

Migraine Headache in Affectively Ill Latino Adults of Mexican American Origin Is Associated With Bipolarity

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Background: The objective of this cross-sectional study was to determine the prevalence of migraine headache among depressed Latino adults of Mexican American origin meeting the criteria for bipolar disorder (BPD) or major depressive disorder (MDD) relative to patients in a psychiatric comparison group.

Method: In a mental health clinic for the indigent, consecutively and systematically evaluated acutely depressed Latino adults received structured diagnostic psychiatric interviews based on modules extracted from the Structured Clinical Interview for *DSM-IV*. All were asked as part of routine assessment whether they had headaches "in the last week." Patients with unilateral, pounding, pulsating headache were classified as having migraine headache. The prevalence of migraine headache among the patients with BPD and MDD was contrasted with that of patients in a psychiatric comparison group composed of patients with disorders other than schizophrenia or schizoaffective disorder. Logistic regression was used to test for associations and control for confounding effects. The data were collected between August 2001 and November 2004.

Results: Eighty-seven patients had BPD and 123 had MDD. Bipolar patients were 2.9 times more likely to have migraine headaches than patients with MDD ($P < .0001$). There was a trend for patients with MDD to have a higher prevalence of migraine than patients in the psychiatric comparison group.

Conclusions: Bipolar patients had a high prevalence of migraine headache relative to patients with MDD. This study suggests that migraine is linked to bipolarity.

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A vast array of idiopathic somatic complaints, including but not limited to pain, are common among depressed persons across the lifespan.¹⁻⁷ Pain as a component of depressive syndromes occurs across cultures.^{8,9} The results of 2 key studies suggest that about 90% of depressed patients experience pain.^{10,11}

Pain stemming from depression exacts a great toll in terms of human suffering, psychosocial impairment, and economic costs. A study of the financial burden posed by pain in a large urban primary care practice compared the direct costs of treating patients with ($n = 207$) and without ($n = 821$) major depressive disorder (MDD) over a 12-month period.¹² The cost of caring for patients with MDD (\$19,838) was over 3-fold greater than that of nondepressed patients (\$6,268). This elevated cost was completely due to an increased demand for services by depressed persons with moderate or greater pain.¹² Headache, including migraine, is a very common form of moderate to severe, debilitating pain experienced by depressed persons, as evident from the review of literature included here. Study of various types of pain, including migraine existing in the context of affective disorders, is accordingly an important topic for investigation.

The first objective of this study was to measure the prevalence of migraine headache among depressed Latino adults of Mexican American origin with bipolar disorder (BPD) and MDD. The second aim was to explore the possibility that the prevalence of migraine headache differs as a function of polarity. The third aim was to contrast the prevalence of migraine headache among patients with affective illness to nonaffectively ill psychiatric comparison patients. Many investigators have studied the relationship between migraine headache and affective disorders,¹³⁻²⁵ and previous authors have reported a high prevalence of migraine among both patients with BPD and MDD but have not found differences in prevalence as a function of polarity.^{13,15,16}

METHOD

This work was done in and through the process of delivering clinical services to patients in an isolated rural

CLINICAL POINTS

- ◆ Patients with bipolar disorder were 2.9 times more likely to have migraine headache than patients with major depressive disorder.
- ◆ Patients with unipolar disorder are not significantly more likely to have migraine headache than non-affectively ill controls.
- ◆ The high prevalence of migraine headache among the bipolar patients relative to the patients with major depressive disorder is consistent with the hypothesis that the association of migraine with bipolar disorder is stronger than its relationship with unipolar disorder.

area. The clinic was created for the delivery of services to indigent persons living in an underserved area. The results are the product of a cross-sectional study based on a retrospective review of the charts of patients receiving services in this clinic.

Clinical Setting

The clinic in which the patients were evaluated was the only vehicle for the delivery of specialized psychiatric services in the community. There were no private-sector psychiatrists.

The clinic served the needs of the populace living in the vast rural expanse of Starr County, Texas. This county, one of the poorest in the United States, rests on the Rio Grande River. The data were collected between August 2001 and November 2004. Starr County was, at least at the time that the data were collected, a semiclosed community. The county had a population of 53,597 persons in the 2000 census. Its racial composition was 99% Hispanic and 1% other at that time.

Patients and Comparison Group

The clinic population covered the lifespan. Youths with any psychiatric disorder were eligible for services. In contrast, the admission of adults was highly restricted. Due to extreme financial constraints, admission of an adult to the clinic required that bachelor's level triage staff classify the prospective patient as meeting the criteria for MDD, BPD, or schizophrenia or schizoaffective disorder according to the *DSM-IV* criteria.²⁶ Further, adults were required to have Medicaid (public health care assistance) in order to gain access to services. Persons with dependent children had this benefit de facto. Many women presenting had dependent children, whereas none of the men did. This accounts for the preponderance of women in the psychiatric comparison group.

The patients included in this study were poorly educated; none of the patients had more than the equivalent of a 12th grade education. All of the patients were Latino persons of Mexican American origin. S.C.D. was the sole practicing psychiatrist in the county and performed all of the assessments.

Inclusion criteria required that patients be between 18 and 65 years of age. The criteria also required that the affectively ill patients not have a known nonpsychiatric basis for headache on the basis of medical history and review of systems and that they met the criteria for major depressive episode²⁶ at the time of evaluation. The non-affectively ill comparison subjects could have histories of any psychiatric disorder other than schizophrenia or schizoaffective disorder, including that of the abuse of stimulants/drugs that can cause vascular headache. The modest number of patients in our database available to serve as comparison patients necessitated this concession. The comparison patients could have no other identifiable cause for migraine headache on the basis of medical history and the review of systems other than the history of the recent abuse of stimulants.

Patients with anxiety disorders, often associated with pain, were eligible for inclusion in the comparison group, but none of our patients had a primary anxiety disorder. Patients with schizophrenia and schizoaffective disorder were excluded as they have a serious psychiatric disorder that may or may not be associated with various types of pain and merit attention in a parallel study. However, a review of our records indicated that none of those patients who were classified as having 1 of these disorders had migraine headache.

Diagnostic Interview

Patients received structured diagnostic interviews to determine the presence of a major depressive episode, hypomania/mania, anxiety disorders, and substance use disorders using modules extracted from the Structured Clinical Interview for *DSM-IV*.²⁷ In the course of the evaluation, patients were presented with the query, "Have you been having headaches in the last week?"

Patients were asked explicit questions about the characteristics of the cephalalgia if they answered this question in the affirmative. The data were not collected in the course of conducting a research study but rather in the course of delivering ordinary, routine, clinical services. Given that the data were not collected in the course of conducting a research project but rather in the process of

Table 1. Demographic Characteristics and Diagnoses of the Latino Patients of Mexican American Origin Included in the Study

Characteristic	Patients With Major Depressive Disorder (n = 123)	Patients With Bipolar Disorder (n = 87) ^a	Patients With an Affective Disorder (n = 210)	Patients With a Nonaffective Disorder (n = 35)	All Patients (N = 245)
Age, mean (SD), y	36.7 (12.0)	36.6 (12.3)	36.7 (12.1)	31.9 (11.3)	36.0 (12.1)
Sex, n (%)					
Male	39 (32)	34 (39)	73 (35)	12 (34)	78 (32)
Female	84 (68)	53 (61)	137 (65)	23 (66)	167 (68)

^aIncluded bipolar depression and mixed states.

delivering ordinary clinical care, time would not allow for formal classification of headache according to the criteria set forth by the International Headache Society (IHS).²⁸

Lipton and colleagues²⁹ reported that headache marked by pain worse on 1 side of the head alone has sensitivity and specificity for IHS-defined migraine of 75% and 50%, respectively. Pounding, pulsating, or throbbing pain has sensitivity and specificity of 87% and 22%, respectively, for IHS-defined migraine.²⁸ Our definition of *migraine* includes pain worse on 1 side of the head and simultaneous concurrent pounding, pulsating, or throbbing pain at that site. It follows that our method of classifying a patient as having migraine has sensitivity of 87% and specificity of 50% for IHS-defined migraine.²⁸ These measures provide acceptable positive and negative predictive value relative to other studies.

A variety of definitions of *migraine* have been used in epidemiologic studies, including that applied here.³⁰ This definition has a chance-corrected agreement (Cohen's κ) with that rendered by a formal interview with a physician of 0.59, which is regarded to be good, and positive and negative predictive values of 84% and 78%, respectively.

We ascertained the prevalence of migraine among patients with a major depressive episode who had BPD and MDD collectively. However, we also separated these groups and determined the prevalence of migraine among those with BPD and MDD separately.

Analysis

Logistic regression was used to test associations and to control for confounding effects (age and gender). The critical value of α was set at .05, 2-tailed. We did not employ a statistical method to determine trends across categories. Data were analyzed using STATA 8.0 (StataCorp LP, College Station, Texas).

RESULTS

Patients with a major depressive episode included 123 persons with MDD and 87 with BPD. Eighty-one of the latter had bipolar I disorder and 6, all women, had bipolar II disorder. There were 35 comparison patients. These patients included individuals with substance use disorders (n = 10), adjustment disorders (n = 4), attention-deficit/

hyperactivity disorder (n = 2), and no known Axis I disorder (n = 19).

The demographic characteristics of the patients are summarized in Table 1. Sixty-eight percent of the patients with MDD, 61% of the patients with BPD, and 66% of the patients in the comparison group were female.

Of the bipolar patients, 54% had migraine headache compared to 29% of the patients with MDD. Patients with BPD were nearly 3 times more likely to have migraine headache than those with MDD (odds ratio [OR] = 2.9, 95% CI, 1.6–5.2, $P < .0001$). Of the comparison patients, 14.2% had migraine headache. The patients with MDD were 2.4 times more likely to have migraine headache than the comparison patients. This constituted a trend (95% CI, 0.85–6.64, $P = .096$). Thus, there was a progression of risk for migraine ranging from 14.2% among the patients who did not meet the criteria for a major depressive episode to 29% among those meeting the criteria for MDD to 54% among those meeting the criteria for BPD, suggesting a trend across these groups.

DISCUSSION

Our data confirm previous findings of an increase in the prevalence of migraine headache among patients with MDD and BPD relative to the general population. The findings suggest that a history of migraine can be regarded to be a "red flag" for the presence of a disorder of mood, particularly BPD.

Fifty-four percent of the patients with BPD and 29% of those with MDD had migraine headache. The OR of a patient with bipolar disorder relative to a patient with MDD of having migraine headache was 2.9. This OR is highly significant. There was a trend for patients with MDD to be more likely to have migraine headache than those in the psychiatric comparison group.

Migraine headaches and affective disorders coexist at a higher prevalence than in the general population. Mahmood et al¹³ were to the best of our knowledge the first investigators to report that migraine is very common among persons with BPD. Thirty percent of their patients with this disorder had a lifetime history of migraine. Fasmer¹⁵ also reported that migraine headaches are common among persons with BPD. However, the lifetime

prevalence of migraine headache among bipolar (44%) and unipolar patients (46%) did not differ. Similarly, Fasmer and Oedegaard¹⁶ did not find that the lifetime prevalence of migraine headaches among bipolar and (57%) and unipolar (45%) patients differ. These studies suggest that there is a strong relationship between migraine and affective illness but do not indicate that the relationship between BPD and migraine is stronger than that between migraine and MDD. The work of these investigators is not inconsistent, however, with the possibility that there are many forms of unipolar disorder (ie, that it is not 1 entity) and that there are variants of it that fall within the bipolar spectrum.²¹

Fasmer and Oedegaard¹⁶ methodically looked at the clinical characteristics of affectively ill persons with migraine in Norway. They used an internationally accepted structured clinical interview supplemented with Akiskal and colleagues' criteria for affective temperaments^{31,32} to diagnose bipolar II disorder. Bipolar I disorder was diagnosed according to the *DSM-IV* criteria, and bipolar II disorder included patients with either discrete hypomanic episodes with discrete periods of a major depressive episode or a cyclothymic or hyperthymic temperament. The critical finding was that patients with bipolar I and bipolar II disorder dramatically differed with respect to the lifetime prevalence of migraine. Eighty-two percent of the patients with bipolar II disorder versus 27% of the patients with bipolar I disorder had a lifetime history of migraine.

It is noteworthy that the patients composing our database were predominantly bipolar I.³³ This renders the finding even more interesting as Fasmer and Oedegaard¹⁶ observed that their bipolar II patients had a substantially higher prevalence of migraine than their bipolar I patients. This suggests that we and the Norwegian investigators simply tapped different genetic pools.

The results of our study suggest that the relationship between migraine headache and BPD is much stronger than that between migraine headache and MDD. Fifty-four percent of our bipolar probands had migraine headaches compared to 29% of our patients with MDD. The magnitude of this difference may stem from the uniqueness of our patient population.

A sample of patients of the type provided by the uniqueness of Starr County has never before been the focus of a study of this nature; there is no preexisting literature to guide us. The county was a semiclosed rural community, at least at the time that the data entering into the analyses making this study possible were collected. A semiclosed community is vulnerable to inbreeding that is conducive to the concentration of genes for an array of illnesses, including migraine in the context of BPD. We have proposed that this is a basis for a high prevalence of bipolar I disorder in the county relative to bipolar II disorder.³³

The study of the genetics of migraine headache has exploded in recent years.³⁴⁻³⁶ We recently reported that simply having a first-degree relative with BPD but not MDD is a risk factor for migraine headache among affectively ill persons.³⁷ The strong association between BPD and migraine headache in the sample subject to study here is consistent with the hypothesis that genes conferring risk for both migraine headache and bipolarity are linked, and they highlight the potential fruitfulness of future studies aimed at determining whether linkage exists.

Methodological Aspects

A major strength of our study is that a highly experienced academic psychiatrist was able to systematically collect a wealth of data in the course of delivering standard, routine services in a community mental health clinic situated in a vast rural expanse. This fact created a unique opportunity. A sociologically "invisible" population that is inaccessible to researchers situated in major academic, tertiary care centers located in large urban settings was the focus of attention.

This is the first clinical study of the prevalence of migraine headache among depressed Latino persons of Mexican American origin with BPD relative to MDD. It is also to the best of our knowledge the first study to reveal a higher prevalence of migraine headache among persons of any ethnic/racial background with BPD relative to MDD. However, despite impressive statistical results, this study, like all studies, has limitations.

Limitations

The focus of the study was exclusively on a Latino population living in a semiclosed community. This focus raises questions about the generalizability of the results. However, the Latino population of Mexican American origin is the most rapidly growing segment of American society. This demographic shift dictates that health care professionals become increasingly aware of the health care attitudes, problems, and needs of this population. Thus, we would propose that although the results may not be generalizable to non-Latino populations, the focus on this demographic group constitutes a virtue rather than a weakness of the study.

The relationship between migraine headache and BPD relative to MDD may not be as robust in other populations. However, that the data were collected in a semiclosed community also presents a potential strength. Starr County may present a unique setting for conducting psychogenetic studies of the relationship between mood disorders, and BPD in particular, and comorbid disorders.

The small sample size of the comparison group constitutes a limitation. Five of the 35 patients in this group reported having a migraine headache.

The most important departure from the ideal is that this is a single-interviewer study. The same psychiatrist who

rendered diagnoses of Axis I disorders also conducted the screen for headache.

CONCLUSIONS

Migraine was remarkably common among our bipolar patients. The prevalence of migraine among them is sufficiently high to suggest that migraine headache is, at least in the population that we studied, a common form of comorbidity with BPD. The findings of the Norwegian investigators cited previously are congruent with this possibility.¹⁶ Efforts at replication in different patient populations hold the promise of fecundity.

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REFERENCES

- Dilsaver SC, Wu X, Akiskal HS, et al. Pain complaints in adolescent patients with affective disorders versus psychiatric controls. *Prim Care Companion J Clin Psychiatry*. 2005;7(4):150–174.
- Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. *N Engl J Med*. 1999;341(18):1329–1335.
- Sartorius N. Physical symptoms of depression as a public health concern. *J Clin Psychiatry*. 2003;64(suppl 7):3–4.
- Greden JF. Physical symptoms in depression: unmet needs. *J Clin Psychiatry*. 2003;64(suppl 7):5–11.
- Moldin SO, Scheftner WA, Rice JP, et al. Association between major depressive disorder and physical illness. *Psychol Med*. 1993;23(3):755–761.
- Masi G, Favilla L, Milepiedi S, et al. Somatic symptoms in children and adolescents referred for emotional and behavioral disorders. *Psychiatry*. 2000;63(2):140–149.
- Stewart DE. Physical symptoms of depression: unmet needs in special populations. *J Clin Psychiatry*. 2003;64(suppl 7):12–16.
- Demyttenaere K, Bonnewyn A, Bruffaerts R, et al. Comorbid painful physical symptoms and depression: prevalence, work loss, and help seeking. *J Affect Disord*. 2006;92(2–3):185–193.
- Arnault DS, Sakamoto S, Moriwaki A. Somatic and depressive symptoms in female Japanese and American students: a preliminary investigation. *Transcult Psychiatry*. 2006;43(2):275–286.
- Dilsaver SC, Benazzi F, Manning JS, et al. Pain complaints in Latino adults of Mexican origin with and without major depressive episode: a cross-sectional study. *Prim Care Companion J Clin Psychiatry*. 2008;10:191–196.
- Corruble E, Guelfi JD. Pain complaints in depressed inpatients. *Psychopathology*. 2000;33(6):307–309.
- Gameroff MJ, Olfson M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. *J Clin Psychiatry*. 2006;67(8):1232–1239.
- Mahmood T, Romans S, Silverstone T. Prevalence of migraine in bipolar disorder. *J Affect Disord*. 1999;52(1–3):239–249.
- Datta SS, Kumar S. Hypomania as an aura in migraine. *Neurol India*. 2006;54(2):205–206.
- Fasmer OB. The prevalence of migraine in patients with bipolar and unipolar affective disorders. *Cephalalgia*. 2001;21(9):894–899.
- Fasmer OB, Oedegaard KJ. Clinical characteristics of patients with major affective disorders and comorbid migraine. *World J Biol Psychiatry*. 2001;2(3):149–155.
- McIntyre RS, Konarski JZ, Wilkins K, et al. The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian Community Health Survey. *Headache*. 2006;46(6):973–982.
- Oedegaard KJ, Fasmer OB. Is migraine in unipolar depressed patients a bipolar spectrum trait? *J Affect Disord*. 2005;84(2–3):233–242.
- Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. *Headache*. 2006;46(9):1327–1333.
- Peterlin BL, Ward TN. Neuropsychiatric aspects of migraine. *Curr Psychiatry Rep*. 2005;7(5):371–375.
- Oedegaard KJ, Angst J, Neckelmann D, et al. Migraine aura without headache compared to migraine with aura in patients with affective disorders. *J Headache Pain*. 2005;6(5):378–386.
- Nuyen J, Sachellevs FG, Satariano WA, et al. Comorbidity associated with neurological and psychiatric diseases: a general practice-based controlled study. *J Clin Epidemiol*. 2006;59(12):1274–1284.
- Endicott NA. Psychophysiological correlates of “bipolarity.” *J Affect Disord*. 1989;17(1):47–56.
- Merikangas KR, Angst J, Isler H. Migraine and psychopathology: results of the Zurich cohort study of young adults. *Arch Gen Psychiatry*. 1990;47(9):849–853.
- Breslau N, Davis GC. Migraine, major depression and panic disorder: a prospective epidemiologic study of young adults. *Cephalalgia*. 2002;12(2):85–90.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
- First MB, Spitzer RL, Gibbon M, et al. *The Structured Clinical Interview of DSM-IV Axis I Disorders: Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Association; 1997.
- International Headache Society Classification Subcommittee. International Classification of Headache Disorders, 2nd Edition. *Cephalalgia* 2004; 24(S): 1–160.
- Lipton RB, Dodrick D, Sadovskey R, et al. A self-administered screen for migraine in primary care: the ID Migraine Validation Study. *Neurology*. 2003;61(3):375–382.
- Hagen K, Zwart JA, Vatten L, et al. Head-HUNT: validity and reliability of a headache questionnaire in a large population-based study in Norway. *Cephalalgia* 2000;20(4):244–251.
- Akiskal HS, Akiskal K. Cyclothymic, hyperthymic, and depressive temperaments as subaffective variants of mood disorders. In: Tasman A and Riba MB, eds. *American Psychiatric Association Review of Psychiatry*, vol 11. Washington, DC: American Psychiatric Association Press; 1992: 43–62.
- Akiskal HS, Mallya G. Criteria for the diagnosis of the “soft” bipolar spectrum: Treatment implications. *Psychopharmacol Bull*. 1987;23(1): 68–73.
- Dilsaver SC, Benazzi F, Akiskal HS, et al. Dose-response relationship between number of comorbid anxiety disorders in adolescent bipolar/unipolar disorders, and psychosis, suicidality, substance abuse and familiarity. *J Affect Disord*. 2006;96(1):249–258.
- Estevez M, Gardner KL. Update on the genetics of migraine. *Hum Genet*. 2004;114(3):225–235.
- Wessman M, Kaunisto MA, Kallela M, et al. The molecular genetics of migraine. *Ann Med*. 2004;36(6):462–467.
- Gardner KL. Genetics of migraine: an update. *Headache*. 2006; 46(suppl 1):S19–S24.
- Dilsaver SC, Benazzi F, Oedegaard K, et al. Is a family history of bipolar disorder a risk factor for migraine among affectively ill patients? *Psychopathology*. 2009;42(2):119–123.