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Better sexual acceptability of agomelatine (25 and 50 mg) compared to escitalopram (20 mg) in healthy volunteers. A 9-week, placebo-controlled study using the PRSexDQ scale

Angel L Montejo¹, JFW Deakin², Raphael Gaillard³, Catherine Harmer⁴, Florent Meyniel⁵, Artin Jabourian⁶, Cecilia Gabriel⁷, Celine Gruget⁷, Corinna Klinge⁴, Christine MacFayden⁴, Holly Milligan², Emma Mullings² and Guy Goodwin⁴

Abstract

The present double-blind, placebo-controlled study evaluates the effects of agomelatine and the selective serotonin reuptake inhibitor escitalopram on sexual dysfunction in healthy men and women.

Methods: A total of 133 healthy volunteers (67 men, 66 women) were randomly assigned to agomelatine (25 or 50 mg) or escitalopram (20 mg) or placebo for nine weeks. Sexual acceptability was evaluated by using the psychotropic-related sexual dysfunction questionnaire 5-items total score and sexual dysfunction relative to each sub-score (in 110 volunteers with sexual activity). Sexual dysfunction was evaluated at baseline and after two, five and eight weeks of treatment and one week after drug discontinuation.

Results: The psychotropic-related sexual dysfunction questionnaire 5-items total score was significantly lower in both agomelatine groups versus escitalopram at all visits ($p < 0.01$ to $p < 0.0001$) with no difference between agomelatine and placebo nor between both agomelatine doses. Similar results were observed after drug discontinuation. The total score was significantly higher in the escitalopram group than in the placebo group at each post-baseline visit ($p < 0.01$ to $p < 0.001$). Similar results were observed regardless of volunteers' gender. Compared to placebo, only escitalopram significantly impaired dysfunction relative to "delayed orgasm or ejaculation" ($p < 0.01$) and "absence of orgasm or ejaculation" ($p < 0.05$ to $p < 0.01$). The percentage of participants with a sexual dysfunction was higher in the escitalopram group than in agomelatine groups ($p < 0.01$ to $p < 0.05$) and placebo ($p < 0.01$).

Conclusion: The study confirms the better sexual acceptability profile of agomelatine (25 or 50 mg) in healthy men and women, compared to escitalopram.

Trial registration name: Evaluation of the effect of agomelatine and escitalopram on emotions and motivation in healthy male and female volunteers.

Trial registration number: ISRCTN75872983.

Keywords

Sexual dysfunction, agomelatine, escitalopram, healthy volunteers, antidepressant, tolerability

Introduction

Sexual dysfunction (SD) remains an underestimated adverse effect of antidepressant drugs and the diagnosis is often missed because, if not directly questioned, patients are disinclined to admit SD for fear of stigmatization. In patients diagnosed with depressive disorders, SD affect all phases of sexual response for about 25–50% of men and 35–90% of women. The most common symptoms include a decline in libido, disorders of sexual arousal in women and erectile dysfunction in men, and it causes abnormal orgasm (anorgasmia or delayed) in both sexes (Angst, 1998). SD can be the result of existing disorders but also side effects of medications (Baldwin and Foong, 2013; Lee et al., 2010; Reichenpfader et al., 2014). While treating mood symptoms, most of the currently available antidepressants can affect all phases of sexual activity of patients, by further decreasing desire, arousal, and orgasm in men and women (Clayton et al., 2002; Delgado et al., 2005; Kennedy et al., 2006; Montejo et al., 2001; Rosen et al., 1999). The risk of SD varies with differing antidepressants, and should be considered when choosing an antidepressant. The incidence of treatment-emergent

SD can be high (50–70%), notably when the mechanism of action encompasses a high profile of 5-HT reuptake blockade (Clayton

¹Hospital Universitario de Salamanca, Nursing School of Salamanca, IBSAL, Salamanca, Spain

²Neuroscience and Psychiatry Unit, The University of Manchester, Manchester, UK

³Centre Hospitalier Sainte Anne, Paris, France

⁴University Department of Psychiatry, Warneford Hospital, Oxford, UK

⁵Institut du Cerveau et de la Moelle Epinière, Hôpital de la Pitié-Salpêtrière, Paris, France

⁶rue Marbeuf, Paris, France

⁷Institut de Recherches Internationales Servier (IRIS), Suresnes, France

Corresponding author:

Angel L Montejo, Hospital Universitario de Salamanca, Servicio de Psiquiatría, Av. Comuneros 27, Salamanca 37003, Spain.
Email: amontejo@usal.es

and Montejo, 2006; Clayton et al., 2014; Serretti and Chiesa, 2009). By comparison, drugs that predominantly increase noradrenaline or dopamine uptake and the 5-HT₂ receptor blockers have fewer negative effects on sexual functioning (Bijlsma et al., 2014; Clayton et al., 2002; Segraves and Balon, 2014).

Agomelatine, the action of which is based on both MT₁/MT₂ receptor agonist and 5-HT_{2C} receptor antagonist properties (Guardiola-Lemaitre et al., 2014), is an effective antidepressant with similar efficacy to standard antidepressants and better tolerability (Taylor et al., 2014). Agomelatine-treated patients are less likely than those receiving other antidepressants to discontinue treatment because of adverse effects (Taylor et al., 2014). In particular, agomelatine preserves sexual function in comparison with venlafaxine, with a significantly lower incidence of sexual disorders affecting either desire-arousal or orgasm (Kennedy et al., 2008). The absence of deleterious side effects on sexual function during antidepressant treatment could be translated into enhanced patient quality of life, compliance to treatment, and may favour recovery from the depressive episode.

That an antidepressant is free per se of sexual side effects can be firmly demonstrated on conditions that the compound is administered to healthy volunteers free of depressive symptoms. There are at least two reasons to sustain this statement. First, when evaluating the effects of an antidepressant on the sexuality of depressed patients, the therapeutic effect on mood can partially mask concomitant negative effects on sexual functioning related to the drug's pharmacodynamic effect. Second, the depression per se can deteriorate the patient's sexuality before any antidepressant intake (Fabre and Smith, 2012; Thakurta et al., 2012), so only patients without SD have to be selected to adequately measure antidepressant-related SD. It is also important to use validated instruments that can provide a baseline to detect SD and measure change over time. To date, only a few studies have explored the impact of antidepressants on populations free of depressed symptoms (Abler et al., 2011; Kennedy et al., 1996; Montejo et al., 2010; Nafziger et al., 1999). One of these studies, using the validated Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Montejo et al., 2000), has confirmed in healthy men the better sexual acceptability profile of agomelatine compared to the selective serotonin reuptake inhibitor (SSRI) paroxetine (Montejo et al., 2010).

The present double-blind, comparative and placebo-controlled study was designed to confirm and complete these findings by assessing the sexual acceptability – using PRSexDQ – and the global safety of agomelatine treatment (at fixed doses of 25 and 50 mg) for nine weeks in healthy men and women. The sensitivity of the trial was validated by using a placebo arm and, as comparator, the SSRI escitalopram (10–20 mg) known to impair sexual function in depressed men and women (Clayton et al., 2007; Reichenpfader et al., 2014; Serretti and Chiesa, 2009; Sidi et al., 2012).

Methods

This phase I study used a randomized, double-blind, 4-group (agomelatine 25 and 50 mg, escitalopram 20 mg, and placebo) parallel design, in healthy men and women, and was conducted in two clinical centres in the United Kingdom in agreement with the principles of good clinical practice and the Declaration of Helsinki. The relevant local ethics committees approved the protocol, and all volunteers freely gave their written informed consent before their selection in the study.

Volunteers

In order to be included, healthy men or women aged 18 to 45 years had to be non-smokers or moderate smokers (< 10 cigarettes/day) with a body mass index between 18.0 and 34.9. To be eligible at the selection visit, clinical examination (structured clinical interview for DSM-IV-TR axis I disorder (SCID)), physical examination and body weight, vital signs (systolic and diastolic blood pressure, standing and supine, heart rate standing and supine after 10 min rest) and laboratory examinations (haematology and blood and urine biochemistry), have to be within the normal ranges and/or clinically acceptable for healthy volunteers according to the investigator judgement. The hepatic parameters (ALAT, ASAT, γ GT, alkaline phosphatase, total and conjugated bilirubin) were to be within the normal ranges (low values were acceptable if not clinically significant). Volunteers had also to have a negative drug screening (amphetamine, methamphetamine, benzodiazepines, cocaine, opioids, cannabis, ecstasy, tricyclic antidepressants) and a negative breath alcohol test. All women had to use a highly effective method of birth control. Blood pregnancy test (at ASSE) and urine pregnancy test (at inclusion) for women of childbearing potential have to be negative.

Any use of sedative hypnotics, including benzodiazepines, or psychotropic substance had to be discontinued at least three months before entering the study. Any other medication, including antidepressants and anti-psychotics, or drugs especially contraindicated to agomelatine (fluvoxamine and ciprofloxacin) and escitalopram (MAO-inhibitors, metoclopramide, furazolidone, pimozone, certain antimicrobial agents, etc.) had to be discontinued at least one month preceding the selection.

Treatment with drugs that could interfere with sexual hormones (hormonal treatment, dopaminergic agonists and antagonists, codeine, and opioid analgesics) or treatments with drugs capable of interfering with sexual intercourse (β -blockers, anti-hypertensive, hypo-cholesterolaemic and psychotropic drugs) had to be discontinued at least three months before entering the study.

No other medications were allowed concomitantly during the study except paracetamol (1.5 g per day) when necessary, and oral contraceptives.

Treatments

Two doses of agomelatine were tested, 25 and 50 mg, versus escitalopram 20 mg (10 mg during the first week of treatment) and placebo was used as a study validator via the comparison escitalopram-placebo. During the study, treatment was taken once a day by oral route in the evening (20:00) in one red capsule containing one or two tablets of agomelatine 25 mg or one or two tablets of escitalopram 10 mg or one tablet of placebo.

Study treatments were of identical appearance (whatever the treatment arm and the dosage) to protect the blinding. No case of unblinding occurred during the study. The blind was broken after database lock.

Study design

Volunteers first underwent a 1–6 weeks selection period without treatment and then were randomized to one of the four treatment

arms: agomelatine 25 mg, agomelatine 50 mg, escitalopram 10–20 mg or placebo. The treatments were assigned at inclusion by a balanced (non adaptive) randomization, with stratification on gender and on centre.

Visits were performed for inclusion, then at week 1 (days 3 and 7), week 2 (day 14), week 5 (day 35) and week 8 (days 55 and 56) during the double-blind treatment period. A follow-up visit (DEND) was performed five to seven days after the treatment discontinuation or after premature treatment withdrawal whatever its time of occurrence.

Sexual acceptability was assessed by the validated PRSexDQ (Montejo et al., 2000). The PRSexDQ consists of seven items pertaining to SD. The first item is a screening item to assess whether the patient has any sort of SD. The second item assesses whether the patient has spontaneously reported any SD to his or her physician. The items 3–7 assess five dimensions of SD according to severity or frequency: loss of libido (0 = nul, 1 = mild, 2 = moderate, 3 = severe), delayed orgasm or ejaculation (0 = nul, 1 = mild, 2 = moderate, 3 = severe), anorgasmia or no ejaculation (0 = never, 1 = occasionally, 2 = often, 3 = always), erectile dysfunction in men/vaginal lubrication dysfunction in women (0 = never, 1 = occasionally 2 = often, 3 = always), and patient's tolerance of the SD (0 = no SD, 1 = good, 2 = fair, 3 = poor). Only items 3–7 account for the total score of the PRSexDQ. As each item was scored from 0 to 3, the total score ranged from 0 (absence of SD) to 15 (maximum level of SD with the worst tolerability by the patient).

In addition to PRSexDQ total score, SD relative to each individual item was also evaluated. SD was defined as at least one sexual impairment in one of the four following items of PRSexDQ: decreased libido (item 3), delayed orgasm/ejaculation (item 4), anorgasmia/no ejaculation (item 5), and erectile dysfunction/vaginal lubrication dysfunction (item 6). A sexual impairment corresponded to a score ≥ 1 for items 4, 5, 6 or a score ≥ 2 for item 3.

A visual analogue scale on sexual functioning satisfaction (VAS-SFS) (Garcia-Portilla et al., 2011) was filled in at the same visits as the PRSexDQ. VAS-SFS measures the volunteer's degree of satisfaction with his/her sexual functioning, from "very satisfied" to "very unsatisfied" on a 100 mm in length vertical line corresponding to his/her current level of satisfaction. The higher the score, the more satisfied the participant was with his/her sexual functioning.

Safety evaluations including collection of adverse events and measurements of blood pressure and heart rate were done at all visits. For each adverse event, emergence (defined as a new or a worsening event under study treatment), intensity (e.g. mild, moderate, severe), seriousness (serious, non serious) and causality (related, not related to treatment) were considered.

Laboratory tests were performed at selection (haematology, blood and urine biochemistry), at weeks 2 and 5, at the follow-up visit or in case of withdrawal. Liver function test (LFT) included ALAT, ASAT, bilirubin (total and conjugated), ALP and γ GT was performed at selection, at weeks 2 and 5, at the follow-up visit or in case of withdrawal.

Statistical analysis

The PRSexDQ mean total score at each visit value, was compared between both agomelatine doses and escitalopram,

between escitalopram and placebo, between both agomelatine doses and placebo and between two agomelatine doses using a linear model studying treatment effect with centre, gender and baseline as covariates (fixed effect), by gender and overall (at the same type one error of 5%). Differences between treatment groups were calculated as escitalopram minus agomelatine 25 mg, escitalopram minus agomelatine 50 mg, escitalopram or agomelatine (25 and 50 mg) minus placebo and agomelatine 25 mg minus 50 mg. An analysis was performed for SD relative to each PRSexDQ individual item (at each visit), and comparisons on percentage of volunteers with SD relative to each item of escitalopram versus agomelatine 25 and 50 mg, escitalopram versus placebo, agomelatine 25 and 50 mg versus placebo and agomelatine 25 mg versus agomelatine 50 mg were performed using logistic regression. Descriptive statistics were provided for safety data.

Descriptive statistics were provided for scores obtained from the VAS-SFS, expressed as value at each visit, and change from baseline to each post-baseline visit and to the last post-baseline value under treatment.

Statistical analyses were performed on SAS® software, version 9.2. (SAS Inc; Cary, NC, USA).

Results

A total of 137 volunteers were selected by two centres in the UK, of which 133 were included and randomly assigned to one of the four treatment groups (33 participants in the agomelatine 25 mg group, 32 in the agomelatine 50 mg group, 36 in the escitalopram 20 mg group and 32 in the placebo group). Of these, 120 volunteers completed the study and 13 discontinued (four volunteers in the agomelatine 25 mg group, seven in the escitalopram group and two in the placebo group). Half of the volunteers (66 participants, 49.6%) were women. In the randomized set (RS) defined as all included and randomized participants, the baseline demographic characteristics of the treatment groups were generally similar, with a mean \pm standard deviation age of 24.0 ± 4.9 , 21.8 ± 3.8 , 24.1 ± 4.1 and 23.0 ± 4.1 years old in the agomelatine 25 mg, agomelatine 50 mg, escitalopram and placebo groups, respectively.

Sexual acceptability was analyzed in a total of 110 participants (82.7%) who had a sexual activity at baseline and at least once until week 8. These participants from the RS have completed the double-blind treatment period at least until week 5, have taken the treatment without protocol deviation. The sexual acceptability at baseline was similar in all treatment groups. The mean (\pm standard deviation) PRSexDQ 5-item total score was 0.5 ± 1.3 at baseline without relevant difference between treatment groups. No relevant differences were observed between genders either (0.8 ± 1.7 in women versus 0.2 ± 0.5 in men). The mean sexual functioning satisfaction VAS score of those volunteers was 88.4 ± 11.1 mm (median 90.0 mm), indicating that participants were satisfied with their sexual functioning. No relevant differences neither between treatment groups nor between genders, were observed for the sexual functioning VAS score.

No clinically relevant difference between groups was observed on the mean treatment duration (59.9 ± 11.9 days). The compliance was satisfactory with all volunteers reporting a compliance $\geq 70\%$.

Sexual acceptability was also analyzed in a subset of 78 participants with the same characteristics as those in our previous study (Montejo et al., 2010), that is, with no SD at baseline and with sexual activity at *each* visit (31 women, 47 males).

5-item total score of PRSexDQ

Volunteers with sexual activity at baseline and at least once until week 8 (n = 110). The mean \pm standard deviation total score was significantly lower in both agomelatine groups compared to escitalopram at each visit during the treatment period (at week 8: 1.1 ± 2.0 for agomelatine 25 mg, 0.8 ± 1.6 for agomelatine 50 mg, versus 3.0 ± 3.1 for escitalopram) and at follow-up visit (5–7 days after the treatment discontinuation: 1.1 ± 2.2 for agomelatine 25 mg, 0.6 ± 1.2 for agomelatine 50 mg, versus 2.5 ± 2.8 for escitalopram).

There was a statistically significant between-drug difference in favour of each agomelatine dose from week 2 (estimates of the differences: 2.8 ± 0.5 points, $p < 0.0001$ at 25 mg; 2.0 ± 0.5 points, $p = 0.0004$ at 50 mg) to the end of the 8-week study period (1.9 ± 0.6 points, $p = 0.0016$ at 25 mg; 2.1 ± 0.6 points, $p = 0.0005$ at 50 mg) and also at follow-up visit (1.4 ± 0.6 points, $p = 0.0169$ at 25 mg; 1.8 ± 0.6 points, $p = 0.04$ at 50 mg). The PRSexDQ 5-item total score observed in the placebo group was 0.3 ± 1.3 at the end of the 8-week study period. No statistically significant differences between each dose of agomelatine and placebo group nor between both agomelatine doses were found at each visit. The mean total scores in the escitalopram group were 3.2 ± 3.3 at week 2, 3.5 ± 3.2 at week 5 and 3.0 ± 3.1 at week 8 and 2.5 ± 2.8 at follow-up visit. At each visit, there was a statistically significant escitalopram-placebo difference ($p < 0.0001$) (estimates of the differences: 2.7 ± 0.5 points at week 2; 2.8 ± 0.5 points at week 5; 2.5 ± 0.6 points at week 8; 1.9 ± 0.6 points) (Figure 1A).

Similar results in favour of both agomelatine doses were observed in both genders (Figure 1B). In men, the 5-item PRSexDQ total scores were significantly lower in both agomelatine groups than in the escitalopram group at each visit (p -values ranging between < 0.01 and < 0.0001) and at follow-up visit ($p < 0.05$). The total score was significantly higher in the escitalopram group than in the placebo group at each visit (p -values ≤ 0.0001) and at follow-up visit ($p < 0.05$). In women, the 5-item PRSexDQ total scores were significantly lower in the agomelatine 25 mg group than in the escitalopram group at week 2 ($p < 0.005$) and week 5 ($p < 0.05$). In women volunteers receiving agomelatine 50 mg, the 5-item PRSexDQ total scores were significantly lower than in the escitalopram group at week 5 ($p < 0.05$). The total score was significantly higher in the escitalopram group than in the placebo group at each visit (p -values ranging from < 0.05 to < 0.005) and at follow-up visit ($p < 0.05$). No statistically significant differences between each dose of agomelatine and placebo group nor between both agomelatine doses were found at each visit (including follow-up visit) in both genders.

Volunteers with sexual activity at baseline and at each post-baseline visit (n = 78). The mean \pm standard deviation total score was significantly lower in both agomelatine groups compared to escitalopram at each visit during the treatment period and at follow-up visit. There was a statistically significant between-drug difference in favour of each agomelatine dose from week 2

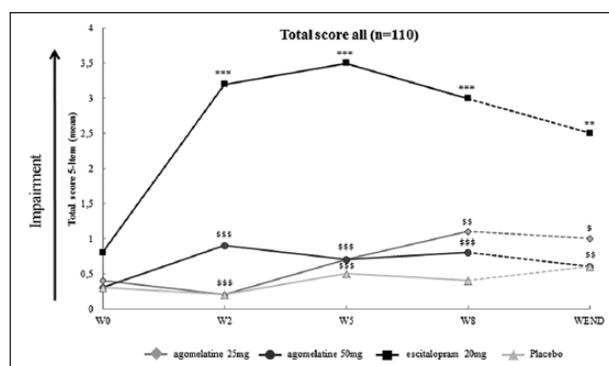


Figure 1A. Evolution by visit of the PRSexDQ total score in volunteers with sexual activity at baseline and at least once until week 8 ($n = 110$). At each visit, the mean PRSexDQ total score was significantly lower in both agomelatine groups compared to escitalopram. PRSexDQ total score was higher in the escitalopram group compared to placebo. $**p < 0.01$; $***p < 0.001$ (escitalopram versus placebo); $^{\$}p < 0.05$; $^{\$\$}p < 0.01$; $^{\$\$\$}p < 0.001$ (escitalopram versus agomelatine 25 or 50 mg); ANCOVA adjusted for centre, gender and baseline; WEND = 5–7 days after the last study drug intake.

(2.4 ± 0.5 points, $p < 0.0001$ at 25 and 50 mg) to the end of the 8-week study period (2.4 ± 0.6 points, $p = 0.0001$ at 25 mg; 2.6 ± 0.6 points, $p < 0.0001$ at 50 mg). The PRSexDQ 5-item total score observed in the placebo group was 0.2 ± 0.7 at the end of the 8-week study period. No statistically significant differences between each dose of agomelatine and placebo group nor between both agomelatine doses were found at each visit. The mean total scores in the escitalopram group were 2.7 ± 2.7 at week 2, 3.6 ± 3.2 at week 5 and 3.3 ± 2.8 at week 8 and 2.8 ± 2.7 at follow-up visit. At each visit, there was a statistically significant escitalopram-placebo difference ($p < 0.0001$) (see supplementary material).

Similar results in favour of both agomelatine doses were observed in both genders (see supplementary material). In men as in women, the 5-item PRSexDQ total scores were significantly lower in both agomelatine groups than in the escitalopram group at each visit (p -values ranging between < 0.01 and < 0.0001 for men; p -values from < 0.05 to < 0.01 for women). The total score was significantly higher in the escitalopram group than in the placebo group at each visit (p -values ≤ 0.0001 from weeks 2 to 8 for men; p -values ranging from < 0.01 to < 0.005 for women). No statistically significant differences between each dose of agomelatine and placebo group nor between both agomelatine doses were found at each visit (including follow-up visit) in both genders.

PRSexDQ: dysfunction relative to each individual item

Volunteers with sexual activity at baseline and at least once until week 8 (n = 110). For dysfunction relative to each PRSexDQ item after eight weeks of treatment, results were in favour of both agomelatine doses compared to the escitalopram group, except for the items “decreased libido” and “erectile dysfunction in men/vaginal lubrication dysfunction in women”. The greatest differences in favour of agomelatine were noted for the dysfunctions “delayed orgasm/ejaculation” and “absence of orgasm/ejaculation”.

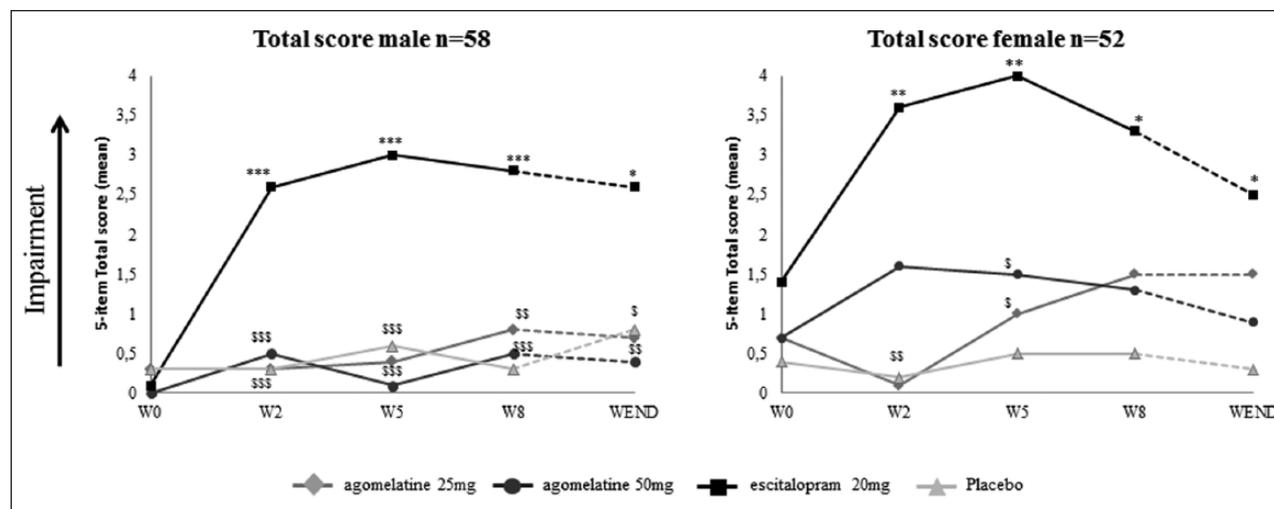


Figure 1B. Evolution by visit of the PRSexDQ total score in volunteers with sexual activity at baseline and at least once until week 8 ($n = 110$).

Analysis per gender.

The mean PRSexDQ total score was significantly lower in both men and women receiving agomelatine than in volunteers receiving escitalopram regardless of the gender. PRSexDQ total score was higher in the escitalopram group compared to placebo.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (escitalopram versus placebo).

§ $p < 0.05$; §§ $p < 0.01$; §§§ $p < 0.001$ (escitalopram versus agomelatine 25 or 50 mg).

ANCOVA adjusted for centre and baseline; WEND = 5–7 days after the last study drug intake.

The dysfunction “delayed orgasm/ejaculation” was reported in four (16.7%), and two (8.3%) volunteers in the agomelatine 25 and 50 mg groups respectively, versus 14 (53.8%) in the escitalopram group ($p < 0.01$ and $p < 0.005$ for agomelatine 25 and 50 mg, respectively for each comparison) at week 8 (Figure 2). Two volunteers (7.1%) in the placebo group reported a dysfunction “delayed orgasm/ejaculation”, a finding not significantly different from those of each agomelatine group and significantly different from those of the escitalopram group ($p < 0.001$).

The “absence of orgasm/ejaculation” was reported in three (12.5%), and one (4.2%) volunteers in the agomelatine 25 and 50 mg groups respectively, versus 12 (46.2%) in the escitalopram group ($p < 0.05$ and $p < 0.01$ for agomelatine 25 and 50 mg respectively, for each comparison) at week 8 (Figure 2). Two volunteers (7.1%) in the placebo group reported a dysfunction “absence of orgasm/ejaculation”, a finding not significantly different from those of the agomelatine groups and significantly different from those of the escitalopram group ($p < 0.004$).

“Tolerance about changes in the sexual relationship” showed that most participants had no SD at baseline in the agomelatine groups 25 and 50 mg (88.9%, 96.0%), and in the escitalopram group (89.3%). During the treatment period, the frequency of participants without SD decreased significantly in the escitalopram group compared to the agomelatine groups ($p < 0.05$ to $p < 0.01$ depending on the visit except for week 2 on agomelatine 25 mg) and to placebo group ($p < 0.01$). Of the volunteers, 19 (76%) and 20 (80.0%) reported no SD in the agomelatine 25 and 50 mg groups respectively, versus 13 (50.0%) in the escitalopram group and 27 (96.4%) in the placebo group at week 8 (Table 1). No statistically significant differences between each dose of agomelatine and placebo group nor between both agomelatine doses were found.

Volunteers with sexual activity at baseline and at each post-baseline visit ($n = 78$). The greatest differences in favour

of agomelatine were noted for the dysfunctions “delayed orgasm/ejaculation” and “absence of orgasm/ejaculation”. The dysfunction “delayed orgasm/ejaculation” was only reported in two (12.5%) volunteers in the agomelatine 25 mg group (none in the agomelatine 50 mg) versus 12 (63.2%) in the escitalopram group at week 8. One volunteer (4.8%) in the placebo group reported a dysfunction, a finding not significantly different from that of the agomelatine group. The “absence of orgasm/ejaculation” was reported in two (12.5%) in the agomelatine 25 mg group versus 10 (52.6%) in the escitalopram group (none in the agomelatine 50 mg and placebo groups) at week 8.

Tolerance about changes in the sexual relationship was significantly better in both agomelatine groups than in the escitalopram group (at week 8: $p < 0.05$ and $p < 0.01$ for agomelatine 25 and 50 mg, respectively). Of the volunteers, 13 (81.3%) and 16 (84.2%) reported no SD in the agomelatine 25 and 50 mg groups respectively, versus seven (36.8%) in the escitalopram group and 20 (95.2%) in the placebo group at week 8.

No statistically significant differences between each dose of agomelatine and placebo group nor between both agomelatine doses were found.

VAS-SFS

In the subset of participants with a sexual activity at baseline and at least at one post-baseline visit until week 8, the sexual functioning satisfaction VAS score did not vary in the agomelatine 25 mg, 50 mg and placebo groups, with mean changes from baseline to week 8 of 0.7 ± 16.1 (median 3.0) mm, -5.4 ± 22.0 (median 0.0) mm and 0.3 ± 6.1 (median 0.0) mm, respectively. Similar results were observed in both genders.

In the escitalopram 20 mg group, in line with PRSexDQ total score, the mean sexual functioning satisfaction score decreased

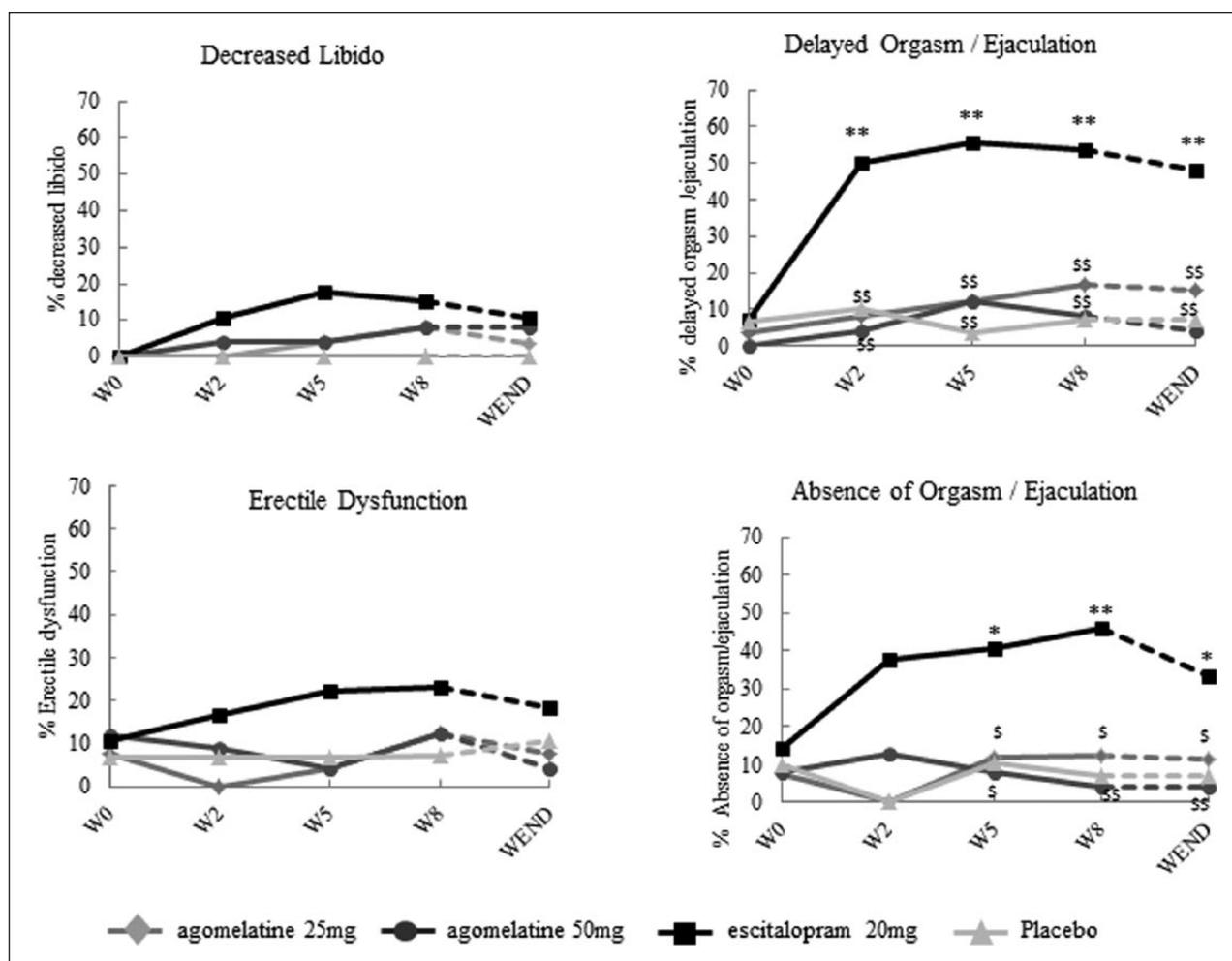


Figure 2. Sexual dysfunction (SD) as per each single PRSexDQ's item in volunteers with sexual activity at baseline and at least once until week 8 ($n = 110$).

After eight weeks of treatment, the frequency of participants with the SD "delayed orgasm/ejaculation" or "absence of orgasm/ejaculation" is statistically significantly lower in both agomelatine groups than in the escitalopram group. On escitalopram, the frequency of participants with "delayed orgasm/ejaculation" or "absence of orgasm/ejaculation" after eight weeks of treatment is significantly higher than on placebo.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (escitalopram versus placebo).

^s $p < 0.05$; ^{ss} $p < 0.01$ (escitalopram versus agomelatine 25 or 50 mg).

Logistic regression; WEND = 5–7 days after the last study drug intake.

during the treatment period, with a mean decrease from baseline of -10.0 ± 18.2 (median -5.0) mm at week 8, particularly in women -15.7 ± 21.6 (median -5.0) mm, and -3.3 ± 10.6 (median -6.0) mm in men versus 0.3 ± 6.1 (median 0.0) mm in the placebo group (1.6 ± 6.6 (median 0.0) mm in men and -0.9 ± 5.5 (median -2.0) mm in women).

Safety

In the safety set ($N = 133$), defined as all included volunteers who took at least one dose of study treatment, the most common treatment-emergent adverse events reported in agomelatine groups were headache, somnolence, upper respiratory tract infection and nasopharyngitis (Table 2). Headache was experienced by six and eight volunteers (18.2% and 25.0%) receiving agomelatine 25 and 50 mg respectively, compared to 13 volunteers (36.1%) receiving escitalopram (10–20 mg), and seven volunteers (21.9%)

in the placebo group. Somnolence, upper respiratory tract infection, abnormal dreams and urinary tract infection were generally more reported by volunteers of the agomelatine 25 mg group.

Most of emergent adverse events in the agomelatine or placebo groups were of mild or moderate intensity. Few participants experienced severe emergent adverse events during the treatment period: two participants in the agomelatine 25 mg group (diarrhoea and nightmare in one subject and ovarian cyst torsion in the other), one participant in the agomelatine 50 mg group (upper respiratory tract infection), one in the escitalopram 20 mg group (headache), and three participants in the placebo group (dry mouth, abnormal dreams and ejaculation failure, respectively).

Two participants, both in the agomelatine 25 mg group (6.1%), had emergent serious adverse events. One participant had two serious adverse events considered as treatment-related by the investigator (ALAT: 3.5 ULN and ASAT: 2.2 ULN) which occurred 14 days after the first intake. The participant recovered after study drug withdrawal (56 days after the last dose intake).

Table 1. PRSexDQ individual item 5: Tolerance about changes in relationship in participants with sexual activity at baseline and at least at one post-baseline visit until week 8 ($N = 110$).

			Agomelatine 25 mg ($N = 27$)	Agomelatine 50 mg ($N = 25$)	Escitalopram ($N = 28$)	Placebo ($N = 30$)
Tolerance about changes in sexual relationship						
Base- line	All	<i>n</i>	27	25	28	30
	No SD	<i>n</i> (%)	24 (88.9)	24 (96.0)	25 (89.3)	30 (100)
	Well	<i>n</i> (%)	3 (11.1)	1 (4.0)	2 (7.1)	–
Week 8	Fair	<i>n</i> (%)	–	–	1 (3.6)	–
	All	<i>n</i>	25	25	26	28
	No SD	<i>n</i> (%)	19 (76.0)	20 (80.0)	13 (50.0)	27 (96.4)
	Well	<i>n</i> (%)	4 (16.0)	3 (12.0)	11 (42.3)	1 (3.6)
p-value	Fair	<i>n</i> (%)	2 (8.0)	1 (4.0)	2 (7.7)	–
	Poor	<i>n</i> (%)	–	1 (4.0)	–	–
			NS	NS	< 0.01 ¹	
DEND	All	<i>n</i>	27	25	28	29
	No SD	<i>n</i> (%)	22 (81.5)	20 (80.0)	14 (50.0)	28 (96.6)
	Well	<i>n</i> (%)	3 (11.1)	4 (16.0)	11 (39.3)	–
	Fair	<i>n</i> (%)	2 (7.4)	–	3 (10.7)	–
	Poor	<i>n</i> (%)	–	1 (4.0)	–	1 (3.4)
p-value			< 0.05 ²	< 0.05 ²	< 0.0005 ¹	

¹versus placebo, ²versus escitalopram, Cochran-Mantel-Haenszel test; NS = non significant.

Table 2. Summary of emergent adverse events during the 8-week treatment period in at least four volunteers of any treatment group (safety set, $N = 133$).

	Agomelatine 25 mg ($N = 33$)	Agomelatine 50 mg ($N = 32$)	Escitalopram 20 mg ($N = 36$)	Placebo ($N = 32$)
Headache	6 (18.2)	8 (25.0)	13 (36.1)	7 (21.9)
Somnolence	7 (21.2)	4 (12.5)	5 (13.9)	2 (6.3)
Upper respiratory tract infection	6 (18.2)	3 (9.4)	4 (11.1)	2 (6.3)
Nasopharyngitis	5 (15.2)	2 (6.3)	6 (16.7)	8 (25.0)
Fatigue	3 (9.1)	2 (6.3)	4 (11.1)	1 (3.1)
Abnormal dreams	4 (12.1)	1 (3.1)	4 (11.1)	2 (6.3)
Urinary tract infection	4 (12.1)	1 (3.1)	1 (2.8)	1 (3.1)
Dizziness	–	1 (3.1)	5 (13.9)	–
Nausea	–	–	10 (27.8)	1 (3.1)

Number of patients (%).

The other participant experienced not treatment-related severe ovarian cyst torsion. For both participants, emergent serious adverse events led to study drug withdrawal and resolved.

During the treatment period, few participants experienced emergent adverse events leading to study treatment discontinuation: two participants in the agomelatine 25 mg group (6.1%) experienced three serious emergent adverse events that led to study drug withdrawal and two participants in the escitalopram 20 mg group (5.6%) experienced seven non-serious emergent adverse events leading to study treatment discontinuation. In the escitalopram group, emergent adverse events leading to study treatment discontinuation were related to nervous system disorders and psychiatric disorders (two participants), and general disorders and administration site conditions (one participant). They were considered as related to study treatment for two participants (agitation and tremor in one participant, dizziness, restlessness legs syndrome and anxiety in the other). In

the agomelatine 25 mg group, two participants had three emergent adverse events leading to study treatment discontinuation. ALAT increased and ASAT increased in one participant (considered as related) and there was an ovarian cyst torsion in the other participant (not related). No participants withdrew from the study due to adverse events in the agomelatine 50 mg and placebo groups.

No clinically relevant change in mean values of biochemical and haematological parameters were found and there were no death reported during the study.

Discussion

The present study is one of the few randomized clinical trials evaluating the sexual acceptability of an antidepressant in a population including both men and women without depressive symptoms, so that pharmacodynamic effects are not masked by

patients' pathology (Abler et al., 2011; Kennedy et al., 1996; Montejo et al., 2010; Nafziger et al., 1999).

The sexual acceptability of agomelatine 25 or 50 mg in healthy participants having a sexual activity at baseline and at least once until week 8 is particularly good and significantly superior to that of escitalopram 20 mg. The level of SD with agomelatine 25 or 50 mg was low and analogous to that of placebo, with no dose-dependent effect. The robust difference between antidepressants, in favour of agomelatine, is obtained from the second week of treatment and maintained up to the follow-up visit. Consistently, the mean PRSexDQ 5-item total score was significantly lower in both agomelatine groups than in the escitalopram group from the second week, and the difference was maintained until the end of the study period. After eight weeks of treatment, the dysfunctions relative to each PRSexDQ individual item (except "decreased libido" and "erectile dysfunction") were significantly less frequent on agomelatine than on escitalopram. After eight weeks of treatment, SD relative to all PRSexDQ items except "erectile dysfunction" and "decreased libido" had a significantly higher level on escitalopram than on placebo. The greatest difference in favour of agomelatine was noted for the dysfunctions "delayed orgasm/ejaculation" and "absence of orgasm/ejaculation", as previously demonstrated in men versus paroxetine (Montejo et al., 2010). Accordingly, the absence of deleterious effect of agomelatine on sexual acceptability using PRSexDQ, particularly on these items was consistently observed in the subset of male volunteers with regular sexual activity at each visit, a population similar to the previous study (Montejo et al., 2010).

The advantage of agomelatine over SSRIs is likely to be related to its antagonist action at 5-HT_{2C} receptors, as compounds sharing this pharmacological property do not delay orgasm/ejaculation in non depressed healthy men (Waldinger et al., 2001, 2003). On the other hand, as decrease in libido and erectile dysfunction appear lately in the chronological sequence of sexual alterations (Clayton and Montejo, 2006; Montejo et al., 1997), a treatment period longer than eight weeks may be needed for studying the impact of antidepressants on the emergence of these two sexual disorders.

In agreement with all above-mentioned results, all participants given both doses of agomelatine (or the placebo) reported a good degree of satisfaction with his/her sexual functioning, as there were no relevant changes in VAS-SFS total score from baseline. These findings substantiate the absence of deleterious effect on sexual function throughout the entire development of agomelatine, and are in line with specific head to head trials (Kennedy et al., 2008; Montejo et al., 2010) and meta-analyses that consistently report that there is no significant difference with placebo regarding treatment-emergent SD caused by agomelatine (Kennedy and Rizvi, 2010; Serretti and Chiesa, 2009; Taylor et al., 2014).

The present study offers the opportunity to explore the sexual acceptability according to the gender of participants as there was a balanced 1:1 ratio of men to women in each treatment arm. In men, agomelatine 25 and 50 mg doses were associated with a statistically significant better sexual acceptability than escitalopram 20 mg at each visit from week 2. The findings either in the whole population or in the subset of volunteers with regular sexual activity at each visit are analogous to previous data obtained versus paroxetine 20 mg in Spanish male volunteers (Montejo et al., 2010). Taken together these results emphasize the better sexual acceptability of agomelatine compared to SSRIs in healthy Caucasian men.

The sexual acceptability of agomelatine is also good in women, regardless of the dose administered, and superior to escitalopram. It is worth mentioning that, for the subset of women, statistical significances for differences with escitalopram were reached at weeks 2 and 5 with agomelatine 25 mg and at week 5 with agomelatine 50 mg. The profile of curves illustrate that the PRSexDQ total scores are slightly higher in women than in men. This is in line with the observations that women may be more prone to SD than men both in untreated and treated patients. Thus, prior to antidepressant treatment, depressed women are more prone to SD than men and they may differ from men not only in incidence but also in the presentation of clinical symptoms associated with sexual adverse effects (Thakurta et al., 2012). During antidepressant treatment, depressed women are also more prone to SD than men (Lee et al., 2010), and a majority of depressed women had SD on all the domains of sexual functioning decreased (desire, arousal, orgasm, satisfaction) (Grover et al., 2012). In this regard, the good sexual acceptability of both doses of agomelatine for women having a regular sexual activity is particularly noteworthy.

The study confirms in healthy volunteers that escitalopram is capable of causing high rates of SD, as already demonstrated in depressed patients (Garnock-Jones and McCormack, 2010; Reichenpfader et al., 2014). In particular, SD with escitalopram treatment was reported to occur to a similar extent as that with paroxetine, to a similar or greater extent as that with the SNRI duloxetine. Accordingly, the deterioration of the sexual acceptability by escitalopram detected here by mean of the PRSexDQ scale is in line, though slightly weaker than that obtained with paroxetine in similar conditions (Montejo et al., 2010), and maintained up to the follow-up visit, one week after drug discontinuation. The results were corroborated on the VAS-SFS scale, and it is worth mentioning that the degree of satisfaction with sexual functioning decreased mainly in women receiving escitalopram. Actually, one third of depressed women report SD on escitalopram (Sidi et al., 2012). This is an important point to consider as depression is much more common among women than men, with women/men risk ratios roughly 2:1 (Kessler, 2003).

The clinical safety profile in healthy volunteers given agomelatine 25 and 50 mg was consistent with that observed in depressive patients (Taylor et al., 2014) and with the agomelatine summary of product characteristics (SmPC); no unexpected adverse event was observed. On both doses of agomelatine, volunteers mainly experienced headache, somnolence, upper respiratory tract infection and nasopharyngitis (mild or moderate in intensity). One case of reversible transaminases increases (> 3 ULN) was reported in the agomelatine 25 mg dose regimen, with return to normal levels upon treatment cessation. Overall, the data give additional support to the good tolerability of both doses of agomelatine. The safety profile of escitalopram was in agreement with the SmPC; patients mainly reported headache, nausea, dizziness and somnolence.

Conclusions

By using validated scales to evaluate SD, the findings demonstrate the good sexual acceptability profile of agomelatine in healthy men and women. Agomelatine is an antidepressant that does not cause SD, which represents an advance in pharmacotherapy for mood disorders as the treatment avoids SD-related impairment of

quality of life, self-esteem, and relationships (Williams et al., 2010). The minimization of SD is an important factor to medication adherence and hence therapeutic success (Montejo et al., 2001) and it should be considered when making decisions about the relative merits and drawbacks of the antidepressant to be prescribed in naïve patients. In addition, such characteristics may also offer a successful alternative for patients who suffer from antidepressant-related SD. Accordingly, patients who previously developed SSRI- or SNRI-related SD and who switch to agomelatine significantly improve on every domain of PRSexDQ over several months of treatment (Montejo et al., 2014).

Author note

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Conflict of interest

AM has received investigational grants over the last 12 months from Eli Lilly, Pfizer, Lundbeck, Otsuka, Roche and Forum Pharmaceuticals. He was the Speaker Bureau for the last 12 months for Lundbeck, Otsuka, Pfizer, Eli Lilly, Glaxo SmithKline and Menarini.

JD currently advises or carries out research funded by Autifony, Sunovion, Lundbeck, AstraZeneca and Servier. All payment is to the University of Manchester. He has share options in P1vital Ltd.

RG has served as consultant, advisor or CME speaker in the last 12 months for AB Sciences, AstraZeneca, Janssen, Eli Lilly, Lundbeck, Otsuka, Roche, Servier and Takeda.

CH has acted as a paid consultant for Servier, P1vital Ltd. and Lundbeck and is a company director of Oxford Psychologists. She has received grant income from Servier, Lundbeck, Sunovion, UCB and Janssen Inc.

GG holds grants from Medical Research Council and Wellcome Trust, and holds shares in P1vital Ltd. and has served as consultant, advisor or CME speaker in the last 12 months for AstraZeneca, Cephalon/Teva, Convergence, Eli Lilly, GSK, Lundbeck, Medscape, Otsuka, Servier, Sunovion and Takeda.

CG and CG are employees at Servier.

Other authors have no conflict of interest.

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