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Review

The use of agomelatine in anxiety disorders: A review

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ABSTRACT

Agomelatine is a novel antidepressant that acts *via* antagonism at the 5HT2C receptor and agonism at the MT1 and MT2 receptors. Besides its use as an antidepressant, there is evidence that agomelatine has an anxiolytic effect as well. Agomelatine is unique because in addition to decreasing anxiety symptoms, it improves the sleep profile of patients by regulating the circadian rhythm. In this study electronic literature search on PubMed was conducted using the following keywords: anxiety, phobia, phobic, panic, fear and agomelatine. Twenty-seven relevant studies and publications on the use of agomelatine for anxiety were identified and are included in this review. Agomelatine was found to be efficacious in alleviating anxiety symptoms and improving sleep quality in patients with generalized anxiety disorder. It also reduced anxiety symptoms in major depressive disorder patients. Furthermore, evidence indicated its effectiveness in treating panic disorder. Agomelatine was well-tolerated with lesser side effects as compared to other antidepressants. Based on the studies that have been done, agomelatine is an efficacious and tolerable antidepressant that is considered beneficial in the management of anxiety. In addition, evidence shows that agomelatine may be more effective in comparison to other antidepressants in patients with severe baseline anxiety.

KEYWORDS: agomelatine, anxiolytic, melatonergic, antidepressant.

1. Introduction

Agomelatine is a novel antidepressant that was recently approved by the European Medicines Agency (EMA) in 2009 [1]. This molecule exerts its unique antidepressant effect by agonizing the MT1 and MT2 melatonin receptors and antagonizing the 5HT2C serotonin receptors. Though initially developed for the management of major depressive disorder, there is increasing interest in its usage for treatment of anxiety disorders. Being a 5HT2C antagonist confers on agomelatine anxiolytic properties [2]. Thus, there is potential for the widespread use of agomelatine in the management of anxiety disorders.

Agomelatine has a unique receptor profile. Animal studies revealed that it has a high affinity as an agonist to MT1 (pKi:10) and MT2 receptors (pKi:9.9) as well as moderate affinity as an antagonist to serotonin receptors 5HT2B (pKi:6.6) and 5HT2C (pKi:6.2) [3]. Upon oral administration, more than 80% of agomelatine is absorbed and its exposure increases proportionally with dose increment. The absolute bioavailability is 1% and it has high first-pass metabolism [4]. The volume of distribution is around 35 litres and the plasma protein binding is 95%, irrespective of concentration, age, and kidney function. Agomelatine is metabolised mainly by the hepatic cytochrome CYP 450 1A2 (90%) and marginally by the CYP 2C9 and the CYP 2C19 (less than 10%). Hydroxylated and demethylated agomelatine are the major metabolites and are considered pharmacologically inactive [5]. Mean half-life is 1-2 hours and elimination is relatively rapid through urine (80%). Prior to elimination, the inactive metabolites undergo glucuronidation and then sulfonation. While data on the use of agomelatine in chronic renal disease is limited, patients with a creatinine clearance of less than 30 ml/min experience a 25% increase in plasma concentration. In hepatic impairment, on the other

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hand, the plasma half-life of agomelatine was found to be 3 times higher, thus making it unsuitable for use in patients with liver cirrhosis or active hepatitis [6]. In patients with depression and decreased cardiac vagal tone, agomelatine confers benefits as it has been shown to increase heart rate variability, and thus is protective against myocardial infarction and heart failure [7]. In light of its pharmacokinetic and pharmacodynamic properties, agomelatine is expected to have favourable tolerability profile and hence improved compliance [6].

Anxiety disorder comprises a broad spectrum of illnesses, including generalized anxiety disorder (GAD), social anxiety disorder, panic disorders and phobic disorders. Initial confidence in the use of agomelatine for management of anxiety was established following the successful treatment of GAD and panic disorder. In fact, the efficacy of agomelatine in treating GAD has been proven in placebo-controlled phase II studies [8]. This is a relevant finding because adequate management involving selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and noradrenaline reuptake inhibitors (SNRIs), has an estimated response rate of 50% [9]. Furthermore, there are some concerns over SSRIs and SNRIs as they have prolonged latency and multiple cognitive side effects [10]. This necessitates newer treatment options. Besides agomelatine, pregabalin [11], and quetiapine [12] are possibilities. However, agomelatine has a potential edge as it appears to reduce anxiety symptoms within two weeks [13]. In this review, we aim to study and summarize the evidence on agomelatine's efficacy and tolerability for management of anxiety.

2. Methods

To recognize studies on agomelatine use in anxiety disorders, a PubMed search was conducted, among research papers published between January 1950 and August 2019, using the following keywords: ***agomelatine*** AND ***anxiety*** OR ***phobia*** OR ***phobic*** OR ***panic*** OR ***fear***. We targeted fully published studies from peer-reviewed journals in the English language. These included controlled trials, review articles, meta-analyses, editorials, commentaries, correspondences and letters to the editor. Relevant articles were selected and reference lists where checked for further studies. The following data were extracted to summarize relevant criteria including authors, year of publication, country of study, study design, number of subjects, outcome measure(s) used and main results.

3. Results

The electronic search identified 27 studies on the use of agomelatine in management of anxiety for inclusion in this review. These studies consisted of review articles, network analyses, clinical trials, letters to the editor and case reports. For the ease of interpreting these results, we will discuss them according to the usage of agomelatine in various anxiety disorders, namely, generalized anxiety disorder (GAD), anxiety symptoms in depression and panic disorder (PD).

3.1. Agomelatine for GAD

Agomelatine was first shown to be efficacious in alleviating anxiety symptoms in animal studies. Antagonism of the 5HT2C receptor was shown to have an anxiolytic effect and mice that had 5HT2C receptor knockout were shown to have reduced anxiety [14-16]. In one study, the anxiolytic effects of agomelatine were compared with that of melatonin, diazepam, and buspirone in anxiety animal models using the Vogel test, the elevated plus-maze test, and the conditioned ultrasonic vocalization test. In these tests, it was found that agomelatine had favourable responses, only slightly weaker than those observed with diazepam and buspirone but stronger anxiolytic response than melatonin [17]. Another animal study examined the chronic use of agomelatine and fluoxetine on various anxiety and depression mice models; the results revealed that agomelatine induced antidepressant and anxiolytic effects comparable to fluoxetine but with the added advantage of regulating sleep [18]. Further examination of agomelatine`s anxiogenic effects in rats in social isolation revealed that male rats were more responsive to therapy compared to female rats. However, hypo-cortisolaemia was not corrected following treatment. Ultimately, behaviour analysis using the open field test, social interaction test, and elevated plus maze extended the evidence base for the anxiolytic effect of agomelatine [19]. In another rather interesting study, the prophylactic effect of agomelatine, venlafaxine and voluntary wheel running was examined on rats under restraint stress. The results revealed that pre-treatment with

both medications and running had a positive impact on the anxious behaviour and the stress-induced memory impairment as indicated by the results of elevated plus-maze, elevated T-maze, open field test (OFT) and Morris water maze (MWM). However, only agomelatine and venlafaxine improved the outcome of the forced swimming test (FST) and the novel object recognition behaviour [20].

Recent clinical trials have also demonstrated the effectiveness of agomelatine in the management of anxiety [21], particularly anxiety and sleep disturbances characterized by mood symptoms. Table 1 summarizes the clinical trials involving the use of agomelatine for GAD. One short term study was a 12-week, double-blinded placebo-controlled study that used agomelatine in doses between 25-50 mg/day [8]. Another study had a similar design but used 10-20 mg of escitalopram per day as the active comparator for assay sensitivity [13]. These studies had a sample population characterized by moderate to severe anxiety as per the HAM-A scores. In these short-term studies, superiority was shown in primary outcomes (a ≥ 50% decrease in HAM-A scores). Secondary outcomes, measured by clinical global impressions-severity (CGI-S) and clinical global impressions-improvement (CGI-I), also showed statistically significant

Table 1. Summary of clinical trials involving the use of agomelatine for GAD.

Author, Year, Country	Study design (No of subjects)	Outcome measures	Main results
Stein *et al*., (2008) South Africa [8]	Double-blinded, placebo-controlled (121)	HAM-A, CGI-S, LSEQ, SDS, DESS	Reduction in HAM-A score from baseline with agomelatine 25-50 mg compared to placebo (E [SE] = -3.28 [1.58]; 95% confidence, estimated from -6.41 to -0.15; p = 0.040).
Stein *et al*., (2014) South Africa [13]	Double-blinded, placebo controlled with active comparator, escitalopram (412)	HAM-A, CGI-S, SDS	Agomelatine significantly reduced mean HAM-A total score (agomelatine-placebo difference: 4.71 [1.03], p < 0.0001) and had significant effects on CGI-S, sleep quality and functional impairment. Escitalopram was as efficacious but with more adverse events.
Stein *et al*., (2012) South Africa [24]	Double-blinded, placebo-controlled, discontinuation study (477)	HAM-A, MADRS	Patients on agomelatine had a lower relapse rate compared to placebo. Risk of relapse was significantly lower for those who continued with agomelatine (p = 0.046).
Stein *et al*., (2018) Canada, Australia, Czech Republic, Finland, Germany, Hungary, Poland, Russia, Slovakia [23]	Double-blind randomized multicentre with active comparator, escitalopram (523)	HAM-A, CGI, THAT, SHAPS, LSEQ	Both medications resulted in a decrease in the HAM-A score. Agomelatine was not inferior to escitalopram, (E(SE) = −0.91(0.69), 95% CI = [−2.26, 0.44], p = 0.195).
Stein *et al*., (2017) Russia, Poland, Slovakia, Ukraine [25]	Double-blind randomised multicentre placebo controlled (412)	HAM-A, CGI, HAD, SDS	Agomelatine 10 and 25 mg resulted in significant lowering in the HAM-A score (difference versus placebo of 7.167 ± 1.00 at 10 mg and 11.087 ± 0.98 at 25 mg, p = 0.0001). A higher placebo agomelatine difference was reported in the agomelatine 25 mg group.

HAM-A: Hamilton anxiety rating scale; CGI-S: Clinical global impressions-severity; LSEQ: Leeds sleep evaluation questionnaire; SD: Sheehan disability score; MADRS: Montgomery-Asberg depressive rating scale; DESS: Discontinuation emergent signs and symptoms scale; THAT: Toronto hospital alertness test, SHAPS: Snaith-Hamilton pleasure scale; HAD: Hospital anxiety and depression; SDS: Sheehan disability scale.

superiority of agomelatine over placebo (0.57; 95% CI 0.30 - 0.84; $p < 0.001$ and 0.51; 95% CI 0.26 - 0.77; $p = 0.003$) [22]. In particular, the study, which included a comparison with active comparator escitalopram showed that agomelatine had similar efficacy as escitalopram in reducing symptoms of anxiety. This study also proved that sleep quality, as shown by the Leeds sleep evaluation questionnaire (LSEQ), is improved by agomelatine as compared with escitalopram. As sleep is an important component in the symptomatology of GAD, amelioration of insomnia will bring about significant relief in anxious patients [22]. Similarly, a larger multicentre study conducted for 12 weeks, evaluated the efficacy of agomelatine (25-50 mg/day) in the management of severe GAD patients using escitalopram (10-20 mg/day) as active comparator. A clinically significant decrease in the HAM-A total score was achieved using both drugs. Agomelatine did not demonstrate significant inferiority in comparison to escitalopram (E(SE) = −0.91(0.69), 95% CI = [−2.26, 0.44], $p = 0.195$). The response rates were 60.9% and 64.8% in the agomelatine and the escitalopram groups, respectively. Both drugs equally decreased the psychic and somatic HAM-A scores, enhanced sleep and alertness parameters and decreased anhedonia. Nevertheless, agomelatine was considered more tolerable due to the lower incidence of adverse events [23]. Another study examined the efficacy of agomelatine in relapse prevention among GAD patients. In this long-term study, patients were treated with agomelatine (25-50 mg/day) for a duration of 16 weeks following which responsive patients were randomized to continue agomelatine therapy or to receive a placebo. During the maintenance period, a lower number of patients relapsed with agomelatine compared to placebo (19.5% vs 30.7%). Risk of relapse was also significantly lower in the treatment group, compared to the placebo group [24].

Given the efficacy of agomelatine in treatment of GAD in several placebo-controlled studies, a clinical trial was conducted to determine the minimum effective agomelatine dose in GAD using 10 and 25 mg/day doses. The HAM-A score was reduced significantly in both groups. However, the effect of the agomelatine dose was more evident in the 25 mg group as indicated by the greater agomelatine placebo difference (7.167 ± 1.00 at 10 mg and 11.087 ± 0.98 at 25 mg, $p < 0.0001$). Additionally, significant improvement was found in the HAM-A somatic and psychic subscales, response and remission rates. Agomelatine was also found to be tolerable with minimal difference from placebo [25].

In addition to these studies which used the HAM-A scale as the primary endpoint measure, agomelatine was also shown to be efficacious in relieving symptoms of GAD, using the DSM IV generalized anxiety disorder severity scale (DGSS), which has been shown to have good construct validity and internal reliability [26]. Agomelatine also improved both psychic and somatic items in the HAM-A, compared to other antidepressants which only improved the psychic component of the HAM-A [8, 13, 27].

3.2. Agomelatine for anxiety symptoms in depression

It is known that anxiety symptoms are seen fairly often in depression [28]. Studies have shown that the existence of anxiety symptoms in depression is associated with a poorer prognosis, evidenced by more severe symptoms, elevated suicide risk and prolonged duration of illness [29]. Table 2 summarizes the clinical trials involving the use of agomelatine for anxiety symptoms in depression. Stein and colleagues pooled data from 6 double-blind, randomized trials of agomelatine in major depressive disorder (MDD) [30]. Three studies were placebo-controlled while the remaining three were controlled using an active comparator, namely fluoxetine, sertraline, and venlafaxine. The Hamilton depression rating scale (HAM-D) was used to measure the primary outcome while the secondary outcome was measured using HAM-A. In the placebo arm, all studies showed the superiority of agomelatine compared to placebo [31-33]. All these trials lasted between 6-8 weeks. In the active comparator arm, there was a significant difference in the HAM-A somatic and psychic subscales, favouring agomelatine over the SSRI and the SNRI [30]. There was also a reduction in the HAM-D anxiety subscore with agomelatine compared to fluoxetine ($p = 0.032$) [34] and sertraline ($p = 0.034$) [35]. Kasper *et al*., also found that there was an improved sleep latency ($p < 0.01$) and sleep efficacy ($p < 0.01$) with agomelatine as compared to sertraline. Over the period of 6 weeks, there was also an improvement in depressive ($p < 0.05$) and anxiety symptoms ($p < 0.05$) as measured with the

Table 2. Summary of clinical trials involving the use of agomelatine for anxiety symptoms in depression.

Author, Year, Country	Study design (No of subjects)	Outcome measures	Main results
Loo *et al*., (2002) Belgium, France, UK [31]	Randomized, double blind, placebo control in comparison with paroxetine (711)	HAM-D, CGI-S	Significant reduction on HAM-D scores with agomelatine.
Olié &Kasper, (2007) France, Finland [32]	Randomized, double blind, placebo control (238)	HAM-D, CGI-S	Significant reduction on HAM-D scores with agomelatine ($p < 0.001$) .
Kennedy &Emsley, (2006) Finland, Canada, South Africa [33]	Randomized, double blind, placebo control (212)	HAM-D, CGI-S	Significant reduction on HAM-D scores with agomelatine ($p = 0.026$) .
Lemoine *et al*., (2007) France, Spain, US [36]	Randomized, double-blind, in comparison with venlafaxine (332)	HAM-D	Antidepressant efficacy was similar to venlafaxine but superior in terms of sleep measures.
Kasper *et al*., (2010) Austria [35]	Randomized, double blind in comparison with sertraline (313)	HAM-D, HAM-A, CGI-S, Sleep actigraphy	Significant improvement with agomelatine with sleep measures as well as depressive ($p < 0.05$) and anxiety symptoms ($p < 0.05$).
Hale *et al*., (2010) Argentina, Brazil, Italy, Spain, UK [34]	Randomized, double-blind, in comparison with sertraline (515)	HAM-D and CGI-S	Agomelatine was superior to sertraline in reducing HAM-D scores ($p = 0.024$) and CGI scores ($p = 0.023$).
Chen & Xie, (2018) China [37]	Randomized single blind, in comparison with paroxetine (99)	HAM-D, HAM-A, ADL	Compared to paroxetine, agomelatine resulted in significantly lower HAM-D ($p = 0.002$, $p = 0.001$) and, HAM-A ($p = 0.00001$, $p = 0.00001$) scores.

HAM-D: Hamilton depression rating scale; CGI-S: Clinical global impressions-severity; HAM-A: Hamilton anxiety rating scale; ADL: Activities of daily living scale.

HAM-A and HAM-D [35]. Agomelatine was also shown to be superior to venlafaxine, but this result did not reach the point of significance on either the HAM-A or HAM-D scores ($p = 0.213$ on the HAM-A psychic subscore and $p = 0.591$ on the HAM-A somatic subscore) [36]. In the study by Stein and colleagues, agomelatine showed significant reductions in the psychic and somatic subscores of the HAM-A compared to sertraline ($p = 0.023$). This finding was replicated in earlier studies as well [8, 24]. Agomelatine was also more efficacious in reducing anxiety and depressive symptoms (based on pooled analysis) in patients who had higher baseline HAM-A and HAM-D scores [30].

Agomelatine was also investigated among stage 2-4 chronic kidney disease (CKD) patients with depressesion and anxiety symptoms [37]. Patients on agomelatine (25-50 mg/day) were found to have significantly lower mean HAM-D and HAM-A scores compared to the patients on paroxetine (20-40 mg/day). The paroxetine group, however, was found to have a higher non-significant score on the ADL scale and a lower non-significant response and remission rates. The adverse events were transitory and mild in both the treatment groups. The researchers concluded that in CKD patients, compared to paroxetine, agomelatine is a preferable option. However, further research is required to confirm this statement.

3.3. Agomelatine for panic disorder

Panic disorder (PD) is traditionally treated with SSRIs and SNRIs, however, it has been shown that 45% of patients with PD do not achieve

significant remission with SSRIs [38]. A total of three papers discussed the role of agomelatine in panic disorders. Among these, two were letters to the editor and one was a case report. The letters to the editor comprised of one open-label trial and one case series. Table 3 summarizes the studies involving the use of agomelatine for panic disorder.

One open-label case series followed up five PD patients with a HAM-A score of 22 at baseline. The study lasted for six weeks and all the patients were given agomelatine in the doses of 25-50 mg/day, depending on their response to treatment. Participants achieved total remission of their symptoms and also reported improvement in sleep measures towards the end of the study period. Sleep quality index and HAM-A scores improved post treatment [39]. Though the sample size is far too small to have adequate power, this finding gives preliminary positive results for the usage of agomelatine in PD. Another open-label trial followed 13 patients who had panic disorder for eight weeks. These patients had never been treated with any other antidepressants other than agomelatine. The primary end-point measure was the panic disorder severity scale (PDSS). The study concluded that 36% of patients met the criteria for response to treatment and 18% of them met the criteria for full remission, based on their post-PDSS scores. The pre-post effect size (Cohen's d) for the PDSS was 1.34, which is large [40]. In some cases, agomelatine might show superiority to SSRIs in treating PD, by virtue of its superior side effect profile. In particular, a case report mentioned that a patient, who responded fairly well with 15 mg/day of paroxetine, had to stop taking the drug due to sexual dysfunction. However, when he was switched to 25 mg/day of agomelatine, he experienced remission of his panic attacks without having any side effects [41]. Thus, the usage of agomelatine in PD seems promising.

4. Side effects

Agomelatine, being a novel antidepressant, has relatively fewer side effects compared to other antidepressants. Huijbregts *et al.* found that the most common side effects among their cohort were decreased sexual need (27%), dizziness and shaking (18%) and muscle stiffness (18%) [40]. Kasper *et al.* on the other hand found the rates of adverse events to be 48% in the agomelatine group, compared to 49% in the sertraline group. The common adverse events were headache, dry mouth and diarrhoea. However, they also noted, rather interestingly, that the number of adverse events that led to treatment discontinuation was 4.5 times higher in the sertraline group compared to the agomelatine group, thus making agomelatine more favourable [35]. Another study also confirmed

Table 3. Summary of studies involving the use of agomelatine for panic disorder.

Author, Year, Country	Study design (No of subjects)	Outcome measures	Main results
Fornaro, (2011), Italy [41]	Case report	Nil	Subject achieved substantial remission with paroxetine (15 mg/day) but had troubling sexual dysfunctions. Subject achieved meaningful remission with 25 mg/day of agomelatine without sexual side effects.
Huijbreghts *et al*., (2015), Netherlands [40]	Open-label trial (13)	PDSS, BDI, BAI, SF-36, SDS	Reduction of scores with primary and secondary outcome measures. The PDSS pre/post effect size was 1.34 (Cohen's d).
Levitan *et al*., (2016), Brazil [39]	Case series (5)	HAM-A, HADS, PASP ACQ, SUDS, PSQI	Improvement in panic symptoms, overall anxiety, and avoidance symptoms at the end of study period.

PDSS: Panic disorder severity scale; BDI: Beck depression inventory; BAI: Beck anxiety inventory; SF-36: Short-form 36; SDS: Sheehan disability scale; HAM-A: Hamilton anxiety rating scale; HADS: Hospital and depression scale; PASP: Panic and agoraphobia scale-patient; ACQ: Agoraphobic cognition questionnaire; SUDS: Subjective units of distress scale; PSQI: Pittsburgh sleep quality index.

that headache (11.3%) and dizziness (8%) were the most common adverse effects of agomelatine therapy and 3.6% had a significant elevation of liver enzymes [24]. In terms of liver enzyme elevation, Buoli *et al.* mentioned that transaminase increase was observed in 1.4% of patients taking 25 mg and 2.5% of patients taking 50 mg of agomelatine [9]. Stein *et al*. reported that the adverse events of agomelatine were almost comparable to those of placebo (38.1% vs 34.5%), while the most commonly reported adverse events associated with agomelatine were dizziness and nausea [8]. Another study concluded that the emergent adverse event symptoms were almost similar between agomelatine, placebo, and escitalopram. Patients who were on agomelatine (0.7%) had fewer severe adverse events compared to placebo (3.1%), and escitalopram (4.3%). Furthermore, adverse events leading to treatment discontinuation was significantly lesser with agomelatine, compared to escitalopram and also placebo [13]. Another positive effect of using agomelatine is that it can potentially reduce the dependence on benzodiazepines, as agomelatine has sedative effects [42] and can also alleviate night-time panic attacks, which are seen in about 40% of patients who suffer from panic disorder. This can also help to reduce the need for benzodiazepine as a rescue medication for patients who experience night-time panic attacks [43].

5. Discussion

Anxiety disorders comprise a broad spectrum of conditions that pose a challenge to treatment. In the past, anxiety disorders were treated with SSRIs and SNRIs, however, a significant proportion of the patients did not show substantial improvement and residual symptomatology remained [44]. While benzodiazepines were credited with quick symptom relief, they have problems with dependence and cognitive impairment upon long term use [45]. Thus, it is imperative to explore new pharmacotherapy options for the treatment of anxiety disorders. Agomelatine, a novel melatonergic antidepressant, works *via* MT1 and MT2 agonism, coupled with 5HT2C antagonism. This cellular level change then leads to improved noradrenaline and dopamine neurotransmission in the frontal cortex, improved neurogenesis and regulation of the circadian rhythm, all of which contribute to its antidepressant effect [46]. Rather interestingly, agomelatine has shown promise as an anxiolytic. Its anxiolytic effect was first demonstrated in various animal studies [17, 18]. As research into this molecule grew, it became apparent that the 5HT2C receptor was key in its anxiolytic effect. Mice who were lacking the 5HT2C receptor were shown to have reduced anxious behaviours. In addition, the antagonism of 5HT2C receptors increases extracellular concentrations of noradrenaline, thus contributing to its anxiolytic effects [47]. As agomelatine has unique melatonergic agonism, it promotes the secretion of melatonin, thus correcting the phase delay in the circadian rhythm of patients who are depressed. This chronobiotic action of agomelatine is one of its unique features which contributes to its efficacy as an anxiolytic [48].

The studies were of a broad spectrum, covering single case reports, case series, randomised control trials, and pooled analyses. All the studies that looked at the efficacy of agomelatine in GAD used HAM-A as one of the primary endpoint measures. It is interesting to note that agomelatine reduced both the psychic and the somatic components of the HAM-A sub scores. This is in contrast with other antidepressants, which only reduced the psychic component of the HAM-A. Although agomelatine's sedative effects could have contributed to the reduction of the somatic sub score of the HAM-A, a similar reduction was noted even after removal of the sleep subscore from the HAM-A scale [27]. There were two studies that compared agomelatine with escitalopram. One study found that agomelatine was as efficacious as escitalopram in moderately anxious patients but with a far lesser adverse event profile (comparable to placebo). Interestingly, patients who had more severe anxiety (as evidenced by their HAM-A scores at baseline), experienced a higher rate of remission compared to those on escitalopram (65% vs 59%). Thus, in patients who can't tolerate the side effects of SSRIs or SNRIs, agomelatine is a tolerable and efficacious choice [13]. Agomelatine has also shown to be more efficacious compared to venlafaxine, fluoxetine, and paroxetine in reducing the psychic and somatic anxiety subscore of the HAM-A scale in patients with higher baseline scores of anxiety [30]. This finding adds to the growing pool of evidence that agomelatine may be more beneficial compared to SSRIs or SNRIs

for subjects with more severe symptoms at baseline [49].

The studies upon which this review was based on have a number of limitations. Firstly, the sample size of most of the studies was small and even included case reports, thus decreasing the power of the studies. Secondly, the scales used in most of the studies above were the HAM-A and HAM-D scales. Next, the study sample consisted of patients who had a singular diagnosis of anxiety disorder. This not reflective of the real-world scenario because a significant number of patients with anxiety disorders also have comorbid depression. Exclusion of these patients may lead to poor generalization of the data pooled [50]. Furthermore, patients with subthreshold GAD, which is seen very often in the primary care setting, were not included in the studies above. Thus, the studies were not naturalistic in nature. Studies, which compared agomelatine with placebo, lacked comparison with an active comparator, thus resulting in a potential bias in the efficacy results. Additionally, the clinical trials that studied agomelatine in patients with panic disorder, were open-label in nature. This makes it difficult to comment on the actual efficacy of agomelatine in panic disorder as an active comparator was absent.

6. Conclusion

Despite the limitations of the studies above, agomelatine has been shown to have therapeutic efficacy and good tolerability among patients who suffer from anxiety disorders. It provides an exciting option, particularly for the subset of patients who cannot tolerate the troubling side effects of SSRIs or SNRIs. More randomized controlled trials with placebo and active comparator arms are required to consolidate the efficacy of agomelatine in the spectrum of anxiety disorders.

CONFLICT OF INTEREST STATEMENT

None.

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