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Do psychiatric comorbidities influence headache treatment outcomes? Results of a naturalistic longitudinal treatment study

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Epidemiologic [1,2,20,29] and clinic-based research [5,7,26] demonstrates that depressive and anxiety disorders are common in persons with headache disorders. Headache patients with psychiatric disorders report greater headache frequency, higher rates of multiple-headache diagnoses, increased physical disability, and poorer life quality compared to patients without psychiatric disorders [5,12,22]. Research also suggests that the presence of a psychiatric disorder contributes to the chronicity and intractability of headache [24].

While it is posited that psychiatric comorbidity contributes to poor treatment outcomes in headache [13,14,15,24], little systematic research has empirically examined the relationship between psychiatric comorbidity and preventive treatment outcomes in headache patients. Two studies [21,28] suggest that patients with psychiatric comorbid disorders demonstrate greater improvements in headache treatment outcomes relative to patients without psychiatric disorders. However, these studies either assessed psychiatric comorbidity using self-report symptom scales in lieu of DSM-based psychiatric diagnoses [28] or used small convenience samples (n=16 and n=52) [21,28].

The relationship between psychiatric comorbidity and headache treatment outcomes may also be more complex than originally thought. Holroyd and colleagues [8] found that improvements in headache activity following treatment with antidepressant medication, stress management therapy, or antidepressant medication plus stress management therapy were not influenced by the presence of a mood or anxiety disorder; however, for the outcome variable of headache disability, the three therapies were more effective in patients with mood or anxiety disorders than in patients with no psychiatric disorders. It must be noted, however, that Holroyd's study was a randomized controlled trial, assessed the treatment efficacy of only amitriptyline/nortriptyline medications, stress management therapy, and amitriptyline/nortriptyline-plus-stress management, and enrolled only patients with chronic tension-type headache (CTTH). It is unclear if the relationship between psychiatric comorbidity and headache treatment outcomes

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observed in controlled trials of CTTH generalize to headache subspecialty centers that provide heterogeneous therapies to patients presenting with diverse headache disorders (i.e., chronic migraine, episodic tension-type headache, etc.).

This study used a prospective naturalistic design to examine how psychiatric comorbidity is related to the effectiveness of a wide variety of preventive headache therapies administered by headache physicians to “typical” patients in headache clinic settings. Because “psychiatric comorbidity” is heterogeneous, analyses examined how comorbid depressive disorders, anxiety disorders, or both were associated with headache treatment outcome. If research can more accurately characterize the relationship between psychiatric disorders and headache treatment outcomes, health care providers can better predict who responds to headache therapies (e.g., headaches may be more or less responsive to treatment when accompanied by certain psychiatric disorders) and better tailor preventive therapies to the specific needs of headache patients with various psychiatric disorders.

Patients and Method

Sample Characteristics and Study Procedures

This study enrolled 311 patients seeking treatment for primary headache disorders in four outpatient headache treatment clinics in Ohio’s four largest cities: Columbus (n=123); Toledo (n=107); Cleveland (n=69); and Cincinnati (n=12). Study inclusion criteria were: (1) 18 years of age or older; (2) satisfying International Headache Society criteria for either episodic migraine, chronic migraine, episodic tension-type headache, chronic tension-type headache, or medication overuse headache [6]; (3) the treating physician judged that the patient should begin new preventive medication therapy (although patients were not required to be “preventive treatment naïve”); and (4) provision of informed consent. Because of the study’s naturalistic design, no exclusion criteria were applied.

Recruitment materials (i.e., brochures and posters) were distributed to participating clinics for display and distribution to patients. Patients were recruited by site physicians and nurses during the initial clinic visit, but only the physician determined patient eligibility. Eligible patients who wished to enroll into the study provided written informed consent in the treatment clinic. The 223 patients who received new preventive medications were the focus of the current study (see Figure 2).

The study’s naturalistic design and its assessment schedule were chosen because they approximated the standard of care at headache treatment centers with the exception of the acute therapy baseline assessment conducted prior to the initiation of new preventive treatment. At the Month 0 Acute Therapy Baseline visit (M_0 AT Baseline), patients’ acute therapies were managed according to the best judgment of treating physicians. At the Month 1 Preventive Therapy Initiation visit (M_1 PT Initiation), new preventive treatment was started based on the best judgment of treating physicians. At the Month 2 Preventive Therapy Adjustment visit (M_2 PT Adjustment) preventive therapies were adjusted or changed. At the Month 6 Evaluation visit (M_6 Evaluation), preventive therapy outcome was evaluated (see Figure 1).

Assessment Methodologies

Demographic Characteristics—At M_0 AT baseline, patients reported their age, race, gender, number of years of education completed, employment status, health insurance status (HMO, PPO, private, SSI), and annual income.

Headache Diagnosis—During the M₀ AT baseline visit, study physicians diagnosed the patient's current headache disorder(s) using International Headache Society criteria [6]. The physician also documented each patient's current and past headache treatments.

Psychiatric Disorder Diagnosis—Psychiatric disorders were diagnosed using the Primary Care Evaluation for Mental Disorders [31]. The PRIME-MD is a structured diagnostic interview that was administered to all patients by trained research staff during a telephone interview conducted within two days after the patient completed the M₀ AT baseline visit. The Prime-MD was used because it was designed specifically for use in medical settings, yields a subset of diagnoses included in the Diagnostic and Statistical Manual of Mental Disorders (including mood and anxiety disorders, the disorders of primary interest in this study), and demonstrates good convergent validity with the Structured Clinical Interview for DSM Disorders [SCID;30]. In this study, the PRIME-MD diagnoses were used to categorize patients into one of four groups: (1) "No Psychiatric Disorder" (n=76); (2) "Depression-Only" (n=46); (3) "Anxiety-Only" (n=29), or (4) "Depression-and-Anxiety" (n=72).

Outcome Measures

Headache Activity—During the 30 days that followed patients' M₀ AT baseline and M₆ evaluation visits, a self-administered, paper-and-pencil daily diary was completed in which patients indicated whether they experienced a headache that day (yes/no) and the severity of the headache (see Figure 1). *Headache days* was operationally defined as the "number of days over the 30-day period during which patients indicated that they experienced a 'mild,' 'moderate,' or 'severe' headache." *Headache severity* was assessed daily for each headache using a 4-point scale (0= "None", 1= "Mild", 2= "Moderate", or 3= "Severe"). Average headache severity scores were calculated by summing all headache severity ratings and dividing this sum by the number of headaches experienced over the 30-day period.

Disability/ Quality of Life—Measures of headache-specific disability and quality of life were completed at the M₀, M₁, M₂ and M₆ clinic visits. The 25-item *Headache Disability Inventory* [HDI;9] measured the impact of one's headaches on emotional functioning and daily activities. The HDI demonstrated good internal consistency ($\alpha=.90$; current study), with higher scores indicating greater headache disability. The HDI has adequate stability: short-term (1 week, $r = .93 - .95$) and longer-term (2 months, $r = .76 - .83$). Patient's report on the HDI also tend to be congruent with spousal reports [9,10]. The 14-item *Headache-Specific Quality of Life Questionnaire* (HSQL) measured the impact of headache disorders on patients' quality of life. Because the original items of the MSQOL refer only to migraines, the term "migraine" was replaced with the more general term of "headache" in relevant items. For example, the original MSQOL item "In the past 4 week, how often have *migraines* interfered with how well you dealt with family, friends and others close to you" was changed to "In the past 4 week, how often have your *headaches* interfered with how well you dealt with family, friends and others close to you." *lower* scores indicating better quality of life.

Analyses: Independent group t-tests for continuous variables and χ^2 tests of association for categorical measures were conducted to (i) test if psychiatric disorder was associated with headache diagnosis, headache characteristics, or demographic measures at the M₀ AT baseline visit, and (ii) identify differences between treatment completers and treatment dropouts on headache diagnosis, headache characteristics, acute and preventive headache therapies, and demographic variables.

The outcome analysis that analyzed changes in headache days, headache severity, HDI, and HSQL were conducted using an intent-to-treat approach and used data provided by patients who received at least one type of preventive therapy and who provided data at one or more

clinic visits. Hierarchical linear modeling (HLM; 27) compared the four groups (No Psychiatric Disorder, Depression-Only, Anxiety-Only, Depression-and-Anxiety) on headache days per month and headache severity at the M₀ AT baseline and M₆ evaluation visits and the HDI and HSQ at the M₀, M₁, M₂, and M₆ clinic visits and determined if the four groups showed similar rates of change on outcome measures. HLM was chosen over traditional ANOVA because HLM compared mean differences between the four groups across each clinic visit, estimated regression lines (used to characterize rates of change over the course of treatment) for patients in all four groups, and formally compared the slopes of these four regression lines. HLM was also considered the preferred technique because it: (1) included all patients in outcome analyses regardless of amount or temporal patterns of missing data; and (2) used a growth curve model approach, which provided a better pre-treatment correction factor than standard ANOVA or ANCOVA [22,27]. Effect size estimates were obtained by using the mean and standard deviation of the rate of change over the six month study for each group. The model-based predicted value was used to determine values for missing data. The effect size was estimated by calculating the mean difference between the two groups and dividing it by the pooled standard deviation. Effect sizes between 0.0 and 0.30 were considered “small,” 0.31 to 0.70 “medium,” and 0.71 and greater “large” [3].

All statistical analyses were performed using SAS for Windows, version 9.1.3 (SAS Inc., Cary, NC, USA) and used an alpha level of .05. HLM analyses used the PROC MIXED procedure. Due to the study's limited number of assessments (e.g., headache activity variables were assessed only twice), a linear change in each outcome measure was assumed. An unstructured variance-covariance matrix was used to model the data. Age and education served as covariates in analyses that compared change in each of the four outcome variables across the four groups. The model shown below characterized treatment response within the four groups:

- Level-1 Model $y_{ij} = \pi_{0j} + \pi_{1j} (\text{time})_{ij} + e_{ij}$ and
- Level-2 Model $\pi_{0j} = Y_{00} + Y_{01} (\text{age})_j + Y_{02} (\text{education})_j + Y_{03} (\text{group})_j + r_{0j}$ $\pi_{1j} = Y_{10} + Y_{11} (\text{age})_j + Y_{12} (\text{education})_j + Y_{13} (\text{group})_j + r_{1j}$.

Results

Participant Characteristics

Table 1 shows the demographic characteristics of the 223 study patients who received new preventive therapies. The average patient was 36.6 ± 10.2 years of age (Range=18 to 66) and completed 14.0 ± 2.2 years of education. Fifty-eight percent of patients were Caucasian and 34% African American/non-Hispanic, 4% Hispanic/Latino, 2% Native American, 2% Asian American/Pacific Islander. Most patients were female (89%) and almost all (99%) had health insurance, most frequently through Medicaid, HMOs, or PPOs. Thirty-three percent reported annual incomes below \$20,000 and 12% reported annual incomes exceeding \$60,000. Most (59%) were diagnosed with only one type of headache disorder. The most common headache diagnosis was “episodic migraine” (either with or without aura). The average patient experienced headaches on 17.5 ± 7.8 days during the past month.

Of the 223 patients, 34% (76/223) received no psychiatric diagnosis, 21% (46/223) received a diagnosis of Depression-Only, 13% (29/223) received a diagnosis of Anxiety-Only, and 32% (72/223) received a diagnosis of Depression-and-Anxiety. A listing of specific diagnoses within the four psychiatric disorder groups is shown in Table 3.

Chi-square tests of association and independent sample t-tests characterized associations among psychiatric disorders and demographics at M₀ AT baseline. Table 1 shows that patients with no psychiatric disorders (M=34.4 years) and patients diagnosed with Anxiety-Only (M=34.5 years) were significantly younger than patients diagnosed with Depression-Only

($M=41.1$ years; $p_s < .05$ in Bonferroni-adjusted post-hoc comparisons). Patients with no psychiatric disorders also completed more years of education ($M=14.7$ years) than patients with Depression-and-Anxiety ($M=13.5$ years, $p < .01$). No associations were found between psychiatric diagnoses and headache diagnosis (all $p_s > .10$).

Prior to enrollment, patients reported having been prescribed the following acute medications: simple and compound analgesics (46%); triptans/ergotamine (45%); adjunctive therapies (e.g., antiemetics; 24%). Patients reported having been prescribed the following preventive medications: anticonvulsants (12%), SSRIs (10%), beta blockers (6%), tricyclic antidepressants (8%), calcium channel blockers (3%), and “other” (B12, magnesium, NSA, Botox; 10%).

Study Therapies

Acute therapies—Table 2 shows that study physicians prescribed triptans or ergotamines for almost 40% of patients, simple and compound analgesics for 27% of patients, and adjunctive treatments such as antiemetics for 26% of patients. No associations were found between psychiatric disorder and acute therapy prescription category.

Preventive therapy—Table 2 shows that study physicians prescribed antidepressants for 36% of patients, anticonvulsants for 34%, and “other” preventive therapies, such as vitamins, magnesium, and nonsteroidal anti-inflammatory medication for 28%. The Depression-Only group was most frequently (52.2% of patients) prescribed antidepressant medications, followed by the Depression-and-Anxiety group (38.9%), the Anxiety-Only (37.9%) group and patients without a psychiatric disorder (22.4%), $\chi^2(3)=11.6$, $p < .01$. Post-hoc comparisons of proportions found that Depression-Only patients, $z=3.41$ and Depression-and-Anxiety patients, $z=2.32$, were significantly more likely to be prescribed antidepressants than patients with no psychiatric disorder (both $p_s < .05$). “Other Preventive Medications” (e.g., Vitamin B₁₂ supplements, Magnesium supplements) were prescribed to 38.2% of patients with no psychiatric disorders, 34.5% of Anxiety-Only patients, 26.4% of Depression-and-Anxiety patients, and 13% of Depression-Only patients, $\chi^2(3)=9.5$, $p < .03$. Post-hoc comparisons of proportions found that patients with Depression-Only were significantly less likely to be prescribed “Other Preventive Medications” compared to patients with no psychiatric disorders, $z=3.5$, patients with Anxiety-Only, $z=2.2$, and patients with Depression-and-Anxiety, $z=2.1$ (all $p_s < .05$).

Attrition

The participant flow chart in Figure 2 shows that 256 patients were judged by their treating physicians to be good candidates for a new preventive therapy. Of these 256 patients, 223 (87%) began preventive therapy: 73% (65/89) in the no psychiatric disorder group, 88% (42/48) in the Depression-Only group, 72% (23/32) in the Anxiety-Only group, and 66% (57/87) in the Depression-and-Anxiety group.

Patients were operationally defined as “dropouts” if they missed one or more scheduled treatment visits and failed to reschedule and complete the missed visit(s). Retention rates for patients who received new preventive therapies were comparable across groups: no psychiatric disorders (56% of patients); Depression-Only (69%); Anxiety-Only (56%); and Depression-and-anxiety (46%), $\chi^2(3) = 6.6$, $p > .08$. Independent sample t-tests and χ^2 tests compared study completers ($n=141$) and dropouts ($n=82$). Drop outs were significantly younger ($M=34.2$ yrs) than completers ($M=38.0$ yrs, $p < .01$), reported less education ($M=14.2$ completers, $M=13.5$ dropouts, $p < .05$) and were more likely to be African -American (46% of African Americans vs. 30% of Caucasians; $p < .03$).

Study dropouts and study completers did not differ in headache days per month, headache severity, HDI or MSQ scores at the M_0 AT baseline. However, diagnoses of chronic tension-type headache and of medication overuse headache were more frequent (26% and 12%, respectively) in study dropouts than in study completers (12% and 4%, respectively, both $p_s < .05$). Drop outs also were more likely to be diagnosed with only one type of headache (67% completers, 46% dropouts, $p < .01$). With respect to preventive medications, patients who discontinued treatment were more likely to be prescribed antidepressants (30% completers, 46% dropouts, $p < .05$) and were more likely to be prescribed compound analgesics with codeine/barbiturate (1% completers, 5% dropouts, $p < .05$).

Outcome

Table 4 shows outcomes by psychiatric disorder on measures of headache days per month and headache severity assessed at M_0 AT baseline and M_6 evaluation.

Headache days per month—Figure 3a and Table 4 show that at M_0 AT baseline, each of the three psychiatric disorder groups recorded approximately 19 headache days per month, while patients with no psychiatric disorder recorded about 15 headache days per month. Only the two depressive disorder groups differed significantly from patients with no psychiatric disorder (both $p_s < .02$). Although patients with Anxiety-Only and no psychiatric disorder did not differ significantly on headache days per month, the small number of Anxiety-Only patients ($n=29$) provided less statistical power for this comparison. Rates of improvement were significant for all four groups but improvements did not differ between groups: no psychiatric disorder (e.g., $b = -0.63$, a reduction of 0.63 headache days per month or a mean reduction of 3.8 headache days between the M_0 baseline and M_6 evaluation visits); Depression-Only, $b = -0.85$, $p < .01$ (a mean reduction of 5.1 headache days between the M_0 and M_6 visits); Anxiety-Only, $b = -1.27$, $p < .01$ (a mean reduction of 7.6 headache days between the M_0 and M_6 visits); and Depression-and-Anxiety, $b = -0.78$, $p < .01$ (a mean reduction of 4.7 headache days between the M_0 and M_6 visits). However, patients with Anxiety-Only ($b = -1.27$) showed twice the rate of improvement compared to patients with no psychiatric disorder ($b = -0.63$, $p < .07$). At M_6 evaluation, the number of headache days was no longer significantly elevated in the three psychiatric disorder groups relative to the no psychiatric disorder group (all $p_s > .10$; see Table 4). It's noteworthy that headache days in the Anxiety-Only and no psychiatric disorder group were virtually identical at the M_6 evaluation ($M = 10.8$ and $M = 11.27$, respectively).

Headache severity—Figure 3b and Table 4 show that at the M_0 AT baseline visit, the mean headache severity ratings for all four groups were within the “mild” to “moderate” severity range and all four groups reported comparable levels of headache severity (all $p_s > .10$). The three psychiatric disorder groups recorded essentially identical rates of improvement in headache severity from M_0 AT baseline to M_6 evaluation (all $b_s = -.03$), although improvement rates were only significant in the two depressive disorder groups. The test comparing the change in Anxiety-Only patients to no psychiatric disorder patients was less powered (power=0.57) than were the tests comparing the Depression-Only and Depression-and-Anxiety groups to no psychiatric disorder (power = 0.66 and 0.77, respectively). Patients with no psychiatric disorders recorded no change in headache severity from M_0 AT baseline to M_6 evaluation. At the M_6 evaluation visit, all four groups recorded comparable headache severity ratings (all $p_s > .10$; see Table 4).

Table 5 shows outcomes by psychiatric disorder on the HDI and HSQ which were assessed at all four clinic visits (M_0 , M_1 , M_2 , and M_6).

HDI—Figure 3c and Table 5 show that at M_0 AT baseline, patients with one or two psychiatric disorders reported greater headache disability than patients with no psychiatric disorders (all

$p_s < .03$). Furthermore, patients with two psychiatric disorders (i.e., Depression-and-Anxiety group) reported greater headache disability than patients with only one (Anxiety-Only and Depression-Only groups; $p < .01$). These differences persisted over the course of treatment (i.e., at the M_1 , M_2 , and M_6 visits). All four groups exhibited significant rates of improvement in headache disability between M_0 AT baseline and M_6 evaluation: no psychiatric disorders ($b = -0.64$, $p < .01$); Depression-Only ($b = -0.58$, $p < .01$); Anxiety-Only ($b = -1.14$, $p < .01$); and Depression-and-Anxiety ($b = -1.12$, $p < .01$), although rates of improvement did not differ significantly between the four groups (i.e., all $p_s > .10$). At the M_6 evaluation, patients in the two depressive disorder groups reported greater headache disability than patients with no psychiatric disorder; however, only patients in the Depression-and-Anxiety group reported greater headache disability than patients with Anxiety-Only. Indeed, patients with Anxiety-Only and no psychiatric disorder reported similar headache disability levels ($M = 43.3$ and $M = 41.2$, respectively).

HSQL—Figure 3d and Table 5 show that at the M_0 AT baseline visit, patients with Anxiety-Only and no psychiatric disorders exhibited similar levels of quality of life and both groups reported better quality of life than patients in the two depressive disorder groups (all $p_s < .05$). All four groups reported significant improvements from M_0 AT baseline to M_6 evaluation: no psychiatric disorders ($b = -0.88$, $p < .01$); Depression-Only ($b = -2.16$, $p < .01$), Anxiety-Only ($b = -2.33$, $p < .01$); and Depression-and-Anxiety ($b = -2.34$, $p < .01$). While the four groups did not differ in rates of improvement, the following “moderate” effects sizes suggest that patients in each of the three psychiatric disorders groups reported greater improvements in quality of life compared to patients with no psychiatric disorders: Depression-Only ($b = -2.16$, $p < .02$, effect size=0.48); Anxiety-Only ($b = -2.33$, $p < .03$, effect size=0.61); and Depression-and-Anxiety ($b = -2.34$, $p < .01$, effect size=0.55). At the M_6 evaluation, only patients with Anxiety-Only continued to have significantly better quality of life than patients with Depression-and-Anxiety ($p < .02$).

Discussion

This is one of the first studies to prospectively examine how psychiatric disorders relate to treatment outcome in patients receiving contemporary, state-of-the-science treatments in headache specialty clinics. Major findings were: (1) two-thirds of patients were diagnosed with one or more psychiatric disorders; (2) patients with psychiatric disorders improved equally as well as patients with no psychiatric disorder (who consistently reported the most modest treatment gains on the four outcome measures); and (3) the presence of a comorbid depressive disorder was associated with more frequent and disabling headaches at treatment initiation and treatment completion.

In the current study, two-thirds of patients had one or more psychiatric disorders at the initiation of preventive therapy, most commonly a depressive disorder. This rate is considerably higher than those observed in headache sufferers in the general population [1,19,25] but comparable to rates observed in patients in headache specialty clinics [21,26,32]. It could be that physician referral patterns to headache specialty clinics led to the formation of a sample that included a disproportionately greater percentage of headache patients with psychiatric disorders. Nonetheless, findings from this study and previous research [21,24] suggest that high rates of psychiatric comorbidity are perhaps the rule (and not the exception) in headache specialty treatment centers and that the assessment of patients for psychiatric disorders should occur routinely in these settings.

Contrary to conventional wisdom, all three psychiatric disorder groups demonstrated significant improvements in headache days per month, headache-related disability, and quality of life over the treatment period. Rates of improvement on these outcome measures rarely

differed by psychiatric disorder group and were similar to patients without a psychiatric disorder, suggesting that patients with psychiatric comorbidities do benefit from headache preventive therapies.

Marked improvements in headache outcomes in patients with psychiatric disorders may have occurred because, at the initiation of treatment, patients with comorbid psychiatric disorders had greater “room for improvement.” Indeed, patients with psychiatric disorders often began treatment with more headache days, more disability, and poorer quality of life than patients with no psychiatric disorder. Additionally, patients with a psychiatric disorder were more likely to be prescribed antidepressant therapies (Depression-Only=52%; Depression-and-Anxiety=39%, Anxiety-Only=38%) compared to patients with no psychiatric disorder (22%) for their headaches (even though--to the best of our knowledge--psychiatric disorders were not assessed by physicians in this study). It could be that the more aggressive prescription of antidepressants to patients with psychiatric disorders yielded significant improvements in headache outcomes. However, because this was a naturalistic study, cause-effect inferences cannot be made regarding the extent to which antidepressant therapies (used alone or in combination with other treatments) produced improvements in headache characteristics in this sample. Future research should examine if, and how, antidepressant medications reduce headache activity in patients with psychiatric disorders.

At baseline, patients with a depressive disorder reported more headache days, greater headache disability, and poorer quality of life compared to patients with no psychiatric disorders. These relationships have been documented in both population- and clinic-based samples [4,7,12, 16]. At the treatment evaluation visit, patients with depressive disorders were comparable to patients with no psychiatric disorders in headache days and headache severity but continued to report greater disability and poorer quality of life than patients with no psychiatric diagnoses. These differences at the evaluation period essentially reflect the disparities that existed prior to the initiation of preventive therapy and suggest that there is heterogeneity in psychosocial treatment outcomes by psychiatric disorders. This heterogeneity appears to be more related to differences that existed at treatment initiation and persisted through treatment evaluation than to differential rates of change by psychiatric group. Specifically, patients with depressive disorders tended to begin and end treatment with more disabling headaches and poorer life quality than patients with no psychiatric disorders. One implication of these findings may be that while preventive (and acute) therapies produced some improvements in psychosocial functioning in patients with depressive disorders, these improvements might be greater if pharmacotherapies are combined with biopsychosocial interventions (e.g., cognitive behavioral stress management interventions) that intervene not only on the patients’ headache characteristics but on important social and emotional aspects of their lives.

The current study has several limitations. All participating headache treatment centers were located in relatively large cities in Ohio; the extent to which study findings generalize to other states and geographic areas (e.g., rural areas) is unclear. The four groups differed in age and education at the acute therapy baseline visit. While these variables were employed as covariates in treatment outcome analyses, the four groups may have differed on other factors that were not assessed in the study. Failure to control for these variables may have influenced study findings. Patients who discontinued treatment (and who dropped out of the study) were significantly younger and had completed fewer years of education, potentially reducing the generalizability of study findings. While the PRIME-MD was used to determine the psychiatric diagnoses in patients, the use of a different diagnostic interview (e.g., CES-D) might have provided different psychiatric diagnoses than those assigned by the PRIME-MD. While this study examined the influence of psychiatric comorbidity on treatment outcome, psychiatric comorbidity was assessed as the “presence” or “absence” of one or more DSM-based

psychiatric disorders. Future research should examine if the severity of one's comorbid psychiatric disorders influences treatment outcome in headache patients.

Patients with psychiatric disorders began treatment with more severe headache characteristics, a finding that is consistent with those reported in the headache literature [4,5,28]. However, differences in headache characteristics between patients with and without psychiatric disorders introduce the possibility that "regression to the mean" accounts for some of the reductions in headache characteristics in patients with comorbid psychiatric disorders. Furthermore, some patients may have been managing their headaches using strategies such as relaxation, meditation, biofeedback, and herbal therapies. These practices were not controlled for in outcome analyses and may have produced some of the improvements observed in key outcome measures. While treatment outcomes were examined in persons with depressive and anxiety disorders, the study did not assess outcomes across other psychiatric disorders, such as bipolar disorder, eating disorders, or substance use disorders. Related to this, the study did not assess outcomes by subgroups of depressive or anxiety disorders (i.e., outcomes may differ between patients with major depressive disorder and minor depressive disorder). Treatment effectiveness may have also varied by patients' adherence to preventive medication regimens, which was not assessed in this study.

In spite of these limitations, this is perhaps the first investigation to prospectively examine how psychiatric disorders are related to treatment outcome in patients receiving a wide variety of contemporary and evidence-based treatments in community-based headache specialty treatment centers. Given that two-thirds of patients were diagnosed with one or more psychiatric disorders, practitioners should identify patients with psychiatric disorders and ensure that both their headache disorder and mental health needs are addressed. Contrary to "conventional wisdom," many patients with psychiatric disorders responded favorably to headache treatment. Additionally, in light of continued high rates of headache days per month in many patients with and without psychiatric comorbid disorders, more effective therapies are needed to produce even greater reductions in headache days per month in patients in headache specialty treatment centers. Finally, given the poorer quality of life in patients with psychiatric disorders (particularly those with depressive disorders), more intensive and comprehensive interventions that go beyond pharmacologic treatment-only are needed to improve quality of life in this group.

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Figure 1.
Study Assessment and Treatment Schedule

Figure 2.
Patient Flow Diagram

Figure 3a.
Growth Curves of Patient Changes in Headache Days Per Month

Figure 3b.
Growth Curves of Patient Changes in Headache Severity

Figure 3c.
Growth Curves of Patient Changes in Headache Disability (HDI)

Figure 3d.
Growth Curves of Patient Changes in Headache Specific Quality of Life (HSQL)

Sociodemographics at the M₀ AT Baseline Visit by Psychiatric Comorbidity Diagnosis

Characteristic	Overall (N=223)	No Psychiatric Disorder (n=76)	Depression Only (n=46)	Anxiety Only (n=29)	Depression- and-Anxiety (n=72)	F or χ^2	p <
Age	36.6 ± 10.2	34.4 ± 9.3	41.1 ± 10.4	34.5 ± 11.5	37.0 ± 9.8	4.8	0.01
Years of Education	14.0 ± 2.2	14.7 ± 2.4	13.9 ± 2.4	13.5 ± 1.9	13.5 ± 2.0	4.2	0.01
Being Caucasian	57.9% (n=129)	67.1% (n=51)	54.4% (n=25)	65.5% (n=19)	47.2% (n=34)	6.9	0.08

Table 2
Study Therapies Prescribed to Headache Patients by Psychiatric Comorbidity Diagnosis

Characteristics	Overall (N=23)		No Psychiatric Disorder (N=76)				Depression Only (N=46)				Anxiety Only (N=29)				Depression- and-Anxiety (N=72)				F or χ^2 p-value											
			N		%		N		%		N		%		N		%													
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%														
Acute Medication																														
Simple & compound analgesics																			59	26.5	22	28.9	10	21.7	8	27.6	19	26.4	0.8	0.85
Compound analgesics with codeine/barbiturates																			5	2.2	2	2.6	1	2.2	0	0.00	2	2.8	0.8	0.84
Triptans and Ergotamines																			88	39.5	35	46.1	18	39.1	13	44.8	22	30.6	4.1	0.25
Adjunctive Therapies (e.g. Antiemetics)																			58	26.0	21	27.6	10	21.7	10	34.5	17	23.6	1.8	0.61
Preventive Medication																														
Antidepressant																			80	35.9	17	22.4	24	52.2	11	37.9	28	38.9	11.6	0.01
Anticonvulsant																			76	34.1	26	34.2	18	39.1	10	34.5	22	30.6	0.9	0.82
Beta Blocker																			27	12.1	12	15.8	4	8.7	3	10.3	8	11.1	1.6	0.65
Calcium Blocker																			7	3.1	4	5.3	1	2.2	0	0.00	2	2.8	2.2	0.52
Other (B12, Magnesium, NSA)																			64	28.7	29	38.2	6	13.0	10	34.5	19	26.4	9.5	0.03

Table 3**Specific Depressive and Anxiety Diagnoses within Psychiatric Disorder Group**

DepressionOnly (n=46)	AnxietyOnly (n=29)	Depression-and-Anxiety * (n=79)
(1) MDD (16/46)	(1) Anxiety Disorder, NOS (19/29)	(1) MDD & Anxiety Disorder, NOS (23/79)
(2) Dysthymic Disorder (6/46)	(2) GAD (6/29)	(2) MDD & GAD (16/79)
(3) MDD, Partial Remission (13/46)	(3) Panic Disorder (3/29)	(3) MDD, Dysthymic Disorder & GAD (10/79)
(4) "1" and "2" (7/46)	(4) "2" and "3" (1/29)	(4) MDD, Dysthymic Disorder & Panic Disorder (6/79)
(5) "2" and "3" (4/46)		

MDD: Major Depressive Disorder; GAD: Generalized Anxiety Disorder; NOS: Not Otherwise Specified

* For the Depression-and-Anxiety Group, only categories that were represented by 5 or more participants were included.

Table 4

Headache Activity Outcomes by Psychiatric Disorder Group

Outcome Measure	Headache Days/Month			Headache Severity (1-3)		
	No Psychiatric Disorder (n=75)	Depression Only (n=46)	Anxiety Only (n=29)	No Psychiatric Disorder (n=75)	Depression Only (n=46)	Anxiety Only (n=29)
M ₀ AT Baseline	15.07 (0.95)	18.95 (1.2)	18.45 (1.6)	1.61 (0.05)	1.75 (0.06)	1.67 (0.08)
M ₆ PT Evaluation	11.27 (1.1)	13.86 (1.4)	10.80 (1.8)	1.61 (0.06)	1.59 (0.07)	1.52 (0.10)
Rate of Change*	-0.63 ^a (0.19)	-0.85 ^a (0.23)	-1.27 ^a (0.30)	-0.00 (0.01)	-0.03 ^b (0.01)	-0.03 ^b (0.02)

Mean (SE)

^a p < .01

^b p < .05

* Rate of Change: Average unit reduction in outcome variable per month

Table 5

Psychosocial Headache Outcomes by Psychiatric Disorder Group

Outcome Measure	Headache Disability Inventory			Headache-Specific Quality of Life		
	No Psychiatric Disorder (n=75)	Anxiety Only (n=29)	Depression and-Anxiety (n=72)	No Psychiatric Disorder (n=75)	Depression Only (n=46)	Anxiety and-Anxiety (n=72)
M ₀ AT Baseline	45.02 (1.1)	50.11 (1.9)	58.62 (1.2)	36.72 (1.5)	48.01 (1.9)	41.54 (2.4)
M ₁ PT Initiation	44.39 (1.2)	48.97 (1.9)	57.50 (1.2)	35.84 (1.4)	45.85 (1.8)	39.21 (2.3)
M ₂ PT Adjustment	43.75 (1.2)	49.55 (1.5)	56.37 (1.2)	34.96 (1.4)	43.69 (1.8)	36.88 (2.2)
M ₆ Evaluation	41.21 (1.5)	47.23 (1.9)	51.87 (1.6)	31.45 (2.0)	35.06 (2.5)	27.54 (3.1)
Rate of Change [*]	- 0.64 ^a (0.21)	- 1.14 ^d (0.33)	- 1.12 ^a (0.22)	- 0.88 ^a (0.33)	- 2.16 ^a (0.42)	- 2.33 ^a (0.53)

Mean (SE)

^a p < .01

^b p < .05

^{*} Rate of Change: Average unit reduction in outcome variable per month