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*REVIEW ARTICLE*

# The effects of agomelatine on sexual function in depressed patients and healthy volunteers

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**Background** Selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor antidepressants are associated with high rates of treatment-emergent sexual dysfunction (TESD) due to stimulation of serotonin receptors.
**Objective** The objective is to evaluate the effect of agomelatine on sexual function in depressed patients.
**Methods** This paper reviews published and unpublished data on sexual function with agomelatine in depressed patients and healthy volunteers.
**Results** Agomelatine, an agonist of melatonergic MT1 and MT2 receptors and antagonist of 5-HT2 receptors, is associated with similar rates of sexual dysfunction compared with placebo and lower rates compared with other antidepressants. Twice as many sexually active depressed patients ($n = 193$) reported a deterioration of sexual function during 12 weeks of treatment with venlafaxine compared with agomelatine (15.2% vs. 8.2%, $p < 0.0001$); however, no differences were found with respect to arousal. Using the Arizona Sexual Experience Scale in depressed patients ($n = 399$), the incidence of treatment-emergent sexual dysfunction (TESD) with agomelatine (3%) was significantly lower than placebo (8.6%) and selective serotonin reuptake inhibitors (10.1%). Among healthy male volunteers ($n = 92$), TESD was not increased compared with placebo in either agomelatine (25 and 50 mg/day) group over 8 weeks, and both were significantly lower than TESD with paroxetine ($p < 0.0001$). Moderate or severe TESD occurred in less than 5% of subjects receiving agomelatine versus 62% who received paroxetine ($p < 0.001$).
**Conclusion** Agomelatine demonstrates favorable sexual acceptability. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—agomelatine; depression; sexual dysfunction; antidepressants; tolerability

## INTRODUCTION

Sexual dysfunction is a prevalent symptom, occurring in more than 70% of patients with major depressive disorder (MDD) (Baldwin, 2001; Bonierbale *et al*., 2003). Underlying causes of sexual dysfunction in the depressed patient are multiple and may be associated with the disorder, its management, or both. Treatment-emergent sexual dysfunction occurs with most currently available antidepressants (Montejo-Gonzalez *et al*., 1997; Montgomery *et al*. 2002; Clayton and Montejo 2006; Basson *et al*., 2010) and represents a significant shortcoming due to adverse effects on treatment adherence and episode recovery (Coryell *et al*., 1993; Hu *et al*., 2004; Papakostas, 2008). In one large follow-up study, 38.3% of patients considered sexual side effects as unacceptable and likely to be associated with non-compliance (Montejo *et al*., 2001). Nevertheless, disturbances in sexual function due to antidepressants are frequently underestimated in clinical practice because of a lack of direct questioning by the clinician and reluctance by patients to spontaneous self-report (Montejo-Gonzalez *et al*., 1997; Montejo *et al*., 2001; Clayton *et al*. 2002; Haberfellner, 2007).

## SEXUAL DYSFUNCTION ASSOCIATED WITH ANTIDEPRESSANT TREATMENT

There are important differences in the incidence of sexual dysfunction associated with the different types of antidepressants, as shown by prospective studies in depressed outpatients with estimates across medications over 50% (Williams *et al*., 2006; Chen *et al*., 2008; Montejo *et al*., 2010).

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In a recent naturalistic study in Spain involving 2000 patients with no prior history of sexual dysfunction, the effects of antidepressant treatment (venlafaxine, duloxetine, escitalopram, citalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, and clomipramine) after 2 months were evaluated. High rates of moderate to severe sexual dysfunction (based on Psychotropic-Related Sexual Dysfunction [PRSexDQ-SALSEX scores]) were reported in more than 70% of patients, with delayed orgasm and reduced libido being most frequent. Treatment discontinuation due to sexual dysfunction occurred in 8.5–23.6% of patients, depending on the antidepressant. Only 44.2% spontaneously reported sexual adverse events, and 19.6% considered discontinuing treatment (Montejo *et al*., 2011a). However, other factors may also contribute to emergent sexual dysfunction. In a 52-week double-blind maintenance trial with the serotonin and norepinephrine reuptake inhibitor (SNRI), duloxetine, the probability of continued sexual dysfunction appeared to be more related to response rather than duloxetine or placebo treatment status (Montejo *et al*., 2011b). There is additional support for lower rates of sexual dysfunction with dual action serotonin and norepinephrine antidepressants including duloxetine (Delgado *et al*., 2005) and milnacipran (Baldwin *et al*., 2008) and desvenlafaxine succinate (Clayton *et al*., 2009). Bupropion, an antidepressant that is devoid of direct effects on the serotonin system, has also demonstrated less sexual dysfunction compared with SSRIs (Thase *et al*., 2005).

This review explores the evidence regarding treatment-emergent sexual dysfunction associated with agomelatine, a novel antidepressant compound, in comparison with placebo and active comparators in depressed and healthy individuals.

## METHODS

Literature searches using PubMed (2002–2011) were restricted to English language publications involving human subjects. Specified keywords were "agomelatine" along with "sexual dysfunction," "sexual function," "depression," "major depression," "major depressive disorder," "antidepressant," "selective serotonin reuptake inhibitor (SSRI)," and "SNRI."

### *Evaluation of sexual function in agomelatine trials*

The new antidepressant agomelatine is a melatonergic agonist at the $MT_1$ and $MT_2$ receptors and a serotonergic (5-hydroxytryptamine, 5-HT) antagonist at the $5\text{-}HT_{2C}$ receptor (Audinot *et al*., 2003; Millan *et al*., 2003). The unique mechanism of action is associated with clinical efficacy in the management of MDD compared with placebo (Loo *et al*., 2002; Kennedy and Emsley, 2006; Olie and Kasper, 2007) and to other antidepressants (Hale *et al*., 2010; Kasper *et al*., 2010). Importantly, agomelatine has no significant affinity for other central receptors or membrane transporters (Millan *et al*., 2003), which suggest a low likelihood for treatment-emergent sexual dysfunction (Keltner *et al*., 2002). Several approaches have been employed to assess sexual function associated with agomelatine treatment, involving spontaneous self-report and structured rating scale methods during placebo-controlled and active comparator trials in depressed patients and in healthy controls.

*Evaluations based on spontaneous self-report in depressed patients.* In an analysis of all the safety data from the agomelatine trial database until 2010 ($N = 5817$), the percentage of patients reporting at least one emergent sexual dysfunction event while receiving 25–50 mg of agomelatine ($n = 3792$), an SNRI ($n = 307$) or placebo ($n = 826$) was similar (1.2%, 1.6, 1.3%, respectively). Patients on an SSRI were more likely to report a treatment-emergent sexual adverse event (4.2%, $N = 892$). In men specifically, spontaneously reported emergent adverse events related to sexual dysfunction with agomelatine compared with placebo or active comparator revealed a rate of 2.7% in the agomelatine group ($n = 1069$), 1.7% in the placebo group ($n = 235$), 9.0% in the group who received an SSRI (fluoxetine, paroxetine, or sertraline; $n = 279$), and 3.1% in the group who received venlafaxine ($n = 96$).In women, the percentage of treatment-emergent sexual dysfunction occurred in 0.6% of the agomelatine group ($n = 2723$), 1.2% of the placebo group ($n = 591$), 2.0% of the SSRI group ($n = 613$), and 1.0% of the venlafaxine group ($n = 211$) (data on file).

Among other published trials comparing antidepressant efficacy between agomelatine and placebo (Stahl *et al*., 2010; Zajecka *et al*., 2010), there was no indication that sexual side effects occurred by spontaneous report in either trial. Neither was sexual dysfunction reported during extended treatment out to 26 weeks in a relapse prevention study (Goodwin *et al*., 2009). Similarly, sexual side effects were not reported in the comparative studies of agomelatine and fluoxetine (Hale *et al*., 2010) or sertraline (Kasper *et al*., 2009) for any drug. There was also no indication of sexual dysfunction during "real world" treatment with agomelatine in a large German open-label trial evaluating efficacy and tolerability in over 3000 patients (Laux, 2011).



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*Evaluations based on standardized rating scales in depressed patients.* In a pooled analysis of three short-term published placebo-controlled studies (Loo *et al*., 2002; Kennedy and Emsley, 2006; Olie and Kasper, 2007), MDD patients were treated with agomelatine, placebo, or an SSRI (fluoxetine or paroxetine) for 6–8 weeks. Sexual functioning was assessed using the Arizona Sexual Experience Scale, and data for men and women were combined and analyzed as a single group across each drug. Treatment-emergent sexual dysfunction occurred significantly less frequently among patients who received agomelatine than with placebo or SSRIs (Figure 1) (Kennedy and Eisfeld, 2006).

Sexual acceptability of agomelatine was the primary outcome measure in a randomized controlled trial involving 276 depressed patients with moderate to severe MDD (Montgomery-Åsberg Depression Rating Scale [MADRS] score ≥20) (Kennedy *et al*., 2008). This trial differed from others in the pre-registration phase of drug development in that: (i) the MADRS scale was used to determine entrance severity and as an outcome measure; (ii) agomelatine was prescribed at a fixed dose of 50 mg rather than a flexible 25–50-mg regimen in comparison with venlafaxine XR 150 mg; and (iii) the duration of the trial was 12 weeks. Changes in sexual function during treatment were evaluated using the Sex Effects (Sex FX) Scale (Kennedy *et al*., 2010).

The reduction in depressive symptoms at study endpoint did not differ statistically between groups. Among patients who were sexually active at baseline ($n = 193$), a decrease in Sex FX total score was reported by 8.2% of the agomelatine group versus 15.2% of the venlafaxine group at 12 weeks ($p < 0.0001$) (Table 1). In women only, a decrease of 9.2% was reported with agomelatine compared with 15.1% with Venlafaxine ($p < .001$), and in men only, 5.2% reported a deterioration with agomelatine compared with 15.2% with venlafaxine ($p < .0001$). Likewise, fewer patients reported any decline on Sex FX items for desire (6.6% versus 16.4%; $p < 0.0001$) or orgasm (9.1% versus 18.5%; $p = 0.001$), respectively, with agomelatine versus venlafaxine; however, no significant differences were reported between drugs for arousal. In sexually active remitted patients ($n = 111$), the most striking differences were in deterioration of desire in men (agomelatine: 3.6% vs. venlafaxine XR: 19.4%, $p < .01$), and in women, the deterioration was 4.3% for agomelatine versus 21.2% for venlafaxine XR ($p < .0001$) (Kennedy *et al*., 2008).

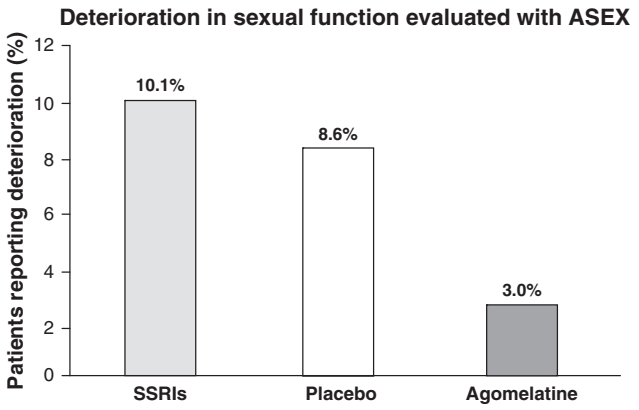


Figure 1. Sexual dysfunction assessed using Arizona Sexual Experience Scale (ASEX) in a pooled analysis of three placebo-controlled trials of depressed patients receiving agomelatine (25–50 mg/day, $n = 168$), selective serotonin reuptake inhibitor (SSRI) ($n = 114$), or placebo ($n = 117$) for 6–8 weeks. Data are from Kennedy and Eisfeld (2006)

Table 1. Crude incidence rate (%): deterioration (defined as a reduction of ≥1 point from baseline in each domain score) in sexual function, assessed by the Sexual Function Questionnaire in patients who were sexually active at baseline

| Domain | Agomelatine 50 mg/d ($n = 103$) | Venlafaxine 150 mg/d ($n = 90$) | $p$-value |
|---|---|---|---|
| Desire | 6.6 | 16.4 | <0.0001 |
| Arousal | 9.2 | 11.4 | 0.322 |
| Orgasm | 9.1 | 18.5 | 0.001 |
| Global satisfaction | 4.9 | 12.8 | 0.005 |
| Total score | 8.2 | 15.2 | <0.0001 |

Modified from Kennedy *et al*. (2008).
[a]Defined as deterioration of ≥1 point from baseline in each domain score.

*Evaluations among healthy volunteers.* For the depression as a confounding factor to be removed, agomelatine's sexual acceptability was examined among non-depressed subjects over 8 weeks using the PRSexDQ-SALSEX scale (Montejo *et al*., 2010). Ninety-two young male volunteers (age 18–30 years) who reported good physical health and a satisfactory sexual life were randomized to receive one of four treatments for 8 weeks: agomelatine 25 mg/day, agomelatine 50 mg/day, paroxetine 20 mg/day, or placebo ($n = 23$ for each group).

At the last observation, the incidence of sexual dysfunction (defined as a score ≥1 on any of PRSexDQ-SALSEX items 3–6) in either of the agomelatine groups (25 mg/day, 22.7% and 50 mg/day, 4.8%) was significantly lower than that in the paroxetine group (85.7%, $p < 0.0001$). This difference in sexual acceptability between the two agents was apparent at each visit from week 2 onwards. The high sexual acceptability of agomelatine was also borne out using other assessment criteria on the PRSexDQ-SALSEX scale. Moderate or severe sexual dysfunction (PRSexDQ-SALSEX item



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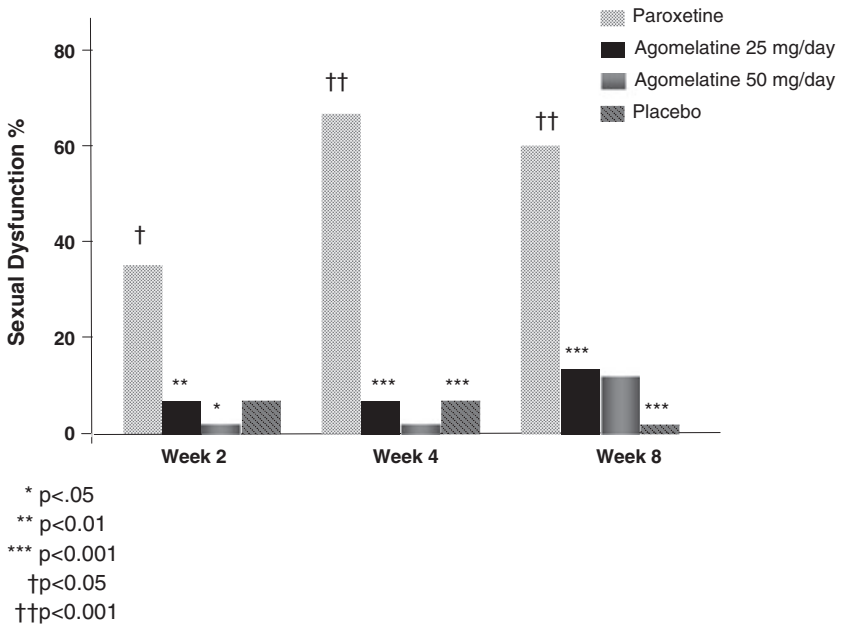


Figure 2. Percentage of healthy male volunteers with moderate or severe sexual dysfunction as assessed by the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ, item 3 = 3, or items 4, 5, or 6 ≥2) during 8-week treatment with agomelatine 25 or 50 mg/day, paroxetine 20 mg/day, or placebo (Montejo *et al*., 2010).*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, for agomelatine 25 or 50 mg/day versus paroxetine; †$p < 0.05$, ††$p < 0.001$ for paroxetine versus placebo

3 = 3, or any of PRSexDQ-SALSEX items 4–6 ≥2) scale was high with paroxetine from 2 weeks but remained close to placebo for both dosages of agomelatine (Figure 2) (Montejo *et al*., 2010). Likewise, mean PRSexDQ-SALSEX total score (i.e., the sum of items 3–7 on PRSexDQ-SALSEX) in both agomelatine treatment groups (25 mg/day, $0.9 \pm 2.0$, 50 mg/day, $0.2 \pm 0.9$) was similar to placebo and significantly lower than paroxetine at each visit and at the last assessment ($5.2 \pm 3.6$, $p < 0.0001$). Concerning the individual PRSexDQ-SALSEX items, the greatest difference in favor of agomelatine was noted for "delayed orgasm/ejaculation," which was reported by 9.1% and 4.8% of the agomelatine 25 and 50 mg/day groups, respectively, compared with 81% of the paroxetine group ($p < 0.0001$ for each comparison). Low libido and erectile dysfunction were significantly different from paroxetine only after week 8, suggesting that paroxetine-related sexual dysfunction may begin with orgasmic complaints and progress into libido and erectile problems a few weeks after the onset of treatment (Montejo *et al*., 2010).

## DISCUSSION

On the basis of published and unpublished trial data, there is support for a favourable sexual side effect profile with agomelatine in depressed and healthy individuals. This is consistent with the generally favorable tolerability profile of this agent (Ghosh and Hellewell, 2007).

In contrast to agomelatine, SSRI and SNRI antidepressants adversely affect sexual function, and this may compromise their effectiveness in the clinical management of depression. The principal mechanism of action of both SSRI and SNRI antidepressants is blockade of serotonin reuptake. The subsequent increase in serotonin activity in the central and peripheral nervous system is associated with a range of side effects including inhibition of libido, ejaculation, and orgasm (Rosen *et al*., 1999). One of the main biochemical mechanisms proposed to underlie these sexual side effects is activation of the 5-$HT_2$ receptors by serotonin (Keltner *et al*., 2002). Clinical evidence supporting this hypothesis includes the therapeutic benefits of the 5-$HT_2$ antagonist, cyproheptadine, as an adjuvant treatment for the management of SSRI-induced sexual dysfunction (Keller *et al*., 1997). Nefazodone and mirtazapine, which are both antagonists of 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, are antidepressants associated with reduced sexual side effects compared with SSRIs (Montejo *et al*., 2001; Taylor *et al*., 2005). The drug flibanserin, a 5HT2A antagonist and 5HT1A agonist, although failed as an antidepressant (Kennedy, 2010), resulted in improved desire within a population of women with hypoactive sexual desire disorder (Clayton *et al*., 2010). Agomelatine's antagonistic action on 5-$HT_{2C}$ receptors may therefore explain its good sexual acceptability compared with the SSRI and SNRI antidepressants. Preclinical studies have also demonstrated



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increased sexual activity with melatonergic agonism (Drago and Busa, 2000), and the action of agomelatine on $MT_1$ and $MT_2$ receptors is another mechanism that could favorably influence sexual function. The lack of difference between agomelatine and venlafaxine in the domain of arousal suggests that serotonin may not affect all domains of sexual function similarly, and arousal may be mediated by other factors such as hormone levels (Davis, 2000).

Sexual side effects of antidepressants severely impact a patient's quality of life and jeopardize long-term compliance with treatment (Burra *et al*., 2007). Switching an antidepressant due to adverse events can also limit positive outcome. There is evidence to suggest that patients who remain on their initial antidepressant therapy are 1.6 times more likely than patients who require changes in therapy to achieve response (Montejo *et al*., 1988). Despite the fact that agomelatine is one of the few antidepressants to have had clinical trials designed specifically to test its effect on sexual function as a primary outcome (Kennedy *et al*., 2008; Montejo *et al*., 2010), there are too few studies, both short term and long term, in which standardized measures of sexual function were applied. In general, the field also suffers from failure to recruit enriched patient samples with minimum frequency of sexual activity prior to treatment.

## CONCLUSION

On the basis of an extensive review of all available data on agomelatine and sexual function, the evidence, from self-report and standardized rating scales, suggests that treatment with agomelatine is associated with a lower risk of sexual dysfunction in contrast to the majority of first-line antidepressants.

## CONFLICT OF INTEREST STATEMENT

Dr. Montejo has received honoraria or research funding from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Servier, and Wyeth. Dr. Kennedy has received honoraria or research funding from AstraZeneca, Boehringer Ingelheim, Brain Cells Inc., Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Pfizer, Servier, and St. Jude Medical. Dr. Majadas has no conflict of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity in conflict with the subject matter or materials discussed in the manuscript.

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