OXFORD

International Journal of Neuropsychopharmacology (2020) 23(9): 571–577

doi:10.1093/ijnp/pyaa035
Advance Access Publication: 4 September 2020
Brief Report

BRIEF REPORT

Clinical Correlates and Outcome of Major Depressive Disorder and Comorbid Migraine: A Report of the European Group for the Study of Resistant Depression

Gernot Fugger, Markus Dold, Lucie Bartova, Marleen M. M. Mitschek, Daniel Souery, Julien Mendlewicz, Alessandro Serretti, Joseph Zohar, Stuart Montgomery, Chiara Fabbri, Richard Frey, Siegfried Kasper

Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria (Drs Fugger, Dold, Bartova, Mitschek, and Frey); Université Libre de Bruxelles, Bruxelles, Belgium (Dr Souery); Psy Pluriel Centre Européen de Psychologie Médicale, Bruxelles, Belgium (Dr Souery); School of Medicine, Free University of Brussels, Bruxelles, Belgium (Dr Mendlewicz); Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy (Drs Serretti and Fabbri); Psychiatric Division, Chaim Sheba Medical Center, Tel Hashomer, Israel (Dr Zohar); Imperial College, University of London, London, United Kingdom (Dr Montgomery); Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom (Dr Fabbri); Center for Brain Research, Medical University of Vienna, Vienna, Austria (Dr Kasper).

Correspondence: Siegfried Kasper, MD, Medical University of Vienna, Center for Brain Research, Spitalgasse 4, A-1090 Vienna, Austria (siegried.kasper@meduniwien.ac.at).

Abstract

Background: The present multicenter study aimed at defining the clinical profile of patients with major depressive disorder (MDD) and comorbid migraine.
Methods: Demographic and clinical information for 1410 MDD patients with vs without concurrent migraine were compared by descriptive statistics, analyses of covariance, and binary logistic regression analyses.
Results: The point prevalence rate for comorbid migraine was 13.5% for female and 6.2% for male patients. MDD + migraine patients were significantly younger, heavier, more likely female, of non-Caucasian origin, outpatient, and suffering from asthma. The presence of MDD + migraine resulted in a significantly higher functional disability. First-line antidepressant treatment strategy revealed a trend towards agomelatine. Second-generation antipsychotics were significantly less often administered for augmentation treatment in migraineurs. Overall, MDD + migraine patients tended to respond worse to their pharmacotherapy.
Conclusion: Treatment guidelines for comorbid depression and migraine are warranted to ensure optimal efficacy and avoid possible pitfalls in psychopharmacotherapy, including serotonin syndrome.

Key Words: Major depressive disorder, migraine, clinical aspects

Received: February 5, 2020; **Revised:** March 22, 2020; **Accepted:** May 14, 2020

Significance Statement

Major depressive disorder (MDD) and migraine are highly prevalent and debilitating disorders when viewed individually. As depicted in our large, real-world sample of 1410 MDD patients, comorbidity of these conditions is frequently encountered in clinical routine. Moreover, the co-occurrence of either disease significantly impacts the related burden and seems to influence both treatment and outcome. Somatic comorbidities have to be thoroughly taken into account regarding treatment plans for depressed individuals in terms of a patient-centered approach to provide rapid and optimal psychopharmacotherapeutic care. In this context, clear treatment guidelines for MDD and comorbid migraine are warranted.

Introduction

Major depressive disorder (MDD) and headache disorders, including migraine, belong to the most prevalent and debilitating diseases worldwide (James et al., 2018). While cross-sectional studies repeatedly provided evidence about their co-occurrence, longitudinal studies indicated a reciprocal or bidirectional relation (Amoozegar, 2017). Shared etiologic mechanisms include alterations in serotonergic and dopaminergic pathways that are partly reflected in treatment options for either disease as well as fluctuations in ovarian hormones and a dysregulation of the hypothalamic-pituitary-adrenal axis (Moschiano et al., 2011). Furthermore, the concept of a genetic overlap between MDD and migraine recently received support (Yang et al., 2018). In summary, existing literature going beyond the concept of epidemiology leaves many questions unanswered. Studies with smaller sample sizes revealed that MDD patients with comorbid migraine appear to be more severely depressed and have a reduced quality of life (Hung et al., 2008). As clinical information of patients suffering from a comorbidity of the disorders is scarce, the present study sought to enrich the existing knowledge by elucidating differences in socio-demographic, clinical, psychopharmacotherapeutic, and response characteristics between MDD individuals with and without comorbid migraine in a large sample of 1410 real-world MDD patients representative for those encountered in daily clinical routine.

Methods

The European Group for the Study of Resistant Depression carried out an international, multicenter, noninterventional, cross-sectional trial in 10 sites across Europe between November 2012 and February 2016 (Bartova et al., 2018, 2019). It is noteworthy that recruitment was performed at both university/academic sites of psychiatric services as well as non-academic outpatient psychiatric services throughout Europe. Most patients were recruited at an Austrian university department comprising an in- and outpatient unit, followed by a non-academic clinical practice in France. Consequently, we are confident that the reported findings of prescription practices are representative for the overall clinical routine of psychiatrists in general. Adult in- and outpatients with MDD according to the Diagnostic and Statistical Manual of Mental Disorders IV-TR criteria (classification code: 296.2x or 296.3x) were included. Patients with any other primary psychiatric disorder than MDD were excluded. Current depressive symptom severity was evaluated by the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and the 17- and 21-item Hamilton Rating Scale for Depression (Hamilton, 1960). Symptom severity at the beginning of the current major depressive episode was estimated by calculating a retrospective MADRS score based on the patients' statements and medical record information. Symptom changes within the current major depressive episode were quantified by MADRS total score changes (retrospective MADRS minus current MADRS). The definition of treatment response was ≥50% MADRS total score reduction during application of 1 antidepressant agent for ≥4 weeks at an adequate dose. Treatment resistance was defined by treatment failure of ≥2 consecutive adequate trials with antidepressants with or without agents for combination/augmentation. The Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was applied to underpin the MDD diagnosis and to evaluate concurrent psychiatric comorbidities. Functional impairment was assessed by the Sheehan Disability Scale (SDS) (Sheehan et al., 1996). Socio-demographic variables and clinical data including details about treatment modalities and response pattern were collected in a detailed clinical interview. Information about any somatic comorbidities was retrieved from the detailed clinical interview and the patients' medical record files. Comorbid migraine was defined by the presence of a history of physician-diagnosed migraine. Patients provided written informed consent before study entry. Ethics committees at each site approved the study. A more detailed description of the study protocol has already been provided (Dold et al., 2018).

Data analysis was performed using IBM SPSS Statistics, Version 22.0 (IBM Corporation 1994, 2018). According to the presence of comorbid migraine, patients were allocated into 2 different groups (MDD with vs without migraine). Descriptive statistics (means, SD, and/or percentages) were applied to show the characteristics of each group. For between-group comparisons, χ^2 tests (categorical variables) and ANCOVA (continuous variables) with the presence of comorbid migraine (fixed effect) as well as age and sex (covariates) as variables were used. In case of a significant between-group difference in these statistics, a binary logistic regression analysis with the relevant independent variable was accomplished to estimate its association with the presence of migraine as dichotomous dependent variable (age and sex as covariates). The significance level for all analyses was set at $P \leq .05$. Bonferroni-Holm adjustment was applied except for socio-demographic variables.

Results

The overall point prevalence rate for comorbid migraine across 1410 patients with MDD was 11.1% (95% confidence interval [CI]: 9.4% to 12.7%). The point prevalence rate for female patients was 13.5% (95% CI: 11.3% to 15.7%) and for male patients was 6.2% (95% CI: 4.0% to 8.4%).

Patients in the MDD + migraine group were significantly younger (mean 46.5 years ± 11.5 SD vs 50.8 years ± 14.3 SD, $P < .001$), heavier (mean 73.4 ± 18.2 kg vs 73.2 ± 16.6 kg, $P = .025$) and more likely to be female (81.4% vs 65.1%, $P < .001$) and of other than Caucasian origin (8.3% vs 3.3%, $P = .002$) than those in the MDD without comorbid migraine group. A higher proportion of patients in the MDD + comorbid migraine group consisted of outpatients (77.6% vs 63.9%, $P = .001$) and suffered from comorbid

asthma (10.9% vs 2.5%, $P < .001$). Furthermore, MDD patients with comorbid migraine exhibited a significantly higher total score at the SDS (20.9 ± 6.4 vs 18.7 ± 7.6, $P < .001$). Overall, monotherapy in patients with MDD and comorbid migraine was more likely than in MDD patients without comorbid migraine (50.0% vs 38.4%, $P = .005$). Whereas the distribution of administered first-line antidepressants did not differ significantly, the augmentation of the ongoing antidepressant pharmacotherapy with at least 1 antipsychotic drug was less often established in MDD patients with comorbid migraine than in those without (16.0% vs 26.8%, $P = .004$). Table 1 displays all assessed variables of the patient groups in detail.

In the binary logistic regression analyses, we found gender (odds ratio [OR] = 0.42, 95% confidence interval [CI]: 0.28 to 0.64; $P < .001$), mean age (OR = 0.98, 95% CI: 0.97 to 0.99; $P < .001$), mean weight (OR = 1.01, 95% CI: 1.00 to 1.02; $P = .021$), non-Caucasian origin (OR = 2.23, 95% CI: 1.15 to 4.32; $P = .018$), outpatient setting (OR = 0.59, 95% CI: 0.40 to 0.88; $P = .010$), comorbid asthma (OR = 3.89, 95% CI: 2.08 to 7.29; $P < .001$), SDS mean total score (OR = 1.05, 95% CI: 1.02 to 1.07; $P < .001$), and augmentation with antipsychotics (OR = 0.59, 95% CI: 0.37 to 0.92, $P = .021$) to be significantly associated with the presence of comorbid migraine in MDD patients (Table 2).

Discussion

According to the results of the present cross-sectional, European multicenter study, patients with MDD and comorbid migraine not only differed from those without comorbid migraine in several socio-demographic variables including a younger age, female gender, and non-Caucasian origin but also regarding the profile of somatic and psychiatric comorbidities. Quality of life was significantly reduced, and the response to the administered antidepressant therapy tended to be worse in patients with MDD and comorbid migraine. In fact, the applied first-line antidepressant therapy tended to be in favor of agomelatine. Augmentation with at least 1 antipsychotic drug was significantly less often applied in migraineurs.

A worldwide meta-analysis taking into account over 300 studies with more than 6 million patients indicated a migraine prevalence rate of 13.8% in the female and 6.9% in the male general population, which almost exactly matches our findings (Woldeamanuel and Cowan, 2017). According to population-based longitudinal research, patients with migraine are 60% more likely to develop MDD compared with those without migraine. However, when inversely MDD was the primary diagnosis and the risk for developing migraine was examined, the association was found to be markedly weaker at around 40%. After correcting for stress and childhood trauma, the link between MDD and migraine even lost significance (Modgill et al., 2012).

The fact that MDD + migraine patients are more likely female, younger, and have a higher BMI has been described previously in the literature (Victor et al., 2010; Louter et al., 2014). Furthermore, we found other than Caucasian origin to be associated with MDD and migraine, which is in line with a study from the United States showing that in contrast to Caucasians, African American people with migraine were at higher risk of comorbid depression (Heckman and Britton, 2015).

Regarding psychiatric comorbidities, anxiety disorders especially seem to be associated with migraine, whereas the temporal sequence is most likely started by migraine followed by anxiety (Hamelsky and Lipton, 2006). The significance of the association regarding our results was lost after correcting for multiple testing. In fact, other authors also found elevated levels of PTSD in migraineurs (Buse et al., 2013), which was not the case in our investigation. In addition, not only psychiatric but also somatic comorbidities were found to be related to MDD + migraine in our sample. Within the scope of a large cohort study involving more than 25 000 individuals, a significantly increased risk for migraine was detected in patients with asthma (Peng et al., 2016). This is of particular importance, since the present study also found a significant association between MDD + migraine and asthma. A possible link between thyroid disease and migraine, in parts supported by our data as well, appears plausible in light of existing evidence linking migraine to hypothyroidism (Rubino et al., 2019). The pathogenetic mechanisms explaining these associations, however, are still in need of elucidation.

Alterations of serotonergic circuits as well as a dysfunction of the hypothalamic-pituitary-adrenal axis, hormonal and genetic factors, inflammatory processes, and sensitization of neuronal networks dealing with emotions and the sensorium, including pain processing, are some but far from all of the suspected conjunctions between migraine and MDD (Minen et al., 2016). Given multiple probable etiologic links, the lack of current guidelines for treating patients with MDD and migraine as comorbid condition is surprising (Amoozegar, 2017) and may even be mirrored in our findings regarding treatment strategies in the patient groups. To sum up, patients with MDD + migraine were prefered to be treated by monotherapy. First line antidepressant therapy depicted a trend towards the prescription of agomelatine. Augmentation with antipsychotics was significantly less frequently administered in that group. According to available evidence, serotonin-norepinephrine reuptake inhibitors (SNRIs) should be regarded as the treatment option of first choice when addressing depression and migraine probably due to their anti-nociceptive potential (Burch, 2019). Tricyclic antidepressants, especially amitriptyline, seem to be most effective in migraine prevention; antidepressant efficacy, however, is inherent to higher required dosages followed by more side effects and less tolerability for most patients (Minen et al., 2016). A recent review highlighted the potential of melatonergic agents, including agomelatine, regarding migraine prevention (Long et al., 2019). This is particularly agomelatine important, since particularly agomelatine was the only first-line antidepressant more frequently prescribed in MDD + migraine patients. Selective-serotonin reuptake inhibitors are proven to be very effective in the course of antidepressant treatment (Cipriani et al., 2018) but not for migraine prophylaxis (Minen et al., 2016). Nevertheless, they were applied as the first-line antidepressant in almost 50% of our patients with MDD and comorbid migraine. As triptans, a group of serotonin receptor agonists, are widely used to treat migraine attacks (Gawel et al., 2001), the possibility of a serotonin syndrome has to be kept in mind in any case of serotonergic polypharmacy. Hereby, it is worth mentioning that the risk of a serotonin syndrome in patients who receive a combination therapy of a triptan and a serotonergic antidepressant appears to be very low (Orlova et al., 2018). Even though it was not evaluated in the present study, repetitive transcranial magnetic stimulation provided evidence for efficacy in treating patients with MDD and migraine (Kumar et al., 2018) and should be considered a safe and advantageous alternative treatment option. Augmentation of the ongoing antidepressant with antipsychotics in patients with MDD + migraine appears intuitively plausible as dopamine antagonists, like metoclopramide or haloperidol, play a crucial role in the management of acute migraine. A recent systematic review demonstrated that atypical

Table 1. Patients' Demographic, Clinical, and Treatment Characteristics for the Comparison MDD With vs Without Comorbid Migraine

Characteristics	MDD total (n = 1410)	MDD with comorbid migraine (n = 156)	MDD without comorbid migraine (n = 1254)	*P* value (ANCOVA/x^2)
Gender, n (%)				
Male	467 (33.1)	29 (18.6)	438 (34.9)	<.001
Female	943 (66.9)	127 (81.4)	816 (65.1)	
Age, mean (SD), years	50.3 (14.1)	46.5 (11.5)	50.8 (14.3)	<.001
Marital status, n (%)				
Partnered	702 (49.8)	79 (50.6)	623 (49.7)	.821
Single/divorced/widowed	708 (50.2)	77 (49.4)	631 (50.3)	
Ethnic origin, n (%)				
Caucasian	1356 (96.2)	143 (91.7)	1213 (96.7)	.002
Weight, mean (SD), kg	73.26 (16.8)	73.44 (18.2)	73.24 (16.6)	.025
Education, n (%)				
lower	640 (45.4)	61 (39.1)	579 (46.2)	.072
higher	755 (53.5)	95 (60.9)	660 (52.6)	
Depressive episode, n (%)				
Single	127 (9.0)	12 (7.7)	115 (9.2)	.543
Recurrent	1283 (91.0)	144 (92.3)	1139 (90.8)	
With psychotic features	154 (10.9)	11 (7.1)	143 (11.4)	.104
With melancholic features	856 (60.7)	94 (60.3)	762 (60.8)	.902
With atypical features	33 (2.3)	4 (2.6)	29 (2.3)	.846
Setting, n (%)				
Inpatient	488 (34.6)	35 (22.4)	453 (36.1)	.001
Outpatient	922 (65.4)	121 (77.6)	801 (63.9)	
Somatic comorbidities, n (%)				
Hypertension	267 (18.9)	28 (17.9)	239 (19.1)	.739
Thyroid disease	204 (14.5)	32 (20.5)	172 (13.7)	.023
Diabetes	84 (6.0)	10 (6.4)	74 (5.9)	.800
Heart disease	72 (5.1)	7 (4.5)	65 (5.2)	.709
Arthritis	65 (4.6)	11 (7.1)	54 (4.3)	.123
Asthma	48 (3.4)	17 (10.9)	31 (2.5)	<.001*
Psychiatric comorbidities, n (%)				
GAD	151 (10.7)	24 (15.4)	127 (10.1)	.045
Panic disorder	114 (8.1)	20 (12.8)	94 (7.5)	.021
Agoraphobia	113 (8.0)	20 (12.8)	93 (7.4)	.019
PTSD	20 (1.4)	4 (2.6)	16 (1.3)	.266
OCD	22 (1.6)	4 (2.6)	18 (1.4)	.291
Current suicide risk (dichotomous)	649 (46.0)	80 (51.3)	569 (45.4)	.163
Depression rating scales				
HAM-D total 21-item, mean (SD)	19.8 (9.1)	19.6 (7.9)	19.8 (9.2)	.799
HAM-D total 17-item, mean (SD)	18.8 (8.7)	18.4 (7.7)	18.8 (8.9)	.529
MADRS total, mean (SD)	24.6 (11.3)	24.8 (9.2)	24.6 (11.5)	.695
MADRS total at onset of current MDD episode, mean (SD)	34.1 (7.7)	32.4 (7.0)	34.3 (7.8)	.014
MADRS total change (present MADRS—retrospective MADRS), mean (SD)	−9.4 (10.8)	−7.6 (9.6)	−9.6 (10.9)	.043
Treatment response (dichotomous), n (%)				
Response (≥50% MADRS total reduction)	346 (24.5)	27 (17.3)	319 (25.4)	.026
Resistance	572 (40.6)	53 (34.0)	519 (41.4)	.075
SDS				
Mean total score (SD)	19.0 (7.5)	20.9 (6.4)	18.7 (7.6)	<.001
Psychopharmacotherapy				
Number of drugs, mean (SD)	2.2 (1.2)	2.0 (1.2)	2.2 (1.2)	.231
Polypharmacy, n (%)	851 (60.4)	78 (50.0)	773 (61.6)	.005*
Monotherapy, n (%)	559 (39.6)	78 (50.0)	481 (38.4)	
Administered first-line antidepressant (in the current MDD episode), n (%)				
SSRI	734 (52.1)	75 (48.1)	659 (52.6)	.291
SNRI	336 (23.8)	39 (25.0)	297 (23.7)	.716
NaSSA	121 (8.6)	9 (5.8)	112 (8.9)	.184
TCA	74 (5.2)	10 (6.4)	64 (5.1)	.490
NDRI	32 (2.3)	2 (1.3)	30 (2.4)	.380
Agomelatin	69 (4.9)	14 (9.0)	55 (4.4)	.012

Table 1. Continued

Characteristics	MDD total (n = 1410)	MDD with comorbid migraine (n = 156)	MDD without comorbid migraine (n = 1254)	P value (ANCOVA/x^2)
Applied psychopharmacological combination and augmentation strategies (in addition to the ongoing antidepressant treatment), n (%)				
Combination with at least 1 additional antidepressant	415 (29.4)	38 (24.4)	377 (30.1)	.140
Augmentation with at least 1 antipsychotic drug	361 (25.6)	25 (16.0)	336 (26.8)	.004*
Augmentation with at least 1 mood stabilizer	158 (11.2)	16 (10.3)	142 (11.3)	.690
Augmentation with at least 1 BZD/BZD-like drug	465 (33.0)	42 (26.9)	423 (33.7)	.088
Augmentation with at least 1 low-potency antipsychotic	91 (6.5)	10 (6.4)	81 (6.5)	.981
Augmentation with pregabalin	102 (7.2)	14 (9.0)	88 (7.0)	.374

Abbreviations: BZD, benzodiazepines; HAM-D, Hamilton Depression Rating Scale; GAD, General Anxiety Disorder; MADRS, Montgomery Åsberg Depression Rating Scale; MAO, monoamine oxidase inhibitor; MDD, major depressive disorder; n, number of participants; NaSSA, noradrenaline and specific serotonergic agent; NDRI, norepinephrine dopamine reuptake inhibitor; OCD, Obsessive Compulsive Disorder; PTSD, Post Traumatic Stress Disorder; SARI, serotonin antagonist and reuptake inhibitor; SDS, Sheehan Disability Scale; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

* Significant after Bonferroni-Holm correction.

antipsychotics, most importantly olanzapine, seem to be beneficial in migraine management (Jimenez et al., 2018), especially regarding pain control. The observed reluctance in using antipsychotics in the MDD and comorbid migraine group in our sample might suggest that treatment options have not been exploited to the full.

As demonstrated in the present study as well as in previous studies with clearly smaller sample sizes, MDD and comorbid migraine has a significant impact on disability (Rammohan et al., 2019), contributing to a high disease burden. In addition, our results support existing evidence about lower remission rates of MDD patients who suffer from comorbid migraine (Hung et al., 2015). In fact, we are only able to refer to a trend because due to correction for multiple testing the statistical significance of the results was forfeited. As only 17% of the migraineurs achieved remission of their depressive symptoms (≥50% MADRS total reduction) compared with 25% of the patients without migraine, the clinical significance of this finding should not be underrated.

The current study has several limitations. It was not originally designed to study migraine, and the International Classification of Headache Disorders was not applied. However, migraine diagnoses made by primary care physicians tend to be correct in the majority of cases (Tepper et al., 2004). Consequently, patients who reported having physician-diagnosed migraine in our investigation most likely had migraine. The evaluation of treatment response by evaluating a retrospective MADRS is less accurate than in prospective trials. However, as our raters were all trained psychiatrists, it is not unusual to retrospectively consider a certain period of time in the course of a clinical investigation or when applying psychometric scales.

The major strength of our study is the naturalistic design allowing a detailed insight about clinical correlates of migraine in a large sample of depressed individuals. Many findings consolidate previous research dealing with this topic, which might be an indirect marker of validity. The impact of migraine on treatment response and disability in MDD appears plausible. A reverse effect in terms of worsening migraine by poorly treated depression is reasonable, too. Consequently, both diseases need to be sufficiently treated, at best as early as possible in terms of a patient-centered approach as described previously in the literature (Oluboka et al., 2018). Nonetheless, treatment guidelines for the optimal management of MDD and comorbid migraine are urgently required. In light of current evidence, SNRIs should be preferred to treat patients with MDD and comorbid migraine, because unlike selective-serotonin reuptake inhibitors or other antidepressant agents, SNRIs have been associated with significance in migraine prevention (Burch, 2019). With respect to particular substances, it is noteworthy that venlafaxine needs to be administered at higher dosages of at least 150 mg to achieve sufficient norepinephrine reuptake inhibition (Gallagher et al., 2015) responsible for synergistic antidepressant and analgesic effects. Importantly, the potential risk of a serotonin syndrome appears to be low when SNRIs are combined with triptans (Orlova et al., 2018), which are known to be among the most effective treatment options regarding acute

Table 2. Binary Logistic Regression Analyses Investigating the Association Between Explanatory Variables and the Presence of Comorbid Migraine.

	B	SE	Adjusted OR	95% CI	P value
Gender (male vs female)	-0.86	0.22	0.42	0.28 – 0.64	<.001
Mean age (years)	–0.02	0.01	0.98	0.97 – 0.99	<.001
Non-Caucasian ethnic origin	0.80	0.34	2.23	1.15 – 4.32	.018
Mean weight (kg)	0.01	0.01	1.01	1.00 – 1.02	.021
Setting (inpatient vs outpatient)	–0.52	0.21	0.59	0.40 – 0.88	.010
Somatic comorbidities					
Asthma	1.36	0.32	3.89	2.08 – 7.29	<.001
SDS					
Mean total score (SD)	0.05	0.01	1.05	1.02 – 1.07	<.001
Psychopharmacotherapy					
Polypharmacy vs monotherapy	–0.31	0.18	0.73	0.52 – 1.03	.076
Augmentation with at least 1 antipsychotic drug	–0.53	0.23	0.59	0.37 – 0.92	.021

Abbreviations: B, coefficient for the constant; CI, confidence interval; OR, odds ratio; SDS, Sheehan Disability Scale; SE, standard error.
The present table displays all variables that are associated with the presence of comorbid migraine. The OR are adjusted for the covariates age and sex.

migraine attacks (Loder, 2010). On the other hand, antidepressant treatment with monoamine oxidase inhibitors should be avoided in MDD patients suffering from comorbid migraine, as triptans like sumatriptan or zolmitriptan are contraindicated in combination with monoamine oxidase inhibitors (Tepper et al., 2003). Considering nonpharmacological treatment approaches, cognitive-behavioral treatment strategies have the most robust evidence and are, hence, also recommended for this challenging patient population (Peck et al., 2015).

Acknowledgments

Dr Fugger contributed to designing the study, statistical analyses, and writing the report, including the first draft of the manuscript. All coauthors contributed to designing the study, critically reviewing, and approving the final manuscript.
This work by the Group for the Study of Resistant Depression (GSRD) was supported by an unrestricted grant sponsored by Lundbeck A/S. The sponsor was not involved in designing the study, data collection, data analyses, interpretation of data, writing of the report, and in the decision to submit the study for publication.

Statement of Interest

Dr Dold has received a travel grant from Janssen-Cilag. Dr Bartova received travel grants and/or consultant/speaker honoraria from AOP Orphan, Medizin Medien Austria, Vertretungsnetz, Janssen, Austroplant and Angelini. Dr Souery has received grant/research support from GlaxoSmithKline and Lundbeck, and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr Serretti is or has been consultant/speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boheringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. Dr Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultantor on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GSK, Jazz, and Solvay. Dr Montgomery has been a consultant or served on advisory boards for Novartis AG, Lundbeck, Neurim, and Richter. Dr Kasper received grants/research support, consulting fees, and/or honoraria within the last 3 years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, and Servier. Dr Frey received speaker honoraria from Janssen and AOP Orphan. All other authors declare that they have no conflicts of interest.

References

Amoozegar F (2017) Depression comorbidity in migraine. Int Rev Psychiatry 29:504–515.
Bartova L, Fugger G, Kautzky A, Souery D, Mendlewicz J, Papadimitriou GN, Dikeos D, Ferentinos P, Porcelli S, Serretti A, Zohar J, Montgomery S, Kasper S (2018) Major depression and the degree of suicidality: results of the European Group for the Study of Resistant Depression (GSRD). Int J Neuropsychopharmacol 21:539–549.
Bartova L, Dold M, Kautzky A, Fabbri C, Spies M, Serretti A, Souery D, Mendlewicz J, Zohar J, Montgomery S, Schosser A, Kasper S (2019) Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice. World J Biol Psychiatry 20:427–448.
Burch R (2019) Antidepressants for preventive treatment of migraine. Curr Treat Options Neurol 21:18.
Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB (2013) Psychiatric comorbidities of episodic and chronic migraine. J Neurol 260:1960–1969.
Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 391:1357–1366.
Dold M, Jimenez XF, Sundararajan T, Covington EC (2018) A systematic review of atypical antipsychotics in chronic pain management: olanzapine demonstrates potential in central sensitization, fibromyalgia, and headache/migraine. Clin J Pain 34:585–591.
Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC (2015) Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev 8:CD011091.
Gawel MJ, Worthington I, Maggisano A (2001) A systematic review of the use of triptans in acute migraine. Can J Neurol Sci 28:30–41.
Hamelsky SW, Lipton RB (2006) Psychiatric comorbidity of migraine. Headache 46:1327–1333.
Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.
Heckman BD, Britton AJ (2015) Headache in African Americans: an overlooked disparity. J Natl Med Assoc 107:39–45.
Hung CI, Wang SJ, Yang CH, Liu CY (2008) The impacts of migraine, anxiety disorders, and chronic depression on quality of life in psychiatric outpatients with major depressive disorder. J Psychosom Res 65:135–142.
Hung CI, Liu CY, Yang CH, Wang SJ (2015) The impacts of migraine among outpatients with major depressive disorder at a two-year follow-up. PloS One 10:e0128087.
James SL, Abate D, Abate KH, et al. (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1789–1858.
Jimenez XF, Sundararajan T, Covington EC (2018) A systematic review of atypical antipsychotics in chronic pain management: olanzapine demonstrates potential in central sensitization, fibromyalgia, and headache/migraine. Clin J Pain 34:585–591. doi: 10.1097/AJP.0000000000000567.
Kumar S, Singh S, Kumar N, Verma R (2018) The effects of repetitive transcranial magnetic stimulation at dorsolateral prefrontal cortex in the treatment of migraine comorbid with depression: a retrospective open study. Clin Psychopharmacol Neurosci 16:62–66.
Loder E (2010) Triptan therapy in migraine. N Engl J Med 363:63–70.
Long R, Zhu Y, Zhou S (2019) Therapeutic role of melatonin in migraine prophylaxis: a systematic review. Medicine (Baltimore) 98:e14099.
Louter MA, Wardenaar KJ, Veen G, van Oosterhout WP, Zitman FG, Ferrari MD, Terwindt GM (2014) Allodynia is associated with a higher prevalence of depression in migraine patients. Cephalalgia 34:1187–1192.
Minen MT, Begasse De Dhaem O, Kroon Van Diest A, Powers S, Schwedt TJ, Lipton R, Silbersweig D (2016) Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 87:741–749.

Modgill G, Jette N, Wang JL, Becker WJ, Patten SB (2012) A population-based longitudinal community study of major depression and migraine. Headache 52:422–432.

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.

Moschiano F, D'Amico D, Canavero I, Pan I, Micieli G, Bussone G (2011) Migraine and depression: common pathogenetic and therapeutic ground? Neurol Sci 32(Suppl 1):S85–S88.

Oluboka OJ, Katzman MA, Habert J, McIntosh D, MacQueen GM, Milev RV, McIntyre RS, Blier P (2018) Functional recovery in major depressive disorder: providing early optimal treatment for the individual patient. Int J Neuropsychopharmacol 21:128–144.

Orlova Y, Rizzoli P, Loder E (2018) Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. JAMA Neurol 75:566–572.

Peck KR, Smitherman TA, Baskin SM (2015) Traditional and alternative treatments for depression: implications for migraine management. Headache 55:351–355.

Peng YH, Chen KF, Kao CH, Chen HJ, Hsia TC, Chen CH, Liao WC (2016) Risk of migraine in patients with asthma: a nationwide cohort study. Medicine (Baltimore) 95:e2911.

Rammohan K, Mundayadan SM, Das S, Shaji CV (2019) Migraine and mood disorders: prevalence, clinical correlations and disability. J Neurosci Rural Pract 10:28–33.

Rubino E, Rainero I, Garino F, Vicentini C, Govone F, Vacca A, Gai A, Gentile S, Govone G, Ragazzoni F, Pinessi L, Giordana MT, Limone P (2019) Subclinical hypothyroidism is associated with migraine: a case-control study. Cephalalgia 39:15–20.

Sheehan DV, Harnett-Sheehan K, Raj BA (1996) The measurement of disability. Int Clin Psychopharmacol 11(Suppl 3):89–95.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(Suppl 20):22–33; quiz 34–57.

Tepper S, Allen C, Sanders D, Greene A, Boccuzzi S (2003) Coprescription of triptans with potentially interacting medications: a cohort study involving 240 268 patients. Headache 43:44–48.

Tepper SJ, Dahlöf CG, Dowson A, Newman L, Mansbach H, Jones M, Pham B, Webster C, Salonen R (2004) Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. Headache 44:856–864.

Victor TW, Hu X, Campbell J, White RE, Buse DC, Lipton RB (2010) Association between migraine, anxiety and depression. Cephalalgia 30:567–575.

Woldeamanuel YW, Cowan RP (2017) Migraine affects 1 in 10 people worldwide featuring recent rise: a systematic review and meta-analysis of community-based studies involving 6 million participants. J Neurol Sci 372:307–315.

Yang Y, Zhao H, Boomsma DI, Ligthart L, Belin AC, Smith GD, Esko T, Freilinger TM, Hansen TF, Ikram MA, Kallela M, Kubisch C, Paraskevi C, Strachan DP, Wessman M, van den Maagdenberg AMJM, Terwindt GM, Nyholt DR; International Headache Genetics Consortium (2018) Molecular genetic overlap between migraine and major depressive disorder. Eur J Hum Genet 26:1202–1216.