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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.

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ABSTRACT

The present double-blind, placebo-controlled study evaluated the effects of agomelatine and the SSRI escitalopram on sexual dysfunction (SD) in healthy men and women.

Methods: 133 healthy volunteers (67 men, 66 women) were randomly assigned to agomelatine (25mg or 50mg) or escitalopram 20mg or placebo for 9 weeks. Sexual acceptability was evaluated by using the Psychotropic Related Sexual Dysfunction Questionnaire (PRSexDQ) 5-items total score and sexual dysfunction relative to each sub-scores (in 110 volunteers with sexual activity). SD was evaluated at baseline and after 2, 5, 8 weeks of treatment and 1 week after drug discontinuation.

Results: The PRSexDQ 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 volounteers' gender. Compared to placebo, only escitalopram significantly impaired dysfunction relative to "delayed orgasm or ejaculation" ($p < 0.01$), "absence of orgasm or ejaculation" ($p < 0.05$ to $p < 0.01$). The percentage of participants with a SD 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 (25mg or 50mg) 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 stigmatisation. 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, erectile dysfunction in men and affects both sexes abnormal orgasm (anorgasmia or delayed) (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;Kennedy et al., 2006;Montejo et al., 2001;Rosen et al., 1999;Delgado et al., 2005;Clayton et al., 2007a). 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 and Montejo, 2006;Clayton et al., 2014;Serretti and Chiesa, 2009). By comparison, drugs that predominantly increase noradrenaline or dopamine uptake and the $5\text{-}HT_2$ receptor blockers have fewer negative effects on sexual functioning (Clayton et al., 2002;Segraves and Balon, 2014;Bijlsma et al., 2014).

Agomelatine, the action of which is based on both MT1/MT2 receptor agonist and $5\text{-}HT_{2C}$ 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's 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 concommitant negative effects on sexual functioning related to the drug pharmacodynamic effect. Second, the depression *per se* can deteriorate the patient' sexuality before any antidepressant intake (Thakurta et al., 2012;Fabre and Smith, 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 few studies have explored the impact of antidepressants on populations free of depressed symptoms (Kennedy et al., 1996;Nafziger et al., 1999;Montejo et al., 2010;Abler et al., 2011). 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 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 25 and 50 mg) for 9 weeks in healthy men and women. The sensitivity of the trial was validated by using a placebo arm

and, as comparator, the SSRI escitalopram (10-20mg) known to impair sexual function in depressed men and women (Sidi et al., 2012;Serretti and Chiesa, 2009;Reichenpfader et al., 2014;Clayton et al., 2007b).

METHODS

This phase I study used a randomised, 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 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 1 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 judgment. The hepatic parameters (ALAT, ASAT, γGT, 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 3 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, pimozide, certain antimicrobial agents…) 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 (ß-blockers, anti-hypertensive, hypo-cholesterolaemic and psychotropic drugs) had to be discontinued at least 3 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 mg 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 (08:00 p.m.) in one red capsule containing one or two tablets of agomelatine 25 mg or one or two tablets of escitalopram 10mg 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 randomised to one of the four treatment arms: agomelatine 25mg, agomelatine 50mg, escitalopram 10-20mg 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 5 to 7 days after the treatment discontinuation or after premature treatment withdrawal whatever its time of occurrence.

Sexual acceptability was assessed by the validated Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Montejo *et al.*, 2000). The PRSexDQ consists of seven items pertaining to sexual dysfunction. The first item is a screening item to assess whether the patient has any sort of sexual dysfunction (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 sexual dysfunction, 1 = good, 2 = fair, 3 = poor). Only items 3 through 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 sexual dysfunction, to 15: maximum level of sexual dysfunction with the worst tolerability by the patient.

In addition to PRSexDQ total score, sexual dysfunction relative to each individual item was also evaluated. Sexual dysfunction was defined as at least one sexual impairment in one of the 4 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 was, the most satisfied with his/her sexual functioning the participant was.

Safety evaluations included 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 γGT 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, were 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 mg and 50mg) minus placebo and agomelatine 25mg minus 50mg. 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 25mg and 50mg, escitalopram *versus* placebo, agomelatine 25mg and 50mg *versus* placebo and agomelatine 25mg *versus* agomelatine 50mg 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, North Carolina).

RESULTS

A total of 137 volunteers were selected by 2 centres in U.K., of which 133 were included and randomly assigned to one of the 4 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). One hundred and twenty volunteers completed the study and 13 discontinued (4 volunteers in the agomelatine 25mg group, 7 in the escitalopram group and 2 in the placebo group). Half volunteers (66 participants, 49.6%) were women. In the randomized set (RS) defined as all included and randomised participants, the baseline demographic characteristics of the treatment groups were generally similar, with a mean ± 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 analysed 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 (± 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 ≥ 70%.

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

5-item total score of PRSexDQ

1) Volunteers with sexual activity at baseline and at least once until week 8 (n=110)

The mean ± 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 differences in favour of each agomelatine dose from week 2 (Estimates of the differences: 2.8 ± 0.5 points, p<0.0001 at 25mg; 2.0 ± 0.5 points, p =0.0004 at 50mg) to the end of the 8-week study period (1.9 ± 0.6 points, p=0.0016 at 25mg; 2.1 ± 0.6 points, p= 0.0005 at 50mg) and also at follow-up visit (1.4 ± 0.6 points, p=0.0169 at 25mg; 1.8 ± 0.6 points, p=0.04 at 50mg). 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 differences (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 25mg group than in the escitalopram group at weeks 2 (p<0.005) and 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 (included follow-up visit) in both genders.

2) V*olunteers with sexual activity at baseline and at each post baseline visit (n=78)*

The mean ± 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 differences in favour of each agomelatine dose from week 2 (2.4 ± 0.5 points, p<0.0001 at 25mg and 50mg) to the end of the 8-week study period (2.4 ± 0.6 points, p=0.0001 at 25mg; 2.6 ± 0.6 points, p< 0.0001 at 50mg). 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 differences ($p<0.0001$). (**Figure 1C supplemental file**).

Similar results in favour of both agomelatine doses were observed in both genders (**Figure 1D supplemental file**). 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 (included follow-up visit) in both genders.

PRSexDQ: dysfunction relative to each individual item

1) Volunteers with sexual activity at baseline and at least once until week 8 (n=110)

For dysfunction relative to each PRSexDQ items after 8 weeks of treatment, results were in favour of both agomelatine doses compared to escitalopram group, except for item "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".

The dysfunction "delayed orgasm/ejaculation" was reported in 4 (16.7%), and 2 (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 25mg and 50mg, 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 escitalopram group (p<0.001).

The "absence of orgasm/ejaculation" was reported in 3 (12.5%), and 1 (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 25mg and 50mg 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 escitalopram group (p<0.004).

"Tolerance about changes in the sexual relationship" showed that most participants had no sexual dysfunction at baseline in each agomelatine groups 25 mg, 50 mg (88.9%, 96.0%), and in the escitalopram group (89.3%). During the treatment period, the frequency of

participants without sexual dysfunction 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 25mg) and to placebo group ($p<0.01$). Nineteen (76%) and 20 (80.0%) volunteers reported no sexual dysfunction 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.

2) V*olunteers with sexual activity at baseline and at each postbaseline 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 2 (12.5%) volunteers in the agomelatine 25mg group (none in the agomelatine 50mg) 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 2 (12.5%) in the agomelatine 25mg group versus 10 (52.6%) in the escitalopram group (none in the agomelatine 50mg 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 25mg and 50mg, respectively). Thirteen (81.3%) and 16 (84.2%) volunteers reported no sexual dysfunction in the agomelatine 25 and 50 mg groups respectively, *versus* 7 (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 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 6 and 8 volunteers (18.2% and 25.0%) receiving agomelatine 25mg and 50mg respectively, compared to 13 volunteers (36.1%) receiving escitalopram (10-20mg), and 7 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 25mg 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: 2 participants in the agomelatine 25 mg group (diarrhoea and nightmare in one subject and ovarian cyst torsion in the other one), 1 participant in the agomelatine 50 mg group (upper respiratory tract infection), 1 in the escitalopram 20 mg groups (headache), and 3 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). 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 an emergent adverse events leading to study treatment discontinuation : two participants in the agomelatine 25mg group (6.1%) experienced 3 serious emergent adverse events that led to study drug withdrawal and two participants in the escitalopram 20 mg group (5.6%), experienced 7 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 (2 participants), and general disorders and administration site conditions (1 participant). They were considered as related to study treatment for 2 participants (agitation and tremor in one participant ; dizziness, restlessness legs syndrome and anxiety in the other one). In the agomelatine 25mg group, 2 participants had 3 emergent adverse events leading to study treatment discontinuation. ALAT increased and ASAT increase in one participant (considered as related) and an ovarion 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 patient's pathology (Kennedy et al., 1996;Nafziger et al., 1999;Montejo et al., 2010;Abler et al., 2011).

The sexual acceptability of agomelatine 25 mg 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 sexual dysfunction with agomelatine 25 mg 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 8 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 8 weeks of treatment, sexual dysfunction relative to each PRSexDQ items but "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 and in 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;Waldinger et al., 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) and a treatment period longer than 8-week 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 was 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 25mg and 50mg 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 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 sexual dysfunction 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, sexual dysfunction with escitalopram treatment was reported to occur to a similar extent to that with paroxetine, to a similar or greater extent to 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 sexual dysfunction 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 mg 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 sexual dysfunction, 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 characteristic 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 improves every domain of PRSexDQ over several months of treatment (Montejo *et al.*, 2014).

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LEGEND TO FIGURES

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 escitalopram group compared to placebo. ** $p < 0.01$; *** $p < 0.001$ (escitalopram *vs* placebo). [$] p <0.05; [$$] p <0.01; [$$$] p <0.001 (escitalopram *vs* agomelatine 25 or 50 mg), ANCOVA adjusted for centre, gender and baseline. WEND : 5-7 days after the last study drug intake

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 the gender. PRSexDQ total score was higher in escitalopram group compared to placebo. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (escitalopram *vs* placebo); [$] p <0.05; [$$] p <0.01; [$$$] p <0.001 (escitalopram *vs* agomelatine 25 or 50 mg). ANCOVA adjusted for centre and baseline. WEND : 5-7 days after the last study drug intake

Supplemental file Figure 1C : Evolution by visit of the PRSexDQ total score in volunteers with sexual activity at baseline and at each visit and without sexual dysfunction at baseline (n = 78). At each visit, the mean PRSexDQ total score was significantly lower in both agomelatine groups compared to escitalopram. PRSexDQ total score was higher in escitalopram group compared to placebo. *** $p < 0.001$ (escitalopram *vs*

placebo) ; $^{\$\$}$ p <0.01; $^{\$\$\$}$ p <0.001 (escitalopram *vs* agomelatine 25 or 50 mg). ANCOVA adjusted for centre, gender and baseline. WEND : 5-7 days after the last study drug intake

Supplemental file Figure 1D : Evolution by visit of the PRSexDQ total score in volunteers with sexual activity at baseline and at each visit and without sexual dysfunction at baseline (n = 78). Analysis per gender. The mean PRSexDQ total score was significantly lower in both men and women receiving agomelatine than in volunteers receiving escitalopram regardless the gender. PRSexDQ total score was higher in escitalopram group compared to placebo. * p < 0.05; **p < 0.01; ***p < 0.001 (escitalopram *vs* placebo); $^{\$}$ p < 0.05; $^{\$\$}$ p < 0.01; $^{\$\$\$}$ p < 0.001 (escitalopram *vs* agomelatine 25 or 50 mg). ANCOVA adjusted for centre and baseline. WEND : 5-7 days after the last study drug intake

Figure 2 : Sexual dysfunction as per each single PRSexDQ's item in volunteers with sexual activity at baseline and at least once until week 8 (n = 110). After 8 weeks of treatment, the frequency of participants with the sexual dysfunction "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 8 weeks of treatment is significantly higher than on placebo. * p < 0.05; ** p < 0.01; ***p < 0.001 (escitalopram *vs* placebo) ; $^{\$}$ p < 0.05; $^{\$\$}$ p <0.01 (escitalopram *vs* agomelatine 25 or 50mg). Logistic regression. WEND : 5-7 days after the last study drug intake.

TABLES

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						
Baseline	All	n	27	25	28	30
	No sexual dysfunction	n (%)	24 (88.9)	24 (96.0)	25 (89.3)	30 (100)
	Well	n (%)	3 (11.1)	1 (4.0)	2 (7.1)	-
	Fair	n (%)	-	-	1 (3.6)	-
Week 8	All	n	25	25	26	28
	No sexual dysfunction	n (%)	19 (76.0)	20 (80.0)	13 (50.0)	27 (96.4)
	Well	n (%)	4 (16.0)	3 (12.0)	11 (42.3)	1 (3.6)
	Fair	n (%)	2 (8.0)	1 (4.0)	2 (7.7)	-
	Poor	n (%)	-	1 (4.0)	-	-
P value			NS	NS	<0.01 [1]	
DEND	All	n	27	25	28	29
	No sexual dysfunction	n (%)	22 (81.5)	20 (80.0)	14 (50.0)	28 (96.6)
	Well	n (%)	3 (11.1)	4 (16.0)	11 (39.3)	-
	Fair	n (%)	2 (7.4)	-	3 (10.7)	-
	Poor	n (%)	-	1 (4.0)	-	1 (3.4)
P value			<0.05 [2]	<0.05 [2]	<0.0005 [1]	

(1) *vs*. placebo, (2) *vs*. escitalopram, Cochran-Mantel-Haenszel test. NS : non significant

Table 2: Summary of emergent adverse events during the 8-week treatment period in at least 4 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 (%)