Assessment of N-acetylcysteine as an Alternative for the Treatment of the Premenstrual Dysphoric Disorder: A Randomized Clinical Trial

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ABSTRACT

Background: Premenstrual dysphoric disorder (PMDD) is a common condition affecting females' quality of life in a significant negative manner. Verities of medical treatments have been investigated for whether the prevention or treatment of this condition with uncertain outcomes. Currently, evidence has shown the role of oxidant and antioxidant agents in the etiology of PMDD. N-acetylcysteine (NAC) is an anti-inflammatory and antioxidant agent that we have aimed to assess its efficacy for the treatment of PMDD, and compare it with fluoxetine, as one of the choice treatment of this disorder.

Methods: The current randomized clinical trial has been conducted on 119 childbearing females, randomly divided into three groups of either treatment with 10 mg of fluoxetine twice daily or 450 mg of NAC twice daily or placebo in 2016-2018. The agents were administered daily for two weeks within the initiation of menstruation cycle for two menstruation cycles. The questionnaires of Hamilton and daily record of severity of problems (DRSP) were filled before and following the interventions for groups, and the results were compared.

Results: The baseline DRSP and Hamilton scores were not statistically different among the three groups (P>0.05) while by the end of the study all of the groups presented significantly improved scores (P<0.001). Comparison of three groups revealed remarkable inferiority of placebo to the other two groups (P<0.05) while no statistical difference was found between N-acetylcysteine with fluoxetine in terms of neither Hamilton (P:0.12) nor DRSP scores (P:0.75).

Conclusion: Findings of our study are in favor of NAC use for the treatment of PMDD. Further studies with larger sample size and elongated duration of treatment and follow-ups are strongly recommended.

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Introduction

Premenstrual syndrome (PMS) is a combination of physical, psychological and behavioral symptoms occurring in up to the 90% of females in reproductive ages (1); 3-8% of them meet the criteria for the premenstrual dysphoric disorder (PMDD) (2). These symptoms occur within a week before the bleeding, in the luteal phase, and improve by the onset of menstruation (3).

PMDD that was considered as a severe form of the PMS based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (4) was revised by the DSM-V and defined as the existence of one of the five affective symptoms, anxiety, irritability, marked anger, affective liability, and depressed mood, plus five or more symptoms related to mentioned affective symptoms (5). Based on this criterion, the most severe symptoms should be presented in

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the 3-4 days before the bleeding and last at most for three days following the menstruation. Moreover, the patients should be symptom-free in the postmenstrual week (6).

Varieties of etiologies have been estimated to play a significant role for the presentations of PMDD, among them serotonin role (5-HT, 5-hydroxytryptamine) is one of the most favored ones. It has been demonstrated that females with PMDD have abnormalities in the total blood serotonin, the transmission of serotonin, lower concentrations of serotonin transporter receptors and depleted amount of tryptophan as the precursor of serotonin (4, 7). Therefore, selective serotonin reuptake inhibitors are considered as the choice of PMDD treatment with approximate respond rate of 60-80% (8, 9).

Fluoxetine is the most common SSRI agent, abundantly used for the treatment of PMDD. Studies in the literature have reported considerable success due to the use of fluoxetine for this aim (1), while similar to other SSRIs, fluoxetine causes adverse effects including nausea, headache, tremor and to a more critical reduction in libido and impotence (10). These adverse effects, reduction in libido and impotence in particular, has made the patients reluctant to use fluoxetine and convinced psychiatrists to search for other agents with better responses and less adverse effects.

The evidence showing either increased levels or the highest levels of proinflammatory components in the blood flow during the luteal phase is increasing. Among the components, interleukin 6, tumor necrosis factor and C-reactive protein can be named (11, 12). On the other hand, some of the studies have raised the theory of the role of oxidative metabolism in the symptoms of PMDD and therefore the value of using anti-oxidant agents whether for the prevention or the treatment, though the evidence is not appropriate enough and controversial (5, 13).

These studies have presented the oxidant/antioxidant effect due to the alterations in the estrogen and progesterone levels (5, 13). In addition, glutathione is the primary endogenous antioxidant produced in the brain from the precursor amino acids, L-glycine, L-cysteine, and L-glutamate in two enzymatic steps. Oxidative stresses trigger the depletion in the glutathione levels (14).

N-acetylcysteine (NAC) is an agent used widely as a mucolytic (15) and antidote of acetaminophen (16), but have shown to act as an anti-inflammatory and anti-oxidant agent, as well (17). Besides, NAC enhances L-cysteine supplies, the rate limiting agent for the endogenous production of glutathione (14). Moreover, there are studies in the literature showing the values of NAC use, as an antioxidant, for the treatment of mood disorders (18). Therefore, we have hypothesized that NAC may help females resenting from PMDD, as well. To best of our knowledge, this is the first study assessing the role of N-acetylcysteine for the treatment of PPMD based on its anti-oxidant effect; therefore we have aimed to compare the efficacy of NAC versus fluoxetine and placebo for the PMDD symptoms relief.

Methods

The current study is a parallel double blinded 1:1:1 allocation ratio randomized-clinical-trial (RCT) conducted on 119 childbearing females referred to university hospitals from May 2016 to April 2018.

Inclusion criteria were as following; Diagnosis of the premenstrual dysphoric disorder based on DSM-V criteria (5); age of 18-45 years old; the body mass index (BMI) of 19.8-25 kg.m-2; normal menstrual cycles of 21-35 days; menstruation duration of 3-10 days; no history of treatment with antidepressant agents, oral contraception and supplemental vitamin drugs in recent two weeks; also, no previous history or concurrent diagnosis of other mood and thought disorders.

Pregnancy, treatment of infertility, unwillingness for participation in the study and use of any supplement were considered as unmet criteria. Those who did not adhere to the treatment schedule or discontinued the use of treatments were excluded.

The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol (No: Ir.mui. rec13396.33.31). We also recorded this study in the Iranian Registry of Clinical Trials and obtained the code of IRCT20180604039970N1 for its conduction.

After that, the study protocol was explained for the participants, and they were reassured about the confidentiality of their personal information. Eventually, the participants were requested to sign the written consent form of participation in this study.

The study population was selected through convenience sampling until achieving the required number of population for the study.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 s_1^2 + s_2^2}{d^2}$$

The formula above was used to measure the sample size in which the $z_{(1-\alpha/2)}$ as 95% confidence interval, and $z_{(1-\beta)}$ as 80% of test power equaled 1.96 and 0.84, respectively. In addition, d, S1 and S2 equaled 1.46, 2 and 2.5, respectively. The eventual measured population for each of the groups was 32 ones.

Then, they were randomly divided into three groups using Random Allocation software. Based on this software, each patient was randomly provided with a particular number attributed her to a group. The participants and the psychiatrist who interviewed them were blinded to the type of the prescribed remedy. As the intervention agents were provided in similar capsules, the patients were unaware about the type of treatment. Besides, the patients' allocation to the groups and the treatment agents were provided by a psychiatrist, but not the psychiatrist who interviewed the patients. The interviewer was blinded to the type of remedies used by the patients.

The first group was treated with 10 mg of fluoxetine twice daily (Abidi Co., Tehran, Iran), the second one with

900 mg of N-Acetyl Cysteine (Acetyl Cysteine STADA, STADA Co., Bing-doung, Vietnam) in divided doses used twice daily. The NAC sachets are only in 200 mg forms that, we have combined four and half of sachets together and then divided them into 450 mg capsule covers similar in shape, color and size to other agents and the third group were treated with placebo similar in shape, color, and size to other agents (Pharmacy Faculty of Isfahan University of Medical Sciences; Iran). The participants used the agents for two weeks following the initiation of menstruation. These treatment approaches performed for two menstrual cycles.

Age, gender, marital status, educational level, medical history, and occupation were recorded in the study checklist for all of the study participants.

They were assessed using two questionnaires of Hamilton and daily record of severity of problems (DRSP) before the study and following the treatments. Hamilton questionnaire is a means of assessing depression symptoms. It contains 21 questions with scorings of zero as no symptom to 4 as severe symptoms. The score of 0-7 is defined as regular, 8-13 as mild, 14-18 as moderate, 19-22 as severe, and >23 as very severe depression (19, 20).

Endicott and colleges in 1996 presented DRSP questionnaire. This questionnaire has the Cronbach's alpha of 0.95 and divides the symptoms into five subtypes of anxiety, depression, emotional, retention, and physical. The scoring system of the symptoms include; no symptoms: zero; notifying symptoms without chores interruption: 1; the

presence of symptoms partially causing an interruption in the daily activity but not job absence: 2 and complete interruption in daily activities: 3. The severity of the symptoms was scored from 7 days before the menstruation to at most four days following the bleeding. The scores of 0-33 were defined as mild, 33-66 as moderate and >66 as severe (21, 22).

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) version 22. The descriptive data were presented in mean and standard deviation, absolute numbers, and percentages. For inferential data, Wilcoxon test, paired T-test, ANOVA, and ANCOVA tests were used. The P-value of less than 0.05 was considered as significant level.

Results

In the current study, 160 patients were initially evaluated. Twenty five of them did not meet the inclusion criteria, and 14 ones refused to participate in the study. Among the studied population, two females treated with N-acetylcysteine left the study because of epigastric discomfort and belching, and 38 ones were adherent to the study protocol. All of the fluoxetine treated (N=40), and placebo-treated (N=41) females ceased the study successfully.

Participants of the three groups were not statistically different regarding demographics, including age, marital status, educational level, and family history of psychiatric illnesses (P>0.05). Table 1 represents the comparison of demographic information in the groups in details.

Table 1. Comparison of demographic characteristics in Intervention groups.

Group Parameter	N-acetylcysteine	Fluoxetine	Placebo	P-value
Age	30.61(7.32)	30.30(30.68)	30.53(7.77)	0.97
Family History of Psychiatric Disorders				
Yes	18(47.4)	23(57.5)	24(58.5)	0.55
No	20(52.6)	17(42.5)	17(41.5)	
Marital Status				
Single	19(50)	21(52.5)	21(51.2)	0.97
Married	19(50)	19(47.5)	20(48.8)	
Education				
Elementary and below	7(18.4)	5(12.5)	2(4.9)	0.64
Secondary education	11(28.9)	15(37.5)	13(31.7)	
Bachelor degree	13(34.2)	13(32.5)	17(41.5)	
Post graduate degrees	7(18.4)	7(17.5)	9(22.0)	
Job				
Housewife/unemployed	20(52.6)	22(55)	16(39)	0.30
Employed	18(47.4)	18(45)	25(61)	

The DRSP and Hamilton questionnaires were assessed before the study. Participants of the three groups were not statistically different regarding their depression status assessed through Hamilton test (P:0.22) and also, their

PMDD severity assessed using DRSP (P:0.72) before the initiation of the intervention. Comparison of each group within the time regarding both Hamilton and DRSP questionnaires showed a significant positive effect of all

of the approaches including N-acetylcysteine (P<0.001), fluoxetine (P<0.001) and placebo (P<0.001). Furthermore, comparison of three groups revealed remarkable inferiority of placebo to the other two groups as the females under treatment of fluoxetine, and N-acetyl cysteine represented significant better scores of both Hamilton and DRSP assessments than placebo following the study performance (P<0.05) (Table 2). Two-by-two comparison of the groups

showed significant differences between placebo-treated group with N-acetyl cysteine (P<0.001 for both Hamilton and DRSP questionnaires) and fluoxetine (P<0.001 for both Hamilton and DRSP questionnaires) treated groups while no statistical difference was found between N-acetyl cysteine with fluoxetine in terms of Hamilton (P:0.12) and DRSP scores (P:0.75).

Table 2. Comparison of daily record of severity of problems (DRSP) and Hamilton scores.

	Group	Before	After	Change	P-value
DRSP score	**N-acetylcysteine**	67.35 (6.42)	23.04(12.79)	44.31(12.81)	<0.001
	Fluoxetine	64.92(8.66)	24.69(14.93)	40.24(15.99)	<0.001
	Placebo	65.60(8.82)	51.15(19.58)	14.45(18.35)	<0.001
	P-value	0.72	<0.001	<0.001	
Hamilton score	**N-acetylcysteine**	10.08(1.02)	3.71(2.08)	6.37(2.01)	<0.001
	Fluoxetine	9.75(0.98)	3.13(1.57)	6.63(1.66)	<0.001
	Placebo	10.07(1.23)	7.32(2.90)	2.76(3.05)	<0.001
	P-value	0.22	<0.001	<0.001	

The other assessment of this study was about the adverse effects presented in the females. Table 3 compares the incidence of adverse effects in three treatment groups.

Comparison of the three groups revealed no significant difference regarding drug-related adverse effects (P>0.05).

Table-3. Drug-related adverse effects among the studied population.

	Gastrointestinal	Headache	Anxiety	Insomnia	Increased vaginal bleeding
Fluoxetine	8 (20%)	9 (22.5%)	7 (17.5%)	6 (15%)	9 (22.5%)
N-acetyl cysteine	6 (15.7%)	3 (7.9%)	3 (7.9%)	4 (10.5%)	3 (7.9%)
Placebo	3 (7.3%)	6 (14.6%)	5 (12.2%)	4 (9.75%)	5 (12.2%)
P value	0.103	0.091	0.711	0.645	0.087

Discussion

In the current study, three approaches of fluoxetine, as conventional medical treatment of PMDD, placebo, as control and N-acetyl cysteine for the treatment of PMDD were assessed. Three groups were similar in terms of demographics, including age, marital status, educational level, and family history of psychiatric illnesses. Therefore probable confounding effects of the demographics were eliminated in the further assessments. Although we observed placebo effect in the control group, NAC administration was as successful as fluoxetine for the treatment of PMDD, whereby the adverse effects of NAC use were negligible.

As mentioned above, 3-8% of the females resent from irritating symptoms of PMDD, a disorder that occurs every month and remarkably affects the person's life in a negative manner (23). Varieties of medical treatment approaches have been used for the treatment of PMDD with diverse outcomes. SSRIs are at the top list of remedies used for the treatment of PMDD (24). Similar to our study, several studies in the literature have demonstrated the moderate to significant satisfactory outcomes of fluoxetine use for the treatment of PMDD (8, 25). Besides, in the current study the successful control of PMDD symptoms were achieved

by use of fluoxetine only for few days within the initiation of menstruation cycle. The significance of this short-term use is better clarified by considering that none of the females represented reduction in libido or impotence as the most note-worthy adverse effect of fluoxetine leading to nonadherence to the long-term treatment. Therefore, the patients are capable to use fluoxetine intermittently, in the luteal phase only (26); a characteristic that probably occurs due to the rapid activation of enzymes converting 5α-dihydro-progesterone (5α-DHP) to allopregnanolone, a neuroactive steroid (27).

To the best of our knowledge, the current study is the first one assessing the use of NAC for the treatment of PMDD. We found significant response to the treatment, while comparison of NAC to fluoxetine as a choice treatment, revealed insignificant difference. There are studies in the literature representing the efficacy of NAC for conditions such as schizophrenia, mood disorders, addiction, obsessive-compulsive and related disorders and substance abuse. Berk et al., conducted their study on patients resenting from bipolarity, experimented the use of 1 gr NAC twice daily in depression phase and represented dramatic response of the patients in contrast to placebo (18). Similar outcomes were

represented by Deepmala et al. (28) who investigated the NAC use in several psychiatric disorders including bipolar disorder, as maintenance therapy in particular, and also depression. These results were confirmed by Fernandes et al. (29) assessing the use of 2-2.4 gr daily NAC for depressed mood regardless of the major psychiatric disorder.

The similarity of symptoms represented by PMDD females to the presentations of depressed mood and affect is the hallmark to administer NAC for the treatment of PMDD. The outcomes of the current study may have been achieved through mechanisms including; 1) acetylated cysteine is capable of passing blood brain barrier, representing higher levels of cysteine, the rate-limiting component of glutathione production pathway, to the brain for the endogenous antioxidant glutathione production and restoration of redox imbalance (30). Not only, the role of glutathione depletion in condition such as depressed mood has been well-established (31), but there are animal studies showing increased levels of glutathione following oral administration of NAC (32, 33). 2) The second mechanism is attributed to the modulation of inflammatory pathways, as elevated levels of C-reactive protein, interlukin-6 and tumor necrosis factor alpha has been detected in various psychiatric disorders (34, 35). NAC may affect the inflammatory cascade either directly or through amelioration of oxidative stress (36).

The other assessment of our study targeted adverse effects of each agent, among which although insignificantly, the least complaints were found among those under NAC treatment, even less than placebo. Increased vaginal bleeding was one of the surprising most common complaint of fluoxetine use, while other ones were presented by other studies, as well. The permanent adverse effects of SSRIs, sexual dysfunction which is the most remarkable reason for discontinuation of the treatment (8) was not presented by the patients, probably due to the intermittent short-term use.

NAC is a well-tolerated agent used orally in various different studies, and even up to 2800mg of dose did not cause significant adverse effects, while similar to our study, gastrointestinal irritation is the most common complaints, other non-specific reported adverse effects include headache, insomnia, elevated blood pressure, fatigue, muscle pain, skin rash and dry mouth (28, 37).

Although it is a limitation of our study not to assess the affected mood entities of PMDD patients in details, but only in general, studies in the literature have shown that short-term administration of fluoxetine can improve PMDD females irritability, mood swings and labile affect (26) , symptoms affected by NAC mechanisms as well. Therefore, further studies in order to detailed assessment of PMDD symptoms and its response to various medical therapies are strongly recommended. Besides, we want to recommend different doses of NAC in the future studies.

In conclusion, this study showed significant improvement in the PMDD symptoms following use of whether placebo or fluoxetine or NAC. Comparison of the agents revealed remarkable superiority of both fluoxetine and NAC to the placebo while NAC and fluoxetine had similar efficacy on the PMDD symptoms relief.

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