Published in final edited form as:

Int J Behav Med. 2017 August ; 24(4): 528–534. doi:10.1007/s12529-016-9620-5.

Comorbidity of Migraine, Major Depressive Disorder, and Generalized Anxiety Disorder in Adolescents and Young Adults

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Abstract

Objectives—This study aims to examine the association between migraine, major depressive disorder (MDD), and generalized anxiety disorder (GAD) in adolescents and young adults.

Background—MDD, GAD, and migraine are often comorbid, with adult migraineurs having twice the rate of MDD as nonmigraineurs and more disabling migraines. Findings in children are less consistent; but anxiety disorders, including GAD, are prevalent among youth. Data on the association between MDD, GAD and migraine in adolescents and young adults are sparse.

Methods—Participants (N=227), between 15 and 20 years old, who were unmedicated or within one month of beginning antidepressant treatment underwent a comprehensive assessment to establish the presence of MDD and GAD, according to the *Diagnostic & Statistical Manual, Fourth Edition, Text Revision*, and to rate their symptom severity using the Longitudinal Interval Follow-up Evaluation for Adolescents. They then completed the ID Migraine. The Student's t test and chi-square test were used to compare continuous and categorical variables, respectively, across participants with vs. without migraine. Logistic regression analysis examined the association between the presence of migraine and psychopathology.

Results—A diagnosis of MDD was associated with significantly increased risk of having migraine. Moreover, more severe and persistent ratings of depression were associated with an even higher likelihood of having migraine. A diagnosis of GAD was also significantly associated with

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The authors report no conflicts of interest.

the presence of migraine. The prevalence of *comorbid* MDD and GAD was significantly higher in participants with migraine than in those without migraine (55% vs. 22%, $p<0.0001$). When examined concurrently, GAD remained significantly associated with migraine, with a statistical trend for MDD to be associated with it. The use of selective serotonin reuptake inhibitors did not significantly alter these findings and serum vitamin D concentration was not associated with any of the disorders.

Conclusions—The comorbidity of migraine, MDD, and GAD has important clinical and research implications. Shared psychological and biological vulnerabilities may be involved in the three conditions. Greater understanding of the shared vulnerabilities can lead to unified treatments.

ClinicalTrials.gov Identifier—NCT02147184

Keywords

migraine; depression; anxiety; adolescents; young adults; vitamin D

Introduction

Internalizing disorders, which include depressive and anxiety disorders, are prevalent. In fact, major depressive disorder (MDD) is a leading cause of disability worldwide and is associated with suicide, substance-use disorders, and social and educational impairment.^{1, 2} In adolescents, the 1-year prevalence of MDD is 4% to 5%; and its lifetime prevalence is upward of 11%.^{2, 3} Anxiety disorders, including generalized anxiety disorder (GAD), are similarly common in adolescents, with a prevalence ranging between 10% and 20%.¹ Notably, anxiety disorders are often comorbid with MDD among youth.¹

Like internalizing disorders, migraine is a chronic condition that significantly impacts quality of life and functioning, including academic performance, in adolescents and college students.⁴ The prevalence of migraine differs by age and sex.⁵ Among females, it increases from 7.0% before the age of 14 years to 9.7% by age 20. In contrast, boys 14 years old and younger have a prevalence of 4.7%, increasing to 6.0% by age 20.

MDD, GAD, and migraine are often comorbid. In fact, adults with migraine have twice the prevalence of MDD of nonmigraineurs.^{6, 7} Moreover, migraine comorbid with MDD is more chronic, disabling, and treatment resistant than migraine without MDD.⁶ In children, the findings regarding the association between MDD and migraine are less consistent; with some studies reporting no association and others finding higher severity of depressive symptoms or a prevalence of MDD as high as 9.5% in those with migraine or chronic daily headaches.^{6, 8–11} As for comorbid anxiety disorders, they predict persistence of migraine and headache-related disability.¹² Notably, this association appears to be bidirectional; as migraineurs have higher prevalence of anxiety disorders.⁶ In contrast to children and adults, less is known about the association between MDD, GAD, and migraine in older adolescents and college-age individuals.¹² Some studies, combining children and adolescents, have shown an association,^{9, 13, 14} with others failing to do so^{15, 16}.

Low serum vitamin D concentration has been associated with MDD symptoms^{17–20}, as well as presence of migraine.²¹ However, most studies have not confirmed that low vitamin D is

associated with migraine or its severity.^{19, 22, 23} Vitamin D is thought to have immunomodulatory effects;^{24, 25} but the exact mechanisms by which vitamin D might influence migraine, MDD, or GAD remain unknown. Furthermore, the association between vitamin D concentration and these disorders has not been investigated in adolescents and young adults, specifically.

We used a well-characterized sample of older adolescents and young adults^{26–28} to examine the association between MDD and migraine. As MDD and GAD are often comorbid, we further investigated the independent association between MDD and GAD on the one hand and migraine on the other. Finally, we also explored whether serum vitamin D concentration is associated with migraine.

Methods

This analysis draws on data from an observational parent study aimed at examining the skeletal effects of selective serotonin reuptake inhibitors (SSRIs).^{26–28} Participants were 15 to 20 years old, recruited from inpatient and outpatient clinical settings, via word of mouth, and by advertisement. Study participation was restricted to individuals who were not taking psychotropics or who were within one month of starting an SSRI. The use of psychotropics within 2 years prior to enrollment led to exclusion, with the exception of benzodiazepines (n=3), trazodone (n=1), α_2 agonists (n=1), or a stable dose of psychostimulants (n=2). Other exclusionary criteria included the presence of eating disorders, substance-use disorders, pregnancy, a significant medical or surgical history, or plans to move out of state in the following year. The University of Iowa Institutional Review Board approved the study, and all adult participants or parents/guardians of minor participants provided written informed consent. The minors also gave written assent and consent.

Procedures

Participants presented for a baseline intake visit, followed by monthly phone contacts. Every 4 months, they returned for an in-person, follow-up visit for a total study participation of 2 years. Demographic, socioeconomic, and substance-use data were collected. In addition, the Beck Depression (BDI) and Anxiety Inventories (BAI), as well as the ID Migraine screener, were completed by the participants.^{29–31} The three-item ID Migraine questionnaire is widely used to screen for migraine headaches in primary care settings. It has a sensitivity of 81%, a specificity of 75%, and a positive predictive value of 93%. The sensitivity and specificity of the screener are not impacted by age or sex.³¹ Of note, while the BDI and BAI were administered at the baseline and first postbaseline in-person visit, which were 0.42±0.24 years apart, the ID Migraine screener was administered only at the first postbaseline in-person visit.

Diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR)*¹ incorporated information from an unstructured interview conducted by a child psychiatrist (CAC), the National Institute of Mental Health Diagnostic Interview Schedule for Children,³² and the review of medical records and the self- and researcher-completed symptom rating scales. As detailed elsewhere,²⁶ MDD and GAD severity was quantified for each week throughout the study, starting at 4 months prior to

enrollment, using the Longitudinal Interval Follow-up Evaluation, modified for use with adolescents (A-LIFE).³³ The A-LIFE Psychiatric Status Rating (PSR) scores range from 1 for no symptoms, to 2 to 4 for varying levels of symptom severity and impairment, and to 5 and 6 for full *DSM-IV-TR* criteria. This allowed generating the proportion of weeks during the observation period, starting 4 months prior to study entry, in which MDD or GAD ratings indicated that diagnostic criteria had been met. At study entry, a fasting blood sample was used to measure 25-OH-Vitamin D concentration (Abbott, Wiesbaden, Germany).

Statistical Analyses

Patients who endorsed at least two of the three items in the ID Migraine screener ($n=31$, 14%) comprised the positive-migraine group.²³ The positive- and negative-migraine groups were compared, using Student's *t*-test for continuous variables and Chi square or Fisher's Exact for categorical ones. While adjusting for relevant confounding variables, we examined the association between the presence of migraine and psychopathology, using logistic regression analysis. The adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) were computed. Body mass index (BMI) was computed as weight/height² (kg/m²); and BMI age-sex-specific Z-scores were generated, based on the 2000 Centers for Disease Control and Prevention normative data.³⁴

All hypothesis tests were two-tailed, with a significance level of $p < 0.05$; and analyses used procedures from SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC).

Results

Table 1 lists the demographic and clinical characteristics of the sample overall and split, based on whether participants had a positive migraine screen. As expected, the positive-migraine group included more females.

Migraine and Depression

After adjusting for female sex (OR = 2.6, 95% CI = 1.0, 6.6, $p < 0.05$), we found that having a diagnosis of MDD was associated with a higher prevalence of migraine (OR = 3.4, 95% CI = 1.1, 10.2, $p < 0.02$). Age did not significantly contribute to the model ($p > 0.60$).

Although SSRIs are commonly used to alleviate migraines and chronic headaches, one of their established acute side-effects is headache. Therefore, we repeated the analysis after excluding participants who stopped ($n=26$) or started ($n=2$) SSRI treatment between study entry and administration of the ID Migraine screener. The association remained significant (OR = 4.9, 95% CI = 1.4, 17.0, $p < 0.02$). Adjusting, instead, for SSRI treatment ($p > 0.10$) also did not alter the magnitude of the association (OR = 3.3, 95% CI = 0.9, 3.0, $p < 0.09$).

When the A-LIFE-based proportion of weeks meeting *DMS-IV-TR* criteria for a major depressive episode (MDE) was substituted for the diagnosis of MDD, the association with migraine became stronger (OR = 5.2, 95% CI = 1.8, 14.8, $p < 0.003$). In other words, after adjusting for sex ($p < 0.08$), we found that being in an MDE for the entire observational period was associated with more than a five-fold increased risk for having migraine. Again,

restricting the analysis to those whose SSRI treatment status did not change between study entry and administration of the ID Migraine screener did not alter the results (OR = 6.0, 95% CI = 2.0, 18.2, $p < 0.002$); nor did adjusting for SSRI treatment status (OR = 4.1, 95% CI = 1.1, 15.2, $p < 0.04$), which itself failed to significantly contribute to the model ($p > 0.20$).

Effect of GAD

After adjusting for sex ($p < 0.06$), we found that having a diagnosis of GAD was significantly associated with the presence of migraine (OR = 2.8, 95% CI = 1.3, 6.2, $p < 0.01$). Again, age was not a significant covariate ($p > 0.60$).

Twenty-six percent of the participants had comorbid MDD and GAD. The prevalence of comorbidity was significantly higher in participants with migraine (55% vs. 22%, $p < 0.0001$). To examine the independent contribution of MDD and GAD to the risk of having migraine, both were concurrently entered in the logistic regression model. After adjusting for sex ($p < 0.09$), we found that GAD remained significantly associated with migraine (OR = 2.4, 95% CI = 1.1, 5.3, $p < 0.04$), with a statistical trend for MDD to be associated with it (OR = 2.7, 95% CI = 0.9, 8.4, $p < 0.08$). When the sample was restricted to those whose SSRI treatment status did not change between study entry and administration of the ID Migraine screener, and after sex ($p < 0.09$) and SSRI treatment status (taking an SSRI OR = 1.9, 95% CI = 0.7, 5.1, $p > 0.10$) were adjusted for, the association between MDD and GAD, on the one hand, and migraine, on the other, failed to reach significance; although the ORs did not significantly change (OR of having MDD = 3.0, 95% CI = 0.8, 11.7, $p > 0.10$ and OR of having GAD = 1.7, 95% CI = 0.7, 4.2, $p > 0.20$). This suggests that the sample size may have limited the study's statistical power.

The A-LIFE-based proportion of weeks meeting GAD criteria was also associated with migraine (OR = 6.2, 95% CI = 2.1, 18.4, $p < 0.002$). When the sample was restricted to those whose SSRI treatment status did not change, and sex ($p < 0.09$) and SSRI treatment status ($p > 0.50$) were adjusted for, proportion of weeks meeting GAD criteria remained significantly associated with migraine (OR = 4.7, 95% CI = 1.1, 19.6, $p < 0.04$) but not proportion of weeks meeting MDE criteria (OR = 2.1, 95% CI = 0.5, 8.7, $p > 0.30$).

25-OH-Vitamin D and Migraine

Vitamin D concentration was measured at study entry and then yearly. However, the ID Migraine screener was completed 0.42 ± 0.24 years after study entry. Therefore, we examined the correlation between the vitamin D concentrations measured at study entry and 1.1 ± 0.4 years later. The intraclass correlation was significant (ICC = 0.694, 95% CI = 0.611, 0.762, $n = 182$, $p < 0.0001$), suggesting that vitamin D concentration was relatively stable over the shorter follow-up period of 0.42 years.

After adjusting for female sex ($p < 0.03$) and age ($p > 0.60$), we found no association between vitamin D concentration and migraine (OR = 0.99, 95% CI = 0.97, 1.02, $p > 0.60$) or between having deficient vitamin D status (i.e., concentration < 20 ng/mL) and migraine ($p > 0.50$). Similarly, neither vitamin D concentration nor deficient vitamin D status was associated with MDD, GAD, or comorbid MDD and GAD (all p values > 0.10).

Discussion

Our analyses extend findings in children and adults to older adolescents and college-age individuals, confirming that the presence of migraine is associated with a higher prevalence of MDD and GAD. The association was more consistent with GAD and was observed whether *DSM-IV-TR-based diagnoses* or A-LIFE-based symptom severity were used. On the other hand, we failed to find a significant association between vitamin D concentration and migraine.

Migraine headaches and MDD are highly comorbid. The two are thought to share some common etiopathological pathways related to psychosocial stress, poor lifestyle habits, avoidance behavior, and biological mechanisms, as well. In this study, a diagnosis of MDD was associated with a 3.4-fold increase in the risk of having migraine. Furthermore, more severe and persistent MDD ratings were associated with an even higher likelihood of having migraine. This difference likely reflects the fact that the *DSM-IV-TR-based* MDD diagnosis does not capture the varying severity levels (i.e., ranging from full remission to severe with psychosis) and duration of MDD, which the A-LIFE was designed to do. This would also be consistent with the fact that adjusting for SSRI treatment, which is a marker of symptom severity (i.e., more severe symptoms will more likely lead to initiating treatment), somewhat attenuated the OR.

SSRIs can both cause and treat headaches. The ID migraine was administered more than 4 months after study entry. As a result, it is unlikely that the participants' reported headaches were exacerbated by SSRIs. If this had been the case, the medication would have been discontinued. Nonetheless, to minimize any potential effect of SSRIs, we 1) restricted the sample to participants whose SSRI status did not change between study entry and administration of the ID migraine and 2) adjusted for SSRI treatment. These additional analyses continued to reveal a three- to four-fold increase in the risk of having migraine in the presence of MDD. It is possible that SSRIs resulted in improved migraine severity. This would attenuate the associations we found.

GAD is often comorbid with MDD and was also strongly associated with migraine. Therefore, we sought to disentangle these associations and, indeed, found that taking GAD into account attenuates the association between MDD and migraine. To our knowledge, the independent association between MDD and GAD, on the one hand, and migraine on the other has not been examined in this age group. The finding that GAD is more strongly associated with migraine than MDD is consistent with other studies showing that pain conditions are more strongly related to anxiety disorders than to MDD³⁵.

One of the main strengths of this study is that the diagnoses of MDD and GAD were made by a child psychiatrist, based on a variety of information, including an unstructured and a structured interview. This differentiates it from many other studies which used only rating scales, with limited sensitivity and specificity. In patients with migraine specifically, the shortcomings of rating scales are exacerbated by the overlap in several symptoms (e.g., nausea, headache, or fatigue) between migraine and MDD or GAD.³⁶ Additionally,

participants were followed prospectively, increasing the accuracy of the psychiatric diagnoses.

There are important clinical implications regarding the associations between migraine, MDD, and GAD. First, this comorbidity is associated with increased risk for suicidality, medication overuse, and disability.^{4, 37, 38} Second, prospective studies indicate the presence of a bidirectional relationship between internalizing disorders on the one hand, and migraine on the other, with each disorder increasing the risk for the onset of the other.^{39, 40} Thus, integrated treatments that target shared underlying vulnerabilities may be valuable. Mechanisms underlying the comorbidity between internalizing disorders and migraine have focused on neurochemical processes.⁴¹ More recently, however, attention has been placed on shared psychological vulnerabilities between pain conditions and psychopathology.⁴² For example, patients with migraine exhibit more avoidance behaviors than healthy controls and those with lower levels of acceptance report more pain-related interference and disengagement from activities.⁴³ Similarly, patients with MDD and/or GAD exhibit more avoidance behaviors, and lower levels of acceptance, than their non-depressed/anxious counterparts.⁴⁴ Thus, integrated psychosocial interventions that focus on reducing avoidance, increasing engagement, and improving acceptance may help with the migraine pain, MDD, and GAD.^{45–47} Thus, in light of their prevalence, finding treatments that help target both migraine and comorbid MDD/GAD will have significant public health implications.

Although vitamin D has been reported to improve migraine in small studies,^{48, 49} most evidence fails to support an association between serum Vitamin D concentration and migraine or migraine severity.^{22, 50, 51} Notably, one study found a positive, although weak, relationship between vitamin D concentration and a measure of migraine severity.⁵⁰ Our findings are consistent with the published literature and suggest that, in this population of older adolescent and young adults, there is no association between vitamin D concentration and migraine.

Although this study offers novel findings, particularly related to the independent association between MDD and GAD with migraine, it suffers from several shortcomings. First, the ID migraine was used to screen for migraine. This screener tool has been validated and has high sensitivity and specificity.³¹ However, it does not distinguish between episodic and chronic migraine and may underestimate the prevalence of episodic migraine (i.e., subjects that have not had a migraine attack in more than 3 months). Additionally, it fails to assess the severity of migraine symptoms. Clearly, a clinician-based diagnosis of migraine would have been optimal. Second, the ID migraine was administered at the first postbaseline visit. While this schedule minimized the risk that migraine would be a side-effect of SSRIs, it resulted in a gap of 0.42 years between when vitamin D was measured and the ID Migraine was administered. Third, a few psychotropic groups were allowed at study entry. Some of these medications may cause headaches. However, only a few participants took them, rendering their potential effect on the findings negligible.

In conclusion, in a group of older adolescents and college-age individuals, migraine was associated with both GAD and MDD, although to a stronger degree with the former. The use

of SSRIs did not appear to significantly alter these findings. Serum vitamin D concentration was not associated with any of the disorders. The psychological⁴⁵ and biological processes that underlie the association between migraine and internalizing disorders deserve further investigation as do interventions to alleviate the increased suffering that marks this comorbidity.

Acknowledgments

This work was funded by the National Institute of Mental Health (R01MH090072) and the National Center for Research Resources (2UL1TR000442-06) through grants to the senior author (C.C). It was also funded by a grant from the National Institute of Mental Health (K23MH097827) to the first author (L.D.) and was partially supported with resources and the use of facilities at the Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (CIN13-413). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies, the Department of Veterans Affairs, the US government, or Baylor College of Medicine. The funding agencies had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review or approval of the manuscript. The authors are grateful for the contributions of the participants and their families, as well as for those of the research team.

Abbreviations

MDD	major depressive disorder
GAD	generalized anxiety disorder
SSRIs	selective serotonin reuptake inhibitors
BDI	Beck Depression Inventory
BAI	Beck Anxiety Inventory
DSM-IV-TR	Diagnostic & Statistical Manual, Fourth Edition, Text Revision Longitudinal Interval Follow-up Evaluation, modified for use with adolescents
A-LIFE PSR	A-LIFE Psychiatric Status Rating
ICC	intraclass correlation coefficient

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Table 1

Demographic and Clinical Characteristics of the Sample Overall and Split Based on the Presence of a Positive ID Migraine Screen. [mean±sd, unless otherwise noted]

	Total sample n=227	ID Migraine + n=31	ID Migraine – n= 196	P-value
Age, years	18.9 ± 1.6	19.0 ± 1.7	18.9 ± 1.6	>0.60
Female Sex, n (%)	141 (62)	25 (81)	116 (59)	<0.03
Hispanic, n (%)	15 (7)	3 (10)	12 (6)	>0.40
Racial Composition, n (%)				>0.20
White	203 (89)	25 (81)	178 (91)	
Asian American	12 (5)	2 (6)	10 (5)	
African American	10 (4)	3 (10)	7 (4)	
Native American	2 (1)	1 (3)	1 (1)	
BMI Z-score	0.44 ± 0.96	0.33 ± 0.93	0.46 ± 0.96	>0.40
Vitamin D, ng/ml	32.9 ± 16.2	33.3 ± 14.0	32.8 ± 16.6	>0.80
Vitamin D < 20 ng/ml, n (%)	43 (19)	4 (13)	39 (20)	>0.30
Cigarette Use, n (%)	33 (15)	5 (16)	28 (14)	>0.70
Cigarettes Smoked per Day	2.2 ± 2.6	4.2 ± 3.9	1.8 ± 2.1	>0.20
Alcohol Use, n (%)	154 (68)	24 (77)	130 (66)	>0.20
Days per Week of Alcohol Consumption	1.0 ± 0.9	0.8 ± 0.7	1.0 ± 0.9	>0.20
Drinks Consumed per Sitting	4.8 ± 2.4	4.2 ± 2.5	4.9 ± 2.4	>0.20
Psychiatric variables:				
Major Depressive Disorder, n (%)	153 (67)	27 (87)	126 (64)	<0.02
Proportion of Weeks Meeting MDE Criteria	0.30 ± 0.34	0.50 ± 0.36	0.27 ± 0.33	0.0007
Beck Depression Inventory Score	11.5 ± 10.7	19.8 ± 12.1	10.3 ± 9.9	<0.0001
Generalized Anxiety Disorder, n (%)	72 (32)	17 (55)	55 (28)	<0.003
Proportion of Weeks Meeting GAD Criteria	0.45 ± 0.40	0.70 ± 0.33	0.40 ± 0.40	0.0001
Beck Anxiety Inventory Score	8.8 ± 8.7	15.6 ± 10.2	7.7 ± 8.0	<0.0001
Taking SSRIs, n (%)				
At Study Entry	110 (48)	22 (71)	88 (45)	0.007
At ID Migraine Administration	86 (38)	18 (58)	68 (35)	<0.02