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Long-term consequences associated with antiepileptic therapy

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One percent of the world’s population – ca. 50 million people, suffer from epilepsy and two million new cases are diagnosed each year [Villanueva et al., Epilepsy Behav, 2010]. Considering the choice of antiepileptic drug (AED), it is necessary to take into account the possible long-term consequences of therapy. Apart from the type of seizure or epileptic syndrome, also age, gender, the need for long-term therapy, co-existing diseases, and possible adverse effects are important factors when planning the antiepileptic therapy. In female patients, an impact of AEDs (especially from the group of inducers of liver enzymes) upon contraception is of pivotal importance in that they may lead to a 6% failure of oral contraceptive drug. Also, hormonal implants and patches may be less effective in women on antiepileptic therapy. It is noteworthy that gabapentin, lacosamide, levetiracetam, pregabalin, valproate, and vigabatrin show no interaction with oral contraception [Pollard and Delanty, Neurology, 2007]. As regards pregnancy, for 1000 pregnant women around 3–4 are epileptic patients on antiepileptic therapy [Morrow et al., J Neurol Neurosurg Psychiat, 2006]. Antiepileptic treatment may be associated with a risk of even serious malformations, pregnancy loss or genetic abnormalities. The risk of malformations is positively correlated with valproate. Therefore, its dosage needs to be maintained below 1000 mg daily and combinations of valproate with lamotrigine are to be avoided. Supplementation with folic acid at 4–5 mg daily is recommended [Artama et al., Neurology, 2005].

Valproate used during pregnancy may have a negative impact upon cognitive functions of children born to epileptic mothers. For instance, 30% of children from mothers treated with valproate usually require special education during school years and this percentage is considerably lower for other monotherapies. Also, the weaker development in children below six years old is observed [Renisch et al., JAMA, 1995; Adab et al., J Neurol Neurosurg Psychiat, 2001; 2004; Gaily et al., Neurology, 2004; Vinien et al., Neurology, 2005].

The frequency of epilepsy occurrence is comparative in men and women. For men, it is associated with a fourfold higher risk of accidents associated with epilepsy in the group with symptomatic etiology than in the case of epilepsy of unknown etiology [Wirrell, Epilepsia, 2006], a higher risk of developing SUDEP (Sudden Unexpected Death in Epilepsy), especially in young men [Nashef and Tomson, Epilepsy. A Comprehensive Textbook, 2007], sexual dysfunction, manifested by loss of libido, impotence and infertility. The presence of sexual dysfunction may occur in 32% of epileptic men, and even 44.7% of patients reported erectile dysfunction [Herzog et al, Neurology, 2005]. Importantly, these mentioned above disorders result not only from adverse effects of AEDs, but may be also associated with the epileptic syndrome, type of seizure (complex partial seizures), duration of illness, sociodemographic factors such as age or the relationship between partners.

AEDs may induce cosmetic side effects such as: a possible weight gain associated with valproate, vigabatrin, gabapentin, or a possible loss of weight following topiramate, hair loss while using of valproate, or allergic reactions. Rash is encountered in 15.9% of patients on antiepileptic therapy [Arif et al., Neurology, 2007]. Interestingly, women are more sensitive than men in this respect [Alvestad et al., Epilepsia, 2007]. The risk of allergic reactions may be reduced by slow and gradual increase in doses of AEDs. This is especially important for lamotrigine, carbamazepine, and phenytoin [Zaccara et al., Epilepsia, 2007]. In limited cases, allergic reactions may be severe – for instance erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (Lyell’s syndrome) [Alvestad et al., Epilepsia, 2007]. Although AED Hypersensitivity Syndrome is rare, it may be a life-threatening condition. The syndrome is characterized with a triad of symptoms: fever, rash, and damage to internal organs and there is a significant risk of cross-reactivity among AEDs.

For allergic patients with generalized seizures, the following AEDs are recommended: levetiracetam, topiramate, and valproate and for those with partial seizures – gabapentin, levetiracetam, pregabalin, or topiramate [Knowles et al., Drug Safety, 1999; Kwong et al., J Ped Child Health, 2006; Alvestad et...
The risk of allergic reactions to AEDs may bear a genetic component. For instance, there is an association between the increased risk of Stennes-Johnson syndrome or toxic epidermal necrolysis after carbamazepine in patients with HLA-B 1502, primarily in Asians – 10–15% of the population. On the other hand, carbamazepine-induced allergic reactions among patients from Northern Europe are more frequent in those who have HLA-A 3101 allele [McCormack et al., N Engl J Med, 2011].

AEDs may exert negative effects on cognitive functions. Phenobarbital or phenytoin produce the most significant impact of in this respect; carbamazepine, valproate, topiramate, zonisamide exert moderate effects whilst and the modest impact may be ascribed to gabapentin, lamotrigine, and levetiracetam [Aldenkamp et al., Epilepsia, 2003; Park and Kwon, J Clin Neurol, 2008]. To minimize the side effects in the form of cognitive impairment resulting from the use of AEDs it is recommended to slowly increase the dose; use the lowest effective dose; if possible, avoid drugs in monotherapy that significantly affect the cognitive functions (such as phenobarbital), if treatment requires the application of polytherapy use the smallest effective dose [Park and Kwon, J Clin Neurol, 2008].

People with epilepsy are thought to be at an increased risk of accidents and injuries. Head injuries, motor vehicle accidents, burns and submersion injuries are among the most feared epilepsy related injuries [Tomson et al., Epilepsy Res, 2004]. In addition to life style circumstances also psychomotor disturbances in course of illness and side effects of antiepileptic drugs may contribute to the risk of injuries in patients with epilepsy [Wirrell, Epilepsia, 2006]. These risks result in stigmatization of patients and contribute to a number of limitations in their daily living activities. Injuries as a result of epilepsy are still an important concern for patients caregivers and employers.

The use of AEDs may produce a risk of suicide among epileptic patients. Suicidal thoughts are observed in 12% of epileptic patients (6% in general population) and this can be even higher in children and adolescents, in whom 20% of patients may be affected. The suicide mortality rate is in the range of 11.5%, which is 10 times higher as compared with the general population [Hesdorffer and Kanner, Epilepsia, 2009]. When patients with temporal lobe epilepsy are considered, the mortality rate can be even 25 times higher [Greydanus et al., Dev Med Child Neurol, 2010; Caplan, Epilepsia, 2005]. Risk factors for suicide include previous psychiatric disorders, poor health, young age of epilepsy occurrence (below 18 years of age), organic brain damage, ineffective treatment, access to firearms and interictal personality disorders [Nilsson, Epilepsia, 2002; Greydanus et al., Dev Med Child Neurol, 2010].

The improper treatment of epilepsy may be associated with the possibility of SUDEP. An increased risk of SUDEP is encountered in patients with frequent seizures; those, who undergo polytherapy; those with a long duration of epilepsy; those with epilepsy of symptomatic aetiology; those treated with lamotrigine; with IGE seizures; with cognitive disorders; with alcohol addiction [Hesdorffer et al., Epilepsia, 2011].

## Risk of injuries in patients with epilepsy

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However, the evidence for increased incidence of injuries in patients with epilepsy has been conflicting, as they derives from previous studies often focused on more severe and poorly controlled epilepsy populations in epilepsy centers or emergency rooms. According to newer, prospective, controlled, unselected and large-samples of patients with epilepsy, most accidental injuries are not severe, but minor and mostly caused by an epileptic clinical condition and associated handicap. Also, several current studies report that the overall and relative rate of injuries limiting activities did not differ between patients with epilepsy and the general population. Often quoted, previous, retro-
pective and population-based Rochester study of 247 people with epilepsy recorded seizure-related injuries that required medical attention in 16% of the group, and the cumulative risk of injuries – 6.8% at 2 years, 14.6% at 10 years and 26.1% at 20 years. The researchers identified five potential risks for seizure-related injury: higher seizure frequency, convulsive seizures or drop attacks, physical disability, less independent living and greater number of antiepileptic drugs used. Although frequent, most (79%) of these injuries were minor cuts, scratches, and bruises [Lawn et al., Neurology, 2004].

Other studies have reported similar rates of injuries (12.6–35%) [Appleton, Epilepsia, 2002; Kirby and Saddler, Epilepsia, 1995; Buck et al., Epilepsia, 1997] but none of them included controls though estimation of comparative risk of injuries in patients with epilepsy and other populations was not possible.

Among recent controlled studies two prospective European multicenter controlled studies provides the most robust data [Beghi and Cornaggia, Epilepsia, 2002; van den Broek and Beghi, Epilepsia, 2004]. The first of them found modestly but significantly higher 2-year rates of injuries in patients with idiopathic, cryptogenic or remote symptomatic epilepsy (21%) than in healthy controls (14%). With few exceptions most of injuries were trivial: in 6% of patients – contusions, in 5%-wounds, in 3%-abrasions or fractures, and in 2%-head contusions or sprains/stains or wishplashes. The risk was higher for concussions, abrasions and wounds in epilepsy group. Domestic accidents prevailed, followed by street and work accidents [van den Broek and Beghi, Epilepsia, 2004]. Nevertheless patients with epilepsy reported more medical action and hospitalization [van den Broek and Beghi, Epilepsia, 2004]. A quarter of the injuries in epileptic patients were seizure related. When these injuries were excluded, the incidence did not differ between patients and controls. Disease characteristics associated with an increased risk of accidents included generalized epilepsy and active disease with at least monthly seizures. The results suggest that patients with epilepsy but under satisfactory pharmacological control are not at any significantly higher risk of accidents and epilepsy in pharmacologic remission carries only a moderate risk of accidents [Beghi and Cornaggia, Epilepsia, 2002; van den Broek and Beghi, Epilepsia, 2004].

A population-based study of Tellez-Zenteno [Epilepsia, 2008] in Canada evaluated the occurrence of injuries in patients with epilepsy that are severe enough to interfere with normal activities and the relative risk of injuries in large sample of unselected patients with epilepsy in general population. The one-year overall rate of injuries was not different in patients with epilepsy and in non-selected general population (14.9% v. 13.3%). Although orthopedic injuries were the most frequent type in both groups (about 60%), no difference in prevalence of fractures (about 17–18%), and dislocations (3.6%) were found. Next most frequent were sprain/strain (42%) and superficial injuries (24%). No significant differences between patients with epilepsy and the general population were seen with regard to place where injury occurred, mechanism of injury and annual number of injuries. Body part injured included mostly hip, thigh and lower leg (above 30%). Falls (37–44%) and over-exertions (11–20%) were the commonest mechanisms of injuries. Places of injuries occurrence were predominantly home and less frequently workplace and street without significant differences between epileptics and non-epileptics. Injuries were significantly three-times more frequent during sports in the general population than in patients with epilepsy, probably because of the lower level of physical activities in epileptics. The proportion of individuals that received any health care was not different between those with epilepsy and the general population (67% vs. 64%). However the researchers found a three-times higher frequency of hospital admission following injuries in patients with epilepsy. This was related strictly to seizures and epilepsy comorbidities, but not to injuries alone and reflected a more cautious attitude of clinicians towards injuries in patients with epilepsy. The main observation of Tellez-Zenteno study (in agreement with the cited European studies) is that the prevalence of injuries overall, and the most specific aspects relating to injuries did not differ between patients with epilepsy and the general population.

Persson et al. [Epilepsia, 2002] studied the incidence of extremity fractures in patients with epilepsy in comparison with the general population. They found that 11% of patients sustained fractures (mostly forearm, tibia and fibula) and significantly higher risk for fractures measured (as a Standardized Morbidity Ratio) equaled 2.39. Risk factors were male sex, age above 45 years with recently diagnosed epilepsy and poor control of generalized tonic-clonic seizures. 43% of the fractures were seizure related. The relative risk of fractures was higher during first and second year.
after diagnosis of epilepsy, probably because epilepsy patients gradually learn to adjust their life styles to avoid risk situations. Authors suggest that efforts should be made to improve seizure control and adjust treatment because side effects of antiepileptic drugs including ataxia and dizziness could lead to falls and fractures independently of seizures.

Even if head injuries are the most common type in some studies they rarely are serious. Among above 27 000 seizures episodes in the survey of Russell-Jones and Shorvon [J Neurol Neurosurg Psychiat, 1989] only 2.7% resulted with head injuries; 45% of them required suturing and only three cases (0.4%) were serious (skull fracture, extra- or subdural hemorrhage).

Although above cited prospective cohort study [van den Broek and Beghi, Epilepsia, 2004] did not demonstrate a significantly greater risk of burns in people with epilepsy, other retrospective studies suggested an increased risk of burns [Spitz et al, Epilepsia, 1994; Josty et al., Epilepsia, 2000]. These researchers estimated 1.6% and 3.7% of burn unit admissions resulted from epilepsy. Most injuries occurred at home during everyday activities while patients were cooking or showering or there were scald injuries and contact burns with heaters, irons, or hair dryers. In surveys of adults with epilepsy about 16% reported sustaining a burn as a result of a seizure [Buck et al., Epilepsia, 1997].

Drowning is a major concern in persons with epilepsy and appears the most likely injury type that leads to death. About 14% of adults reported sustaining a seizure while bathing or swimming in the preceding year [Buck et al., Epilepsia 1997]. Mortality ratio for accidental drowning in adults with epilepsy was 4.4 [Sheth et al., Neurology, 2004]. In children and adolescent epileptic persons was a relative risk of 13.9% for drowning and of 13.8% for fatal drowning compared to matched population without epilepsy. The most common sites for submersion were predominantly the bathtub (relative risk – 96) or swimming pool (relative risk – 23) [Diekema et al, Pediatrics, 1993]. Another study found that children with epilepsy were 7.5 times more likely to experience submersion injury than those without epilepsy [Ryan and Dowling, CMAJ, 1993]. Nearly all deaths resulting from drowning unsupervised. No child with epilepsy died of submersion when an adult witnessed the event. The data suggest that supervision may reduce drowning accidents and deaths.

Motor accidents or driving and epilepsy is a particularly sensitive topic in adult neurology practices. Theoretically, seizures may occur while driving and cause serious crashes, potentially injuring passengers, other drivers and pedestrians. Driving restrictions, specified by law are nearly universal for people with epilepsy. A patient must have controlled seizures to be allowed to drive. Some types of epilepsies (with auras or nocturnal seizures only during sleep) may reduce the risk of seizure-related crashes. The seizure-free periods that determinate whether a patient is controlled ranges between particular countries and even between particular states in some countries from 3 to 24 months [Krumholz et al., JAMA, 1991]. In a study of 400 drivers with epilepsy, 33% admitted to having had seizures while driving, and 55% had an accident resulting from a seizure. This study found that the most important factor associated with crashes was a short seizure-free interval [Krauss et al, Neurology, 1999]. In a recent European cohort study the risk for street accidents was 5% and 7% at 12 and 24 months for all epileptic persons and 4% and 6% after exclusion of seizure related events. The difference between both groups of patients and controls was significant, although authors analyzed mainly circumstances of accidents, but not exactly motor crashes during driving motor vehicle by epileptic persons [van den Broek and Beghi, Epilepsia, 2004]. On the other hand, in a current population study of injuries in epileptic persons by Tellez-Zenteno [Epilepsia, 2008] transportation and traffic related injuries (but not exactly motor crashes during driving) did not differ between epileptics (5.8%) and general population (6.7%). This was in keeping with studies questioning the role of driving motor vehicle by epileptic persons [van den Broek and Beghi, Epilepsia, 2004].

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Neurology, 2004]. Seizure-related driving fatalities were rare, accounting for only 0.2% of total 44,000 annual driving fatalities in the United States. In contrast, alcohol was responsible for 10% of accidents [Sheth et al., Neurology, 2004]. The use of cellular phones increased the risk of a collision fourfold, and these drivers posed a greater risk to public safety than drivers with epilepsy [Redelmeier et al., N Engl J Med 1997]. On the other hand, drivers with epilepsy had an increased risk of fatal crashes (8.6 per 100,000) compared to those with other medical conditions such as cardiovascular disease (accordingly 3.74) or diabetes (1.88) [Taylor et al., J Neurol Neurosurg Psychiat, 1996].

Evidence from literature would suggest that injury risk in epilepsy is only moderately greater than in the general population but not the same in all patients. Persons with generalized seizures, and particularly those leading to falls, as well as more frequent seizures appeared to be at a higher risk. Comorbid neurologic physical deficit or cognitive handicap likely also increased the risk. Patients with epilepsy had more home, street, and work accidents, and the home is the commonest place of injury. Minor soft tissue injuries are the most commonly seen following seizures. Rare, but potentially much more serious injuries include drowning, burns, severe head injuries and severe motor vehicle accidents. When seizure-related events are excluded, patients with epilepsy are only at a higher risk of accidents and injuries than in the general population. This means that proper treatment of epilepsy that minimize fits and does not cause neurotoxic side effects influencing attention and motor coordination should be an important factor in diminishing injuries in epileptic persons.

Influence of caffeine upon the anticonvulsant activity of newer antiepileptic drugs against 6 Hz psychomotor seizure model of partial seizures in mice

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Caffeine (a methylxanthine derivative) apart from possessing a seizure inducing potential in high doses (>200 mg/kg) [Chu, Epilepsia, 1981], has been also shown to reduce the protective activity of a number of antiepileptic drugs – classical (carbamazepine, phenobarbital, phenytoin, valproate) [Czuczwar et al., Epilepsia, 1990] and newer (topiramate) against maximal electroshock-induced convulsions in mice [Chrościńska-Krawczyk et al., Pharmacol Rep, 2009]. Interestingly, this particular activity of caffeine has not disappeared over time – chronic administration of the methylxanthine even resulted in enhanced negative effects towards some antiepileptic drugs protecting against maximal electroshock and participation of pharmacokinetic factors was excluded in these particular interactions [Gąsior et al., Epilepsia, 1996; Pharmacol Biochem Behav, 1996]. Although the convulsive potential of caffeine is mainly related to the blockade of A1 adenosine receptors, the participation of A1 receptor blockade in the negative interaction between caffeine and antiepileptic drugs is not that clear [Chrościńska-Krawczyk et al., Pharmacol Rep, 2011]. Although many antiepileptic drugs are susceptible to this interaction with caffeine in the test of maximal electroshock in mice, there are some exemptions to the rule, for instance lamotrigine and oxcarbazepine, which were even resistant to the chronic administration of caffeine [Chrościńska-Krawczyk et al., Pharmacol Rep, 2009]. A question thus arises, whether these antiepileptic drugs retain their resistance to caffeine in another test of experimental seizures – 6 Hz psychomotor seizure test, assumed as a model of partial seizures, contrary to maximal electroshock-induced convulsions, a model of generalized tonic-
clonic seizures [Borowicz and Czuczwar, Future Med, 2011]. Also, antiepileptic drugs, inactive against maximal electroshock (levetiracetam and tiagabine) [Barton et al., Epilepsy Res, 2001], were included in this study.

Caffeine was administered ip acutely or chronically (twice daily for two weeks) to Swiss mice in a dose of 46.2 mg (or lower doses) which is an equivalent to 50 mg/kg of aminophylline. Neurotoxic potential of combinations of caffeine with antiepileptic drugs was evaluated in the chimney test and grip-strength test.

The most susceptible drug to the untoward effect of caffeine was levetiracetam, whose protective activity against 6 Hz current (32 mA) was reduced by ca 50%, both after acute and chronic caffeine at 46.2 mg/kg. The methylxanthine was ineffective in lower doses in this regard. Only chronic caffeine (at 46.2 mg/kg) significantly reduced the protective action of oxcarbazepine and as regards lamotrigine or tiagabine, they were unaffected by acute or chronic caffeine. In the chimney test, only acute caffeine (46.2 mg/kg) potentiated the neurotoxic potential of oxcarbazepine and tiagabine. No negative interaction was noted in the grip-strength test.

The obtained results indicate that the negative influence of caffeine upon some antiepileptic drugs may be extended to another test of experimental seizures. Lamotrigine and tiagabine seem resistant to the untoward activity of caffeine. This observation is particularly important, because lamotrigine was also resistant to caffeine in the maximal electroshock test, and tiagabine – in the threshold electroconvulsive test [Chrościńska-Krawczyk et al., Pharmacol Rep, 2009].

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Caffeine and antiepileptic drugs in patients with epilepsy

Roman Chwedorowicz

Caffeine has been documented to induce seizures per se in experimental animals [Chu, Epilepsia, 1981]. Moreover, this methylxanthine derivative in lower doses (< 50 mg/kg) has been shown to distinctly lower the protective potential of classical (carbamazepine, phenobarbital, phenytoin, valproate) and newer antiepileptic drugs (topiramate) in experimental models of epilepsy, maximal electroshock-induced convulsions in mice being the most frequent model [Czuczwar et al., Epilepsia, 1990; Chrościńska-Krawczyk et al., Pharmacol Rep, 2009]. Interestingly, lamotrigine and oxcarbazepine were resistant towards this hazardous influence of caffeine [Chrościńska-Krawczyk et al., Pharmacol Rep, 2009].

The estimated mean caffeine intake per capita in USA is in the range of 3 mg/kg, which may produce pharmacologically relevant caffeine plasma concentrations [Fredholm et al., Pharmacol Rev, 1999]. Higher intake (in the range of 5–6 cups of coffee per day, which amounts to ca 500–600 mg of caffeine) may result in nervousness, irritability, headache, excitation or insomnia [Fredholm et al., Pharmacol Rev, 1999]. Considering the world’s widespread use of caffeine containing drinks or beverages and the preclinical data, an important question arises whether caffeine may have a negative impact on the efficacy of antiepileptic drugs in clinical conditions.

Limited clinical evidence indicates that the assumed untoward effect of caffeine in epileptic patients may be actually the case. The available reports point to the good efficacy of the existing antiepileptic treatment in the pre-caffeine period – in some patients the seizure-free stated was observed. A considerable increase in seizure frequency was noted when the patients started heavy coffee drinking – ca. 4–10 cups daily. Interestingly, all the patients, who stopped coffee intake, returned to their baselines [Kaufman and Sachdeo, Seizure, 2003; Bonilha and Lee, Seizure, 2004; Błaszczyk, Pharmacol Rep, 2007]. However, it is remarkable that 71 moderate coffee drinkers did not find any correlation between their drinking habit and seizure frequency. In contrast, 7 epileptic patients us-
ing at least 4 cups of coffee daily restored their seizure frequency to baseline when quitting the habit [Błaszczyk, Pharmacol Rep, 2007].

 Apparently, more clinical studies are necessary to characterize the influence of caffeine upon the effectiveness of antiepileptic therapy. At present, it seems very likely that at least heavy coffee drinking may reduce the efficacy of antiepileptic drugs. It would be also of particular interest to find out, whether patients taking antiepileptic drugs, which are not susceptible to the negative impact of caffeine (lamotrigine, oxcarbazepine) in preclinical studies, are resistant to this methylxatnine in that their seizure frequency is not dramatically increased.

Newer antiepileptic drugs: pregabalin and retigabine

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Despite many novel antiepileptic drugs, one third of epileptic patients suffer from pharmacoresistant seizures [Lason et al., Pharmacol Rep., 2011]. In recent years, two more antiepileptic drugs are available – pregabalin and retigabine. The former shares a mechanism of action identical to its precursor – gabapentin. Specifically, pregabalin is an antagonist of α2δ subunit of voltage-operated calcium channel. Preclinical data indicate that combinations of pregabalin with lamotrigine, topiramate, or oxcarbazepine result in an additive interaction [Luszczki et al., Epilepsy Res, 2010]. Clinical data provide evidences that the maximal plasma concentration is encountered 1 h following its oral administration, bioavailability is in the range of 90%, its t1/2 reaches ca 6 h. Pregabalin’s pharmacokinetics is linear and the drug does not undergo any significant metabolism, being eliminated through the kidneys [Ben-Menachem, Epilepsia, 2004]. This antiepileptic drug is recommended with good results as an adjunct in patients with partial epilepsy and against neuropathic pain [Taylor et al., Epilepsy Res, 2007; Beydoun et al., Exp Rev Neurother, 2008]. Among adverse effects, patients report dizziness, cognitive deficit, euphoria, fatigue, and constipation [Zaccara et al., Epilepsia, 2011].

Retigabine displays a completely different mechanism of action, which is not shared by any antiepileptic drug. Specifically, retigabine activates neuronal potassium channels (Kv7.2–7.3) in as low concentration as 0.1 μmol. Enhancement of GABA-dependent chloride current has been also noted for this drug but in much higher concentration of 10 μmol [Czuczwar et al., Pharmacol Rep, 2010]. Preclinical evaluation of retigabine’s combinations with other antiepileptic drugs has revealed a synergy for the combination with valproate and an addition for combined treatments with carbamazepine or lamotrigine [Luszczki et al., Naunyn-Schmiedeb Arch Pharmacol, 2009]. Following a single dose of 200 mg in healthy volunteers, retigabine has reached its maximal concentration of 420 ng/ml within 2h. Its t1/2 time is around 8.5 h [Czuczwar et al., Pharmacol Rep, 2010]. The metabolic degradation of retigabine occurs via glucuronidation and acetylation. Interestingly, when retigabine is combined with lamotrigine, the t1/2 time of the latter is decreased by 15% [Czuczwar et al., Pharmacol Rep, 2010]. Retigabine has been found very effective as an adjunct in patients with partial seizures. Clinical data also points to its effectiveness in Alzheimer’s patients. Preclinical evidence suggest its potential activity against neuropathic pain, bipolar disease, dystonia, and cocaine addiction [Czuczwar et al., Ther Clin Risk Manag, 2012]. Adverse effects of this antiepileptic include dizziness, somnolence, fatigue, confusion, dysarthria, and nausea [Czuczwar et al., Pharmacol Rep, 2010].
Influence of new antiepileptic drugs on cognitive functions in epileptic patients

Albena Grabowska-Grzyb

In addition to seizure frequency, cognitive functioning is a key factor of interest to physicians involved in the treatment of epilepsy. In everyday clinical routine essential source of information is an interview. Based on data obtained with the interview, the progress in treatment is assessed. Beside the information obtained in the interview, more objective and accurate is the use of specialized neuropsychological testing, allowing for accurate observation of the dynamics of the cognitive problems that occur during treatment and to establish a point of view on these problems. At last part of the cognitive impairments are already present in people with epilepsy, before the start of their antiepileptic treatment. Consequently, it is not caused by antiepileptic drugs (AEDs) or accumulating effects of seizures and may result from epileptogenesis [Taylor et al., Epilepsia, 2010]. These impairments may be encountered across several cognitive domains, in previously untreated patients with newly diagnosed epilepsy who perform worse than healthy volunteers on measures of attention, concentration, motor function, mental flexibility, memory and learning. But it is proportion of 30% of patients with epilepsy that demonstrated subtle memory and attention dysfunction. Equally, anxiety and depression may have affected patient’s performance [Kalviainen et al., Seizure, 1992].

Patients with epilepsy are often tested for their intelligence and cognitive function. Impact on cognitive functions is one of the criteria when evaluating AEDs. For this purpose, psychological tests are frequently used. Advances in the psychological functioning of patients are often a key element in evaluating the effectiveness of therapeutic intervention and have considerable bearing on the patients quality of life. Only compartment of the results of cognitive functions before and during epilepsy would enable a precise measure of the impact of epilepsy on a variety of cognitive functions that assemble human intelligence. Thus, it should be noted that all research conducted so far give indirect evidence, which do not provide accurate and precise estimates of the impact of epilepsy on the functioning of the central nervous system in the field of cognitive performance. The neuropsychological test battery should be selected to be most able to detect a difference between drugs in randomized clinical trial [Baker and Marson, Epilepsy Res, 2001].

Many patients, elderly and specially young with epilepsy experience disturbances of cognition and behavior. Cognitive impairments are frequently reported by people with epilepsy, but when these cognitive impairments arise in the course of the disease is an important issue. These disturbances are increased by AEDs [Carpay et al., Seizure, 2005]. The impact of the older AEDs on cognitive functions is very diverse: benzodiazepines and barbiturates often have negative effects on cognitive functions and behavior in all age groups [Grabowska-Grzyb et al., Epilepsy Behav, 2006]. Valproate and phenytoin have impact on cognitive functions only in elderly patients [Craig and Tallis, Epilepsia, 1994]. For young group, only VPA may have negative effect on memory and concentration [Gareri et al., Prog Neurobiol, 1999]. As far as the new AEDs are concerned, a positive influence or at least a lack of negative influences on cognition ie: memory, calculia, lexia and concentration is mainly reported for lamotrigine, also for gabapentin, levetiracetam and oxcarbazepine [Froescher and Trinka, Epileptologia,2006]. In his review on special issues regarding the treatment of the elderly, Bergey [Neurology, 2004] mentions gabapentin, lamotrigine, levetiracetam and valproate as the AEDs with the best cognitive profiles. In the double-blind randomized comparison between lamotrigine and carbamazepine in elderly patients [Brodie et al., Epilepsy Res, 1999], lamotrigine was significantly less likely to produce somnolence than carbamazepine and making memory disturbances. In several studies, topiramate had a negative impact on cognition [Blum et al., Neurology, 2006] but the results are inconsistent – Majkowski et al. [Epilepsia, 2005] demonstrated that most of the more common adverse effects in a topiramate adjunctive therapy were transient. At a topiramate dosage of more than 100 mg, the majority of patients with topiramate combination therapy suffered from side effects and the most common of them were abnormality of thinking and impairment of concentration [Froescher et al., Epileptic Disord, 2005]. The literature analysis...
by Lathers et al. [J Clin Pharmacol, 2003], comparing lamotrigine, topiramate and phenobarbital, shows an equal degree of sedation for phenobarbital and topiramate and significantly higher degree of sedation for phenobarbital and topiramate than for lamotrigine. In a systematic review of adults with epilepsy [Cramer et al., Epilepsy Behav 2003], incidences of affective adverse effects (agitation, antisocial reaction, anxiety, apathy depression, emotional lability, euphoria, nervousness) induced by new AEDs were compared. The lowest rates were noted for gabapentin, followed by lamotrigine and levetiracetam. Higher rates of nervousness were noted for tiagabine and topiramate, high rates of hostility or irritability were noted for zonisamide. The antidepressant and mood-stabilizing effects were exerted by gabapentin and lamotrigine [Schmidt et al., Nervenheilkunde, 2004]. Influence of new AEDs on cognitive functions is associated with their dosages. Also, positive and negative side effects may coexist.

In the future, neuropsychological tests should therefore be performed before and during the intake of any AED (monitoring of cognitive functions and of behaviour) [Froscher, Epileptologia, 2008].

### Epilepsy and driving license – new regulations

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In Poland, approximately 400,000 people suffer from epilepsy. The annual prevalence of epilepsy is roughly 40 to 70 in 100,000 people. However, common knowledge on etiology, signs and symptoms, ways of treatment and various types of possible assistance to sufferers still remain insufficient. Negative attitudes and misbelieves on epilepsy result in concealing the disease by sufferers [Majkowski J: Epilepsy – diagnostics, treatment, prevention. PZWL Warszawa, 1986].

PRO-EPI is the first complex Polish opinion poll on social aspects of epilepsy which was initiated by the Polish Society of Epileptology and the pharmaceutical company UCB and realized by Pentor Research Institute. The survey was performed from February to March in 2009, on a representative group of Poles (N = 1042) among neurologists (N = 179), among adult epilepsy patients (N = 1019), among parents of children having epilepsy (N = 313) as well as headmasters of primary schools and junior secondary schools (N = 200) [Research PRO-EPI-Pentor, PTE, UCB 2009].

According to PRO-EPI study young and active patients having seizures very rarely (once a year or less frequently), and being treated properly are most aggrieved not being able to have a driving license. Nearly every neurologist dealing with epilepsy patients discusses with them about a possibility of getting a driving license. However, it is usually the patient who starts the topic. Every fourth neurologist claims that they issued their patients a certificate necessary to apply for a driving license [Research PRO-EPI-Pentor, PTE, UCB 2009].

The actual situation of patients with epilepsy concerning driving license based on PRO-EPI is as follows:
- 35 percent of adult patients have a driving license but 28 percent received the document before diagnosing the disease, and 7 percent after the diagnosis of epilepsy.
- 23 percent of adults with epilepsy drive mechanical vehicles, usually in daily situations, on short and familiar routes and in exceptional cases.
- Every third adult patient admits that they would like to have a license in the future.
The American study of drivers’ death in car accidents showed that young drivers cause accidents 123 times more often than people with epilepsy while alcohol is the reason for fatal accidents 156 times more often than epilepsy. In the general population, the risk of death in a car accident is 2.6 times higher than in the population with epilepsy. A seizure as a cause of accident is outnumbered by alcohol, driver’s mistake and road conditions [Sheth et al., Neurology 2004].

In different countries, there are significant differences in legal regulations related to driving license acquisition. In Great Britain, a seizure-free period before issuing or lengthening a non-professional driver’s license is as long as one year, in other countries of the EU it is two years. In case of asleep seizures, it is a one-year seizure-free period required. To restore a driving license, a three-year period of only asleep seizures is demanded in Great Britain, a two-year one in Belgium, and a one-year period in Holland and Ireland. In France, it is possible to have a driving license if there are only awake seizures. In Great Britain, a professional driving license is issued if a patient is not on antiepileptic drugs and is free of seizures for at least 10 years, however if there is a single seizure, a patient is not allowed to drive a car for a year. An occurrence of 3 Hz spike and wave discharges in EEG results in a one-year driving prohibition in Great Britain [Beghi and Sander, Br Med J, 2005]. The regulations vary in the USA, depending on a state and they also stay different in provinces of Canada. For instance, a seizure-free period required for a non-professional driving license in the States ranges from 3, through 6 or 12 up to 18 months, depending on a state. However, in ten states the period has not been defined explicitly. It is possible to hold a driving license after the first attack if the period free of seizures is from 3 to 6 months in different states. Moreover, a driving license can be held by a patient who has only nocturnal seizures for five years. Professional or commercial driving license cannot be issued if a patient is on antiepileptic drugs [Lipman and Lehman, Epilepsia, 1994; Salinsky et al., Epilepsia, 1992].

On diagnosing epilepsy, both the doctor and the patient have some commitments. The information about the disease must be provided to the doctor who certifies fitness to drive and to the Department of Communication. The patient has to be aware of the fact that they lose their license and insurance in case of withholding the information on the disease. The doctor diagnosing epilepsy is obliged to inform the patient about their duty to report the disease to the Department of Communication provided the patient is a holder of a driving license. The doctor has to tell the patient that concealing the disease may cause a loss of a driving license and insurance. The requirements should be noted in medical documentation.

In Poland, the former regulations and a common practice made epileptic patients unable to hold a license. On 25 August 2009, a European Commission Directive 2009/112/EC amending Council Directive 91/439/EEC on driving licenses was implemented. It has changed legal regulations on applying for a driving license by people with epilepsy in countries of the EU. Member States had to bring into force the laws and regulations. In Poland, the legal basis is a government order of the Minister of Health of the 15th of April, 2011 amending the order on applicants’ and drivers’ medical examination [Dz.U. nr 8; 2011].

On 29 June 2011, the government adapted the Polish laws to the European directive 2009/112/EC on regulations concerning driving licenses for people with epilepsy. The annex no 4 of the regulation determines THE WAY OF HEALTH ASSESSMENT OF A PERSON WITH EPILEPSY IN CASE OF STATING THE EXISTANCE OR A LACK OF CONTRAINDICATIONS FOR DRIVING VEHICLES and it sounds as follows:

In case of an applicant for a driving license of a category A, A1, B, B1, B + E, T or a holder of a driving license of a category A, A1, B, B1, B + E, T, it is possible to issue a license or lengthen its validity:

1. When a person is on antiepileptic drugs – after presenting a neurological opinion confirming a lack of seizures for the last two years of treatment. After the period the patient is obliged to have check-ups every six months for two years, afterwards every year for three consecutive years and then depending on medical indications.

2. When a person has had the first seizure – after presenting a neurological opinion confirming a twelve-month seizure-free period.

In case of therapy cessation, driving is definitely contraindicated for the first six months. After this time, the patient has to undergo appropriate medical follow-ups every six months for two years and then every year for next three years, later depending on medical requirements.

When anti-epileptic therapy is being changed, a neurologist can determine a period during which a patient is not able to drive. A seizure during the last two years of the disease is an absolute contraindica-
tion for driving. Re-applying for a license is possible after putting forward a neurologist’s opinion to confirm a seizure-free period of two-year therapy. After that a patient has appropriate neurological follow-ups every six months for two years, then every year for the next three years, and then depending on medical requirements. A holder of a driving license of a category A, A1, B, B1, B + E, T who has had epilepsy diagnosed or has had an epileptic-like seizure is not fit to drive as a professional driver.

An applicant or holder of a driving license of a category C, C1, D, D1, C + E, C1 + E, D + E, D1 + E, of a tram endorsement or of a certificate of vocational qualifications who has had epilepsy diagnosed or who has ever had an epileptic-like seizure cannot be stated to be fit to drive the vehicles.

The current regulations include the necessity for presenting an authorized doctor an opinion of a neurologist in charge. The opinion has a form of a NEUROLOGICAL OBSERVATION CHART FOR APPLICANTS’ AND DRIVERS’ MEDICAL EXAMINATION.

To summarize, liberalizations of the regulations have been introduced for epilepsy patients who apply for driving licenses. On the other hand, regulations for doctors have become stricter. Having suspected or diagnosed epilepsy in patients with driving licenses or applying for them, doctors are obliged to inform immediately the authority which issues driving licenses about the necessity for evaluating health predisposition to driving. The amendment has aroused controversy because it is contradictory to medical confidentiality. However, the legislator cites the act of 5 December 1996 on professions of doctors and dentists: article 40; section 2; clause 3 according to which doctors are exempted from the duty if the patient’s or other people’s safety is endangered. All the above changes in legislation are caused by the objective of Member States to unify requirements on driving in order to make travelling in the EU countries easier. Patients should be advised of different legislation in the European Union countries so as to adjust their rights to legal regulations of a country.

Anticonvulsant effects of combinations among three antiepileptic drugs – an isobolographic analysis

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Isobolographic analysis is a mathematical method allowing for a determination and characterization of pharmacodynamic interactions of drugs used both in clinical and preclinical studies. With isobolography, one can graphically illustrate the interactions exerted by drugs administered in mixtures at various dose-ratios. In preclinical studies one can distinguish two types of isobolographic analysis: the type I – is reserved for drugs in mixture, which administered separately produce a defined effect, and the type II – is reserved for drugs used in mixture of which at least one drug when administered singly is considered as virtually ineffective [Łuszczki, Naunyn Schmiedebergs Arch Pharmacol, 2008]. Pharmacodynamic interactions between drugs in the isobolographic analysis are classified as follows: supra-additivity (synergy), additivity, sub-additivity (relative antagonism) and infra-additivity (absolute antagonism). Generally, in the type I of isobolographic analysis all interactions are plotted into the Cartesian system of coordinates. In preclinical studies, median effective doses (ED₅₀ values) of drugs administered singly are placed on axes of the Cartesian system of coordinates (usually on X and Y for two-drug combinations and on X, Y and Z for three-drug combinations). The diagonal lines connecting the ED₅₀ values on axes are considered as the lines of additivity and each point placed on these lines reflects a median effective dose of a drug mixture (at a fixed-ratio combination), whose effect is considered as additive (ED₅₀ add). Supra-additivity (synergy) between drugs is observed when the final effect of the drug mixture is stronger than that theoretically expected, based on the sum of individual effects of the component drugs. Supra-additive interactions are ob-
observed if points corresponding to the experimentally determined median effective doses for drug mixtures (ED$_{50\text{ mix}}$ values) are plotted significantly below the lines of additivity. Additivity is present if the experimentally-derived effect of the drug mixture is the sum of the partial effects of individual component drugs. The additive interactions are graphically illustrated when points corresponding to the experimentally determined ED$_{50\text{ mix}}$ values are plotted close to or on the lines of additivity. Sub-additivity (relative antagonism) is observed if the effects produced by a drug mixture are lower than the effects produced by the respective fractions of the ED$_{50}$ values for drugs administered separately. Sub-additive interactions are illustrated if points corresponding to the experimentally determined ED$_{50\text{ mix}}$ values for drug mixtures are plotted significantly above the lines of additivity. The last pharmacodynamic interaction that is isobolographically characterized – infra-additivity (absolute antagonism) is observed if drugs used in a mixture produce the opposite effects (for instance: pro- and anticonvulsant effects). In such a situation, the infra-additive interactions are illustrated graphically if points corresponding to the experimentally determined ED$_{50\text{ mix}}$ values for drug mixtures are plotted above the ED$_{50}$ values for drugs administered separately. The type I isobolographic analysis characterizes the interactions that occur between drugs used at fixed drug dose ratio combinations, which are usually based on fractions of ED$_{50}$ values of drugs used in mixture. In other words, the drugs in mixture are combined at fixed proportions that correspond to the fractions of ED$_{50}$ values of drugs used separately. More specifically, the fixed-ratio two-drug combination of 1:1 reflects a mixture of two drugs used at equivalent fractions of their ED$_{50}$ values (i.e., 1/2 ED$_{50}$ value of the first drug and 1/2 ED$_{50}$ value of the second drug). Similarly, a three-drug mixture at the fixed-ratio of 1:1:1 consisted of 1/3 ED$_{50}$ value of the first drug, 1/3 ED$_{50}$ value of the second drug, and 1/3 ED$_{50}$ value of the third drug. Additionally, with isobolographic analysis one can readily determine a power of interactions existing among drugs by the use of an interaction index ($\alpha$) [Luszczki and Czuczwar, Epilepsia, 2004]. This index is calculated by dividing the experimentally determined ED$_{50\text{ mix}}$ values by their respective theoretically denoted ED$_{50\text{ add}}$ values. The interaction index values equal to or lower than 0.7 reflect supra-additivity ($\alpha \leq 0.7$). Additivity is observed if values of the interaction index are higher than 0.7 and simultaneously lower than 1.3 (1.3 > $\alpha$ > 0.7). Sub-additivity is observed when the interaction index values are equal to or higher than 1.3 ($\alpha \geq 1.3$).

Despite advanced knowledge of the pathophysiological processes involved in seizure initiation, amplification and propagation in the brain, as well as the introduction of several novel (second- and third-generation) antiepileptic drugs (AEDs) into the therapy of epilepsy, there are still ~30% of patients unsuccessfully medicated with currently available AEDs in monotherapy [Kwan and Brodie, N Engl J Med, 2000]. Refractory epilepsy in ~30% of patients is still a significant clinical problem and a challenging issue for clinicians and researchers. Once monotherapy with AED of choice has failed, clinicians are expected to replace the ineffective drug with another AED as an alternative monotherapy. If alternative monotherapy fails twice, the primary concern is to find a highly efficacious combination of two or more AEDs in an attempt to enhance seizure control. Generally, the addition of a second or a third AED (as polytherapy) may provide enhanced seizure control in ~14% of these patients [Kwan and Brodie, Seizure, 2000]. In such cases, the clinicians are expected to adequately combine some AEDs in order to provide the patients with a state of seizure freedom. To date, only several two-drug and three-drug combinations have been approved as efficacious against specific form of epileptic attacks [Stephen and Brodie, Seizure, 2002]. Because of the ethical and methodological difficulties during the evaluation of AED combinations in the clinical setting, preclinical studies in animals can provide invaluable information allowing a selection of useful AED combinations.

The aim of the present study was to determine the exact characteristics of interactions among four various three-drug combinations in the mouse maximal electroshock-induced seizure (MES) model using the type I of isobolographic analysis. Generally, the MES test is thought to be an experimental model of tonic-clonic seizures and, to a certain extent, of partial convulsions with or without secondary generalization in humans [Löschler et al., Epilepsy Res, 1991]. In this study, the three-drug combinations of carbamazepine + phenobarbital + topiramate, lamotrigine + valproate + topiramate, carbamazepine + valproate + pregabalin, and phenytoin + phenobarbital + pregabalin were examined only at a fixed-ratio of 1:1:1. All experiments were performed on adult male albino Swiss mice. The experimental protocols and procedures...
were approved by the Second Local Ethics Committee at the University of Life Sciences in Lublin (License No.: 18/2011).

Isobolographic analysis of interaction for all the studied combinations at the fixed-ratio of 1:1:1 (i.e., carbamazepine + phenobarbital + topiramate; lamotrigine + valproate + topiramate; carbamazepine + valproate + pregabalin; and phenytoin + phenobarbital + pregabalin) revealed that the experimentally-derived \( ED_{50 \text{ mix}} \) values in the mouse MES model considerably differed than the theoretically calculated \( ED_{50 \text{ add}} \) values. Specifically, the interaction index value for the combination of carbamazepine + phenobarbital + topiramate at the fixed-ratio of 1:1:1 was 0.4, indicating supra-additive interaction among drugs. Similarly, the interaction index value for the combination of lamotrigine + valproate + topiramate at the fixed-ratio of 1:1:1 was 0.7, and also indicated supra-additive interaction among drugs. The interaction index value for the combination of carbamazepine + valproate + pregabalin at the fixed-ratio of 1:1:1 was 0.6, indicating supra-additive interaction among drugs. Similarly, the interaction index value for the combination of phenytoin + phenobarbital + pregabalin at the fixed-ratio of 1:1:1 was 0.5 and indicated supra-additive interaction among drugs.

Summing up, based on the results from this isobolographic study one can ascertain that the three-drug combinations of carbamazepine + phenobarbital + topiramate, lamotrigine + valproate + topiramate, carbamazepine + valproate + pregabalin, and phenytoin + phenobarbital + pregabalin tested at the fixed-ratio of 1:1:1 exerted supra-additive (synergistic) interactions in the mouse MES model. Considering the interaction index values, one can readily arrange and classify the synergistic AED combinations from the most effective combinations in the mouse MES model. From a preclinical point of view, the combination of carbamazepine + phenobarbital + topiramate was the most favorable with the interaction index value of 0.4. The second supra-additive combination with the interaction index value of 0.5 was that for phenytoin + phenobarbital + pregabalin. The third supra-additive combination with the interaction index value of 0.6 was that for carbamazepine + valproate + pregabalin. The last beneficial combination tested in this study was that for lamotrigine + valproate + topiramate with the interaction index value of 0.7. Although the results from this study cannot be directly extrapolated into clinical practice, they may be valuable clues suggesting the combination of selected AEDs in three-drug mixture to treat the patients with refractory epilepsy.

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**Influence of sildenafil on the anticonvulsant activity of some antiepileptic drugs in the pentylenetetrazole test in mice**

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Sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, is predominantly used in the treatment of erectile dysfunctions of various etiologies. Its pharmacological action is strictly connected to the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway. PDE5 catalyzes the breakdown of cGMP to guanosine monophosphate (GMP). Inhibition of PDE5 with sildenafil leads to the increase in intracellular cGMP level which causes smooth muscle relaxation and improves blood flow to the penis. The ability of sildenafil to cross the blood-brain barrier and presence of PDE5 in different brain structures suggests that sildenafil might affect some central nervous system functions [Milman and Arnold, Ann Pharmacother, 2002; Uthayathas et al., Pharmacol Rep, 2007].

Animal studies have revealed that sildenafil improves memory and learning processes, exhibits prodepressant, anxiogenic and proaggressive potential.
Furthermore, sildenafil induces neurogenesis and promotes functional recovery after stroke. Sildenafil was also reported to produce antinociceptive effects in animal models of pain [Uthayathas et al., Pharmacol Rep, 2007].

The growing number of recent studies indicates that sildenafil affects convulsant activity in both humans and experimental animals. Proconvulsant activity of sildenafil was firstly noted in two otherwise healthy men who experienced generalized tonic-clonic seizures soon after taking Viagra [Gilad et al., BMJ, 2002]. Proconvulsant potential of sildenafil was later confirmed in the mice models of seizures. This drug dose-dependently decreases threshold for pentylenetetrazole (PTZ)-induced [Riazi et al., Br J Pharmacol, 2006; Nieoczym et al., Pharmcol Rep, 2010; Montaser-Kouhsari et al., Seizure, 2011] and bicuculline-induced [Riazi et al., Br J Pharmacol, 2006] clonic convulsions. Furthermore, sildenafil was also reported to reverse anticonvulsant activity of diazepam [Gholipour et al., Eur J Pharmacol, 2009] and lithium chloride [Bahremand et al., Epilepsy Res, 2010] in PTZ-induced clonic seizure paradigm in mice. Conversely, sildenafil increases threshold for electroconvulsions in a dose-dependent manner and intensifies anticonvulsant activity of carbamazepine (CBZ), valproate (VPA) and topiramate (TPM) in the maximal electroshock seizure test in mice [Nieoczym et al., Epilepsia, 2010].

Sildenafil also limited duration of behavioral seizures and afterdischarges in the amygdala-kindling in rats [Nieoczym et al., Pharmacol Rep, 2010] but did not reveal any statistically significant effect in the cocaine-induced convulsions test in mice [Nieoczym et al., Pharmcol Rep, 2009].

Sexual dysfunctions are one of the most common disturbances in the interictal period in both men and women with epilepsy. While 3–9% of healthy men have erectile dysfunctions, male epilepsy patients experience this in 57% [Smaldone et al., Seizure, 2004]. Sexual dysfunctions in people with epilepsy might be caused by epilepsy itself, antiepileptic drugs (AEDs) and psychiatric/psychotic problems [Smaldone et al., Seizure, 2004; Stimmel and Gutierrez, CNS Spectr, 2006]. Co-existence of epilepsy and erectile dysfunctions in male epileptic patients requires safe and effective medication. Sildenafil has been recognized as adequate in the treatment of erectile dysfunctions in men with epilepsy. However, according to recent reports sildenafil might affect convulsant activity in both humans [Gilad et al., BMJ, 2002] and experimental animals [Riazi et al., Br J Pharmacol, 2006; Nieoczym et al., Pharmcol Rep, 2010; Nieoczym et al., Epilepsia, 2010; Montaser-Kouhsari et al., Seizure, 2011]. In addition, co-administration of sildenafil with antiepileptic drugs (AEDs) might lead to the pharmacodynamic and/or pharmacokinetic interactions between these medications and to the reduction of the therapeutic activity of AEDs [Nieoczym et al., Epilepsia, 2010].

We examined the effect of sildenafil on threshold for clonic seizures and on the anticonvulsant activity of some AEDs, i.e., clonazepam (CZP), phenobarbital (PB), VPA, tiagabine (TGB) and ethosuximide (ETS), in the subcutaneous (sc) PTZ test in mice. Furthermore, its influence on gabapentin (GBP) and vigabatrin (VGB) activity was investigated in the timed intravenous (iv) PTZ infusion test in mice.

We noted that sildenafil did not affect threshold for clonic seizures in the sc PTZ test and it also did not change anticonvulsant activity of CZP, PB, VPA and TGB in this paradigm. Statistically significant decrease in the median effective dose (ED50); i.e., dose of the AED that protects 50% of the mice against PTZ-induced clonic convulsions, was noted only in the case of ETS. Sildenafil at a dose of 20 mg/kg reduced the ED50 of ETS by about 22% while a dose of 40 mg/kg decreased the ED50 by 53%. Moreover, changes in the ED50 produced by sildenafil were not paralleled by the alterations in the brain concentration of ETS which suggests pharmacodynamic nature of these interactions.

Our studies revealed that GBP increase threshold for tonic seizures, while VGB increases thresholds for both myoclonic and clonic seizures. Sildenafil influenced neither GBP nor VGB activity. Moreover, it did not change brain concentration of these antiepileptic drugs. Our studies did not reveal any changes in long-term memory (passive-avoidance test), motor coordination (the chimney test) and muscle strength (the grip-strength test) in mice provoked by sildenafil itself and its combination with the studied AEDs.

In conclusion, our data have shown that sildenafil does not influence threshold for clonic seizures induced by sc administration of PTZ in mice. PTZ-induced seizures are mediated by blocking of GABAergic neurotransmission in the central nervous system, but it is well known that the sc PTZ seizure test is less sensitive than the timed iv PTZ infusion paradigm. It might be supposed that the lack of effect of sildenafil in our research eventuated from the little sensitivity of...
Despite major progress in the understanding of basic mechanisms of epilepsy there are still problems to be resolved. The discovery of new therapies effective in refractory epilepsy and modulating the natural course of the disease as well as elucidation of the mechanism of epileptogenesis are the biggest challenges for the future [Jacobs et al., Epilepsy Behav, 2009]. There is accumulating evidence that currently available new generation drugs have not fully met expectations. The proportion of patients with uncontrolled seizures reaches up to 30% and is similar to that reported in the past [Löscher and Schmidt, Epilepsia, 2011]. Another unresolved issue remains refractory status epilepticus (SE) as the basic mechanisms of the transformation from drug responsive into drug resistant SE are poorly understood. New generation drugs were not formally tested in that condition what limits our therapeutic options. Preliminary results, however do not support their efficacy with that regard [Rossetti and Lowenstein, Lancet Neurol, 2011].

This leads to somewhat frustrating conclusion that novel and more effective next-generation antiepileptic drugs (AEDs) are needed. All new drugs passed quite thorough pre-clinical evaluation based on currently available experimental models. However, it is increasingly understood that possibly these classic models may fail to indentify drugs with novel mechanisms of action.

That is why there is still need and space for novel models with unique characteristics mimicking the human conditions of pharmacoresistant epilepsy as well as of refractory SE.

Recently, we described a new model of generalized convulsive SE induced with orphenadrine (ORPH) [Rejdak et al., Brain Res Bull, 2011]. The drug in therapeutic, relatively low doses, exerts antagonistic activity against muscarinic and histaminic receptors, what was the basis for its clinical usage in Parkinson’s disease, pain and as a myorelaxant in neuromuscular disorders [Slordal and Gjerden, Br J Psychiatry, 1999; Rizzatti-Barbosa et al., Cranio, 2003; Gold, Clin Ther, 1978]. In addition, ORPH acts also as a ‘mild’, non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors by binding to the phencyclidine site [Kornhuber et al., J Neural Transm, 1995] and prevented the neurotoxicity induced by kainic acid [Sureda et al., Neuropsychopharmacology, 1999] and 3-nitropropionic acid [Pubill et al., Br J Pharmacol, 2001] in rats but when used in low dose range. One of the newer studies demonstrated another important mechanism consisting of concentration, voltage, and frequency-dependent blockade of voltage gated subtypes of human sodium channels [Desaphy et al., Pain, 2009]. All above mechanisms are typically anticonvulsant and the activity of ORPH in our model seems paradoxical.

Indeed, systemic administration of ORPH dose-dependently (dose range of 50–80 mg/kg) produced seizures in adult rats. The $CD_{50}$ value for the occurrence of SE was 60.2 (52.2–69.5) mg/kg while $CD_{97}$ value was 79.4 mg/kg. Thus, the maximal dose of...
80 mg/kg was used for further experiments and was proven to produce SE in 100% of animals. ORPH induced seizures starting from complex partial fits consisting of stereotyped behavior, limb movements, head shaking and myoclonic twitches of the body. The mean duration of single seizure episode was 23 ± 10 s (with average number of single seizure episodes of 7 ± 5) and mean total time of intervals between the single seizure episodes was 255 ± 192 s. After that period, an overt generalized convulsive SE appeared and lasted for approximately 2 hours. During the status there were intermittent breaks with seizure suppression associated with hyperventilation but without return to consciousness. The mortality rate was very
low and typically all animals survived the SE after doses ranging from 50 to 70 mg/kg. The maximal dose of 80 mg/kg was associated with 15% mortality. The death of animals appeared to be not a direct result of convulsions and could be related to peripheral effects of ORPH on cardio-vascular or respiratory systems. Animals recovering from SE appeared relatively normal, returning to full motor activity within subsequent several hours. EEG recording confirmed epileptic nature of behavioral changes and demonstrated that fully expressed SE appears usually after 30 min as shown in Figure 1. Studying the effects of different drugs on seizure activity, we found that among conventional AEDs only phenobarbital, valproate and diazepam but not carbamazepine, ethosuximide and phenytoin, dose-dependently diminished the incidence of seizures in rats, what corresponds with treatment effects observed in the clinical practice of human SE [Rejdak et al., Brain Res Bull, 2011]. Among new generation AEDs: felbamate, levetiracetam, topiramate, lamotrigine and progabide did not affect the seizure incidence. In the group of experimental drugs, only dizocilpine dose-dependently affected the occurrence of the SE while scopolamine and mecamylamine were not effective [unpublished data].

Based on the above findings, the mechanism how ORPH induces seizures in rats remains elusive and seems complex. The experiments performed so far, seem to exclude the possibility that typically studied mechanisms including sodium and calcium channels, cholinergic, GABA-ergic and glutamatergic transmission would be the primary in seizure initiation by ORPH. In particular, based on the effects exerted by drugs acting on NMDA receptors may indicate that NMDA activation is rather secondary event in the mechanism of proconvulsant activity of ORPH. It is of note that the drug per se is also a weak NMDA antagonist in low doses.

The interesting concept in elucidation of the proconvulsive activity by ORPH would refer to KCNH2-encoded human “ether-à-go-go-related gene” potassium channels (ERG). This is supported by the study, which demonstrated that the ORPH inhibited ERG, which could explain proarrhythmic side effects noted in patients exposed to the drug [Scholz et al., Naunyn Schmiedeberg’s Arch Pharmacol, 2007]. However, the activity of ORPH may also involve brain located channels. Indeed the widespread distribution of ERG potassium channels in rat brain with particular predilection for glia is extensively founded [Papa et al., J Comp Neurol, 2003]. This is a part of the mechanism regulating potassium homeostasis in hippocampal glia. Pharmacologic studies have also shown a relationship between preventing voltage-dependent potassium buffering in astrocytes and the development of epileptiform activity in the hippocampus. Voltage dependent buffering refers to the neurologic process whereby glia control the potassium concentration in the extraneuronal space in order to maintain normal neuronal conduction of action potentials. There has to be a constant extraneuronal potassium concentration in order for the action potential to effectively start and stop as needed. If this is perturbed, there is enhanced susceptibility for epileptic activity. Interestingly, blocking ERG potassium channels in astrocytes changes potassium concentrations extraneuronally, and such changes in potassium concentrations extraneuronally have been shown to be epileptogenic. This has clinical implications as post-traumatic changes in hippocampal glia mimic the effects of acute blockade by external antagonists, including loss of potassium conductance with subsequent failure of glial potassium homeostasis, which in turn promotes abnormal neuronal excitation [D’Ambrosio et al., J Neurosci, 1999]. Further research should focus on this interesting mechanism as it might prove to be an important component of the complex pathophysiology of drug refractoriness in epilepsy.

We propose the new model, thanks to its unique characteristics, as an interesting option for studying novel targets for pharmacological intervention in refractory epilepsy and drug resistant SE.