



# Epilepsy and co-morbid depression

## Clinical significance too often underestimated

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# Epilepsy and co-morbid depression

## Clinical significance too often underestimated

Between half and a quarter of all patients suffering with epilepsy also suffer from an affective disorder. In many cases, however, this goes undiagnosed and untreated. One of the reasons for this is the still widely held misconception that the symptoms of the affective disorder are a “logical” reaction to chronic epilepsy and its social consequences. In fact, however, a co-morbid depression will have more effect on the patient’s quality of life than the epilepsy itself. In addition, there is compelling evidence that there are common pathophysiological features present in both illnesses in terms of a disorder of the cerebral network.

### Include affective vulnerability in the therapy concept

*Considering the high risk of psychiatric co-morbidity for epilepsy patients, the factor of “affect” should always be taken into account in making decisions about possible treatment options. The use of anti-convulsants with a potential to cause depressive symptoms should be rejected in order to avoid the onset of, or activating, in a more or less iatrogenic manner, any already manifest or latent affective disorder. Alternative treatments with demonstrated mood-stabilising or even antidepressant properties are valproate and carbamazepine as well as lamotrigine and oxcarbazepine. Additionally, in many cases a specific psycho-pharmacological intervention and socio-therapeutic care may be necessary.*

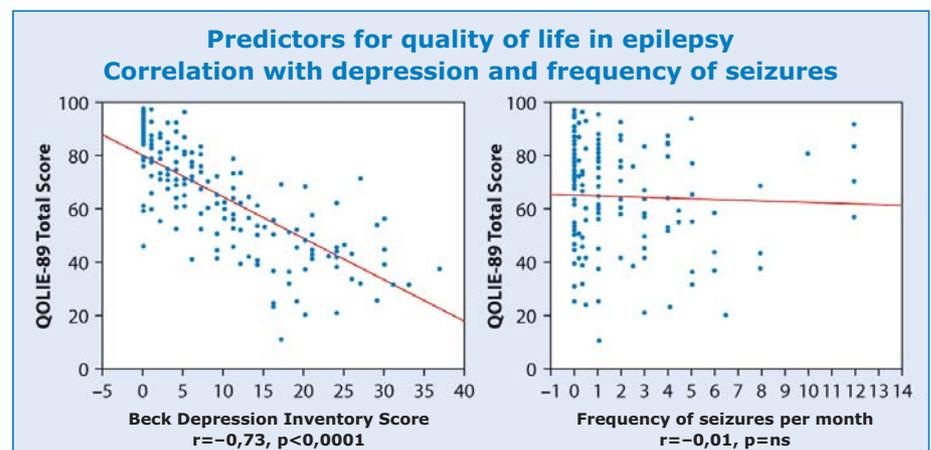
Psychological disorders are between five and ten times more common amongst people with epilepsy in comparison with the general population. The prevalence of depressive disorders is particularly high. The available data in the literature range from 29% (representative sample testing (1)) to 44% (candidates for epilepsy surgery (2)) and 72% (patients with temporal lobe epilepsy (3)) depending on the characteristics of the study population.

### The mood state is more significant for quality of life than seizure frequency

The data on the influence of affective disorders on the life of

someone already suffering from epilepsy are significantly more consistent. In comparison to patients with stable mood and independent from the epilepsy syndrome, patients with epilepsy and an affective disorder

- feel that their epileptic seizures are more severe and have a greater adverse effect on their everyday lives (4),
- have a statistically significantly poorer quality of life in all areas (5),
- have two to three times more frequent contact with doctors (excluding psychiatrists) (6).
- On the whole, the mood state of patients with epilepsy has



**Fig. 1:** The quality of life of people suffering from epilepsy (n=194) is correlated with the patient’s mood, but not with the frequency of seizures (according to Gilliam [7])

more of an impact on their quality of life than the frequency of their seizures (Fig.1) (7).

In the opinion of Prof. Bettina Schmitz, Berlin, it is regrettable that the psychological problems of people suffering from epilepsy too seldom receive adequate treatment or, in some cases, are frequently not recognised until a late stage if at all. This opinion was borne out not just by her own clinical experience, but by a great deal of scientific evidence. This diagnostic deficit is probably attributable to the fact that many patients suffering from epilepsy will not talk about their mood state or complain about symptoms which do not fall into the typical spectrum of depression, as defined by ICD-10, partly out of a fear of further stigmatisation.

**“Dysphoric disorders” are mostly temporarily independent of the seizure event**

The factors which most influence the quality of life of patients with epilepsy are primarily psychological disturbances which are not in temporal correlation with seizure activity and which affect the majority of all cases (8). In contrast to the periictal changes in affect, which in general are of short duration and are self-limiting, these psychic disturbances constitute a chronically fluctuating event (Fig. 2).

The clinical picture is multifaceted and includes flat mood, lack of motivation and feelings

of anxiety on the one hand, and explosive irritability, low tolerance of frustration and emotional lability on the other, as well as somatic symptoms, which manifest themselves as unusual pains, sleeplessness and cogni-

lobe epilepsy, in which seizures originate in the brain’s limbic system, which is responsible for the processing of signals concerned with the emotions, the incidence of depression is unusually high (8, 9)

<p><b>Unstable depressive symptoms</b></p> <ul style="list-style-type: none"> <li>➤ Low mood</li> <li>➤ Anergia</li> <li>➤ Pains</li> <li>➤ Insomnia</li> </ul> <p><b>Unstable affective symptoms</b></p> <ul style="list-style-type: none"> <li>➤ Phobia</li> <li>➤ Anxiety</li> </ul> <p><b>Specific symptoms</b></p> <ul style="list-style-type: none"> <li>➤ Paroxysmal irritability</li> <li>➤ Euphoria/irritability</li> </ul>
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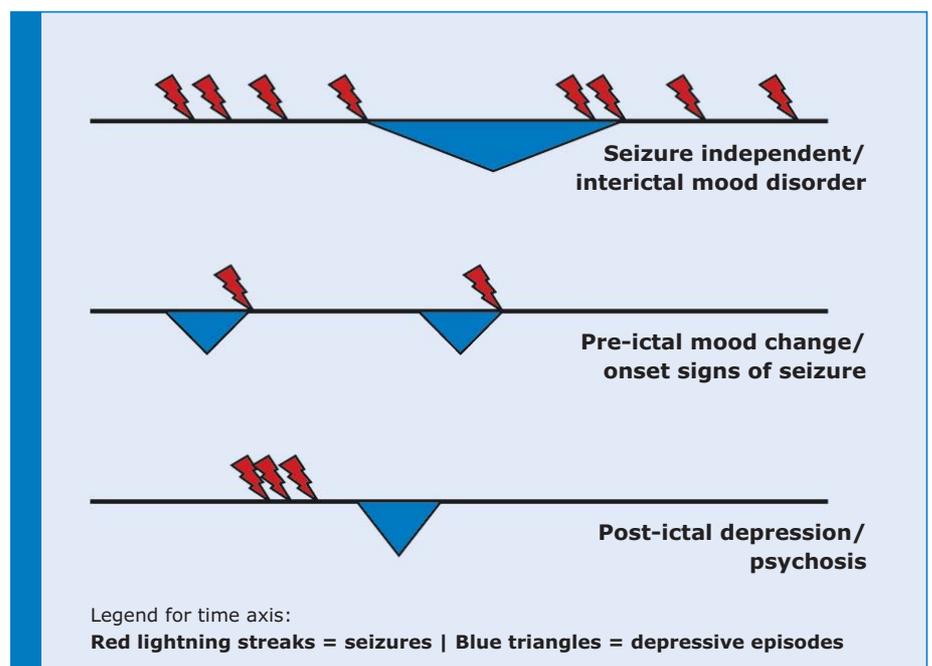
**Table 1:** Typical epileptic syndrome of “interictal dysphoric disorder” (According to Blumer et al. (2))

tive deficits. In this connection one may also speak of an “interictal dysphoric disorder” (Table 1) (2).

In patients suffering from focal epilepsy, and especially temporal

This observation speaks against the possibility of a psychological reaction to the chronic illness and its social consequences. The hypothesis of a pathophysiological connection is supported by the fact that neuropsychological tests (10) and functional

imaging (11) have demonstrated that, in patients with epilepsy, there is a reduced level of activity in the frontal lobes which are responsible for the executive modulation of the emotions. In



**Fig. 2:** Forms of affective co-morbidity in epilepsy. Where does the seizure begin, and where does it end? (according to Schmitz)

primary generalised epilepsy syndromes one would expect to find affective disorders above all in patients with juvenile myoclonic epilepsy (12). These affective disorders are probably also caused by the presence of functional and subtle structural deficits in the mesial and lateral frontal regions of the brain (13). According to *Schmitz*, depression is nowadays understood as being an epileptogenous disorder in regions of the brain which are connected functionally but are anatomically distant from one another. As a further argument for a common pathological mechanism we could cite the bi-directional aetiological connection. It has been demonstrated many times in epidemiological studies that patients with epilepsy were three to four times more likely to have suffered from depression before their first seizure occurred compared to the general population (14).

### Avoid antiepileptics with depressiogenic potential ...

The first step in the treatment of a co-morbid depression in an individual suffering from epilepsy is to optimise pharmacotherapy.

*»Emotion and affect are still too often neglected in patients suffering from epilepsy. The executive modulation of emotions is located in the orbito-frontal cortex (in red), the processing of emotions takes place in the amygdala (in blue).«*

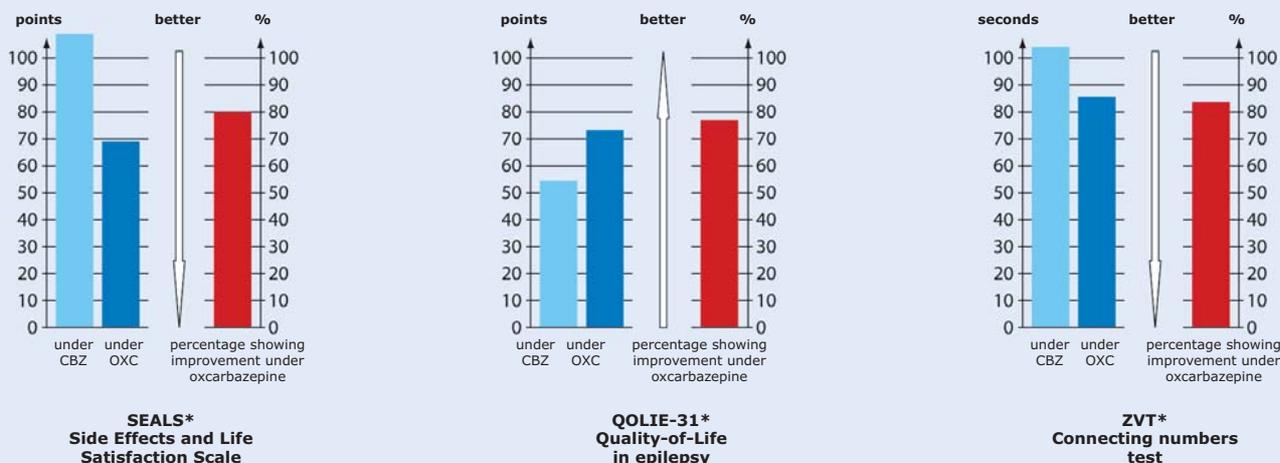
In a consecutive study of the cases of one hundred patients it was found that a clinically significant depression had been induced by intake of anti-convulsant medication in 28% of cases (15). The risk of developing a depression is substance-

dependent. We can expect to find an adverse psychotropic effect in the use of phenobarbital, phenytoin and primidone as well as in felbamate, tiagabine, topiramate and vigabatrin. *Schmitz* is therefore convinced that in all patients suffering from epilepsy before starting or changing anti-convulsant therapy the psychiatric baseline status should be determined, or at least attention should be paid to the possibility of affective vulnerability. This would help to avoid a situation arising, which is to some extent iatrogenic, i.e. in which the choice of a patient's medication actually made their mental state worse.

### ... in favour of alternatives with positive psychotropic properties

Mood-stabilising or even anti-depressant effects should be

### Switchover to oxcarbazepine after pretreatment with carbamazepine (n=93)



**Fig. 3:** Higher quality of life following change in anticonvulsant therapy. During a prospective standardised clinical observational study, 136 patients with focal epilepsy who had been taking an ineffective therapy were switched to oxcarbazepine (OXC) therapy. Within four months this produced total freedom from seizures in 35% or 30% of cases (pretreatment with carbamazepine (CBZ) or other antiepileptics). Even in the cases in which the improvement of seizure situation was less distinctive, or in which there was no reduction in the numbers of seizures, there were benefits from the change in therapy: It was possible to demonstrate a statistically significant improvement in the patients' quality of life in 80% of cases (17).

expected during the use of drugs such as valproic acid (e.g. *Orfiril® long*), lamotrigine (e.g. *Plexxo®*, *Lamotrigin Desitin®*), carbamazepine (e.g. *T(r)imonil®*) or oxcarbazepine (e.g. *Apydan®\**). The marketing authorisation for the treatment of patients with bipolar disorder with the established anticonvulsants valproic acid and carbamazepine endorses these findings. The advantages of valproic acid over carbamazepine are that it has a broader therapeutic range, in both the control of epilepsy (focal and primary generalised seizures) as well as in affective disorders (dysthymia, manic-psychotic and manic-depressive states), and it is better tolerated by the patient. Valproic acid is also easier to use in that there are fewer risks of interactions with other drugs (no enzyme induction) and because it is available in patient-convenient

pharmaceutical forms (such as *Orfiril®* long sustained release mini tablets which have the advantage that they can be taken only once a day and independent from meals).

Although lamotrigine and oxcarbazepine are classified amongst the newer antiepileptics, they have long since been standard treatments for epilepsy and have been in world-wide clinical use for over fifteen years. They even appear to be the equals of the "classical" antiepileptics in terms of their psychotropic profile. Lamotrigine, like valproic acid, may be used to treat patients with both focal and generalised types of epilepsy, and is also authorised for the prophylactic treatment of depressive episodes in bipolar disorders. Oxcarbazepine is now extensively replacing carbamazepine as

the treatment of choice for focal epilepsy because, whilst its success rate in treating focal epilepsy is more or less identical to that of carbamazepine, but it is much better tolerated. In addition, there is now a lot of promising data from clinical studies for its mood-stabilising qualities (16) and additional effects in improving cognition (17) (see Fig. 3).

### Affective co-morbidity requires a multimodal treatment concept

The fear of reducing the myoclonic threshold should not, in the opinion of *Dr Thomas Dorn*, Zurich, stop us from treating patients with epilepsy and a comorbid depression with psychopharmacological methods. Relatively little is understood about

#### Aims

- Improvement in social integration
- Improvement in ability to relate to others
- Improvement in coping strategies
- More understanding of the connections between epilepsy and affective disorder
- Reduction in stigmatisation
- Prevention of renewed depressive episodes
- Prevention of thoughts of suicide

#### Problems

- Psychiatric treatment centres are poorly equipped to deal with the needs of people suffering from epilepsy.
- Epilepsy is viewed primarily as a neurological disease which has little to do with a person's psychological or psychiatric state.
- Fear of double stigmatisation because of seizures and psychiatric symptoms

#### Prejudices

- People suffering from epilepsy are unpredictable
- Epilepsy always produces a change in personality
- Epilepsy signifies that a person is less gifted than others

**Table 2:** Socio-therapy in psychiatric co-morbidity (according to Deister)

\* ) Apydan® is available in Denmark, Estonia, Finland, Poland, Hungary.

the pro-convulsive mechanisms of antidepressant drugs, though these effects occur usually only in high serum concentrations of the active ingredients. Local anaesthetic, antihistaminergic or antimuscarinergic qualities are all under investigation as being possible mechanisms (18). The risk presented by the more modern drugs, which intervene more selectively in the imbalance of monoamines seems to be less than that presented by the older tricyclic antidepressants. An anticonvulsant effect has even been described in the selective serotonin re-uptake inhibiting drugs fluoxetine and citalopram (19,20). *Dorn* reminds us that particular attention must be paid when selecting a psychopharmaceutical drug that it should not increase the severity of the side-effects of the medication which is required to control the patient's seizures. In addition, the starting doses and the target doses of the medication should be somewhat lower, and the rate of titration slower than in patients who do not suffer from epilepsy.

The third pillar in seeking to improve the quality of life for people suffering from epilepsy with an affective co-morbidity is psychotherapy. There has been a great conceptual shift over recent years, according to *Prof. Arno Deister*, Itzehoe. Instead of placing the emphasis on "protection", as was the case in previous decades, the emphasis has now shifted to "empowerment". This emphasis still, however, re-

gretfully leads to problems and prejudices (*Table 2*). The central features of this approach are the strengthening of:

- *Autonomy – the ability to act as an independent person*
- *Courage – the will to take risks and to dare to move forward*
- *The taking of responsibility – for oneself (and others)*

Possible forms of treatment for the various forms of affective co-morbidity range from cognitive behavioural therapy and psycho-education to courses designed to help patients improve their daily time-planning skills and their ability to make social contact right up to supported living and supported employment schemes.

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