

ORIGINAL ARTICLE

FREQUENCY OF DEPRESSION AND ANXIETY AMONG
ADULT EPILEPTIC PATIENTS

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ABSTRACT

Epilepsy is a common neurological disease that greatly affects quality of life. Although not cured but easily managed by anti-epileptic medications, it is known to be associated with many other psychiatric co-morbid conditions including depression and anxiety. These psychiatric morbidities are often overlooked thus complicating the disease prognosis. The object of this study was to determine the frequency of depression and anxiety among adult epileptic patients. This study has been conducted in the Outpatient Department of Neurology, Dr Ruth K. M. Pfau Civil Hospital Karachi, Pakistan during November 20, 2016 to May 28, 2017. A total of 171 patients were enrolled during this period. Hamilton rating scale for depression (HRSD) and Hamilton anxiety rating scale (HAM-A) were used for assessment and the data was analyzed statistically. Among 171 patients, mean age was found to be 38.05 ± 6.42 years with majority of the patients were female i.e. 103 (60.2%). Depression has been noted in 105 (61.4%) patients with majority cases having moderate severity 47 (44.7%). On the other hand, anxiety has been diagnosed in almost all selected patients. Similar to depression, it has also been found to be of moderate severity i.e. 83/171 (48.5%). In a stigmatized society like Pakistan, living with epilepsy is a problem. It is further aggravated by having associated psychiatric co-morbid conditions. This study revealed a high prevalence of depression and anxiety among epileptic patients living in Pakistan. Therefore, it is suggested that epileptic patients may also be investigated and treated for such co-morbid conditions for better clinical outcome.

Keywords: Anxiety, depression, epilepsy, Hamilton rating scale for anxiety and depression.

1. INTRODUCTION

Epilepsy is a group of neurological diseases characterized by recurrent short episodes of signs or symptoms due to abnormal excessive neuronal activity in the brain^{1,2}. It may vary from brief untraceable³ to long periods of vigorous shaking movements⁴ that may result in physical injuries⁵. It may also be associated with loss of sphincter (bowel or bladder) control or tongue bite^{6,7}. It is usually of idiopathic cause but may also result due to infection, trauma, drugs/toxins, inflammatory or space occupying lesions in the brain^{8,9}. Genetic mutations may also contribute to some extent¹⁰⁻¹². Epilepsy cannot be cured but it is managed efficiently most of the times^{13,14}. Its worldwide prevalence in 2013 was around 22 million¹⁵, with majority of the cases occurring in the developing countries⁶. In developing countries, it is associated with discriminatory attitude

of the society⁵ that ultimately affects social and psychological well-being of the patients⁴. It is reported that around 20–30% of the epileptic patients have psychiatric disturbances^{16,17}. Certain psychiatric disorders are more commonly observed in epileptic patients like depression, anxiety, obsessive compulsive disorder and migraine¹⁸⁻²¹.

Many recent epidemiological trials have reported a high prevalence of depression (9–37%) and anxiety (11–25%) in epileptic patients^{22,23}. These figures further exceeds in the treatment of refractory epilepsy such as temporal lobe epilepsy²⁴⁻²⁸. Suicide and suicidal behavior are more common among epileptic patients with co-morbid depression or anxiety²⁹⁻³². In Pakistan, a study reported 60% depression in such epileptic patients³³ while on the contrary another study reported only 13% depression³⁴. The prevalence of anxiety is

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also higher in epileptic patients than that of general population^{28,35}. Depression and anxiety may often be present simultaneously in epileptic patients³⁶⁻³⁸. The co-morbidity of depression and anxiety in epilepsy is considered to be bidirectional phenomenon because these share common pathophysiological conditions such as structural abnormalities, monoamine pathways³⁹⁻⁴¹, cerebral glucose metabolism⁴²⁻⁴⁴, hypothalamic-pituitary-adrenal axis⁴⁵, gabaaminobutyric acid suppression⁴⁶, amygdala hyperreactivity^{45,47,48}, antiepileptic drug related psychological disturbances⁴⁹⁻⁵³ and psychosocial factors⁵⁴. Depression and anxiety may have variable signs in the epileptic phase (preictal, ictal, interictal or postictal). Anxiety is commonly present in the form of fears and panic attacks^{55,56} while depression as disinterest, fatigue, and irritability⁵⁷. Depression and anxiety are often untreated in many epileptic patients in Pakistan due to negligence or unawareness⁵⁸. The amelioration of the symptoms of depression or anxiety is quite likely to reduce the symptoms of epilepsy⁵⁹. The International League Against Epilepsy (ILAE) has recommended to screen the epileptic population on regular basis for depression and anxiety. They have also suggested supportive counseling and therapy to both patient and family. Among drugs, antidepressants such as selective serotonin reuptake inhibitors (SSRI) are recommended for use. Drug interactions and psychiatric effects of antiepileptic drugs should also be considered before their administration⁶⁰.

The object of the present investigation is to determine the frequency of depression and anxiety among adult epileptic patients as these disorders are very likely to be present in such patients and are most likely to remain undiagnosed during the treatment. The presence of such co-morbidities complicates the prognosis by directly increasing the morbidity and mortality and indirectly compromising the economical and health resources of the person, family and society at large.

2. METHOD

2.1. Study Design

The study included adult epileptic patients who

visited the Outpatient Department of Neurology, Dr Ruth K. M. Pfau Civil Hospital Karachi, Pakistan during November 20, 2016 to May 28, 2017. A total of 171 patients were enrolled for the study during this period. An estimated prevalence of depression and anxiety in epileptic patients was considered as 20%⁶¹ with a confidence level of 95% (standard value of 1.96) and margin of error at 6%.

2.2. Selection Criteria

Both male and female patients of age between 18–60 years and diagnosed with epilepsy for at least 6 months were selected for the study. The selected patients were taking their medicines regularly for more than five months and have visited the OPD for follow up at least once every month. All selected patients were proficient in Urdu language and prior consent from each patient was taken before enrolling them to the study.

All those patients who had known history of medical disorders like diabetes mellitus, hypertension, and hypercholesterolemia; psychiatric disorders like schizophrenia, obsessive compulsive, and eating disorders; addiction of drugs like cannabis, alcohol, benzodiazepine, opioids, and stimulants; recent death in the family within a month's duration, or any other traumatic event like robbery, etc. were excluded from the study.

2.3. Patient's Assessment

All patients were interviewed and their demographic details including marital status, education, occupation, monthly income, etc. were taken. The depression was assessed by Hamilton Rating Scale for Depression (HRSD) and anxiety by Hamilton Anxiety Rating Scale (HAM-A). Both scales include a psychological questionnaire that is used by clinicians to rate the severity of depression and anxiety in patients.

The HRSD was a 17 question scale and each of them was scored on a 0 to 2 or 4 point scale, depending on the questions. A total score of 0–7 was considered to be normal while scores of 8–13 indicated mild depression, 14–18 moderate

depression, 19–22 severe depression, and ≥ 23 was considered to be very severe depression⁶².

In case of HAM-A, a 14 itemed questionnaire was used and each item was scored on 0 to 4 point scale for no anxiety to severe anxiety. The total score range was 0–56, where a score of 14–17 indicated mild anxiety, 18–24 moderate anxiety, and 25–30 pointed towards severe anxiety⁶³.

2.4. Statistical Analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 20.0. (IBM, New York, USA). The mean and standard deviation was calculated for age, duration of disease, and HRSD/HAM-A scores. While the frequency was calculated for gender, level of education, occupation, marital status, type of family (nuclear/joint), monthly

income (less than 10,000, 10,000–25,000, more than 25,000), depression and anxiety. Stratification with respect to age, gender, level of education, marital status, occupation, type of family, monthly income and duration of illness was also performed. Post stratification, Chi-square test was applied and p -value of ≤ 0.05 was considered as significant.

3. RESULTS

Among 171 patients, about 60% of the patients were females ($n=103$) with mean age of 38.05 ± 6.42 years and mean illness duration of 3.50 ± 5.3 years. Most of the patients were single 77 (45%) and unemployed 122 (71%) with majority either illiterate 53 (31%) or having only primary education 40 (23%). The details of the demographic data of the selected patients are reported in Table 1.

Table 1. Demographic data of epileptic patients ($n=171$)

Demographics		Frequency (n)	Percentage (%)
Gender	Male	68	39.8
	Female	103	60.2
Marital status	Married	59	34.5
	Single	77	45.0
	Widow	4	2.3
	Divorced	31	18.2
Education	Illiterate	53	31.0
	Primary	40	23.4
	Secondary	38	22.2
	Intermediate	27	15.8
	Graduate	11	6.4
	Postgraduate	2	1.2
Occupation	Self employed	29	17.0
	Govt. employed	20	11.7
	Unemployed	122	71.3
Type of family	Nuclear	103	60.3
	Joint	68	39.7
Monthly income	Less than 10,000	85	49.9
	10,000–25,000	53	30.9
	Great than 25,000	33	19.2

Depression has been observed in about 61% (105/171) of the patients (Table 2). Among the patients diagnosed for depression, females are found to be the predominant sufferer (58%) as compared to male epileptic patients (42%). Depression is high among singles (41%), illiterate (39%), and unemployed epileptic patients (73%). Only education and unemployment of epileptic patients against depression was found to be statistically significant ($p < 0.05$) (Table 2).

The frequency and severity of depressive disorder in epileptic patients according to their demographic details is reported in Table 3. In majority of the patients, the severity of depression has been found of moderate level (Table 3). On the other hand, anxiety has been noted in all 171 epileptic patients with vast majority having a moderate level of its severity (~48%). The frequency and severity of anxiety in epileptic patients according to their demographic details is reported in Table 4.

Table 2. Frequency of depressive disorder among epileptic patients

Demographic Details		Depressive Disorder				
		Yes (%) ^a	No (%) ^a	Total (%)	<i>p</i> value ^b	Chi square
Gender	Male	44 (41.9%)	24 (36.4%)	68 (39.7%)	0.275	1.190
	Female	61 (58.1%)	42 (63.6%)	103 (60.3%)		
Marital status	Married	30 (28.6%)	29 (44.0%)	59 (34.5%)	0.215	7.081
	Single	43 (40.9%)	34 (51.5%)	77 (45.0%)		
	Widowed	2 (1.9%)	2 (3.0%)	4 (2.3%)		
	Divorced	30 (28.6%)	1 (1.5%)	31 (18.1%)		
Education	Illiterate	41 (39.0%)	12 (18.2%)	53 (31.0%)	0.003	15.943
	Primary	30 (28.6%)	10 (15.1%)	40 (23.4%)		
	Secondary	20 (19.1%)	18 (27.3%)	38 (22.2%)		
	Intermediate	9 (8.6%)	18 (27.3%)	27 (15.8%)		
	Graduate	4 (3.8%)	7 (10.6%)	11 (6.4%)		
	Postgraduate	1 (0.9%)	1 (1.5%)	2 (1.2%)		
Occupation	Self employed	17 (16.2%)	12 (18.2%)	29 (17.0%)	0.0015	5.763
	Govt. employed	11 (10.5%)	9 (13.6%)	20 (11.7%)		
	Unemployed	77 (73.3%)	45 (68.2%)	122 (71.3%)		
Type of family	Joint	37 (35.2%)	31 (47.0%)	68 (39.8%)	0.197	1.663
	Nuclear	68 (64.8%)	35 (53.0%)	103 (60.2%)		

^a 105 epileptic patients out of 171 identified as depressive whereas no depression has been observed in the remaining 66 patients. The percentages of each column are calculated from the respective total.

^b p value < 0.005 was considered significant.

Table 3. Frequency and severity of depressive disorder in epileptic patients (n=105)

Demographic Details		Severity of Depression (%)				
		Mild	Moderate	Severe	Very Severe	Total
Gender	Male	15 (53.5%)	20 (42.5%)	8 (29.7%)	1 (33.3%)	44 (42%)
	Female	13 (46.5%)	27 (57.5%)	19 (70.3%)	2 (66.7%)	61 (58%)
Marital status	Married	9 (32.1%)	12 (25.5%)	7 (26%)	2 (66.7%)	30 (28.5%)
	Single	11 (39.2%)	15 (32%)	16 (59.2%)	1 (33.3%)	43 (41%)
	Widowed	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)	2 (1.9%)
	Divorced	8 (28.7%)	18 (38.3%)	4 (14.8%)	0 (0%)	30 (28.6%)
Education	Illiterate	12 (42.8%)	12 (25.5%)	15 (55.5%)	2 (66.7%)	41 (39%)
	Primary	4 (14.2%)	20 (42.5%)	6 (22.2%)	0 (0%)	30 (28.5%)
	Secondary	5 (17.8%)	11 (23.4%)	4 (14.9%)	0 (0%)	20 (19%)
	Intermediate	6 (21.4%)	2 (4.3%)	1 (3.7%)	0 (0%)	9 (8.5%)
	Graduate	1 (3.8%)	2 (4.3%)	1 (3.7%)	0 (0%)	4 (3.8%)
	Postgraduate	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)	1 (1.2)
Occupation	Self employed	7 (25%)	7 (14.9%)	2 (7.4%)	1 (33.3%)	17 (16.1%)
	Govt employed	5 (17.8%)	3 (6.4%)	3 (11.1%)	0 (0%)	11 (10.4%)
	Unemployed	16 (57.2%)	37 (78.7%)	22 (81.2%)	2 (66.7%)	77 (73.3%)
Type of family	Joint	10 (35.7%)	20 (42.5%)	7 (26%)	0 (0%)	37 (35.2%)
	Nuclear	18 (64.3%)	27 (57.5%)	20 (74%)	3 (100%)	68 (64.8%)

Table 4. Frequency and severity of anxiety in epileptic patients (n=171)

Demographic Details		Severity of Anxiety (%)				
		Mild	Moderate	Severe	Very Severe	Total
Gender	Male	25 (52%)	29 (35%)	14 (35%)	68 (42%)	25 (52%)
	Female	23 (48%)	54 (65%)	26 (65%)	103 (58%)	23 (48%)
Marital status	Married	15 (31.2%)	31 (37.3%)	13 (32.5%)	59 (34.5%)	15 (31.2%)
	Single	23 (48%)	33 (39.7%)	21 (52.5%)	77 (45%)	23 (48%)
	Widowed	0 (0%)	4 (4.8%)	0 (0%)	4 (2.3%)	0 (0%)
	Divorced	10 (20.8%)	15 (18.2%)	6 (15%)	31 (18.2%)	10 (20.8%)
Education	Illiterate	13 (27%)	19 (22.9%)	21 (52.5%)	53 (31%)	13 (27%)
	Primary	5 (10.4%)	25 (30.1%)	10 (25%)	40 (23.3%)	5 (10.4%)
	Secondary	12 (25%)	21 (25.3%)	5 (12.5%)	38 (22.2%)	12 (25%)
	Intermediate	13 (27.1%)	13 (15.7%)	1 (2.5%)	27 (15.8%)	13 (27.1%)
	Graduate	4 (8.3%)	5 (6 %)	2 (5%)	11 (6.4%)	4 (8.3%)
	Postgraduate	1 (2.2%)	0 (0%)	1 (2.5%)	2 (1.3)	1 (2.2%)
Occupation	Self employed	11 (23%)	16 (19.2%)	2 (5%)	29 (17%)	11 (23%)
	Govt employed	11 (23%)	4 (4.8%)	5 (12.5%)	20 (11.7%)	11 (23%)
	Unemployed	26 (54%)	63 (76%)	33 (82.5%)	122 (71.3%)	26 (54%)
Type of family	Joint	25 (52%)	66 (79.5%)	12 (30%)	103 (58%)	25 (52%)
	Nuclear	23 (48%)	17 (20.5%)	28 (70%)	68 (42%)	23 (48%)

4. DISCUSSION

Epilepsy is a worldwide distressing neurological disorder that is often considered displeasing in developing countries like Pakistan. The estimated frequency of epilepsy in Pakistan is about 9.99 per 1000 people³³. There is no particular gender bias known for occurrence of epilepsy, however, Usman et al.³⁴ reported a higher prevalence of epilepsy in Pakistani males as compared to females. Similar gender findings were also noted in another study⁶⁴. On the contrary, in this study epilepsy has been found to be more prevalent in females as compared to males (Table 2), which might be due to large female sample size (Table 1).

Development of either depression or anxiety or both is very common among epileptic patients^{65,66} as they experience depression twice more commonly than non-epileptics with an incidence of suicide and self-harm five-times higher than the general population⁶⁷. This study has diagnosed about 61% of the epileptic patients with depression (Table 2). A lifetime prevalence of depression between 6–30% has been reported in a population-based study with up to 55% among patients followed in tertiary centers⁶⁸. The findings of this study are in agreement with another study that was also conducted in Pakistan, which has reported 60% prevalence of depression among epileptic patients³³. Such high percentage of depression in epileptic patients can be attributed to many risk factors including seizure control, type, and severity of epilepsy, etc⁶⁹⁻⁷¹. Moreover, in low income countries like Pakistan social stigma, fear, and lifelong adjustment issues are also major factors^{33,68}. Furthermore, lack of basic psychiatric services and facilities in developing countries like Pakistan, account for an additional factor of such high prevalence⁷².

The results of this study further indicated that all the epileptic patients are also suffering from anxiety with majority of them being diagnosed with its moderate form (Table 4). This finding is consistent with a high prevalence of anxiety reported earlier⁶⁸. The study revealed that unmarried or single patients are more depressed (Table 2) and have high prevalence of moderate type of depression (Table 3) and anxiety (Table 4) as compared to married

patients. These findings are in agreement with the findings of Khalid et al.⁶⁸ who also reported a high prevalence of depression and anxiety among unmarried patients. This could be because of the reason that most people in Pakistan, especially in rural areas, consider epilepsy as insanity and, therefore, do not marry. This could be one reason that there is remarkable psychosocial stress among females in Pakistan^{72,73}.

Education and unemployment are also found to be statistically significant risk factors for depression among epileptic patients in this study (Table 2). The poor and low socioeconomic background of epileptic patients could be a major reason for developing depression and anxiety. This factor is in agreement with the observations of other studies where more depression and anxiety was found among epileptic patients belonging to lower socioeconomic status^{34,68}. Along with poor or low socioeconomic status, lack of education may prevent epileptics from recognizing symptoms of depression and anxiety leading to under diagnosis by physicians.

This study has addressed a very important and quite underestimated issue in the Pakistani society. Efforts have been made to create awareness among epileptic patients regarding their own wellbeing by making them identify and accept their co-morbid depression and anxiety. This study makes strong and basic recommendations for proper diagnosis and recognition of these co-morbid conditions by physicians while treating their epileptic patients. Proper public health interventions and awareness campaigns among epileptic patients may also in turn help to diagnose these co-morbid conditions and facilitate initiation of proper treatment for such patients. The sample size of this study was quite small and collected from one specific site only, male and female disproportion has also limited the study findings to be generalized and overestimated the findings in females.

5. CONCLUSION

In Pakistan, limited community-based mental health facilities and low socio-economic condition make it difficult for epileptic patients to understand and

recognize co-morbid psychiatric conditions like depression and anxiety. This study has revealed a high prevalence of depression and anxiety among epileptic patients associated with multiple factors like low education, unemployment and unmarried status. To overcome these conditions, physicians especially neurologists should recognize and identify the signs and symptoms of psychiatric co-morbidities during routine follow up. Health policies should be implemented in the medical setups to work along with epileptic patients during their long term treatment in terms of arranging support groups, awareness and educational seminars and psychotherapy. Overall quality of life of an epileptic patient can be improved with better compliance to treatment and psychological wellbeing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

The study was approved by the Ethical Review Committee of Department of Psychiatry and Behavioral Sciences, Dow Medical College and Dr. Ruth K. M. Pfau Civil Hospital, Karachi.

REFERENCES

1. Chang BS, Lowenstein DH. Epilepsy. *N Engl J Med*. 2003;349:1257-1266.
2. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55:475-482.
3. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet*. 2006;367:1087-1100.
4. Devlin AL, Odell M, L Charlton JL, Koppel S. Epilepsy and driving: current status of research. *Epilepsy Res*. 2012;102:135-152.
5. World Health Organization. Epilepsy. Available at <http://www.who.int/mediacentre/factsheets/fs999/en/> (Last accessed on July 2018).
6. Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL. *Bradley's Neurology in Clinical Practice*, 7th ed., Elsevier Inc., 2016.
7. National Clinical Guideline Centre. *The Epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care*. National Clinical Guideline Centre, London, UK, 2011. Available at www.nice.org.uk.
8. Berkovic SF, Mulley JC, Scheffer IE, Petrou S. Human epilepsies: interaction of genetic and acquired factors. *Trends Neurosci*. 2006;29:391-397.
9. Bhalla D, Godet B, Druet-Cabanac M, Preux PM. Etiologies of epilepsy: a comprehensive review. *Expert Rev Neurother*. 2011;11:861-876.
10. Hammer GD, McPhee SJ. *Pathophysiology of Disease – An Introduction to Clinical Medicine*, 7th ed., The McGraw-Hill Companies, Inc., New York, USA, 2014.
11. Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. *Nat Rev Neurosci*. 2013;14:337-349.
12. Pandolfo M. Genetics of epilepsy. *Semin Neurol*. 2011;31:506-518.
13. Eadie MJ. Shortcomings in the current treatment of epilepsy. *Expert Rev Neurother*. 2012;12:1419-1427.
14. Epilepsy Foundation North West. *Seizure types*. Available at <https://www.epilepsynw.org/about-epilepsy/seizure-types> (Last accessed on July 2018).
15. Mula M, Sander JW. Suicide risk in people with epilepsy taking antiepileptic drugs. *Bipolar disord*. 2013;15:622-627.
16. Vuilleumier P, Jallon P. Epilepsy and psychiatric disorders: epidemiological data. *Rev Neurol*. 1998;154:305-317.
17. Tucker GJ. Seizure disorders presenting with psychiatric symptomatology. *Psychiatr Clin North Am*. 1998;21:625-635.
18. Wheless JW, Willmore LJ, Brumback RA.

- Advanced Therapy in Epilepsy, People's Medical Publishing House, Shelton, USA, 2009.
19. Larner AJ. A Dictionary of Neurological Signs, Springer-Verlag, New York, USA, 2011.
 20. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia*. 2007;48:2336-2344.
 21. Jobe PC. Common pathogenic mechanisms between depression and epilepsy: an experimental perspective. *Epilepsy Behav*. 2003;4:S14-S24.
 22. Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. The clinical course of epilepsy and its psychosocial correlates: findings from a UK community study. *Epilepsia*. 1996;37:148-161.
 23. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:617-627.
 24. O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. *Br J Gen Pract*. 1999;49:211-214.
 25. Kwon OY, Park SP. Frequency of affective symptoms and their psychosocial impact in Korean people with epilepsy: a survey at two tertiary care hospitals. *Epilepsy Behav*. 2013;26:51-56.
 26. Manchanda R, Schaefer B, McLachlan RS, Blume WT, Wiebe S, Girvin JP, Parrent A, Derry PA. Psychiatric disorders in candidates for surgery for epilepsy. *J Neurol Neurosurg Psychiatry*. 1996;61:82-89.
 27. Kobau R, Gilliam F, Thurman DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 Health Styles Survey. *Epilepsia*. 2006;47:1915-1921.
 28. Edeh J, Toone B. Relationship between interictal psychopathology and the type of epilepsy. Results of a survey in general practice. *Br J Psychiatry*. 1987;151:95-101.
 29. Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy Behav*. 2003;4: S31-S38.
 30. Lim HW, Song HS, Hwang YH, Lee HW, Suh CK, Park SP, Kwon SH. Predictors of suicidal ideation in people with epilepsy living in Korea. *J Clin Neurol*. 2010;6:81-88.
 31. Jacoby A. Felt versus enacted stigma: a concept revisited. Evidence from a study of people with epilepsy in remission. *Soc Sci Med*. 1994;38: 269-274.
 32. Taylor J, Baker GA, Jacoby A. Levels of epilepsy stigma in an incident population and associated factors. *Epilepsy Behav*. 2011;21:255-260.
 33. Yousafzai AR, Yousafzai AW, Taj R. Frequency of depression in epilepsy: a hospital based study. *J Ayub Med Coll Abbottabad*. 2009;21:73-75.
 34. Usman S, Chaudhry HR, Asif A, Yousaf A, Jahangir SF, Gul H, Butt MG, Akhtar M. Demographic profile of patients with epilepsy in a community clinic. *Pak J Med Sci*. 2007;23:873-876.
 35. Kanner AM. Depression and epilepsy: a new perspective on two closely related disorders. *Epilepsy Curr*. 2006;6:141-146.
 36. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J Abnorm Psychol*. 1991;100:316-336.
 37. Olino TM, Klein DN, Lewinsohn PM, Rohde P, Seeley JR. Longitudinal associations between depressive and anxiety disorders: a comparison of two trait models. *Psychol Med*. 2008;38: 353-363.
 38. Jones JE, Herman BP, Berry JJ, Gilliam F, Kanner AM, Meador KJ. Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation. *J Neuropsychiatry Clin Neurosci*. 2005;17:172-179.
 39. Toczek MT, Carson RE, Lang L, Ma Y, Spanaki MV, Der MG, Fazilat S, Kopylev L, Herscovitch P, Eckelman WC, Theodore WH. PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. *Neurology*. 2003;60: 749-756.

40. Savic I, Lindstrom P, Gulyas B, Halldin C, Andree B, Farde L. Limbic reductions of 5-HT1A receptor binding in human temporal lobe epilepsy. *Neurology*. 2004;62:1343-1351.
41. Merlet I, Ostrowsky K, Costes N, Ryvlin P, Isnard J, Faillenot I, Lavenne F, Dufournel D, Le Bars D, Mauguière F. 5-HT1A receptor binding and intracerebral activity in temporal lobe epilepsy: an [18F]MPPF-PET study. *Brain*. 2004;127:900-913.
42. Bromfield EB, Altshuler L, Leiderman DB, Balish M, Ketter TA, Devinsky O, Post RM, Theodore WH. Cerebral metabolism and depression in patients with complex partial seizures. *Arch Neurol*. 1992;49:617-623.
43. Victoroff JJ, Benson F, Grafton ST, Engel J, Jr, Mazziotta JC. Depression in complex partial seizures. *Electroencephalography and cerebral metabolic correlates*. *Arch Neurol*. 1994;51:155-163.
44. Salzberg M, Taher T, Davie M, Carne R, Hicks RJ, Cook M, Murphy M, Vinton A, O'Brien TJ. Depression in temporal lobe epilepsy surgery patients: an FDG-PET study. *Epilepsia*. 2006;47:2125-2130.
45. Mazarati AM, Shin D, Kwon YS, Bragin A, Pineda E, Tio D, Taylor A, Sankar R. Elevated plasma corticosterone level and depressive behavior in experimental temporal lobe epilepsy. *Neurobiol Dis*. 2009;34:457-461.
46. Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. *J Clin Psychopharmacol*. 2007;27:263-272.
47. Stahl SM. Brainstorms: symptoms and circuits, part 2: anxiety disorders. *J Clin Psychiatry*. 2003;64:1408-1409.
48. Rogawski MA, Loscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nat Med*. 2004;10:685-692.
49. Kanner AM, Barry JJ, Gilliam F, Hermann B, Meador KJ. Depressive and anxiety disorders in epilepsy: do they differ in their potential to worsen common antiepileptic drug-related adverse events? *Epilepsia*. 2012;53:1104-1108.
50. Park SP. Depression in patients with newly diagnosed epilepsy predicts lamotrigine-induced rash: a short-term observational study. *Epilepsy Behav*. 2013;28:88-90.
51. Liik M, Vahter L, Gross-Paju K, Haldre S. Subjective complaints compared to the results of neuropsychological assessment in patients with epilepsy: The influence of comorbid depression. *Epilepsy Res*. 2009;84:194-200.
52. Marino SE, Meador KJ, Loring DW, Okun MS, Fernandez HH, Fessler AJ, Kustra RP, Miller JM, Ray PG, Roy A, Schoenberg MR, Vahle VJ, Werz MA. Subjective perception of cognition is related to mood and not performance. *Epilepsy Behav*. 2009;14:459-464.
53. Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? *Neurology*. 2002;58:S27-S39.
54. Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Ann Neurol*. 1982;12:129-144.
55. Devinsky O. A 48-year-old man with temporal lobe epilepsy and psychiatric illness. *JAMA*. 2003;290:381-392.
56. Kanner AM, Kozak AM, Frey M. The use of sertraline in patients with epilepsy: is it safe? *Epilepsy Behav*. 2000;1:100-105.
57. Aziz H, Akhtar SW, Hasan KZ. Depression and epilepsy: how closely related are they? *Neurology*. 2002;58:S27-S39.
58. Zung WW, Magruder-Habib K, Velez R, Alling W. The comorbidity of anxiety and depression in general medical patients: a longitudinal study. *J Clin Psychiatry*. 1990;51:77-80.
59. Kerr MP, Mensah S, Besag F, de Toffol B, Ettinger A, Kanemoto K, Kanner A, Kemp S, Krishnamoorthy E, LaFrance WC Jr, Mula M, Schmitz B, van Elst LT, Trollor J, Wilson SJ; International League of Epilepsy (ILAE) Commission on the Neuropsychiatric Aspects of Epilepsy. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia*. 2011;52:2133-2138.
60. Phabphal K, Sattawatcharawanich S,

- Sathirapunya P, Limapichart K. Anxiety and depression in Thai epileptic patients. *J Med Assoc Thai*. 2007;90:2010-2015.
61. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1989;45:742-747.
 62. Clark DB, Donovan JE. Reliability and validity of the Hamilton Anxiety Rating Scale in an adolescent sample. *J Am Acad Child Adolesc Psychiatry*. 1994;33:354-360.
 63. Sander JWAS. Some aspects of prognosis in the epilepsies: a review. *Epilepsia*. 1993;34:1007-1016.
 64. Ventola CL. Epilepsy management: newer agents, unmet needs, and future treatment strategies. *P T*. 2014;39:776-792.
 65. Kanner AM, Nieto JC. Depressive disorder in epilepsy. *Neurology*. 1999;53:S26-S32.
 66. Goldstein LH. Effectiveness of psychological interventions for people with poorly controlled epilepsy. *J Neurol Neurosurg Psychiatry*. 1997;63:137-142.
 67. Mendez MF, Doss RC, Taylor JL, Salguero P. Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. *J Nerv Ment Dis*. 1993;181:444-447.
 68. Khalid A, Aslam N. Psychological distress among patients with epilepsy. *Indian J Psychol Med*. 2011;33:45-48.
 69. Malingo L, Marasco C, Fiorilli ACM, Guarneri M, Maj M. The impact of professional and social network support on the burden of families of patients with schizophrenia in Italy. *Acta Psychiatr Scand*. 2002;106:291-298.
 70. Hawton K, Fagg J, Marsack P. Association between epilepsy and attempted suicide. *J Neurol Neurosurg Psychiatry*. 1980;43:168-170.
 71. Thompson PI, Oxley J. Socioeconomic accompaniment of severe epilepsy. *Epilepsia*. 1988;29:S9-S18.
 72. Taj R, Hameed S, Mufti M, Khan A, Rahman G. Depression among primary caregivers of Schizophrenic patients. *Ann Pak Ins Med Sci*. 2005;1:101-104.
 73. Basher S, Niazi RS, Minhas FA, Ali W, Najam N. Depression and anxiety in the caregivers of mentally ill patients. *J Pak Psychiatr Soc*. 2005;2:27-33.