

Psychiatric Comorbidity of Migraine: A descriptive Study

Saadoun Dawood Ahmed

Department of Medicine, College of Medicine, Kirkuk University

Date of submission: 6 October 2015

Accepted for publication: 1 December 2015

Abstract:

Background: Migraine is frequently associated with psychiatric disorders and comorbidity with psychiatric disorders raises the global burden of migraine.

Objectives: To detect psychiatric comorbidity in patients suffering from migraine.

Patients and Methods: A descriptive study involving 192 patients with migraine who fulfilled the International Classification of Headache Disorders-2 2004 (ICHD-2). Diagnostic and Statistical Manual of mental disorders, 4th Text Revised (DSM-IVTR) was used to classify the psychiatric disorders, among them. All patients were interviewed by means of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for identification of the content of obsessive compulsive symptoms.

Results: The majority of the migraineurs were with throbbing unilateral headache (79.1%), (31.3%) of the patients were with one per month in frequency of attack and (41.7%) of them had family history of migraine. The provoking factors of the attack were reported in (37.5%) of the migraineurs. (75%) of the patients had psychiatric disorders. The commonest psychiatric disorders were generalized anxiety disorder (31.25%) followed by depressive disorder (19.8%).

Conclusion : (75%) of patients with migraine of the present study had psychiatric disorders.

Keywords: Migraine, Psychiatric comorbidity.

Introduction:

Migraine is a common, debilitating disorder that imposes a large personal burden on sufferers and high economic costs on society. The one year prevalence of migraine was quoted to be (14.7%). Population based studies have consistently shown that about (5%) of men and (15% -17%) of women suffer from migraine attacks ^(1, 2). Migraine usually begins on one side of the head (often behind the eye) and spread to the whole head⁽³⁾. The highest prevalence occurs between the ages of 25 and 55 years, potentially the most productive period of life ⁽⁴⁾. Previous studies have found that migraine occurs together with other illnesses at a greater coincidental rate than is seen in the general population ⁽⁵⁻⁷⁾. These occurrences are

called "comorbidities". The term comorbidities is used to refer to the statistical association of two distinct diseases in the same individuals at a rate higher than expected by chance ⁽⁸⁾. The comorbid illnesses in patients with migraine include; stroke, vascular brain lesions, heart disease, hypertension, psychiatric disorders (depression, anxiety disorders and bipolar disorder), restless legs syndrome, epilepsy and asthma ⁽⁵⁻¹⁰⁾. Prodromal and accompanying symptoms of migraine attacks often are psychiatric in nature, such as depression, elation, irritability, anxiety, over activity, difficulty thinking, and anorexia or increased appetite ⁽¹¹⁾. In addition, psychosocial stress is the most common precipitating factor for a

migraine attack⁽¹²⁾. In further studies, general distress, anxiety, fear of impending doom, depression, irritability, fatigue, lethargy, apathy, dullness, changes in motor activity, appetite and sleep have been reported⁽¹³⁻¹⁸⁾. Hudson and colleagues claimed that migraine headache is associated with other psychiatric and medical conditions including major depressive disorder, attention- deficit/ hyperactivity disorder, bulimia, cataplexy, dysthymic disorder, generalized anxiety disorder, irritable bowel syndrome, premenstrual dysphoric disorder, social phobia, fibromyalgia, and obsessive compulsive disorder (OCD)⁽¹⁹⁾.

Comorbidity between migraine and psychiatric disorders has been extensively studied, but the mechanisms underlying this phenomenon are far from clear. The evidence from literatures⁽²⁰⁻²²⁾ points to three main potential mechanisms, as follows;

1. Psychiatric disorders are causal factors in the development of migraine. In this case, psychiatric disturbances are responsible for a full expression of migraine, and under particular circumstances for the evolution of migraine in a daily pattern (chronic migraine)

2. Migraine is a causal factor in the development of psychiatric disorders. In this case, the repetition of intense and/ or long lasting pain episodes may facilitate the development of anticipatory anxiety and /or depression.

3. Shared aetiological factors and common determinants explain the co-occurrence of both entities. In this case, there is no clear causal association, and a common substrate (e.g., deranged activity of neurotransmitters or receptors) may cause both migraine and the comorbid psychiatric disorder.

Increasing evidence suggests that migraine in comorbidity with psychiatric disorders associated with poorer health-related outcomes⁽²³⁾. Several studies have so far examined health – related outcomes of migraine, investigating variables such as disability, restriction of activity, quality of life or mental health care utilizations⁽²⁴⁻²⁷⁾. The aim of the study is to detect psychiatric comorbidity in patients suffering from migraine.

Materials and Methods:

This descriptive study involved 192 patients with migraine who fulfilled the International Classification of Headache Disorders-2 (ICHD-2) 2004⁽²⁸⁾. The ICHD-2 (table 1) tabulates the criteria for headache classification and diagnosis. This allows a systematic approach to a range of disorders that present with headache. The sample consisted of 40 male patients, 152 female patients, aged between 16 – 56 years. The study was conducted in the private clinic and psychiatric outpatient at Azadi Teaching Hospital, during the period between April 2014 and February 2015. Sociodemographic profile such as; age, sex, marital status, educational level, occupation, characteristic of migraine, psychiatric history, and detailed physical examination as well as mental status examination were recorded. The patients were subjected to specialists opinion (e.g., neurologist, ENT or ophthalmologist specialist) and relevant investigations (e.g., fundoscopy, C.T. Scan, EEG, blood sugar etc.,) whenever required to exclude an organic lesion. The cases suffering from organic mental disorders, chronic psychiatric disorders, epilepsy or substances related disorders were excluded from the study. Diagnostic and

Statistical Manual of mental disorders, 4th Text Revised (DSM-IVTR) ⁽²⁹⁾ was used to classify the psychiatric disorders. All patients were then interviewed by means of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) ⁽³⁰⁾ for identification of the content of obsessive compulsive symptoms. The scale is a clinician – rated 10-item scale. Each item is rated 0 (not significant) to 4 (extreme symptoms). If the patient met the full criteria for obsessive compulsive disorder (OCD) according to the OCD module of the DSM-IVTR, then a diagnosis of OCD was applied. If the patient met the full criteria with exception that the disability or distress was judged to be below the diagnostic threshold, then a diagnosis of subclinical OCD was applied ⁽³¹⁾. Verbal consent was obtained from all subjects after full explanation of the study procedure. Descriptive statistical analysis was done by, mean \pm standard deviation (SD), frequency and percentage. Using, SPSS 17, levels of statistical significance differences were obtained in regarding some sociodemographic data, (sex, marital status and age) and type of headache.

Table 1a. ICHD-2 diagnostic criteria for 1.1 migraine without aura ⁽²⁸⁾.

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
 - 1. Unilateral location
 - 2. Pulsating quality
 - 3. Moderated or severe pain intensity
 - 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache at least one of the following

- 1. Nausea and/or vomiting
- 2. Photophobia and phonophobia
- E. Not attributed to another disorder

Table 1b. ICHD-2 diagnostic criteria for 1.2.1 Typical aura with migraine ⁽²⁸⁾.

- A. At least two attacks fulfilling criteria B-D
- B. Aura consisting of at least one of the following , but no motor weakness:
 - 1. Fully reversible visual symptoms including positive features (flickering lights, spots, or lines) and / or negative features (i.e. loss of vision)
 - 2. Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/ or negative features (i.e. numbness)
 - 3. Fully reversible dysphasic speech disturbance.
- C. At least two of the following:
 - 1. Homonymous visual symptoms and/ or unilateral sensory symptoms.
 - 2. At least one aura symptom develops gradually over ≥ 5 minutes and/ or different aura symptoms occur in succession over 5 minutes.
 - 3. Each symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache fulfilling criteria B- D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes.
- E. Not attributed to another disorder.

Results:

A total of 192 patients were interviewed, 152(79.2%) were female patients and 40(20.8%) male patients. The mean age of the patients was 33.3 years (standard deviation; SD= ± 8.7) and the mean age of migraine onset 21 years.

The sociodemographic characteristics of the patients are shown in table (2). The majority of the patients, with high

significant difference than others were married (61.5%) ($P < 0.001$) and housewife (54.2%). Maximum patients belong to age group 31-45 (56.3%) with high significant difference ($P < 0.001$) years followed by 16-30 years (37.5%), female outnumbered the males significantly ($P < 0.002$) (79.2% versus 20.8%) and in the educational level of Illiterate and primary schools (52%).

Table (3) show the characteristic symptoms of migraineurs. The majority of the patients were with throbbing unilateral headache (79.1%) with high significant difference than bilateral throbbing headache ($P < 0.001$), 31.3% of

the patients were with one per month in frequency of attack and 41.7% of them had family history of migraine.

Table (4); show the provoking factors of migraine. The provoking factors were reported in 37.5% of the migraineurs. The commonest provoking factors were fatigue and stress (20.8%) followed by change in weather (18.8%).

Table (5); show the psychiatric disorders in migraineurs. (75%) of the patients had psychiatric disorders. The commonest psychiatric disorders were generalized anxiety disorder (31.25%) followed by depressive disorder (19.8%).

Table (2): Sociodemographic characteristics of patients.

Variables	No.	%	P-value
Gender			
Male	40	20.8	$P < 0.002$
Female	152	79.2	
Marital state			
Single	68	35.4	$P < 0.001$
Married	118	61.5	
Divorced	6	3.1	
Age (years)			
16-30	72	37.5	$P < 0.001$
31-45	108	56.3	
46-60	12	6.3	
Education level			
Illiterate and primary schools	100	52	
Intermediate and secondary schools	76	39.6	
Institutions and University	16	8.3	
Employment			
Housewife	104	54.2	
Student	40	20.8	
Government employee	24	12.5	
Skilled worker	16	8.3	
Unemployed	8	4.2	

Table (3): Characteristic symptoms of migraineurs.

Variables	No.	Percentage	P-value
Type of headache			
Throbbing headache (Unilateral)	152	79.1	P< 0.001
Throbbing headache (Bilateral)	20	10.4	
Non- throbbing headache (Unilateral)	12	6.3	
Non- throbbing headache (Bilateral)	8	4.2	
Frequency			
2-3 per week	22	11.5	
1-2 per week	50	26	
2-3 per month	40	20.8	
1 per month	60	31.3	
Attack in more than one month	20	10.4	
Family history of migraine	80	41.7	

Table (4): Provoking factors of migraine.

Provoking factors	Freq	%
Present	72	37.5
Fatigue and stress	40	20.8
Menstruation	20	10.4
Change in weather (coldness, hotness, high attitude)	36	18.8
Changes in wake- sleep pattern, missing sleep (as jet lag) or lack of adequate sleep, or getting too much sleep	22	11.5
Food: food contain a chemical called tyramine (aged cheese and cooked cheese, dairy product, yogurt, food rich in concentrated tomato paste), fermented pickled food, onion, banana, chocolate	32	16.7
Skipping meals or fasting	28	14.6
Beverages: alcohol, highly caffeinated beverage	10	5.2
Strong odor: perfume, paint thinner	12	6.3
Sexual activity (questioned male only)	6	3.1
Drugs: oral contraceptive, nitroglycerine, secondhand smoke	18	9.4
Not reported	120	62.5

Table (5): Psychiatric disorders among subjects with migraine

Psychiatric disorders	Frequency	Percentage
Generalized Anxiety Disorder	60	31.25
Depression	38	19.8
Subclinical Obsessive – Compulsive Disorder	24	12.5
Phobic and Panic Disorder	22	11.5
Total	144	75

Discussion:

Migraine is reported to be more common in persons between the age of 31 and 40 years (Waters WE, O'Connor PP)⁽³²⁾, and (Bhatia M.S, Gupta R)⁽³³⁾. In the present study, migraine was found to be more common among age group of 31-45 years (56.3%) that is significantly higher than the other age groups. Females (79.2%) were found to suffer more commonly with high significant difference than males (20.8), this is similar with other studies (Waters WE, O'Connor PP)⁽³²⁾, (Bhatia M.S, Gupta R)⁽³³⁾, ((Crip AH, et al)⁽³⁴⁾, (Linnet MS, Stewart WF)⁽³⁵⁾ and (Jette N, et al)⁽³⁶⁾. The majority of patients were married with high significant difference than other marital status; this may be because of the age group commonly affected by migraine, which was the average age of marriage.

The characteristics symptoms of migraineurs were, higher prevalence of unilateral throbbing type of headache (79.1%) with high significant difference than bilateral, and this is similar to other studies (Lipton RB, et al)⁽²⁵⁾, (Bhatia M.S, Gupta R)⁽³³⁾ and (Merikangas KR, et al)⁽³⁷⁾. The frequency of migraine most commonly reported (31.3%) was one per month. The explanation of this may be, because the sample is more among female, and the provoking factor of menses or may be due to time in which the patients exposed to other provoking factors. Family history of migraine (41.7%) was similar to study of Tan H J et al⁽³⁸⁾.

The provoking factors of migraine were reported by (37.5%) of patients which were similar in other studies (Bhatia M.S, Gupta R)⁽³³⁾, (Merikangas KR, et al)⁽³⁷⁾ and (Blau JN)⁽³⁹⁾.

(75%) of migraineurs were associated with psychiatric disorders and

generalized anxiety disorder (31.25%) was the commonest psychiatric disorders followed by depressive disorder (19.8%). This finding was in agreement with results of other studies (Bhatia M.S, Gupta R)⁽³³⁾. Previous clinical and community studies (Merikangas KR, et al)⁽³⁷⁾, (Hussain AM, et al)⁽⁴⁰⁾, (Ortiz A et al)⁽⁴¹⁾, and (Lal V, Singla M)⁽⁴²⁾ have also reported a strong association between migraine and depression as well as anxiety disorders and also vice versa (Ortiz A et al)⁽⁴¹⁾ and (Torreli P, D'Amico D.)⁽⁴³⁾. Other psychiatric disorders were subclinical obsessive compulsive disorder (12.5%) and phobic with panic disorders (11.5%). A diagnosis of subclinical OCD was given if characteristic OCD symptoms are present but the criterion of significant distress or impairment or duration (>1 hour per day) was not met (Stein MB, et al.)⁽³¹⁾ and (Mataix-Cols D, et al.)⁽⁴⁴⁾.

To explain the nature of the relationship between migraine and psychiatric disorders, Breslau et al.⁽¹²⁾ reviewed the 1007 subjects interviewed in 1989 three and a half years later. They found that migraineurs had a more than three-fold relative risk of developing depression compared with non-migraine patients; in turn, depressive patients that had not previously suffered from migraine had a more than three-fold relative risk of developing migraine compared with non-depressed patients. The association seems to arise from the two conditions reciprocally affecting each other in a "bidirectional" relationship rather than resulting from a one way action, thus ruling out the possibility that mood disturbances may be secondary to repeated migraine attacks (Breslau N, et al. 1994)⁽⁴⁵⁾. Findings of a

bidirectional influence between migraine and major depression suggest a common neurobiology. There is evidence for involvement of both monoamine (serotonin and dopamine) and peptide (endorphin and enkephalin) neurotransmitters in depression. Endorphins and enkephalins are involved in both mood and pain control. Serotonin (5HT) in particular has been implicated in mood disorders, anxiety disorders, sleep disorders, eating disorders, obsessive-compulsive disorder, migraine, and tension type headache. There is good evidence for the involvement of 5HT₁ receptor (Dubovsky SL.)⁽⁴⁶⁾ and (Marcus DA)⁽⁴⁷⁾. Evidence is accumulating that dopamine is also intimately involved in migraine. Migraine prodrome is often characterized by dopaminergic symptoms and antidopaminergic compounds can often be helpful in treatment (Seligman MEP)⁽⁴⁸⁾. According to these data, it can be hypothesized that severe headache, severe somatic symptoms and major depression may be linked through dysfunction of the serotonergic and dopaminergic systems.

Conclusion:

In the present study, (75%) of patients with migraine had psychiatric disorders. The more frequent psychiatric disorders were generalized anxiety disorder (31.25%) followed by depression (19.8%). Psychiatric consultation is needed for migraineurs to detect psychiatric disorders and appropriate psychiatric intervention to treat them will be taken on.

References:

[1]. Stewart WF, Shechter A, Rasmussen BK. Migraine Prevalence. A review of population-based studies. *Neurology* 1994; 44 (6 suppl 4): S17-23. Comment in: *Neurology* 1995; 45:1030.

[2]. Celentano DD, Stewart WF, Lipton RB, Reed ML. Medication use and disability among migraineurs: a national probability sample survey. *Headache* 1992; 32: 223- 8.

[3]. Merikangas KR, Angst J, Isler H. Migraine and psychopathology: Results of the Zurich cohort study of the young adults. *Arch Gen Psychiatry*. 1990; 47: 849-853.

[4]. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, Income, race and other sociodemographic factors. *JAMA*. 1992; 292: 64-69.

[5]. Breslau N, & Rasmussen BK. The impact of migraine: Epidemiology, risk factors, and co-morbidities. *Neurology*. 2001; 65: 4-12.

[6]. Franchini L, Bongiorno F, Dotoli D, Rainero I, Pinessi L, Smeraldi E. Migraine headache and mood disorders: A descriptive study in an outpatient psychiatric population. *J Affect Disord*. 2004; 81: 157- 160.

[7]. Breslau N, & Davis GC. Migraine, physical health and psychiatric disorders: a prospective epidemiologic study of young adults. *J Psychiatr Res*. 1993; 27: 211- 21.

[8]. Lipton RB & Silberstein SD. The role of headache-related disability in migraine management: Implications for headache treatment guidelines. *Neurology*. 2001; 56: 35- 42.

[9]. Lipton RB, & Pan J. Is migraine a progressive brain disease? *JAMA*. 2004; 291: 493-4.

[10]. Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, & et al. Case-control study of migraine and risk of ischemic stroke in young women. *Br Med J*. 1995; 310: 830-3.

[11]. Low Nancy CP, du Fort, Guillaume G, & Cervantes P. Prevalence, Clinical Correlates, and Treatment of Migraine in Bipolar Disorder. *Headache: The Journal of Head and Face Pain*. 2003; 43(9): 940-949. Doi: 10.1046/j.526—4610.2003.03184

- [12]. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM. Headache and major depression. Is the association specific to migraine? *Neurology*. 2000; 54: 308-13.
- [13]. Moersck FP. Psychic manifestations in migraine. *Am J Psychiatry* 1974; 3:698-716.
- [14]. Crisp AH, Kaluck RS, McGuinness B, Ralph PC, Harris G. Some clinical, social and psychological characteristics of migraine subjects in the general population. *Postgrad Med J* 1977; 53:691-7.
- [15]. Kudrow L. Current aspects of migraine headache. *Psychosomatics* 1978; 19:48-57.
- [16]. Garvey MJ, Tollefson GD, Schaffer CB. Migraine headaches and depression. *Am J Psychiatry* 1984; 141: 986-8.
- [17]. Evans RW, Rosen N. Migraine, psychiatric comorbidities and treatment. *Headache* 2008; 48:952- 8.
- [18]. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life and depression: A population- based case- control study. *Neurology* 2000; 55: 629- 35.
- [19]. Hudson JI, Mangweth B, Pope HG Jr, Hausman A, De Col C, Laird NM, Beibl W, Tsuang MT. Family study of affective spectrum disorder. *Arch Gen Psychiatry* 2003; 60: 170-7.
- [20]. Radat F, Swendsen J. Psychiatric Comorbidity in Migraine: a review. *Cephalalgia*. 2005 Mar; 25(3): 165-78.
- [21]. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain* 111 (2004): 77- 83.
- [22]. Lipton RB, Silberstein SD (1994) why study the comorbidity of migraine? *Neurology* 44: S4-S5.
- [23]. Jette N, Patten S, Williams J, Becker W, Wiebe S (2008) Comorbidity of migraine and psychiatric disorders – A national Population – Based Study. *Headache* 48: 501-16.
- [24]. Edmeads J, Finally H, Tugwell P, Pryse-Phillips W, Nelson RF, Murray TJ. Impact of migraine and tension- type headache on life- style, consulting behavior, and medication use: a Canadian population survey, *Can J NeurolSci* 1993; 20: 131- 7.
- [25]. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002; 58: 885-94.
- [26]. Lipton RB, Bigal ME, Kolodner K, Stewart WF, Liberman JN, Steiner TJ. The family impact of migraine: population-based studies in the USA and UK. *Cephalalgia* 2003; 23: 429- 40.
- [27]. Jelinski SE, Becker WJ, Christie SN. Chord Study Group Demographics and clinical features of patients referred to headache specialists. *Can J NeurolSci* 2006; 33: 228-34
- [28]. Lipton RB, Bigal ME, Steiner TJ, Silberstein SD, Olesen J. Classification of primary headaches. *Neurology* 2004; 63: 427-35.
- [29]. American Psychiatric Association (APA): Diagnostic and Statistical Manual of mental disorders, 4th Text Revised (DSM-IVTR). American Psychiatric Press, Washington, DC, 2000.
- [30]. American Psychiatric Association. Handbook of psychiatric measures, Washington, DC: The institute; 2000.
- [31]. Stein MB, Forde DR, Anderson G, Walker JR. Obsessive- compulsive disorder in the community: An epidemiologic survey with clinical reappraisal. *Am J Psychiatry*. 1997; 154: 1120-6.
- [32]. Waters WE, O'Connor PP. Prevalence of migraine. *J Neurosurg Psychiatry* 1957; 38: 613-6.
- [33]. Bhatia M.S, Gupta R. Migraine: clinical pattern and psychiatric comorbidity. *Industrial Psychiatry Journal*; Jan-Jun 2012 V 21(1)
- [34]. Crip AH, Kalucy RS, McGuinness B, Ralph PC, Harris G. Some Clinical, Social and Psychological Characteristics of

Migraine Subjects in the General Population. *Postgrad Med J* 1977; 53: 671-7.

[35]. Linet MS, Stewart WF, Migraine headache: Epidemiologic Perspectives, *Epidemiol Rev* 1984;6: 107-39.

[36]. Jette N, Petten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric disorders- A national population- based study. *Headache* 2008; 48:501-16.

[37]. Merikangas KR, Risch NJ, Merikanga JR, Welssman MM, Kidd KK. Migraine and depression; association and familial transmission. *J Psychiatr Res* 1988; 22:119-29.

[38]. Tan H J et al. The coexistence of anxiety and depressive personality traits in migraine. *Singapore Med J* 2007; 48(4): 307.

[39]. Blau JN, Premonitory symptoms of migraine. In :Olesen J, Edvinson L, editors. *Basic mechanisms of Headache*. New York: Elsevier; 1988: 345-51.

[40]. Hussain AM, Mohit MA, Ahad MA, Alim MA. A study on psychiatric comorbidity among the patients with migraine. *TAJ* 2008; 21:108-11.

[41]. Ortiz A, Cervantes P, Zlotnik G, van de Velde C, Slaney C, Garnham J, et al.

Cross- prevalence of migraine and bipolar disorder. *Bipolar Disord* 2010; 12: 397-403.

[42]. Lal V, Singla M. Migraine comorbidities – a discussion. *J Assoc Physicians India* 2010; 54:18-20.

[43]. Torrelli P, D' Amico D. An updated review of migraine and comorbid psychiatric disorders. *NeurolSci* 2004; 25: s234-5.

[44]. Mataix –Cols D, Junque C, Sanchez-Turet M, Vallejo J, Veger K, Barrios M. Neuropsychological functioning in a subclinical obsessive-compulsive sample. *Biol Psychiatry*. 1999; 45: 498-904

[45]. Breslau N, Davis GC, Schultz LR, Peterson EL (1994) Migraine and major depression: a longitudinal study. *Headache* 34: 387-93

[46]. Dubovsky SL (1994). Beyond the serotonin reuptake inhibitors: rationales for the development of new serotonergic agents. *J Clin Psychiatry* 55(Suppl): 34-44.

[47]. Marcus DA (1993) serotonin and its role in headache pathogenesis and treatment. *Clin J Pain* 9: 159-67.

[48]. Seligman MEP (1975) Helplessness: on depression development and death. WH Freeman and Company, San Francisco.