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Depressive symptoms during the different phases of a migraine attack: A prospective diary study

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ABSTRACT

Background: The relationship between migraine and depression has been thoroughly investigated, indicating a bidirectional comorbidity. The exact temporal relationship between acute depressive symptoms (mood changes) and the various phases of the migraine attack has not yet been examined.
Methods: We performed a prospective diary study in $n = 487$ participants with migraine. Participants filled out a daily diary on migraine and acute depressive symptoms during a 1-month period. We randomly selected one migraine attack per participant, consisting of six days around an attack, including the interictal, premonitory, ictal, and postdromal phases. Acute depressive symptoms covered five major items from the DSM-5 classification. Primary analysis was performed using a mixed model with post-hoc testing. We also tested whether lifetime depression influenced the presence of acute depressive symptoms.
Results: During a migraine headache day, patients scored higher on acute depressive symptoms than on all other days of the migraine attack ($p < 0.001$). There were no early warning signs for an upcoming headache attack through acute depressive symptomatology. Migraine patients with lifetime depression scored overall higher during the migraine attack than those without lifetime depression ($p < 0.001$).
Limitations: Migraine attacks were based on self-reported migraine and one migraine attack per patient was randomly selected.
Conclusion: We now clearly demonstrate that during the migraine headache phase, but not in the prodromal phase, patients report increased depressive symptomatology. No evidence was found for mood changes as an early warning sign for an upcoming migraine attack.

1. Introduction

Migraine patients have a three to six times increased risk of depression compared with controls without a history of severe headaches (Merikangas et al., 1990; Breslau et al., 2003). The relationship between migraine and depression has been thoroughly investigated, indicating a bidirectional comorbidity (Breslau et al., 2003; Breslau et al., 2000). Shared etiological factors have been proposed to underlie this comorbidity, pointing towards a shared genetic background for both diseases (Consortium, 2018; Schur et al., 2009; Stam et al., 2010; Yang et al., 2018). Thus, a clear relationship between lifetime depression and lifetime migraine has been proven, as well as the associations of depression with risk for migraine chronification, medication overuse headache, and cutaneous allodynia (Louter et al., 2013; Ashina et al., 2012; Viana et al., 2018; Louter et al., 2014). The temporal relationship, however, between acute depressive symptoms (mood changes) and the various phases of a migraine attack, has not yet been examined. Premonitory symptoms of migraine are defined by the International Classification of Headache Disorders (ICHD-3) as "symptoms preceding and forewarning of a migraine attack by 2–48 h, occurring before the aura phase in migraine with aura and before the onset of pain in migraine without aura" (Headache Classification Committee of the International

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Headache Society et al., 2018). Acute depressive symptoms (mood changes, lethargy, difficulty with concentration, changes in appetite) have been reported as a premonitory phenomenon preceding a migraine attack, but almost all studies were cross-sectional and only few and very small longitudinal studies were performed (Giffin et al., 2003; Laurell et al., 2016; Maniyar et al., 2015).Understanding how acute depressive symptoms may fluctuate in migraine patients will be important to uncover the balance between "the trait" lifetime depression in migraine patients, and "the state" acute depressive symptoms during a migraine attack and at the moment of a forthcoming attack. In the current study our main objective was to gain more insight in acute depressive symptoms during the different phases of a migraine attack and to evaluate whether acute depressive symptoms increase in the days preceding a migraine headache as an early warning sign of an upcoming attack or develops during the headache phase, by using a prospective diary in a large well-defined group of patients with migraine.

2. Methods

2.1. Lumina

Migraine patients were recruited from the LUMINA (Leiden University Migraine Neuro-Analysis) project (van Oosterhout et al., 2011). Using a dedicated website and validated web-based screening and diagnostic questionnaires, Dutch speaking adults with migraine (with or without aura) according to the International Headache Disorders criteria (ICHD-3) were invited to participate in research on migraine. Details of recruitment and validation of migraine diagnoses are published earlier (van Oosterhout et al., 2011). In short, Dutch adult migraine patients were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). Patients were considered eligible after a two-step inclusion process using validated questionnaires via our dedicated Leiden University Migraine Neuro-Analysis (LUMINA) website. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36. Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire, based on the ICHD-3 criteria. The specificity of the second questionnaire was 0.95 and sensitivity was 0.45. This questionnaire is described in English in detail (van Oosterhout et al., 2011). We consider the cohort a well-defined web-based cohort. Of all participants, ≈90% were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, additional aura and headache characteristics, acute and prophylactic headache medication use, and current and lifetime depression.

Approval for the present study was obtained from the Medical Ethics Committee of the Leiden University Medical centre and all patients signed informed consent.

2.2. Participants and study design

For the present study, patients were eligible if they had at least one migraine attack, but not more than eight migraine days/month. Patients with a higher migraine frequency were excluded in order to assure interictal days could be assessed. In addition, patients were excluded in case of medication overuse headache (as defined by the MOH criteria of ICHD-3) (Headache Classification Committee of the International Headache Society et al., 2018). Eligible patients received an email invitation to participate in a prospective diary study on (premonitory symptoms of) migraine for a period of one month. Patients were not given any restrictions regarding acute or preventive headache medication.

2.3. Daily questions on migraine status

The daily diary contained questions on headache status during the past day: (1) 'Did you experience headache today?' If yes was answered on this question, the participant answered a sequel question: (2) 'was this a migraine headache?' Migraine days were defined as days on which the second question was answered with 'yes'. A 'normal headache day' was defined as a day in which a patient experienced a headache, but answered the sequel question ('was this a migraine headache?') with 'no'. As patients received the daily diary at the end of the day, in every diary participants were asked if anything had changed after having filled in the diary of the day before (i.e. participants might have developed a migraine attack after they went to bed, but before midnight). If so, the headache status of that previous day was adapted. A total migraine attack was defined as a series of six days: five consecutive days, being one inter-ictal day, followed by three pre-ictal days (premonitory phase) and one migraine day. The sixth day was the recovery day (postdromal phase), defined as the first headache-free day. Even though interictal days are normally not counted as a phase of a migraine attack, for the purpose of this paper it was considered to be important to define a pre-ictal and post-ictal headache free day.

2.4. Daily questions on depressive symptoms

The complete daily online questionnaire consisted of $n = 50$ questions designed to assess premonitory symptoms, which had to be answered with a five-point Likert scale, scoring from 0 (not at all) to 4 (very severe). No short validated questionnaire has been published to assess daily fluctuations in depressive symptoms, thus we chose five questions in order to address acute depressive symptoms (according to the DSM-5 criteria for depression (American Psychiatric Association et al., 2013)): (1) Did you feel sad or depressed today? (2) Did you experience a diminished interest or pleasure in your daily activities today? (3) Did you feel tired today (not related to physical efforts)? (4) Did you feel hopeless, worthless and/or guilty today? (5) Did you struggle with remembering information today? These five questions comprise the two core symptoms of depression and three of the remaining seven criteria for DSM-5 defined depression. We considered the sum of these five questions (ranging from 0 to 20) as an indication for the severity of acute depressive symptoms during the concerning day (depression score).

2.5. Lifetime depression

As part of the LUMINA questionnaire, patients had filled out questionnaires on depression. We defined lifetime depression as a dichotomous variable. We used our previously published algorithm for lifetime depression combining the validated cut-off scores for the Hospital Anxiety and Depression Scale (HADS-D) and the centre for Epidemiologic Studies Depression scale (CES-D), with additional questions on depression diagnoses in the past. We defined lifetime depression as positive (yes) when a participant indicated: to have 1) HADS-$D \geq 8$; and/or to have 2) CES-$D \geq 16$; and/or 3) use of antidepressants with depression as indication; and/or 4) current or past diagnosis of depression (Stam et al., 2010; Louter et al., 2014; Bjellanda et al., 2002; Radloff, 1977).

2.6. Statistical analysis

We tested differences in mean sum scores on the acute depressive symptoms questionnaire between the six different days of the migraine attack using a repeated measures ANOVA model (Field, 2013), with the mean score on the acute depressive symptoms scale as the dependent variable, and the phase in the migraine attack as the independent, within-subjects variable. As a secondary analysis differences in mean sum scores on the acute depressive symptoms scale were tested again,

but with lifetime depression as the between-subject factor, using a mixed effects ANOVA model. As an exploratory analysis we used the sum score of the two core symptoms of acute depressive symptoms (depressive mood and loss of interest) and performed the same ANOVA analyses again. Furthermore, to evaluate if all inquired symptoms were contributing to the overall acute depressive symptoms score, we analyzed the mean score of all symptoms separately in the same manner. For all ANOVA models we applied Greenhouse-Geisser correction of degrees of freedom due to violation of the assumption of sphericity and Bonferroni corrections for multiple comparisons.

For all analyses *p*-values (two-tailed) of < 0.05 were considered statistically significant. All analyses have been performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

3. Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

4. Results

4.1. Patient characteristics

Of the $n = 755$ LUMINA migraine patients that were randomly selected from the LUMINA cohort and who participated in the diary study we included $n = 487$ participants who had at least one migraine attack during the study period of one month and filled out enough data to enable us to use one complete migraine attack. This group was a good representation for the total LUMINA cohort regarding gender and age, but average migraine frequency was lower compared to the total LUMINA cohort as this was a specific criterium for this particular study (van Oosterhout et al., 2011). With this lifetime depression in this group may be a bit lower, as no chronic migraine patients were allowed for this current analysis. Days on which patients did not report a migraine headache but did indicate to have taken a triptan were excluded from the analyses. Although most participants suffered more than one migraine attack during the study period of one month (mean ± SD = 3.1 ± 1.2) only one attack was randomly selected for analysis. Therefore, $n = 487$ migraine attacks from $n = 487$ participants were eligible for analysis. The depression questionnaires for determining lifetime depression were filled out on average one month prior to starting the daily diary. In total $n = 216/487$ (44%) patients fulfilled the criteria for lifetime depression. Patients with and without lifetime depression did not differ in number of reported migraine attacks (both groups mean ± SD: 3.1 ± 1.2, $p = 0.48$). Baseline characteristics and number of self-reported migraine attacks and migraine days are reported in Table 1.

Table 1
Baseline characteristics of the total study population ($n = 487$).

Variable	Value
Female, n (%)	426 (88%)
Age, years (mean ± SD)	46.6 ± 10.8
BMI (kg/m^2 mean ± SD)	24.3 ± 3.7
Migraine without aura, n (%)	314 (65%)
Age at onset migraine, years (mean ± SD)	19.8 ± 11.0
Number of days with a diary (mean ± SD)	27.7 ± 4.0
Number of self-reported migraine attacks (mean ± SD)	3.1 ± 1.2
Number of self-reported migraine headache days (mean ± SD)	6.7 ± 3.3
Lifetime depression, n (%)	216 (44%)

BMI = Body Mass Index. Lifetime depression = HADS-*D* ≥ 8, and/or CES-*D* ≥ 16, and/or use of antidepressants with depression as indication, and/or current or past diagnosis of depression.

4.2. Acute depressive symptoms

Patients had a higher acute depressive symptoms score on the migraine day than on all other days ($p < 0.001$). The interictal day differed from the first premonitory day (migraine day – 3) ($p = 0.02$), but not from the other premonitory days (migraine day – 2 and migraine day −1) (respectively $p = 0.08$ and 0.66) (Fig. 1A, table 2). Compared with patients without a lifetime depression, migraine patients with a lifetime depression had a higher score on all days for acute depressive symptoms (all days $p < 0.001$) (Fig. 1B, Table 2). When analyzing the acute depressive symptoms separately, every item independently was shown to be increased on the migraine day compared to all other days ($p < 0.001$) (Fig. 2), and all item scores were higher in patients with lifetime depression, compared to patients without lifetime depression ($p < 0.001$) (Fig. 3)

In addition, when analyzing the sum score of the two core symptoms of acute depressive symptoms (feeling depressed and loss of interest, total sum ranging from 0 to 8), patients scored higher on the migraine day compared to all other days ($p < 0.001$) and patients with lifetime depression scored higher on all days of the migraine attack compared to patients without lifetime depression (all days $p < 0.001$) (Fig. 4A and B).

5. Discussion

This study investigated the temporal relationship between acute depressive symptoms before, during and after a migraine attack. Migraine patients reported more acute depressive symptoms during their migraine headache day than on all other days of attack. No increase in acute depressive symptoms was observed in the days preceding the migraine headache and after the headache day acute depressive symptoms normalized back to comparable levels as before. Migraine patients who fulfilled the criteria for lifetime depression, reported more acute depressive symptoms on every day of the migraine attack.

Previous studies have described mood changes, concentration problems, fatigue, and other psychiatric symptoms as premonitory symptoms for migraine (Giffin et al., 2003; Laurell et al., 2016; Maniyar et al., 2015), but most of those studies had a cross-sectional design, with retrospective reporting of premonitory symptoms with the risk of recall bias. One small prospective study was performed in a selected group of patients who regularly experienced premonitory symptoms prior to migraine headache. The authors found emotional changes, difficulty with concentration, and irritability in the premonitory phase, the headache phase, and the postdromal phase (Giffin et al., 2003). The interictal prevalence of those symptoms was not described which makes it difficult to conclude if these symptoms indeed forewarned migraine headache. The symptoms with the highest predictive value for a migraine attack in that study were yawning, difficulties in speech and reading, and emotional disturbance, predicting migraine attacks in two thirds of patients. A strength of that study was that premonitory symptoms could be related to the migraine headache with a resolution of hours. In our diary study we estimated acute depressive and premonitory symptoms on a daily basis in regard to attacks. However, we did not select patients based on premonitory symptoms, which may have introduced a selection bias in the previous small studies (Giffin et al., 2003).

The fact that migraine patients report more acute depressive symptoms during their migraine headache day does not indicate that they fulfil the full criteria for depression, but most of all indicates a mood disturbance and loss of interest on that particular moment. In general, the diagnosis “depression” is based on mood changes with functional impairment for at least two weeks. Our questionnaire measured five out of nine symptoms of the DSM-5 criteria for depressive symptoms, thus only giving an indication of acute fluctuations in these symptoms as our aim was a daily evaluation. That our five selected items are well chosen is shown by the fact that participants with a lifetime depression had increased scores on all days of the migraine cycle, indicating that our

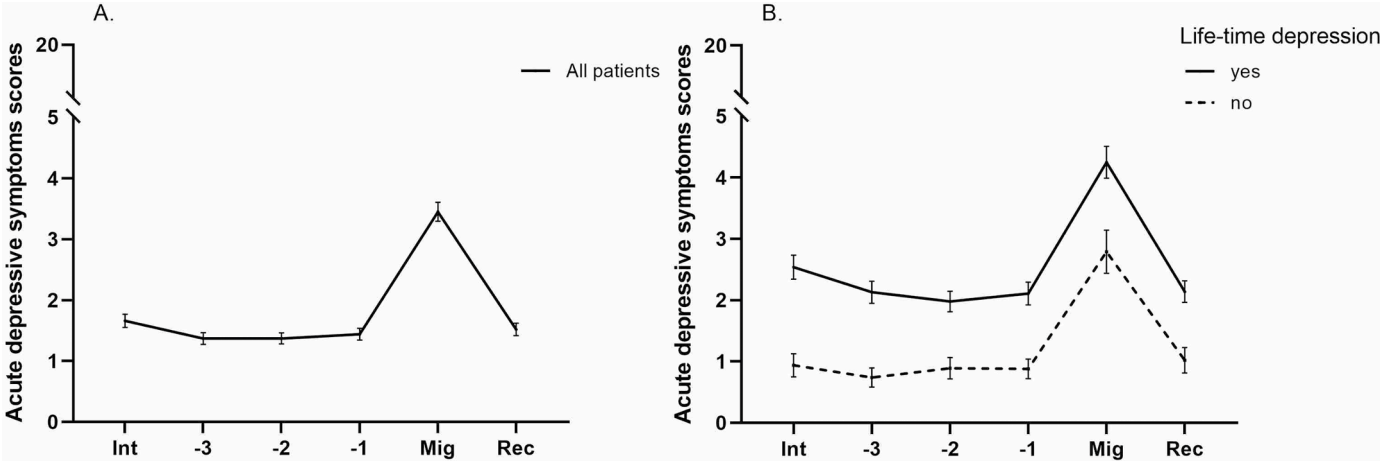

Fig. 1. Total acute depressive symptoms scores development during a migraine attack.
Acute depressive symptoms scores consist of 5 items answered on a five-point Likert scale, scoring from 0 (not at all) to 4 (very severe) (total range 0–20). Lifetime depression = HADS-$D \geq 8$, and/or CES-$D \geq 16$, and/or use of antidepressants with depression as indication, and/or current or past diagnosis of depression. Data presented in mean ± 95% CI. Int = interictal day, −3, −2 and −1 = premonitory days, Mig = migraine day, Rec = recovery day. A. mean score for all patients. B. mean score compared between patients with and without lifetime depression (all days $p < 0.001$).

Table 2
Acute depressive symptoms scores during a migraine attack.

	Total (n = 487)		Lifetime depression (n = 216)		No life time depression (n = 271)	
	Mean	SD	Mean	SD	Mean	SD
Interictal	1.66	2.38	2.54	2.89	0.940	1.57
Migraine day −3	1.37	2.16	2.13	2.65	.740	1.29
Migraine day −2	1.37	2.02	1.98	2.45	.890	1.44
Migraine day −1	1.44	2.17	2.11	2.73	.88	1.33
Migraine day	3.45	3.41	4.25	3.83	2.79	2.90
Recovery day	1.52	2.22	2.14	2.59	1.02	1.72

Acute depressive symptoms scores consist of 5 items answered on a five-point Likert scale, scoring from 0 (not at all) to 4 (very severe) (total range 0–20). Lifetime depression = HADS-$D \geq 8$, and/or CES-$D \geq 16$, and/or use of antidepressants with depression as indication, and/or current or past diagnosis of depression.
Data are presented in mean ± SD.

scoring of daily depressive symptoms is related to depression. Furthermore, when analyzing the five symptoms separately, all items contributed to the increased score on the migraine headache day.

Since we only included patients with relatively low migraine frequency, our results are not generalizable to the entire migraine population, especially not to patients with chronic migraine. However, in order to investigate the pre-ictal and interictal phase of the migraine attack reliably regarding changes in premonitory symptoms, a clear distinction between the postdromal phase of one attack and the pre-ictal phase of the subsequent attack was regarded essential. Furthermore, we fully realize that selecting only one migraine attack per patient leads to loss of data. However, including an unequal amount of attacks per patient would have caused an unbalanced weight for patients with a higher attack frequency. By studying a large cohort and selecting one attack per patient randomly, we avoided this problem.

A limitation of the present study is that a migraine day was based on self-reported migraine, as is common practice in most e-diaries. Recently, we developed a new time-locked electronic headache diary for the Leiden Headache Clinic in which the migraine status is determined using an algorithm based on the exact and individual ICHD-3 criteria

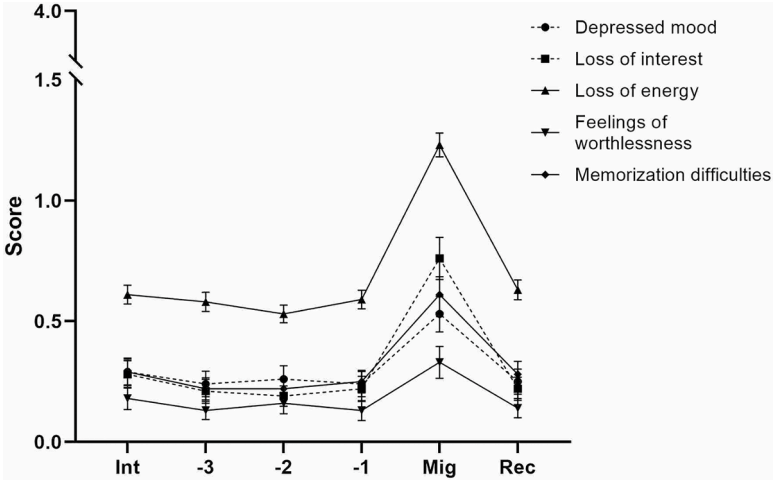

Fig. 2. Acute depressive symptoms scores development during a migraine attack, separately for each item
Acute depressive symptoms scores consist of 5 items answered on a five-point Likert scale, scoring from 0 (not at all) to 4 (very severe) (total range 0–20). Data presented in mean ± 95% CI. Int = interictal day, −3, −2 and −1 = premonitory days, Mig = migraine day, Rec = recovery day.

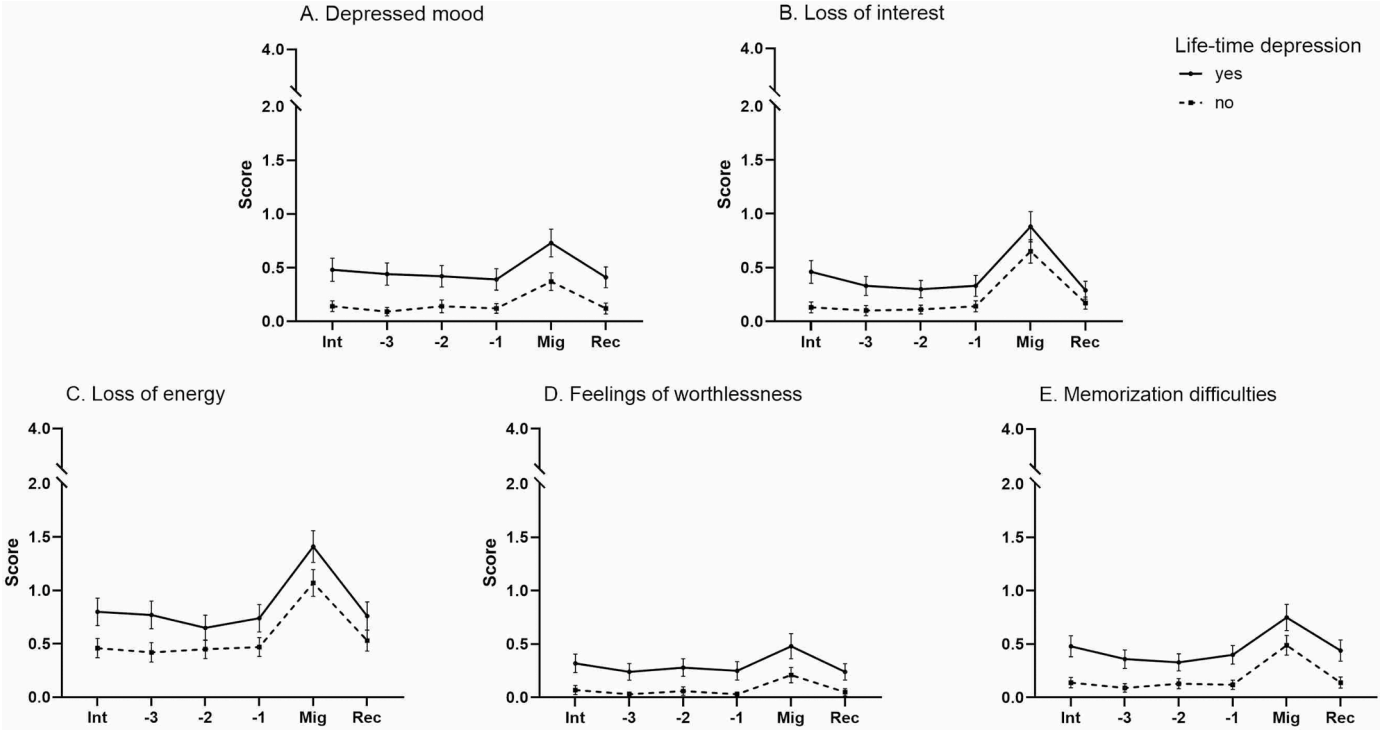

Fig. 3. Comparing patients with and without lifetime depression for each item of acute depressive symptom scores during a migraine attack
Acute depressive symptoms scores consist of 5 items answered on a five-point Likert scale, scoring from 0 (not at all) to 4 (very severe) (total range 0–20). Lifetime depression = HADS-*D* ≥ 8, and/or CES-*D* ≥ 16, and/or use of antidepressants with depression as indication, and/or current or past diagnosis of depression. Data presented in mean ± 95% CI. Int = interictal day, −3, −2 and −1 = premonitory days, Mig = migraine day, Rec = recovery day.

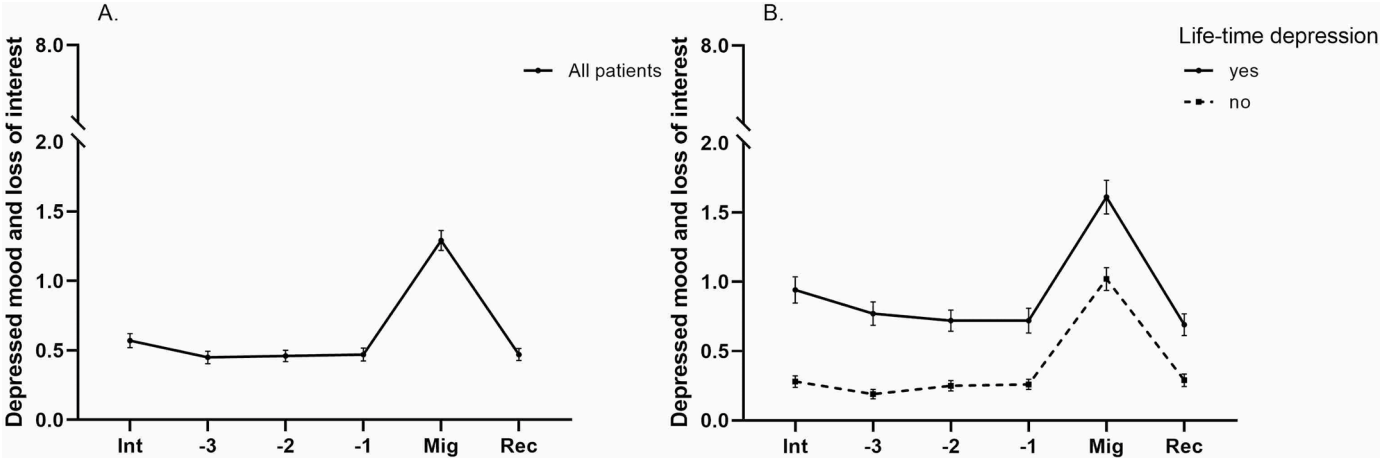

Fig. 4. Sum scores of core items for acute depressive symptoms (depressed mood and loss of interest) development during a migraine attack
Core symptoms of acute depressives symptoms (depressed mood and loss of interest) answered on a five-point Likert scale, scoring from 0 (not at all) to 4 (very severe) (total range 0–8). Lifetime depression = HADS-*D* ≥ 8, and/or CES-*D* ≥ 16, and/or use of antidepressants with depression as indication, and/or current or past diagnosis of depression. Data presented in mean ± 95% CI. Int = interictal day, −3, −2 and −1 = premonitory days, Mig = migraine day, Rec = recovery day. A. mean score for all patients. B. mean score compared between patients with and without lifetime depression (all days $p < 0.001$).

(van Casteren et al., 2021). In future research we will implement this migraine e-diary that can be filled out on a mobile device to make an even more reliable assessment of the different phases in the migraine attack. More frequent input by patients may lead to more accurate reporting of fluctuations in premonitory, acute depressive, and migraine symptoms during a migraine attack. In addition, analyzing more datapoints per patient in future studies using artificial intelligence may give us a more comprehensive insight in the timing of depressive symptoms and the temporal relation to attacks.

Acute depressive symptoms (especially mood changes and loss of interest) are not "early warning" signals that precede a migraine headache, but migraine patients do experience more acute depressive symptoms during a migraine headache, independent of life time depression. There is currently no evidence for an association between acute depressive symptoms during migraine and the risk for developing new onset of depression. However, migraine patients do have an increased risk of developing a depression, with a risk for chronification (Ashina et al., 2012). It is thus of utmost importance for physicians to be alert to depressive symptoms in patients with migraine. In case of migraine patients who are already filling out daily diaries about their

headache characteristics and accompanying symptoms, it is important to limit the burden of daily questions. Adding only two short questions concerning the core of acute depressive symptoms (feeling depressed and loss of interest) to a daily diary would likely be sufficient to get more insight into a patient's mood during and outside attacks.

6. Conclusion

Acute depressive symptoms are, in an episodic migraine population, not increased in the days before a migraine headache and don't seem an early warning sign for an upcoming migraine attack. Migraine patients report more depressive symptoms during their migraine headache day than on all other days of the migraine attack and patients who fulfil the criteria for lifetime depression score higher on depressive symptoms on every day of a migraine attack.

Abbreviations

ICHD: International Classification of Headache Disorders; LUMINA: Leiden University Migraine Neuro-Analysis; DSM: Diagnostic and Statistical Manual of Mental Disorders; HADS: Hospital Anxiety and Depression Scale; CES-D: centre for Epidemiologic Studies Depression scale; SMS: short-message-services

Contributions

SdVL, MAL, WPJvO, EWZ, MSN and GMT were involved in the study design and interpretation of results. EWZ advised on statistical analyses. SdVL wrote the initial draft. MAL, WPJvO, EWZ, MSN and GMT revised the manuscript.

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