

## Pharmacological and non-pharmacological approaches to life threatening conditions in epilepsy

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### SUMMARY

**Background.** A higher degree of mortality may be attributed to patients with epilepsy. There are several main reasons responsible – sudden unexpected death in epilepsy (SUDEP), status epilepticus (SE) and central nervous system damage. Also, epilepsy associated accidents and suicidal attempts have to be highlighted.

**Aim.** Epidemiology and therapeutic or preventive (pharmacological or non-pharmacological strategies) of the conditions increasing mortality have been reviewed so as to minimize the mortality rate in patients with epilepsy.

**Discussion and Conclusions.** Generally, the treatment of convulsive SE entails the need to achieve rapid stabilization of a patient and an appropriate choice of antiepileptic drugs (AEDs) so as to stop seizure activity. In the event of no response the treatment has to be continued under general anaesthesia. For minimizing the risk of SUDEP in young adults or patients with childhood epilepsy, adequate treatments with AEDs must be initiated or possible surgery considered. Patients with uncontrolled epilepsy require AED optimization. Although a possible link between taking AEDs and increased suicidality is questionable, patients with epilepsy are advised to be evaluated for possible symptoms of depression or anxiety. Surgical treatment of epilepsy may increase the risk of depression development, so a careful psychiatric examination is recommended prior to surgery.

**Key words:** status epilepticus • sudden • unexpected death in epilepsy • depression • suicide • injuries • epilepsy

### BACKGROUND

Mortality in the cohort of epileptic patients is considerably higher than in the general population. It is estimated to be 1.6–11.4 times higher than in healthy people and the ratio for epileptic children may be between

5.3 and up to 9.0 times higher (Lathoo, Sander, 2005). The bigger risk of death in epileptic patients is attributed to a variety of factors, which may be classified into several types.

Among the most frequently listed factors there is the course of the epilepsy underlying disease (damages of the central nervous system [CNS]), sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE). Other factors include seizure-resulting accidents (injuries, drowning, burns, choking, aspiration pneumonia after seizures), suicidal attempts of epileptic patients or the adverse impact of pharmacotherapy (Lathoo, Sander, 2005; Devinsky et al., 2016; Konopko, Rola, 2017).

Lathoo and Sander (2005) have proposed a classification which includes the following categories: epilepsy-related deaths, underlying disease-related deaths and unrelated deaths. The first category, epilepsy-related deaths, involves directly related diseases, SUDEP, SE, accidents being the outcome of seizures, suicidal attempts of epileptic patients or the adverse impact of pharmacotherapy (drug toxicity or idiosyncratic reactions to a treatment). The second category – underlying disease-related deaths – comprises such causes as primary and secondary CNS neoplasia, cerebrovascular disease, CNS infection and inherited neurodegenerative disorders. Finally, there are epilepsy-unrelated deaths, which include non-CNS neoplasia, ischemic heart disease, pneumonia and accidents unrelated to seizures (Lathoo, Sander, 2005; Devinsky et al., 2016).

## DISCUSSION

### Status epilepticus

#### *Epidemiology of SE*

Amare et al. (2008) have stated that the occurrence of SE reaches between 18 and 61 instances per 100,000 per year, with 70% of convulsive SE, secondary generalized CSE being more frequent than the primary generalized one. SE is the first symptom of epilepsy in approximately 10% of cases (Amare et al., 2008). Epileptic patients display a higher risk of SE when they withdraw from taking AEDs. Other contributing factors include additional diseases or co-occurring metabolic dysfunctions (Towne et al., 1994). The risk of the occurrence of SE in individuals who had not been identified as epileptics could be increased by structural brain disturbances, metabolic disorders as well as toxic substances and addictions (Lowenstein, 1999).

The frequency of SE is claimed to be 9.9 per year per 100 000 of the inhabitants of the French-speaking regions in Switzerland (Coyetaux et al., 2000), 13.1 – 16.5 in Italy (Vignatelli et al., 2003; 2005), and 15.8 in Germany (Knake et al., 2001). Mortality as a result of SE

has been determined to reach 20–40% and it depends on its cause, duration, patient's age, co-occurring diseases, etc. (Lowenstein, 1999).

Epileptic patients are clearly more prone to risk of death induced by SE, but some of them more than the others. The risk factors linked with higher probability of decease include old age, being male, prolonged SE, as well as acute symptomatic aetiology (nervous system infections, stroke or metabolic dysfunctions; Beghi et al., 2005; Devinsky et al., 2016). Lower mortality in SE is found with idiopathic etiology or AEDs withdrawal (Amare et al., 2008).

#### *Propositions for a new definition of SE*

One of the first definitions of the SE was presented in 1876 by Trousseau, who wrote “In the SE when the convulsive condition is almost continuous, something special takes place which requires an explanation” (Trinka et al., 2015).

In 1964, Gastaut and colleagues coined a more modern and precise definition of SE, described as a “seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition” (Trinka et al., 2015). SE is considered to take place if there were recurring seizures and a patient remains unconscious for 60 minutes between seizures. A similar concept was proposed in 1983 by the International League Against Epilepsy (ILAE) and the World Federation of Neurology. More recent definitions specify the seizure duration as 30 minutes (Trinka et al., 2015). The most recent definition of SE, formulated by Trinka et al. (2015), specifies time point t1 and t2 and it describes SE as a disorder resulting from failure of mechanisms responsible for seizure termination or initiation of mechanisms leading to prolonged seizure duration beyond time point t1. Time point t1 is an indicator of a period during which treatment of SE should be initiated, whereas time point t2 indicates the border after which there is a risk of long-term consequences of SE. These consequences may include neuronal death, neuronal injury or alteration of neuronal networks, depending upon the type and duration of seizures (Beghi et al., 2005).

The convulsive SE is considered to occur when a time point t1 is equal to 5 minutes, and t2 reaches 30 minutes. A focal SE with impaired consciousness is considered to occur if the time values for time points t1 and t2 are 10 minutes and more than 60 minutes respectively (Beghi et al., 2005). As highlighted previously, Trin-

ka et al. (2015) developed a concept of two time points,  $t_1$  and  $t_2$ . Those two points indicate at possible consequences of the SE if their duration is exceeded. The time limits are varied for different types of SE. For the tonic-clonic SE, the values of each time point is 5 and 30 minutes respectively. In case of focal SE with impaired consciousness, the duration of  $t_1$  is 10 minutes, whereas the value for  $t_2$  is longer than 60 minutes. As regards the absence SE, the value for the first time point is considered to be 5–10 minutes, and it is unknown for  $t_2$ . However, the scientific evidence for the time frame is currently not sufficient and potential findings in the future may modify these current values.

### **Treatment of SE**

Based on a variety of input data from patients' observations, Trinka et al. (2015) postulate that treatment of convulsive seizures should begin within approximately 5 minutes. Regardless of the above information, it must be stressed that time limits provided are constructed mainly for operational purposes only and the onset timing may vary significantly in different clinical circumstances (Lathoo, Sander, 2005; Devinsky et al., 2016). It is estimated that at least half of the patients with SE do not have epilepsy or do not demonstrate specific epilepsy syndromes. A new classification of SE, proposed by Trinka et al. (2015) incorporates four underlying elements: semiology, etiology, electro-encephalographic (EEG) correlates and age. These elements are considered to provide a framework so that it is possible to establish clinical diagnosis and carry out a specific therapeutic approach for each patient (Trinka et al., 2015). The classification takes into account extremely important non-convulsive SE. It is a descriptive term denoting instances of SE with very little or no clinical signs of ongoing seizures except for obtundation or subtle motor phenomena (Kinney et al., 2017).

The primary goal of treating convulsive SE is quick termination of seizure activity, stabilization of a patient and instituting a proper anticonvulsive treatment to prevent pulmonary edema and arrhythmia (Stölberger, Finsterer, 2004; Jones et al., 2014). The variety of causes and symptoms in SE require a careful and complex procedure to design efficient treatment. Taking care of SE incorporates the treatment of early SE (according to the old definition, 30 minutes as of its onset), established SE (30 – 120 minutes as of the onset), refractory SE (more than 120 minutes) and super-refractory SE (exceeding 24 hours; Trinka et al., 2015; Glauser et al., 2016).

Glauser et al. (2016) have developed and proposed an algorithm for treating SE at various stages, corresponding to the time values presented above. According to the model, stage 1 is the treatment of the early SE. At this stage, it is recommended to administer benzodiazepines (e.g. intravenously (IV) lorazepam, buccal midazolam, IV or rectal diazepam). The second stage is the established SE. The recommended agents during this stage are IV AEDs – such as phenytoin, phenobarbital or valproate. If the SE continues and the patient does not respond to stage 1 and stage 2 treatments, then the advised course is to continue treatment under general anaesthesia (recommended agents include propofol, midazolam, thiopental/pentobarbital; Glauser et al., 2016).

A loading dose of valproate or levetiracetam may be administered IV. However, only 7% of patients who have not responded to timely and appropriate AED doses during previous stages will then respond to any AED during the third stage (Treiman et al., 1998). Third-line AEDs are used mainly to avoid intubation. Stage 4 occurs when the SE continues or recurs for 24 hours or more even though a general therapy with anaesthesia had been utilized (Treiman et al., 1998).

Glauser et al. (2016) have developed and proposed the following protocol for treating SE. The first stage is called the Stabilization Phase and its duration is five minutes. The primary task during this stage is to stabilize the patient, checking airways, breathing and circulation function and perform neurological examination in order to identify any disability. While continuing monitoring vital signs, assess patient's oxygenation, providing oxygen by means of nasal mask. If respiratory assistance is required, it might be necessary to utilize intubation. The following steps at this stage are initiating ECG monitoring and checking blood glucose level. If it is below 60 mg/dl, it is recommended to administer thiamine (adults 100 mg IV, then 50 ml D50W IV; children older than 2: 2ml/kg D25W IV, less than 2 years old: 4 mg/kg D12.5W). The final step is to try gaining IV access and check the level of electrolytes, haematology, perform a toxicology screen and measure anticonvulsant drug levels (Glauser et al., 2016). The following stage is called Initial Therapy Phase and it takes between 5 and 20 minutes from the onset. The recommended course of action at this stage is administering benzodiazepines. If seizures do not stop, then the treatment with recommended AEDs and dosages should be continued. Otherwise, if patient is at the baseline, then employing symptomatic medical care is recommended

(Glauser et al., 2016). The second stage therapy phase takes place during the 20–40-minute time bracket. However, during this phase, there is no preferred evidence-based procedure. The recommended courses to be followed and agents to be administered to patients include fosphenytoin, valproate, levetiracetam (IV) or if these are not available, then IV phenobarbital should be used. Note, that only one second line option should be chosen and administered as a single dose (Glauser et al., 2016). The third stage therapy phase occurs between 40 and 60 minutes from SE onset. Again, at this stage, there are no evidence-based therapies to be recommended, but it is suggested to repeat the second line therapy with general anaesthetics (using thiopental, midazolam, pentobarbital or propofol). Also, EEG monitoring must be performed continuously. As in the above phases, if seizures do not stop, continue the therapy and if the patient is at the baseline, then employ symptomatic medical care (Glauser et al., 2016).

Other recommendations for treating SE in adult patients were proposed by Jones et al. (2014) in the In-Hospital Emergency Drug Management of Convulsive SE in Adults. The first treatment step in the event of SE is administering benzodiazepines for longer than five minutes. The first-choice drugs at this stage are lorazepam (IV), diazepam (IV) or clonazepam (IV). If IV administration is not possible or difficult, then buccal midazolam may be given (alternatively – injection through a buccal route or intramuscular injection). If the above methods are difficult or impossible then the alternative is administering diazepam rectally. Even if the seizures stop, the recurrence rate after this stage is relatively high. Therefore, it is recommended that most patients receive an IV stage 2 AED to prevent further seizures (Jones et al., 2014). The second step of the protocol proposed by Jones et al. (2014) should be implemented when no response to Step 1 treatment is visible within 10 minutes. The recommended agents at this stage include one of the following: phenytoin, levetiracetam, sodium valproate or phenobarbital. These agents should be considered as alternatives and administered intravenously (Jones et al., 2014). If phenytoin is given, patient should constantly have electrocardiogram (ECG) and blood pressure monitored due to a risk of hypotension and bradycardia. As regards sodium valproate, it should be avoided in SE of an unknown cause in young patients. Also, caution is recommended for pregnant women or if patients suffer from acute liver failure. In such situations, alternative agents are

recommended. In case of phenobarbital, it is extremely important to monitor blood pressure, ECG and respiratory function. The latter function is of paramount importance since phenobarbital may induce respiratory depression. Therefore, it should be administered only if ventilator support is available. One of the requirements at this stage is informing a neurointensivist or experienced anaesthetist about the patient and his or her condition (Jones et al., 2014). Step 3 is implemented when there is no response to Step 2 within 30 minutes as of the onset. If patients are hemodynamically stable at that stage, it is recommended to optimize the dose of the initial second stage AED and consider administering an alternative second stage drug. Patients should receive anaesthesia (with intubation and ventilation) and be admitted to the intensive care unit. Also, like in the previous step, a neurointensivist or an experienced anaesthetist should be made aware of the patient and his or her condition. During this stage, patients should be administered propofol, thiopentone or midazolam (if patients are already ventilated; Jones et al., 2014).

The American Epilepsy Society recommends the following currently available AEDs to be used for treating convulsive SE in adult patients and in children during post-neonatal period. The first line AEDs to be used as primary agents include midazolam (IM), diazepam (IV) and lorazepam (IV), and if these are not possible to utilise, then alternatives are recommended: diazepam (rectally), phenobarbital (IV), midazolam (buccally) or midazolam (nasally). The second line AEDs include valproic acid (IV), levetiracetam (IV), phenytoin (IV), fosphenytoin (IV), as a primary choice. The alternatives comprise phenobarbital (IV) (Glauser et al., 2016). As highlighted above, if SE lasts 120 minutes or longer, it is referred to as the refractory SE. This stage is assumed to occur in approximately 25–35% of epileptic patients. In the event of refractory SE, the recommended protocol is either repeating the second-line therapy or administering general anaesthesia (recommended agents include propofol, midazolam, thiopental/ pentobarbital). Patient must be EEG monitored at all times and the treatment should take place in an intensive care unit (Glauser et al., 2016).

If the SE does not stop or recurs after 24 hours from onset, despite administering timely and appropriate doses of AEDs with general anaesthesia, it is referred to as the super-refractory SE. The options that may be employed as a part of therapy include enteral administration of topiramate (up to 1600 mg/d), IV la-

cosamide (200–600 mg), ketamine (0.9–3 mg/kg – 0.3–7.5 mg/kg/h), or magnesium sulphate (IV, saturation dose; 3–6 g). Other substances and methods that may be considered include corticosteroids (IVIG), plasmapheresis, but also ketogenic diet, VNS (Vagus Nerve Stimulation), ECT (Electroconvulsive therapy) and rTMS (Repetitive Transcranial Magnetic Stimulation; Glauser et al., 2016).

### Sudden unexpected death in epilepsy (sudep)

#### *Definition and criteria*

The acronym SUDEP refers to the disorder known as Sudden Unexpected Death in Epilepsy, or “death in the shadows”, as some authors call it (Thom et al., 2016; Shankar et al., 2017). Nashef et al. (2012) defined SUDEP as a sudden, unexpected death of an individual with recognized epilepsy. Death is not related to trauma or drowning, and it may be witnessed or not, also, it may be with or without evidence for a seizure (Nashef et al., 2012; Laxer et al., 2014). Annegers (1997) defined SUDEP by providing criteria for its identification. SUDEP may be recognized if the victim had epilepsy, understood as recurrent unprovoked seizures. The second criterion of possible SUDEP is when the patients are dying unexpectedly even though their health condition could be described as reasonable. Another distinguishing factor is when the patient died suddenly and also when death occurred during normal life activities and regular circumstances. A strong prerequisite for possible SUDEP identification is a lack of obvious medical causes of death. Based on the above criteria, SUDEP has been classified into the following types. When all the above criteria have been met and confirmed in a post-mortem medical examination, it may be described as a definite SUDEP. Probable SUDEP also meets those criteria but it lacks sufficient medical post-mortem evidence. SUDEP is considered possible when the circumstances as to the patient’s death are unclear and could have been caused by other factors. Finally, SUDEP is regarded unlikely when the cause of death has been clearly determined or the circumstances indicate that the cause of death could not have been SUDEP (Annegers, 1997; Bell, Sander, 2006). Nashef et al. (2012) also distinguished the category of Definite SUDEP plus and the Experienced SUDEP whilst Shankar et al. (2017) are of the opinion that there are even more categories of this particular condition.

#### *SUDEP epidemiology*

The estimated occurrence of SUDEP in the overall population of epileptic patients, expressed as a ratio, accounts for 0.58 per 1000 patient-years (the ratio may range within 95% confidence intervals: 0.31 and 1.08). The incidence ratio in childhood patients is assessed to be 0.22 per 1000 patient-years (the range may vary between 0.16 and 0.31), whereas in adult patients it is 1.2 (0.64–2.32). Based on the findings, it may be considered that SUDEP is the cause of death in 8–17% of patients with epilepsy (Hesdorffer et al., 2011; Harden et al., 2017).

#### *Hypotheses on the SUDEP pathomechanism*

The literature presents various hypotheses regarding the pathomechanisms of SUDEP, defining them as underlying causes of the disorder. However, it must be stressed that current knowledge of pathophysiology and underlying neurobiology is insufficient, and these hypotheses may, and probably will, be subject to change in the future.

One of the possible pathomechanisms of SUDEP is the Central Sleep Apnoea, being the result of seizure activity propagation onto the respiratory centre and its blockage with secondary hypoxia (Walczak, 2003; So, 2006; Richerson et al., 2016). Another mechanism is the impairment of the respiratory ducts patency as a result of larynx spasm with secondary asphyxia (Hesdorffer, Tomson, 2013; Kennedy et al., 2015). It is also suggested that SUDEP may be caused by neurogenic pulmonary oedema, which is the result of severe  $\alpha$  adrenergic response, generalized contraction of pulmonary vessel and increased pulmonary pressure (Leestma et al., 1997; Walczak, 2003).

SUDEP may also be induced by cardiac rhythm disorders, mainly tachyarrhythmia and bradyarrhythmia, which are caused by dysfunction of the autonomous nervous system. There is evidence which indicates that SUDEP may overlap with sudden cardiac death or sudden infant death syndrome. An important thing to remember is the fact that life-threatening cardiac disorders can demonstrate in a very similar manner to epilepsy (Walczak, 2003; Lee, Devinsky, 2005; Lamberts et al., 2012; Goldman et al., 2016). It is often recommended that in case of epileptic patients a cardiac history and ECG should be obtained and the family history of sudden or unexpected deaths should be investigated (Nousiainen et al., 1989; Bergfeldt, 2003; Lee, Devinsky, 2005; Lamberts et al., 2012). One of the possible patho-

mechanisms of SUDEP is suboptimal AED concentrations or rapid withdrawal of AEDs. Similar effect may be caused by some AEDs, especially those modifying the action of sodium channels, which affect the functions of the autonomous nervous system (Nousiainen et al., 1989; Bergfeldt, 2003; Lee, Devinsky, 2005; Lamberts et al., 2012). Some authors also indicate at genetic predispositions, especially those linked with mutations in the genes responsible for developing the long QT syndrome (Konopko, Rola, 2017). Certain findings reveal that mutations in genetic epilepsies may increase predisposition to sudden death and susceptibility in acquired epilepsies (Konopko, Rola, 2017).

Apart from SUDEP pathomechanisms, there are also risk factors which are hypothesized to increase the probability of the SUDEP occurrence. There are the following risk factors that seem to foster SUDEP: male, young age (less than 45), long time (chronic) epilepsy (15–30 years), early onset of a disease, insufficient treatment history, epilepsy with tonic-clonic seizure, night time seizures, high frequency of epileptic seizures, multiple drug therapy and frequent changes of pharmacotherapy, excessive use of alcohol, frontal lobe epilepsy, mental dysfunctions, co-occurring anxiety and depression disorders, and using lamotrigine (women in particular) (Tomson, 2000; Tomson et al., 2005; Hesdorffer, Tomson, 2013; Tomson et al., 2013; Holst et al., 2013; Granbichler et al., 2015; Tomson et al., 2016). According to Walczak (2003), the results of most studies have not revealed a relationship between any AED and SUDEP. There are, however, suggestions that carbamazepine may be a risk factor due to its association with arrhythmia or disturbed cardiac autonomic function (Walczak, 2003).

#### **Potential strategies for preventing SUDEP in high-risk patients**

As highlighted above, the various factors could indicate a higher probability of SUDEP occurrence. Therefore, it is advisable to develop strategies that will provide the optimum results should a specific risk factor or potentially terminal circumstances occur (Kiani et al., 2014). For young adults suffering from epilepsy or for individuals with childhood epilepsy onset, it is advisable to provide immediate medical and surgical treatment that will minimize the risk of SUDEP (Bell, Sander, 2006; Johnston, Smith, 2007). For patients suffering from uncontrolled epilepsy or those displaying generalized tonic-clonic seizures the advisable strate-

gy is AED optimization. It may also be recommended to consider epilepsy surgery. In case of suboptimal AED concentrations, the recommended course is improving drug compliance and providing patient supervision. The recommended strategy for patients taking multiple AEDs is decreasing AED administration, whereas frequent changes/adjustments in pharmacotherapy may require regimen stabilization. As regards other risk factors, the abuse of alcohol (or other substances) may require abstention (if possible), whereas the recommended strategy for mental disorders or retardation is increased supervision (Ryvlin et al., 2011; 2013; Maguire et al., 2016).

In case of potentially terminal events, the strategies aim at reducing the impact of a given event and prevent patient's death. Therefore, a recommended strategy for seizure occurrence is increased supervision and seizure alarm; pulmonary oedema should be identified and treated; the strategy for apnea or hypoxia is monitoring of pulse oximetry as well as stimulation and oxygenation (Hirsch, 2009; Nashef, Richardson, 2016). Cardiac monitor and pacemaker are recommended if asystole occurs and the strategy for suffocation is changing the environment in which the patient is currently placed or changing patient's location (Klenerman et al., 1993; Rugg-Gun et al., 2016).

#### **Discussing the issue of SUDEP with epilepsy patients**

Despite its extremely significant impact upon patients' well-being and a potentially lethal outcome, physicians rarely discuss SUDEP with their patients. According to some authors, only 2.7% of neurologists and child neurologists in Austria, Germany and Switzerland address this issue with their patients (Strzelczyk et al., 2016). On the other hand, 92.9% of neurologists pass on the information that operating mechanical vehicles is prohibited and 81.5% pass on information regarding the everyday problems and limitations experienced and faced by epileptic patients (Kroner et al., 2014; Miller et al., 2014; Strzelczyk et al., 2016).

Donner et al. (2016) present the outcome of a survey carried out in a group of British physicians in 2006. The results indicate that only 4.7% of them highlight the issue of SUDEP to all patients, whereas 25.6% discuss it with the majority of patients and 7.6% never bring it to the attention of anyone. In 2015, 20% of physicians were noted to pass important information to all families, whereas 7% never brought it to the attention of any patient (Donner et al., 2015).

## Suicides

The problem of suicide is extremely urgent in the population of epileptic patients. It is estimated that suicidal thoughts are twice as frequent in epileptics as in general population, with 12% found in epileptic children and 20% in adolescents. When compared with the general population, other suicide-related symptoms are also higher in epileptic patients. It has been reported that suicidal attempts were more frequent by 4.6–30%, whereas actually committed suicides were more frequent by 2.3–14%. The mortality rate as a result of suicidal attempts is ten times higher than in the general population. This value is even larger in case of frontal lobe epilepsy patients, with a staggering 25 times higher value (Bell, Sander, 2009; Hesdorffer, Kanner, 2009; Bell et al., 2009; Greydanus et al., 2010; Bagary, 2011; Mula, Sander, 2013; Mula et al., 2013).

Between 2003 and 2011, an analysis was carried out of the suicidal incidents among epileptic patients in 17 US states. The annual suicide ratio amounted to 16.89/100,000, and the risk of committing suicide in this group was 22% higher than in general population, in particular in the 40–49 age bracket – suicides committed by poisoning (Tian et al., 2016).

### *Risk factors of suicide in epileptic patients*

It is possible to identify a variety of general and epilepsy-specific factors which frequently occur in suicide attempts. The general ones include the sense of solitude, suicidal attempts in close family or friends, suicidal thoughts and mental disorders. The epilepsy-specific risk factors linked with suicide comprise such aspects as stigmatization and discrimination, but also taking medicines which may induce depression effects as well as easy access to a large number of toxic drugs (Grabowska-Grzyb, 2005; Ferrer et al., 2014).

### *Is there an association between taking AEDs and the suicide rate?*

The issue of increased suicidality induced by AEDs still triggers controversies and requires further investigation. In 2008, an alert was issued by the U.S Food and Drug Administration (FDA) about the increased risk of committing suicides for 11 AEDs after conducting 199 clinical trials. Actually, “an increased risk of suicidal thoughts and behaviors (suicidality)” was postulated in patients prescribed AEDs. The FDA postulated a warning to be placed on the labels. In the end, it has not been introduced due to insufficient data, an ex-

tremely heterogeneous nature of risk linked with different AEDs and positive effects of the drugs offsetting rather minor adversities and potential suicidality (Mula, 2018). It was recommended, however, that epileptic patients undergo a routine evaluation for symptoms of depression or anxiety that may eventually lead to a suicide (Maguire et al., 2014).

Undoubtedly, the FDA alert stimulated attempts to evaluate the possible relationship between taking AEDs and suicidal ideation – the number of publications on this issue has sharply increased, starting from 2008 (Mula, 2018). Also, drug companies are interested in gathering the respective data from clinical trials with the use of AEDs. Among an increasing number of clinicians, this problem seems to be adequately considered although still many of them do not properly screen patients with epilepsy for the occurrence of depression or possible suicidal thoughts (Mula, 2018).

### **Epilepsy and depression – epidemiology**

The higher probability of epileptic patients developing depression is a well-grounded fact, proven by the following data. Depression occurs in 9–37% of epileptic patients compared to 9–10% of individuals with other diseases and 6–19% of the general population, as indicated by the studies carried out in Canada, the US and the UK. Similar studies in South Korea reveal a ratio of 27.8% in epileptic patients vs 8.8% in healthy population. Depression is almost six times more likely in the cohort of epileptic patients with frequent seizures than in those in remission (33% vs 6% respectively). It occurs more often in patients with poor seizure control compared to patients that are well-controlled (54.3% vs 23.8% respectively). There is also a contrast between epileptic individuals with well controlled epilepsy and healthy population – approximately 14% of the former may experience depression compared to 8.8% in the latter group (Kwon, Park, 2014).

### **Depression and anxiety in people with epilepsy**

As highlighted above, epileptic patients are significantly more likely to experience depression than the general healthy population. There are numerous risk factors that are found in epileptics which may be associated with potential occurrence of depression. These include complex partial seizures, large frequency of seizures, seizure focus in the temporal lobe of a brain's dominating hemisphere, use of barbiturates and benzodiazepines or the condition of seizure-free patients

after temporal lobe resection. Interestingly, risk factors need not be of a medical or health-related nature. Depression and anxiety could be triggered and intensified as a result of social isolation/exclusion (Grabowska-Grzyb, 2005).

Patients with epilepsy who undergo surgical treatment are susceptible to a higher risk of developing depression. The treatment may lead to a depression or anxiety in one out of 2–3 patients (up to 30%) (Kanner, Balabanov, 2008). Personality disorders and psychoses are less frequent (Koch-Stoecker, 2002). It is therefore recommended to carry out a scrupulous psychiatric examination before the procedure so that such risks could be eliminated or minimized.

### **Injuries and body damage**

Epilepsy patients are more prone to experiencing injuries, with a probability ratio estimated to be on average 3.42 (2.5–4.69) higher than in the general population. The most susceptible patients are those with generalised tonic-clonic seizures as well as those with poorly controlled seizures (Ficker, 2000; Asadi-Pooya et al., 2012; Sajjan et al., 2016).

After a 24-year observation, it was found that 1 out of 10 children with epilepsy experienced serious injuries as a result of seizures. The majority of injuries occurred in the patients with frequent seizures. Therefore, it may be emphasised that the best way to prevent injuries is to ensure better seizure control (Forsgren et al., 2005; Wirrell, 2006; Beghi, 2009; Camfield, Camfield, 2015).

While analysing different types of injury, it becomes evident that patients with epilepsy demonstrate a higher probability of experiencing almost all types of injury compared to the control group. Expressed as total values, both groups present a relatively low risk of having burns (4.5% in epileptic patients vs 1.4% in the control group), fractures (5.3% vs 2.8%), head injury (1.9% vs 0.7%) and dental injuries (4.5% vs 1.7%). The differences and total values are significant in soft tissue injuries, with 43.6% of epileptic patients and 10% in the control group exposed to the risk. Interestingly, the individuals from the control group are more likely to be involved in car accidents when compared to epileptic patients (1% vs 0.4% respectively), but this may be the result of driving restrictions introduced for epileptic patients (Tomson et al., 2004; Tellez-Zenteno et al., 2010; Asadi-Pooya et al., 2012).

Preventing injuries in patients with epilepsy may not always be easy, but there are certain guidelines

that could be applied, depending on patients' lifestyle and everyday activities. Some procedures for all patients include aggressive treatment of epilepsy, minimization of drug-related ataxia, but also regular physical activity in order to maintain bone mass or swimming in the presence of another person. For higher risk patients, the preventive measures include bathing under supervision, avoiding hot objects so as to prevent burns, wearing helmets (for some patients) and avoiding high places (Spitz, 1998; Ficker, 2000; Nei, Bagla, 2007; Gayatri et al., 2010).

### **CONCLUSIONS**

Epilepsy-related deaths comprise cases of SUDEP, SE, suicides and accidents associated with seizure activity. In order to reduce the possibility of SUDEP, the occurrence of generalized tonic-clonic seizures must be reduced because these seizures are the main risk for SUDEP. According to Harden et al. (2017), a reduction in the risk of SUDEP may be treated as an additional benefit to other obvious benefits. Considering that nocturnal seizures associated with postictal respiratory depression may also result in SUDEP, a presence of a bedroom observer would be recommended (Harden et al., 2017).

It is remarkable that the number of patients without epilepsy, in whom SE may occur, is close to 50%. As a serious life-threatening condition, the treatment of SE must begin as soon as possible, and the main goal of treatment is aimed on the cessation of seizure activity. In the early stage of SE, benzodiazepines (preferably intravenously) are recommended and if the seizure activity does not stop then, in the next stage, IV phenytoin, phenobarbital or valproate may be administered. General anaesthesia may be required if the above treatments fail.

Although a possible association between taking some AEDs and committing suicides has been postulated, this negative relationship has not been proven. Nevertheless, patients with epilepsy require continuous monitoring for the occurrence of depression or suicidal ideation. One has to consider that these patients have been found particularly prone to depression and suicide and serotonin reuptake inhibitors may be considered for the treatment of depression in such patients (Błaszczyk, Czuczwar, 2016). Usually, these drugs do not lower the convulsive threshold and some of them may even elevate this parameter (Błaszczyk, Czuczwar, 2016).

Epilepsy may be well controlled in the majority of epileptic patients, and apart from certain disease-relat-

ed inconveniences, these people can have normal lives. However, epilepsy can show a different and more dangerous face, which can bring a significant risk to patients and lead to their death. The particularly dangerous disorders are SE, SUDEP or higher risk of suicides.

It is extremely important to promote awareness of such risks and develop knowledge of the symptoms, and identification and proper procedures if they occur. It is not an exaggeration to claim that such knowledge and procedures can save many lives.

The problem of AED misuse may significantly interfere with the issues discussed in this review. Usually, drug misuse in patients with epilepsy may be related to irregular AED consumption, omissions of single doses and even self-dependent changes in the daily drug load which may be elevated or reduced. Noteworthy, the fraction of non-compliant patients ranges from 20 to even 80%, the most frequently encountered type of misuse being drug omissions (Piskorska et al., 2013). Evidently, this particular problem seems responsible for the significant increases in seizure frequency or AED toxicity, eventually leading to an elevated probability of life-threatening conditions. Worsened quality of life or poor professional or educational performance may further provoke untoward ideation in patients with epilepsy. Evidently, good compliance means that the possibility of life-threatening events will be considerably reduced.

Osteoporotic patients with epilepsy may pose a complex clinical problem as mostly endangered with serious pathological fractures and some AEDs may actually be responsible for the reduction of bone mineral density. In particular enzyme inducing AEDs have been well documented in this respect. On the other hand, lamotrigine, and to a lower degree – levetiracetam, seem one of the most recommended AEDs to patients with epilepsy facing the problem of osteoporosis (Miziak et al., 2016). It is quite obvious that tailoring AEDs showing the best protective activity against a given type(s) of seizures and lowest adverse potential is not always possible. Therefore, in patients with ongoing osteoporosis and prescribed hepatic enzyme inducing AEDs (carbamazepine, phenobarbital or phenytoin), preventing measures are recommended (treatment with bisphosphonates). Possibly, bisphosphonates can also be used in patients with epilepsy in whom osteoporosis is diagnosed (Miziak et al., 2016).

Although there are many antidepressant drugs which can be safely administered to patients with epilepsy

with depression, there are some antidepressants, identified pre-clinically, as potentially hazardous to this patient population with similar clinical data on this issue. These antidepressants include bupropion, clomipramine and maprotiline and their use in patients with epilepsy should be discouraged (Banach et al., 2016). The probability of pharmacokinetic interactions between AEDs and antidepressant drugs need to be considered. Although some combinations of these drugs display such interactions, dose adjustments may be only necessary on an individual basis. However, drug monitoring may prove inevitable when the combined treatment with AEDs and antidepressants leads to an increase in seizure frequency or evident drug toxicity. On this basis, dose adjustments may be implemented (Banach et al., 2016).

#### CONFLICT OF INTERESTS DISCLOSURE

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