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Depressive Symptoms in Epilepsy

Prevalence, Impact, Aetiology, Biological Correlates and Effect of Treatment with Antiepileptic Drugs

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Contents

Abstract

Occurring in up to 80% of patients with epilepsy, depression in epilepsy may manifest as (i) major depressive disorder, meeting Diagnostic and Statistical Manual, 4th edition (DSM-IV) diagnostic criteria; (ii) atypical depression or dysthymia; or (iii) a dysthymic-like disorder with intermittent symptoms that can be milder than those of major depression. Depressive symptoms impair patients' health-related quality of life and may affect the clinical course of epilepsy. Depressive symptoms in epilepsy have been attributed to several causes, including endocrine and/or metabolic effects of seizures; the psychological response to epilepsy and its associated mental, physical and social challenges; common pathogenic mechanisms between depression and epilepsy; and the adverse effects of certain antiepileptic drugs (AEDs), particularly GABAergic agents, such as vigabatrin, tiagabine, topiramate and phenobarbital. Whereas some AEDs impair mood, others appear to improve aspects of mood or are mood neutral. Demonstrable antidepressant efficacy of AEDs used to manage seizures could have a significant impact on the care of patients with epilepsy. The AED lamotrigine has been demonstrated to be effective in the treatment of depressive symptoms in patients with epilepsy. In randomized, double-blind, clinical trials in patients with

epilepsy, depressive symptoms improved more with lamotrigine monotherapy than valproate monotherapy and more with lamotrigine adjunctive therapy than placebo. Results of open-label studies of lamotrigine monotherapy and adjunctive therapy are consistent with the results of double-blind clinical trials. Lamotrigine-associated improvement in depressive symptoms is independent of its anticonvulsant efficacy. In prospective assessments, gabapentin, levetiracetam and oxcarbazepine each exhibited potentially beneficial effects on depressive symptoms in patients with epilepsy. However, evidence for the efficacy of gabapentin, levetiracetam and oxcarbazepine in the treatment of depressive symptoms in epilepsy is inconclusive at present because the effects of each agent have only been reported in single studies of an open-label design and with small sample sizes.

1. Depressive Symptoms in Epilepsy

The frequency of depression in patients with epilepsy is higher than that in the general population, matched samples of healthy control individuals or patients with other chronic conditions.[1-4] Depressive symptoms in epilepsy impair patients' health-related quality of life (QOL) and may affect the clinical course of epilepsy. Because the choice of antiepileptic drugs (AEDs) can significantly affect mood, the psychotropic properties of AEDs are an important consideration in the choice of therapy. Some AEDs appear to cause or aggravate depression, some appear to be mood neutral and others appear to improve aspects of mood.[5] The demonstration that AEDs used to manage seizures are also effective at alleviating depressive symptoms could significantly impact the care of patients with epilepsy. The AED lamotrigine appears to improve depressive symptoms in epilepsy. Positive effects of lamotrigine on mood were observed initially in early epilepsy clinical trials in which lamotrigine was anecdotally noted to improve patients' mood, social interaction and well-being. These early observations were corroborated by the demonstration of improvement in health-related QOL with lamotrigine monotherapy or adjunctive therapy in patients with epilepsy compared with pretreatment baseline, placebo treatment and treatment with other AEDs,[6-11] as well as demonstration of the antidepressant efficacy of lamotrigine monotherapy or adjunctive therapy in randomized, double-blind, controlled clinical trials.[12,13] The present article discusses the manifestations, impact, possible aetiologies and current treatment of epilepsy-associated depressive symptoms, and reviews data on the efficacy of AEDs for depressive symptoms in epilepsy.

2. Clinical Manifestations

Depressive symptoms are categorized according to their relationship with seizures as being ictal (depressive symptoms are a manifestation of a seizure), peri-ictal (depressive symptoms are an aspect of the seizure prodrome and/or occur after the seizure) or interictal (depressive symptoms occur independently of seizures).[3] Interictal depression is the most common form of depression in epilepsy; peri-ictal and ictal depression appear to occur infrequently.[3]

Depressive symptoms in epilepsy can manifest as major depressive disorder, atypical depression or dysthymia, or a dysthymic-like disorder with intermittent symptoms that can be milder than those characterizing major depression.[3,14,15] Studies suggest that between one-quarter and one-half of patients with depressive symptoms in epilepsy have depression not meeting diagnostic criteria for major depression.[14-16] The frequent presence in epilepsy of depressive symptoms that may be milder and more intermittent than those of major depressive disorder could contribute to the under-recognition of depression in epilepsy.[2] On the basis of the evaluation of mood symptoms in patients with epilepsy, Blumer and colleagues[16] proposed the existence of 'interictal dysphoric disorder', an epilepsy-specific

mood disorder characterized by intermittent depression with a chronic course and associated with irritability, anhedonia, hopelessness, fear and anxiety. Other research refutes the idea of an epilepsy-specific mood disorder and suggests that depressive symptoms in epilepsy are similar to those measured in populations without epilepsy.[17] Overall, the data suggest that the constellation of depressive symptoms in patients with epilepsy overlaps that of patients with major depression, although specific features (e.g. anhedonia without sadness) may be more prominent or likely in depression in epilepsy.

3. Prevalence

Estimates of the prevalence of depressive symptoms in epilepsy vary widely among studies, ranging from approximately 6% to 80%, and depend on the means of defining depressive symptoms (e.g. depressive symptomatology, illness meeting diagnostic criteria for major depression), the means of assessing depressive symptoms (e.g. questionnaire, self-report, clinical interview), and the nature and characteristics of study samples (e.g. community or population based, clinic based, hospital based). Between-study variations in prevalence rates notwithstanding, the data consistently show a higher incidence of depressive symptoms in patients with epilepsy than in the general population, matched samples of healthy control individuals or patients with other chronic conditions.[1-4] Compared with the general population, patients with epilepsy may be four to five times more likely to experience depression.[2] An elevated frequency of depression in epilepsy has been found across age groups, including in children, adolescents, adults and the elderly, and across studies using various means of defining and assessing depression.[3,18-22] Depression is exceedingly common in epilepsy, even in studies defining depression as full syndromal illness and using rigorous methods to assess its presence. For example, the point-to-6-month prevalence of major depression in adults with epilepsy was nearly 4-fold greater that in the general population in a 2006 report of seven studies that used internationally accepted diagnostic criteria for major depressive disorder, validated diagnostic structured interviews to assess for depression and samples not originating from psychiatric settings.[22]

4. Consequences

Depressive symptoms in epilepsy have far-reaching consequences, including impairment of patients' health-related QOL, high rates of healthcare resource utilization and elevated rates of suicide. Depressive symptoms also appear to impact on the clinical course of epilepsy.

Patients with epilepsy and depressive symptoms are at high risk of poor perceived health status, as measured by standardized QOL instruments.[23-25] In a survey of 501 patients with epilepsy, QOL in patients with depressive symptoms was impaired relative to patients without depressive symptoms, regardless of seizure type.[23] Patients with co-morbid mild/moderate depression or severe depression based on Center for Epidemiology Studies-Depression Scale (CES-D)[26] scores had poorer QOL, as measured by the Quality of Life in Epilepsy Inventory-89 (QOLIE-89),[25] compared with non-depressed patients. The magnitude of the impairment in QOL was directly related to the severity of the depression.

Depressive symptoms more strongly predict QOL than seizures in patients with active epilepsy.[27-31] For example, among 87 patients with temporal lobe epilepsy, the effect of depression on health-related QOL exceeded, and was independent of, the effect of frequent, severe and chronic seizures.[30] Similarly, among 122 patients with refractory epilepsy, depression, which was present in 54% of patients, strongly predicted QOL impairment, whereas there was no correlation between QOL and seizure frequency.[29] In a study of 257 patients with epilepsy at 25 US clinics, scores on mood inventories were stronger predictors of health-related QOL measured with QOLIE-89 than were scores on tests of memory, verbal ability, spatial function, psychomotor and cognitive processing speed, or cognitive flexibility.[27] In patients with epilepsy screened at the Washington University outpatient epilepsy clinics (St Louis, MO, USA), QOL mea-

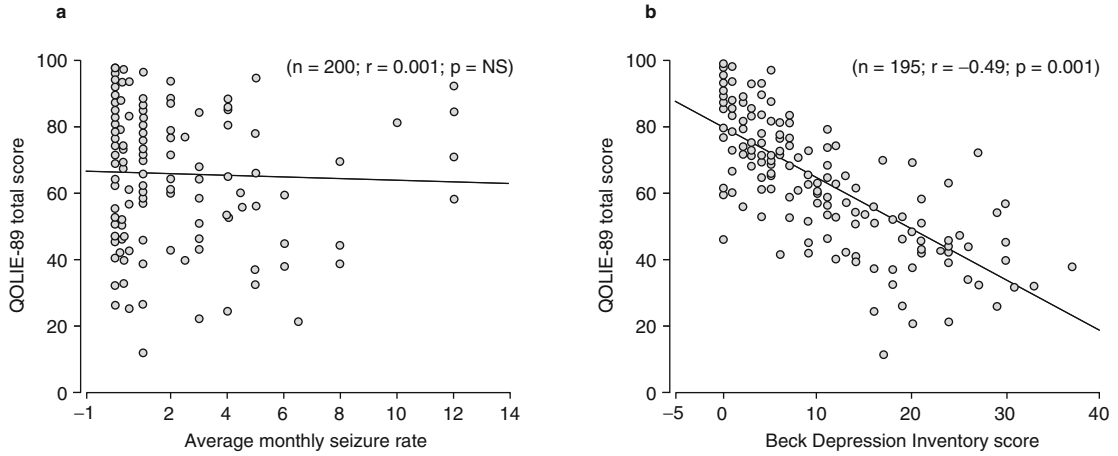

Fig. 1. Depressive symptoms more strongly predict quality of life than seizures. Quality of life versus (**a**) seizures and (**b**) depressive symptoms (reproduced from Gilliam,[28] with permission). **NS** = not significant; **QOLIE-89** = Quality of Life in Epilepsy Inventory-89.

sured with QOLIE-89 was significantly predicted by the Beck Depression Inventory (BDI)[32] score, but not by average monthly seizure rate (figure 1).[28]

Depressive symptoms may affect the clinical course of epilepsy. In a nationwide community-based sample in the US, patients with epilepsy and clinical depression, as measured on the CES-D, reported greater severity of, and bother from, seizures and more problems with recovery from seizures than non-depressed respondents reporting similar seizure types.[23] Patients with epilepsy and severe depression reported more difficulty with cognitive, emotional and physical aspects of seizure recovery, rated in terms of frequency, severity and bothersomeness, than patients with epilepsy and no depression.

Depression in epilepsy is associated with higher health resource utilization than epilepsy without concurrent depressive symptoms. In a US community-based sample of people with epilepsy, compared with patients with no depression, the frequency of visits to medical doctors was 2-fold higher among patients with mild/moderate depression and 4-fold higher among patients with severe depression.[10] Patients with epilepsy and severe depression reported more psychiatric visits, emergency care visits and days in hospital than patients with mild or no depression. Results did not differ after data were adjusted for seizure type, seizure recency or the number of days with epilepsy symptoms.

Depression in epilepsy is associated with a high rate of suicide. Although the incidence of suicide in epilepsy varies from study to study, data consistently show a higher risk of suicide in patients with epilepsy than in the general population.[1,33,34] In a review of 17 studies, the average incidence of suicide was 9- to 10-fold higher in patients with epilepsy (13.2%) than the general population (1.4%).[35] The risk of suicide appears to be particularly high in patients with temporal lobe epilepsy, who have been reported to be at up to 25-fold higher risk of suicide than patients in the general population.[1,36] A possible link between the use of certain AEDs and suicide has been suggested.[37] The US FDA recently asked manufacturers of AEDs to examine their databases from controlled clinical trials for evidence of suicidality in order to determine whether AEDs, individually or as a class, are linked to a heightened risk of suicide.[38,39]

5. Aetiology

Depressive symptoms in epilepsy have been attributed to several causes, including (i) endocrine and/or metabolic effects of seizures; (ii) the psychological response to epilepsy and its associated mental, physical and social challenges; (iii) common pathogenic mechanisms between depression and epilepsy; and (iv) the adverse effects of certain AEDs,

particularly GABAergic drugs, such as vigabatrin, tiagabine, topiramate and phenobarbital (discussed further in section 9).[1,4,40] These factors are not mutually exclusive and one or more may operate to varying extents depending on the individual. In clinical studies, depressive symptoms in epilepsy have been associated with variables such as recent seizures,[41] patients' perception of poor seizure control,[42] duration of epilepsy,[43] having complex partial seizures,[44] having temporal lobe epilepsy,[45] unemployment[41,44] and antiepileptic polytherapy.[46]

Although epilepsy-associated depressive symptoms can be secondary to epilepsy, several lines of evidence refute the idea that depressive symptoms are primarily epiphenomena of seizures or a psychological response to having epilepsy. The elevated incidence of depression among patients with epilepsy relative to those with other chronic, impactful conditions is consistent with the possibility that depression in epilepsy is not simply a consequence of having a chronic disorder.[47,48] The fact that depression is not always secondary to epilepsy or seizures is supported by the observations that the onset of depression can predate the onset of epilepsy[49,50] and that seizure intractability does not predict the presence of depressive symptoms.[51] However, associations between seizure recency and/or severity and depressive symptoms have been demonstrated in some studies.[41]

6. Biological Correlates

The high prevalence of depressive symptoms in epilepsy may be attributed to a common pathogenic mechanism underlying the two disorders. Common biological substrates that may explain the co-occurrence of depressive symptoms and epilepsy include reduced noradrenergic and/or serotonergic function, temporal lobe abnormalities and frontal lobe abnormalities.

Reduced functioning of the serotonergic and noradrenergic systems plays an important role in depression and the putative mechanism of action of many antidepressants is enhancement of noradrenergic and/or serotonergic neurotransmission.[52] Reduced serotonergic and noradrenergic function also facilitates kindling of seizures, increases the severity of seizures and reduces seizure threshold in animal models of epilepsy.[3,53,54] These observations are consistent with the possibility that monoaminergic abnormalities contribute to both depressive symptoms and epilepsy in patients with the co-morbid disorders.

Temporal limbic structures, such as the hippocampus and amygdala, are important in regulating both mood and seizure activity.[55,56] The particularly high prevalence of depression among patients with temporal lobe epilepsy,[57] which affects these limbic structures, is consistent with a potential role of these structures in both seizures and depressive symptoms in patients with the co-morbid disorders. Such a role is also supported by the finding that the severity of depression in patients with epilepsy is correlated with the extent of abnormalities in temporal limbic structures, including the hippocampus, in neuroimaging studies.[58,59] Recent data are consistent with important roles for both the amygdala and the hippocampus in depression associated with temporal lobe epilepsy.[58,60,61]

Patients with temporal lobe epilepsy, including those with co-morbid depression, also manifest frontal lobe dysfunction in neuroimaging studies and perform poorly on frontal lobe-mediated tasks.[54,62-66] Frontal lobe dysfunction is also present in patients with major depression with no co-morbid epilepsy.[67] Frontal lobe hypometabolism in patients with depression associated with epilepsy, as well as in those with primary depression, is consistent with the possibility that similar frontal lobe metabolic disturbances could contribute to depressive symptoms and epilepsy in patients with the co-morbid conditions.

7. Current Treatment

Their high prevalence notwithstanding, depressive symptoms in epilepsy are undertreated. In a sample of 70 consecutive patients with temporal lobe epilepsy, one-third (34%) had significant depression, as assessed by standardized psychiatric interviews, but none of the patients were receiving

antidepressant therapy.[68] In another study of 32 adult epilepsy patients with a history of chronic depression, 82% were experiencing major or minor depressive episodes at the time of the study but were not receiving treatment for depression.[15] Similarly low rates of antidepressant use in patients with epilepsy and co-morbid depression have been documented in other studies.[69,70] Factors potentially explaining the undertreatment of depressive symptoms in epilepsy include failure to recognize depression and/or to understand its impact, concern about antidepressant-associated exacerbation of seizures, concern about drug interactions and the lack of an evidence base to support prescribing decisions.[4,71]

The efficacy and safety of conventional antidepressants for depressive symptoms in epilepsy have been demonstrated in only a handful of studies.[72-75] Selective serotonin reuptake inhibitors have been demonstrated to be effective in the treatment of depressive symptoms in epilepsy.[73,75] Although tricyclic antidepressants may also be effective, they decrease seizure threshold and potentially exacerbate seizures in patients with epilepsy.[76] In addition, drug interactions are a concern given that most antidepressants are metabolized by the liver. Metabolism of enzyme-inducing AEDs, including phenytoin, carbamazepine, phenobarbital and primidone, can increase the metabolism of antidepressants that undergo hepatic metabolism.[3,77] Moreover, several antidepressants inhibit cytochrome P450 enzymes and could influence the metabolism of AEDs.

8. Efficacy of Antiepileptic Drugs (AEDs) for Depressive Symptoms in Epilepsy

Although AEDs are not currently primary treatments for the management of depressive symptoms in epilepsy, several AEDs appear to affect mood and could have potential in this regard.[4,5] The demonstration that an AED used to manage seizures is also effective in alleviating depressive symptoms could significantly impact on the care of patients with epilepsy and co-morbid depressive symptoms. In this section, evidence regarding the effects of AEDs on depressive symptoms in patients with epilepsy is reviewed. Data were identified from searches of MEDLINE using PubMed with no date limits. Two sets of searches, one having an AED name and 'depression' as keywords, and another having an AED name and 'mood' as keywords, were conducted. AED names included carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate and zonisamide. Congress abstracts or presentations not published as full papers were not included as reference sources. The literature searches revealed that, although the antidepressant effects of virtually all AEDs have been investigated in bipolar disorder and/or major depressive disorder, prospective assessments of the efficacy of AEDs for depressive symptoms in patients with epilepsy have been documented only for gabapentin, lamotrigine, levetiracetam and oxcarbazepine.

8.1 Gabapentin

The efficacy of gabapentin for depressive symptoms in patients with epilepsy was investigated in a prospective, nonrandomized, open-label study.[78] Adults with partial seizures taking stable doses of one to four AEDs were given adjunctive gabapentin (n = 20) or no adjunctive therapy (n = 20) after they completed baseline mood scales. On follow-up assessments approximately 3 months later, improvement in scores on the Cornell Dysthmia Rating Scale (CDRS) were significantly greater in patients treated with gabapentin than in patients not treated with adjunctive gabapentin ($p = 0.04$). However, the groups did not differ with respect to change from baseline in scores on the BDI or the Hamilton Scale for Depression (HAM-D). Seizure frequency during the study period did not differ between patients treated with adjunctive gabapentin and those not treated with adjunctive gabapentin. The average gabapentin dosage at follow-up was 1615 mg/day.

8.2 Lamotrigine

The efficacy of lamotrigine for depressive symptoms in patients with epilepsy was assessed in both double-blind controlled and open-label studies.

Table I summarizes the characteristics and results of these studies.[12,13,79-82]

Standard mood assessments, including the BDI 2nd edition (BDI-II),[83] the Profile of Mood States (POMS)[84] and the CDRS-Self Report (CDRS-SR),[85,86] were incorporated as prospective secondary measures in a randomized double-blind clinical trial designed primarily to compare the effects of lamotrigine monotherapy with valproate monotherapy on bodyweight (table I).[12] The study enrolled patients aged ≥12 years who were newly diagnosed with epilepsy and experiencing any seizure type classifiable by the International Classification of Seizures.[87] The study comprised a 2-week screening phase, an 8-week dose-escalation phase and a 24-week maintenance phase. Lamotrigine or valproate was administered in double-dummy fashion during the dose-escalation and maintenance phases. Target dosages for the maintenance phase were 200 mg/day for lamotrigine (range 100–500 mg/day depending on clinical response) and 20 mg/kg/day for valproate (range 10–60 mg/kg/day depending on clinical response). Patients completed the BDI-II, POMS and CDRS-SR assessments at screening (baseline), week 10 (the second week of the maintenance phase) and week 32 (the last week of the maintenance phase). The study did not require minimum baseline scores on the mood questionnaires and was not powered to assess differences between lamotrigine and valproate with respect to mood; therefore, no formal statistical analyses were performed on the mood data.

Mean scores on the BDI-II at screening reflected low/mild depressive symptoms and were similar between groups (lamotrigine 10.4 [SD ± 9.3], valproate 11.9 [SD ± 10.7]). Scores on the mood assessments improved for patients in the lamotrigine group, but not in the valproate group, beginning with the first post-treatment assessment at week 10 (figure 2).[12] Lamotrigine-associated improvement was maintained at week 32.

Although lamotrigine improved depressive symptoms more than valproate, seizure control was similar between the two groups. The proportion of patients who were free of seizures during the dose-escalation and maintenance phases was 29% for lamotrigine and 26% for valproate. The similar rates of seizure control between the two groups in the context of the greater improvement in mood with lamotrigine suggest that lamotrigine-associated improvement in depressive symptoms was not secondary to its effect on seizures.

Standard mood assessments, including BDI-II, POMS and CDRS-SR, were incorporated as prospective secondary measures in a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy and tolerability of adjunctive lamotrigine for the treatment of primary generalized tonic-clonic seizures (table I).[13] The study enrolled patients aged ≥2 years with a diagnosis of epilepsy with primary generalized tonic-clonic seizures (with or without other idiopathic generalized seizure types) classifiable by the International Classification of Seizures;[87] however, mood assessments involved only English-speaking patients aged ≥16 years.

The study comprised a ≤2-week screening phase, an 8-week baseline phase, a 7-week dose-escalation phase and a 12-week maintenance phase for those aged ≥16 years. Patients meeting the seizure criterion for study inclusion (at least three primary generalized tonic-clonic seizures with at least one primary generalized tonic-clonic seizure in each 4-week period during the baseline phase) were randomized 1 : 1 to receive either lamotrigine or placebo during the escalation and maintenance phases. During the escalation phase, lamotrigine was introduced and titrated while the number and doses of concomitant AEDs were maintained. During the maintenance phase, the dose of lamotrigine was maintained at a target level that depended on patient age and concomitant AEDs. During the maintenance phase, doses of concomitant AEDs were to be kept as constant as possible, and neither discontinuation of the concomitant AEDs nor addition of new AEDs was permitted. Use of antidepressants was not exclusionary. Patients completed BDI-II, POMS and CDRS-SR assessments at screening and at the end of the maintenance phase.

Table I. Studies of lamotrigine for depressive symptoms in patients with epilepsy

Study (year)	Design	Patients	Treatments	Mood assessments	Results of mood assessments
Double-blind studies					
Edwards et al.[12] (2001)	Randomized, double-blind, active-comparator trial 8-wk dose-escalation followed by 24-wk maintenance	≥12 y of age newly diagnosed with epilepsy and experiencing any seizure type	Lamotrigine monotherapy [target 200 mg/day] (n = 65) Valproate monotherapy [target 20 mg/kg/day] (n = 68)	BDI-II, POMS, CDRS-SR	Scores on all mood assessments improved with lamotrigine, but not valproate, beginning on the first assessment at treatment wk 10. Improvement was maintained at the last treatment wk 32. No hypothesis testing was undertaken
Ettinger et al.[13] (2007)	Randomized, double-blind, placebo-controlled 7-wk dose-escalation followed by 12-wk maintenance	≥16 y of age with a diagnosis of epilepsy with primary generalized tonic-clonic seizures	Lamotrigine adjunctive therapy [target dose dependent on concomitant AEDs] (n = 32) Placebo (n = 38)	BDI-II, POMS, CDRS-SR	At the end of the maintenance phase, mean improvement from baseline was significantly greater with lamotrigine than placebo for BDI-II score ($p = 0.01$) and POMS total score ($p = 0.03$), and numerically greater with lamotrigine than placebo for CDRS-SR score, although the difference did not reach statistical significance ($p = 0.50$)
Open-label studies					
Martinović et al.[79] (2004)	Open-label assessment after 2–3 mo of treatment	≥16 y old with partial epilepsy resistant to at least two standard AEDs	Lamotrigine adjunctive therapy (n = 56) Adjunctive therapy with other AEDs (n = 56)	CDRS, 17-item HAM-D, BDI	After 2–3 mo of treatment, the improvement in depressive symptoms was significantly greater in the lamotrigine group than the control group across all assessments ($p < 0.05$)

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Table I. Contd

Study (year)	Design	Patients	Treatments	Mood assessments	Results of mood assessments
Kalogjera-Sackellares and Sackellares[80] (2002)	Open-label	Adults with uncontrolled partial seizures and concomitant depressive symptoms that did not meet DSM-IV criteria for major depressive disorder	Lamotrigine monotherapy or adjunctive therapy titrated over 9 wk to a maximum of 250 mg bid for patients not taking concomitant valproate and a maximum of 75 mg bid for patients taking concomitant valproate (n = 13)	MADRS, MMPI	At wk 5 and mo 3, scores improved compared with baseline on the MADRS total score ($p = 0.002$ at wk 5, $p = 0.010$ at mo 3). Similar improvements were observed in individual MADRS items. At mo 3, but not at wk 5, the mean score on the depression scale of the MMPI was improved ($p = 0.033$)
Fakhoury et al.[81] (2007)	Open-label	Patients who had low to moderate depressive symptoms (CES-D score ≥12) and required a change in AED therapy. Patients with major depressive disorder as measured by the MINI or taking antidepressant medication were excluded	Lamotrigine adjunctive therapy (n = 158) for 19 wk followed by lamotrigine monotherapy for 36 wk	BDI-II, CDRS-SR, POMS	BDI-II score improved vs baseline at the end of adjunctive therapy and monotherapy ($p < 0.0001$ vs baseline). Similar results were observed with the other scales
Kustra et al.[82] (2005)	Open-label	Patients with partial seizures who required a change in AED therapy	Lamotrigine adjunctive therapy for 16 wk (n = 547). Those taking a single enzyme-inducing AED could then convert to lamotrigine monotherapy for an additional 12 wk	POMS	Mean total mood disturbance score on the POMS improved from baseline to the end of adjunctive therapy ($p < 0.001$ vs baseline) and to the end of monotherapy ($p < 0.001$ vs baseline). Improvements in each of the six domains of the POMS were observed

AEDs = antiepileptic drugs; **BDI** = Beck Depression Inventory; **BDI-II** = Beck Depression Inventory, 2nd edition; **bid** = twice daily; **CDRS** = Cornell Dysthymia Rating Scale; **CDRS-SR** = Cornell Dysthymia Rating Scale–Self Report; **CES-D** = Center for Epidemiology Studies–Depression Scale; **DSM-IV** = Diagnostic and Statistical Manual, 4th edition; **HAM-D** = Hamilton Scale for Depression; **MADRS** = Montgomery Asberg Depression Rating Scale; **MINI** = Mini International Neuropsychiatric Interview; **MMPI** = Minnesota Multiphasic Personality Inventory; **POMS** = Profile of Mood States.

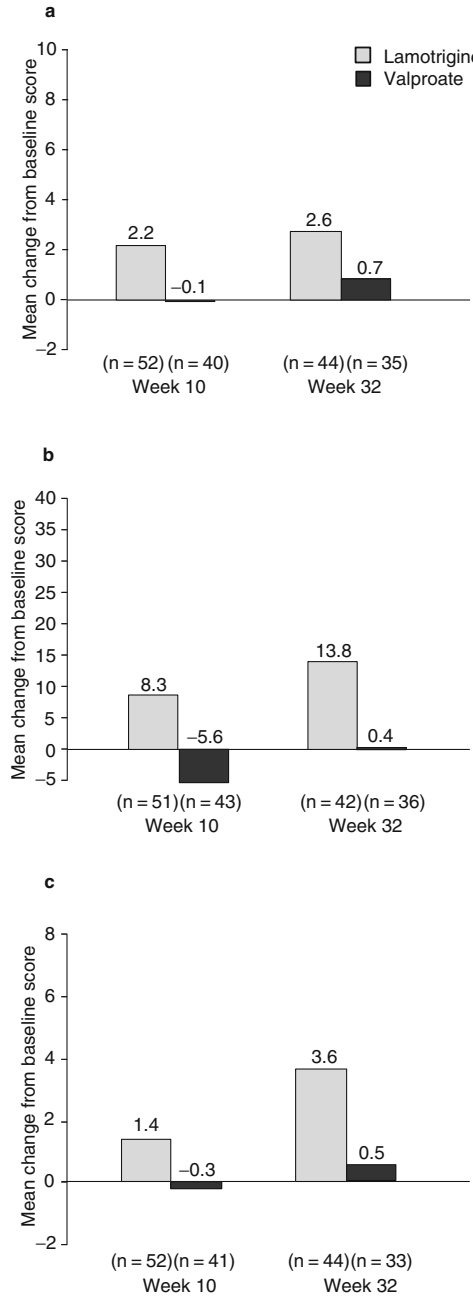

Fig. 2. Mean change from baseline scores on the (**a**) Beck Depression Inventory, (**b**) Profile of Mood States and (**c**) Cornell Dysthymia Rating Scale–Self Report assessments in patients treated with lamotrigine monotherapy or valproate monotherapy (reprinted from Edwards et al.,[12] © 2001, with permission from Elsevier).

Mean scores on the BDI-II at screening reflected mild depressive symptoms and were similar between groups. At the end of the maintenance phase, mean improvement from baseline was significantly greater with lamotrigine than placebo for BDI-II score ($p = 0.01$) and POMS total score ($p = 0.03$), and numerically greater with lamotrigine than placebo for CDRS-SR score, although this difference did not reach statistical significance ($p = 0.5$) [figure 3].[13]

Median percentage reductions in seizure frequency were significantly greater with lamotrigine than placebo during the escalation phase, the maintenance phase, and the escalation and maintenance phases combined for primary generalized tonic-clonic seizures and all generalized seizures. However, improvement in seizure frequency was not correlated with improvement in mood ($r = 0.1$, p-value not significant).

The results of these randomized double-blind clinical trials are consistent with data from four open-label studies of the effects of lamotrigine on depressive symptoms in epilepsy (table I).

In the first open-label study, the effects of adjunctive lamotrigine versus adjunctive treatment with other AEDs on mood symptoms and seizure control were assessed prospectively in patients aged ≥16 years with partial epilepsy resistant to at least two standard AEDs.[79] The lamotrigine group comprised 56 patients, of whom 31 had at least mild depressive symptoms (i.e. minor depressive disorder, dysthymic disorder, interictal dysphoric disorder). The control group, which was administered AEDs other than lamotrigine, comprised 56 patients, of whom 32 had at least mild depressive symptoms. After 2–3 months of treatment, improvement in depressive symptoms was significantly greater in the lamotrigine group than in the control group across assessments, including the CDRS, the 17-item HAM-D and the BDI (figure 4).[79] The incidence of improvement in seizures was higher in the lamotrigine group (≥50% improvement in 51.7% of patients) than in the control group (≥50% improvement in 25.2% of patients).

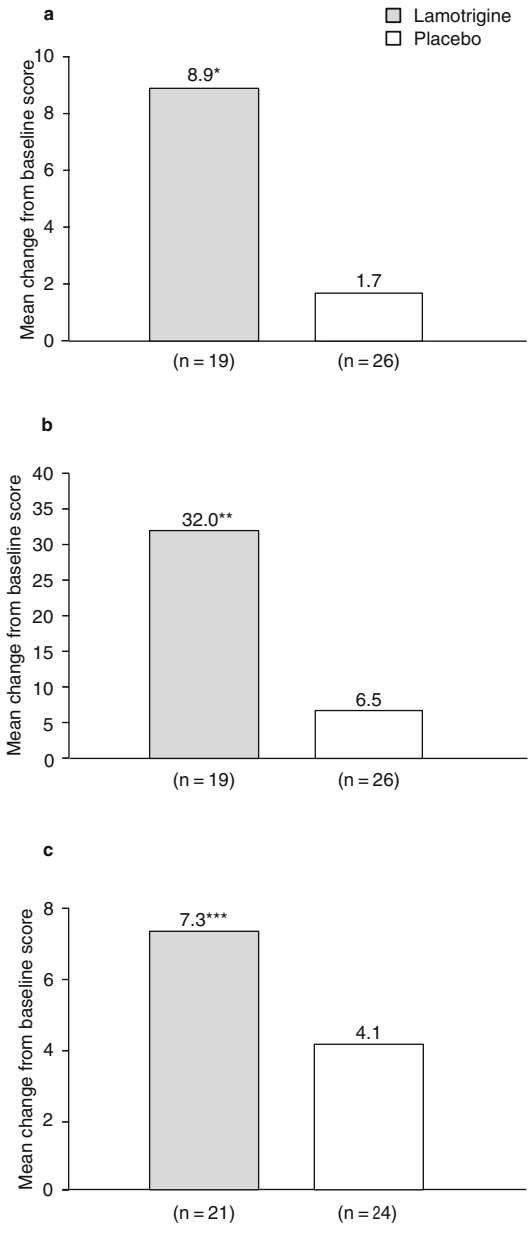

Fig. 3. Mean change from baseline scores on the (**a**) Beck Depression Inventory, 2nd edition, (**b**) Profile of Mood States and (**c**) Cornell Dysthymia Rating Scale–Self Report assessments in patients treated with lamotrigine adjunctive therapy or placebo. For all scales, increases in score reflect improvement. The number of subjects differs between groups and for different tests because analyses were performed on patients with evaluable data (reprinted from Ettinger et al.,[13] © 2007, with permission from Elsevier). * p = 0.01, ** p = 0.03, *** p = 0.05 vs baseline.

The second open-label study involved 13 adults with uncontrolled partial seizures and concomitant depressive symptoms who did not meet Diagnostic and Statistical Manual, 4th edition (DSM-IV) criteria for major depressive disorder.[80] Patients were considered to have depressive symptoms if they indicated the presence of a mood disturbance that affected their QOL. Patients with DSM-IV-defined major depression were excluded on the basis of revised HAM-D scores obtained at screening. Thus, the sample comprised patients having the subsyndromal depressive symptoms often documented in patients with epilepsy.

Lamotrigine, initiated as monotherapy or adjunctive therapy immediately after completion of screening procedures, was titrated over 9 weeks to a maximum of 250 mg twice daily for patients not taking concomitant valproate and a maximum of 75 mg twice daily for patients taking concomitant valproate. Mood assessments, completed at baseline and after 5 weeks and 3 months of treatment with lamotrigine, included the Montgomery Asberg Depression Rating Scale (MADRS)[88] and the Minnesota Multiphasic Personality Inventory (MMPI),[89] which includes a depression scale.

At screening, total MADRS scores reflected mild depression in 62% of patients and moderate depression in 38% of patients. Of the 11 patients with reading skills sufficient to complete the MMPI, the depression scale was elevated in 82%. At week 5 and month 3, significant improvement compared with baseline was observed on the MADRS total score ($p = 0.002$ at week 5; $p = 0.010$ at month 3). Similar improvements were observed in individual MADRS items. At month 3, but not at week 5, the mean score on the depression scale of the MMPI was significantly improved ($p = 0.033$).

Average seizure frequency based on data from daily seizure diaries was reduced by ≥50% in 6 of 11 patients with evaluable data at month 3. Overall seizure frequency was reduced from baseline by an average of 29% during the lamotrigine treatment period.

A third open-label study enrolled patients who had low to moderate depressive symptoms (CES-D

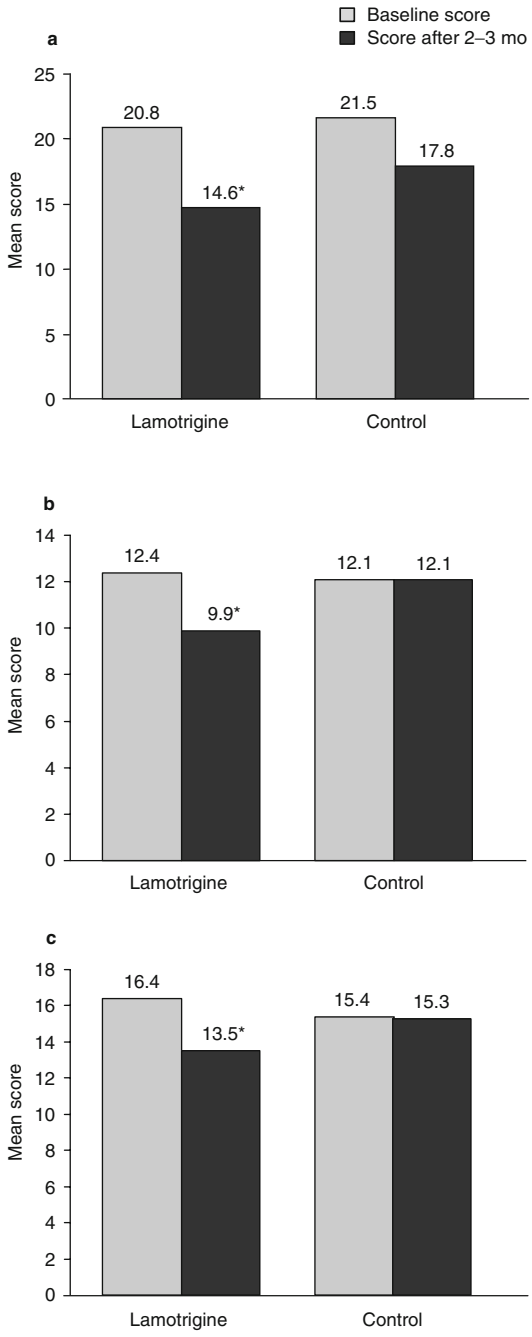

Fig. 4. Mean scores on (**a**) Cornell Dysthymia Rating Scale, (**b**) Hamilton Scale for Depression and (**c**) Beck Depression Inventory mood assessments at baseline and after 2–3 months of adjunctive treatment with lamotrigine or other antiepileptic drugs.[79] * $p < 0.05$ vs control.

score ≥12) and required a change in AED therapy.[81] Patients with major depressive disorder, as measured by the Mini International Neuropsychiatric Interview, or taking antidepressant medication were excluded. Lamotrigine was added to a stable AED regimen and patients were then converted to lamotrigine monotherapy. To evaluate changes in mood, the self-report instruments BDI-II, CDRS-SR and POMS were administered at baseline, at the end of 19 weeks of adjunctive treatment with lamotrigine and 36 weeks after conversion to lamotrigine monotherapy.

The number of patients completing the adjunctive therapy and monotherapy phases was 96 and 66, respectively. The mean BDI-II baseline score was 17.4, reflecting mild depression. Following initiation of lamotrigine, the mean BDI-II score decreased to 12.0 at the end of adjunctive treatment ($p < 0.0001$ vs baseline). Improvement continued during the monotherapy phase, at the end of which the mean BDI-II score was 8.9 ($p < 0.0001$ vs baseline). Improvement in depressive symptoms versus baseline was also observed on the other scales at the end of adjunctive therapy and further improvement was observed 36 weeks after conversion to lamotrigine monotherapy (table II).[81] These data suggest that lamotrigine may have an antidepressant action in patients with epilepsy and comorbid low to moderate depressive symptoms.

A fourth open-label study enrolled patients with partial seizures who required a change in AED therapy.[82] Patients received lamotrigine adjunctive therapy for 16 weeks. Those taking a single enzyme-inducing AED could then convert to lamotrigine monotherapy for an additional 12 weeks. Patients completed the POMS at baseline, and at the end of the adjunctive therapy and monotherapy phases.

The number of patients completing the POMS at baseline, at the end of adjunctive therapy and at the end of monotherapy was 198, 158 and 52, respectively. Mean total mood disturbance score on the POMS improved from 54 at baseline to 33 at the end of adjunctive therapy ($p < 0.001$ vs baseline) and to 31 at the end of monotherapy ($p < 0.001$ vs base-

Table II. Mean (SD) scores or change-from-baseline scores on mood assessments for patients receiving lamotrigine adjunctive therapy followed by lamotrigine monotherapy (reprinted from Fakhoury et al.,[81] © 2007, with permission from Elsevier)[a]

Assessment	Score				
	baseline (n = 158)	adjunctive phase (n = 158)	mean change*	monotherapy phase (n = 88)	mean change*
CES-D	24.4 (9.3)	16.2 (10.0)	−8.2 (10.3)	13.5 (10.5)	−12.4 (10.3)
CDRS-SR	59.8 (11.9)	53.7 (12.6)	−6.3 (11.9)	50.4 (13.0)	−11.4 (13.3)
POMS					
tension-anxiety	14.9 (7.1)	12.6 (7.7)	−2.2 (7.5)†	10.9 (7.5)	−4.5 (7.6)
depression-dejection	17.8 (11.5)	13.5 (11.4)	−4.3 (10.9)	11.4 (11.0)	−9.0 (11.0)
anger-hostility	12.2 (9.0)	10.1 (8.9)	−2.1 (7.7)‡	9.7 (8.7)	−4.3 (8.4)
vigour-activity	12.7 (5.6)	15.8 (6.5)	3.1 (6.8)	18.0 (6.5)	5.8 (6.5)
fatigue-inertia	12.6 (6.7)	10.1 (6.7)	−2.6 (6.9)	8.7 (6.4)	−4.2 (7.0)
confusion-bewilderment	11.4 (5.3)	9.6 (5.5)	−1.8 (5.5)	8.8 (5.9)	−2.9 (5.2)
total mood	56.2 (34.1)	40.1 (38.0)	−16 (36.4)	31.4 (38.9)	−31 (37.0)

a For all scales except vigour-activity, higher scores reflect more severe symptoms. For vigour-activity, higher scores reflect less severe symptoms.

CDRS-SR = Cornell Dysthymia Rating Scale–Self Report; **CES-D** = Center for Epidemiology Studies–Depression Scale; **POMS** = Profile of Mood States; * $p < 0.0001$ except where noted, † $p < 0.001$, ‡ $p < 0.01$ vs baseline.

line). Improvements in each of the six domains of the POMS were observed.

8.3 Levetiracetam

The efficacy of levetiracetam for depressive symptoms in patients with epilepsy was investigated in a prospective open-label study in 25 adults with uncontrolled partial seizures and depressive symptoms.[90] The study excluded patients meeting DSM-IV criteria for major depressive disorder. Patients were considered to be depressed if they affirmed having symptoms of mood disturbance that affected their QOL. The MADRS, HAM-D and Zung Self-Rating Scale for Depression were used to assess depressive symptoms after 5 weeks and 3 months of treatment with levetiracetam. The results show that scores on all three measures were significantly improved from baseline at both week 5 and month 3. Levetiracetam was also associated with a reduction in the frequency of seizures. Over 3 months of treatment, the average seizure frequency was reduced by 38%. The average seizure frequency was reduced by at least 50% from baseline in 12 of 25 patients. Because baseline seizure frequencies were determined retrospectively and, in some cases, appeared unusually low, the seizure data should be interpreted cautiously.

8.4 Oxcarbazepine

The efficacy of oxcarbazepine for depressive symptoms in adults with epilepsy was investigated in a prospective open-label study.[91] Patients with partial seizures received adjunctive oxcarbazepine (n = 40) or AEDs other than oxcarbazepine (n = 40). The study did not exclude patients with a psychiatric history who were taking stable doses of antidepressants. The CDRS, HAM-D and BDI were used to assess depressive symptoms at time 1 (baseline; for oxcarbazepine-treated patients, at least 2 weeks after a stable dose of oxcarbazepine had been achieved) and approximately 3 months thereafter (time 2). Scores on the CDRS, but not the HAM-D or BDI, improved significantly more after 3 months in oxcarbazepine-treated patients than in patients treated with other AEDs. Among the 28 oxcarbazepine-treated patients who, at study entry, were dysthymic (defined by a CDRS score of at least 20), 19 (68%) were euthymic (i.e. CDRS score <20) after oxcarbazepine treatment. Although 31 of the oxcarbazepine-treated patients reported a decrease in seizure frequency from time 1 to time 2, no significant difference in seizure frequency was found between time 1 and time 2 or between the oxcarbazepine and control groups. There was no correla-

tion found for changes in mood scales and changes in seizure frequency.

8.5 Summary: Efficacy of AEDs for Depressive Symptoms in Epilepsy

In prospective assessments, gabapentin, lamotrigine, levetiracetam and oxcarbazepine were each shown to have a potentially beneficial impact on depressive symptoms in patients with epilepsy. The evidence for the efficacy of gabapentin, levetiracetam and oxcarbazepine for depressive symptoms in epilepsy is inconclusive to date, because the effects of each agent have been reported only in single studies having an open-label design and small sample sizes. The evidence base for lamotrigine is more extensive than for the other agents and includes data from prospective, randomized, double-blind research.

With the exception of one open-label study that recruited patients with epilepsy and co-morbid depression, and had improvement of depressive symptoms as a primary endpoint,[81] lamotrigine-associated improvements in depressive symptoms were observed under conditions not necessarily conducive to demonstrating such improvements. The double-blind trials were not designed primarily, nor were they statistically powered, to assess the antidepressant effects of lamotrigine; mood assessments were prospective, secondary measures. Furthermore, those studies did not enrol patients selected for the presence of depressive symptoms at baseline. The inclusion of non-depressed patients in the samples may have increased the difficulty of demonstrating an antidepressant effect of lamotrigine. These results would be complemented by controlled prospective studies designed to evaluate the effects of lamotrigine on depressive symptoms in a sample of patients with epilepsy selected specifically for depressive symptomatology at baseline.

Although the results with lamotrigine consistently support its efficacy for depressive symptoms in epilepsy, several limitations of the studies should be borne in mind when interpreting the data. First, the studies of lamotrigine in patients with epilepsy assessed depressive symptoms >8 weeks after initiation of lamotrigine, whereas studies of the acute treatment of depression typically assess symptoms ≤8 weeks after initiation of treatment. The effects of lamotrigine on depressive symptoms in epilepsy during the early weeks after initiation of treatment remain to be delineated. Second, attrition may have impacted the results because data analyses included only results from patients with evaluable data both at baseline and at the end of the treatment period. If patients who withdrew from the studies early differed from those who did not withdraw prematurely with respect to depressive symptomatology or response to lamotrigine, then the mood data may be compromised. In the randomized, double-blind, placebo-controlled study,[13] lamotrigine was significantly more effective than placebo at improving depressive symptoms in the context of similar attrition rates between groups. Attrition rates ranged from 34% to 41% in the lamotrigine group and from 32% to 37% in the placebo group, depending on the mood instrument.[13]

9. Negative Impact of AEDs on Depressive Symptoms in Epilepsy

Whereas gabapentin, lamotrigine, levetiracetam and oxcarbazepine have been associated (with varying degrees of robustness) with an improvement of depressive symptoms in epilepsy, other AEDs have been associated with provocation or exacerbation of depressive symptoms in epilepsy.[92] Provocation or exacerbation of depressive symptoms has been reported with GABAergic drugs, including vigabatrin, tiagabine, topiramate and phenobarbital.[1,4,40] Phenobarbital and primidone are associated with an elevated incidence of depressive symptoms in studies designed to assess mood symptoms.[93,94] In children with epilepsy, in those taking phenobarbital (n = 15) compared with those taking carbamazepine (n = 24), a higher prevalence of major depressive disorder (40% vs 4%) and suicidal ideation (47% vs 4%) has been observed.[93] The two groups did not differ with respect to seizure-related variables. In a cross-sectional study of 241 patients with epilepsy, primidone was significantly associated with interictal depressive symptoms.[94] Depressive syndrome

was diagnosed in 43% of patients (n = 107) on the basis of scores on the MADRS and HAM-D. The use of primidone and inadequate seizure control were each significantly associated with the presence of depressive symptoms in both univariate and multivariate analyses.

10. Conclusions

Depressive symptoms are common in patients with epilepsy. Depression in epilepsy may manifest as major depressive disorder meeting diagnostic criteria, atypical depression or dysthymia, or a dysthymic-like disorder with intermittent symptoms that can be milder than those of major depression. Depressive symptoms in epilepsy impact on patients' QOL and are associated with a high risk of suicide.

Lamotrigine, an effective antiseizure medication, also appears to be effective in the treatment of depressive symptoms in patients with epilepsy. In randomized, double-blind, clinical trials, depressive symptoms improved more with lamotrigine monotherapy than valproate monotherapy and more with lamotrigine adjunctive therapy than placebo. The lamotrigine-associated improvement in depressive symptoms was independent of its anticonvulsant efficacy. Results of open-label studies of lamotrigine monotherapy and adjunctive therapy are consistent with the results of double-blind clinical trials. In prospective assessments, gabapentin, levetiracetam and oxcarbazepine each had potentially beneficial effects on depressive symptoms in patients with epilepsy. The evidence for the efficacy of gabapentin, levetiracetam and oxcarbazepine in treating depressive symptoms in epilepsy is inconclusive to date, because the effects of each agent have been reported only in single studies that had an open-label design and small sample sizes.

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