigators enrolled 2,876 outpatients from 18 primary care clinics and 23 psychiatric clinics.[5] The protocol had relatively few exclusion criteria, which included bipolar disorder, psychosis, obsessive-compulsive disorder, eating disorder, and past history of seizures. In comparing the eventual sample in this study with select samples obtained during pharmaceutical trials, Wisniewski et al[6] estimated that only 22.2 percent of participants in the STAR*D study would have met study entry criteria for typical Phase III trials for depression. The STAR*D study took place over a six-year study period and cost $35 million.[4]

As indicated by the unabridged name of the study, participants were subjected to sequential treatment options or levels of intervention, consisting of both pharmacological therapy (antidepressant monotherapy as well as augmentation strategies) and psychological therapy (i.e., cognitive behavioral therapy) for depression—if initial and subsequent treatment options failed. There were four general intervention levels, but at each level, with the exception of the first, there was the possibility of various treatment alternatives. At the first level of intervention, all participants underwent a trial with citalopram.

At the end of the study, investigators determined the cumulative remission rates, which represent the overall remission rates for the entire sample at a given level of treatment. For levels 1 through 4, these rates were 33, 57, 63, and 67 percent, respectively.[5] Given that the last percentage represents the overall remission rate for the entire sample, which for many participants entailed exposure to several treatment trials, approximately two-thirds of participants in this study eventually experienced remission. However, it is important to note that one-third of participants failed these various treatments. Investigators identified lower response rates among patients with comorbid Axis I psychiatric disorders and mood disorders with anxious/melancholic features,[7] alcohol and drug use,[8] and depression accompanied by somatic symptomatology[9]—all relatively common characteristics of patients seen in primary care settings.

Conclusions from the STAR*D study were as follows: 1) with an initial antidepressant course, only one-third of participants experienced remission, 2) two-thirds of participants achieved cumulative remission through sequential treatment undertakings; and 3) even after various therapeutic interventions, one-third of participants remained ineffectively treated for depression. In other words, depression can be daunting to treat. These findings segue into the anticipated arrival of the novel antidepressant, agomelatine.

AGOMELATINE

Description. Agomelatine is a structural analog of melatonin[10] and was developed by the European pharmaceutical company Servier Laboratories Ltd (Neuilly-sur-Seine, France).[11] Agomelatine was first approved for clinical use in the European Union in 2009,[11] where it is marketed under the names Valdoxan™ or Thymanax.™ Novartis, who purchased the marketing rights from Servier, is currently seeking United States Food and Drug Administration (FDA) approval for the drug in the United States.

Agomelatine is in a unique pharmacological class. Explicitly, unlike other available antidepressants, agomelatine is a melatonin agonist (i.e., MT_1 and MT_2 receptor-site agonism) and a $5HT_{2c}$ antagonist.[12] The melatonergic effect is purported to resynchronize circadian rhythms.[12] The serotonergic action is not as imagined. To explain this, the $5HT_{2c}$ receptor inhibits the release of norepinephrine and dopamine. By antagonizing this receptor, agomelatine disrupts the previous inhibition effect, which results in the release of norepinephrine and dopamine (i.e., the overall neurotransmitter effect is that agomelatine is a noradrenergic/dopaminergic antidepressant).[13]

Pharmacology. Agomelatine is well absorbed orally, with greater bioavailability in women compared with men.[12] Food intake does not

appear to alter the absorption or bioavailability of agomelatine.[12] The drug is 95-percent plasma-protein bound and is metabolized predominantly by hepatic cytochrome 1A2 of the P450 isoenzyme system (90%).[12] Because of this hepatic pathway, drugs that inhibit cytochrome 1A2 (e.g., fluvoxamine, estrogens, propranolol) may slow the metabolism of agomelatine, resulting in increased agomelatine levels. The elimination of agomelatine is rapid, with a plasma half-life between 1 and 2 hours.[12]

Efficacy studies of agomelatine. Agomelatine has been examined in a number of different types of clinical studies. In a six-week, randomized, double-blind study of 332 patients with major depression, Lemoine et al[14] reported beneficial effects of agomelatine 25 to 50mg per day from the first week of treatment, with overall better responses than the comparator antidepressant, venlafaxine extended release. Olie and Kasper[15] reported the efficacy of agomelatine 25 to 50mg per day in a six-week double-blind trial of 238 patients. In an eight-week, double-blind, placebo-controlled trial of 711 patients with major depression, Loo and Hale[16] reported the efficacy of agomelatine (doses between 1 and 25mg per day), using paroxetine as a comparator.[16]

In addition to acute treatment effects, agomelatine demonstrated efficacy in a maintenance trial.[17] In this study, Goodwin et al[17] examined the sustained efficacy of agomelatine in 165 patients in a randomized, placebo-controlled, double-blind trial of 24 weeks. During the study period, depression relapse was significantly lower among the active treatment group.

Agomelatine has been empirically compared with a number of other antidepressants, including venlafaxine,[14] paroxetine,[16] and fluoxetine,[18] with generally comparable clinical results. Additional studies[19–21] attest to the general antidepressant efficacy of agomelatine, which has also been effective in the treatment of anxiety[22,23] and seasonal affective disorder.[24]

Because of its effects on melatonin receptors, agomelatine purportedly improves overall sleep quality without daytime sedation.[14,25,26] This effect is paralleled by changes in sleep electroencephalograms, which indicate improvements in overall sleep architecture.[27] It appears that the global effect of agomelatine with regard to sleep is a resynchronization of circadian rhythms.

Dosing and side-effect profile. Agomelatine is manufactured as a 25mg tablet,[12] which is the initial dose and is administered at bedtime. If there is no response, the dose of agomelatine is to be increased to 50mg at bedtime (two 25mg tablets).

General side effects with agomelatine are mild and transient, and typically emerge within the first two weeks of treatment. Side effects may include nausea and dizziness, which are most commonly reported, as well as somnolence, insomnia, migraine headaches, anxiety, constipation, diarrhea, fatigue, back pain, and hyperhidrosis.[12]

Importantly, agomelatine may also cause an increase in serum hepatic transaminases, as high as three times the upper limit of the normal range, in up to one percent of individuals.[12] While the prompt discontinuation of agomelatine has resulted in the normalization of hepatic transaminases, this potential side effect warrants further investigation, particularly with regard to any long-term risks. At the present time, the manufacturer recommends baseline liver function tests with follow-up testing at six, 12, and 24 weeks.[12]

Like other antidepressants, the induction of suicide and/or hypomania/mania is a potential risk when prescribing agomelatine.[12] Because agomelatine does not enhance serotonin, there is no apparent risk of serotonin syndrome, abnormal bleeding due to serotonergic effects on platelets or the upper gastrointestinal tract, or discontinuation syndrome[12] according to a 12-week[28] and a 24-week study.[17]

Agomelatine apparently has little consequence on sexual functioning.[12] In this regard, agomelatine was significantly less likely to cause sexual dysfunction in comparison with either paroxetine[29] or venlafaxine extended-release.[30] In addition to minimal sexual dysfunction, in a 24-week study, agomelatine was weight neutral at all doses.[17]

Being a new antidepressant, there is limited information on the safety of agomelatine in overdose.[12] Available reports suggest that overdoses with agomelatine are characterized by somnolence, fatigue, agitation, anxiety, tension, dizziness, and/or malaise.[12] One individual overdosed on 2,450mg of agomelatine and spontaneously recovered without medical incident.[12]

CONCLUSIONS

Depression is highly prevalent both in the community and primary care samples. While numerous and diverse treatments are available for depressed patients, data from STAR*D indicate that only one-third of patients experience remission with an initial antidepressant trial and only two-thirds achieve remission after multiple interventions (i.e., one-third of patients never experienced remission of depression in this study). Given this complex clinical terrain, an antidepressant with a novel mechanism of action is appealing. Agomelatine is a novel agent with

melatonin-agonist and $5HT_{2c}$-antagonist activity. The latter activity results in the release of norepinephrine and dopamine (i.e., the drug does not affect serotonin levels). Agomelatine appears to be well tolerated, have low rates of sexual dysfunction, exhibit no discontinuation syndrome, and be weight neutral. Agomelatine improves sleep and, at present, seems to be relatively safe in overdose. However, this antidepressant may cause elevations in hepatic enzymes—a finding that warrants further investigation. If agomelatine is reasonably safe in terms of drug interactions and hepatic effects, the cost is competitive, and clinical exposure in the United States parallels current findings, agomelatine may be a useful addition to the current pharmacological armamentarium in the clinical war against depression.

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