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Professor Zdzisław Kleinrok, In Memoriam

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## Effect of antiepileptic drugs on the immune and endocrine systems

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Accumulating data indicate that besides the central nervous system, antiepileptic drugs may also affect the immune and endocrine functions. As the three homeostasis-keeping systems communicate between one another *via* neuromediators, hormones and cytokines, some studies focused on antiepileptic drug effects on these parameters. Preclinical studies showed that some antiepileptic drugs might influence peripheral immunological parameters in rodents. Thus, phenytoin and carbamazepine were reported to decrease both humoral and cellular response, and an involvement of CD8 cells in these effects was postulated. Other investigators found that valproate and phenobarbital decreased humoral response and lymphocyte T cytotoxicity in mice, respectively. Moreover, carbamazepine and phenytoin enhanced autoimmune response in experimental encephalomyelitis after withdrawal of these drugs in mice [Black et al., *Ann Neurol*, 2007]. Only scarce data on the effects of new generation anticonvulsants on the immune system are available. In particular, it was reported that topiramate reversed kainate-induced decrease in lymphocyte T proliferative activity in rats [Kubera et al., *Pol J Pharmacol*, 2004]. Clinical data indicate that phenytoin, carbamazepine, valproate, predominantly possess immunosuppressive activity, inhibit protein synthesis in lymphocytes, decrease CD4/CD8 ratio, decrease the level of (Ig)A, and decrease or elevate the level of IgG and IgM [Basaran et al., *Int J Immunopharmacol*, 1994; Bostantjopoulou et al., *Funct Neurol*, 1994; Sorrel and Forbes, *Clin Exp Immunol*, 1975]. Antiepileptic drugs also exert profound effect on cytokine production. It was found that *in vitro* carbamazepine inhibited interleukin (IL)-2 and IL-4 but enhanced IL-10 and transforming growth factor- $\beta$  (TGF- $\beta$ ) production. In epileptic patients treated with carbamazepine and phenytoin, an increase in IL-2, and IL-1 blood level was observed, respectively. On the other hand, *in vitro* valproate inhibited tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-6 production probably *via* its action on the nuclear transcription factor  $\kappa$ B (NF- $\kappa$ B), whereas in patients this drug enhanced IL-1, IL-6 and IL-5 level. Hypersensitivity of the immune

system has been described in some patients treated with lamotrigine, carbamazepine, phenobarbital and phenytoin. The postulated mechanism of this phenomenon involves the activation of drug specific CD4<sup>+</sup> and CD8<sup>+</sup>, increase in IL-4 and IL-5 level, receptor T polymorphism or a direct effect of the drug on lymphocyte T receptors.

Regarding endocrine effects of anticonvulsants, an interaction of these drugs with thyroid, gonadal and adrenal axis merits attention [Benedetti et al., *Eur J Clin Pharmacol*, 2005; Isojarvi et al., *Epilepsia*, 2001; Lofgren et al., *Epilepsia*, 2006; Motta, *Neurol Neurochir Pol*, 2000]. Indeed, carbamazepine, oxcarbazepine or simultaneous administration of carbamazepine and valproate reversibly decrease thyroxine (T4) level in patients, without effect on thyroid-stimulating hormone (TSH). While valproate given alone has no effect on T4, phenytoin, phenobarbital and primidone, as metabolic enzyme inducers, may decrease the level of free and bound thyroxine. No effects of new antiepileptics such as levetiracetam, tiagabine, vigabatrin or lamotrigine on thyroid hormones were observed. Other data showed that valproate enhanced leptin and insulin blood level and increased body weight, whereas topiramate showed an opposite effect. An influence of anticonvulsants on hypothalamic-pituitary-gonadal axis is partially sex-dependent. In males, valproate decreased follicular-stimulating hormone (FSH) and luteotropin (LH) but enhanced dehydroepiandrosterone sulfate (DHEAS) concentrations. Carbamazepine decreased testosterone/sex hormone-binding globulin (SHBG) ratio, whereas oxcarbazepine had no effect on androgens. In females, valproate reduced FSH-stimulated estradiol release, elevated testosterone level and had an androgenic effect. Carbamazepine decreased testosterone level but enhanced SHGB concentration. In comparison with thyroid and gonadal hormones, only a few data concern antiepileptic drug interaction with hypothalamic-pituitary-adrenal axis (HPA). No effects of antiepileptic drugs on ACTH/cortisol circadian rhythmicity were found. Valproate *via* GABA<sub>A</sub> receptors decreased corticotropin-releasing factor (CRF) release

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in rats, whereas lamotrigine was reported to stabilize ACTH/cortisol secretion. Furthermore, felbamate was found to inhibit stress-induced corticosterone release in mice. Interestingly, recent data suggest that some

antiepileptic drugs may inhibit functional activity of glucocorticoid receptors [Basta-Kaim et al., *Pharmacol Rep*, 2007].

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## Teratogenic effects of antiepileptic drugs

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Epilepsy is a chronic neurological condition with prevalence of 4 to 10 people per 1000. It occurs with comparable frequency in men and women. A significant part of epileptic women are those in childbearing age and 3 to 4 of every 1000 pregnant women have active epilepsy [Morrow et al., *J Neurol Neurosurg Psychiatry*, 2005]. Although the risk of major congenital malformation (MCM) caused by prenatal exposure to antiepileptic drugs (AEDs) is 4–9% (the background risk of MCM is 1–2%), more than 90% of children born from mothers receiving AEDs are healthy.

The association of fetal malformation with prenatal AEDs exposure was first noticed by Mullers-Kuppers in 1963 [*Acta Paedopsychiatr*, 1963] and by Meadow in 1968 in a letter to *The Lancet* [Brodie, *J Neurol Neurosurg Psychiatry*, 2006].

From this time on more attention has been paid to teratogenicity of AEDs [Oguni and Osawa, *Epilepsia*, 2004]. In 1975, Hanson and Smith [*J Pediatr*, 1975] described “fetal hydantoin syndrome“ (facio-cranial anomalies, microcephalia, brain retardation, cleft hypoplasia). Retrospective investigations of Kaneko et al. [*Epilepsy Res*, 1999] have shown a higher risk of malformation in children born to mothers taking higher dose of phenytoin or phenobarbital in the first pregnancy trimester.

Despite the widespread use of AEDs, the underlying mechanisms by which they cause teratogenicity and embryopathy still remain unclear. The term fetal antiepileptic drug syndrome has been proposed to refer to the constellation of anomalies seen with different AEDs as a group. As similar malformations are seen with different AEDs, it is possible that the malformation may be caused by common underlying mechanisms. Proposed mechanisms can be attributed

to either direct drug toxicity, drug-induced folate deficiency, alteration in thyroid hormone status, oxidation of the drug to free radical intermediates or genetic predisposition leading to deficiency of drug detoxifying enzyme epoxide hydrolase [Leppert and Wieser, *Nervenarzt*, 1993]. A recent theory is that AEDs cause embryonic cardiac bradyarrhythmia and hypoxic damage. These fetal episodes of hypoxia and ischemia lead to reperfusion injury and generation of oxygen species [Azarbayjani and Danielsson, *Epilepsia*, 2002].

The first report of the North American AED Pregnancy Registry (1997–2002) showed a significant risk of major malformation in the offspring of mothers taking phenobarbital monotherapy in early pregnancy (6.5% of pregnancies, indicating a significant relative risk of 4.2 times the expected rate). The second report from the North American AED Pregnancy Registry (1997–2003) reported an increased rate of MCMs with valproate monotherapy, used in the first trimester (10.7% of pregnancies, indicating a significant relative risk of 7.3 times the expected rate). All other AEDs combined in this registry have a MCM rate of 2.9%. The Australian Registry of Antiepileptic Drugs in Pregnancy showed a MCM rate for valproate monotherapy of 17.1%. The incidence of MCMs in offspring not exposed to AEDs was 3.6%, exposed to valproate polytherapy was 13%, to phenytoin – 4.7%, and to carbamazepine – 4.5%. [Perucca, *Lancet Neurol*, 2005]. The UK Epilepsy and Pregnancy Registry showed the overall rate for all AEDs exposed cases was 4.2% and was significantly higher for offspring exposed to polytherapy at 6.0% compared with monotherapy at 3.7%. The MCM rate for women with epilepsy who had not taken AEDs during pregnancy was 3.5%. The MCM rate was significantly greater for

pregnancies exposed to valproate (6.2%), compared with those exposed only to carbamazepine (2.2%) [Tomson, *Epilepsy Behav*, 2007]. Aratama et al. [Neurology, 2005] have concluded that the risk of monotherapy and polytherapy, excluding valproate, was not associated with an increased risk of MCMs.

Other surveys have shown similar results, especially with regards to valproate. International survey of malformations (MADRE study) of 299 patients with AEDs exposure revealed oral clefts associated with phenobarbital and methylphenobarbital [Arpino et al., *Epilepsia*, 2000]. Cardiac malformations were associated with phenobarbital, methylphenobarbital, valproate and carbamazepine. Valproate was associated with spina bifida, hypospadias, porencephaly, other brain anomalies, and limb reduction defects. In addition, a dose-related increase in MCMs has been found with valproate; doses higher than 1000 mg per day were associated with an increased risk of congenital malformations. Similarly, lamotrigine at doses exceeding 200 mg per day, causes a higher risk of MCMs [Morrow et al., *J Neurol Neurosurg Psychiatry*, 2006]. Polytherapy with AEDs has also been as-

sociated with an increased risk. Polytherapy elevates the overall risk of congenital malformations up to four times, compared to monotherapy [Kaaja et al., *Neurology*, 2003].

Recent studies have hinted at neurocognitive deficits in children exposed to AEDs *in-utero*. A direct evidence for the neurocognitive effects of intrauterine exposure to AEDs is difficult to obtain, since multiple influences like maternal intelligence quotient (IQ) and social environment determine final intellectual outcome after birth. Several studies have been carefully performed to assess the risk [Adab et al., *J Neurol Neurosurg Psychiatry*, 2001, 2004; Gaily et al., *Neurology*, 2004; Reinisch et al., *JAMA*, 1995; Sanjeev et al., *Epilepsia*, 2007; Vinten et al., *Neurology*, 2005]. A risk of significantly lower verbal IQ and special educational needs in children exposed to valproate especially in high doses as compared to other AEDs exposure or non-exposed children has been documented [Gaily et al., *Neurology*, 2004; Vinten et al., *Neurology*, 2005]. However, there has been no risk of impaired intelligence with the carbamazepine use [Gaily et al., *Neurology*, 2004].

## Influence of antidepressants on the efficacy of antiepileptic drug treatment

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The bidirectional relationship between epilepsy and depression has been recognized in ancient times by Hippocrates [Lewis, *J Mental Sci*, 1934]. This observation was confirmed nowadays in a number of investigations [Forsgren and Nystrom, *Epilepsy Res*, 1999]. Among patients with epilepsy, 36.5% of them reported symptoms of depression, compared to 11.8% of controls [Blum et al., *Neurology*, 2002].

Affective disorders and epilepsies share partially similar pathogenesis. The common predisposition appears to arise from noradrenergic and serotonergic deficits [Schildkraut, *Am J Psychiatry*, 1965]. Moreover, GABAergic deficits associated with glutamatergic and CRH excess may trigger and maintain sei-

zures as well as depressive episodes [Jobe, *Epilepsy Behav*, 2003].

Appropriate treatment of depression in people with epilepsy can improve mood, energy and functioning. Additionally, it can help reduce seizure risk and frequency. Nevertheless, depression in epileptic patients is still underdiagnosed and undertreated [Hermann et al., *Epilepsia*, 2000; Wiegartz et al., *Neurology*, 1999]. Substantial progress has been made in reducing the adverse effect liability of the antidepressants. Their possible proconvulsant properties are no longer considered to stem from therapeutic mechanisms [Jobe, *Clin EEG Neurosci*, 2004]. Actually, an overdose of tetracyclic and tricyclic antidepressants may lower the

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seizure threshold through the influence on the glutamatergic, GABAergic, and histaminergic neurotransmission, activity of G-protein-coupled K<sup>+</sup> channels, and synthesis of brain-derived neurotrophic factor (BDNF) [Jobe and Browning, *Epilepsy Behav*, 2005]. The safest antidepressant drugs are the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [Kanner and Nieto, *Neurology*, 1999].

The influence of four antidepressant drugs on the anticonvulsant activity of conventional antiepileptics against the maximal electroshock in mice was evaluated in our lab. Fluoxetine is the most prominent representative of SSRIs. Mianserin blocks presynaptic  $\alpha_2$ -, postsynaptic  $\alpha_1$ -adrenoreceptors, and postsynaptic 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. Venlafaxine and milnacipran belong to the class of SNRIs [Saxena, *Pharmacol Ther*, 1995].

Acute treatment with fluoxetine increased the electroconvulsive threshold, and, when given at the subprotective dose, it potentiated the anticonvulsant action of valproate, carbamazepine, phenytoin and phenobarbital [Borowicz et al., *Pharmacol Rep*, 2006]. Chronic administration (maintained for 14 days) of fluoxetine failed to affect the threshold for electroconvulsions, but enhanced the efficacy of valproate, car-

bamazepine and phenytoin. However, the interactions between this antidepressant and antiepileptics could be partially due to pharmacokinetic factors [Borowicz et al., *Eur J Pharmacol*, 2007]. Acute mianserin raised the electroconvulsive threshold and potentiated the action of valproate, carbamazepine and phenytoin. In contrast, chronic therapy with mianserin lowered the threshold and reduced efficacy of valproate and phenytoin. In this case pharmacokinetic contribution to the observed interaction is not probable [Borowicz et al., *Psychopharmacology (Berl)*, 2007]. Venlafaxine and milnacipran given acutely increased the threshold for electroconvulsions and enhanced the action of valproate, carbamazepine and phenobarbital. Effect of the chronic treatment of the two antidepressants on seizure phenomena and brain concentrations of antiepileptic drugs is currently investigated.

In conclusion, antidepressant drugs from various classes can influence the conventional antiepileptic treatment. The final effects depend not only on the mechanism of action, but also the treatment duration with individual antidepressants. Although the presented data are still incomplete, it is not unreasonable to postulate that the use of mianserin in epileptic patients should be at least limited.

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## Psychological sequelae of switching from an original to a generic agent in drug-resistant epilepsy – a prospective study

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Although 50% of epilepsy patients accept a decrease in the cost of their therapy, the majority of them are afraid of changing drugs, being mostly concerned with effectiveness and safety of generic drugs [Berg et al., *Epilepsy Behav*, 2006; Haskins et al., *Epilepsy Behav*, 2005].

Approximately 1/3 of physicians are anxious to employ generic drugs in epilepsy treatment, 2/3 fear deteriorated seizure control following a switch, recurrent seizures or poorer tolerance of a new drug [Berg et al., *Epilepsy Behav*, 2006; Haskins et al., *Epilepsy Behav*, 2005]. The prospective studies included 441

patients aged 18–58 years with drug-resistant epilepsy with partial seizures treated with lamotrigine (n = 224), topiramate (n = 104) or gabapentin (n = 113) in Epilepsy and Migraine Treatment Centre, Kraków, Poland. In each patient, the frequency and degree of troublesomeness of epileptic seizures, quality and frequency of adverse effects and quality of life were assessed (the QOLIE-31-P scale). The subjects were tested prior to changing the medication and three months after the switch.

The investigations have demonstrated that there is no significant difference in the frequency and trouble-

someness of epileptic seizures in particular groups treated with original or generic lamotrigine, original or generic topiramate and original or generic gabapentin. After the switch, there were no differences in the frequency and quality of adverse effects. A switch

from an original to a generic drug did not affect the quality of life, either.

It appears that the use of generic drugs in patients with drug-resistant epilepsy is fully justified.

## Clinical application of new generation drug combinations in refractory epilepsy

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Approximately 20–30% of patients treated for epilepsy require polytherapy due to unsuccessful monotherapy [Kwan et al., *N Engl J Med*, 2000]. Combinations of new generation antiepileptic drugs are justified in cases of resistance to classic drugs, combinations of classic and new generation drugs or when drug interactions have to be avoided [Stephen et al., *Seizure*, 2002]. To-date, clinical information on combinations of new generation agents are scarce and most commonly describe the addition of another drug to the first, ineffective agent [Deckers et al., *Epilepsia*, 2000; Łuszczki et al., *Epilepsia*, 2004].

In a 6-month follow-up study, 197 two-drug combinations were assessed, in patients with epilepsy treated in Epilepsy and Migraine Treatment Centre in Kraków, Poland, using 5 new generation drugs: tiagabine (TGB), lamotrigine (LTG), vigabatrin (VGB), gabapentin (GBP) and topiramate (TPM). The inclusion criteria were: refractory epilepsy with partial seizures, at least two seizure episodes/month and therapeutic failure of treatment with either of two drugs forming a combination. At the time of the second drug addition, the patients were on the first drug monotherapy. The second agent was given at the minimal effective dose (MED.), i.e. TGB = 30 mg, LTG = 200 mg, VGB = 2,000 mg, GBP = 1,800 mg and TPM = 200 mg. The measure of combination effectiveness was the percentage of responders (at least 50% seizure reduction), percentage of seizure-free patients and dose of drugs used in combination. Safety was measured by the percentage of patients excluded from the study due to unacceptable adverse effects. The results are shown in Table 1.

**Tab. 1.** Drug combinations, number of patients in groups, results of effectiveness and safety evaluation of drug combinations

| Drug combination | Number of patients | % of responders | % of seizure-free patients | % of withdrawals |
|------------------|--------------------|-----------------|----------------------------|------------------|
| TGB + VGB        | n = 28             | 28.6            | 14.3                       | 35.7             |
| TPM              | n = 16             | 43.7            | 25.0                       | 50.0             |
| GBP              | n = 14             | 50.0            | 21.4                       | 14.3             |
| LTG              | n = 17             | 35.3            | 11.8                       | 5.9              |
| VGB + TPM        | n = 13             | 53.8            | 30.8                       | 46.2             |
| GBP              | n = 18             | 44.4            | 22.2                       | 11.1             |
| LTG              | n = 30             | 60.0            | 20.0                       | 16.6             |
| TPM + GBP        | n = 20             | 60.0            | 30.0                       | 20.0             |
| LTG              | n = 18             | 38.9            | 11.1                       | 22.2             |
| GBP + LTG        | n = 23             | 60.9            | 30.4                       | 4.3              |

The most effective combinations were GBP + LTG, TPM + GBP, VGB + LTG, VGB + TPM and TGB + GBP. The safest combinations were GBP + LTG, TGB + LTG, VGB + GBP, TGB + GPB and VGB + LTG. The following combinations were found to be of little safety: TGB + TPM, VGB + TPM and TGB + VGB. The most effective combinations required lower doses of individual drugs, which were slightly in excess of MED.

The most effective combinations include agents that the best approximate the ideal from the pharmacokinetic viewpoint. The effect of these combinations requires low or medium doses. Combinations of drugs affecting the GABAergic system are of low safety and often are the cause of treatment cessation, even when highly effective.

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# Levetiracetam – a newer antiepileptic drug with unique properties

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Levetiracetam has a bunch of properties, clearly differentiating this drug from other, conventional and novel antiepileptic drugs. Specifically, in contrast to all antiepileptic drugs, the drug is not effective in major screening models of seizures in rodents – for instance in maximal electroshock or pentetrazole-induced convulsions [Czapiński et al., *Curr Top Med Chem*, 2005]. Interestingly, levetiracetam has been shown to protect against kainate- or pilocarpine-induced seizure activity as well as against electrically kindled convulsions [De Smedt et al., *CNS Drug Rev*, 2007]. Also, the drug seems effective in reducing the severity of pilocarpine-induced status epilepticus and subsequent mortality [Oliveira et al., *Neurosci Lett*, 2005]. Following its detailed protective activity against kindling development, a conclusion may be drawn that levetiracetam, apart from acute anticonvulsant effects, has also antiepileptogenic activity [Löscher et al., *J Pharmacol Exp Ther*, 1998]. In a model of prolonged status epilepticus, levetiracetam has been found neuroprotective by reducing mitochondrial dysfunction when given 15 min after the onset of status epilepticus [Gibbs et al., *Epilepsia*, 2006]. However, there are also data available that this antiepileptic drug is not antiepileptogenic or neuroprotective when given after a prolonged status epilepticus in rats [Brandt et al., *Neuropharmacology*, 2007].

Levetiracetam's anticonvulsant activity may be associated with an inhibition of N-type voltage-dependent calcium channels and, unlike other antiepileptics, binding to a very special site within the brain which is the synaptic vesicle protein 2A [De Smedt et al., *CNS Drug Rev*, 2007]. However, the detailed levetiracetam's mechanisms of action *via* this binding site is unknown. There are no data available that levetiracetam

directly affects GABAergic or glutamatergic receptors which are the main targets for a majority of antiepileptic drugs. However, there are some assumptions that this antiepileptic drug may indirectly enhance GABA-mediated events [De Smedt et al., *CNS Drug Rev*, 2007].

Preclinical studies indicate that its combination with other antiepileptic drugs may result in synergy which is pharmacodynamic in nature [Łuszczki et al., *Epilepsia*, 2006]. Specifically, an isobolographic analysis of interactions of levetiracetam with numerous antiepileptic drugs against maximal electroshock-induced convulsions in mice has revealed that combinations of levetiracetam with topiramate, carbamazepine or oxcarbazepine were synergistic and those with phenytoin, phenobarbital, valproate or lamotrigine – additive. None of the evaluated combinations affected motor coordination or long-term memory [Łuszczki et al., *Epilepsia*, 2006]. Again, a synergy was evident for a combined treatment of levetiracetam with felbamate against electroconvulsions in mice, however, felbamate elevated brain concentration of levetiracetam pointing to a pharmacokinetic contribution in this particular interaction [Łuszczki et al., *Epilepsia*, 2007].

However, levetiracetam is very rarely associated with pharmacokinetic interactions. This is because it possesses minimal metabolism and protein binding. Also, this antiepileptic displays good bioavailability and a relatively short time to steady-state concentrations [Patsalos, *Pharmacol Ther*, 2000]. Levetiracetam, as an antiepileptic showing an efficient clinical response and promising long-term retention rate may be recommended as monotherapy or adjuvant therapy for different types of seizures [De Smedt et al., *CNS Drug Rev*, 2007].

## The progress in EEG recordings in diagnosis of epilepsy

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The progress of EEG recordings in diagnostics of epilepsy is closely connected with science development and technological progress. Progress in these two fields (science and technology) allowed for producing modern EEG apparatuses for: digital detection, amplification and registration of bioelectrical activity, prolonged registration, monitoring (video-EEG, ambulatory cassette monitoring), continuous EEG, quantitative EEG analyses and analyses of EEG data in the combination with MRI data.

The relationship between EEG changes and epilepsy was revealed by Berger H. (who found the connection between an unilateral spike and a seizure of the limb on the contralateral side) and by Gibbs F. (who found that absence attack was connected with generalized discharges of complex spike-and-3Hz-slow-wave [Majkowski, *Elektroencefalografia Kliniczna*, 1989]).

Polish Society of Clinical Neurophysiology proposes a schema of diagnosis of epilepsy [Niedzielska et al., *Aktualności Neurologiczne*, 2001]. The basic schema includes a routine EEG (with hyperventilation and photic stimulation) lasting 20–30 min. The expanded schema contains: EEG after sleep deprivation and monitoring registration (video-EEG, ambulatory cassette recording).

Pre-surgical noninvasive diagnosis of epilepsy includes quantitative analyses of EEG activity (to define the epileptic focus), whereas invasive examinations use routine EEG registration connected with electrocorticography (ECoG) with electrodes implanted in deep structures of the brain.

Long-term monitoring (LTM) in diagnosis of epilepsy refers to the simultaneous recording of EEG and behavior over extended periods of time to evaluate patients with paroxysmal disturbances of cerebral function. EEG recording of long duration may be useful in a variety of situations where patients have disturbances that are difficult to record during routine examinations. The main indications for LTM are: diagnosis (recording and identification of epileptiform activity and/or behavioral abnormalities in patients with normal or equivocal standard EEG examinations and verification of the epileptic nature of the new

“spells”), classification (types of clinical seizures, characterization of EEG ictal and interictal abnormalities), characterization of the relationship of seizures with specific precipitating circumstances or stimuli and characterization of the behavioral consequences of epileptiform discharges as measured by psychological tests. For LTM, a video-EEG recording is used (it is the most effective method of behavioral monitoring, patient’s behavior is continuously recorded on videotape simultaneously with EEG) and ambulatory cassette EEG (especially to analyze EEG during subjective feelings and disorders) [Engel, Report of an IFCN committee, 1993; Mizrahi and Lesser, In: *Current Practice of Clinical Electroencephalography*, 2003].

The EEG recording after sleep deprivation (SD) is used in the patients with suspected epilepsy in whom standard EEG recording was normal or had some unspecific abnormalities. EEG after SD is longer in time than standard EEG and also includes typical activating method (hyperventilation and photic stimulation) [Majkowski, *Elektroencefalografia Kliniczna*, 1989; Niedermeyer and Lopes da Silva, *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, 1999]. Sleep deprivation has been used to activate the occurrence of seizure discharges [Bazil and Walczak, *Epilepsia*, 1997; Rowan et al., *Electroencephalogr Clin Neurophysiol*, 1982]. This method is effective in 30–70% of the time and can increase the diagnostic yield even if sleep does not occur [Fountain et al., *J Clin Neurophysiol*, 1998].

Magnetoencephalography (MEG) is an imaging method used to measure the magnetic fields produced by electrical activity in the brain. These measurements are commonly used in both clinical evaluation and research. In clinical practice, MEG is used for epilepsy diagnosis to detect and localize epileptiform activity for surgical planning. In pre-surgical evaluation of epileptic patients, it is important to know whether the epileptic discharges are focal, how many brain areas are involved, what is the relative timing between the foci [Niedermeyer and Lopes da Silva, *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, 1999].



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The method of three-dimensional mapping (3D) connects data from various modalities, such as EEG and MRI scans. Such a connection of two features in one examination can give new functionalities, such as for example, a pre-surgical, noninvasive diagnosis of an epileptic focus. The three-dimensional scans obtained through imposition enable a precise analysis of the discharge spreading point [Walerian, *Epileptologia*, 2003].

Continuous EEG monitoring (CEEG) in intensive care unit is the best available method for detecting epileptiform activity. CEEG has documented high in-

cidence of nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) in patients with acute cerebral ischemia, intracranial hemorrhages, head trauma, and convulsive status epilepticus [Claassen et al., *J Clin Neurophysiol*, 2005; Jordan, *Neurology*, 1992; *J Clin Neurophysiol*, 1993; Privitera et al., *Epilepsy Res*, 1994; Vespa, *J Neurosurg*, 1999]. In the absence of CEEG, the diagnosis of NCS and NCSE is likely to be delayed or missed [Drislane, *Neurology*, 1998]. The possibility of psychogenic status epilepticus also must be kept in mind [Engel, *Seizure and Epilepsy*, 1989; Luther et al., *Ann Neurol*, 1982].

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## The assessment of determinants of psychiatric disorders in children and adolescents with epilepsy

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A variety of comorbid psychiatric disorders can accompany epilepsy in children and adolescents, including mood disorder, anxiety, adjustment disorder, psychosis, autism spectrum disorders and attention-deficit hyperactivity disorder. Children and adolescents with seizures are at increased risk of psychiatric disorders. The prevalence rates of psychiatric disorders in epileptic children have fluctuated in the wide ranges from 12% to 77% [Caplan et al., *Epilepsia*, 2005; Dunn et al., *Dev Med Child Neurol*, 2003; Ettinger et al., *Epilepsia*, 1998; Kanner, *Epilepsy Behav*, 2000; Pellock, *Epilepsy Behav*, 2004; Piazzini et al., *Epilepsy Behav*, 2001; Plioplys, *Epilepsy Behav*, 2003; Plioplys et al., *J Am Acad Child Adolesc Psychiatry*, 2007; Steffenburg et al., *Dev Med Child Neurol*, 2003; Williams et al., *Epilepsy Behav*, 2003]. The risk for comorbid psychopathology in pediatric epilepsy is three to six times higher than that of general population and significantly higher than that of children with other chronic pediatric disorders [Austin et al., *Epilepsia*, 1996, 2000; Davies et al., *Dev Med Child Neurol*, 2003]. Children with developmental disabilities are more likely than healthy children to develop epilepsy [Goulden et al., *Epilepsia*, 1991; Steffenburg et al., *Dev Med Child Neurol*, 2003]. A number of approaches have been developed to explain the multi-

factorial etiology of psychiatric comorbidity in epilepsy in children and adolescents and it was found to involve both neurobiological and psychosocial factors, taking into account the interference of biological, genetic, psychological and family factors [Baki et al., *Epilepsy Behav*, 2004; Piazzini et al., *Epilepsy Behav*, 2001]. There are many controversies as to which factors may play an important role in the different types of psychiatric disorders in developmental age [Thome-Souza et al., *Epilepsy Behav*, 2004]. The relationship between pediatric epilepsy and psychiatric disorders appears to be complex, illustrating current conceptualization of adjustment to chronic pediatric disorders. The presence of one or more comorbid psychiatric symptoms may complicate seizure control. The developmental variations of age-specific psychiatric disorders in childhood and adolescence, their specific clinical manifestations and tendency to comorbidity, predictors of clinical course should be considered in every case. Potential epilepsy-related variables include: age of onset, frequency and severity of seizures, type of seizure disorder, and antiepileptic drugs [Devinsky, *Epilepsia*, 1995; Lambert et al., *Epilepsia*, 1999]. A question asked by many clinicians is whether a child with focal epilepsy or one with generalized epilepsy is more likely to exhibit a behavioral

disturbance. Location of the seizure focus may affect predisposition to psychiatric comorbidity. Patients with seizures that are of temporal and frontal lobe origin are disproportionately affected by psychiatric comorbidity [Kanner, *Epilepsia*, 2003]. Focal epilepsy was significantly more frequent in children and adolescents with epilepsy [Thome-Souza et al., *Epilepsy Behav*, 2004]. Potential psychosocial determinants include different aspects, like increased perceivability of stigma, elevated number of stressful life events during the past year, poor adjustment to epilepsy, financial stress, external locus of control, and an earlier onset of epilepsy [Hermann et al., *Br J Psychiatry*, 1990]. The effectiveness of psychological interventions in reducing seizure frequency and improving psychological adjustment in children and adolescents has been documented [Dahl et al., *Epilepsia*, 1985; McCusker et al., *Seizure*, 1999; Reiter et al., *Seizure* 2000; Wagner et al., *Epilepsy Behav*, 2006].

The primary goal of pharmacological therapy in pediatric epilepsy and comorbid psychiatric disorders is to optimize management with multidisciplinary management strategies, in order to identify and treat comorbid psychiatric disorders. Age is an important factor in determining the type of psychiatric disorder, with a predominance of ADHD, pervasive disorder in children and depressive disorder in adolescents. In children and adolescents with epilepsy, a study of the family is also important in order to analyze family structure and genetic predisposition. Optimal diagnosis, clinical evaluation, and choice of comprehensive as well as tailored treatment are predicated based on the proper identification of coexisting psychiatric and behavioral disorders. Increased current knowledge of the clinical presentation of psychiatric developmental disorders in pediatric epilepsy may facilitate development of effective prevention and intervention strategies to improve the outcome of disorders and quality of life of children and adolescents with epilepsy.

## Novel seizure models – progress in experimental epileptology

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The molecular and cellular events underlying development and progress of epileptic changes in the brain are still not fully understood. Among epileptic patients, at least 1/3 does not respond well to pharmacotherapy. Therefore, identifying novel mechanisms involved in the generation and propagation of seizures is the issue of continuous studies. Department of Pharmacology of Medical University in Lublin, headed by Professor Zdzisław Kleinrok during the years 1967–1999, had been a prominent and dynamic centre of intense research in experimental pharmacology. Numerous valuable scientific contributions stimulated by Professor Kleinrok included the development of three novel seizure models: pilocarpine-, aminooxyacetic acid (AOAA)- and 3-nitropropionic acid (3-NPA)-induced seizures.

The pilocarpine seizure model was described in 1983 [Turski et al., *Behav Brain Res*, 1983]. Pilocarpine, a muscarinic agonist, upon administration to ro-

duents either intracerebrally or peripherally, induces a pattern of behavioral and electroencephalographic changes resembling limbic seizures in humans [Turski et al., *Behav Brain Res* 1983; Turski et al., *Brain Res*, 1987, Turski et al., *Synapse*, 1989]. Repetitive seizures are followed by status epilepticus which can last for several hours. The development of neuronal loss within the hippocampus with neuropathological pattern is similar to temporal lobe sclerosis observed in humans with epilepsy and ensuing status epilepticus [Leite et al., *Epilepsy Res*, 2002; Turski et al., *Behav Brain Res*, 1983]. Latent period of variable length (from 4–45 days) precedes the occurrence of spontaneous limbic seizures [Cavalheiro et al., *Epilepsia*, 1991; Leite et al., *Neurosci Biobehav Rev*, 1990]. During acute phase, application of phenobarbital, pentobarbital, diazepam, clonazepam or valproate may prevent the seizure development. Pretreatment with lithium chloride prior to pilocarpine injection po-

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tentiates the epileptogenic action of pilocarpine and reduces the mortality associated with the occurrence of status epilepticus [Honchar et al., *Science*, 1983]. The pilocarpine- and lithium-pilocarpine seizure models became especially valuable tools in the search for drugs effective against status epilepticus (during acute phase) and for the research on the mechanisms underlying epileptogenesis (during chronic phase). Studies in various laboratories exploiting pilocarpine model have been described in approximately 900 publications within the last 25 years.

Further discoveries in experimental epileptology made in the Department of Pharmacology involved studies on the action of mitochondrial toxins, AOAA and 3-NPA. Mitochondrial toxins are known to inhibit the oxidative phosphorylation what leads to impaired energy production. A number of substances may disturb mitochondrial respiratory chain, e.g. 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>), AOAA or 3-NPA. MPP<sup>+</sup>, the metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), blocks the activity of complex I and IV [Nicklas et al., *Life Sci*, 1985], 3-NPA is an irreversible inhibitor of succinate dehydrogenase [Alston et al., *Proc Natl Acad Sci USA*, 1977], and AOAA disrupts function of aspartate-malate shuttle [Kauppinen et al., *Biochim Biophys Acta*, 1987]. In 1991, it was demonstrated that AOAA acts as a potent convulsant [Turski et al., *Synapse*, 1991]. AOAA evokes clonic seizures (not followed by the tonic phase) in rodents, as demonstrated after peripheral or central application. AOAA-induced seizures do not progress into status epilepticus. Intracerebral injection of AOAA precipitates convulsions with a latency period of approximately 7–8 min, what suggests that the triggering mechanisms do not involve a direct receptor activation. The susceptibility to seizures depends on the age of experimental animals, with the highest susceptibility among young animals [Turski et al., *Brain Res Dev Brain Res*, 1992]. AOAA-induced seizures

may be prevented by diazepam, valproate and phenobarbital, whereas carbamazepine and phenytoin are inactive. Seizures can be also abolished with the use of N-methyl-D-aspartate (NMDA) antagonists [Turski et al., *Synapse*, 1991]. AOAA model revealed novel mechanism of epileptogenesis, indicating that an impaired mitochondrial function may be an important aspect contributing to seizure development. Studies using the AOAA model were described in approximately 40 publications.

In 1998, it was reported that the acute 3-NPA application, either peripheral or intracerebral, might also trigger seizures in rodents [Urbańska et al., *Eur J Pharmacol*, 1998] Analogically as observed with AOAA or MPP<sup>+</sup>, seizures evoked by intracerebral administration of 3-NPA are delayed and occur 8–9 min after application of the compound. Seizures include only clonic component and may progress into status epilepticus. Anticonvulsant protection is offered by only a few drugs including benzodiazepines, phenobarbital, valproate, non-NMDA glutamate receptor antagonists and adenosine antagonists [Urbańska et al., *Eur J Pharmacol*, 1998, 1999; Zuchora et al., *Neurosci Lett*, 2001; Zuchora et al., *Eur Neuropsychopharmacol*, 2005]. 3-NPA was demonstrated to display also proconvulsive effects, i.e. it lowered the threshold for kainate-, AMPA- and 4-aminopyridine-induced convulsions [Haberek et al., *Eur J Pharmacol*, 2000]. 3-NPA seizure model seems to be useful in studies of pharmacoresistant epilepsy associated with congenital or acquired disturbances of mitochondrial function. Research data based on the 3-NPA-induced seizures were reported in 9 publications.

In summary, novel seizure models developed in the Department of Pharmacology, Medical University in Lublin extend our knowledge on the mechanisms governing initiation and propagation of seizures and are valuable tools in the search for more effective antiepileptic drugs.

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