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Myo-inositol in the treatment of premenstrual dysphoric disorder

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Objective Premenstrual dysphoric disorder (PMDD) is a mood disorder disrupting social and/or occupational life of affected women. Premenstrual dysphoric disorder etiology is unknown, although a pivotal role is played by the serotoninergic system. Indeed, one of the most effective treatments is selective serotonin reuptake inhibitors. Several studies have proposed a selective serotonin reuptake inhibitor-like role for myo-inositol, likely due to the fact that myo-inositol is the second messenger of serotonin. In the present study, we aimed to investigate the effect of myo-inositol in the treatment of PMDD.
Methods We used a two-phase clinical trial approach (phase I: placebo washout; phase II: comparisons between treatment and placebo) and treated PMMD patients with two different myo-inositol formulations: powder or soft gel capsules. We decided to test these two formulations because according to the manufacturer, 0.6 g of myo-inositol in soft gel capsule has a pharmacokinetic equivalent to 2 g of myo-inositol in powder.
Results Our results showed a significant improvement of three different scales: a reduction in the Daily Symptoms Records scale and an improvement of the Hamilton Depression Rating and Clinical Global Impression—Severity of Illness scales. Results were similar for both formulations.
Conclusions In the present study, by using a new pharmaceutical formulation, we were able to clearly prove the efficacy of myo-inositol in PMDD. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—myo-inositol; premenstrual dysphoric disorder; selective serotonin reuptake inhibitors; soft gel capsules

INTRODUCTION

Among all the natural molecules claiming to have an effect on mood disorders, myo-inositol is one of the few that has been proven effective (Saeed *et al*., 2007). The main challenge to the adoption of myo-inositol into clinical practice was the dosage. Indeed, several trials were performed using myo-inositol preparations ranging from 12 to 30 g, resulting in gastrointestinal side effects and reduced patients' compliance (Rosel *et al*., 2000, Levine *et al*., 1995, Benjamin *et al*., 1995b, Carlomagno and Unfer, 2011).

Premenstrual dysphoric disorder (PMDD) is a mood disorder affecting women during the last week of luteal phase (Zukov *et al*., 2010, Pearlstein and Steiner, 2008, Yang *et al*., 2008). PMDD is characterized by physical, affective, and behavioral symptoms, particularly anxiety and depressed mood that disrupt social and/or occupational functioning (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) (Halbreich *et al*., 2003, Chawla *et al*., 2002) (Borenstein *et al*., 2005). PMDD affects from 2 to 8% of US or European women, and its diagnosis is based on two full monthly cycles of daily symptom charting (Cunningham *et al*., 2009).

Several studies suggest that the etiology of PMDD relies at least in part on decreases in serum progesterone and oestradiol levels; therefore, PMDD has been considered to be a consequence of steroid withdrawal (Schmidt *et al*., 1998). Both animal experiments and clinical studies suggest that androgens may exaggerate irritability and aggression (Schmidt *et al*., 1998). Therefore, because irritability is the main symptom of PMDD (Schmidt *et al*., 1998), it has been suggested that PMDD may be partially due to enhanced androgenicity.

Two lines of evidence support the assumption that the pathogenesis of PMDD may be related to changes in serotoninergic activity: first, the main symptoms of PMDD, such as irritability, anger, depressed mood, and carbohydrate craving are serotonin-dependent behaviors; second, aberrations in serotonergic transmission were found in women with premenstrual syndrome/

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PMDD (Su *et al*., 1997, Steinberg *et al*., 1999, Eriksson *et al*., 2006), with symptomatic women having lower density of serotonin transporter receptors than controls (Melke *et al*., 2003).

Several treatment strategies have been used to treat PMDD, including hormones, diuretics, and serotonergic antidepressants (Cunningham *et al*., 2009).

Because myo-inositol antidepressant activity is well known (Carlomagno and Unfer, 2011) (Kaplan *et al*., 1996, Benjamin *et al*., 1995a, Chengappa *et al*., 2000, Benjamin *et al*., 1995b, Levine *et al*., 1995), we decided to test myo-inositol effectiveness in the treatment of PMDD.

Recently, a new pharmaceutical formulation of myo-inositol (soft gel capsule) was developed. According to the manufacturer, 0.6 g of myo-inositol in soft gel capsule ensures the same pharmacokinetic of 2 g of myo-inositol in powder (data not shown).

The present study shows preliminary data of a two-phase double-blind trial, aiming to study the effectiveness of the two formulation of myo-inositol in patients who met the criteria for PMDD.

METHODS

Patients

The study consisted of 90 patients (aged 18–45 years) who were enrolled at both the AGUNCO Obstetrics and Gynacology Center (Rome, Italy) and at the Casa di Cura Psichiatrica Colle Cesarano, Villa Adriana (Tivoli, Italy).

Premenstrual dysphoric disorder diagnosis was given according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Women were enrolled for the study if they had an age between 18 and 45 years, a menstrual cycle length between 24 and 35 days, and a diagnosis of PMDD. On the other hand, women were excluded from the study if they were taking oral contraceptives, if they had irregular menstrual cycles, if they were pregnant, or lactating. Women who met diagnostic criteria for a major psychiatric syndrome, or who were taking any other medication to treat premenstrual symptoms were excluded from the study.

SIFIOG (Italian Society of Phytotherapy and Dietary Supplements in obstetrics and Gynecology) ethical committee approved the present study.

Study Design

Patients were randomly assigned to one of the two treatment groups: powder (4 g of myo-inositol 3 times per day, Lo.Li. Pharma s.r.l.) or soft gel capsule (1,2 g of myo-inositol 3 times per day, Lo.Li. pharma s.r.l, Rome; patent pending). The study consisted of two phases. In the first part, a single-blind placebo "washout" was carried out for two menstrual cycles during which women were treated with a placebo (powder or soft gel capsule according to the assigned group). Subjects responding to the placebo treatment (patients who showed significant improvement in one of the scales used for evaluations) were excluded from the study. The second phase was carried out for six menstrual cycles. Eligible patients were randomized, either in placebo or treatment group for both formulations (Figure 1).

Procedure

All patients were evaluated using the Hamilton Depression Rating (HAM-D) scale, Penn Daily Symptoms Records (DSR) scale, and Clinical Global Impression—Severity of Illness (CGI-SI) scale. Measurements were taken at baseline and at the end point of each phase. The main outcome measure was the premenstrual score from the DSR, HAM-D, and CGI-SI.

Statistical analysis

Statistical analysis was performed using the GraphPad software. Results were analyzed via one-way ANOVA followed by Bonferroni's correction test. To compare the effectiveness of the two treatments, we analyzed percent differences to respective T0 between the two formulations by Student's *t*-test. The confidence interval was accepted as $p < 0.05$.

RESULTS

Out of the 90 patients enrolled for the study, only 71 were still eligible after the "washout" placebo period.

All patients completed the study. At baseline (T0), there were no differences among groups for the analyzed parameters (Table 1).

After the observation period (phase II), patients were evaluated using the same parameters used at enrollment.

Results clearly showed that myo-inositol was able to reduce several aspects of the PMDD syndrome. Indeed, all scores improved in the myo-inositol-treated groups compared with the baseline and with the placebo phase II (Table 2).

In particular, there was no difference between the two pharmaceutical formulations (powder or soft gel capsule): 3.6 g/day myo-inositol in soft gel capsule showed similar improvement of DSR, HAM-D, and CGI-SI scales compared with 12 g/day myo-inositol in powder. The percent difference to respective T0 between the two formulations did not differ (DSR: $p > 0.05$; HAM-D: $p > 0.05$; CGI-SI: $p > 0.05$).

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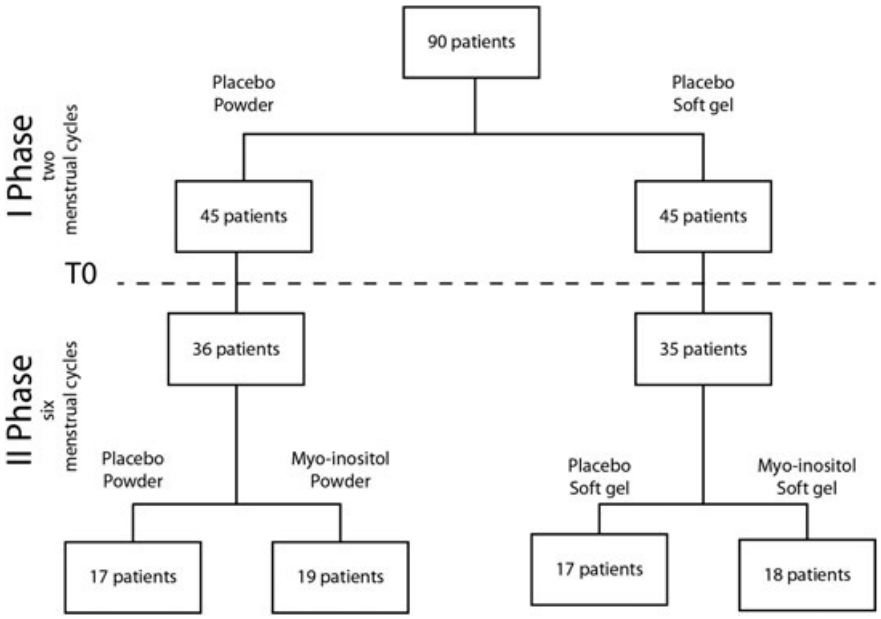

Figure 1. Study flow chart

Table 1. Analyzed parameters at T0 between the groups

	MI-powder				MI-soft gel			
	placebo		treated		placebo		treated	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
DSR	178.4	43.54	182.7	51.23	182.9	47.09	181.4	45.12
HAM-D	15.76	5.64	15.79	4.56	16.00	5.51	16.28	5.08
CGI-SI	4.53	1.51	4.21	1.84	4.12	1.76	4.33	2.11

DSR, Daily Symptoms Records scale; HAM-D, Hamilton Depression Rating scale; CGI-SI, Clinical Global Impression—Severity of Illness scale.

No severe side effects were reported during the study; only one patient belonging to the myo-inositol powder group reported mild gastrointestinal side effects, but she decided to continue with the treatment.

DISCUSSION

This preliminary study shows that myo-inostitol is able to improve several aspects of the PMDD syndrome.

Indeed, we were able to show that the DSR score was significantly reduced after myo-inositol

Table 2. Values of the analyzed parameters at T0 and the end of phase II for all the groups

	MI-powder									
	Placebo T0		Placebo phase II		Treated T0		Treated phase II			
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	*p*-value MI PhII *vs* MI T0	*p*-value MI Tr *vs* plac
DSR	178.4	43.5	173.4	50.0	182.7	51.2	77.0	47.2	**	**
HAM-D	15.8	5.6	15.8	4.6	15.8	4.6	8.2	3.8	**	**
CGI-SI	4.5	1.5	4.2	2.0	4.2	1.8	1.8	0.8	**	**
	MI-soft gel									
	Placebo T0		Placebo phase II		Treated T0		Treated phase II			
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
DSR	182.9	47.1	169.1	59.9	181.4	45.1	79.4	33.7	**	**
HAM-D	16.0	5.5	16.0	5.6	16.3	5.1	8.2	3.1	**	**
CGI-SI	4.1	1.8	4.1	1.6	4.3	2.1	2.0	0.7	**	**

Comparisons were performed in the MI-treated group at T0 and at the end of phase II, and between Placebo phase II and MI treated phase II.
DSR, Daily Symptoms Records; HAM-D, Hamilton Depression Rating scale; CGI-SI, Clinical Global Impression—Severity of Illness scale.
** $p < 0.01$.

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supplementation for a period of six menstrual cycles. The dosage of the myo-inositol powder used in the study was administrated during the day to minimize the chance of gastrointestinal side effects.

In parallel, we checked the effect of myo-inositol in a soft gel capsule pharmaceutical formulation. According to the manufacturer, the pharmacokinetic of one capsule containing 0.6 g of myo-inositol is equivalent to the pharmacokinetic of 2 g of myo-inositol in powder (data not shown).

Myo-inositol antidepressant activity is well known (Carlomagno and Unfer, 2011) (Kaplan *et al*., 1996, Benjamin *et al*., 1995a, Chengappa *et al*., 2000, Benjamin *et al*., 1995b, Levine *et al*., 1995), and several studies have been performed to better understand its mechanism of action. In particular, it was shown that the noradrenergic neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) was not able to block the antidepressant activity of myo-inositol (Einat *et al*., 2001). Additional data suggested that myo-inositol antidepressant activity was mediated by the serotoninergic system (Einat *et al*., 2001). In particular, it was shown that two serotonin antagonists acting on 5-HT_{1A} and 5-HT_{2A}/5-HT_{2c} receptors (Lejeune and Millan, 2000, Viola *et al*., 2002) have opposite effects. Indeed, although administration of the 5-HT_{2A}/5-HT_{2c} antagonist ritaserin abolished myo-inositol antidepressant effect, the administration of the 5-HT_{1A} antagonist pindolol did not (Einat *et al*., 2001).

These data suggested that a specific pathway is involved in myo-inositol antidepressant activity, likely a signaling that involves the 5-HT_{2A}/5-HT_{2c} receptors (Einat *et al*., 2001).

Furthermore, the authors showed that there was no synergistic action between myo-inositol and the direct serotonin agonist 8-OH-DPAT (Einat *et al*., 2001). Unfortunately, these data are based on animal models, and therefore, further research is needed to fully understand MI mechanism of action in humans.

In the present study, we show that 0.6 g of myo-inositol in a soft gel capsule formulation have therapeutic equivalence to 2 g of myo-inositol in powder.

Indeed, a comparable clinical improvement of the PMDD measured using scales such as DSR, HAM-D, and CG1-S1 was observed in both myo-inositol-treated groups.

The clinical relevance of these results is that this new myo-inositol formulation overcomes all the gastrointestinal side effects previously described (Carlomagno and Unfer, 2011). Therefore, this myo-inositol formulation represents a new pharmacological tool that could be routinely used in the clinical practice to treat mood disorders.

Previous data by Nemets and coworkers claimed that myo-inositol has no beneficial effect on PMDD. In their study, 12 g of myo-inositol in powder were administrated, with no indication of multiple administration (Nemets *et al*., 2002). Their study was a crossover clinical trial (placebo and MI) during which the treatments were administered during the luteal phase of the menstrual cycle.

The discrepancy between their study and our study could be also due to the different study design. Indeed, in our study, we adopted the protocol already used by Steiner *et al*. (Steiner *et al*., 1995), where a selective serotonin reuptake inhibitor was used as PMDD treatment, and a placebo washout phase was introduced. Furthermore, in our study, a chronic treatment schedule was adopted.

In conclusion, our data demonstrate that myo-inositol could be a valuable treatment for PMDD. Furthermore, by using a new myo-inositol formulation, it is possible to bypass the gastrointestinal side effects that in the past limited the clinical use on myo-inositol in the treatment of mood disorders.

CONFLICT OF INTEREST

G. C., S. B. and F. D. A. declare no conflict of interest; V. U. is a Lo.Li. pharma consultant.

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