Tenth Conference

on

PROGRESS
IN ETIOPATHOGENESIS
OF SEIZURES

Lublin, November 25, 2006

Organized by: Department of Pathophysiology
Medical University of Lublin

Section of Pharmacology
Polish Academy of Sciences

Sponsored by: Sanofi-Aventis
UCB Pharma and Janssen-Cilag

Chronic administration of bupropion enhances the anticonvulsant activity of new antiepileptic drugs in mice

Bartłomiej Barczyński, Tomasz Mróz, Marian Wielosz, Piotr Tutka

Department of Experimental and Clinical Pharmacology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland

Bupropion hydrochloride (BUP) is a safe and effective antidepressant with comparable efficacy to selective serotonin reuptake inhibitors (SSRIs) [Foley et al., Expert Rev Neurother, 2006]. It is approved for use as first line smoking cessation aid and treatment of depression or seasonal affective disorder. The mechanism of antidepressant action of BUP, although not clearly understood, is now considered to be a result of dopamine and norepinephrine reuptake inhibition. It has been documented that BUP noncompetively blocks several different isoforms of nicotinic acetylcholine receptors [Slemmer et al., J Pharmacol Exp Ther, 2000]. Clinical data show that BUP even in doses considered to be therapeutic, may produce seizures in humans [Johnston et al., J Clin Psychiatry, 1991; Pesola and Avasarala, J Emerg Med, 2002]. Convulsions develop in 15–37% of all intentional BUP exposures [Spiller et al., Am J Emerg Med, 1994]. When used at recommended doses, it poses the same risk of seizures as other antidepressants [Dunner et al., J Clin Psychiatry, 1998]. However, the mechanism of this serious adverse effect still remains unclear. The treatment of BUP-evoked convulsions is empirical and based on a general knowledge of seizure treatment [Belson and Kelley, J Emerg Med, 2002]. We have recently demonstrated in mice that BUP-induced convulsions are antagonized by a variety of antiepileptic drugs, with clonazepam being the most effective [Tutka et al., Epilepsy Res, 2005]. In another study, we have shown that a 14-day BUP administration in a dose of 5 mg/kg, does not affect or even, in some cases, inhibits the anticonvulsant activity of conventional antiepileptic drugs in maximal electroshock model (MES) in mice [Barczyński et al., Pharmacol Rep, 2006]

The aim of the present study was to evaluate whether BUP administered intraperitoneally (*ip*) influenced anticonvulsant activity and motor toxicity of three new antiepileptic drugs.

Our research was performed on male Swiss mice weighing at the beginning of the experiments 19–25 g which were kept in standard laboratory conditions.

The experimental groups, consisting of eight animals, were chosen by means of a randomized schedule. BUP (Zyban®, GlaxoSmithKline) was administered for two weeks, twice daily, every 12 hours, at certain periods of time, i.e. 7–8 a.m. and 7–8 p.m. The drug was suspended in a 1% solution of Tween 81 and administered *ip* in a volume of 10 ml/kg of body weight. The following antiepileptic drugs were used: felbamate (Felbamate®, Tocris Neuramin), topiramate (Topamax®, Janssen Cilag) and lamotrigine (Lamitrin®, GlaxoSmithKline). Electroconvulsions were produced according to Swinyard et al. [Swinyard et al., J Pharmacol Exp Ther, 1952] with the use of ear-clip electrodes. Tonic extension of the hind limbs was the criterion for convulsions. BUP was applied in a dose of 5 mg/kg, which was previously determined as not affecting the convulsive threshold during chronic administration. Control groups of mice received sterile saline. In order to assess impairment of motor coordination of mice, the rotarod test [Dunham and Miya, J Am Pharmacol Assoc, 1957] was applied.

Chronic administration of BUP enhanced the protective activity of all novel antiepileptics. The respective ED_{50} values were reduced from 60.7 to 41.6 for topiramate (p < 0.01), from 4.6 to 3.0 for lamotrigine (p < 0.01) and from 48.7 to 37.3 mg/kg for felbamate (p < 0.05). The dose of 2.5 mg/kg of BUP administered for 14 days did not change the protective activity of all above drugs studied. BUP (5 mg/kg) did not affect motor impairment induced by felbamate and topiramate. BUP in the dose of 5 mg/kg slightly increased the TD_{50} value of lamotrigine from 19.2 to 26.3 (p < 0.05) whereas the dose of 2.5 mg/kg showed no such effect.

The study shows that chronic administration of BUP enhances the anticonvulsant activity of felbamate, topiramate and lamotrigine. Patients suffering from both, seasonal affective disorder and epilepsy might benefit from the use of combined treatment with BUP and one of the antiepileptic drugs studied. However, to support the conclusion, more preclinical experiments have to be performed.

Caffeine and management of epilepsy – a clinical evidence

Barbara Błaszczyk[1,2]

[1]Department of Neurology, Neuropsychiatric Hospital, Grunwaldzka 47, PL 25-736 Kielce, Poland
[2]Department of Neurological Diseases, Institute of Medical Education, Świętokrzyska Academy, IX Wieków Kielc 19, PL 25-517 Kielce, Poland

Numerous experimental data clearly indicate that either acute or chronic caffeine may reduce the anti-convulsant activity of conventional antiepileptic drugs against electroconvulsions in mice [for review: Czuczwar and Kleinrok, Pharmacol Res, 1990; Gąsior et al., Epilepsia, 1996; Pharmacol Biochem Behav, 1996]. There are only limited clinical reports on this issue. For instance, Kaufman and Sachdeo [Seizure, 2003] reported on an increased seizure frequency in a patient with mixed seizures (grand mal, absence, atonic, and myoclonic seizures). The plasma concentrations of antiepileptic drugs were within therapeutic limits, sleep patterns were normal and the patient was not exposed to stress. It came out that the patient started to drink a diet caffeinated beverage. When the diet beverage was substituted by the decaffeinated one, the seizure frequency reached baseline. A similar case report was documented by Bonilha and Li [Seizure, 2004] who found a dramatic increase in seizure frequency associated with heavy coffee drinking in a patient with symptomatic partial epilepsy. Stopping coffee ingestion resulted in a considerable reduction in this parameter.

A hundred of epileptic patients (F – 62; M – 38 in the age of 20–79 yrs.) were questioned about coffee drinking and it turned out that 78 (F – 52; M – 26) used to drink coffee. Twenty two patients (F – 12; M – 10) would drink more than two cups daily. Interestingly, 71 patients (F – 51; M – 20) could detect no association between their coffee drinking habit and seizure frequency. In patients, whose seizure frequency was considerably increased, quitting the habit restored their frequency to baseline without any change of antiepileptic medication.

It may be concluded that ingestion of caffeine can impair the therapeutic effect of antiepileptic drugs in some patients, usually heavy coffee drinkers (4–5 cups daily). Elimination of excessive caffeine intake returns the affected patients' seizure frequency to baseline.

Do antiepileptics influence the efficacy of antidepressants?

Kinga Borowicz

Department of Pathophysiology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland

Epilepsy is associated with increased risk of psychiatric illness, particularly depression. This relationship has been recognized since Hippocrates observed a relatively high frequency of "melancholia" among those with epilepsy, as well as "melancholics" were prone to develop epilepsy [Lewis, J Mental Sci, 1934]. Depression is often underdiagnosed and under-treated in people with epilepsy [Hermann et al., Epilepsia, 2000; Wiegartz et al., Neurology, 1999]. Depressive disorders can be sometimes the side effect of antiepileptic drugs, such as barbiturates. They can be also related to the cause of the secondary epilepsy, like brain injury in the course of stroke, head trauma, meningitis or encephalitis. The relationship between epilepsy and depression seems to be bidirectional, since patients with depression also have higher frequency of epilepsy [Forsgren and Nystrom, Epilepsy Res, 1999]. In epileptic patients, depressive disorders can present as unipolar, bipolar or dysthymic disorders. More characteristically, however, patients develop atypical depression. Although antidepressant drugs (ADDs) have been used in epileptic patients for

a long time, to date there has been only one controlled study. Drugs of the family of selective serotonin reuptake inhibitors (SSRIs) should be considered as initial therapy for depressive disorders in these patients [Kanner and Nieto, Neurology, 1999].

Depression affects about 5.3% and epilepsy about 0.5–1% of general population. Among patients with epilepsy, 36.5% reported symptoms of depression, compared to 11.8% of controls [Jacoby et al., Epilepsia, 1996; Blum et al., Neurology, 2002]. The impact of depression on people with epilepsy include greater seizure frequency, less seizure control, and increased risk of suicide. It suggests that depression could be a biological marker for a more severe form of epilepsy [Kanner and Nieto, Neurology, 1999]. It is also interesting that epileptics may experience an increased occurrence of depressive episodes when seizure frequency falls in response to therapy with antiepileptic drugs (AEDs). People with epilepsy were 5 time more likely to commit suicide. For patients with temporal-lobe epilepsy, the risk of suicide is 25-fold higher [Risdale et al., Br J Gen Pract, 1996].

Reduction in serotonergic, noradrenergic and GABA-ergic functions have been marked as pivotal pathogenic mechanisms of depression and have served as the bases for antidepressant pharmacological treatments [Schildkraut, Am J Psychiatry, 1965]. Likewise, a lessened activity of these neurotransmitters has been reported to facilitate kindling, to exacerbate seizure severity, and intensify seizure predisposition in some animal models [Jobe et al., Crit Rev Neurobiol, 1999].

All classes of ADDs are reportedly successful in treating epilepsy-related depression. However, ADDs may bidirectionally affect the seizure control [Jobe et al., Epilepsy Int Symp Abstr, 1983]. Some of them lower the seizure threshold. Fortunately, they do so in varying degrees. The highest risk is characteristic for tetracyclic antidepressants, e.g., bupropion, maproti-

line, mianserin, and tricyclic anidepressans, e.g., doxepin, imipramine and amitriptyline [Dailey and Naritoku, Biochem Pharmacol, 1996]. The proconvulsant action of ADDs may be due to its influence on glutamatergic, GABA-ergic, and histaminergic neurotransmission, effects on G-protein-coupled K^+ channels, and effects on brain-derived neurotrophic factor (BDNF) [Jobe and Browning, Epilepsy Behav, 2005]. It should be underlined that lowering the seizure threshold with therapeutic doses of aforementioned drugs rarely has clinical significance. In fact, seizures appear when ADDs are overdosed. Nevertheless, the most safe class of ADDs to prescribe in people with epilepsy and those with abnormal EEGs are the selective serotonin reuptake inhibitors (SSRIs). Additional benefits could be related with SSRIs therapy. According to Jobe and Browning [Epilepsy Behav, 2005] this class of ADDs reduces the incidence of respiratory arrest in DBA/2 mice. Respiratory arrest has been associated with sudden unexpected death in epilepsy, and the DBA/2 mouse model of epilepsy is also considered as a model for this disorder.

In terms of drug interactions ADDs may cause slight increases in AED levels. This effect is usually not clinically significant and in some cases my account for better seizure control. However, AED levels should be monitored. The effect of AEDs on ADDs concentrations is usually reversed. Some AEDs lower antidepressant concentrations by up to 50%. Higher-than-usual antidepressant requirements have not been necessary [Kanner, Biol Psychiatry, 2003].

In conclusion, depression in epileptic patients is more than only a reactive disorder. ADDs may influence the treatment with AEDs. Current guidelines for management of depression in people with epilepsy recommend choosing agents with a low seizure potential (the most frequently SSRIs), using the lowest effective dose, and avoiding sudden dose changes.

Inluence of caffeine on the protective action of some conventional and novel antiepileptic drugs – an experimental evidence

Magdalena Chrościńska[1], Małgorzata Jargiełło[1], Stanisław J. Czuczwar[1,2]

[1]Department of Pathophysiology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland
[2]Department of Physiopathology, Institute of Agricultural Medicine, Jaczewskiego 2, PL 20-950 Lublin, Poland

Methylxanthines, caffeine and theophylline may be ingested in tea or coffee which leads to pharmacologically relevant plasma concentrations [Gilbert et al., Can Med Assoc, 1976; Smith et al., Lancet, 1982]. Both drugs, when given in high doses, induce severe seizure activity in rodents [Czuczwar et al., Eur J Pharmacol, 1987; Epilepsia, 1990] and the seizure activity can be hardly affected by antiepileptic drugs [Czuczwar et al., Eur J Pharmacol, 1987]. It is thus of pivotal importance to establish whether caffeine, at non-convulsive doses, may affect the protective potential of antiepileptic drugs. Any undesired interaction between caffeine and antiepileptic drugs can be of clinical significance.

A broad experimental evidence exists, pointing to the hazardous effects of caffeine upon the anticonvulsant activity of conventional antiepileptic drugs against maximal electroshock-induced convulsions in mice. The methylxanthine, administered acutely at doses below its convulsant potential, diminished the protective action of carbamazepine, phenobarbital, phenytoin, and valproate which was generally not accompanied by pharmacokinetic interactions [Czuczwar et al., Epilepsia, 1990]. Interestingly, when given chronically for two weeks, caffeine retained this particular activity, significantly reducing the protection offered by the above mentioned antiepileptics. Again, pharmacokinetic interactions did not account for these data and especially, in the case of valproate and phenobarbital, chronic caffeine was much more potent than given acutely [Gasior et al., Epilepsia, 1996; Pharmacol Biochem Behav, 1996]. A central effect of caffeine is very likely to be involved since 8-(p-sulfophenyl)theophylline, which cannot enter the brain through the blood-brain barrier, was completely ineffective in this respect [Borowicz et al., J Neural Transm, 1993].

The results published so far clearly indicate that caffeine may actually reduce the effectiveness of conventional antiepileptic drugs. To the degree, the experimental data may be transferred to clinical conditions, these results also indicate that caffeine may interfere with the efficacy of epilepsy management. In fact, some case-report studies seem to support such a conclusion [Kaufman and Sachdeo, Seizure, 2003; Bonilha and Li, Seizure, 2004].

An important question arises on whether the methylxanthine may also decrease the anticonvulsant activity of some newer antiepileptic drugs – gabapentin, tiagabine, and topiramate. In a series of unpublished data, caffeine (23.1 and 46.2 mg/kg), both given acutely or chronically, significantly attenuated the anticonvulsant action of topiramate against maximal electroshock-induced seizures in mice. An ED_{50} of the antiepileptic against maximal electroshock was increased from 44.8 mg/kg by acute or chronic caffeine (23.1 mg/kg) to 72.1 and 78.4 mg/kg, respectively. For acute or chronic caffeine at 46.2 mg/kg, the respective ED_{50}s of topiramate were 82.5 and 95.3 mg/kg. Also, the acute and chronic methylxanthine (at 46.2 mg/kg) impaired the protective activity of gabapentin which was reflected by a decrease in the electroconvulsive threshold elevated by the antiepileptic drug at 200 mg/kg. At the dose of 23.1 mg/kg, only chronic caffeine was effective in this respect. In contrast, neither acute nor chronic caffeine (up to 46.2 mg/kg) affected the anticonvulsant action of lamotrigine against maximal electroshock in mice. Similarly, the acute and chronic methylxanthine remained without a significant effect upon the elevated electroconvulsive threshold by tiagabine (4 mg/kg). In no case, pharmacokinetic interactions could explain the data on the newer antiepileptic drugs.

In conclusion, some newer antiepileptic drugs (lamotrigine and tiagabine) seem resistant to the undesired interaction with caffeine in experimental animals. A possibility exists that this may be also true for epileptic patients.

Epileptic seizures in progress of multiple sclerosis

Iwona Halczuk

Department of Neurology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland

The occurrence of epileptic seizures in patients with multiple sclerosis (MS) is relatively rare, but prevalence of epilepsy in MS, in majority of papers, ranges between 0.5–10.8%, and it is at least three times higher than in the general adult population. There is no characteristic plaque distribution pattern in patients with MS and epilepsy [Sokic et al., Epilepsia, 2001]. The most probable anatomic basis for the seizures is areas of inflammation and demyelination in the cortex and juxtacortical white matter and cytotoxic edema, that accompanies an active plaque. Other factors, some of which are still not clearly understood, such as the fibre, electrolytic changes, size of the plaque, or reactive gliosis seem also to play a part in the production mechanism [Buttner et al., Nervenarz, 1989; Lapenna et al., Epilepsia, 2004].

Partial epilepsies with focal seizures often with atypical symptoms and with or without secondary generalization are the usual pattern [Bertol et al., Rev Neurol, 1997; Engelsen and Gronning, Seizure, 1997]. Also a status of tonic-clonic seizures is often observed [Moreau et al., Epilepsia, 1998; Striano et al., Multiple Sclerosis, 2003]. There are also reports of nonconvulsiv status epilepticus with periodic lateralized epileptiform discharges (PLED) [Maingueneau et al., Neurophysiol Clin, 1999; Striano et al., Multiple Sclerosis, 2003]. The epileptic seizures are more frequent during secondary progressive course, than in the relapsing-remitting or primary progressive course of MS, and during secondary progressive phase of MS the seizures are associated with brain atrophy and high lesion load [Mehrabian et al., Epilepsia, 2004; Sokic et al., Epilepsia, 2001]. Furthermore, epileptic seizures more frequently occur in the cerebral than in spinal form of MS [Cendrowski, Clinical Neuroepidemiology, Volumed Publications, Wrocław 1997].

Seizures can be observed as the first symptom of MS, or during relapses, with a direct correlation between paroxysmal phenomena and plaques demonstrated by brain MRI. Sometimes epileptic activity is the only clinical manifestation of MS, and sometimes epileptic seizures occur several years before clinical signs of MS are manifested. But in most patients, epileptic seizures occur when the diagnosis MS is already known. The longer the interval from the first episode of the MS to the first epileptic seizure the more probable epilepsy is caused by other reasons than the MS [Buttner et al., Nervenarzt, 1989; Mehrabian et al., Epilepsia, 2004].

Up to 60% patients with MS show unspecific changes in electroencephalographic records like a slowing of basic rhythm and focal abnormalities [Striano et al., Neurol Sci, 2003]. The EEG of patients with MS and epilepsy shows slowing background rhythms, focal ativity and focal or generalized epileptiform activity. The frequency of bilateral and generalized abnormalities is significantly higher with brain stem localization of clinical signs. In the progressive phase of the disease, there is a significantly greater occurrence of bilateral slow EEG abnormalities and bilateral potentially epileptic signs (sharp waves, bilateral paroxysms). Paroxysmal discharges occurred more often in EEG examination, than clinical seizures [Cendrowski and Majkowski, J Neurol Sci, 1972; Ghezzi et al., Eur Neurol, 1990; Moreau et al., Epilepsia, 1998; Sokic et al., Epilepsia, 2001]. According to the literature periodic lateralized epileptiform discharges (PLEDs) are relatively often to be observed in the EEG of patients with MS and epilepsy [Spatt et al., J Neurol, 2001].

There are some non-epileptic paroxysmal symptoms, such as tonic spasm, paroxysmal akinesia, paroxysmal dystonia, paroxysmal dysarthria and ataxia, diplopia, paroxysmal sensory disturbances and pains which may be confused with epileptic seizures. The mechanisms of these attacks are still unknown, probably they are caused by ephaptic transmission due to myelinoaxonal dissociation within the demyelinated plaque [Spatt et al., J Neurol, 2001; Twomey et al., J Neurol Neurosurg Psychiatry, 1980]. These non-epileptic paroxysmal symptoms correspond to active disease phases but they are not accompanied by EEG changes [Spatt et al., J Neurol, 2001]. The antiepileptic drugs are the agent of choice for therapy non-epileptic paroxysmal symptoms [Kesselring, Schweiz Med Wschr, 1985; Spatt et al., J Neurol, 2001].

Generally, the prognosis of epilepsy in multiple sclerosis patients is estimated to be good, without spe-

cial recommendations or consensus for the choice of anti-epileptic drug. If seizures are symptoms of MS relapse, the combined treatment with antiepileptic drugs and intravenous administration of steroids is recommended [Merabian et al., Epilepsia, 2004; Spatt et al., J Neurol, 2001].

Depression disorders in children and adolescents with epilepsy: etiology, clinical semiology and treatment

Marta Kaczyńska-Haładyj

Neuropsychiatric Department for Children, Neuropsychiatry Hospital, Abramowicka 2, PL 20-442 Lublin, Poland.

Depression is the common comorbid psychiatric disorder associated with epilepsy in the developmental age. Children and adolescents with seizures are at increased risk for psychiatric disorders. The prevalence rates of depressive disorders in children and adolescents with epilepsy have fluctuated in the wide range from 12 to 33% [Alwash et al., Seizure, 2000; Caplan et al., Epilepsia, 2005; Dunn et al., J Am Acad Child Adolesc Psychiatry, 1999; Ettinger et al., Epilepsia, 1998; Oguz et al., J Child Neurol, 2002]. Depressive disorders are much more likely in children and adolescents with chronic disorders, such as diabetes and epilepsy [Brent and Birmaher, N Eng J Med, 2002]. The existence of the strong correlation between epilepsy and depression has been recently demonstrated in a variety of studies. A number of approaches have been developed to explain the multifactorial etiology of pediatric depression in epilepsy. Multiple risks for depression in epilepsy include genetic, neurotransmitter, neurological, iatrogenic and psychological factors. Depressive disorders have a prevalence of about 2% in school age children and 4–8% in adolescents, with the markedly increasing incidence after puberty [Birmaher et al., J Am Acad Child Adolesc Psychiatry, 1996; Flemming and Offord, J Am Acad Child Adolesc Psychiatry, 1990; Kroes et al., J Am Acad Child Adolesc Psychiatry, 2001; Lewinsohn et al., J Am Acad Child Adolesc Psychiatry, 1994]. Pediatric depression is associated with a significant impairment of global functioning [Puig-Antich et al., J Am Acad Child Adolesc Psychiatry, 1993]. Numerous researchers have concluded that these disorders tend to possess chronic courses and long term outcome with multiple relapses [Kovacs et al., Arch Gen Psychiatry, 1984; Kovacs et al., J Am Acad Child Adolesc Psychiatry, 1996]. Current knowledge obtained from adults with mood disorders and epilepsy has been used to understand children with depressive disorders. However, the studies of children with epilepsy revealed some similarities and many differences. The same diagnostic criteria are used in pediatric depression as in adult depression. Although, the developmental variations in symptom manifestations of depressive disorders in childhood and adolescent phase, semiology, pathomechanism and etiology, predictors of clinical course as well as comorbidities need to be considered. Younger children have higher frequency of comorbid separation anxiety, phobias, somatic complaints and as comorbid behavioral problems [Ryan et al., Arch Gen Psychiatry, 1987]. Adolescents develop hopelessness, guilt, and suicidal ideation. A family history of mood disorders may be an important clue to the diagnosis of depression in children with epilepsy [Plioplys, Epilepsy Behav, 2003]. The diagnosis of depressive disorders in pediatric patients is difficult and complex. At the time of the initial diagnostic evaluation, the physician who is managing a patient with seizure disorder should make a psychiatric and psychological assessment to identify the patient's risk for depression. This approach enables to assess the impact of epilepsy on the patient and to detect developmental variations of clinical pictures in depressive disorders. Depression and other disorders remain underdiagnosed and undertreated in children and young people with epilepsy [Caplan et al., Epilep-

sia, 2005; Dunn and Austin, Neurology, 1999; Ott et al., Epilepsia, 2003; Pellock, Epilepsy Behav, 2004].

Early identification of depressive disorders of pediatric epilepsy and as tailored treatment are essential to prevent development of a chronic course and improve their quality of life. Pediatric depression is treatable with both psychotherapeutic and pharmacotherapeutic approaches. Medication should be used cautiously because some of the antidepressant may lower the sei-

zure threshold. The serotonin reuptake inhibitors SSRIs appear to be safe for treatment of children with depression and epilepsy and seem first-line agents for treatment of moderate and severe depression in children with epilepsy. The goal of pharmacological therapy in childhood epilepsy and comorbid depressive disorders is to prevent seizures and maintain remission of depression.

Pharmacogenomics in epilepsy treatment

Władysław Lasoń

Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Science, Smętna 12, PL 31-343 Kraków

Pharmacogenomics investigates possible associations between variances in genomic sequences and individual response to a given drug. The aim of pharmacogenomics is to enhance drug efficacy and to decrease its undesired effect [Spurr, Trends in Genetics, 2006; Tate et al., Epilepsy Curr, 2005; Szoeke et al., Lancet Neurol, 2006]. It is expected that pharmacogenomics will play an important role in developing risk reduction strategies, targeted therapies, resistance testing and dose optimization. The methods of pharmacogenomic diagnostics, such as PCR-RFLP, AS-PCR, TaqMan PCR, Invader, linear arrays, microsphere arrays, high density oligonucleotide arrays, and electrophoretic sequencing enable quantification of mRNA, genotyping of single nucleotide polymorphisms, or DNA sequencing and re-sequencing. Pharmacogenomic approach is thought to be especially useful in epilepsy because of its commonality (ca. 1% of human population), frequent drug resistance (25–30% of patients), variable response to drugs and availability of reliable tests for evaluation of efficacy and undesired effects of antiepileptic drugs. The candidate genes are these which encode proteins involved in antiepileptic drug pharmacokinetics (drug transporters, drug-metabolizing enzymes), pharmacodynamics (receptors, ion channels, enzymes, regulatory proteins, second messengers) or hypersensitivity (immunological agents) [Depondt, Eur J Paediatr Neurol, 2006]. However, results of few studies have been controversial [Szoeke et al., Lancet Neurol, 2006]. An as-

sociation between drug resistance with genotype of 3435CC of MDR1/ABCB1 has been found by some investigators [Siddiqui et al., N Engl J Med, 2003; Zimprich et al., Neurology, 2004; Hung et al., Pharmacogenomics, 2005], whereas other authors failed to confirm these findings [Tan et al., Neurology, 2004; Sills et al., Epilepsia, 2005]. The possible role of MRP1, MRP2, OCTN2 drug transporter polymorphisms has also been studied [Kerb et al., Pharmacogenomics, 2001]. With regard to metabolic enzymes, an association has been found between CYP2C19 and/or CYP2C9 polymorphism and decrease in phenytoin hydroxylation [Mamiya et al., Epilepsia, 1998), reduction of phenobarbital clearance [Mamiya et al., Eur J Clin Pharmacol, 2000], inhibition of phenytoin elimination [Odani et al., Clin Pharmacol Ther, 1997] and decreased metabolism of S-mephenytoin [Xiao et al., J Pharmacol Exp Ther, 1997]. Furthermore, an association between CYP2C9 polymorphism and maximal dose of phenytoin and decrease in valproate biotransformation in patients with CYP2C9*2 and CYP2C9*3 polymorphism have also been reported [Tate et al., Proc Natl Acad Sci USA, 2005; Ho et al., Pharmacogenomics, 2003]. Less is known about polymorphism of protein targets for anticonvulsants. Nevertheless, Tate et al. [Proc Natl Acad Sci USA, 2005] reported that polymorphism in 5(-91) intron of SCN1A was associated with an increase in maximal dose of carbamazepine and phenytoin. On the other hand, Scheffield et al. [Bull

Hum Genet Soc of Australia, 2005] found an association between gene polymorphism and the maximal dose of valproate but not that of carbamazepine. Apart from sodium channels, an association was observed between polymorphism of G1R65A in GABA$_B$ receptor and enhanced risk of drug resistant temporal lobe epilepsy [Gambardella et al., Neurology, 2003]. Hypersensitivity to antiepileptic drugs was also a subject of few pharmacogenomic studies. To this end, Pirmohamed et al. [Neurology, 2001] found an association between TNF- alleles and hypersensitivity to carbamazepine, whereas Chung et al. [Nature, 2004] observed an association between HLA-B31502 alleles and Stevens-Johnson syndrome in Chinese patients treated with carbamazepine. The main problems with pharmacogenomics of epilepsy is

early phase of study (only few candidate genes were studied so far), multifactorial character of this disease and variable drug response, which decrease predictive validity of a single test. Moreover, discrepancy in results of association studies are thought to result from differences in size of patient groups under study, ethnic factors, heterogeneity of epilepsy, and difficulties in interpretation of polymorphism data. It has been postulated that future endeavors to develop pharmacogenomics of epilepsy should take into account evaluation of interaction of multiple genetic variants with exogenous factors, prospective clinical studies on large groups of patients and introducing better and cheaper diagnostic tools for genotyping of epileptic patients.

Antiepileptic drugs and quality of life

Krzysztof Owczarek

Department of Medical Psychology, Medical Academy of Warsaw, Trojdena 2, PL 02-109 Warszawa, Poland

Considerable progress in the pharmacotherapy of epilepsy has been achieved within the last few years. Evidence of this progress can be found in the findings of research on the safety and clinical efficacy of new antiepileptic drugs. A considerable proportion of epileptic patients now experience significantly less discomfort and restriction due to their illness. Better motor efficiency, well-being and cognitive functioning have all contributed to the fact that many patients do not experience adverse clinical effects of their conditions in their everyday lives. One of the natural consequences of the new therapeutic options is the increasing number of patients who function well as long as they remain in medical care. Improved self-reliance and well-being have encouraged the natural wish to participate in the mainstream of social life in many patients.
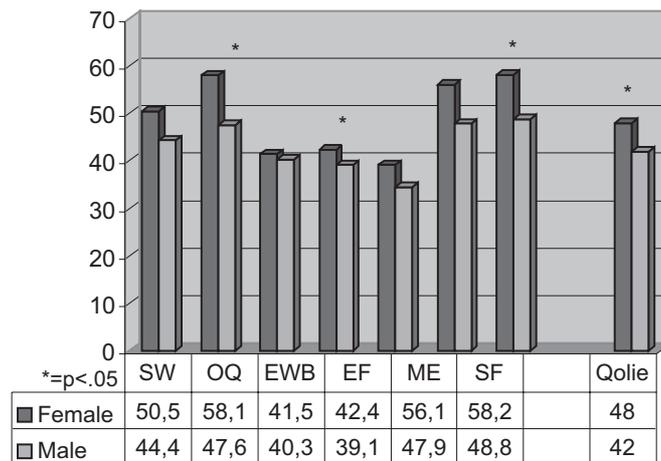
Progress in the medical sciences is not accompanied, however, by analogous positive re-evaluation of social awareness. The social situation of epileptic patients has still not normalized and health considerations have nothing to do with this unfortunate state of affairs. The poor social functioning of these patients is

often caused by centuries-long prejudice, myths and biases which force this group into isolation.

Surveys conducted in various European countries suggest that very negative character traits are attributed to epileptic patients. For example, in the United Kingdom these patients are often perceived as hostile and aggressive, anxious and with feelings of entitlement or mentally retarded, asocial and physically repugnant [Jacoby, Ictal, 1998]. Studies of social attitudes towards epileptic patients in France have shown that the vast majority of the population are unwilling to work with them, see no possibility of spending leisure time with them (sport, recreation) and do not want to live near "such people" [Dulac, Ictal, 1996].

We must therefore trace the causes of social prejudice and stigmatisation of epilepsy to the prevailing and deficient elements of social mores. In many countries this state of affairs is apparently rooted in years-long neglect of efforts to develop tolerant social attitude patterns and to popularise reliable information concerning epilepsy [Owczarek, Epileptology (in Polish), 1999].

In their day to day lives men and women afflicted with epilepsy are forced to cope with various objec-

	SW	OQ	EWB	EF	ME	SF		Qolie
■ Female	50,5	58,1	41,5	42,4	56,1	58,2		48
□ Male	44,4	47,6	40,3	39,1	47,9	48,8		42

Fig. 1. Scores on QOLIE-31 scales by gender. SW – Seizure Worry; OQ – Overall Quality of Life; EWB – Emotional Well-Being; EF – Energy/Fatigue; COG – Cognitive Functioning; ME – Medication Effects; SF – Social Functioning; QOLIE-3 – Total Score
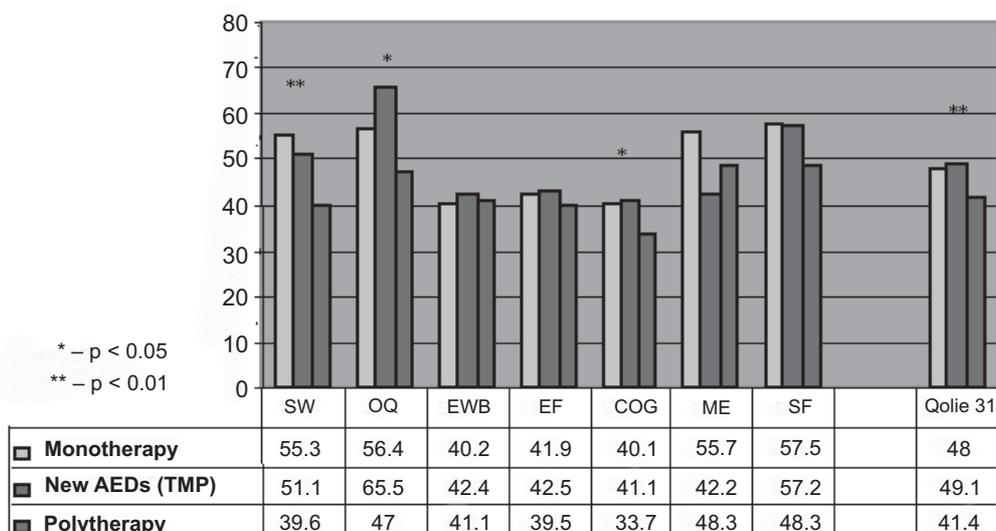
tive and subjective limitations relating to their incapacity. Satisfaction with quality and standard of living depend on the effectiveness with which people are able to overcome various deeply rooted prejudices in social awareness. One of the causes of stress and depression in epileptic patients is the feeling of stigmatisation which springs from lack of acceptance or even intolerance.

Within the last decade the concept of quality of life (QOL) has become an important indicator of patient health. Many physicians who specialise in the treatment of epilepsy now express increasing concern with quality of life and the use of various measures of this variable is increasingly widespread. Most researchers agree that global QOL is a combination of four different components: physical fitness, psychological well-being, social relations and economic status. These four basic components are widely recognised as sufficient for assessment of QOL.

Assessment of quality of life

Physical fitness – general health, efficiency of coping with day-to-day activities, frequency and gravity of

	SW	OQ	EWB	EF	COG	ME	SF		Qolie 31
□ Monotherapy	55.3	56.4	40.2	41.9	40.1	55.7	57.5		48
■ New AEDs (TMP)	51.1	65.5	42.4	42.5	41.1	42.2	57.2		49.1
■ Polytherapy	39.6	47	41.1	39.5	33.7	48.3	48.3		41.4

Fig. 2. Scores on QOLIE-3 scales by type of treatment. For abbreviations cf. Fig. 1.

disease aggravation, experienced side-effects of medication;

Psychological well-being – subjective well-being, subjective fitness (depressive ideation, anxiety), problems with cognitive functioning (attention, memory etc.);

Social functioning – family, friends, acquaintances, social relations at work (superiors, subordinates);

Economic status – financial independence, personal income, employment.

QOLIE-31 is a questionnaire used to assess quality of life in individuals with epilepsy. It is a highly reliable and valid diagnostic instrument. The questionnaire measures such dimensions as: fear related to epileptic seizures, depleted energy and vital activity, depressive ideation, locomotive and driving problems, problems relating to cognitive functioning, academic and occupational limitations, social and socialising problems, the adverse physical and psychological effects of AEDs, and overall opinions concerning one's satisfaction with life.

The author's own research

This study tested the effects of the kind of pharmacotherapy received by epileptic patients on the component factors of quality of life assessed by means of QOLIE-31. The mean male and female scores on quality of life factors were also compared. The study was run on 58 women (55%) and 48 men (45%) whose mean age was 38. The mean male and female scores on all the QOLIE-31 factors were compared. Analysis of variance (one-way) and the Sheffe Test

for Multiple Comparisons were used to assess differences between all of our groups. Figure 1 shows that, on the average, women scored higher than men on the Overall QOL, Energy/Fatigue and Social Functioning. These results suggest that the upbringing of boys is seriously deficient. Overprotection, maternal in particular, causes epileptic boys to withdraw from everyday life. Women are better prepared to cope with life independently and that is why they rate their quality of life more highly.

Mean scores on all QOLIE-31 factors were compared for groups receiving AEDs in monotherapy – either classic (carbamazepine, valproate) or new generation (topiramate) – and patients receiving AEDs in polytherapy (Fig. 2). Statistically significant differences between groups emerged for the following factors: Seizure Worry (SW); Overall Quality of Life (OQ), Cognitive Functioning (COG) and the Total QOLIE-31 score. Patients receiving AEDs in polytherapy had the lowest means. These patients rated their cognitive functioning most poorly compared with the other scales. The differences between the means for the remaining factors were non-significant at $p \leq 0.05$.

We must refrain from definitive and final conclusions, however, due to certain methodological considerations. We need to select more homogeneous groups with respect to factors which may confound our logical inferences (e.g., number and type of epileptic seizures). It would therefore be worthwhile testing all AEDs and determining their effects, in a methodologically precise and clear way, on quality of life as measured by each and every factor of the QOLIE-31.