Online Supplement

Ambulatory Assessment Characteristics Predict the Clinical Course of Premenstrual Dysphoric Disorder (Letter to the Editor)

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Supplementary Materials and Methods

Participants

Women with Premenstrual Dysphoric Disorder (PMDD) were recruited using different sources (e.g., newspapers, gynecologists practices, homepage of the Central Institute of Mental Health (CIMH). They underwent a clinical baseline interview to assess study in- and exclusion criteria and baseline sociodemographic and clinical variables. Inclusion criteria were fulfilling the DSM-5 criteria for PMDD A to E using the Structured Interview for DSM-IV TR Defined PMDD (SCID-PMDD [1]) with the diagnostic algorithm adapted for DSM-5. To avoid further participant burden, criterion F (prospective daily ratings during at least two symptomatic cycles before study inclusion) was not required. Exclusion criteria included age < 20 and > 42, a reported cycle length of < 22 or > 34 days, a reported variation of cycle length of more than five days, use of hormonal contraceptives, psychotropic medication or other medication affecting the HPAA during the last three months, heavy exercise (≥1 h per day), late evening or night shifts, body mass index <18 or >35, birth of a child or lactation/breastfeeding during the last 6 months, history of gynecological diseases, bipolar or psychotic disorders, and substance dependence, or current substance abuse.

In total, n=61 women with PMDD completed the baseline interview including the Ambulatory Assessment (AA). One woman dropped out during the four-month interval between baseline assessment and follow-up, resulting in a sample of n=60 PMDD women for the present paper.

Study Procedure

Data were collected from 3/2016 to 12/2018. During the baseline session at the CIMH the Structured Clinical Interview for DSM-IV TR PMDD (SCID-PMDD [1]) was administered to assess inclusion and exclusion criteria for PMDD. The SCID-PMDD is a structured clinical interview modeled after SCID-I that includes all symptom criteria relevant for DSM-5 together with the required impairment and exclusion criterions. The interview has shown high interrater reliability (kappa=0.96 [1])). Interviews were performed by a trained research psychologist.

For each woman individual calendars were prepared based on the date of her last menstruation onset and the average length of her menstruation and of her menstrual cycle. The menstrual cycle was divided into the menstrual, follicular, ovulatory, and late luteal phase (see [2]). Assessments during the *menstrual phase* took place on the second and third day of menstruation, and the *follicular phase* was examined on the second and third day after the end

of menstruation. The *ovulatory phase* was determined by a chromatographic ovulation test (gabControl hlH Ovulationsteststreifen, gabmed, Cologne). Participants started testing a few days before the predicted ovulation and continued daily testing until the ovulation test was positive. The AA for the ovulatory phase was then performed on the two days following ovulation. Assessments of the *luteal phase* took place on the fourth and third day before the next menstruation was expected. The calendar specified the exact days on which the respective AA was to be carried out and when to begin with the ovulation test. Participants were asked to repeat assessments during the next cycle if the assessment days were not accurate (e.g., if the actual menses onset was several days earlier or later than expected). To prevent sequential effects, women started the AA in different phases of their menstrual cycle. Four months after completion of the AA procedure, participants underwent a clinical follow-up interview at the CIMH where the SCID-PMDD was reassessed. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants gave written informed consent.

Measures

Interview and questionnaire scores

For the present analysis, the sum score of PMDD symptoms assessed with the SCID-PMDD (see above) was used as a predictor variable at baseline and as the dependent variable at follow-up. Furthermore, depressive symptoms were measured at baseline and at follow-up with the 21-item Beck Depression Inventory (BDI-II, German version [3]).

Ambulatory Assessment (AA)

The AA took place following the diagnostic baseline interview. It was carried out using Motorola Moto G 2nd Generation smartphones with the software My Experience movisensXS, Version 0.6.3658 (movisens GmbH, Karlsruhe, Germany). There were eight subjective assessments per day, with the first at 9 am and the last at 9:30 pm. Inter-assessment intervals were semi-randomized and varied between 45 and 120 min. Each assessment was announced by a beep and took 3-4 min to complete. Participants had 5 min to respond, and assessments could be delayed by 15 min. If participants were unable to respond or rejected the alarm, the assessment was saved as missing. At each assessment participants rated momentary mood and rumination on 7-point likert scales (1=not at all, 7=very much).

Momentary negative and positive affect were assessed with six items each which were balanced with respect to arousal (negative affect: upset, irritated, nervous, listless, down, bored; positive affect: cheerful, energetic, enthusiastic, satisfied, relaxed, calm). Outcomes for

negative and positive affect were calculated by averaging the respective item scores. Rumination was assessed with the item "at the moment I am stuck on negative thoughts and cannot disengage from them", thereby capturing the uncontrollability facet of rumination. In accordance with other AA studies on daily life stress (e.g. [4,5]), stress appraisal of recent daily life events was measured as the degree of unpleasantness of the most important event subjects encountered since the last beep (ranging from -3=very pleasant to +3=very unpleasant).

Twenty minutes after the subjective ratings, participants collected saliva cortisol samples with standard salivettes (Sarstedt, Germany). Participants were instructed to refrain from strenuous exercise during the AA day and not to eat, drink other than water, smoke, physically exercise or brush their teeth 20 min before completing saliva sampling (further details see [6]). Three further samples were collected after awakening (without subjective ratings) to determine the cortisol awakening response [6]. These samples were excluded from the present analyses. Saliva cortisol concentrations were measured using commercially available chemiluminescence-immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were <8%.

Data analytic strategy

Data were analyzed using SAS and IBM SPSS version 23. Stress appraisal was transformed by centering around the person mean, thereby varying within but not between individuals [7]). With this approach, interindividual differences in mean stress appraisal do not affect the parameter estimates but are controlled (see [8], p. 365), and the predictor indicates higher/lower stress appraisal than usual. Cortisol data were log-transformed to adjust for skewness. Log cortisol data were examined for outliers, and outliers more than three standard deviations from the group mean were winsorized to 3 standard deviations (cf. [9,10]).

Predictor analysis followed a two-step procedure. In a first step, random effects parameters (i.e., intercepts, slopes of stress appraisal) for four AA variables (negative affect (average of six items), positive affect (average of six items), rumination, and salivary cortisol secretion) over the total menstrual cycle[1] for each woman were estimated with Restricted Maximum Likelihood using the PROC MIXED procedure of SAS with time, time-squared (if significant), sampling day and stress appraisal as fixed effects. Hence, the estimated person specific intercept values reflect interindividual differences in the average level of momentary negative affect, positive affect, rumination and cortisol secretion over the menstrual cycle,

[1] Outcomes were aggregated across the menstrual cycle to avoid loss of statistical power and to limit type 1 errors due to alpha inflation.

while the estimated slope values reflect interindividual differences in the effect of stress appraisal levels on these state variables over the menstrual cycle.

All random effects for AA variables were then standardized and these standardized parameters were entered as predictors of the intensity of PMDD symptomatology at follow-up. For this purpose, regression analyses were carried out in SPSS in a second step. The standardized SCID-PMDD symptom score at follow up served as the outcome variable while controlling for baseline SCID-PMDD symptom scores and baseline BDI-II scores (raw means and standard deviations of these variables see Table S1). In addition, we included further possible confounding variables: age, psychotropic medication intake at follow-up (selective serotonin reuptake inhibitors: n = 2, tricyclic antidepressants: n = 1, methylphenidate: n=1), oral contraceptive use (n = 4), and time lag in days between the last day of AA and follow up (Mean = 134, SD = 20, Min = 104, Max = 206). If any of these variables were significant or showed a trend ($p \leq .10$), they were retained in the regression models. This was true for age and psychotropic medication intake, indicating lower PMDD symptom scores in younger women and in those taking respective medication at follow-up.

Thus, all following regression models were corrected for age, baseline PMDD symptoms, baseline depressive symptoms and psychotropic medication intake, which were entered as standardized covariates in a single step. This model including only baseline predictors without any AA variables served as the control model.

Finally, the standardized random effects for all AA variables were used as predictors 1) in separate regression analyses to analyze the incremental effect of each predictor compared with the control model in terms of proportion of explained variance separately, and 2) in a stepwise multiple regression analysis to identify significant independent predictors of follow-up PMDD symptomatology compared with the control model.

Supplementary Results

Sample characteristics

Compliance with AA was high (3381 of 3904 = 86.6% completed prompts). Sociodemographic and clinical characteristics of the sample (n=60) together with mean levels of the AA variables are presented in Table S1.

Variation of mood, rumination, and cortisol over the menstrual cycle

Multilevel analyses with cycle phase, time, time^2 (if significant) and day as fixed effects showed significant effects of cycle phase on mood, rumination and cortisol in the PMDD sample. The cycle phase effect was significant in predicting NA ($F(3,412) = 34.0$, $p<.001$),

PA (F (3,418) = 30.2, p<.001), rumination (F (3,413) =19.7, p≤.005) and cortisol (F (3,395) = 2.6, p=.05). Post hoc tests using Bonferroni correction revealed higher negative affect and rumination as well as lower positive affect during the luteal phase compared to all other cycle phases (ps ≤ .005) but no differences in cortisol levels between the late luteal and other cycle phases (p ≥ .082).

Predictors of PMDD symptomatology at follow-up

Online Table 2 shows the results of separate regression models of random effect parameters of individual AA variables as predictors of PMDD symptoms at follow up. Table S3 shows the results of the stepwise multiple regression model of random effect parameters of negative affect and cortisol as the remaining independent predictors of PMDD symptoms at follow up after stepwise regression. Further explanations see main text.

Supplementary section: Strengths and limitations of the study

Strengths of the present study include the investigation of a relatively large sample size of women with PMDD, the validation of ovulatory cycles through an ovulation test, and the combination of data assessed on the micro (AA) and macro (clinical symptom) level within the framework of a longitudinal study. Here, we could show that AA-variables at baseline yielded unique predictive information and did not merely reflect clinical symptoms but additionally contributed to these known risk factors in affecting the clinical course of PMDD. AA of daily life experiences have also been proposed to provide greater sensitivity for connecting psychological with biological processes than retrospectively assessed symptoms and traits (cf. [11]), which we could previously show in a study with depressed patients [12]. The AA approach may similarly help to advance knowledge regarding psychological and biological mechanisms and their interplay involved in PMDD [13]. Finally, AA may constitute a fruitful tool for identifying possible transdiagnostic risk factors at the micro-level of experience which can eventually be addressed by transdiagnostic therapy approaches.

A limitation of the study is the provisional diagnosis of PMDD, since we did not request prospective daily ratings of PMDD symptoms over at least two symptomatic cycles prior to study entry to prevent participant burden. Therefore, the PMDD diagnosis has to be regarded as provisional. However, this approach is in line with a majority of studies using retrospective reports to assess PMDD, and prevalence rates of moderate to severe premenstrual symptoms derived from retrospective epidemiological studies have been found to be consistent with those using prospective ratings (cf. [14]). The use of a single item to assess uncontrollable rumination, although it has already shown good sensitivity as well as construct and predictive

validity in previous studies [15,16,17], may be regarded as a potential further limitation of the study.

Supplementary References

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Table S1. Sample characteristics of women with PMDD (n=60)

Variables	% / M (SD)
Demographic variables	
Age	29.4 (5.8)
Education level (% with high school degree)	73.3%
Marital status (% married or living with partner)	60.0%
Children (%)	23.3%
Clinical variables	
SCID-PMDD[1] symptom score at baseline	7.7 (1.6)
SCID-PMDD[1] symptom score at follow-up	6.8 (2.2)
BDI-II[2] score at baseline	11.0 (9.0)
BDI-II[2] score at follow-up	11.5 (8.9)
Psychotropic treatment at baseline[3]	0%
Psychotropic treatment at follow-up	6.7%
Ambulatory Assessment variables (baseline)	
Compliance Rate	86.5%
Negative affect[4]	2.8 (0.5)
Positive affect[4]	4.2 (0.6)
Rumination[4]	2.4 (0.7)
Stress appraisal[4]	-0.7 (0.5)
Cortisol levels (nmol/l)[4]	11.0 (4.9)

[1]SCID-PMDD = Structured Interview for DSM-IV TR Defined Premenstrual Dysphoric Disorder. [2]BDI-II = Beck Depression Inventory-Revised. [3]Psychotropic treatment at baseline was an exclusion criterion. [4]For illustrative purposes, AA-variables are presented as aggregated variables at the person level.

Table S2. Results of simple regression models of random effect parameters of AA variables as predictors of PMDD symptoms at follow up

Predictors[1]	*df*	$F_{increase}$	Beta	SE	*p*	Explained variance
Random Intercepts (AA[2])						
Negative Affect	(1,53)	8.489	0.330	0.113	0.005	9.6%
Positive Affect	(1,53)	6.376	-0.298	0.118	0.015	7.5%
Rumination	(1,53)	4.783	0.265	0.121	0.033	5.8%
Cortisol	(1,53)	2.846	-0.197	0.117	0.098	3.5%
Random Slopes for stress reactivity (AA[2])						
Stress on Negative Affect	(1,53)	0.861	0.114	0.123	0.358	1.1%
Stress on Positive Affect	(1,53)	1.100	-0.129	0.123	0.299	1.4%
Stress on Rumination	(1,53)	4.458	0.240	0.114	0.039	5.4%
Stress on Cortisol	(1,53)	0.293	0.064	0.119	0.590	0.4%

[1]All models include baseline PMDD symptom scores (Structured Interview for DSM-IV TR Defined Premenstrual Dysphoric Disorder, SCID-PMDD), baseline depressive symptom scores (Beck Depression Inventory II, BDI-II), age, and psychotropic medication intake (0=no, 1=yes) at follow up.
[2]AA = Ambulatory Assessment.

Table S3. Results of the stepwise multiple regression model of random effect parameters of AA variables as predictors of PMDD symptoms at follow up

Predictors[1]	Beta	SE	*p*	*df*	$F_{increase}$	*p*	Explained variance
Random Intercepts (AA[2]**)**				(2,52)	7.36	0.002	15.4%
Negative Affect	0.370	0.110	0.001				
Cortisol	-0.254	0.108	0.023				

[1]Model includes baseline PMDD symptom scores (Structured Interview for DSM-IV TR Defined Premenstrual Dysphoric Disorder, SCID-PMDD), baseline depressive symptom scores (Beck Depression Inventory II, BDI-II), age, and psychotropic medication intake (0=no, 1=yes) at follow up.
[2]AA = Ambulatory Assessment.