



# The Relationship Between Late Luteal Phase Dysphoric Disorder and Anxiety Disorders

AREND T. VEENINGA, M.D., PH.D.

*Psychiatric Hospital 'De Grote Rivieren', Gorinchem, The Netherlands*

CORINE DE RUITER, PH.D. AND FLORIS W. KRAAIMAAT, PH.D.

*Department Psychology, University of Amsterdam, The Netherlands*

**Abstract** — Thirty-two women with the diagnosis 'late luteal phase dysphoric disorder' (LLPDD), thirty-two women with the diagnosis panic disorder (PD) or panic disorder with agoraphobia (PDA), and twenty-eight controls were compared on current and lifetime psychiatric diagnoses according to DSM-III-R criteria, using a structured interview. Anxiety disorders were largely found in the LLPDD patient group. LLPDD patients reported, as assessed with a self-report questionnaire, cyclical fluctuations in anxiety and depression, their levels being generally higher during the cycle than the controls. However, anxiety and depression rates in LLPDD patients did not reach levels reported by PD(A) patients.

## INTRODUCTION

The relationship between PMS and affective disorders has received much attention because alterations in mood seem to be the most prominent complaints during premenstruum (Roy-Byrne, Hoban, & Rubinow, 1987). Anxiety is another psychological symptom reported with greater frequency premenstrually than at other times during the cycle. Recently, some findings have been published on the co-occurrence between panic anxiety and the menstrual cycle. Breier, Charney, & Henninger (1986) found that 51% of women with

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Correspondence should be addressed to Arend T. Veeninga, Psychiatric Hospital 'De Grote Rivieren', Wijkoperstraat 2, 4204 HK Gorinchem, The Netherlands.

panic disorder retrospectively reported a premenstrual exacerbation of anxiety symptoms. Cameron, Kuttesch, McPhee, & Curtis (1988) found that women with panic attacks reported, again rated retrospectively, substantial anxiety fluctuations, the premenstrual week being most severe. Prospective assessment of the same subjects, however, showed much smaller fluctuation (Cameron et al., 1988). Stein, Schmidt, Rubinow, & Udhe (1989) found that prospective evaluation showed a premenstrual increase of anxiety in PMS patients without psychiatric illness, but not in patients with panic disorder. Thus, there is no clear evidence that the menstrual cycle influences fluctuations in anxiety in patients with panic disorder.

A pattern of relatively severe dysphoric complaints in some women during the last week of the luteal phase has led to the inclusion of a new proposed diagnostic category, the 'late luteal phase dysphoric disorder' (LLPDD), in the appendix of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R; American Psychiatric Association, 1987). To be useful as an instrument for research and clinical purposes, it must be possible to make a reliable differential diagnosis with the LLPDD criteria. There is, however, up to the present no empirical evidence that such a differentiation can be achieved (Gallant, Popiel, Hoffman, Chakraborty, & Hamilton, 1992). It appears that the criteria for LLPDD, major depression, dysthymia, and anxiety disorders, overlap substantially. A careful examination of patients with premenstrual affective symptoms is still needed to determine not only whether LLPDD can exist as a separate entity, but also to develop reliable procedures for differential diagnosis between LLPDD and psychiatric disorders.

We undertook this study to assess the comorbidity of LLPDD and anxiety and affective disorders. Patients who met prospectively confirmed criteria for LLPDD were examined on coexisting psychiatric disorders, using DSM-III-R criteria and a structured interview, and were compared with controls. A distinction was made between current and past psychopathology.

Since DSM-III-R criteria for LLPDD and panic disorder substantially overlap, patients with LLPDD were also compared on current and lifetime prevalence of psychiatric disorders with a group of patients having panic disorder (PD), or panic disorder with agoraphobia (PDA). Little is known about the severity of anxiety and depression in LLPDD compared to PD(A). Therefore, LLPDD patients, PD(A) patients, and controls were compared on levels of anxiety and depression as measured with a self-report questionnaire.

## MATERIAL AND METHODS

### *Subjects*

Thirty-two patients with the diagnosis LLPDD, 32 women with a primary diagnosis PD or PDA, and 26 healthy controls participated in the study. LLPDD patients and PD(A) patients were all seeking treatment for their disorder. They were diagnosed on the basis of chronic complaints of at least six months. Mean duration of illness in the LLPDD group was 6.9 years ( $SD = 4.9$ ) and in the PD(A) group 6.1 years ( $SD = 5.4$ ).

### *Selection Procedure*

*LLPDD patients.* Subjects with histories of premenstrual symptoms between the ages of 18 and 45 with regular menses (not less than 27 or more than 31 days), not taking contraceptives, not undergoing treatment for menstrual problems and other physical diseases, were recruited by newspaper advertisement requesting participants for a research and treatment project on premenstrual complaints. Premenstrual fluctuations in complaints were prospectively confirmed with the Menstrual Distress Questionnaire (MDQ; Moos, 1985) on the 4th, 12th, 22nd, and 26th day of the menstrual cycle during two consecutive cycles. A detailed description of the selection procedure is reported elsewhere (Veeninga & Westenberg, 1992). Thirty-eight patients participated in the study.

The provisional diagnosis LLPDD was made by clinical interview using the DSM-III-R criteria. To confirm the symptom criteria of the LLPDD prospectively, measurements with the MDQ were again conducted on the 12th and 26th days of the menstrual cycle for two consecutive cycles. A 30% criterion of change in negative symptoms recommended at the NIMH conference (Blume, 1983) was used, as measured with the subscales considering negative affect, water retention, impaired concentration, and autonomic reactions of the MDQ. In our opinion, these subscales reflect the symptom criteria of LLPDD.

Thirty-two patients completed the interview and the self-report questionnaires, and met prospective symptom criteria for the LLPDD diagnosis. Six patients completed the self-report questionnaires but refused to participate in the interview.

Ovulation detection was performed by sonography on the 12th and the 22nd day of two cycles. All patients had ovulatory cycles.

*PD(A) patients.* A sample of 32 women with a primary PD or PDA diagnosis, diagnosed according to DSM-III-R criteria, was taken from a larger sample of patients who were referred to a research and treatment project on anxiety disorders (De Ruiter, 1989). The PD(A) and the LLPDD groups were matched by age, education, and marital status. None of the PD(A) patients fulfilled criteria for LLPDD. All women had regular menstrual cycles and none was undergoing treatment for menstrual problems or other physical diseases.

*Controls.* Controls included 26 women without histories of premenstrual complaints. Their participation in the study was requested by advertisement in an internal newsletter distributed to health professionals in a hospital. Women between the ages of 18 and 45 with regular menses (no fewer than 27 or more than 31 days), not taking oral contraceptives, and not undergoing treatment for menstrual problems and other physical diseases, were asked to participate in the control group. The diagnosis LLPDD was excluded by clinical interview. Absence of premenstrual complaints was confirmed prospectively with the MDQ on the 12th and 26th day of the menstrual cycle for two consecutive cycles.

### *Measures*

LLPDD patients and controls were interviewed by a psychiatrist in the intermenstrual period. Psychiatric diagnoses were assessed using the Anxiety

Disorders Interview Schedule-Revised (ADIS-R; DiNardo, O'Brien, Barlow, Waddell, & Blanchard, 1983). The ADIS-R is a structured interview designed for making a differential diagnosis of anxiety and affective disorders according to DSM-III-R criteria. The reliability of the ADIS-R proved to be adequate in an American (DiNardo et al., 1983) as well as in a Dutch population (De Ruiter, Rijken, Garssen, van Schaik, & Kraaimaat, 1989). A section on eating disorders (anorexia and bulimia) according to DSM-III-R criteria was added to the ADIS-R for this study. A distinction was made between current psychiatric morbidity and a lifetime prevalence of psychiatric disorders. Patients referred to the research project for anxiety disorders were interviewed on their first visit using the ADIS-R.

In addition to classification of affective and anxiety disorders according to DSM-III-R criteria, the groups were compared on the scores of the Symptom Checklist-90 (SCL-90; Derogatis, 1977). Only the total score and the subscales for anxiety and depression were used. LLPDD patients and controls rated each of the SCL-90 items on the 12th and the 26th day of the menstrual cycle, describing the degree of symptom distress over the most recent seven-day period. The SCL-90 was randomly administered over the menstrual cycle in the PD(A) patient group. There is evidence that the cycle has little or no influence on fluctuations in anxiety in PDA patients (Cameron et al., 1988; Stein et al., 1989). Therefore, it was considered not to be necessary to assess SCL-90 data in PDA patients in the premenstrual as well as the menstrual phase of the cycle.

## RESULTS

Mean age of the LLPDD group was 36.5 years ( $SD = 7.4$ ), of the PD(A) group 32.7 years ( $SD = 6.5$ ), and of the control group 35.1 years ( $SD = 6.1$ ). No significant differences were found between LLPDD patients, controls, and PD(A) patients with regard to age ( $F = 1.69$ ,  $df = 2$ ,  $p > .05$ ), marital status ( $\chi^2 = 12.31$ ,  $df = 6$ ,  $p > .05$ ), and educational level ( $\chi^2 = 4.16$ ,  $df = 8$ ,  $p > .05$ ).

### *Classification of Psychiatric Disorders According to DSM-III-R Criteria*

In Table 1 the distribution of the diagnoses according to DSM-III-R criteria is given for the LLPDD patient group, the PD(A) patient group, and the control group. A distinction is made between current diagnoses and the lifetime prevalence of psychiatric disorders. It has to be noted that some of the patients met diagnostic criteria for two or more diagnoses. Table 2 shows the number of diagnoses for the subjects in the samples. The distribution of the number of additional diagnoses in the LLPDD and the PD(A) samples did not differ ( $\chi^2 = 4.21$ ,  $df = 3$ ,  $p < .05$ ). This means that the LLPDD patient group bears a certain resemblance to the PD(A) patient group in types of additional diagnoses.

Simple phobia is by far the most frequently occurring diagnosis in all groups. Inspection of the data further revealed that ten women in the LLPDD patient group (31 %) had no additional current psychiatric diagnosis. Twenty-two women (69%) had one or more additional psychiatric diagnoses.

TABLE 1  
THE PREVALENCE OF PSYCHIATRIC DISORDERS IN LLPDD PATIENTS, PD(A) PATIENTS, AND  
CONTROLS DIAGNOSED ACCORDING TO DSM-III-R CRITERIA (PERCENTAGES IN PARENTHESES)

	Current Psychiatric Disorders			Lifetime Psychiatric Disorders		
	LLPDD (n = 32)	PD(A) (n = 32)	Contr. (n = 26)	LLPDD (n = 32)	PD(A) (n = 32)	Contr. (n = 26)
PD	—	4 (13%)	—	3 (9%)	4 (13%)	—
PDA	9 (28%)	28 (87%)	—	9 (28%)	28 (87%)	—
Social phobia	3 (9%)	4	—	3 (9%)	4	—
Simple phobia	14 (44%)	12 (38%)	8 (31%)	14 (44%)	12 (38%)	8 (31%)
AG	1 (3%)	—	—	1 (3%)	—	—
OCD	—	3 (9%)	—	1 (3%)	4 (13%)	—
PTSD	—	—	—	2 (6%)	1	—
Total number of anxiety disorders	27	51	8	33	53	8
Dysthymia	—	2 (6%)	—	—	2 (6%)	—
Major depression	—	4 (13%)	—	18 (56%)	19 (59%)	4 (15%)
Bipolar disorder	—	—	—	1 (3%)	—	—
Mania	—	—	—	1 (3%)	—	—
Total number of affective disorders	—	6	—	20	21	4
Psychosis	—	—	—	1 (3%)	1 (3%)	—
Somatization	1 (3%)	—	—	1 (3%)	—	—
Bulimia	4 (13%)	1 (3%)	—	4 (13%)	1 (3%)	—
Substance abuse	—	1 (3%)	—	2 (6%)	2 (6%)	2 (8%)
Total number of other disorders	5	2	—	8	4	2

PD = Panic disorder without agoraphobia. PDA = Panic disorder with agoraphobia. AG = Agoraphobia without a history of panic disorder. OCD = Obsessive compulsive disorder. PTSD = Posttraumatic stress disorder.

Current additional diagnoses in this group were mainly anxiety disorders. Nineteen women (59%) had one or more anxiety disorders. As can be observed, PDA was the second most frequently assigned additional diagnosis with nine women (28%) suffering from PDA. Three women met criteria for

TABLE 2  
NUMBER OF DIAGNOSES FOR LLPDD PATIENTS, PD(A) PATIENTS, AND CONTROLS

Sample	Number of Current Diagnoses				
	None	One	Two	Three	Four
LLPDD patients	—	10	14	7	1
PD(A) patients	—	17	7	4	4
Controls	18	8	—	—	—

social phobia. One patient had agoraphobia without a history of panic attacks. Bulimia was present in four women (13%), and one woman met diagnostic criteria for somatisation disorder. No current affective and psychotic disorders were diagnosed among the LLPDD patients. In the PD(A) sample, no current additional diagnoses were assigned in seventeen cases (53% of the sample). Fourteen women (47%) had one or more additional diagnoses. Four patients met DSM-III-R criteria for social phobia and twelve for simple phobia. Nineteen percent of the PD(A) patients (6) received an additional diagnosis of affective disorder (either major depression or dysthymia). One patient had bulimia and one a substance abuse disorder. Current psychiatric diagnoses in the control group were limited to simple phobias (31%). With regard to the lifetime prevalence of psychiatric disorders, it appeared that three LLPDD patients had a history of PD, two patients a history of posttraumatic stress disorder (PTSD), and one patient a history of obsessive-compulsive disorder (OCD). Affective disorders appeared to have occurred relatively frequently in the psychiatric history of LLPDD patients. At least eighteen patients (56%) reported one or more past episodes of major depression. Lifetime prevalence of psychiatric disorders in the PD(A) group revealed that one patient had a history of OCD and one a history of PTSD. Fourteen PD(A) patients (44%) had a history of major depression. One patient had suffered from a psychosis in the past, and one other patient had had an episode of substance abuse. In the control group, four women (15%) had had a past episode of major depression.

#### *Symptom Profiles for the Groups as Measured With the SCL-90*

In Table 3 the scores on the SCL-90 dimensions are shown for LLPDD patients and controls on the 12th and the 26th day of the cycle, and for PD(A) patients at random over the cycle.

TABLE 3  
MEANS AND STANDARD DEVIATIONS (IN PARENTHESES) OF THE SCL-90 SCALES  
FOR LLPDD PATIENTS, PD(A) PATIENTS, AND CONTROLS

	LLPDD Patients		Controls		PD(A) Patients
	Day 12	Day 26	Day 12	Day 26	Random
SCL anxiety	12.22 (2.15)	15.09 (4.89)	10.31 (0.47)	10.31 (0.68)	32.13 (10.33)
SCL depression	20.25 (5.38)	25.59 (10.03)	16.50 (0.68)	16.81 (1.39)	44.03 (17.94)
SCL total	111.03 (21.58)	134.09 (41.69)	92.69 (2.35)	93.77 (6.56)	234.87 (74.20)

*Note:* LLPDD patients and controls were tested on the 12th and 26th day of the cycle, and PD(A) patients were tested at random over the cycle. Results of statistical analyses are given in the section on the results.

Differences in SCL-90 scores on the 12th and the 26th days of the cycle were analyzed within LLPDD patients and controls (within-subject effects), and between LLPDD patients and controls on the 12th as well as the 26th day of the cycle (between-subject effects). After examining group means, it was decided that comparison of PD(A) scores to LLPDD-Day 12 scores would be significant if Day 26 scores would be, so first differences between PD(A) and LLPDD-Day 26 scores were analyzed.

Variances in the groups were found to differ so that nonparametric tests were used to analyze the data. Significant differences were found in the LLPDD patient group between the 12th and the 26th days of the cycle on the total score of the SCL-90 (Wilcoxon test,  $Z = -3.95$ ,  $p < .001$ ) and on the anxiety (Wilcoxon test,  $Z = -3.54$ ,  $p < .001$ ) and depression (Wilcoxon test,  $Z = -3.72$ ,  $p < .001$ ) subscales. No differences were found in the control group between the 12th and the 26th day on the SCL-90 total (Wilcoxon test,  $Z = -0.12$ ,  $p = .90$ ), the SCL-90 anxiety (Wilcoxon test,  $Z = 0.00$ ,  $p = 1.00$ ), and the SCL-90 depression scale (Wilcoxon test,  $Z = -0.98$ ,  $p = .33$ ).

LLPDD patients significantly differed from controls not only on the 26th day of the cycle on the SCL-90 dimensions (SCL-90 total: Mann-Whitney- $U$  test,  $Z = -5.74$ ,  $p < .001$ ; SCL-90 anxiety: Mann-Whitney- $U$  test,  $Z = -5.54$ ,  $p < .001$ ; SCL-90 depression: Mann-Whitney- $U$  test,  $Z = -5.43$ ,  $p < .001$ ), but also on the 12th day (SCL-90 total: Mann-Whitney- $U$  test,  $Z = -5.06$ ,  $p < .001$ ; SCL-90 anxiety: Mann-Whitney- $U$  test,  $Z = -4.58$ ,  $p < .001$ ; SCL-90 depression: Mann-Whitney- $U$  test,  $Z = -4.16$ ,  $p < .001$ ). This means that LLPDD patients not only had cyclic fluctuations in SCL-90 scores, but also showed higher levels of psychological distress, anxiety, and depression in general during the cycle. The scores of the PD(A) patients on the SCL-90 dimensions (at random over the cycle) appeared to be significantly higher than the SCL-90 scores of the LLPDD patients on the 26th day of the cycle (SCL-90 total: Mann-Whitney- $U$  test,  $Z = -5.57$ ,  $p < .001$ ; SCL-90 anxiety: Mann-Whitney- $U$  test,  $Z = -5.98$ ,  $p < .001$ ; SCL-90 depression: Mann-Whitney- $U$  test,  $Z = -4.48$ ,  $p < .001$ ). Thus, fluctuations in general psychological distress, anxiety, and depression in LLPDD patients do not reach the levels reported by PD(A) patients.

## DISCUSSION

We found that concurrent psychiatric morbidity among patients with chronic premenstrual complaints, who met DSM-III-R criteria for the LLPDD diagnosis, consisted mainly of anxiety disorders. Fifty-nine percent of the sample had one or more anxiety disorders. No current affective disorders were diagnosed in the LLPDD patient group. However, more than 50% of these patients gave histories of one or more major depressive episodes. The current finding that mainly anxiety disorders and no affective disorders were diagnosed in our LLPDD patients group is somewhat contradictory to prior results, mainly reporting high frequencies of affective disorders in relation to premenstrual symptomatology (Wetzel, Reich, McClure, & Wald, 1975; Schuckit, Daly, Herrman, & Hineman, 1975; DeJong, Rubinow, Roy-Byrne, Hoban, Grover, & Post, 1985; Mackenzie, Wilcox, & Baron, 1986; Stout, Steege, Blazer, &

George, 1986; Harrison, Endicott, Nee, Glick, & Rabkin, 1989). Our findings emphasize that LLPDD is strongly related to anxiety disorders. This is in line with more recent investigations (Facchinetti, Romano, Fava, & Genazzani, 1992; Fava, Pedrazzi, & Guaraldi, 1992).

LLPDD patients reported significantly higher levels of anxiety and depression in the premenstrual period compared with the intermenstrual period. However, even in the intermenstrual period, LLPDD patients scored higher than controls on the SCL-90 anxiety and depression dimensions. These higher levels of anxiety and depression in the LLPDD group in the intermenstrual period may be due to the number of LLPDD patients who also had PD(A). However, a post hoc analysis of the data revealed that the difference in SCL-90 anxiety and depression scores between LLPDD patients with a secondary diagnosis of PDA (9) and LLPDD patients without PDA (23) failed to reach conventional levels of significance.

SCL-90 scores in the LLPDD group in the premenstrual period did not reach the level of severity reported by PD(A) patients. This means that LLPDD is a rather mild disorder when symptom profiles of anxiety and depression are compared to those of patients with PD(A). Furthermore, the variance in scores on the 26th day appeared to be rather high, which means that the LLPDD group was not a homogeneous group in terms of severity of premenstrual symptoms.

Almost one third of the LLPDD patients had no additional psychiatric diagnosis. This means that it is possible to identify women with premenstrual mood complaints who fulfil DSM-III-R criteria for LLPDD only, free of other current DSM-III-R diagnoses. The finding of a relatively high comorbidity of LLPDD and anxiety disorders, differences in symptom severity between PDA and LLPDD, and the ability to differentiate between LLPDD and other psychiatric disorders provides some support for the proposal to include an LLPDD category in DSM-III-R. Our findings also emphasize the importance of measuring symptom profiles with self-report questionnaires for diagnosing psychopathology, in addition to classification with DSM-III-R criteria and a structured interview.

Results also emphasize the importance of careful assessment of coexisting psychiatric disorders in women with premenstrual symptoms who seek treatment for this problem. In future research on LLPDD, more attention should be devoted to the exclusion of coexisting psychiatric morbidity in LLPDD patient samples. Furthermore, the need for an index of severity, both for clinical and research purposes, should be stressed.

Finally, it should be emphasized that the conclusions drawn from this study are somewhat limited. The number of subjects in all groups was relatively small and the control group was selected from health professionals only. Moreover, assessment of SCL-90 scores in the PD(A) group was made at different times during the cycle than in the other groups.

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