WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 7, 1323-1334. Review Article ISSN 2277– 7105

COMPARATIVE REVIEW OF A NOVEL MELATONERGIC ANTIDEPRESSANT DRUG- AGOMELATINE

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Article Received on
30 April 2015,

Revised on 22 May 2015,
Accepted on 12 June 2015

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ABSTRACT

Depression significantly affects patients and their families. Thus, there is need for more effective and well tolerated antidepressants to treat this condition. Agomelatine is a novel antidepressant that works on melatonergic and serotonin receptors. Published studies claim it is a useful alternative pharmacological strategy to the existing antidepressant drugs while unpublished studies prefer the older antidepressants as safer option. This review aims to elucidate current evidences on safety and efficacy of agomelatine and also tries comparing it with other antidepressant drug classes existing in the market.

KEYWORDS: Agomelatine, Antidepressants, Major depressive disorder, Melatonin, Serotonin.

INTRODUCTION

Depressive disorders are one of the most common mental disorders around the world. Globally an estimated 350 million people suffer from some form of depression and the number is steadily increasing by approximately 20% per year.[1,2] Depression can be long-lasting or recurrent, substantially impairing the individual's ability to function at work or school or cope with daily life.[3] The drugs used to treat patients diagnosed with depression are called "Anti-depressant agents". Several antidepressant drugs have been introduced

during the past decade. These drugs differ from each other in terms of their chemical structure and putative mechanism of action.[4]

THE NEED FOR A NEWER THERAPEUTIC AGENT

The currently available antidepressant drug classes are monoamine oxidase (MAO) inhibitors, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRI). These drugs act by increasing the levels of serotonin, nor-epinephrine and/or dopamine within the central nervous system.[5] Their mechanism of action supports the monoamine hypothesis of depression. Although their use have led to the alleviation of depressive symptoms,[6] these agents also act at non-target receptor sites, contributing to the development of serious adverse events that could in turn lead to decreased adherence, thereby warranting the research for a safer and effective therapeutic agent.[5]

NEWLY IDENTIFIED PATHOPHYSIOLOGY OF DEPRESSION AND THE ROLE OF AGOMELATINE

Recently, the study conducted by UC Irvine Health researchers identified genes controlling the circadian clock rhythms. Findings from this study revealed that the clock gene rhythms varied in synchrony across six regions of normal human brain and that these rhythms were significantly disrupted in depressed patients. This finding identifies that monoamine deficiency/disruption may not be the only pathway involved and disruption of the normal circadian rhythms/ sleep-wake cycles could also be a possible underlying mechanism for the pathophysiology of depression. This finding lead to the development of a newer class of compound with different mechanism of action than that of the currently available antidepressants which could reset this abnormal clock genes and normalize circadian rhythms thereby treating depression.[7, 8]

Agomelatine (beta-methyl-6-chloromelatonin), a naphthalene analogue of melatonin, was developed by the European pharmaceutical company Servier Laboratories Ltd. It gained entry into the European antidepressant market in 2009.[9] Servier later sold the marketing rights of agomelatine in the United States to Novartis. It was undergoing several Phase III clinical trials in the United States until October 2011, however when the results from the last of those trials became available, the development of the drug for the United States market was discontinued.[10] Currently it is now on the market in 41 countries.[11]

ALTERNATE MECHANISM OF ACTION THAN TRADITION ANTIDEPRESSANT

Agomelatine produces antidepressant action by affecting the melatonergic and serotonergic system. It acts as a potent agonist of melatonin MT1 and MT2 receptors in the suprachiasmatic nucleus (SCN) of the hypothalamus and reverses the disease related abnormality of melatonin secretions, thereby, restoring the normal circadian rhythm and promoting sleep in depressed patients. At the same time, it also acts as an anxiolytic by antagonizing the serotonin 5-HT(2C) receptors.[12] It has no measurable affinity to any other known receptor, hence, limiting the side effects caused, in comparison to the currently available antidepressant drug classes.[13-19]

COMPARATIVE EFFICACY AND SAFETY OF AGOMELATINE

Since its approval in February 2009 and subsequent release for use as an antidepressant in the European Union, many studies regarding the efficacy, tolerance and safety profile of the drug in comparison with other available antidepressant agents have been conducted.[20] However, the results from individual studies arrived at varying conclusions. For this review, 24 such studies were reviewed, from which the following results were drawn.

1. Agomelatine vs placebo

Agomelatine was statistically superior to placebo in the acute treatment of major depressive disorder (MDD) in adults.[21,22] Patients on agomelatine were also found to have higher response rates. However, there were no significant statistical difference between the drug and placebo when remission rates were taken into consideration.[23] Also, data from 3 long term studies failed to show significant effects of agomelatine over placebo.[24]

2. Agomelatine vs other anti-depressants

Agomelatine was mainly compared with SSRIs and SNRIs for the treatment of MDD and generalised anxiety disorder (GAD).

(1) Efficacy as an antidepressant

Agomelatine showed an early achievement of response for depressive symptoms along with other dimensions of clinical and functional status.[25] It significantly improved the sleep quality in depressed patients when compared to SSRIs and SNRIs. Furthermore, any discontinuation of the drug due to its inefficacy in comparison to other drugs was not seen.[26,27] Clinical response was observed within a week of initiating the therapy.[25] However, it did not seem to provide a significant advantage over other antidepressants in terms of

efficacy or remission for the acute phase treatment (6-12 weeks), as no statistical difference in therapeutic outcome was seen when compared to paroxetine, fluoxetine, sertraline, escitalopram and venlafaxine.[23,26,28-30] Conversely, a greater symptom relief with agomelatine at 6th week in comparison to venlafaxine was seen.[27] In one study, 80% of patients in the treatment group remained free from relapse after 10 months of treatment, possibly suggesting that the antidepressant benefits of agomelatine may be long term.[27] However, since the data regarding long term outcome (> 12 months) is lacking and only a limited number of long term studies with agomelatine are conducted, conclusions regarding neither treatment remission nor relapse can be drawn.

(2) Efficacy as an anxiolytic

Agomelatine is effective for the treatment of both somatic anxiety and GAD. It was found to exhibit comparable efficacy and was superior in tolerability than escitalopram with no more adverse events than placebo for acute treatment.[31,32] Majority of evidence from studies suggest agomelatine to be a potential treatment for anxiety disorders (AD), particularly GAD. However, since limited studies are available regarding the use of agomelatine for the treatment of GAD, consideration should be made prior to prescribing.[33]

(3) Safety and tolerability profile of agomelatine

All antidepressant drugs can induce adverse reactions.[34] The most common adverse reactions observed with agomelatine are nausea and dizziness. These reactions are usually transient, occurring within the first two weeks of therapy, and generally does not require cessation of therapy. Other adverse effects include headache, somnolence, rhinitis, back pain, nausea, dizziness, nasopharyngitis, influenza, dry mouth, diarrhoea, somnolence, fatigue, upper abdominal pain and increased ALT and/or AST levels.[22,24,25,27,28,35,36] When a head on comparison of agomelatine with paroxetine, fluoxetine, sertraline, escitalopram and venlafaxine was made, those patients receiving agomelatine were less likely to discontinue the treatment due to adverse drug reactions.[26] In a long term study (6 month), treatment discontinuation with agomelatine was significantly lower than with either venlafaxine or sertraline.[37] Agomelatine has a lower prevalence of dizziness, sexual dysfunction and weight gain than venlafaxine and was well tolerated than paroxetine and other SSRIs in terms of the overall side effect profile.[22,29] No withdrawal symptoms were seen on abrupt discontinuation and no significant differences in suicidal or self-injurious behaviour were observed in comparison to SSRIs (paroxetine, escitalopram, fluoxetine and sertraline).[38,39] The only

downside of agomelatine use seem to be hepatotoxicity.[37] Although rare, it has the potential to cause severe hepatotoxic reactions.[25,40] It is due to this very reason that European Medicines Agency (EMA) has listed agomelatine associated "hepatotoxic reactions" as a new safety concern.[41] Agomelatine related liver injury is usually unpredictable and mainly asymptomatic. It is mostly hepatocellular and dose dependent in nature and neither cholestatic nor hypersensitive reactions have been reported. Elevations in hepatic transaminases develop during the initial months of treatment and mostly recover with or without treatment discontinuation.[42]

A meta-analysis of published and unpublished studies of agomelatine showed it to be equally efficacious to standard antidepressant agents for the treatment of MDD, but, its efficacy is overestimated when only published studies are considered.[22] In all published studies, agomelatine was found to be better in safety and had superior tolerability profile than any other comparator antidepressants.[22,23,43] However, no firm conclusions can be drawn regarding the safety, efficacy and tolerability of agomelatine, as the comparisons were made with only a small number of antidepressants and the total number of studies were limited.[29] Therefore, agomelatine should be considered only as an alternative for those patients who do not respond to, or, who are prone or suffering from adverse drug reactions from other antidepressants.[30,44]

PLACE IN THERAPY FOR AGOMELATINE

The latest NICE guideline (2015) on depression recommends the use of agomelatine when there is an inadequate response to an SSRI. However, the Maudsley Prescribing Guidelines in Psychiatry suggest agomelatine as a possible choice of treatment after treatment failure with two previous antidepressant drugs.[23]

PHARMACOKINETICS

Agomelatine undergoes rapid and almost complete (80%) absorption following oral administration.[45-48] The bioavailability is more in women compared to men and it is increased by use of oral contraceptives and reduced by smoking.[45,47] The peak plasma concentration can be achieved within 1 to 2 hours.[45,48] Although food intake does not alter the bioavailability or the absorption rate of agomelatine, the variability increases with high fat food intake.[45,49] The steady state volume of distribution of agomelatine is about 351 L and plasma protein binding is 95% irrespective of the concentration.[45-48] The protein binding is not altered with age nor in patients with renal impairment but the free fraction is doubled in

patients with hepatic impairment.[45,49] Agomelatine is rapidly metabolized mainly via hepatic enzyme CYP1A2. CYP2C9 and CYP2C19 isoenzymes are also involved, but to a small extent. The major metabolites, hydroxylated and demethylated agomelatine, are inactive and are rapidly conjugated and excreted primarily (80%) through urine. [45,47-50]

INDICATIONS

Agomelatine has been approved for the treatment of MDD in adults.[20,45] It has also been used for the treatment of GAD, bipolar depression, sleep disturbances, cluster headaches and migraine.[45]

UNIQUE PROPERTIES OF AGOMELATINE[12,22,32,36,37]

- It improves sleep quality.
- It does not cause day time sedation.
- It has no withdrawal symptoms on abrupt discontinuation.
- It does not cause sexual dysfunction.
- It has least effect on weight gain.
- It does not have significant cardiovascular effects.
- It improves symptoms of anhedonia.
- It does not interfere with the neuronal reuptake of serotonin, norepinephrine, or dopamine.

DOSE AND PRECAUTIONS

i. Adults

The recommended adult dose of agomelatine is 25 mg once daily taken orally at bedtime irrespective of food intake. After two weeks of treatment, if there is no improvement in clinical symptoms, the dose can be increased to 50 mg once daily. Liver function tests must be performed in all patients initially at the treatment initiation, and then periodically after about six weeks, twelve weeks and twenty four weeks and thereafter when clinically indicated. Patients diagnosed with depression should be treated for a sufficient time period of at least 6 months to ensure that they are symptom free.[45]

ii. Children and adolescents

Agomelatine is not approved for the treatment of depression in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.[45,49]

iii. Elderly patients

Limited clinical data is available on the safety and efficacy of agomelatine in elderly patients with MDD.[45,48,49]

iv. Pregnancy and lactation

No clinical data on agomelatine exposed pregnancies are available. Although animal studies have not identified any direct or indirect harmful effects with respect to pregnancy, caution should be advised while prescribing agomelatine to pregnant women. Potential effects of agomelatine on the breastfeeding infant have also not been established. If treatment with agomelatine is necessary, breastfeeding should be discontinued.[45,48,49]

v. Patients with renal impairment

Limited clinical data is available on the use of agomelatine in depressed patients with moderate to severe renal impairment. Thus, caution should be advised when prescribing agomelatine to these patients.[45,49]

vi. Patients with hepatic impairment

Agomelatine is contraindicated in patients with hepatic insufficiency.[45,46,49]

DRUG INTERACTIONS

Agomelatine is primarily metabolized by cytochrome P450 CYP1A2 (90%) and by CYP2C9/19 (10%).[45,46,49,50] Therefore, those drugs that interact with these isoenzymes may alter the bioavailability of agomelatine. For example, fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase to agomelatine exposure. Thus, concomitant administrations with potent CYP1A2 inhibitors (examples: fluvoxamine, ciprofloxacin) are contraindicated. Use of agomelatine with moderate CYP1A2 inhibitors like estrogens also results in a several fold increased exposure to agomelatine. Those drugs that moderately inhibit CYP1A2 (examples: propranolol, grepafloxacine) may be used with caution.[45,47-49] Co-administration of agomelatine with CYP1A2 inducers such as caffeine or nicotine are likely to reduce the plasma concentration of agomelatine.[47-50] Agomelatine does not alter the free concentrations of drugs highly bound to plasma proteins or vice versa. The concomitant use of agomelatine with alcohol is not recommended.[45, 49]

CONTRAINDICATIONS[45,49]

- Hypersensitivity to agomelatine or to any of the excipients.
- Hepatic impairment.
- Hepatic transaminases more than three times the upper limit of normal.
- Concomitant use with potent CYP1A2 inhibitors.

SPECIAL WARNINGS[45,49]

(i) Mania / Hypomania

Agomelatine should be used cautiously in patients with a history of mania or hypomania and should be discontinued if patient develops any manic symptoms.

(ii) Suicide/suicidal thoughts

Close observation of patients who are at high risk of suicide is required, especially during the early phase of therapy and immediately following dose changes.

(iii) Lactose intolerance

Those patients with certain rare hereditary disorders of galactose intolerance or glucose-galactose malabsorption, should not take agomelatine as it contains lactose.

CONCLUSION

Agomelatine is an effective antidepressant with a unique pharmacology. It is well tolerated and has a low adverse effect burden. The good safety profile of agomelatine, due to its unique receptor profile, thus predicts a higher patient acceptability and a better adherence. It offers an exciting addition to the ever expanding therapeutic armamentarium for MDD.

ACKNOWLEDGEMENTS

The authors would like to thank support from JSS University and JSS College of Pharmacy for their constant encouragement. We would also like to extend our heartfelt thanks to Dr. Herve Le Louet, Professor of Clinical Pharmacology, Head of the Pharmacovigilance and Risk Management Department, University Hospital Henri Mondor, France and Co-opted Member of the PRAC, European Medicines Agency, United Kingdom, for his valuable suggestions and constant support throughout the study.

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