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## Epilepsy and suicide: a narrative review

### Summary

*The epilepsy represents a challenge for life expectancy and quality of life either for social and relational consequences due to stigma and for the consequences of the disorder itself. Suicidal behaviors are more frequent in the persons with epilepsy than in the general population. In addition to those shared with other chronic diseases, the condition of a person with epilepsy recognizes particular risk factors related to the clinical characteristics, demographic, socioeconomic and relational conditions. The frequent comorbidity with psychiatric disorders, first of all depression, complicates the clinical picture both because of neurobiological underpinnings underlying the two disorders and the negative interaction on the quality of life. The hopelessness is strongly correlated to suicidal ideation and its evaluation can be considered a relevant and reliable tool for measuring suicidal ideation. A careful evaluation of suicidal ideation, taking into account demographic and psychological conditions of patients, as well as clinical, social, economic situations, is warranted. The diagnosis and treatment of the disease has to take into account a bio-psycho-social approach that allows the integration of medical, psychological and social aspects.*

### Key words

Epilepsy • Suicidal ideation • Hopelessness • Beck Hopelessness Scale • Bio-psycho-social approach

### The epilepsy burden

The epilepsy affects the quality and expectations of life, with existential repercussions, both for the clinical characteristics and for the social consequences of the disease <sup>1</sup>. The impact of epilepsy is multiform. The unpredictability and the danger of seizures increase the risk of trauma, hospitalization and mortality and frequently alter the mental health of the person resulting in anxiety, depression, cognitive disorders. Seizures also involve stigma, marginalization and social exclusion with negative effects on self-confidence and self-esteem. However, the weight of epilepsy extends beyond the effects of seizures <sup>2</sup>: as a matter of facts epilepsy is more than just seizures. All multiple and interacting medical, psychological, economic and social repercussions must be considered to fully understand the impact of the disease. The psychosocial impact and stigma surrounding epilepsy can contribute to the increased risk of unnatural death. In addition, treatment with anti-epileptic drugs is often associated with side effects that further impairs quality of life.

### The epilepsy and the suicide

In comparison with people without epilepsy, those with epilepsy present a 2 to 3 times greater risk of unnatural death and should be adequately warned about the prevention of trauma and monitored for suicidal thoughts and behaviors. Numerous epidemiological data point to a link between epilepsy and suicide. Andrijc et al. <sup>3</sup> report the presence of suicidal ideation and thoughts of death in 38% of epileptic patients. Tellez-Zenteno et al. <sup>4</sup> showed a twice higher prevalence of suicidal ideation in persons with epilepsy than controls. Christensen et al. <sup>5</sup> found a suicide risk three times higher than controls.

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OPEN ACCESS

Received: June 24, 2019

Accepted: July 15, 2019

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Suicide is a global health problem and includes a wide range of self-aggressive behaviors including complete suicides, suicide attempts and suicidal ideation. In addition to suicides and suicide attempts, ignored, disguised, hidden, sub intentional suicides and suicidal equivalents have also to be taken into account. Suicidal ideation is a medical term that indicates thoughts, desires and plans to commit suicide and can range from passive ideas to ideas with detailed plans and intent to commit suicide.

We report a narrative review of literature on studies on suicidal behaviors in persons with epilepsy.

### Suicidal risks factors

In the general population, suicide risk is higher in the presence of certain demographic, psychopathological and socioeconomic factors <sup>6</sup>. The older males, the singles, immigrants, the unemployed, the Protestants, middle-upper classes, residents in urban areas, the socially and emotionally isolated, chronic pain sufferers seem to be more predisposed <sup>7</sup>. Seasonal variables (spring, summer) the presence of severe frustrations (sentimental disappointments, death of relatives, economic losses, changes in social role and working activity) may be triggering factors <sup>8</sup>. Many psychopathological, psychodynamic, socio-economic and cultural factors contribute to the ethology of suicide. In terms of psychopathological substrate, psychiatric symptoms (especially depressive symptoms, less psychotic or otherwise) are frequent <sup>9</sup>.

The diagnosis of "suicide risk" or rather the risk assessment of self-aggressive behavior is based on: history (suicide familiarity, previous attempts, childhood affective deficiencies or neglect, family problems), general and biological data (age, chronic painful and/or incurable diseases, puberty, puerperium, involution and climate), psychopathological data (depressive syndromes, personality traits, anxiety symptoms, guilt feelings, self-accusation, alcoholism and drug addiction), subjective statements (general or explicit boredom for life, statements, projects or structured resolutions, preparations), socio-economic, interpersonal and family conditions (loss of emotional, economic, social balances). Efforts to identify the so-called "suicidal syndrome" have failed and, as a result, the recognition of suicidal potential is based on the empathic abilities and diagnostic insights of the physician. In view of the lack of "tests based on evidence" many risk factors have been considered, especially in aggregation between them, but the translation from studies on groups to the individual may hesitate in a high percentage of false positives and false negatives. Poor validity and reliability in the prediction of suicide may also depend on the rarity of suicidal events as well as the complexity of clinical,

psychological, cultural and environmental variables. The history of previous suicide attempts seems to be the strongest predictor of a successful future suicide <sup>10</sup>. Psychosocial factors include stigma <sup>11</sup>, fear of crises, discrimination, job loss, lack of support. Psychopathological factors such as mood disorders, cognitive flexibility, inhibitory control, personality traits, alterations in problem solving abilities may increase the suicidal risk. Most of these risk factors are relevant for persons with epilepsy too <sup>12</sup>. The suicidal risk was found higher at the onset of the disease, in the first six months immediately after diagnosis and more frequently in adolescents <sup>13</sup>. The location of the epileptogenic focus in the temporal lobe, the rate of seizures, surgical therapy, psychiatric comorbidity and personality disorders <sup>14</sup>, the history of suicide attempts, depression and substance abuse in family members <sup>15</sup> appear to play a significant role in increasing the risk of suicide. Anti-epileptic drugs, especially those with a GABAergic mechanism of action, appear to increase the presence of suicidal ideation at the beginning of treatment. Based on analysis of randomized controlled studies of 11 anti-epileptic drugs <sup>16</sup>, the Food and Drugs Administration issued an alert regarding a double risk of suicidal events (behavior and ideation) in patients treated with anti-epileptic drugs compared to placebo. The risk appears to be more relevant right after the start of treatment, for about two weeks and appears to be independent of the type of medication used. However, meta-analysis studies suffer from the lack of a standardized definition of suicidal behavior and ideation. The real impact on suicide of anti-epileptic drugs as an independent factor remains uncertain <sup>17</sup>.

### The psychiatric comorbidity in persons with epilepsy

Individuals with epilepsy are more likely to develop psychiatric comorbidity and this comorbidity is strongly related to the negative impact on the subjective state of health and quality of life. The greater tendency to suicide during epilepsy was often justified by the fact that it is the impaired quality of life of the person with epilepsy that makes him more prone to depressive disorders and, therefore to suicidal ideation and behaviors. As a matter of fact, 6% of the people with epilepsy also suffers from a psychiatric disorder <sup>18</sup>. The percentage rises to 10-20% in the case of temporal epilepsy and drug resistant epilepsy. The most common disorders are mood disorders (24-74%), especially depression (30%), followed by anxiety disorders (10-25%), psychosis (2-7%) and personality disorders (1-2%). This comorbidity is linked to endogenous and exogenous factors (including iatrogenic ones) and to the severity and chronicity of epilepsy. Psychiatric disorders comorbidity may precede,

be concomitant or follow the diagnosis of epilepsy. With respect to the seizures can be inter-ictal, ictal, postictal. Epilepsy is a chronic disease that alters social function, so that one could conclude that depression in epileptics is simply reactive or situational but the association may underlie the sharing or contribution of genetic and environmental common pathogenic mechanisms. However, the prevalence of depression in epilepsy is higher than in other chronic diseases of similar severity. For example, a population-based study of 181,000 individuals<sup>19</sup> found a prevalence of depression in epilepsy of 29%, compared to 17% in diabetes, 16% in asthma, 8.7% in other chronic diseases. Furthermore, not only is epilepsy a risk factor for depression, but depression can be a risk factor for epilepsy. In a case/control study in patients with new diagnosis of epilepsy a history of depression prior to seizures was found in epileptics, seven times greater than controls<sup>20</sup>. Neurological factors, including the site and lateralization of the epileptogenic focus may be important for the development of depression<sup>21</sup>. They include features of epilepsy that involve limbic structures and produce mood changes. Forced normalization<sup>22</sup> may be a paradoxical factor in the development of depression in those persons in whom seizures become abruptly well controlled by therapy. Based on these data, the role of “auto convulsive therapy” against depression or an excess of post-critical electrophysiological inhibition involving dopaminergic neurotransmitter systems have been hypothesized. Chronic subclinical limbic and para limbic seizures were believed to contribute to the genesis of affective disorders<sup>23</sup>. Also lowering the level of folic acid due to anti-epileptic drugs can influence the expression of depression in persons with epilepsy.

Inter-ictal depression is more common in focal and especially temporal lobe epilepsy. The association is based on the structural and functional relationships between the temporal regions that mediate the emotions and the frontal areas. Results of neuropsychological studies<sup>24</sup> and SPECT findings of reduced metabolism in bilateral lower frontal areas in persons with temporal lobe epilepsy and depression suggest that the development of frontal dysfunction is a necessary component in the genesis of depression in temporal lobe epileptic patients<sup>25</sup>. In the temporal lobe epilepsy, the limbic epileptogenic areas, such as amygdala, are involved in social behavior, including impulse control, anxiety, emotional memory<sup>26</sup>. Subjects with suicidal behavior often have problems with cognitive inhibition<sup>27</sup> and serotonin projection abnormalities to the prefrontal cortex.

A possible link between epilepsy, impulsivity, suicide and depression is possible. It has been proposed<sup>28</sup> that the neurophysiological substratum of seizures may predispose to a state of neuronal hyper excitability respon-

sible for the impulsiveness in epilepsy. Persons with epilepsy are four times more likely to have attempted suicide before having seizures<sup>29</sup>.

The tendency to suicide and depression cannot simply be a consequence of the poor quality of life of the persons with epilepsy and seem to indicate the role of common mechanisms underlying suicidal and epilepsy behavior. Conversely depression and suicide could be related to different mechanisms.

### Hopelessness as risk factor for suicidal ideation

The hopelessness, defined as a set of cognitive patterns leading to negative life expectancy, is an aspect of demoralization and this is a relevant risk factor for self-injurious and suicidal behavior, especially at a young age. Beck's Hopelessness Scale (BHS)<sup>30</sup> consisting of twenty items, self-administered, multidimensional, originally developed and validated in 294 patients who attempted suicide has proven to be a valuable and reliable tool for measuring suicidal risk. It measures the predisposition of persons with various mental disorders to suicidal behavior. Studies on the structure of BHS have identified three main factors of evaluation: 1) feelings towards the future, 2) loss of motivation, 3) future expectations. The long-term predictive sensitivity of BHS suggests that hopelessness is a relatively stable trait in patients who are developing a suicide risk. Further evidence indicates that hopelessness is a useful variable in determining the possibility of long-term suicide by adding credibility to the hypothesis that it is helpful in predicting suicidal risk regardless from the measures of depression<sup>31</sup>. In this case the role of emotional dysregulation must also be considered. Studies on the relationship between negative emotions and suicide, considering hopelessness as a risk factor for both ideation and suicidal behavior<sup>32</sup> are needed. Although the correlation between hopelessness and suicide is relatively high, it is not always related to actual suicidal behavior, but it may be present in people who will never attempt suicide in their lives as well as be absent in those who do.

### Hopelessness as a link between epilepsy and suicidal behaviors

Suicide and epilepsy have been hypothesized to share common neuro-physio-pathological mechanisms<sup>33</sup> that may explain the increased risk of suicide. The relationship between suicidality and epilepsy is complex, multifactorial and bi-directional. Not only do people with epilepsy present a higher risk of suicide, but, conversely, population-based studies show a five-fold greater risk of developing epilepsy among persons who experienced suicidal behavior prior to the onset of epilepsy<sup>34</sup>.

The risk seems independent from the history of depressive disorder. Population-based studies<sup>35</sup> found that people with a history of depression are four to seven times more likely to develop epilepsy. These data were explained by a common abnormal brain serotonin activity<sup>36</sup>. Epilepsy and depression may both be symptoms of superimposable neuronal network dysfunction (limbic regions). Christensen et al.<sup>5</sup> show that the risk of suicide in epileptics is 14 times higher in the presence of psychiatric comorbidity, particularly depressive disorders (32 times) and anxiety disorders (14 times). Kanner et al.<sup>37</sup> reported the frequency of post-critical suicidal ideation also in relation to post-stroke psychotic episodes. Increased risk 6 to 25-fold was reported to be associated with temporal lobe epilepsy<sup>38</sup>.

Evaluation of Hopelessness by BHS may complement the clinical approach to the epileptic patient<sup>39</sup>. The level of hopelessness may have predictive value for significant suicidal ideation in epileptic patients. Andrić et al.<sup>3</sup> found that suicidal ideation in persons with epilepsy is independently and significantly related to the level of hopelessness and unemployment as an important psychosocial factor.

In a recent study our research group investigated the association of hopelessness with demographic, social and clinical variables, in people with epilepsy without comorbidity with psychiatric disorders (Tab. I)<sup>40</sup>.

Four of the variables studied, such as temporal lobe localization, more frequent seizures rate, higher intellectual level, low socio-economical level, significantly predicted the Hopelessness evaluation. These results can be considered in agreement with the recent observation of the dissociation between function and cognitive performance, showing people with suicidal ideation worse functioning but with higher cognitive performance. It may suggest that high intelligence cannot be seen by physicians as a protective factor from

suicidal ideation<sup>41</sup>. High intellectual level could be related to higher insight of having a severe illness, above all if the seizures are very frequent and polypharmacy is needed. So, a better insight can paradoxically not lead to an advantage but can be related to depression and hopelessness eventually. This is also the case of a severe mental illness, such as schizophrenia, where the so-called 'insight paradox' is related to depression, including demoralization, decreased self-esteem, hopelessness and suicidal ideation<sup>42</sup>. Although several studies indicate that hopelessness is well conceptualized as a risk factor for suicide ideation, this does not mean that it is able to distinguish attempters from ideators, i.e. the progression from ideation to attempt<sup>43</sup>. As a matter of fact, suicidal ideation is not directly linked to the real suicidal behavior. It can be present in people that will never attempt to their life and lack in those who really commit suicides; hopelessness has not been found as a strong predictor of suicide risk, as previously imagined<sup>44</sup>. Furthermore, recent systematic literature researches on suicide prediction models have shown a very limited accuracy of prediction and practical utility<sup>45</sup>.

Although speculatively, if hopelessness, along Beck's formulation can be considered as a link between depression and suicide<sup>46</sup>, it can at least be hypothesized as link between epilepsy and suicidal ideation. These warning flags for suicidal ideation need to be coped with a complex bio-psycho-social approach<sup>47</sup>.

### Suicidal behaviors in persons with epilepsy: which interventions?

The management of the person with epilepsy, even more if suicidal ideation has been shown, is complex. The pharmacological treatment itself could become a possible risk factor for the suicide, both in relation to the timing (at the beginning or when changes in therapy are done) and related to pharmacodynamics. Possible cognitive adverse effects that may affect the socio-relational status and quality of life of the patient, should be carefully assessed. The drug resistance decreases the patient's compliance and leads to a worsening of the psychic state with accentuation of the tendency to self-injurious behaviors. Alternative treatments, such as ketogenic diet, also lead to less motivation and adherence to prescription. Surgical treatment, although directed to the etiological causes of epilepsy, is conditioned by the motivation and collaboration of the patient. In addition, the phenomenon of forced normalization with depressive reactions, even of a severe degree, is described for both pharmacological and surgical therapy. Psychiatric comorbidity, mostly with anxiety and depression, but not infrequently with personality disorders and with psychosis, requires attention especially with regard to

**TABLE I.** Risk factors for suicide behavior found associated with higher Beck Hopelessness Scale score in persons with epilepsy without psychiatric comorbidity<sup>40</sup>.

Demographic	Clinical	Socio-cultural
Female gender	Right side	High intellectual level
Young age	Temporal focus	Low socio-economic level
	Higher seizure frequency	
	Disease at onset	
	Higher number of drugs	



drug combinations so as to avoid negative interference on the effectiveness of both the treatment of seizures and of the psychopathological symptoms. Alternative techniques to drug therapy such as neuromodulation can be considered as useful therapeutic tools in people with epilepsy, even more so if with depressive psychiatric comorbidity. PET studies in people with epilepsy undergoing vagus nerve stimulation (VNS) have shown a relative activation of areas associated with depression (prefrontal dorsolateral cortex, insula, orbitofrontal cortex, cingulate gyrus)<sup>48</sup>. The proposed mechanisms for the effectiveness of the VNS are the induction of neuron plasticity at the level of the hippocampus<sup>49</sup> and the stimulation of serotonin and noradrenergic systems<sup>50</sup>. The results of an observational study of 4.5 years in depressed patients resistant to drug therapy treated with VNS confirmed its effectiveness<sup>51</sup>. Likewise, in patients with epilepsy the treatment can be considered.

The diagnosis and treatment of epilepsy are difficult to accept. Once the therapeutic process is started, psychosocial problems, which are the cause of mainly anxious and depressive disorders, often become relevant. Seizures have an extremely traumatic impact due to their sudden character. Anxious symptoms can sometimes become so overwhelming that they require psychotherapeutic intervention. It is necessary to share the patient will into the decision-making process for each stage of disease management through appropriate empowerment, or an interactive process between subject and environment suitable for improving health and well-being. A good level of empowerment allows the person with epilepsy to develop tools, safety and knowledge to interact functionally with the environment and improve the health by moving from a passive to active condition. Cognitive impairment should be evaluated in order to monitor the patient's ability to understand his condition and to implement appropriate tools both for the individual wellness and for his or her family and social context. Epilepsy punctuates everyday life and requires adaptation to the new condition. So it is necessary to remodel habits and expectations about the future, reformulate its own identity and the social role.

For many years, research has shown how in people suffering from chronic diseases, the incidence of psychopathological conditions is frequent. This not only leads to a significant deterioration in the quality of life of the patient, but also affects adherence to care. The emotional, cognitive and behavioral responses to the marked existential changes imposed by a chronic illness could be relevant. These can be expressed in various forms of psychic suffering, some of which assume the characteristics of true psychopathological pictures. Often, those who experience a disease such as epilepsy manifest depression, anxiety, high stress that make it

more difficult to cope with the new condition of life and the course of illness. The psychological management in epilepsy consists in a first phase of assessment of the subject's difficulties and resources and in planning appropriate strategies<sup>52</sup>. The psychological approach must necessarily consider the patient and its family as well as the environmental context. It is not easy to consider the perception that the patient has of his clinical condition, of his experience, of the whole family, of the possible stigma<sup>53</sup>. The epilepsy cannot only involve a risk in terms of cognitive functions but also emotional and behavioral. Both overprotection and the tendency to hide the diagnosis in the family and in the social environment could worsen the burden of epilepsy. The seizures restrict the autonomy and the chance of social integration. The social discriminations born from the fear not to know whether to do during a seizure. The psychological support is recommended at the onset of the disease. The so-called baseline from which to take the movements to check during time the functions such as attention, memory and language is needed. Difficulty of adaptation and the emotional impairment can be present at the diagnosis. It is opportune to repeat the psychological evaluation in the time, particularly during the evolutionary passages with the purpose to foresee the therapies and the necessary supports.

The psychological support is always suitable: it promotes the mechanisms of reinforcement and adaptation, it favors the adherence to the therapies and the indications of the referent neurologist, it reduces the fears and the imaginations of death tied to the seizures. It protects from the isolation and from emotional troubles. A qualitative observation and a detailed interview about cognitive and behavioral changes can result useful during the modifications of the rate of the seizures or during the variations of the therapy with the purpose to contribute to future decisions on the pharmacological and psychological treatments. From a first evaluation suitable psychological interventions will can emerge, such as support or cognitive-behavioral therapies. Focus groups and the empowerment projects could improve the management of the illness. The comparison with the group promotes personal strategies of psychological adaptation, coping and resilience, the ability to react to difficulties. The crucial problem for persons with epilepsy is to live with a chronic disease that damages autonomy, implies the fear of being alone, about the future and acceptance by others. Talking about it transforms the group into an instrument of protection, awareness and information and makes person's life more reassuring.

## Conclusions

The link between epilepsy and increased risk of suicide is evident. Either neurobiological factors related to the

site of the epileptogenic outbreak and neurotransmitters alterations as well as psychiatric comorbidity, social consequences of the illness, its unpredictable course, the incapacity resulting from the seizures and the stigma, play an important role in the patient's quality of life and in possible self-harm and suicide drifts.

This is a narrative review on the relationship between epilepsy and suicide. This kind of review presents limitations due to a lack of systematic methods in literature selections. Being the number of sources employed incomplete, a possible risk is that of having a limited knowledge base from which to draw conclusions. Although taking into account this non-negligible pitfall, this narrative review summarizes primary studies from which conclusions can be drawn into a holistic interpretation contributed by relevant existing theories and models.

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**How to cite this article:** Ciuffini R, Marrelli A, Perilli E, et al. *Epilepsy and suicide: a narrative review*. *Journal of Psychopathology* 2019;25:155-61.

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