Review Article :

Agomelatine : A Clinical Review and Its Role in the Management of Depression

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ABSTRACT:

The present review article looks at the role of Agomelatine as an antidepressant drugs while elucidating its unique mechanisms of action compared to other traditional antidepressants. The article examines the present literature on agomelatine and provides the busy clinician an overview of this drug along with its pharmacodynamic and pharmacokinetic properties. Clinical trials and studies involving agomelatine have been reviewed and the analysis presented.

Key words: ***Agomelatine, antidepressant.***

INTRODUCTION

Major depressive disorder (MDD) carries an enormous personal, social, and economic burden. Despite a better understanding of disease mechanisms and neurobiological consequences of treatments, the effectiveness and tolerability of currently available antidepressants remain suboptimal [1-2]. The current search for therapeutic targets has shifted from selective monoamine systems to monoamine and non-monoamine networks [3]. Although many individuals experience the disorder, only a small proportion of patients with MDD present for treatment. Older antidepressants such as the tricyclic antidepressants (TCAs), although effective, have significant and sometimes life-threatening adverse effects that limit their use. The newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) tend to be better tolerated, but still have significant adverse effects, e.g. sexual dysfunction and nausea, which may limit compliance. Among the various strategies to help patients with new, more effective and better tolerated treatments, the re-synchronization of biological rhythms appears to be particularly attractive given that a disruption of circadian rhythms is characteristic of a large number of mood disorders [4-5].

Agomelatine is a new antidepressant that is a potent agonist of melatonin receptors and an antagonist of the serotonin 5-HT_{2C} receptor subtype. It is in late-phase trials for the treatment of major depressive disorder.

AGOMELATINE : A MELATONIN AGONIST

Melatonin is a pineal hormone which has a fundamental role in the synchronization of circadian rhythms [6-7] that are disorganized in central nervous system disorders such as depression [8-11]. There are three types of melatonin receptors: MT-1, MT-2 & MT-3. The MT-1 and MT-2 receptors belong to the super family of G-protein coupled membrane receptors linked to the inhibition of the adenylyl cyclase and the subsequent decrease of cAMP [12]. These two receptors are expressed by almost all structures of the CNS, especially hypothalamic suprachiasmatic nucleus. The SCN is an endogenous clock which controls the rhythmic secretion of melatonin in our body with low circulating levels during the day, and high plasma concentrations of hormones at night [13]. It is now clearly recognized that disorganized internal rhythmicity is characteristic of a large variety of affective disorders, including unipolar and bipolar depression, mania, seasonal affective disorder and premenstrual dysphoric disorder [14-18].

MECHANISM OF ACTION OF AGOMELATINE

Agomelatine, a naphthalene derivative of melatonin, potently binds to melatonin receptors MT-1 and MT-2, suppresses cAMP formation and mimics the actions of melatonin by dose dependent inhibition of suprachiasmatic neurons [19]. Agomelatine possesses sleep wake cycle regulating properties, and as affective disorders involve a disorganization of circadian rhythms, agomelatine is suggested to play an important role in the pathophysiology of major depression.

5-HT2C receptors are present in the suprachiasmatic nucleus (SCN), ventrotegmental area, locus ceruleus and limbic system. A polysynaptic circuit runs from the SCN to the ventrotegmental nucleus, the origin of mesocortical and mesolimbic dopaminergic pathways [20]. Also, 5-HT2C receptors cause excitation of GABA interneurons. GABA excitation via 5-HT2C receptors leads to inhibition of adrenergic and dopaminergic pathways resulting in depressive symptoms. 5-HT2C antagonists hence improve the depressive symptoms by increasing dopaminergic and adrenergic transmission.

5-HT2C receptors are also concentrated in limbic structures such as the frontal cortex, the amygdala, the hippocampus and the septum, which have major roles in the control of mood and in the aetiology of anxio-depressive states [21-22].

Activity at 5-HT2C receptors seems to be enhanced in depression. Being a selective 5-HT2C antagonist, agomelatine displays antidepressant and anxiolytic properties. It also promotes slow wave sleep [23-24] and libido [25-26]. Collectively, these observations suggest that 5-HT2C receptor antagonists such as agomelatine should favourably influence mood, circadian synchronization and sleep quality, while preserving sexual function.

PHARMACODYNAMICS

As already mentioned agomelatine is a potent melatonin receptor agonist at MT1 and MT2 receptors in the SCN. It also antagonises the serotonin 5 HT2C receptors with weak action on 5 HT1A and 5 HT2A with negligible activity on other serotonergic receptor subtypes [27]. It is important to note that agomelatine has a dual phased action. Its melatonergic sleep promoting action prevails during the night, whereas during the day its antidepressant action via 5HT2C inhibition is uncoupled from its nocturnal action (this may also be considered as an advantage of agomelatine versus the other classes of antidepressants) [28]. Agomelatine does not directly affect the uptake of serotonin, norepinephrine, or dopamine. By inhibiting 5 HT2C receptors, however, it secondarily increases norepinephrine and dopamine in the frontal cortex of the brain. [27]. This effect might contribute to its antidepressant activity. Agomelatine does not bind to adrenergic, cholinergic, or histamine receptors.

The dentate gyrus of the hippocampal formation is a site of continuous neurogenesis during adult life. Chronic stress can result in decreased neurogenesis (nerve cell growth) [29]. Remodelling of hippocampal formation may be a factor in development of depression and is the basis for neuroplasticity hypothesis of major depression [30]. A recent study published has shown that chronic treatment with agomelatine increased cell proliferation and neurogenesis in the ventral dentate gyrus, a region implicated in response to anxiety and emotion. This implies the antidepressant and anxiolytic effects of agomelatine may be partially due to effects on the ventral dentate gyrus [31].

The animal studies demonstrate that agomelatine is able to resynchronize a disrupted circadian rhythm. Agomelatine shows regulation of sleep wake rhythm, increasing the duration of slow wave sleep and normalizing its distribution throughout the night [32]. In contrast, it does not change rapid eye movement (REM) latency, amount of REM or REM density [33].

PHARMACOKINETICS

Agomelatine is rapidly and well absorbed after oral administration, from the gastrointestinal tract [34]. However, its absolute bioavailabilty is relatively low due to high first pass metabolism [35]. With maximum plasma concentration being observed between 1 and 2 hours after administration, the absorbed fraction is greater than 78 % [34].

Agomelatine is moderately distributed throughout the body with a volume of distribution at a steady state of about 35 L. It is highly protein bound (its plasma protein binding is greater than 95%) [36].

Agomelatine is almost entirely metabolized through the liver, and it undergoes extensive first pass hepatic metabolism. The major cytochrome P-450 (CYP-450) enzyme involved in the metabolism of agomelatine is CYP-1A2 (accounting for about 90% of its metabolism), with minor metabolic contributions by CYP-2C9 and CYP-2C19 [37]. Agomelatine has at least four main metabolites. None of the metabolites have any known toxic effects. Agomelatine and its metabolites are mainly excreted through the kidneys. The elimination half-life of agomelatine is very short (about 2–3 hours) [34]

AGOMELATINE AS AN ANTIDEPRESSANT

The efficacy of agomelatine as an antidepressant has been demonstrated in many animal (preclinical) and human (clinical) trials. Various behavioural models in animals are based on the reversal of the deleterious effects

caused by stress situations, be it acute, sub-chronic or chronic [38]. These preclinical models have shown almost equal efficacy of agomelatine with other antidepressants such as fluoxetine and imipramine.

However, an important point to note is the role of agomelatine in the chronic mild stress paradigm. The chronic mild stress paradigm is considered the most relevant animal model for providing evidence of antidepressant properties of a drug because it focuses on anhedonia, one of the key symptoms of depression. Agomelatine reverses the anhedonia seen in this model, irrespective of the time of day of its administration. There is no withdrawal relapse even one week after cessation of treatment [39].

Agomelatine, in addition to its antidepressant activity, exerts a clear-cut anxiolytic action in various animal models, and mechanistic studies in rats provide compelling evidence for a role of 5-HT2C receptor blockade in this anxiolytic action.

Clinical trials have demonstrated efficacy and safety of agomelatine for the treatment of depression and anxiety. A meta-analysis of the severely depressed subpopulations, using increasing cut offs of the HAMD scale at inclusion, showed agomelatine was also effective in management of severe depression [40]. The antidepressant efficacy of agomelatine is associated with an early improvement in depressive symptoms (approximately 2 weeks) and an excellent acceptability [41]. Patient oriented evidence suggests better improvement on subjective getting to sleep and on subjective quality of sleep compared to venlafaxine [42]. Agomelatine is as effective as paroxetine and venlafaxine when compared with respect to response to treatment as well as remission after treatment [43-45]. Agomelatine is more effective than placebo and as effective as paroxetine or venlafaxine in reducing depressive symptoms correlated with symptom relief in terms of HAM-D reduction [44-46].

Agomelatine also appeared to be effective in anxiety associated with depression as demonstrated by reductions in Hamilton's Anxiety Rating Scale (HARS) when compared to placebo [41].

TOLERABILITY AND SAFETY OF AGOMELATINE

A dose-ranging multinational study, double blind and randomised study examined the antidepressant efficacy of three different doses of agomelatine (1, 5 or 25 mg) in more than 700 patients with MDD. The antidepressant efficacy of 25 mg agomelatine was demonstrated in both the mean efficacy criterion (decrease in the HAMD-17 total score) and in secondary outcome measures (MADRS, CGI-S, number of responders). The most common side effects associated with agomelatine are headache, nausea, dizziness, dry mouth, diarrhea, somnolence, fatigue, upper abdominal pain, and anxiety. The most common serious adverse events were suicide attempts (agomelatine 0.6% versus placebo 0.4%), depression (agomelatine 0.5% versus placebo 0.8%), and falls (agomelatine 0.3% versus placebo 0.3%) [47].

Inspite of these effects, agomelatine has a relatively benign side effect profile. A notable advantage is the lack of clinically significant weight gain, the low risk of sexual dysfunction, the low incidence of gastrointestinal symptoms, absence of ECG abnormalities and the absence of discontinuation symptoms. In this manner, agomelatine compares favourably to SSRI and SNRI drugs.

Comparative studies with venlafaxine show that sexual dysfunction with respect to desire-arousal factor, and orgasm dysfunction occur in a lower percentage of patients treated with agomelatine than treated with venlafaxine. However these results were found not to be statistically significant [47].

When the overall tolerability of agomelatine in head-to-head comparisons with other active drug comparators was done; results showes that agomelatine was not substantially better, as evidenced by the roughly similar rates of discontinuation. Of special concern with the use of agomelatine, is liver function. Significant elevations of liver enzymes are common, at times including rare and serious cases of hepatitis. Monitoring of liver enzyme levels of all patients has been recommended before starting treatment, after 6, 12, and 24 weeks of treatment, and thereafter based on clinical judgement. For this reason, agomelatine is contraindicated in patients with any degree of liver impairment. The liver precautions and the need for laboratory monitoring are a distinct disadvantage for the use of agomelatine compared to many other antidepressant drugs. Agomelatine however, does not significantly affect renal function [47].

As per one study, no statistically significant difference in the number of emergent discontinuation symptoms was seen one week after treatment interruption between patients discontinuing agomelatine and those who continued it [47]. This was in contrast to patients

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CONCLUSIO

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