Epileptologie | 32. Jahrgang

Juni | 2015 ISSN 1660-3656

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Inhalt

Schweizerische Liga gegen Epilepsie
Ligue Suisse contre l'Epilepsie
Lega Svizzera contro l'Epilessia
Swiss League Against Epilepsy

Généralités

Le journal « Epileptologie » publie des articles adressés au journal, commandés ou non, se rapportant à tous les thèmes de l'épileptologie. Dans la règle, seuls les articles qui n'ont pas encore été publiés sont acceptés. Les articles, ou parties intégrantes d'articles, ne doivent pas avoir été soumis parallèlement à d'autres éditeurs, ni avoir été déjà acceptés par d'autres éditeurs. Tous les manuscrits feront l'objet de deux expertises. Il n'y aura pas de tirages à part des articles, par contre ils seront publiés sur la page web de la Ligue (www.epi.ch) et disponibles pour téléchargement sous forme de fichier « pdf ».

Correspondance

Les manuscrits non commandés (ainsi que la correspondance à l'éditeur) doivent être envoyés à: Madame M. Becker, Rédaction Epileptologie, Ligue Suisse contre l'Epilepsie, Seefeldstrasse 84, Case postale 1084, 8034 Zurich. Tél. 043/488 67 79, fax 043/488 67 78, e-mail: becker@epi.ch.

Indications pour la rédaction des manuscrits

Seuls les manuscrits correspondant aux critères suivants seront acceptés. Les manuscrits qui ne seront pas rédigés correctement seront renvoyés avant l'expertise.

1. **Langue:** En plus de l'allemand, les articles en français et en anglais sont acceptés.
2. **Style:** En allemand, les formes alémaniques avec « z » et « k » (par exemple « Karzinom ») sont valables, les termes spécialisés en latin conservent leur orthographe (par ex. arteria carotis).
3. **Format:** L'ensemble du texte, y compris les références littéraires, les tableaux et légendes, doit être dactylographié et formaté de la façon suivante:
- Papier DIN-A4, recto (interligne 1 1/2 ou 2 avec un maximum de 30 lignes par page)
- Renvoi à la littérature dans l'ordre d'apparition dans le texte, numérotation arabe apparaissant dans le texte dans des parenthèses carrées.
- Les tableaux et illustrations doivent être numérotés consécutivement par des chiffres arabes.
4. **Ordre:** 1. Page de titre (incluant le cas échéant, les remerciements aux personnes et/ou institutions qui ont contribués au travail), 2. Résumé en allemand, français et abstract en anglais. Mots clés des trois langues. 3. Texte. 4. Littérature. 5. Tableaux. 6. Légendes des illustrations. 7. Illustrations.
- La page de garde contient le titre entier du travail (français et anglais), les noms et titres des auteurs, les institutions pour lesquelles les auteurs travaillent ainsi que les coordonnées complètes de l'auteur principal, avec numéro de téléphone, fax et e-mail.
- Résumé et abstract en anglais (avec le titre du travail): Sans référence, ni acronyme, ni abréviation inhabituelle (maximum 250 mots).
- 3 à 6 mots clés.
- **Texte:** Disposition dans les travaux originaux : Introduction, méthodes (y compris matériel d'examen, patients, animaux de laboratoire, le cas échéant les autorisations, resp. respect de la Déclaration d'Helsinki, y compris le vote du comité d'éthique), résultats et discussion. Les abréviations doivent être écrites en entier à leur première apparition dans le texte.
- **Références:** Les références à la littérature doivent être citées à la fin du travail dans l'ordre d'apparition dans le texte et citées suivant le modèle ci-dessous. Les communications personnelles, les résultats non publiés et/ou les manuscrits adressés à la publication ne sont pas acceptés, mais doivent être mentionnés de façon appropriée dans le texte. Les citations « à l'impression » resp. « in press » ne se rapportent qu'aux travaux qui ont été acceptés (en ajoutant le nom du journal, le numéro et l'année de parution, si connus). La citation de travaux « en préparation » n'est pas autorisée. Les communications de congrès ne seront prises en considération que sous forme d'abstract ou d'article de « Proceedings-Journal ».
- **Tableau :** Chaque tableau doit apparaître sur une nouvelle page avec un titre explicatif court. Les abréviations et les signes doivent être expliqués en pied de page.
- **Légendes d'illustrations :** La légende de chaque illustration doit être sur une nouvelle page ; les abréviations et les signes doivent y être expliqués.
- **Illustrations :** Dessins, dessins en dégradé ou photographies (noir/blanc ou couleurs).
- **Modèle de citation :** Article de journal : Daoud AS, Batieha A, Abu-Ekteish F et al. Iron status: a possible risk factor for the first febrile seizure. Epilepsia 2002; 43: 740-743 (nommer les 4 premiers auteurs; abréviation des journaux selon la « List of Journals indexed in Index Medicus »); Livres: Shorvon S. Status Epilepticus. Its Clinical Features and Treatment in Children and Adults. Cambridge: Cambridge University Press, 1994; Chapitres de livres: Holthausen H, Tuxhorn I, Pieper T et al. Hemispherectomy in the treatment of neuronal migrational disorders. In: Kotagal P, Lüders HO (eds): The Epilepsies. Etiologies and Prevention. San Diego, London, Boston et al: Academic Press, 1999: 93-102

Que devez-vous envoyer à la rédaction?

Tous les manuscrits doivent être envoyés en trois exemplaires, y compris les illustrations et tableaux. L'envoi de fichiers électroniques (MS Word) est préférable, comme alternative, l'envoi de trois exemplaires imprimés et d'une CDRom (pour les illustrations et les tableaux mentionner le programme utilisé) est possible.

PD Dr. med. Andrea O. Rossetti

Cari lettori,

Questo numero di “Epileptologie” è consacrato alla farmacologia; i medicamenti antiepilettici rappresentano in fatti la prima colonna del trattamento dei pazienti con epilessia, e sono l’oggetto di un interesse millenario. Senza entrare in ambiti storici (già trattati in “Epileptologie” 4/2014) e tralasciando l’aspetto infiammatorio (cf. “Epileptologie” 2/2014), i contributi proposti si concentrano sull’approccio terapeutico farmacologico all’inizio del terzo millennio. Questo da una parte si caratterizza in uno sviluppo incessante (ma, purtroppo, non ancora veramente soddisfacente) di nuove sostanze. Dall’altra, però, vi è una crescente presa di coscenza degli effetti indesiderati a lungo termine, e di aspetti legati al trattamento di popolazioni potenzialmente vulnerabili, quali ad esempio i bambini, le donne in età procreativa, o i pazienti con molte comorbidità. Infine, si assiste a un certo ritorno in voga del monitoraggio terapeutico, che anche grazie ad innovazioni tecniche porta potenzialemente ad una migliore gestione dei pazienti in situazioni particolari.

Per permettere una comprensione la più vasta possibile, il numero è interamente scritto in inglese, “latino” del 20. e 21. secolo, ma in un periodo di globalizzazione galoppante, la redazione dell’editoriale e dei riassunti nelle tre lingue nazionali principali vuol essere un omaggio alla bellezza e alla ricchezza delle particolarità linguistiche e culturali del nostro Paese.

Ringrazio di cuore tutti i miei colleghi e amici che hanno contribuito in maniera così eccellente a questa edizione, e auguro un’interessante e (spero) istruttiva lettura!

Andrea O. Rossetti

Oltre ai contributi presentati e curati prima da Andrea Rossetti, sono lieto di potervi annunciare un interessante lavoro del nostro membro corrispondente pluriennale Ernst A. Rodin di Salt Lake City, USA. Nato e cresciuto in Austria, vive negli Stati Uniti dagli anni ‘50. Per lungo tempo è stato Professore di neurologia a Detroit e Direttore medico del Centro di epilessia del Michigan. Dal 1991 Professore associato presso il Dipartimento di neurologia dell’Università dello Utah, fino al 2000 è stato consulente del programma sull’epilessia presso il Children’s Medical Center di Salt Lake City, Utah. Si è sempre occupato intensamente dell’EEG, tra l’altro negli ultimi anni dell’attività infralenta inferiore a 0,1 Hz, che ci presenta in questa sede.

Günter Krämer

PD Dr. med. Andrea O. Rossetti

Chers lecteurs,

Ce numéro d'Epileptologie est consacré à la pharmacologie; les médicaments antiépileptiques représentent en effet la colonne primordiale du traitement des patients avec épilepsie, et font l'objet d'un intérêt millénaire. Sans rentrer dans le domaine historique (déjà abordé dans "Epileptologie" 4/2014) et laissant de côté les aspects inflammatoires (cf. "Epileptologie" 2/2014), les contributions proposées se concentrent sur l'approche thérapeutique pharmacologique au début du 3ème millénaire. Ceci se caractérise d'un part par le développement incessant (mais hélas pas toujours satisfaisant) de nouvelles substances. D'autre part, cependant, il y a une prise de conscience croissante par rapport aux effets indésirables sur le long terme, ainsi que concernant les aspects en relation avec le traitement de populations potentiellement vulnérables, tels que les enfants, les femmes en âge de procréer, ou les sujets avec nombreuses comorbidités. Aussi, on assiste à un certain retour du monitoring thérapeutique, qui aussi grâce à des innovations techniques peut améliorer la gestion clinique de patients dans certaines situations particulières.

Afin de permettre une compréhension la plus vaste possible, ce numéro a été entièrement écrit en anglais, sorte de latin du 20ème et 21ème siècle ; dans une période de globalisation incessante, la rédaction de l'éditorial et des résumés dans les trois langues nationales principales est un hommage à la beauté et à la richesse de la diversité linguistique et culturelle de notre Pays.

Tout en remerciant très cordialement les collègues et amis qui ont rendu possible ce numéro grâce à leurs excellentes contributions, je vous souhaite une intéressante et (j'espère) instructive lecture !

Andrea O. Rossetti

Outre les articles susmentionnés, présentés et gérés par Andrea Rossetti, j'ai le plaisir de vous annoncer un exposé passionnant d'Ernst A. Rodin, notre membre correspondant de longue date à Salt Lake City, aux Etats-Unis. Né et élevé en Autriche, il vit depuis les années 50 en Amérique, a été de nombreuses années Professeur de neurologie à Détroit et directeur médical du Centre d'épilepsie du Michigan ; il est professeur associé au Département de neurologie de l'Université d'Utah depuis 1991 et a été consultant du programme Epilepsie du Children's Medical Center à Salt Lake City, Utah, jusqu'en 2000. Il s'est toujours fortement intéressé à l'EEG et a, ces dernières années, étudié plus particulièrement l'activité infralente en deçà de 0,1 Hz, qu'il nous présente ici.

Günter Krämer

PD Dr. med. Andrea O. Rossetti

Werte Leser/innen,

Diese “Epileptologie”-Ausgabe ist der Pharmakologie gewidmet: Antiepileptika stellen ja die erste Säule der Epilepsietherapie dar und werden seit Jahrtausenden untersucht. Da die historischen (“Epileptologie” 4/2014) und entzündlichen (“Epileptologie” 2/2014) Aspekte vor kurzer Zeit behandelt wurden, fokussieren die vorliegenden Beiträge auf die antiepileptische Behandlung am Anfang des 21. Jahrhunderts. Diese wird einerseits von der ständigen (aber leider nicht immer befriedigenden) Entwicklung neuer Mittel charakterisiert. Auf der anderen Seite gewinnen die Erkennung von Langzeit-Nebenwirkungen und die spezifischen Aspekte der Behandlung von potenziell vulnerablen Patientengruppen (wie Kinder, Frauen im gebärfähigen Alter und Personen mit mehreren Komorbiditäten), ständig an Wichtigkeit. Auch das therapeutische Monitoring erlebt eine gewisse Wiederbelebung und könnte dank technischen Neuerungen die Therapiesteuerung bei besonderen Patienten erleichtern.

Um eine breites Verständnis zu ermöglichen, ist diese Ausgabe ganz auf Englisch verfasst (also, in „Neu-Latein“); in einer Periode der ungehinderten Globalisierung ist jedoch die Vorbereitung des Editorials und der Zusammenfassungen in den drei wichtigsten Landessprachen eine Hommage an die Schönheit und den Reichtum der Sprachen- und Kulturvielfältigkeit unseres Landes.

Ich bedanke mich ganz herzlich bei den Kollegen und Freunden, die bei dieser Ausgabe so ausgezeichnet gewirkt haben, und wünsche Ihnen allen eine interessante und hoffentlich lehrreiche Lektüre!

Andrea O. Rossetti

Zusätzlich zu den vorstehend von Andrea Rossetti vorgestellten und betreuten Beiträgen freue ich mich, Ihnen eine interessante Arbeit unseres langjährigen korrespondierenden Mitgliedes Ernst A. Rodin aus Salt Lake City, USA, ankündigen zu dürfen. In Österreich geboren und aufgewachsen, lebt er seit den fünfziger Jahren in den USA, war über lange Jahre Professor für Neurologie in Detroit und Medizinischer Direktor des Epilepsie-Zentrums von Michigan, seit 1991 dann Adjunct Professor am Department of Neurology der Universität von Utah, und bis 2000 Consultant des Epilepsieprogramms am Children’s Medical Center in Salt Lake City, Utah. Er hat sich schon immer intensiv mit dem EEG beschäftigt, in den letzten Jahren u.a. mit der infralangsamen Aktivität unterhalb von 0,1 Hz, die er uns hier vorstellt.

Günter Krämer

PD Dr. med. Andrea O. Rossetti

Dear reader,

This "Epileptologie" issue is dedicated to pharmacology: antiepileptic medications represent in fact the most important milestone in the treatment of the epilepsies, and have fascinated scholars since millennia. Since historical ("Epileptologie" 4/2014) and inflammatory ("Epileptologie" 2/2014) aspects have been addressed recently, the proposed contributions focus on antiepileptic treatment in the beginning of the 21st Century. On one hand, this is characterized by an incessant (but unfortunately not always satisfactory) development of newer compounds. On the other hand, however, there is an increasing awareness regarding long-term side effects and therapeutic issues in potentially vulnerable populations, such as children, women in childbearing age, or subjects with several comorbidities. Furthermore, therapeutic drug monitoring enjoys a sort of revival, and also following some technical innovation may allow a better patient management in specific clinical situations.

In order to achieve a broad understanding, this number is entirely written in English, a sort of "new Latin" of the last decades. Conversely, in an era of increasing globalization, the editorial and abstracts in the three principal languages of Switzerland represent an homage to the beauty and richness of the linguistic and cultural variations of our country.

I would like to thank warmly the colleagues and friends who contributed to this issue for their excellent work, and wish you an interesting and hopefully instructive reading!

Andrea O. Rossetti

In addition to the contributions previously presented and treated by Andrea Rossetti, I am pleased to be able to announce to you that we have an interesting work by our corresponding member of many years Ernst A. Rodin from Salt Lake City, USA. Born and raised in Austria, he has lived in the USA since the 1950s, for many years was Professor of Neurology in Detroit and Medical Director of the Epilepsy Center of Michigan, then from 1991 Adjunct Professor in the Department of Neurology of the University of Utah, and until 2000 Consultant of the Epilepsy Program at the Children's Medical Center in Salt Lake City, Utah. He has always concentrated intensively on the EEG, including in recent years on infraslow activity below 0.1 Hz, which he presents to us here.

Günter Krämer

Iris Unterberger
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Summary

Since the last 20 years, more than 12 new antiepileptic drugs (AEDs) have been introduced on the market. Several randomized controlled trials confirmed the efficacy of these newer AEDs as add-on for polytherapy or (less frequently) as monotherapy in patients with epilepsy. However, about one third of patients still do not achieve sustained seizure control, creating the need to further generate novel AEDs with novel acting mechanisms and routes of administration, and to develop disease-modifying drugs.

Epileptologie 2015; 32: 51 – 57

Key words: Epilepsy, medical treatment, AED

Der Vorzug „neuer“ versus „alter“ Antiepileptika: Wo liegt die Evidenz?

In den letzten 20 Jahren sind mehr als 12 Antiepileptika auf dem Markt eingeführt worden. Mehrere randomiserte Studien haben die Wirksamkeit dieser neuen Substanzen als zusätzliche Mittel oder (seltener) als Monotherapie der Epilepsie bestätigt. Trotzdem haben weiterhin etwa ein Drittel der Patienten unkontrollierte Anfälle; deswegen sind weitere Antiepileptika mit innovativen Verabreichungsmethoden und Wirkungsmechanismen, als auch mit Krankheit-beeinflussenden Eigenschaften, dringend benötigt.

Schlüsselwörter: Neue Antiepileptika, randomisierte Studien, Evidenz-basierte Medizin

Choix des nouveaux antiépileptiques par rapport aux anciens : où est l‘évidence ?

Lors des 20 dernières années, plus de 12 nouveaux médicaments antiépileptiques ont été introduits sur le marché. Plusieurs essais randomisés ont prouvé l’efficacité de ces substances en tant que « add-on » avec d’autres antiépileptiques, voir même (plus rarement) comme monothérapies. Cependant, environ un tiers des personnes avec épilepsie reste pharmacorésistante ; cet aspect illustre le besoin impérieux de développer de nouveaux moyens pharmacologiques avec des mécanismes d’action et modes d’administration innovatifs, ainsi qu’avec des propriétés pouvant influencer la maladie épileptique.

Mots clés : Epilepsie, traitement médical, MAE

Scelta dei nuovi antiepilettici: dov‘è l‘evidenza?

Negli ultimi 20 anni sono stati introdotti sul mercato più di 12 nuovi medicamenti antiepilettici. Diversi studi randomizzati ne hanno dimostrato l’efficacia, soprattutto come “add-on” in politerapia, molto meno frequentemente come monoterapia. Purtroppo un terzo delle persone che vivono con l’epilessia continua comunque ad essere farmacoresistente; questo aspetto dimostra chiaramente il bisogno interrogabile di sviluppare nuovi mezzi farmacologici con meccanismi d’azione innovativi, che permettano vie d’amministrazione alternative, e – non da ultimo – con proprietà che possano influenzare l’epilettogenicità.

Parole chiave: Epilessia, trattamento, MAE

Background

Epilepsy is a heterogeneous brain disorder with an annual incidence between 50 and 120 per 100 000 and a prevalence of around 700 per 100 000 [1]. Hence, epilepsy is one of the most common serious neurological disorders, and the burden of disease is comparable with lung cancer, and breast cancer in women [2]. Moreover, epilepsy is associated with other comorbidities, including depression, anxiety, increased morbidity and mortality, seizure-related falls and injuries, and psychosocial stigmatization. Pharmacological therapy with antiepileptic drugs (AEDs) constitutes the backbone of the treatment of epilepsy. About two thirds of adults with newly diagnosed epilepsy will achieve sustained seizure control while taking AEDs [3]. However, approximately half of these patients experience mild to moderate adverse events (AEs) under medical treatment [4, 5]. Moreover, drug resistant epilepsy occurs in 20-30%

of patients with newly diagnosed epilepsy. The choice of drug is primarily based on evidence of efficacy and effectiveness for the respective patient´s seizure type or epilepsy syndrome and by tolerability considerations. For the optimum selection of these drugs, other patient-specific variables have to be considered, including age, gender, comorbidities, drug-drug interactions, childbearing potential or intellectual impairment. The „ideal AED" should have broad spectrum efficacy, provide sustained seizure control, be well tolerated without any safety concerns, be easy to take, and be available in several formulations.

Currently, more than 20 classical (so called „older") and newer AEDs are available to treat epilepsy in adults, with each drug having its potential advantages and disadvantages (**Table 1**).

This review will focus on the body of evidence on the use of newer versus older AEDs in the treatment of epilepsy.

Body of Evidence

Monotherapy

In 2006, the International League Against Epilepsy (ILAE) report provided an evidence-based analysis of AED efficacy / effectiveness as initial monotherapy for epileptic seizures and syndromes, including 50 randomized controlled trials (RCTs) and seven metaanalyses [6]. A very recent update of this review identified additional three class I and 11 class III studies since 2005 [7]. The combined analysis now encompasses a total of 64 trials (class I evidence in 7, class II evidence in 2) and 11 metaanalyses. The clinical trial rating has been related to distinct levels of evidence (**Table 2**).

The authors concluded that there are major methodological weaknesses in the quality of available evidence, especially there is a lack of adequately designed RCTs for patients with generalized seizures/epilepsies, and in children. Many RCTs cannot answer crucial clinical questions creating a need for additional multicenter clinically relevant RCTs answering the unmet questions.

Additional evidence

A recent randomized, open-label, controlled, parallel group, multicenter trial was conducted to test the superiority of the LEV over the LTG as initial monotherapy for epilepsy [8]. The primary endpoint was the rate of seizure-controlled patients in the first 6 weeks. Furthermore, efficacy, tolerability and quality of life were evaluated. Six weeks after randomisation the proportions of seizure-controlled patients were 67.5% (LEV) versus 64.0% (LTG) (p=0.47). Adverse events occurred in 74.5% (LEV) versus 70.6% (LTG) of the patients (p=0.38). There were no significant differences with regard to efficacy and tolerability of LEV and LTG in newly diagnosed focal and generalised epilepsy. Another unblinded randomized study compared the effectiveness of levetiracetam (LEV) with controlled release carbamazepine (CBZ-CR) as monotherapy for focal seizures or extended release valproate (VPA-ER) for generalized seizures in patients with newly diagnosed epilepsy [9]. The hazard ratio for time to treatment withdrawal was 1.02 (0.74 to 1.41) for LEV compared to VPA-ER and 0.84 (0.66 to 1.07) for LEV compared to CBZ-CR. Similar proportions of patients within each treatment arm reported at least one adverse event: 66.1% LEV versus 62.0% VPA-ER; 73.4% LEV versus 72.5% CBZ-CR. The authors concluded that LEV monotherapy was not superior to CBZ-CR/VPA-CR in terms of global outcome.

Drug resistant epilepsy

The clinical comparability of new AEDs in partial refractory epilepsy was evaluated including 62 placebo-controlled, and eight head-to-head RCTs [10]. A random-effect metaanalysis was used to derive pooled estimates of odds ratios (OR) and number needed to treat / harm (NNT/NNH). Indirect comparisons of responder rate based on relative measurements of treatment effect (ORs) favored topiramate (1.52; 1.06-2.20) in comparison to all other AEDs, whereas gabapentin (0.67; 0.46-0.97) and lacosamide (0.66; 0.48-0.92) were less efficacious, without significant heterogeneity. Topiramate and levetiracetam were more efficacious, whereas gabapentin and tiagabine were less efficacious when analyses were based on absolute estimates (NNTs). Withdrawal rate was higher with oxcarbazepine (OR 1.60; 1.12-2.29) and topiramate (OR 1.68; 1.07-2.63), and lower with gabapentin (OR 0.65; 0.42-1.00) and levetiracetam (OR 0.62; 0.43-0.89). The authors pointed out that the differences were too small to derive any conclusions about which new AED(s) has superior effectiveness. Moreover, a recent metaanalysis of 54 randomized controlled add-on studies in patients with drug resistant epilepsy elucidated a benefit in efficacy between add-on treatment with a new AEDs versus add-on treatment with placebo in only 6% for seizure freedom and 21% for a 50% reduction in seizure frequency, suggesting a need for developing more effective AEDs for drug resistant epilepsy [11].

Despite the introduction of more than 12 new AEDs over the past 20 years, there is limited evidence supporting better outcomes for people with epilepsy. In a recent study performed in Scotland, the proportion of patients achieving seizure freedom rose only from 64% to 68% with the use of new AEDs [12].

Table 1: Overview of available antiepileptic drugs.

Drug (year of first approval)	Mechanism of	Potential advantages	Potential disadvantages
Older antiepileptic drugs			
Bromide (1857)	GABA potentiation	Broad spectrum action	CNS-related AEs, acneiform rashes, loss of appetite
Carbamazepine (1964)	Na^+ channel blockade	Highly effective, extensively studied	CNS related AEs, rash, hyponatriaemia, enzyme induction, osteoporosis, leucopenia
Phenobarbital (1912)	GABA potentiation	Broad spectrum action, once daily, attractive costs	CNS related AEs, rash, osteoporosis, enzyme induction, folate deficiency, enzyme induction, Dupuytren's contractures, hematological toxicity
Ethosuximide (1958)	Calcium channel blockade (T-type)	Well proven in childhood absence epilepsy	Gastrointestinal and CNS-related AEs, idiosyncratic reactions, narrow spectrum efficacy
Phenytoin (1938)	Na^+ channel blockade	Rapid titration, intravenous formulation available, attractive costs	CNS-related AEs, gingival hyperplasia, hirsutism, osteoporosis, enzym induction, idiosyncratic reactions
Valproate (1967)	Multiple (GABA potentiation, NMDA inhibition, sodium channel and calcium channel blockade (T-type))	Broad spectrum action, rapid titration, few interactions, intravenous formulation available	Hair loss, weight gain, gastrointestinal AEs, teratogenicity, hepato-toxicity, hyperammonemia, thrombocytopenia, extrapyramidal symptoms
Newer antiepileptic drugs			
Eslicarbazepine (2009)	Na^+ channel blockade	Once daily	CNS-related AEs, rash, hyponatraemia, interaction with combined oral contraceptives
Felbamate (1993)	NMDA inhibiton	Broad spectrum action	CNS-related AEs, aplastic anemia, fulminate hepatic failure, weight loss, interaction with combined oral contraceptives, last-resort drug
Gabapentin (1993)	Calcium channel blockade	Low risk of allergic reactions, Low risk of drug interaction, good tolerability	Mild CNS-related AEs, weight gain
Lacosamide (2008)	Enhanced slow inactivation of voltage-gated Na^+ channels	Low risk of drug interaction, intravenous formulation available	CNS-related AEs, nausea

Table 1: Overview of available antiepileptic drugs.

Drug (year of first approval)	Mechanism of	Potential advantages	Potential disadvantages
Lamotrigine (1990)	Na^+ channel blockade	Broad spectrum action, few interactions, good tolerability	CNS-related AEs, rash, hypersensitivity reactions, interaction with combined oral contraceptives
Levetiracetam (2000)	SV2A modulation	Broad spectrum action, intravenous formulation available, low risk of drug interaction	CNS-related AEs, neuropsychiatric and behavioural effects
Oxcarbazepine (1990)	Na^+ channel blockade	Good tolerability	CNS-related AEs, rash, hyponatraemia, interaction with combined oral contraceptives
Perampanel (2012)	AMPA antagonist	Novel mechanism of action, once daily	CNS-related AEs, neuropsychiatric and behavioural effects
Pregabalin (2004)	Calcium blockade	Low risk of allergic reactions, low risk of drug interaction	CNS-related AEs, weight gain
Retigabine (2011)	K^+ channel opener	Novel mechanism of action	Urinary retention, CNS-related AEs, blue skin discoloration and retinal pigmentary changes, retinal dystrophy, last-resort drug
Rufinamide (2004)	Na^+ channel blockade	Orphan drug for Lennox-Gastaut syndrome	CNS-related and gastrointestinal AEs
Stiripentol (2007)	GABA potentiation	Dravet Syndrome in children	Drowsiness, hyperactivity, weiht loss, dystonia, ataxia, tremor, enzyme inhibitor
Topiramate (1995)	Multiple (GABA potentiation, AMPA inhibition, sodium and calcium channel blockade)	Broad spectrum action	CNS-related AEs, paraesthesia, fatigue, weight loss, renal stones, neuropsychiatric effects, interaction with combined oral contraceptives
Vigabatrin (1989)	GABA potentiation	Well proven efficacy in infantile spasms in tuberous sclerosis	CNS-related AEs, irreversible concentric visual field deficits, last-resort drug
Zonisamide (2000)	Na^+ channel blockade	Broad spectrum action	CNS-related AEs, anorexia, weight loss, renal stones, rash, neuropsychiatric effects

AEs : adverse events

Table 2: Level of evidence for particular seizure types and epilepsy syndromes (adapted from [7]). Of note, these ratings may differ from common clinical practice.

Seizure type/epilepsy syndrome	Level of evidence (efficacy/effectiveness of AED)
Partial onset seizures (adults)	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXc, PB, TPM, VGB Level D: CLZ, PRM
Partial onset seizures (children)	Level A: OXC Level B: none Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB,CLZ,LTG, ZNS
Partial onset seizures (elderly)	Level A: GBP, LTG Level B: none Level C: CBZ Level D: TPM, VPA
Generalized tonic-clonic seizures (adults)	Level A: none Level B: none Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Generalized tonic-clonic seizures (children)	Level A: none Level B: none Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Absence seizures (children)	Level A: ESM, VPA Level B: none Level C: LTG Level D: none
Benign epilepsy with centrotemporal spikes	Level A: none Level B: none Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy	Level A: none Level B: none Level C: none Level D: TPM, VPA

Clarifications of terms: Level A: ≥ 1 Class I studies, or metaanalysis meeting class I criteria sources, or ≥ 2 Class II studies; Level B: 1 Class II study, or metaanalysis meeting class II criteria; Level C: ≥ 2 Class II double-blind or open-label studies; Level D: 1 Class III double-blind or open-label study or ≥ 1 class IV clinical studies or data from expert committee reports, or opinions from experienced clinicians.

Further Considerations

Women with childbearing potential

If clinically possible, AEDs known to be associated with congenital malformations in offspring of women with epilepsy, including valproic acid, as well as a combination of AEDs, should be avoided during pregnancy, especially during the first trimester. The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) reported the lowest malformation rates with lamotrigine < 300mg/day, or carbamazepine < 400mg/day compared with valproic acid and phenobarbital at all doses and with carbamazepine ≥ 400mg/day [13]. A recent guideline for treatment of women with epilepsy further suggested that intrauterine exposure to valproic acid, phenytoin and phenobarbital reduces cognitive outcomes in offspring and should therefore be avoided [14]. Moreover, very recently the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) has further recommended strengthening the restrictions on the use of valproate in women with childbearing potential due to the above mentioned risk of malformations and developmental problems in children exposed to valproate in uterus [15]. Lamotrigine is an appropriate choice, although it might be less efficacious than valproic acid [5].

Elderly people

Aging is associated with changes in pharmacokinetics and pharmacodynamics, implying a more cautious choice of drugs and dosing regimen in elderly patients with epilepsy. Additionally, concomitant internistic diseases including hypertension, renal insufficiency and cardiovascular problems, are common and require further medical treatment. The likelihood of drug interactions is increasing and therefore, monotherapy with a well tolerated drug without the potential of drug-drug interactions is aimed. Although class I evidence is lacking, gabapentin and lamotrigine, as well as topiramate and levetiracetam, might be appropriate choices [16 -19]. Furthermore, an easy-to-use drug is preferable due to probable cognitive impairment resulting in potential non-adherence.

Comorbidities

For the optimum choice of AED treatment, comorbidities have to be taken into consideration. Psychiatric comorbidities, especially depression and generalized anxiety disorders are very common in patients with epilepsy. Lamotrigine is beneficial in bipolar depression, valproic acid and carbamazepine are used as mood stabilizer [20] and pregabalin is appropriate in patients with coexisting generalized anxiety disorder [21]. A recent special report on antiepileptic drugs and suicidality pointed out that although some (but not all) AEDs can be associated with treatment-emergent psychiatric problems possibly leading to suicidal ideation and behavior, the actual suicidal risk is yet to be established, but it seems to be very low [22]. Clinicians should be aware of risk factors and if necessary, patients should be referred for a psychiatric evaluation, but AED treatment should not be withheld, even in subjects with suicidal risks. Not least, pregabalin is well-studied for the treatment of neuropathic pain [23], and valproic acid and topiramate are effective in migraine prophylaxis, respectively [24].

Formulations

Intravenous loading doses, if needed, can be given with older AEDs, including valproic acid, and phenytoin, and newer AEDs such as levetiracetam and lacosamide. Both of the newer AEDs have the advantage of a favorable tolerability profile without sedation, cardiovascular adverse events, or toxic local effects.

Enzyme induction / inhibition

A main advantage for many of the newer AEDs, especially gabapentin, pregabalin, lamotrigine, levetiracetam and lacosamide, is that they do not induce or inhibit hepatic enzyme function (see **Table 1**). This clearly reduces the potential for drug-drug inter-action which is particularly favorable for patients taking non-AED drugs or AED polytherapy.

Conclusion

Several randomized, double-blind, controlled trials confirm the efficacy of new AEDs in monotherapy and polytherapy [7, 10]. However, no class I evidence has demonstrated superior efficacy/tolerability for any specific AED for treating drug resistant epilepsy. Compared with classical AEDs, some of the newer drugs offer the advantage of not affecting the hepatic enzyme function (GBP, PRG,LTG, LEV, LCM) , rapid onset of action (GBP, OXC, LEV and LCM), intravenous loading (LEV and LCM), broad spectrum efficacy (LTG, TPM, ZNS and LEV) or use for treating comorbidities.

The fact that over one third of patients with epilepsy still do not achieve seizure freedom with available AEDs gives rise to further research with a view to develop AEDs with novel mecanisms of action and novel modes of administrations. The novel generation of AEDs has certainly expanded the treatment options; however, these drugs neither reduce the prevalence of drug resistant epilepsy, nor prevent the development of epilepsy in patients at high risk.

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Newer Anti-Epileptic Drugs in Children

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Summary

The introduction of new anti-epileptic drugs (AED) provides more options for treatment of children with epilepsy. We review indications, safety and tolerability of ten new AEDs (lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentin and perampanel). We also make a short review of the most recent new AEDs not yet approved in pediatrics. Many issues specific for children are not addressed during the development of new AEDs, like the impact on the developing brain. New AEDs are usually approved as adjunctive therapy based on adult clinical trial. In pediatrics, the choice of a new AED for children depends on many factors including age, cognitive development, epileptic syndrome and its etiology, as well as concomitant medication.

Epileptologie 2015; 32: 58 – 64

Key words: Newer anti-epileptic drug, childhood epilepsies, side effects

Neuere Antiepileptika für Kinder

Die Entwicklung neuer Antiepileptika (AE) hat breite therapeutische Möglichkeiten in der Epilepsiebehandlung pädiatrischer Patienten eröffnet. In diesem Beitrag werden zehn AE der neuen Generation vorgestellt (lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentine, und perampanel), gefolgt von einer kurzer Zusammenfassung zweier für Kinder noch nicht anerkannten Medikamente. Auch wenn die neuen AE einige Besserungen in der Neuro-Pädiatrie hervorbringen konnten, werden leider spezifische Probleme, insbesondere die Folgen auf die Gehirnentwicklung, vor und bei der Vermarktung nicht untersucht. Die neuen AE sind generell als „add-on"-Mittel zugelassen, meistens nach Studien an Erwachsenen. Beim pädiatrischen Patienten ist die Wahl eines AE vom Alter, der kognitiven Entwicklung, dem epileptischen Syndrom, den Ko-Medikationen, und der unterliegenden Ätiologie der Epilepsie abhängig.

Schlüsselwörter: Neuere Antiepileptika, Epilepsien des Kindesalters, Nebenwirkungen

Nouveaux médicaments antiépileptiques pour les enfants

Le développement d'anti-épileptiques (AE) de nouvelle génération a fourni de nouvelles options thérapeutiques dans la prise en charge des épilepsies de l'enfant. Dans cet article, dix AE de nouvelle génération sont passés en revue (lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentine et perampanel) en plus d'un court résumé des plus récentes drogues, non encore approuvés en pédiatrie. Malgré des avancées significatives, de nombreux problèmes spécifiques à l'enfant ne sont pas pris en compte lors du développement de ces drogues, comme l'impact sur le cerveau en développement. Les nouveaux AE sont habituellement approuvé en complément à d'autres AE, basé sur des essais cliniques adultes. En pédiatrie, le choix d'un nouvel AE dépend de différents facteurs incluant l'âge, le développement cognitif, le syndrome épileptique, les co-médications, et l'etiologie sous-jacente de l'épilepsie.

Mots clés : Nouveaux antiépileptiques, épilepsies de l'enfance, effets indésirables

Nuovi medicamenti antiepilettici per i bambini

Lo sviluppo dei medicamenti antiepilettici (AE) delle nuova generazione ha permesso di espandere le possibilità terapeutiche in neuropediatria. Dieci nuovi AE approvati per l'uso pediatrico (lamotrigina, oxcarbazepina, vigabatrina, levetiracetam, topiramato, zonisamide, felbamato, rufinamide, gabapentina e perampanel), oltra a due sostanze non ancora ammesse in questa fascia d'età, saranno passati in rassegna in questo contributo. Purtroppo, durante l'iter che porta alla messa sul mercato dei farmaci antiepilettici, l'industria ha poco interesse per aspetti molto importanti, particolarmente quelli che riguardano lo sviluppo del cervello nel'in-

fanzia. I nuovi AE sono generalmente approvati quali "add-on" in base a studi condotti sugli adulti. Nell'ambito pediatrico, la scelta del medicamento dipende da diversi fattori, quali l'età, lo sviluppo cognitivo, la sindrome epilettica, la sua eziologia, e la co-medicazione.

Parole chiave: Nuovi antiepilettici, epilessie dell'infanzia, effetti indesiderati

Introduction

Epilepsy is a common pediatric neurologic disorder, affecting 0.5 to 1% of all children [1]. The failure rate of a first anti-epileptic drug (AED) with a newly diagnosed epilepsy remains high, around 20% to 40%. This has been attributed to poor effectiveness and/or high frequency of adverse effects, and stimulated the search for new drugs [2, 3]. Although there is poor evidence that the newer AEDs are more effective than the older ones [4] they are usually better tolerated, have fewer interactions with other drugs, need less serum level checks and some may potentially have some neuroprotective effects [5]. These features are obvious advantages, but evidence-based data on their effectiveness and safety in children are often lacking. Hence, their use often depends on the clinician's experience [1].

We review here 10 new AEDs, i.e. lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentin and perampanel. We focus on their use in pediatric epileptic syndromes (**Table**) and briefly review the most recent AEDs not yet approved in pediatrics.

Lamotrigine

Lamotrigine (LTG) prolongs the slow inactivation of voltage-gated sodium channels and blocks NMDA receptors [3]. It acts on generalized and focal seizures. It was initially indicated as an adjunctive therapy in Lennox-Gastaut syndrome (LGS) (Class I evidence). Since then, its efficacy was demonstrated in infantile spasms (IS), absence epilepsy (Class II evidence), epilepsy with myoclono-atonic seizures (MAE), juvenile myoclonic epilepsy (JME) and idiopathic epilepsy [7]. It has, pharmacodynamically, a synergic effect with valproic acid (VPA) in myoclonic and absence epilepsy [8]. LTG is well tolerated and may be efficacious for focal seizures in patients as young as 1 month old [9].

The clearance of LTG is increased by carbamazepine (CBZ) and phenytoin (PHT) and decreased by VPA [3]. Besides common side effects like dizziness, somnolence, headache or ataxia, severe immune-allergic skin reaction like Stevens-Johnson syndrome can occur more commonly in children. A rapid titration or the simultaneous use of VPA are risk factors [10, 11]. Worsening of myoclonic seizures was reported in JME and Dravet syndrome (DS) but is not an absolute contraindication in these syndromes [4, 12].

Oxcarbazepine

Oxcarbazepine (OXC) is a keto derivative of CBZ. It blocks voltage-gated sodium channels. Potassium conduction potentiation, inhibition of calcium channels and inhibition of NMDA receptors are additional described mechanisms [3, 4]. It is indicated in adjunctive therapy for focal seizures in children ≥ 2 years of age and in monotherapy in children ≥ 4 years of age (Class I evidence) [13]. OXC was shown to be equivalent to CBZ and PHT in its efficacy with a higher tolerability (Class I and II evidences) [14-16].

Acting on different liver cytochromes, OXC may decrease phenobarbital (PB) and PHT levels [3]. Side effects include somnolence, ataxia, diplopia, tremor, dizziness and gastro intestinal disturbances. CBZ-induced severe cutaneous adverse reactions, like Stevens-Johnson syndrome, have been associated with HLA-B*1502 in Asian populations. About 25-33% of patients with a hypersensitivity reaction to CBZ also have an allergic reaction to OXC [17]. Expert opinion recommend HLA-testing in patients from Southeast Asia before initiating OXC. For patients who test positive for B*1502, OXC should be avoided [18].

Hyponatremia is a well-known side effect of OXC due to its effects on anti-diuretic hormone, distal convoluted tubule in the kidney and vasopressin. It is usually asymptomatic and rare in children. Natremia returns to normal levels with dose reduction, drug discontinuation or fluid restriction [7, 17, 19]. OXC can worsen myoclonic and absence epilepsy.

Vigabatrin

Vigabatrin (VGB) is an inhibitor of GABA-aminotransferase increasing GABA levels in the central nervous system [20]. Its main indication in children is in IS. Its efficacy was demonstrated whatever the cause of the IS [21], but especially in tuberous sclerosis complex (TSC), with more than 90% of good responders [4, 22]. It can also be used as an adjunctive therapy in focal and generalized seizures [4, 20]. It has no major drug interaction.

The most serious potential side effect is an irreversible visual field constriction (VFC) [23]. In an observational cohort study of children with IS, the authors showed VFC diagnosed by electro-retinogram (ERG) in 5.3% of children after 6 months of VGB-exposure and 13.3% after 12 months [24]. The occurrence of VFC was not influenced by age at initiation of VGB, gender, or dosage. Authors recommend minimizing VGB treatment to 6 months to reduce the prevalence of VFC in children with IS [25]. When VGB is the only efficient

Table: Use of newer anti-epileptic drugs in pediatric epilepsy syndromes: preferred treatment options based on expert consensus [6]

Syndrome	AED	Dose	Treatment line
Infantile Spasms	VGB	50 to 150 mg/kg/d	1st (TSC)
	TPM	1 to 10 mg/kg/d	2nd-3rd
	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Dravet Syndrome	TPM	1 to 7-8 mg/kg/d	1st-2nd
	LEV	20 to 50 mg/kg/d	2nd-3rd
Epilepsy with Myoclonic Atonic Seizures	LTG	1 to 7.5 mg/kg/d	2nd-3rd
	TPM	1 to 7-8 mg/kg/d	2nd-3rd
	LEV	20 to 50 mg/kg/d	1st-2nd
Lennox-Gastaut Syndrome	RUF	10 to 45 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	1st-2nd
	FBM	15 to 45 mg/kg/d	2nd-3rd
	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Idiopathic and Non Idiopathic Focal Epilepsies	LEV	20 to 50 mg/kg/d	1st-2nd
	OXC	8 to 45 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	2nd-3rd
	GBP	10 to 90 mg/kg/d	1st-2nd
Genetic (Idiopathic) Generalized Epilepsies			
Childhood Absence Epilepsy	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Epilepsy with Myoclonic Absence	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Epilepsy with Tonic Clonic Seizures Alone	LTG	1 to 7.5 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	1st-2nd
	ZNS	1-2 to 5-8 mg/kg/d	1st-2nd
Juvenile Myoclonic Epilepsy	LTG	1 to 7.5 mg/kg/d	1st-2nd
	LEV	20 to 50 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	1st-2nd
	ZNS	1-2 to 5-8 mg/kg/d	1st-2nd

Legend: AED: anti epileptic drug, VGB: vigabatrin, TPM: topiramate, LTG: lamotrigine, LEV: levetiracetam, RUF: rufinamide, FBM: felbamate, OXC: oxcarbamazepine, GBP: gabapentin, ZNS: zonisamide, TSC: Tuberous Sclerosis Complex

drug, like it can be the case in TSC, an ophthalmologic examination is recommended 3 months after initiation, then every 3 months. In children ≤ 5-6 years, an ERG should be considered; since this test requires sedation, risks and benefits should be evaluated for each infant [20, 26]. If seizures are not controlled within 4 weeks for IS and 3 months for focal seizures, VGB should be discontinued and an ophthalmological examination performed 3-6 months after VGB discontinuation [26].

Common side effects like weight gain, behavioral changes, headaches, sleep disturbances, drowsiness and ataxia are reported. VGB may exacerbate myoclonic seizures [20]. Abnormal signal on T2 and diffusion weighted imaging localized in basal ganglia, brainstem and dentate nucleus, were noticed on the brain MRIs of one third of infants treated by VGB for IS. They are related to younger ages and higher doses. The mechanism remains unclear [24]. Children are asymptomatic and signal abnormalities are reversible after drug discontinuation [27].

Levetiracetam

Levetiracetam (LEV) is a pyrrolidine derivative, structurally similar to the piracetam. Its exact mechanism of action is unknown. Its binding to synaptic vesicle protein 2A may play a role. Inhibition of voltage-gated calcium channels and reduction of GABA and glycin-mediated are postulated [4, 28]. Its major metabolic pathway is independent on any liver CYP450 isoenzymes and it has a low plasma proteins bounding, therefore interactions with other drugs are very unlikely [29].

LEV is indicated as an adjunctive treatment for focal seizures in children >4 years old (Class III evidence) [30] and myoclonic seizures in JME (Class IV evidence) [7]. There are growing evidences of its broad-spectrum action on generalized and focal seizures [28]. High dose IV LEV (40-60mg/kg) has been shown to be effective in childhood refractory status epilepticus. It offers an interesting alternative to benzodiazepine especially in children with severe encephalopathy and/or cerebral palsy at higher risk of cardio-respiratory failure [31, 32].

LEV is well-tolerated [28]. A major side effect is behavorial change with aggressiveness, obsessive or psychotic behavior [33]. These signs usually manifest in children with pre-existing cognitive or behavioral/emotional disorders. Their incidence is higher in children [29].

Topiramate

Topiramate (TPM) is a sulfamate-substitued monosaccharide. Its exact mechanism is unknown. It may inhibit voltage-gated sodium and calcium channels, potentiate GABA-mediated chloride currents, block glutamate-mediated excitatory transmission, and inhibit carbonic anhydrase enzymes [3, 4].

Current indications are as an adjunctive therapy for children of 2-12 years of age with focal seizures or idiopathic generalized tonic-clonic seizures (Class I evidence) [7]. It has also shown efficacy in IS, LGS (Class IV evidence) [34], JME (Class IV evidence) and refractory focal seizures (Class I evidence) [35-37]. It decreases the frequency of status epilepticus in DS.

TPM levels can be decreased by PHT and CBZ [3]. TPM can cause nephrolithiasis and metabolic acidosis, usually asymptomatic but requiring caution in patients with renal failure. Hyperthermia due to hypohydrosis is a risk with febrile illnesses or hot weather. Somnolence, paresthesia, nystagmus, glaucoma, anorexia and weight loss were reported. TPM may reduce expressive language or verbal fluency; this side effect can be difficult to ascertain in children with developmental delay/intellectual disability. A drug discontinuation should be considered if there is any doubt [37].

Zonisamide

Zonisamide (ZNS) is a sulfonamide derivative. The proposed mechanisms of action are inhibition of sodium and T-type calcium channels and inhibition of potassium-evoked glutamate synaptic transmission. It also acts on the dopamine and serotonin transmission facilitation and is a weak carbonic anhydrase inhibitor [3]. ZNS is approved for patients >16 years as an add-on therapy for focal seizures. It has shown efficacy and safety in children [38, 39]. It has a good effect in JME (Class IV evidence), absence or myoclonic epilepsies [40, 41]. It can be effective and safe at high dose in IS [42].

ZNS is metabolized by the CYP450 3A4, hence levels are decreased by enzyme inducers like PHT, PB and CBZ [4, 40]. ZNS is well-tolerated; side effects are similar to TPM. Cases with Stevens-Johnson syndrome were reported [40].

Rufinamide

Rufinamide (RUF) is a triazole derivative with a novel chemical structure. Its mechanism of action is unknown; a prolongation of the inactivation phase of voltage-gated sodium channels is postulated [3]. RUF was approved as an adjunctive therapy for tonic/atonic seizures in LGS in children ≥ 4 years [43, 44]. A favorable safety and tolerability profile of RUF for children with intractable epilepsy was shown [45, 46]. Kluger et al. report good effect of RUF in MAE [47]. A retrospective European multicenter study evaluated the efficacy and tolerability of RUF in DS. The retention rate decreased from 45% after 6 months of treatment to 15% after 34 months. RUF was stopped due to seizure aggravation in about 30% of patients and side effects in 10%. Therefore the authors state that RUF does not seem to be a suitable option for long-term treatment in DS [48].

A lower maximal daily dose of RUF is required in case of concomitant use of VPA. It is of special importance in children weighing less than 30kg who may have larger interindividual pharmacokinetic variability [45, 47]. Common side effects, like fatigue, somnolence, ataxia, dizziness, vomiting and headaches, can be reduced by slow titration (every 5-7 days) and subside with maintenance dosing [47]. A hypersensitivity syndrome was reported in children ≤ 12 years of age. They all recovered quickly after drug discontinuation [45].

Felbamate

Felbamate (FBM) is a dicarbamate. Suggested mechanisms of action are: sodium channels antagonism, inhibition of voltage-gated calcium channels and NMDA receptors and potentiation of GABAergic activity [4, 49]. It was the first drug to be tested in a placebo-controlled trial in children with LGS [50] where it was approved for adjunctive therapy (Class I evidence) [51]. There is Class III evidence for its use in IS, absence seizures, JME and Landau-Kleffner syndrome. FBM may be effective in MAE (Class IV evidence) [49].

FBM is a CYP2C19 inhibitor; hence PHT, PB, VPA and OXC levels are increased [7]. Common adverse effects like anorexia, gastro-intestinal complaints, sleep disturbances and gait abnormality were reported. FBM is related to rare but serious, not dose-related, potentially fatal hepatotoxicity and aplastic anemia. A slow drug titration may reduce this risk. Blood cell counts and hepatic enzymes' levels should be performed before the initiation of FBM and monitored regularly [52].

Gabapentin

Gabapentin (GBP) mimicks the structure of GABA and increases the seizure threshold. Its exact mechanism of action is unknown. GBP binds to an auxiliary subunit of voltage-gated calcium channels [4]. It has a short elimination half-time, so it is preferably divided into 3 or 4 doses per day [7]. It is approved as an adjunctive therapy for treatment of focal seizures in children ≥12 years [4]. There is Class I evidence of its efficacy and tolerability in newly diagnosed focal epilepsy and refractory focal epilepsy [14, 34]. One class III double blind trial showed its efficacy in benign rolandic epilepsy [6].

GBP is usually well-tolerated with common side effects including behavioral changes, weight gain, dizziness, somnolence and fatigue. Ataxia, nystagmus and choreoathetosis have been reported [7].

Perampanel

Perampanel (PER) is a non-competitive selective AMPA receptor antagonist acting on post-synaptic glutamate transmission [53]. PER was recently approved by the European Medicines Agency and FDA for adjunctive treatment of children ≥ 12 years of age with focal epilepsy [54, 55]. Double blind drug trials showed a responder rate between 15 and 38%, 2 to 5% of patients being seizure free at 3 months. Long-term safety study showed good tolerability during up to 3 years of exposure [56]. Its long half-life allows a single daily dose.

PER is primarily metabolized via tCYP450, hence, CYP450 inhibitors/inducers may affect their levels. PER could induce liver enzymes and interact with concomitant AEDs like PHT, PB or RUF [57]. Adverse events include dizziness, somnolence, irritability, headache and ataxia [58]. One case of drug reaction with eosinophilia and systemic symptoms was reported [59].

Lacosamide, Brivaracetam

No pediatric studies are available for these drugs. However, they offer interesting perspectives for pediatric use. The following summaries are based on adult studies.

Lacosamide (LCM)

LCM is a functionalized amino acid molecule thought to inactivate voltage-gated sodium channels and interact with the Collapsing-Response Mediator Protein 2 (CRMP-2) involved in neuronal differentiation, polarization and axonal outgrowth [60]. LCM have been FDA-approved for the adjunctive treatment of focal epilepsy [61-63]. Case reports suggest an efficacy in refractory status epilepticus [64, 65]. The effect of LCM on CRMP-2 was postulated to be responsible for neuroprotective effects in animal models. Of particular concern for children is the possible impact of LCM on normal brain development in very young children, given the known interaction with CRMP-2 highly expressed during early development in the CNS [60, 66].

Brivaracetam (BRV)

This (S)-isomer of LEV appears to have a low side effect profile and a potent broad spectrum of action which makes it appealing for use in children [67].

Conclusion

The introduction of a new AED is always welcomed with enthusiasm. In the pediatric population, they are usually first approved as add-on therapies based on adult clinical trials. These extrapolated data do not allow addressing specific pediatric issues. Drug doses often differ from the adult and must be adjusted according to age and weight at diagnosis and at follow-up. Side effects are potentially different in the developing child with possible impact on cognition. Drug and dosage forms are often not suited to pediatric use especially in infancy and neonates. The choice of an appropriate AED requires not only knowledge of pharmacokinetics according to age, drug interactions and best formulation for children but also of the age-related epileptic syndromes, underlying etiology and co-existing medical problems/and cognitive disorders.

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Long Term Somatic Adverse Events of Antiepileptic Drugs

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Summary

Long term antiepileptic drugs (AEDs) side effects are a common concern in people with epilepsy. AEDs are suspected to be associated with several somatic and psychiatric adverse events. This review focuses on long term somatic adverse events and the difficulties of assessing their exact association with AEDs. Most AEDs have been suggested to induce, at varying degrees, bone metabolism changes, increased cardiovascular risk factors, or endocrine disturbances. These findings are however probably biased by the fact that epilepsy itself is associated with a greater burden of somatic co-morbidities, regardless to the exposure to AEDs.

Epileptologie 2015; 32: 65 – 69

Key words: bone metabolism, cardiovascular risk factors, endocrine disturbances, co-morbidities

Langzeitnebenwirkungen von Antiepileptika

Langzeitnebenwirkungen von Antiepileptika (AE) stellen ein häufiges Problem dar, sowohl somatischer als auch psychischer Natur. Dieser Beitrag fokussiert auf somatische Aspekte und auf die Schwierigkeiten, deren Zusammenhang mit der pharmakologischen Behandlung zu erfassen. Veränderungen im Knochenmetabolismus, Erhöhung der kardiovaskulären Risiken und endokrinologische Entgleisungen wurden bei Patienten unter verschiedenen AE beschrieben. Diese Befunde sind jedoch im Hinblick auf die Möglichkeit zu betrachten, dass im Vergleich mit der Allgemeinbevölkerung Epilepsie-Patienten mehrere somatische Komorbiditäten ohne direkte Kausalität mit der medikamentösen Behandlung aufweisen können.

Schlüsselwörter: Knochenmetabolismus, kardiovaskuläre Risikofaktoren, endokrine Störungen, Komorbiditäten

Les effets secondaires à long terme des médicaments antiépileptiques

Les effets secondaires à long terme des médicaments antiépileptiques chez les gens souffrant d'épilepsie sont un problème fréquent. Plusieurs complications somatiques et psychiatriques sont suspectes d'être liés aux médicaments antiépileptiques. Cette revue se concentre sur les complications somatiques à long terme et les difficultés d'explorer leur association avec les traitements de l'épilepsie. Des changements du métabolisme osseux, une augmentation des facteurs de risques cardiovasculaires et des dérangements endocriniens ont été rapporté avec la plupart des antiépileptiques. Ces trouvailles sont au moins en partie biaisées par le fait que l'épilepsie elle-même peut être liée à une fréquence de comorbidités augmenté, sans lien avec l'exposition au traitement.

Mots clés : Métabolisme osseux, facteurs de risques cardiovasculaires, dérangements endocriniens, comorbidités

Gli effetti secondari a lungo termine dei medicamenti antiepilettici

Gli effetti secondari a lungo termine dei medicamenti antiepilettici (AE) rappresentano una problematica frequente nei pazienti con epilessia, siano essi di natura somatica o psichiatrica. In questo contributo ci si concentrerà sulle complicazioni somatiche e sulle difficoltà metodologiche nell' esplorare il legame di causalità con il trattamento farmacologico. La maggiorparte degli AE sono stati messi in relazione con perturbazioni della salute ossea, aumento dei fattori di rischio cardiovascolare, e con alterazioni endocrinologiche. Questi dati, però, sono almeno in parte distorti dalla presenza di comorbidità somatiche pre-esistenti, che sono più frequenti in pazienti con epilessia rispetto alla popolazione controllo.

Parole chiave: Perturbazioni della salute ossea, fattori di rischio cardiovascolare, alterazioni endocrinologiche, comorbidità

Long term side effects represent often a legitimate concern of people with epilepsy requiring an antiepileptic drug (AED) treatment on a long course. A wide range of adverse events (somatic and psychiatric) have been described in people on AEDs, though they may not only be the exclusive consequences of the treatment. This review will focus on somatic long term adverse events, and on confounding factors biasing the relationship between AEDs exposure and these effects. Well known short term adverse events of AEDs will not be discussed here.

Bone metabolism

Long term exposure to AEDs has been known for long to be associated with a decrease in bone density [1-3]. Older age, female gender, lower weight, longer exposure to AEDs, and AED polytherapy have been shown to be independent risk factors [4, 5]. Exposure to a wide range of AEDs was found to be associated with non-traumatic fractures, even after adjusting for demographic and socio-economic factors [6]. Enzyme-inducing AEDs were most implicated, though not exclusively, in the occurrence of osteoporosis [7], supposedly because of increasing the clearance of dihydroxylated vitamin D [8]. This may not be the (only) relevant mechanism, as decreased bone density was found to be independent of low vitamin D level [9-11], and calcium and vitamin D supplementation had little effect in the prevention of fractures in people taking AEDs [12]. An effect on sex hormones may be more important: decreased oestradiol in women taking enzyme-inducing AEDs was associated with decreased bone density, independently of vitamin D levels [13]. Pragmatically, a recent study suggested that switching from enzyme-inducing AEDs (phenytoin) to non-enzyme-inducing AEDs (levetiracetam) not only stops the progressive decrease but also increases bone density after two years of therapy [14]. Among newer AEDs, topiramate has also been suggested as potentially having long term effects on bones, as it decreases parathyroid hormone while increasing markers of bone turnover [15]. Lamotrigine and levetiracetam seem to not have (though not unequivocally [16]) significant effects on bone metabolism, while gabapentin was suggested to decrease bone density [17, 18], but it was not clear whether previous exposure to inducing AEDs was taken into account.

Cardiovascular risk factors

Enzyme-inducing AEDs have been shown to also play a role on cardiovascular risk factors. People on inducing AEDs show significantly higher total cholesterol, low-density lipoprotein cholesterol and triglyceride levels in the long term [19-21], which can be improved by switching to non-inducing AEDs [22]. Increased lipid synthesis is probably mediated by increased clearance of cholesterol metabolites, attenuating the negative feedback on cholesterol synthesis [23]. Levels of other cardiovascular risk factors markers such as lipoprotein (a), CRP [22] and homocysteine [24] were also found to be increased in people taking enzyme-inducing AEDs. A study in children [25] suggested that carotid artery intimal media thickness was significantly greater in children on phenytoin and carbamazepine than in healthy controls. Another study [26] prospectively found a significantly increased incidence of stroke in people taking phenytoin compared to valproate but also to carbamazepine. There is less experience with newer AEDs, and little is known about whether those agents can contribute to the occurrence of somatic conditions. Newer AEDs are either less potent liver enzyme-inducers (e.g. topiramate or oxcarbazepine) or devoid of inducing properties (e.g. levetiracetam, lamotrigine, pregabalin, gabapentin) [27]. Weakly inducing AEDs (topiramate and oxcarbazepine) and non-inducing AEDs (levetiracetam) also increase cardiovascular risk factors such as LDL cholesterol, homocysteinemia, and apolipoprotein B after six months of monotherapy [28]. This actually suggests that liver enzyme induction is not the exclusive mechanism implicated in cardiovascular risk factors, though non-inducing AEDs seem to have a more favourable profile [22]. Valproate was shown to be associated with increased insulin levels independent of weight, compared with healthy controls [29] or people on lamotrigine [30]; a young age at valproate initiation is a risk factor. It was suggested that valproate caused impaired liver insulin metabolism independently of weight [31]. Total cholesterol and triglyceride have also been described as significantly higher in people on valproate than on other AEDs, or healthy controls, even after adjustment for obesity [32]. Valproate, like the enzyme-inducing AEDs, has been suggested to induce persistently raised lipoprotein(a) [33], which is increasingly recognised as an independent cardiovascular risk factor [34, 35].

There is evidence, however, that treatment does not fully explain the increased burden of cardiovascular conditions in people with epilepsy. Increased intimal thickness was shown in patients on carbamazepine or valproate, but was also significantly increased in people with untreated epilepsy, though to lesser extent [36]; it was however not clear whether the latter had been previously exposed to AEDs. A large population study [37] showed that being on AEDs had only small effects on stroke and myocardial infarction incidence, or cardiovascular death. Excluding those with previous stroke, people with epilepsy, whether or not on AEDs, had significantly increased risk for vascular events compared with people without epilepsy. Despite many AEDs being associated with weight gain, the prevalence of being overweight and obesity were found to be only indirectly related to AED treatment. Among 554 people with epilepsy assessed in hospital settings in a

US study [38], no specific monotherapy was associated with weight gain and obesity, but the authors did not report whether they had considered all AEDs the person was exposed to. Previous exposure to AEDs favouring weight gain may have confounded the association with AEDs at the time of the assessment. Polytherapy and drug resistance were found to be associated with weight gain and obesity. This matter is further complicated by the fact that the choice of AEDs may depend on the socioeconomic level of the people being treated. A Swedish study recently showed in a paediatric population that newer AEDs (such as levetiracetam) are more often prescribed to children whose families have a higher socioeconomic level [39]. A higher rate of prescription of liver enzyme-inducers in people with lower socioeconomic levels may worsen further the already higher burden of somatic co-morbidities in people with lower socio-economic level.

Endocrine disturbances

Enzyme-inducing AEDs are also reported to decrease thyroid hormone levels (T3 and T4); this is not, however, associated with any change of TSH and therefore thought to be subclinical [40-42]. Enzyme-inducing AEDs have also been shown to decrease testosterone in men [43] and induce sexual dysfunction [44]. In women, these treatments also decrease levels of oestradiol and dehydroepiandrosterone (DHEA), which has been linked again with sexual dysfunction [45].

Valproate has also been recognised as a risk factor in the development of polycystic ovary syndrome for a long time. The mechanisms by which it can induce polycystic ovaries are probably multiple; hyperinsulinism/weight gain, combined with inhibition of testosterone conversion to oestradiol, alongside theca cell stimulation, result in increased testosterone levels and obesity [46]. Switching to lamotrigine improves the lipid profile, weight, fasting serum insulin, testosterone level and the number of cysts seen on ultrasonography [47]. These changes appear to be linked with the maturation of the reproductive system, as polycystic ovary syndrome has been shown to be more common (80% in one series [48]) if valproate was started before age 20.

Cancer

An association between AEDs and the occurrence of tumors in people with epilepsy has long been questioned [49, 50]. Older AEDs such as phenobarbital and phenytoin, have been incriminated as potential carcinogens [51]. Long-term prescription studies did not, however, find an association [52, 53]. Phenobarbital was particularly implicated in the occurrence of hepatocellular carcinoma [54]. This association is potentially biased by the early use of the carcinogenic contrast medium thorotrast [55]. Phenytoin exposure was suggested as being associated with the occurrence of lymphoma and multiple myeloma in small series [56, 57]. The lympho-proliferative processes can be mimicked by an acute drug reaction to phenytoin [58-61] and extensive investigations may be needed to distinguish between those two conditions [62, 63]. The occurrence of lymphoma was found to be increased in several epidemiological studies of epilepsy [50, 55], but no association with phenytoin exposure was found. Valproate was suggested experimentally as having a cancer protective effect [64-67]. Large epidemiological studies, however, failed to show a preventive effect of valproate exposure [68, 69]; the numbers of individual cancer types were, however, too small to assess a more specific effect. Newer AEDs have not shown carcinogenic properties in in vitro testing fulfilling regulatory requirement [51], but long term clinical experience is still limited.

Conclusion

Medical treatment of epilepsy is associated with the occurrence of several somatic long term complications. Newer AEDs inducing less metabolic consequences may have a more favourable profile. It is however difficult to disentangle the effects of the treatment from the somatic co-morbidities associated with epilepsy itself. Further, long-term and well designed studies are required to shed more light on these very important aspects.

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Tailored Choice of Antiepileptic Drugs in Patients with Epilepsy

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Summary

Antiepileptic compounds represent the first-line of treatment in patients with epilepsy, allowing seizures' control in about 70% of cases. To date, there are more than 25 registered agents, and a new medication is marketed almost yearly. There are no relevant differences among the existing medications in terms of efficacy against seizures (with the limitation of the "wide" versus "narrow" spectrum of action towards seizures types in specific syndromes), as opposed to the profiles of side effects, which may differ considerably. The aim of this article is to illustrate how the treating physician, taking into account a triad represented by the biological background of the patient, pharmacodynamic and -kinetic properties, as well as clinical experience, may reach a tailored specific choice.

Epileptologie 2015; 32: 70 – 77

Key words: Newer AEDs, comorbidities, depression, anxiety

Die massgeschneiderte Wahl von Antiepileptika bei Epilepsiepatienten

Antiepileptische Mittel stellen die erste Wahl der Epilepsietherapie dar und haben eine Chance von etwa 70%, Anfälle erfolgreich zu kontrollieren. Zurzeit gibt es mehr als 25 Arzneien auf dem Markt, und neue werden fast jährlich eingeführt. Es gibt keinen relevanten Unterschied zwischen den verschiedenen Mitteln punkto Anfallskontrolle (abgesehen vom Konzept von Breit- und Engspektrum in Bezug auf die Anfallstypen in den verschiedenen Syndromen); im Gegensatz dazu haben Antiepileptika zum Teil sehr spezifische erwünschte und unerwünschte Nebenwirkungsprofile. Ziel dieser Arbeit ist es zu zeigen, wie sich der/die verschreibende Neurologe/in für die Wahl einer angepassten Medikation an drei Axen rationell orientieren kann: die biologische Grundlage des Patienten, die pharmakodynamischen und -kinetischen Eigenschaften und die klinische Erfahrung.

Schlüsselwörter: Neuere Antiepileptika, Komorbiditäten, Depression, Ängstlichkeit

Choix adapté des médicaments antiépileptiques auprès des patients avec épilepsie

Les médicaments antiépileptiques représentent la première ligne de traitement de l'épilepsie, permettant un contrôle des crises chez environ 70% des malades. On dispose à ce stade de plus de 25 médicaments, et pratiquement chaque année une nouvelle substance est mise sur le marché. Parmi les différentes substances, il n'existe pratiquement pas de différence majeure au niveau de l'efficacité sur les crises (mis à part le concept de spectre « étroit » ou « large » par rapport aux types de crises des différents syndromes épileptiques), au contraire des profils d'effets désirables et indésirables qui peuvent varier considérablement. Cette contribution a pour but d'illustrer comment le soignant peut s'orienter rationnellement vers un choix spécifique adapté, à l'aide de trois axes principaux: le terrain biologique du malade, les propriétés pharmacodynamiques et -cinétiques, ainsi que l'expérience clinique.

Mots clés : Nouveaux antiépileptiques, comorbidités, dépression, anxiété

La scelta appropriata dei medicamenti antiepilettici nei pazienti con epilessia

I medicamenti antiepilettici rappresentano la prima linea nel trattamento dell'epilessia, permettendo un controllo delle crisi in circa il 70% dei pazienti. Attualmente, sul mercato vi sono più di 25 sostanze, e praticamente ogni anno ne appare una nuova. A dispetto di questa panoplia impressionante, non vi è alcuna differenza significativa in termini di efficacia (a parte il concetto di "largo" spettro e "spettro" ristretto, relativo al tipo di crisi delle differenti sindromi epilettiche), al contrario del profilo degli effetti indesiderati. Questo contributo mira ad illustrare come il curante possa orientarsi razionalmente e fare una scelta adattata al signolo caso, prendendo in considerazione tre assi principali: il terreno biologico del malato, le proprietà farmaco-dinamiche e -cinetiche, e la sua esperienza clinica.

Parole chiave: Nuovi antiepilettici, comorbidità, depressione, ansia

Introduction

Epilepsy has a prevalence of 0.5%-1% in the general population, and thus represents one of the most frequent chronic neurological disorders [1]. It has been recently proposed that an at least putative diagnosis of epilepsy, an important requirement to initiate and orient pharmacologic treatment, relies on the occurrence of at least 2 unprovoked seizures, or one unprovoked seizure occurring along with a supposed risk of recurrence of >60% over 10 years, or a defined epilepsy syndrome [2]. In fact, provoked or isolated seizures do not justify starting an antiepileptic drug (AED): once the underlying cause will be reversed or controlled, the patient won't be exposed to any further risk of seizures.

It has been demonstrated that in patients with an epilepsy diagnosis, any first AED will have a chance of about 50% to control recurrences, a second agent will add an additional 10-15%, and any subsequent medication will lead to seizures control in less than 10% of cases [3-6]. Having this in mind, the specific AED choice will be influenced by three principal axes, reflecting a comprehensive approach: first, the patient's biological background, including epilepsy syndrome, age, co-medications, co-morbidities; second, the AED characteristics, including pharmaco-dynamics and -kinetics; and, third, the experience of the prescribing physician. The latter disposes on a steadily increasing number of antiseizure compounds: this constitutes a potential advantage in terms of choices, but is also undoubtedly related to an increasing challenge regarding the knowledge of the different medications, as the epileptologist becomes more and more a sort of "disguised" (epilepto-)pharmacologist.

This contribution will briefly review the most important AED, which are usually categorized into "classical" and "newer" ones (**Tables 1 and 2**, [7]), as well as into "narrow spectrum" and "wide spectrum" of action (the former are suitable for generalized convulsive and focal seizures only, while the latter also prevent myoclonic and absence seizures). Subsequently, a pragmatic categorization into variable groups tailored to different clinical situations will be attempted. This exercise cannot aim at exhaustiveness, but is intended to provide the reader with some tools that may prove useful in clinical practice. The use of AEDs in the pediatric age is discussed in another contribution in this issue [8].

« Classical » AEDs

Since these agents have been on the market for several decades, their main advantages are a robust clinical experience and the modest costs, as all these substances exist as generics; most are also available in intravenous formulations, an esteemed option in ICU- and emergency settings. Conversely, several pitfalls have to be recognized, such as pharmacokinetic issues (interactions, major protein binding), and medication-specific aspects.

Phenobarbital (PB): has been prescribed for over one century (it was developed by Alfred Hauptmann in Germany just before WWI), and it represents the most used AED worldwide in view of the limited costs, and of the wide spectrum of action (apart from absence seizures). However, its popularity in the Western world is decreasing, due to cognitive and sedation side-effects, and its very long-half-life renders withdrawals very delicate. It is a potent enzyme inducer and has been related to increased risk of osteoporosis and worsening of serum lipid profiles upon long-term use [9].

Phenytoin (PHT): still broadly used in the USA, where it was marketed almost 80 years ago, it is a AED with narrow-spectrum efficacy and all the risks related to enzyme induction [9]. It has a narrow therapeutic window with complicated pharmacokinetics (i.e., a saturation of the catabolism leads to nearly unpredictable variations of serum levels upon slight adjustments of the dosage). Furthermore, it is tightly bound to proteins (>90%), which allows for additional interactions with compounds having similar properties; however, this aspect may be beneficial in patients with severe renal disease, as the bound fraction serves as a "buffer" reducing fluctuations in the free fraction during and after dialysis. Furthermore, gingival hyperplasia, anti-folate properties, cerebellar atrophy, neuropathy, as well as systemic (cardiac arrhythmias) and local reactions (purple glove syndrome) upon intravenous loading, represent further possible side effects.

Carbamazepine (CBZ): this Swiss drug, marketed by Novartis in the Seventies, has also a narrow spectrum of efficacy and is also a mood stabilizer; prescription of long-acting oral forms, which is standard in Europe, allows a reduction of side-effects related to the central nervous system, such as dizziness, ataxia, and diplopia [10]. An issue, especially for elderly people, regards the risk of hyponatremia [11], but to a lower extent as compared to the similarly acting oxcarbazepine (OXC) [12]; while leucopenia appears to be much rarer (it is however forbidden to combine CBZ with clozapine). It is an enzyme inducer, as the two above mentioned compounds. The recommendation by the manufacturer in Switzerland to determine HLA A3101 before treatment initiation (in order to rule out a genetic predisposition to skin reactions) has lead to some decrease of its popularity. While this testing appears of limited clinical use (as recently discussed also among the Swiss League against Epilepsy), determination of HLA B1502 in Asian patients is mandatory.

Valproate (VPA): this agent that was discovered in France to exert antiseizure properties by serendipity, represents the best example of wide spectrum efficacy, as it can be used in any seizure type [13, 14]; moreover it is also a mood stabilizer. It is an enzyme inhibitor, and is also highly bound to proteins. Most important side-effects are weight gain and tremor, while the risk of

Table 1: « older » AED (*= broad spectrum of action)

Year of marketing	Agent (abbreviation)	Mechanism of action
1857	bromide	GABA
1912	phenobarbital (PB)	GABA, GLU, Ca
1938	phenytoin (PHT)	Na
1954	primidone (PRM)	Na, GABA
1960	ethosuximide (ESM)	Ca
1961	diazepam (DZP)*	GABA
1967	valproate (VPA)*	Na, Ca, GABA
1974	carbamazepine (CBZ)	Na

Table 2: « newer » AED (*= broad spectrum of action)

Year of marketing	Agent (abbreviation)	Mechanism of action
1993	felbamate (FBM)	Na, Ca, GLU
1993	vigabatrin (VGB)	GABA
1993	gabapentin (GBP)	Ca, GABA
1995	lamotrigine (LTG)*	Na, Ca
1996	topiramate (TPM)*	Na, Ca, GLU, CA
1997	tiagabine (TGB)	GABA
1998	oxcarbazepine (OXC)	Na
2000	levetiracetam (LEV)*	SV2
2005	pregabalin (PGB)	Ca, Na
2007	zonisamide (ZNS)*	Na, Ca, GLU, CA
2009	lacosamide (LCM)	Na, collapsin
2009	rufinamide (RUF)	Na
2011	retigabine/ezogabine (RTG)	K
2013	perampanel (PER)	AMPA (GLU)

Abbreviations: AMPA = alpha-amino-hydroxy-methylisoazol-proprionate receptor modulation; Ca = calcium channels modulation; CA = carboanhydrase; GABA = gamma-amino-butyric acid receptor modulation; GLU = glutamate ; K = potassium channels modulation; Na = sodium channels modulation; SV2 = synaptic vesicle 2.

fulminant hepatitis or pancreatitis, especially in infants (but much less prevalent in adults), and hyperammonemic encephalopathy (especially in an ICU or emergency setting) may severely impact on the patients. However, the perhaps most relevant aspect is the teratogenic effect, which has been consistently recognized over the last decade, and represents an up to 4-fold risk as compared to other AEDs [15, 16]; furthermore, the IQ of the offspring appears also to be impaired [17, 18].

« Newer » AEDs

There is currently no robust evidence on a better efficacy of these compounds as compared to the « classical » ones [3], however, often, the effectiveness results improved as their tolerability is enhanced. These aspects are detailed in another article of this issue [19]. Here follows a brief overview of the most used and the newest compounds.

Lamotrigine (LTG): has a relatively large spectrum of action, apart from some risk of worsening of myoclonias [20]. A slow titration minimizes the risk of skin reactions, which is particularly feared in co-medication with VPA (leading to inhibition of LTG catabolism). Conversely, it is an "inducible" compound, not only from classical cytochrome enzyme inducers, but also from sexual hormones during pregnancy and even under oral contraceptives (OC) [21]. On the other side, LTG does not impair the efficacy of OC. Due to its favorable tolerability profile and antidepressant properties, it represents an excellent choice for the elderly [22] and for patients with concomitant depression, and has been found to be the most effective option in localization-related epilepsies [23]. Regarding its use in pregnancy, the remarkable safety profile has to be underscored [15].

Topiramate (TPM): also having a large action spectrum (apart from absences), it has been related to neuropsychological impairment, particularly on the verbal side, and to psychiatric issues, especially at higher dosages [24-26]. Furthermore, the association with VPA not only may enhance the risk of hyperammonemia, but also teratogenicity [15, 27]. Its inhibition of the carboanhydrase may enhance the risk of narrow-angle glaucoma, as well as nephrolithiasis. Above a dosage of 200mg/day, induction of OC is possible. Acral tingling sensations are easily countered by potassium intake (dried fruits, juices). Finally, it is a valuable agent in migraine prophylaxis and essential tremor [28], and its weight-lowering properties (also due to the carboanhydrase inhibition) is an interesting characteristic of this compound.

Oxcarbazepine (OXC): this prodrug of the biologically active mono-hydroxy-derivative is a narrow-spectrum AED. It has pharmacodynamic properties comparable to CBZ, but with a reduced risk of central-nervous system related side-effects and allergic cross reaction in about 30%. Since there is no broadly acknowledged genetic testing available to predict this issue, OXC has emerged in the last couple of years as an interesting alternative to CBZ (see above regarding HLA testing in Switzerland), especially since it also has mood stabilizing properties. It has mixed inducing/inhibiting properties on cytochromes, and it may lower the efficacy of the OC. Since it undergoes glucuronization, it may be, conversely, induced by the OC and also by pregnancy. As mentioned, the risk of hyponatremia is higher as compared to carbamazepine [12].

Levetiracetam (LEV): this drug, chemically derived from piracetam, is again a wide-spectrum agent, apart for absences. In view of this consideration, and the lack of relevant drug-drug interactions, it probably is the most frequently used AED in an emergency and ICU setting in the Western world, given its easiness of loading and the intravenous formulation [29-31]. However, over the years, behavioral and psychiatric side-effects have been increasingly recognized, mostly in terms of irritability (often related rather by the family than by the patient) [32, 33]. It is the opinion of several experts that these aspects may limit LEV use on a long-term basis. Sexual hormones lower its bioavailability, and this aspect may result in a sudden loss of seizure control [34, 35], implying a tight therapeutic drug monitoring during pregnancy, in analogy with LTG. Recently, reassuring data on the teratogenic risk have been published [16, 36].

Pregabalin (PGB) (and gabapentin): this agent has a narrow spectrum of action. It acts pharmacodynamically in an almost analogous way as gabapentin (marketed 10 years earlier), but has the advantage, being of higher potency, not to be subject to a saturable resorption in the gastro-intestinal tract, allowing a linear dose/blood level ratio. Also, it does not undergo any hepatic metabolism, a considerable feature regarding pharmacokinetic interactions [37]; this is especially relevant in populations prone to polymedication, such as elderly subjects, or oncologic patients [38]. One of the relatively common side effects is weight gain and edema of the lower extremities, and some sedation. Conversely, it has anxiolytic properties [39], allows preservation of (or even enhances) slow-wave sleep, and is indicated in restless legs syndrome [40]. There are practically no data regarding teratogenicity in humans, but data seem reassuring from studies involving gabapentin [16, 36]. The latter (but not PGB) has some efficacy in the treatment of essential tremor [28].

Zonisamide (ZNS): this is a large-spectrum AED, particularly regarding myoclonia. Having a long half-life, it allows a once daily dose, but titration has to occur slowly to prevent side effects related to the central nervous system, such as dizziness, sedation, and at times headache. Inhibition of the carboanhydrase explains similar profile of side effects and the tendency to weight loss as with TPM. It has also been related to psychiatric side effects (incidence of about 7%), but this effect seems clearly less pronounced than with TPM [41, 42]. ZNS

has been related to a mixed induction/inhibition effect on hepatic enzymes, but the interaction with OC seems of no clinical significance. There are few, but somewhat reassuring data on teratogenicity [16, 36].

Lacosamide (LCM): launched together with the intravenous formulation, it is a narrow-spectrum agent that is increasingly used in emergency and ICU settings [43]. For the moment, its use is only allowed as an add-on; side effects are mostly related to dizziness and sedation, particularly in patients already on sodium-channel blockers [44, 45]. Despite a non-neutral effect on cytochromes, the clinical impact of these interactions appears very limited, including with OC. Data on teratogenicity are lacking so far.

Rufinamide (RUF): this AED has an indication in add-on for tonic seizures; its use is thus relatively infrequent in patients outside specific epileptic encephalopathy syndromes. As every sodium channel blocker, its side-effect profile is characterized by impregnation of the central nervous system; furthermore, its bioavailability may be relatively variable, and its metabolism can be induced or inhibited by concomitant medication [46].

Retigabine (RTG): with a profile of narrow-spectrum action, this compound approved as an add-on was potentially interesting due to its peculiar mechanism of action (targeting potassium channels). Undergoing glucuronidation, its catabolism is expected to be inducible by sex hormones, in analogy with LTG and OXC. The side effects are basically dizziness and sedation, as well as at times psychiatric issues. However, pigmentation of the retina and the skin, still of unknown significance, has recently emerged in a still unclear proportion of treated patients [47]; it is thus generally recommended to screen treated subjects periodically with an ophthalmological examination. Understandably, these issues have greatly reduced the diffusion of RTG.

Perampanel (PER): is the "newborn" of the currently available AED, as it was introduced in 2013. It has a specific action on AMPA receptors, and is marketed as add-on for focal and generalized seizures [48]. Its very long half-life allows a once-daily dosage, but also implies a (very) slow titration. It is also highly bound to proteins. Side effects are. As usual, related to dizziness and sedation; more recently some data on psychiatric and behavioral issues have been reported [49]. While it has enzyme-inducing properties that interfere with the efficacy of OC and perhaps also with some AEDs [50], it may have a – yet formally not demonstrated – interesting efficacy on patients with epilepsy related to cortical dysplasia.

Other compounds

Despite of the availability of more than 25 AEDs, in clinical practice the treatment choice is more or less restricted to the majority of compounds presented above. There are however further drugs. Benzodiazepines, especially clonazepam and clobazam, are used as add-on for difficult to treat epileptic encephalopathies; their use outside these indications (which was relatively popular up to two decades ago) has however decreased recently, in view of concomitant sedation, cognitive issues and, maybe more importantly, habituation. Primidone may be interesting in patients with additional essential tremor, but since it is metabolized to PB to a considerable extent, it is also challenged with similar side effects on the long-term. Ethosuximide is well established in childhood absence epilepsy [14], but does not have any place in the treatment of other seizure forms. Felbamate and vigabatrin may be at times prescribed in patients with Lennox-Gastaut, respectively West-syndrome (especially if related to tuberous scle-

Table 3: monthly costs for a mean daily dose of antiepileptic drugs (2014, CHF)

phenobarbital	100mg	:	4.30
phenytoin	300mg	:	8.80
valproate	1000mg	:	15.60 - 28.50
carbamazepine	800mg	:	19.10 - 21.00
topiramate	100mg	:	49.90 - 59.85
levetiracetam	1000mg	:	48.30 - 73.65
lamotrigine	200mg	:	64.30 - 77.60
oxcarbazepine	1200mg	:	79.50 - 102.80
pregabalin	300mg	:	118.45
gabapentin	1800mg	:	105.5 - 137.40
zonisamide	200mg	:	116.30
lacosamide	200mg	:	158.00
retigabine	600mg	:	136.00
perampanel	6mg	:	251.70
rufinamide	1600mg	:	364.30

Table 4: Examples of antiepileptic treatments according to different clinical settings

(modified after [7])

Situation	Compounds to be favored	Compounds to avoid
Depression	lamotrigine, valproate, carbamazepine, oxcarbazepine	levetiracetam, topiramate
Anxiety	pregabalin, gabapentin	levetiracetam
Insomnia	pregabalin, gabapentin	lamotrigine
Restless legs	pregabalin, clonazepam	
Overweight	topiramate, zonisamide	valproate, carbamazepine, pregabaline
Anorexia	valproate, lamotrigine	topiramate, zonisamide
Migraine	topiramate, valproate	
Neuropathic pain	pregabalin, gabapentin	
Essential tremor	primidone, topiramate, gabapentin	valproate
Women in childbearing age (and pregnancy)	lamotrigine, levetiracetam	valproate (topiramate, phenobarbital)
Oral contraceptive efficacy	pregabalin, gabapentin, levetiracetam, lamotrigine, zonisamide, lacosamide	phenobarbital, phenytoin, carbamazepine, oxcarbazepine, primidone, topiramate if >200mg/day, perampanel
Neuro-oncologic patients	lamotrigine, pregabalin, gabapentin, levetiracetam, lacosamide (valproate)	phenobarbital, phenytoin, carbamazepine, oxcarbazepine, primidone, perampanel
Patients with several comedications	lamotrigine, pregabalin, gabapentin, levetiracetam	phenobarbital, phenytoin, carbamazepine, oxcarbazepine, primidone, perampanel
Osteoporosis	lamotrigine, levetiracetam	phenobarbital, phenytoin, carbamazepine, primodine, valproate
End-stage renal disease	valproate, phenytoin (perampanel)	
Nephrolithiasis		topiramate, zonisamide
Dementia	lamotrigine	phenobarbital, benzodiazepines (phenytoin, valproate)
Patients without insurance	carbamazepine, valproate (phenobarbital)	all newer antiepileptic drugs

rosis), but their use is otherwise limited by their potentially severe adverse reaction profiles (hepato- and myelotoxicity, respectively visual field defects). Finally, tiagabine has been nearly abandoned, as it has a relatively limited efficacy and has been related to induction of non-convulsive status epilepticus.

Practical choices according to different clinical situations

Besides the « three axes » mentioned in the introduction (biological background, pharmacological properties, experience), the choice of the medication has also to take into account financial issues. **Table 3** summarizes the cost of a medium daily dosage of the most important AEDs; despite being clearly less expensive, "classical" compounds have significantly more pharmacodynamic interactions, which may enhance hidden costs related to the expenses of the co-medications or complications. Whether this justifies differences of up to a factor 9 cannot be answered in this overview, but is certainly matter for reflection. Furthermore, the balance between all these aspects is very delicate and changes from patient to patient.

These considerations have indeed to be taken into account in a comprehensive way. The prescribing physician has to be steadily aware of the balance between efficacy and tolerability, in order to allow the optimization of the effectiveness for the treated patients. **Table 4** illustrates some more or less common situations and is intended to represent an orientation for the reader, basically reflecting the opinion of the author. Of relevance, medication choices within an efficacy group are oriented on the one side by potential side effects, and on the other by existing co-morbidities: this latter point highlights how among more than 25 compounds it is still possible to offer some rationale in the selection of medical therapy. In this context, a continuous therapeutic alliance of the epileptologist with the patiens, his/her relatives, and the general practitioner, represents the condition to success, together with a good dose of humility and eagerness to continuously learn from colleagues. It is in fact not unusual to be confronted with patients whose response to medication goes against common knowledge. One example is represented by those few subjects well controlled on phenytoin since several years that simply do not tolerate – in terms of seizure control – any change to any other AED with supposedly fewer side effects. As most fields of medicine, the pharmacological treatment of the epilepsies is definitely not an exact science!

Disclosure:
Dr Rossetti received unrestricted research grants from Sage Therapeutics, UCB Pharma and Eisai over the last 3 years.

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Therapeutic Drug Monitoring of Antiepileptic Drugs in the 21st Century

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Summary

Therapeutic drug monitoring (TDM) is only useful if certain criteria are fulfilled and its limitations are known. Ideal candidate drugs are those with significant inter-individual pharmacokinetic (PK) variability, low intra-individual PK variability and a good correlation between blood level and clinical response or side effects. Although the clinical contribution of TDM for some older antiepileptic drugs (AEDs) is well established (phenytoin, valproic acid, carbamazepine, phenobarbital), its relevance for the newer AEDs is hardly documented, in part because their PK characteristics make them questionable TDM candidates. Nevertheless, a majority of them could theoretically benefit from monitoring under specific situations. We summarize here the strategies proposed regarding TDM for currently available AEDs. Future developments include AEDs measurement in saliva, sharper tailoring of TDM (individual therapeutic intervals), availability of point of care TDM tools, and randomized controlled TDM trials for the newer AEDs.

Epileptologie 2015; 32: 78 – 84

Key words: TDM, AEDs, therapeutic management, pharmacokinetics

Therapeutisches Monitoring der Antiepileptika im 21. Jahrhundert

Die Serumspiegelbestimmung von Medikamenten ist nur sinnvoll, wenn bestimmte Kriterien und Grenzen bekannt sind. Ideale Kandidaten sollten eine signifikante inter-individuelle, aber eine bescheidene intra-individuelle Variabilität und eine gute Korrelation zwischen Spiegeln und biologischer Antwort aufweisen. Obwohl die Serumspiegelbestimmung für ältere Antiepileptika (Phenytoin, Phenobarbital, Vaproat, Carbamazepin) seit langer Zeit breit anerkannt ist, ist die Indikation bezüglich neue Antiepileptika bisher nicht klar bewiesen, dies auch in Hinsicht auf ihre pharmakokinetischen Charakteristika. Nichts desto trotz könnte die Serumkonzentrationsbestimmung theoretisch der Mehrheit der neuen Antiepileptika dienen, zumindest in spezifischen klinischen Lagen. Hier werden die Ansätze vorgestellt, welche für ein Monitoring der Antiepileptika vorgeschlagen werden. Weitere mögliche Entwicklungen sind Speichelanalysen, die Individualisation der therapeutischen Referenzen, die Verfügbarkeit von Automaten in der Nähe der Patienten, als auch randomisierte kontrollierte Studien, um die neuesten Substanzen besser zu erfassen.

Schlüsselwörter: Therapeutisches Monitoring, Antiepileptika, therapeutisches Management, Pharmakokinetik

„Monitoring thérapeutique“ des médicaments antiépileptiques au 21ème siècle

Le suivi pharmacologique ou « monitoring thérapeutique des médicaments » est utile si certains critères sont remplis et ses limites connues. Les médicaments candidats idéaux présentent une variabilité pharmacocinétique interindividuelle significative, une faible variabilité intraindividuelle, et une bonne corrélation entre les concentrations sanguines et la réponse clinique ou les effets secondaires. Bien que la contribution clinique du monitoring pour certains anciens antiépileptiques soit établie (phénytoïne, acide valproïque, carbamazépine, phénobarbital), sa pertinence pour les médicaments plus récents est clairement moins bien documentée, entre autres parce que leurs caractéristiques cinétiques ne les désignent pas comme de bons candidats. Néanmoins, une majorité d’entre eux pourraient théoriquement bénéficier d’un suivi des concentrations dans certaines situations spécifiques. Nous ré-

sumons ici les stratégies proposées concernant le suivi thérapeutique individuel des antiépileptiques actuels. Parmi les évolutions souhaitables figurent le dosage des médicaments dans la salive, une individualisation des concentrations cibles (intervalles thérapeutiques individuels), la disponibilité d'outils de monitoring sur le lieu de soin, et des essais cliniques contrôlés pour le monitoring des antiépileptiques les plus récents.

Mots clés : Monitoring thérapeutique, antiépileptiques, gestion thérapeutique, pharmacocinétique

Monitoring terapeutico dei medicamenti antiepilettici nel 21. secolo

Il controllo farmacologico o "monitoraggio terapeutico dei medicamenti" è utile unicamente se criteri ben determinati e i relativi limiti sono conosciuti. I medicamenti candidati ideali si distinguono per una significativa variabilità farmacocinetica interindivuale, una limitata variabilità intraindividuale, e una correlazione ragionevole tra le concentrazioni sanguigne e la risposta clinica o gli effetti secondari. Se la contribuzione clinica del monitoraggio terapeutico per la maggiorparte dei medicamenti "classici" (fenitoina, valproato, carbamazepina, fenobarbital) è chiaramente riconosciuta da tempo, il ruolo relativo alle sostanze più recenti è molto meno documentato, anche a causa delle loro caratteristiche cinetiche. Ciò nonostante, la maggioranza dei nuovi antiepilettici potrebbe teoricamente beneficiare d'un monitoraggio delle concentrazioni, soprattuto in situazioni particolari. Si riassumono in questo contributo le strategie proposte in questo senso, e tra le evoluzioni all'orizzonte si menzioneranno il dosaggio salivario, un'individualizzazione delle concentrazioni ottimali, e lo sviluppo di macchine di misura portatili che permettano un utilizzo in prossimità del paziente. Infine, è importante sottolineare il bisogno di studi prospettici in questo ambito.

Parole chiave: Monitoring terapeutico, antiepilettici, gestione terapeutica, farmacocinetica

When can drug levels be useful to measure?

The concept of therapeutic drug monitoring (TDM) in blood, and potentially in other biological matrices, is led by the assumption that the pharmacodynamic effects of some drugs correlate better with circulating concentrations than with administered doses. TDM encompasses both drug quantification in a sample and pharmacological interpretation for dosage adjustment.

Measurement requests for antiepileptic drugs (AEDs) and interpretation of the results are usually made by the prescribing physician. His challenges are both to decide appropriately on sampling, and to adjust drug dosage in consequence. Development of high performance analytic technologies now gives potential access to quantification of a large number of drugs. Yet not all are good candidates for TDM. Drugs of choice to allow for reliable monitoring are those that display large inter-individual and low intra-individual pharmacokinetic (PK) variability, and good correlation between blood concentrations and the clinical response or side effects [1].

In defining TDM strategies, three situations can be distinguished. There can be either an indication for systematic TDM on a regular basis, or a need for initial adjustment up to finding the right dose, or solely an indication for "on-need" control when confronted with clinical issues such as treatment resistance, side effects, or drug interactions. In the case of AEDs, systematic TDM is not usually advised, while the two later strategies are more widely used in epilepsy management. Initial adjustment measures are mostly requested in acute situations (emergency settings and after a loading dose), whereas TDM use in chronic follow-up of patients with epilepsy is mostly resorted to on an "on-need" basis. A drug level should only be requested if the result is expected to contribute to the patient's management in answering a specific question, such as "is my patient having seizures despite circulating drug exposure within the generally acknowledged therapeutic interval? If not, how to modify the dosing regimen? Or should the patient be prescribed another drug?", "will this measure help answer doubts about compliance?", "will it help to support or refute clinically suspected toxicity?".

What are the potential pitfalls in drug level interpretation?

Some of these specific questions raised by the physician hoping for a contribution of the drug level in the therapeutic decision may be poorly answered, or the level erroneously interpreted, if potential limitations are not considered. Concentration-effect data and intra-individual variability are often lacking in the early post-marketing years of a drug, leaving the question of the value of TDM unanswered. Exploratory TDM can be deemed of interest in some "on-need" situations, but the reference concentration interval must be considered as tentative, as opposed to a validated therapeutic interval based on available concentration-effect (PK-PD) data for a given indication. A blood level may not help predict future levels with or without dosage modification if the intra-individual variability is significant. The time or mode of blood sampling may lead to biases. For a blood concentration to be representative of exposure at a given dose regimen, it must be sampled ideally just prior to the next dose (trough level), or at least after the distribution phase. There also must be enough time given to reach the steady state, so that no further accumulation (or decrease resulting from autoinduction or following a dosage reduction) is expected.

Depending on the drug, steady state may be reached only after several days to weeks following treatment initiation, dosage modification, or introduction/interruption of an interacting drug. Co-medications should be known when interpreting a drug level, as well as the stage of a possible ongoing pregnancy. Other aspects also of importance, but usually of less concern in outpatient practice, are accurate dose calculation (intravenous administrations), physico-chemical compatibility with nutrients or drugs given through the same line, sampling route (risk for dilution or contamination), and the possible need to correct a total concentration level for dysproteinaemia.

Classical antiepileptic agents: the "good old TDM"

AEDs are historically represented in TDM for a fair number of reasons, notably the complexity and heterogeneity of epilepsy, the lack of biological markers or specific clinical signs aside from frequency of seizures to assess treatment efficacy or toxicity, and the complex pharmacokinetics of early drugs [2].

Yet AEDs aren't a homogenous therapeutic class. **Table 1** [3-20] displays those currently available in Switzerland, according to generation of marketing, with their mean PK characteristics, peculiarities, suggested sampling timeline, reference interval and our estimate of the level of evidence for TDM usefulness.

TDM of first and second generation AEDs will not be discussed in detail. Those of interest for TDM remain phenytoin, valproic acid, carbamazepine and phenobarbital, as they are yet prescribed and their reference interval is defined (narrow interval in particular for phenytoin). Their high inter-individual variability can be explained by a hepatic metabolism mediated by cytochromes P450, subject to genetic polymorphism (non-functional CYP 2C8/9 or 2C19 allelic variants with consequently high blood levels at conventional dosages), and to a significant potential for drug interactions (CYP 2C8/9, 2C19, 3A4, 2E1). Enzyme auto-induction can also contribute to this variability (carbamazepine, phenobarbital, phenytoin), as well as saturable metabolism (phenytoin, valproic acid). Furthermore, if highly protein bound drugs with low hepatic extraction (mostly phenytoin and valproic acid) are given to a patient presenting hypoproteinaemia, a low total drug concentration may falsely encourage the clinician to increase the dose, while the free (biologically active) drug concentration is in fact already in the target range. Quantification of free phenytoin or free valproic acid concentrations may therefore prove useful, on a case to case basis, when a significant discrepancy between the total and free serum concentrations is suspected [21-22]. Eventually, metabolites of AEDs can contribute to toxic effects, such as is the case of neurotoxicity caused by epoxy-10-11 carbamazepine.

Only one randomized controlled trial on TDM usefulness for AEDs could be identified [23-24], which failed to show a significant benefit of TDM over therapeutic decisions without drug monitoring, based on seizure control at 12 months. But this study had several limitations (small number of patients, inclusion restricted to patients naïve from previous AED therapy with indication to initiate monotherapy). The lack of robust randomized controlled studies for classical AEDs TDM is mainly explained by historical problems, and does not jeopardize our appreciation that TDM remains useful for initial dose-finding in phenytoin and phenobarbital therapy, especially in ICU or -emergency settings, while it should be used on a more "on-need" basis in answer to a clinical question (poor control, suspected adverse effect) in valproic acid or carbamazepine use.

Should TDM be generalized to the more recent generation of antiepileptic drugs?

Few sources address third generation AEDs TDM and its relevance. Only one group has estimated TDM usefulness for these drugs, which they considered to range between "possibly useful", "remains to evaluate" or "not useful", based on very limited data (French Society of Pharmacology and Therapeutic (FSPT)).

Some of the third generation AEDs show significant interindividual PK variability, in part due to metabolic interactions or polymorphisms as they are hepatic cytochrome or glucuronidase substrates (**Table 1**). These drugs appear of theoretical interest for TDM: lamotrigine, lacosamide, zonisamide, felbamate, and possibly perampanel and retigabine. However, aside from felbamate [25] and lamotrigine [26-27], a clear correlation between blood level and clinical response or side effects has not yet been demonstrated for these drugs. To our best knowledge, TDM of perampanel and retigabine were never explored to this date.

Other third generation drugs are hypothesized to show low inter-individual variability, or more easily predictable variability, as they are almost exclusively eliminated unchanged through the kidney in proportion to renal function (gabapentin, pregabalin and levetiracetam) or metabolized by cytochrome- or glucuronidase-independent pathways (**Table 1**). Although expected of limited interest for TDM, some may show unexpected higher interindividual PK variability, and "on-need" monitoring may be of use in specific situations such as in children or during pregnancy [28-29]. This explains some discrepancies between available pharmacological characteristics and estimated usefulness of TDM: in fact levetiracetam, topiramate, oxcarbazepine, rufinamide and perhaps gabapentin [30] could yet be explored as TDM candidates (current literature only reports a dose-effect relationship for rufinamide). Low interindividual PK variability has been described for topiramate, but a correlation between blood level and clinical response/side effects has been suggested, TDM being therefore

Table 1: Main pharmacokinetics parameters, metabolism and therapeutic drug monitoring recommandations for antiepileptic drugs

		Clinical Pharmacology			Metabolism						TDM			
					Cytochrome P-450 Isoenzyme Associated with Metabolism			UGT	Other	Active Metabolites				
Generation	DCI	$t_{1/2}$ (h)	Protein Binding (%)	Renal Excretion Unchanged (%)	CYP2C8/9	CYP2C19	CYP3A4/5				Interindividual variability in PK	Suggested sampling timeline (d)	Therapeutic Range (mg/L)	Usefulness for the treatment management
1 (1850-1959)	primidone	3-12	~10	~65	-	-	-	-	-	PEMA Phenobarbital	++	2-4 15-29	5-10 10-40	exploratory
	phenobarbital	70-140	~55	20-25	Substrate Major (auto)Inducer	Substrate (auto)Inducer	Inducer	-	Substrate CYP2E1	No	+++	15-29	10-40	recommended
	phenytoin	Variable, ↑ with ↑ blood concentration	~90	~5	Substrate Inducer	Substrate Inducer	Inducer	Inducer	-	No	+++	6-21	10-20 ff 1-2	recommended
	ethosuccinimide	40-60	0	~20	Substrate	Substrate	Substrate Major	Substrate	Substrate CYP2E1	No	+++	8-12	(40-100)	exploratory
2 (1960-1979)	clobazam	10-30*	85	<1	-	Substrate	Substrate Major	-	Substrate CYP2B6	Yes	+++	2-8	(0.03–0.30)	uncertain
	clonazepam	17-56	86	<1	-	-	Substrate	-	After CYP1A4 Nacetyltransf.	No	++	4-10	0.013-0.070	uncertain
	carbamazepine	8-20*	75	<2	Substrate Inducer	Inducer	Substrate (auto)Inducer	-	-	Yes	+++	2-5	4-12	recommended
	valproate	12-16	~90 saturable, ↓ with ↑ concentration	1-3	Substrate Inhibitor	Substrate	-	Substrate Inhibitor	-	No	+++	2-4	50-100 ff 5-15	recommended
	sulthiame	8-15	29	32	?	Substrate? Inhibitor?	?	?	?	No	?	2-4	(2-10)	uncertain
3 (1980-now)	lacosamide	13	<30	40	?	Substrate Major	?	?	?	No	+	2-3	(10-20)	uncertain
	perampanel	66-90	~95	~2	-	-	Substrate	Substrate	-	No	++	14	?	uncertain
	felbamate	16-22	25	50	Inhibitor	Substrate Inhibitor	Inducer	-	Substrate CYP2E1	No	++	3-5	(30-60)	possibly useful
	retigabine	8-10	~80	20-30	-	-	-	Substrate	-	Yes	+	2	?	uncertain
	oxcarbazepine	2*	60	~1	-	Inhibitor	Inducer	Inducer	Arylketone reductase	Yes	++	2-3	(3-35)	possibly useful
	rufinamide	6-10	~35	~2	-	-	Weak Inducer ?	-	Enzymatic Hydrolysis	No	+	1-2	(30-40)	possibly useful
	vigabatrin	5-8	0	60-80	Inducer ?	Inducer ?	-	-	-	No	+	2	(0.8-36)	uncertain
	topiramate	20-30	9-17	40-70	?	? Inhibitor	?	?	-	No	+	4-5	(5-20)	possibly useful
	gabapentin	5-9	0	~100	-	-	-	-	-	No	+	2	(2-20)	possibly useful
	pregabalin	5-7	0	~100	-	-	-	-	-	No	+	2	?	exploratory
	levetiracetam	6-8	<10	66 + Tubular Reabsorption	-	-	-	-	Enzymatic Hydrolysis	No	+	2	(12-46)	possibly useful
	zonisamide	50-70	40-60 *CA	15-30	-	Substrate	Substrate Major	-	-	No	++	10-15	10-40	possibly useful
	lamotrigine	15-35	55	10	-	-	-	Substrate (auto)Inducer	-	No	++	3-7	3-15	possibly useful

Interindividual variability is quantified by the number of + (+++ for high, + for low)
Therapeutic range between brackets if there is no clear correlation between blood concentration and clinical effect
*Active metabolite with prolonged half-life

Table 2: Antiepileptic drugs for which therapeutic drug monitoring could be contemplated in saliva

		Saliva monitoring	
Generation	DCI	Free fraction	Total serum
1 (1850-1959)	phenytoin	S	C
	ethosuximide	/	S
2 (1960-1979)	clobazam Ndesmethyl-clobazam	S	S
	carbamazepine epoxide CBZ	C	C
	valproic acid	no correlation	no correlation
3 (1980-now)	lacosamide	S	?
	oxcarbazepine 10-HOcarbazepine	?	S
	topiramate	?	S

C: Correlation between blood and saliva levels ($r^2 > 0.8$)
S. Blood and saliva levels are similar (concordance > 0.8)

considered "possibly useful" in this case.

Our estimation of TDM usefulness is based on the above considerations as well as the FSPT publications. We would practically recommend "on-need" TDM for any of the third generation AEDs for which TDM is considered "possibly useful" in **Table 1**. Of note, an isolated measurement of any drug can inform about compliance (if the concentration is undetectable, especially in case of seizure recurrence) or about frank toxicity (markedly high concentration).

Do pregnant women require extra considerations when monitoring AED treatment?

Data and indication to further tailor drug monitoring in certain populations are growing, such as in pregnancy. As evidence for a low teratogenic potential of some new AEDs becomes available [31], pharmacokinetic observations suggest a need for close measurement and adjustment (dose increase) in advanced pregnancy for several of these agents as a consequence of increased renal elimination, accelerated metabolism and body fluid increase. This is notably the case for lamotrigine, for which TDM in pregnancy is part of practice parameters according to the American Academy of Neurology and the American Epilepsy Society [32]. Phenytoin, and to a lesser extent carbamazepine, as well as levetiracetam and oxcarbazepine, are likely to require a dose increase in pregnancy [33]. Scarce data on topiramate suggest that its clearance is also increased in pregnancy, but this drug should be given only in mandatory situations, as its teratogenic potential has been insufficiently studied (with conflicting results).

Do practical tools exist to help with TDM of AEDs?

Various computer applications are already available on the market to help guide in treatment adaptation, however they are not intuitive to use and expensive. There is a real need for a practical bedside tool to help ascertain reliable sampling (when and how to sample?) and level interpretation (how to modify the treatment?). Such software is being developed and should be available within the next couple of years.

Future developments

The concept of TDM is an approach to personalized medicine. But one step ahead, individualized therapeutic intervals for AED may be defined, thus refining the concept of pharmaco-sensitive or -resistant epilepsy [4]. Pharmacodynamic variability within a same type of epilepsy supports the rationale for an individual targeted interval [34]. A patient-specific, relatively narrow concentration interval could be determined based on two blood samplings performed during satisfactory control of seizures, at some distance to take the variability into consideration. Such clinically guided targets might be of particular interest for third generation AEDs, or in the context of polytherapy, where therapeutic intervals are poorly defined. For example, lower target levels have been suggested for the combination of valproic acid and lamotrigine or carbamazepine [35], as a pharmacodynamic interaction has been suggested.

Drug dosing in saliva is another development direction of AEDs TDM [36]. As it can be performed by a non-medically trained person and is less invasive and better accepted. The salivary concentration of some AEDs (**Table 2**) was shown to be proportional ("correlated") to the plasma level in about one third of available AEDs (e.g. phenytoin, carbamazepine), and in a

few cases the blood to saliva ratio nears 1, (e.g. ethosuximide, oxcarbazepine, topiramate and possibly levetiracetam). Similarity between salivary and plasma or serum free levels was documented also for phenytoin.

Conclusion

TDM of AEDs is a tricky exercise, requiring background knowledge on criteria for requesting a measure, standardized sampling times and procedures, and principles as well as potential pitfalls regarding its interpretation. TDM remains recommended for initial adjustment and "on-need" situations for phenytoin and phenobarbital, and on a mere "on-need" basis for valproic acid and carbamazepine. Although best explored for lamotrigine, TDM of the newer AEDs remains of uncertain clinical contribution. It could be of value in particular situations for at least half of these new drugs. Because the real benefit of TDM over therapeutic choice based purely on clinical follow-up remains unknown, it would be acceptable to consider randomizing patients into TDM versus no-TDM clinical trials. Further research is necessary to better define the usefulness of TDM for those increasingly prescribed drugs.

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Multiplex Mass Spectrometry Analysis of Latest-Generation Antiepileptic Drugs: A Clinically Useful Laboratory Tool for Improved Real-Time Patients' Care

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Summary

This article is a brief overview of the recent developments in clinical laboratories opening the way to a facilitated access to real-time Therapeutic Drug Monitoring (TDM) of newer antiepileptic drugs (AEDs). New highly sensitive and selective methods by mass spectrometry make it now possible to analyze arrays of several structurally unrelated AEDs simultaneously. Drug-levels quantification and expert TDM interpretation can be available within 6-24 hours, therefore improving real-time patients' care. Further analytical developments may include the measurement of AEDs in saliva, improving patients' convenience. In the future, TDM might involve miniaturized automates for point-of-care testing in analogy with glucose measurements in patients with diabetes.

Epileptologie 2015; 32: 85 – 89

Keywords: Therapeutic drug monitoring, effectiveness, AEDs

Analyse durch Multiplex Massenspektrometrie bei Antiepileptika der letzten Generation: ein klinisch interessantes Werkzeug für ein verbessertes Patientenmanagement

Dieser Artikel stellt eine Übersicht der neuen Entwicklungen der Laboranalysen dar, welche eine vereinfachte Messung der Plasmaspiegel von den neuen Antiepileptika erlauben. Hochsensitive Leistungen durch Massenspektrometrie können eine rasche Spiegelmessung von strukturell unterschiedlichen Substanzen in der gleichen Zeit gewährleisten; dies führt dazu, dass Resultate innerhalb von 6 - 24h zu Verfügung stehen, mit einer signifikanten Besserung des Patientenmanagements. Eine weitere mögliche Entwicklung betrifft die Benutzung des Speichels anstatt des Blutes als Substrat, mit einem erhöhten Komfort für die Patienten. Schliesslich, sind in der Zukunft miniaturisierte Automaten vorstellbar, die Messungen in unmittelbarer Nähe der Patienten erlauben, in Analogie mit den Glukometern bei diabetischen Patienten.

Schlüsselwörter: Therapeutisches Monitoring, Effektivität, Antiepileptika

Analyses en multiplex des nouveaux médicaments antiépileptiques par spectrométrie de masse : un nouvel outil de laboratoire pour une meilleure prise en charge des patients en temps réel

Cet article est une revue des récents développements réalisés au laboratoire pour l'analyse par spectrométrie de masse des nouveaux médicaments antiépileptiques. L'application de cette technologie permet d'avoir un accès facilité aux mesures de concentrations plasmatiques de médicaments. La sensibilité et la sélectivité des méthodes par spectrométrie de masse en tandem permettent de quantifier en temps réel plusieurs médicaments antiépileptiques simultanément. Les résultats analytiques et leurs interprétations TDM par des experts en pharmacologie clinique sont disponibles dans les 6 à 24 h, ce qui permet d'améliorer la qualité de la prise en charge des patients. Les développements futurs s'orientent sur la mesure des taux d'antiépileptiques dans la salive ce qui va également faciliter le suivi des patients. Dans le futur, il est aussi envisageable de disposer d'automates miniaturisés permettant la mesure des taux d'antiépileptiques au chevet du patient, par analogie à ce qui se fait déjà avec la mesure de la glycémie chez les patients diabétiques.

Mots clés : Suivi Thérapeutique des Médicaments, efficacité, antiépileptiques

Analisi dei nuovi medicamenti antiepilettici per spettrometria di massa multipla: un approccio clinicamente interessante per una migliore gestione dei pazienti

Questo articolo passa in rassegna in modo mirato gli sviluppi recenti concernenti le analisi di laboratorio tese a facilitare il monitoraggio in tempo reale dei tassi plasmatici dei nuovi medicamenti antiepilettici. La spettrometria di massa ad alta sensibilità permette l'analisi contemporanea di diverse sostanze senza relazione strutturale reciproca. La quantificazione delle concentrazioni e l'intepretazione farmacologica sono così disponibili nelle 6 - 24 ore, con un indubbio impatto favorevole sulla gestione del paziente. Gli sviluppi futuri dovrebbero permettere l'analisi della saliva al posto del sangue, nonché la possibilità d'utilizzare apparecchi miniaturizzati per un monitoraggio "al letto del malato", in analogia con i glucometri diffusi da anni presso i pazienti con diabete.

Parole chiave: Monitoring terapeutico, effettività, antiepilettici.

Therapeutic Drug Monitoring (TDM) for antiepileptic drugs (AEDs)

It has been established over the last decades that the therapeutic use of AEDs could be optimized by an individualization of their dosage, based on blood (plasma) concentrations measurement. This is done via Therapeutic Drug Monitoring (TDM), which represents current practice for the "classical" antiepileptic drugs, namely phenytoin, phenobarbital, carbamazepine and valproate, all of them being characterized by relatively narrow therapeutic indexes and significant inter-individual pharmacokinetic variability. These last years, a large number of "newer" AEDs, belonging to various unrelated chemical classes, have emerged [1], and additional agents are at a late stage of development. This continuously growing armamentarium constitutes a formidable wealth of new therapeutic options for patients with epilepsy. While these last generation drugs are characterized by more favorable safety and tolerability profiles as compared to "classical" AEDs, a number of issues remain, including unpredictable pharmacokinetics influenced notably by patients' patho-physiological conditions, such as renal or hepatic function fluctuations or alterations, especially in special patient sub-groups (elderly, pregnancy, etc).

If TDM is considered for the efficient clinical use of the latest-generation AEDs, information on plasma levels must be available to the treating clinician within a few hours for dose adjustment. Rapid, sensitive and selective laboratory methods are therefore needed for an efficient TDM.

New powerful clinical laboratory methods

A comprehensive review has been recently published on the advances of both commercial and laboratory-developed AEDs testing [1]. Over the last 30 years, plasma levels of the most common AEDs, especially the "classical" generation, have been measured in clinical laboratories by gas chromatography [2] or by high performance liquid chromatography (HPLC) [3-5], as well as by immunoassays [6-8]. However, immunoassays and HPLC methods that have been mostly used so far have several recognized limitations. Immunoassays are known not to be specific to the parent drug only but also capture the signal of structurally related metabolites. HPLC methods with UV detection are probably more specific but still remain vulnerable to components that may co-elute chromatographically with the target analyte. Increased selectivity may be achieved by slowing the chromatographic gradient program, resulting however in prolonged analytical times and Turn-Around-Times (TAT). In addition, immunoassays are restricted to the measurement of one single drug at a time.

All these limitations have been circumvented by the recent development of high- or ultra-performance Liquid Chromatography coupled to tandem Mass Spectrometry (LC-MS/MS) that qualifies for the rapid, highly specific analysis of arrays of structurally unrelated AEDs simultaneously. However, it is only recently that this technological advance has been formally exploited for the TDM of latest-generation AEDs. Recent assays imply most generally the measurement by LC-MS/MS of a single drug (including, but not restricted to, lacosamide [9]; lamotrigine [10, 11]; zonisamide [12]; levetiracetam [13] and its metabolite [14]; topiramate [15-17]) determined in plasma, and for some of them, in the saliva [18] and even in dried blood spots [19]. Recently, assays by HPLC or UPLC-MS/MS have been proposed for the determination of several compounds simultaneously [20-22], even up to as many as 22 AEDs (including "classical" and "newer" ones) [23]. However, this method used only a limited number of [21] or a single [22] or no [20, 23] stable isotopically-labelled internal standards that are needed to fully compensate for the potential deleterious influence of plasma matrix variability. Since highly variable plasma or serum matrices do occur in special conditions, such as pregnancy and pediatric patients, or in the heterogeneous patients' populations in the ICU or emergency settings, this point is relevant. These patients are frequently polymedicated and/or characterized by significant alteration of renal and hepatic function that likely affects blood and plasma matrix composition.

Last year an assay for six AEDs by UPLC-MS/MS was published, which included the use of stable, isotopically labeled internal standards for all drugs [24]. This landmark publication was the first report of a comprehensively validated assay for the most frequently used

last generation AEDs. In general, short analytical runs, typically lasting less than 10 minutes, are required to provide clinicians in a timely manner with plasma levels results and TDM interpretations.

A comprehensive analytical service for real time TDM of last generation AEDs

Following a request arising from our epileptologists, we have developed in our laboratory an ultra-performance liquid chromatography-tandem mass spectrometry method (UPLC-MS/MS) requiring as low as 100 µL of plasma (or serum) for simultaneous quantification within 7 min of the five frequently used AEDs, namely levetiracetam, zonisamide, lacosamide, lamotrigine and topiramate.

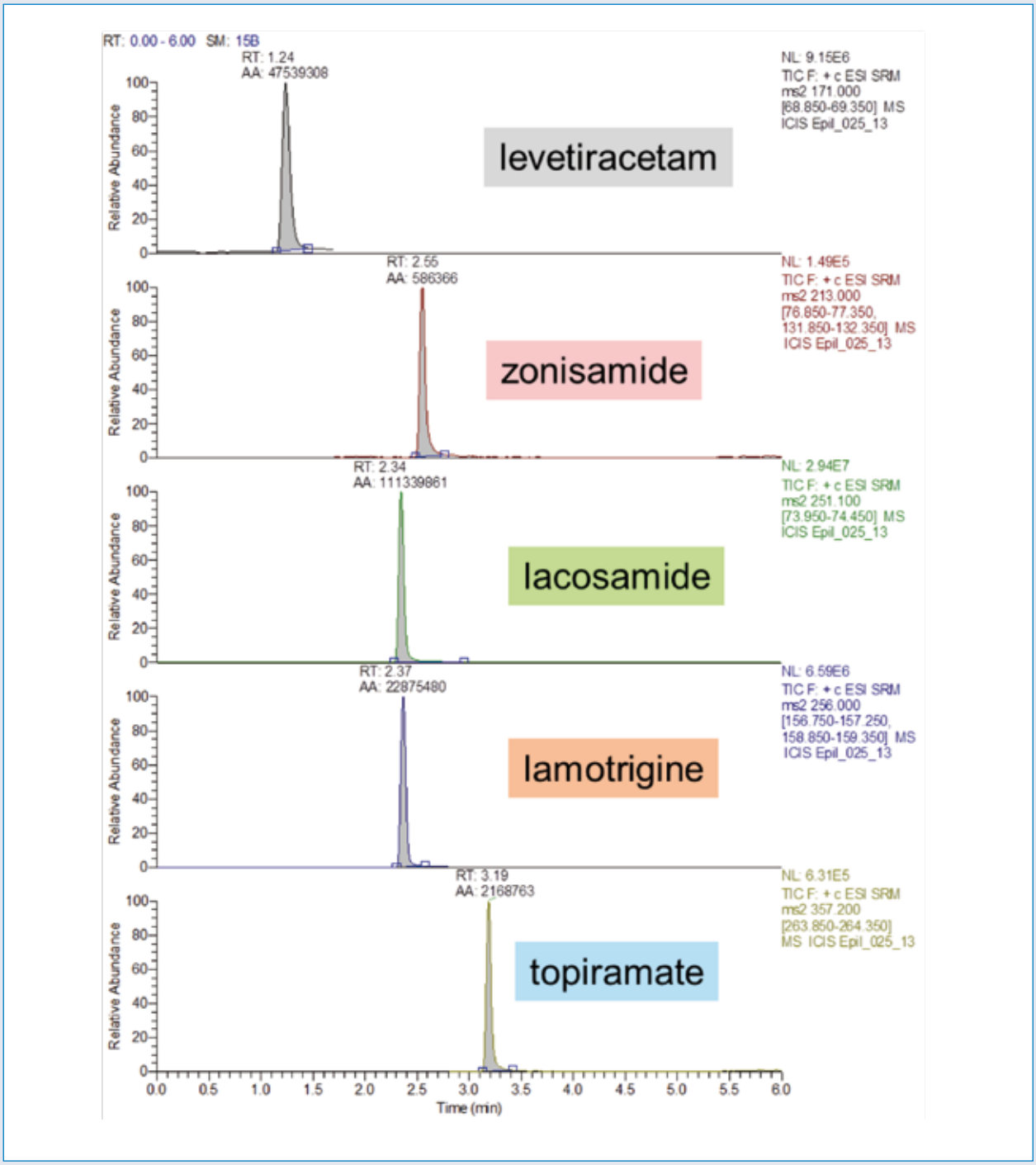

Figure 1: Multiplex analysis by ultra-performance liquid chromatography-tandem mass spectrometry method (UPLC-MS/MS) of "newer" antiepileptic agents. Chromatographic profiles of a plasma calibration sample at 10 µg/ml.

An example of the chromatographic profile of our multiplex assay is shown in **Figure 1**. Each AED is monitored using its specific *m/z* mass spectrometry transition (i.e. the chemical footprint of the molecule). When the drug is eluted from the chromatographic column, a signal presents as a peak, whose intensity is a function of the concentration in the plasma. Each drug signal is normalized with its corresponding stable, isotopically-labelled internal standards added to the patient's sample for correcting potential matrix effects (i.e. levetiracetam-d6, zonisamide-d4,^{15}N, lacosamide-^{13}C,d3, lamotrigine-^{13}C7^{15}N, and topiramate-d12 (not shown in **Figure 1**). The calibration is established within the clinically relevant range of concentration, generally comprised between 0.1 µg/ml (limit of quantification) and 50 µg/ml. This multiplex assay using a simplified extraction procedure followed by simultaneous quantification of multiple AEDs is highly efficient for rapidly providing TDM results, allowing real-time processing of blood samples from patients receiving either different single-drug or combined regimens. Of note, we participate in an external quality program for AEDs where our laboratory performs very well (100 % correct results in the last 4 rounds).

One of the major advantages of mass spectrometry assays is their flexibility to adapt them, if necessary also integrating the analysis of newer drugs (e.g., perampanel). Thus, the list of agents included in the multiplex assay is likely to evolve according to the new therapeutic options and recommendations that may emerge in the future.

Practical considerations

Fortunately, the current five AEDs included in our assay have been shown to be stable for at least 3 days in whole blood at +4°C and at room temperature [24], which is particularly convenient when considering sending samples by post throughout Switzerland, as delivery time to the laboratory for fast post (*"courrier A"*) is 24 - 48h (opening days). Blood samples (2.7 ml) containing citrate as anticoagulant is preferred (for example, in Monovettes®, Sarstedt, Nümbrecht, Germany), but serum or plasma EDTA are also acceptable. It is recommended to send the whole blood samples by post in protective plastic tubes for minimizing the risk of blood spilling. Besides, the blood sample needs to be accompanied with all information required for an expert TDM interpretation: this information has to be carefully recorded in dedicated TDM request forms, an example thereof can be downloaded from the Division of Clinical Pharmacology website [25].

Perspective

Less invasive methods for "newer" AEDs monitoring are needed to improve clinical care and patients' convenience, especially in an emergency and ICU environment, but also in an out-patient setting. The drug determination in saliva (i.e. oral fluid) that reflects the free (unbound, pharmacologically active) concentration in plasma constitutes an attractive option, but requires the high sensitivity provided by UPLC-MS/MS technology notably for drugs highly bound to circulating plasma proteins (i.e. with low free fractions). Nevertheless, before saliva can be considered as a suitable fluid for TDM implementation on large-scale, the strength of the correlation between saliva and free and total plasma levels should be evaluated; this is the subject of an ongoing prospective observational study in our Hospital.

In the future, the current reliance of TDM on large central laboratories equipped with costly LC-MS/MS apparatus will possibly be challenged by the development of miniaturized devices designed for point-of-care testing. Innovative « lab-on-chip » technologies, coupled with intelligent computer-assisted interpretation of concentration results, might indeed revolutionize the practice of TDM and contribute to extend it largely to everyday patients' care. It is highly conceivable that this approach will be applied to blood as well as saliva samples, provided its accuracy, precision and clinical usefulness have been rigorously established. We are currently participating in research efforts aimed at establishing such a concept [26].

Conclusion

This robust, sensitive and selective multiplex UPLC-MS/MS method allows the accurate and precise quantification of plasma concentrations of five of the most frequently used "newer" AEDs simultaneously, with high throughput, i.e. with a single plasma extraction and analytical runs lasting a few minutes. This new method is characterized by an excellent extraction yield and by the use of isotopically-labeled internal standards that can confidently compensate for any matrix effect variability. This approach allows providing TDM service with rapid turn-around time. The developed assay is also flexible, being able to evolve by also including, after slight adjustments, any new drugs for the treatment and prevention of epilepsy. This new method providing analytical results within 6 to 24h offers an efficient tool for a tailored drug dosing and optimization of efficacy and safety in patients with epilepsy.

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A Review of Cerebral Electromagnetic Infraslow Activity

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Summary

Digital EEG systems have a low frequency filter of at least 0.1 Hz. This allows viewing of ictal onset baseline shifts, formerly referred to as "DC shifts." They are most pronounced with "electrodecremental" seizure onsets and have localizing value. In seizures which start with rhythmic buildup pre-existing infraslow activity (ISA; 0.01-0.1 Hz) increases in amplitude, which is at times quite wide-spread. Maximum amplitude (mV) is usually reached during the transition from partial to tonic-clonic seizures. Brief partial seizures may not be accompanied by ISA increase. But if prolonged seizures (>30 seconds) fail to show ictal onset ISA increase, it is likely that the available electrodes have not sampled the critical area(s) of ictogenesis because of ISA's small electromagnetic field. ISA is a normal component of the EEG/MEG frequency spectrum and in long-term intracranial as well as scalp recordings intermittent interictal focal buildup from lower amplitude background activity can be seen.

The smaller electromagnetic ISA field leads to a better delineation of the epileptogenic zone(s) and also may have prognostic value. Long term postoperative follow-up studies of patients, which take ISA information into account, should be undertaken. MEG studies of ISA are currently in progress and so is ISA relationship to mental activity. With a DC-EEG system wave forms extending beyond 20 minutes were seen in normal persons, but possible technical artifacts have not yet been ruled out.

ISA is an important aspect of the electromagnetic spectrum and further investigations by clinicians as well as basic scientists should be undertaken.

Epileptologie 2015; 32: 90 – 107

Key words: Epilepsy, EEG, infraslow, MEG, DC, glia

Eine Übersicht über langsamste elektromagnetische Aktivität des Grosshirns

Digitale EEG-Geräte haben einen unteren Frequenzfilter zwischen 0,016- 0,1 Hz. Dadurch kann man jetzt in archivierten EEGs das untersuchen, was als "DC shift" bei einem Anfallsbeginn bezeichnet wurde. Diese "shifts" sind bei elektrodekrementalem Anfallsbeginn bestens sichtbar und lokalisatorisch wertvoll. Bei rhythmischem Anfallsbeginn nimmt die normal vorhandene infralangsame Aktivität (infraslow activity [ISA], 0,01-0,1 Hz) fokal zu. Das kann manchmal vor dem Auftreten von Veränderungen im 0,5-70 Hz-Bereich gesehen werden. Die höchsten Amplituden (mV) werden bei einem Übergang von fokalen zu tonisch-klonischen Anfällen erreicht. Bei kurzen Anfällen kann die ISA-Zunahme fehlen. Wenn sie aber bei längeren fokalen Anfällen (>30 Sekunden) nicht eintritt, wurde wahrscheinlich der iktogene Hirnbereich wegen der geringeren ISA-Feldausbreitung von den vorhandenen Elektroden nicht erfasst. Bei Langzeituntersuchungen können intermittierende fokale ISA-Zunahmen sowohl im intrakraniellen als auch im Oberflächen-EEG gesehen werden.

Die geringere ISA-Feldverteilung erlaubt eine bessere Abgrenzung der epileptogenen Zone(n). Sie könnte auch prognostisch wertvoll sein, und es sollten postoperative langzeitige Nachuntersuchungen von Epilepsiepatienten, unter Berücksichtigung von ISA, durchgeführt werden. ISA-Vergleiche zwischen EEG und MEG werden derzeit ebenso wie psychophysiologische Untersuchungen durchgeführt. Mittels eines DC-EEG-Gerätes wurden bei gesunden Probanden Wellenlängen von mehr als 20 Minuten beobachtet, technische Artefakte konnten aber noch nicht ausgeschlossen werden.

Zusammenfassend kann festgestellt werden, dass ISA ein wichtiges Element des elektromagnetischen Spektrums darstellt, und dass weitere Untersuchungen sowohl von Klinikern als auch Grundlagenforschern vorgenommen werden sollten.

Schlüsselwörter: Epilepsie, EEG, infralangsam, MEG, DC, glia

Un aperçu de l'activité électromagnétique la plus lente du cerveau

Les EEG numériques disposent d'un filtre de basses fréquences entre 0,016 et 0,1 Hz. Ainsi, il est désormais possible d'examiner dans les EEG archivés ce que l'on appelle les « DC shifts », des déflexions de courant survenant en début de crise. Ces « shifts » sont parfaitement visibles lors d'un début de crise électrodécrémental et précieux pour la localisation. Lors d'un début de crise rythmique, l'activité lente à très basses fréquences (infraslow activity [ISA], 0,01-=0,1 Hz) norma-

lement présente augmente de manière focale. Parfois, cela peut être perçu avant la survenue de modifications dans la plage 0,5-70 Hz. Les plus grandes amplitudes (mV) sont atteintes lors d'un passage d'une crise focale à une crise tonico-clonique. L'augmentation de l'ISA peut ne pas se produire lors des crises courtes. Cependant, si elle ne survient pas lors de crises focales plus longues (>30 secondes), la dimension ictogène du cerveau n'a vraisemblablement pas été enregistrée par les électrodes disponibles en raison de la propagation plus faible du champ de l'ISA. Lors des examens de longue durée, des augmentations d'ISA focales intermittentes ont pu être observées aussi bien en intracrânien que sur l'EEG de surface.

La plus faible propagation du champ de l'ISA permet une meilleure délimitation de la (des) zone(s) épileptogène(s). Elle pourrait également être très utile pour le pronostic et il faudrait procéder à des examens de suivi postopératoires à long terme chez les patients épileptiques, en prenant en compte l'ISA. Des comparaisons d'ISA entre EEG et MEG sont actuellement réalisées tout comme des examens psychophysiologiques. Des longueurs d'ondes de plus de 20 minutes ont été observées à l'aide d'un EEG DC chez des sujets sains, des artefacts techniques ne pouvaient cependant pas encore être exclus.

En résumé, on constate que l'ISA représente un élément important du spectre électromagnétique et que d'autres examens doivent être entrepris aussi bien par des cliniciens que par des chercheurs fondamentalistes.

Mots clés : Epilepsie, EEG, infraslow, MEG, DC, glie

The purpose of this review is to acquaint the readership with this still under-investigated frequency band of the brain's electromagnetic spectrum. This is all the more urgent, since the data exist, to varying extents, in EEG laboratories around the world and can be readily accessed by "mouse clicks." It will be shown that infraslow activity (ISA; <0.1 Hz) can provide valuable information for the clinician as well as the basic scientist and that its assessment should be included especially when long-term monitoring for pre-surgical evaluation is performed.

Historical Introduction

DC shifts

In the middle of the past century a great deal of experimental work was carried out utilizing DC amplifiers, but its significance in regard to current work tends not to be fully appreciated. Keeping in mind the purpose of "Epileptologie", I shall only present some key aspects of papers that have direct relevance to modern studies.

The consensus of all investigators was that the onset of induced seizures (regardless of means) was always associated with a negative shift from the previously stable baseline, which frequently preceded the appearance of electrical changes in the conventional frequency range. In most seizures, the shift subsequently became positive and the seizures terminated when the shift returned to negativity.

Most of the studies limited themselves to exploring portions of the lateral surface of the cerebrum but Vanasupa, Goldring and O'Leary, who reported on the effects of a variety of systemically administered convulsant agents in rabbits, included the cerebellum. Marked differential effects, depending on the drug that was used, were observed at the beginning of the seizure, but they subsequently tended to coalesce toward the previously mentioned sequence [1]. The importance of the paper resides in demonstrating the differential effect of drugs on cerebrum and cerebellum. The latter is currently largely omitted from the studies of ictal activity, although its marked participation in some seizures is well documented.

Apart from chemically induced seizures, Goldring and O'Leary investigated the direct and recruiting responses from thalamic stimulation and noted that with midline stimulation each recruiting spike was followed by slower positive - negative waves. This phenomenon was more pronounced in the rabbit than in the cat. A variety of drugs were then used in order to determine their effect on this phenomenon. It was observed that not all depressant agents had the same effect. They also noted that these slow changes were less pronounced when lateral relay nuclei of the thalamus were stimulated. If intense repetitive stimulation did lead to cortical paroxysms, the baseline shifted into the positive direction, while it always shifted negative with midline stimuli [2]. I am bringing this paper to attention because the thalamus is again under investigation for infraslow activity [3, 4].

Johnson et al. expanded previous studies [1] on methionine sulfoximine seizures. Acute as well as chronic experiments were performed. In the acute situation recordings were obtained from the cerebral cortex and a depth micropipette recorded unit activity. For chronic recordings only cortical activity was studied in relation to the behavior of the rabbit. When the negative shift occurred on the surface it was mirrored by a positive one in the depth. Occasionally depth positivity preceded surface negativity. "During this phase there may be a decrease in unit discharge, but the striking change in unit behavior appears as the depth record shifts in the negative direction. Then a burst of unit activity occurs." There was, however, some variation. The initial depth positivity was at times missing and the first shift was negative. Unit firing rate could also be increased, steady, or decreased, testifying to the complexity of the event. In the chronic preparations the shifts usually occurred after other signs of seizure activity were already

present. They were much smaller in amplitude and considerably less frequent than in the acute experiments. When present, they accompanied tonic-clonic seizures rather than unilateral partial ones [5]. While the depth results are of interest in regard to current depth-electrode studies, which will be mentioned later, they failed to provide information on the approximate cortical layer they were recorded from.

A review article limited to DC changes in seizures was published by O'Leary and Goldring in 1959 [6]. It was expanded in 1964 to cover all aspects of DC changes under a variety of conditions as well as infraslow activity [7]. In regard to the latter the authors mentioned the work of Aladjhalova and co-workers, which will be reported on separately.

Caspers and Simmich, working with rats, added important information in regard to metrazol seizures [8]. The main finding was that a long-lasting negative shift developed within 30-60 seconds, passed a flat peak between the fifth and tenth minute, and then returned gradually to the baseline within half an hour. Paroxysmal spike activity was superimposed upon an additional negative shift and there was no subsequent positivity. But with repeated doses a negative positive sequence was observed. The important finding for our time was the observation that not only respiration increased but also cerebral blood flow. Although the authors did not discuss this aspect in detail, Figure 1 is instructive. The time window appears to be about 30 minutes and within seconds after drug administration one can see the beginning of the negative shift accompanied by some increase in respiration. A minor increase in blood flow can be seen after about 1 minute which lasts about 4 minutes. This is followed by another small peak of about 3 minutes duration and the major change which keeps increasing for the duration of the picture starts at about 10 minutes after the injection. If one were to extrapolate these data to the clinical situation, they suggest that since major ictal fMRI changes are likely to be delayed in relation to the electrical onset they will represent the spread of ictal activity rather than the area of onset.

While these studies dealt largely with a single electrode pair, Gumnit and co-workers concentrated on ascertaining the electrical field of local DC changes. Initially Gumnit studied the effects of sound on the DC response in cats and noted that the DC shifts were not only limited to auditory cortex but also had a very discrete electrical field. A shift observed at one point could be absent at a distance of 3 mm. The shifts arose suddenly with the onset of the stimulus and terminated equally abruptly at its end. In most experiments the electrodes were placed on the dura, but in some instances a depth electrode was inserted. On basis of the latter it was estimated that the shifts were generated within the upper or the middle third of the cortex [9].

Gumnit then expanded his studies to focal seizure generation via local penicillin application to the cortex. These revealed that sustained discharges were associated with an abrupt negative shift at the center of the field. In the periphery the onset was more gradual and became positive. The total radius was about 1 cm. The peak of the negative shift "was then observed to 'march' across the cortex at a speed of 5-20 mm/min". After the paroxysm and during electrical silence "the DC level decayed to the previous baseline over a period 3-30 seconds". Interictal sharp waves had a similar distribution: monophasic negative at the center; briefer, polyphasic and usually predominantly positive at the periphery. Sharp wave activity appeared in the opposite hemisphere within 5-30 minutes. Once established, the center of the mirror field showed "only small negative shifts or, rarely, was isopotential". Positive shifts were relatively more prominent in the periphery of the mirror field than in that of the primary area and could even be larger than the central negative shift [10]. This information is likely to be important in regard to currently seen ictal onset shifts which may have negative or positive polarities.

Since in the previous study a depth recording had shown no reversal of polarity within the cortex, a detailed investigation was then performed in 45 cats. The focus was again produced by penicillin and the area was explored to a depth of 4 mm below the cortical surface. There was no phase reversal and the largest shift was observed at 1 mm, which was regarded as having represented layer V. "In the periphery of the focus, where positive shifts can be recorded from the surface, the shifts reverse sign in the upper 300-500 µ of the cortex, and the maximum negativity also was located in layer V [11]."

All of these studies dealt with animals and there were only three reports on DC shifts in patients with epilepsy. They dealt with absence seizures and demonstrated negative ictal shifts [12-14]. In as much as these were not seen when AC amplifiers with a low frequency filter of 0.5 Hz were used it was felt that DC amplifiers were required to record slower frequencies. This statement, although reasonable at the time, had an unfortunate impact when digital EEG technology and improved amplifiers became available for clinical use.

Infraslow activity

As mentioned above, O'Leary and Goldring [7] had drawn attention to the work by Aladjhalova (also spelled Aladzhalova and Aladjalova in PubMed) who was probably the first to describe the phenomenon in a series of papers between 1954 and 1978. Unfortunately nearly all of the publications were in Russian and no abstracts are available for this time period. Two articles did appear, however, in English translation. Although the 1957 article was published in "Nature" it did not show up among the references in the O'Leary-Goldring review, which may well have stemmed from the prob-

lem when Cyrillic characters are made to fit the Latin alphabet. Nevertheless it appears that O'Leary and Goldring had access to the information cited in their two Russian references and since this is the first information on the phenomenon under discussion I shall quote the relevant paragraphs in their entirety.

There is a segment of spontaneous brain activity which occurs in both man and animals at the unusually slow frequency of 0.5- 8/minute. Aladjhalova has also observed considerably slower potential oscillations which do not develop spontaneously but instead appear 20 to 30 minutes after intense sensory stimulation. These may persist for several hours and are called "horary swings".

Not all brain parts yield slow waves with the dimensions of infraslow rhythmic oscillations of potential (ISOP). For example they occur in the hypothalamus and cerebral cortex but not in brain-stem reticular formation, central gray matter, or thalamus. However, such infraslow activity can be elicited in central gray by the intravenous injection of epinephrine, and acetylcholine will cause it to appear in the reticular formation. Curiously, ISOP waves are not observed throughout the thickness of the cerebral cortex, but are confined to the superficial dendritic lamina and the cortical depths where the cell bodies of the pyramidal neurons predominate.

According to Aladjhalova, ISOP waves are depressed by narcosis, metabolic aberrations, and brain trauma and exaggerated by repeated sensory stimulation and by systemic administration of certain hormones and pharmacologic substances. The exaggeration of ISOP by repetitive sensory stimulation occurs after an interval of 20 to 40 minutes, the change not being limited to the specific projection zone of the sensory receptor but appearing in other regions of cortex as well. With fluctuations in ISOP concurrent changes occur in the spontaneous rhythm of the usual electrocorticogram. For example, at the maximum infraslow wave activity the usual electrocorticogram shows higher amplitude and slower frequency. It is also important that spontaneous infraslow activity appears in neuronally isolated cortical slabs where it can be modified by stimulation of the hypothalamus and by intravenous injection of hormonal substances.

Aladjhalova views ISOP as dependent on humoral factors and not related to the immediate effects of nervous excitation. She says: "Electrical phenomena of infraslow order are defined by processes which are connected with a protracted change of excitatory properties. They do not reflect the immediate changes of excitation although inseparably related to them. The excitability of the cortical neuron depends not only upon action on it of impulses from other excited elements, but also upon non-impulse processes which are caused by humoral factors and influence the "metabolic tonus" of nervous tissue." Her studies are intriguing and may represent an important contribution toward the understanding of brain functioning. However, appraisal of the ultimate impact must await additional investigations and confirmation by others.

In as much as the above quoted review did not contain technical details I searched PubMed for "Aladjhalova" and found one English language article, "Hypnosis in Man and Very Slow Potentials". The paper is written in narrative style and does not contain figures, which would allow one to check the validity of the statements. The most important technical details were a) that DC amplifiers were used and the frequencies below 0.5 Hz were considered; b) that three sets of frontal, temporal and occipital electrodes were employed in bipolar connections on both hemispheres. Fifteen women patients with "neurosis" undergoing hypnotherapy were investigated during 50 sessions. Infraslow changes, called Very Slow Brain Potentials (VSBP) in this paper, were observed. In the waking state "second" potentials (quotation marks are in the original text) "with a period (T) of 7-10 seconds and an amplitude of 0.1 mV predominated all regions of the brain", although the periods differed somewhat in the various regions. At the beginning of the session "with somnolence ... homogeneous slow waves (T=30-40 sec) resembling the waves during drowsiness, spread over the hemispheres. Moreover, during somnolence, in some regions of the brain, potentials with a period of several minutes (T=2-4 min, A=0.5-0.8 mV), characteristic of changes in the level of wakefulness appeared. These phenomena were observed more frequently when a particularly deep hypnotic state was reached" [15].

The paper, which was published in "Nature" [16], did not appear in PubMed under the mentioned spelling of the author's name but it was cited by Hughes' et al. in their study of "Infraslow oscillations (<0.1 Hz) in thalamic nuclei" [3]. PubMed lists it under Aladjalova and is the only one that shows up with this spelling of the name. In the text Hughes et al. wrote:

"ISOs [Infraslow Oscillations] were first described in the animal brain in a study published over 50 years ago detailing gross electrophysiological recordings from the neocortex of rabbits (Aladjalova 1957). In this seminal study two main oscillations were described having periodicities of around 10 and 30-90 seconds, respectively (Figure 2A). These oscillations were present at distinct cortical sites, were not synchronized between hemispheres and, in the case of the faster rhythm, could group periods of more conventional EEG oscillations."

Aladjalova's paper in "Nature" also mentioned that two silver electrodes were implanted in the frontal and two in the occipital area. Differences in frequencies and amplitudes were noted not only between these brain areas when a variety of stimuli, as well as drugs, were administered but a non-polarizable microelectrode showed in a curarized animal differences between surface and the depth with slowest and highest amplitude in the superficial layers (I-IV) of the sensory cortex. During sleep, spindle bursts were seen riding on the

ascending slope and near the top of slow waves. Aladjalova concluded that, "Many other aspects of the infraslow rhythmical potential change also indicate that metabolic changes should be considered". This is also the current explanation of the phenomenon, and the phase relationship of sleep K complexes to infraslow was confirmed in humans by Vanhatalo et al. in 2004 [17], who had been unaware of the Russian studies.

Modern studies

The modern era of ISA investigations in epilepsy patients can be dated to the seminal studies by Ikeda et al. Initially the authors reported on 3 patients with subdural implanted electrodes recorded on a Nihon Kohden (NK) EEG system that has a low frequency filter of 0.016 Hz [18]. Subsequently the patient series was expanded to 6 intracranial recorded patients, 3 additional ones had only scalp recordings [19]. "DC shifts" were present in 85% of 89 seizures recorded from subdural electrodes.

"[These] were localized to one or two electrodes at which the conventional initial ictal EEG change was also observed. They were closely accompanied by the electrodecremental pattern in all patients except for one in whom 1 Hz rhythmic activity was superimposed on clear negative slow shifts. ... Scalp-recorded ictal slow shifts were observed in 23% of all the recorded seizures (60 seizures) among the three patients. They were, like the subdural recorded ones, mainly surface-negative in polarity, closely related to the electrodecremental pattern and consistent in their location."

In addition, it was noted that the shifts were mainly observed in "clinically intense seizures, while no slow shifts were observed in small seizures". In the discussion the low sensitivity of scalp recordings was explained by the small electrical field observed in the intracranial records and that scalp-recordings require activation of at least 6 cm^2 to be detectable. The authors also pointed out that they had avoided studying patients with temporal lobe seizures since these usually are characterized by rhythmic onset of 4-7 Hz activity and ictal automatisms, especially chewing motions would obscure shifts even if they were present. Nevertheless, they felt that reliable recordings might be obtained if movement artifact could be overcome. The authors concluded that, "at least subdural-recorded ictal slow shifts are clinically useful before epilepsy surgery to delineate more specifically an epileptogenic area as well as to further confirm the conventional initial ictal EEG change, and the scalp-recorded slow shifts also have high specificity although their low sensitivity is to be taken into account".

I have discussed this paper in *extenso*, not only because it was the first modern study but because, with one exception, the information has been replicated by all subsequent authors. The term "DC shift", which as the authors admitted was not quite appropriate because AC amplifiers were used, has subsequently led to some confusion and obscured the fundamental fact that DC amplifiers are not needed to demonstrate the phenomenon. This depends only on the low frequency filter of a given EEG system. Since the low frequency filter of most digital systems is at least 0.1 Hz and most scalp-recorded shifts tend to last between 2 and 10 seconds, it is obvious that they can be seen in digitally acquired recordings with the simple technique of opening the low filter to the maximum the system is certified for. Since the filters are not sharp but show gradual decay even slower activity is recorded, albeit at reduced amplitudes and duration.

Gross et al. were the first to attempt to replicate Ikeda's initial intracranial observations but concluded that "Our study failed to demonstrate any clinical advantage of intracranial telemetry recordings with a high-pass filter of 0.01 Hz over conventional recordings with regard to determining the timing and location of seizure onset and propagation" [20]. The statement was based on 47 seizures of 4 patients who had been recorded with epidural and/or depth-electrodes made of stainless steel. Very low frequency activity (VLFA) was not observed in 29 seizures. It occurred with onset of movement in one instance and in those where VLFA was present, "the timing and location of VLFA were not consistent with those of the conventional seizure onset or propagation".

A detailed study of the paper revealed that 30 of the 47 seizures had occurred in one patient and the electrode coverage was relatively limited. Three points, therefore, need to be considered which may have had a bearing on the negative conclusions. 1) The electrodes used were of stainless steel, which has lower low frequency conductance than platinum. 2) None of the seizures started with the electrodecremental pattern, which tends to be most commonly associated with a sudden baseline shift. 3) The problem of defining the precise moment of seizure onset. This is demonstrated by a study of Figures 1 and 3. Figure 1 shows that rhythmic activity at seizure onset is distributed to varying extent over at least 8 electrodes, while the slow shift is limited to 3. Electrode contact 4 which appears to have the highest amplitude rhythmic activity also had the highest amplitude slow wave. But the authors considered, apparently based on DC literature, only the negative portion of the slow wave and neglected to mention an earlier positive component which preceded the rhythmic discharges. This problem is also highlighted in Figure 3 B. Since, as will be shown later, ictal baseline shifts frequently do not arise de novo, but can be an increase of preexisting interictal and preictal infraslow activity, the precise onset of ictal ISA can at times be difficult to ascertain. This is exemplified in Figure 3 B where preictal slow activity is clearly present in some electrodes, including phase reversals. The practical importance of this observation is that one needs at times

at least a 5 or 10 minute preictal segment to ascertain ictal baseline shifts rather than the commonly shown seconds.

Since the work had been carried out a prestigious site and the authors had referred to previous DC work, dealing with ictal shifts, it was subsequently tacitly assumed that AC amplifiers cannot be used for exploration of ISA, especially since Ikeda's 1999 publication overlapped that of Gross et al. and, therefore, was not referenced in their paper.

The need for DC amplifiers to demonstrate ictal onset baseline shifts was subsequently again emphasized by Vanhatalo et al. [21]. The introduction stated, "They [ictal baseline shifts] are, however, not detected by conventional clinical EEG techniques owing to high-pass (i.e. low-cut) filtering. Recording of these low frequencies requires a genuine DC-EEG amplifier and non-polarizable (i.e. Ag/AgCl) electrodes". Seven patients with scalp recorded temporal lobe seizures were presented and "DC shifts were defined as a clear baseline deviation with a duration of longer than five seconds, and in close temporal proximity to ictal electrographic discharge". Thirty-five seizures were recorded all of which were at some point associated with DC shifts, which allowed definitive lateralization even when the conventional EEG frequencies showed bilaterality. "Polarity was either positive or negative (referred to vertex) at the beginning but always negative during later bilateral seizure activity. ... It commenced a few seconds after the beginning of the high voltage spiking." The amplitude ranged between 30 and 150 µV. The authors concluded that, "scalp-recorded DC-EEG might provide an invaluable tool in noninvasive determination of the site of seizure origin in these [mesial temporal lobe] patients". They also recommended further prospective studies.

The latter was echoed in an editorial by Lagerlund and Gross, which accompanied the paper [22]. The headline raised the question: "DC-EEG recording – A paradigm shift in seizure localization?" The authors emphasized the importance of the paper but agreed that further studies are needed to "assess its reliability in more patients and to demonstrate how frequently it provides additional independent information in temporal lobe seizure patients whose scalp recorded ictal EEG gives unclear lateralization". But since DC amplifiers are still not used in routine clinical long-term monitoring sessions, the suggestion could not be followed except for two studies from one institution [23, 24]. But before considering those, the emphasis on DC amplifiers for demonstrating infraslow may well have had a retarding influence on investigations of the frequency band between 0.016 and 0.5 Hz. It is especially regrettable that it is even contained in the most recent edition of "Niedermeyer's Electroencephalography" [25]. This is curious because, although for instance, a DC system was used for data generation, the data were then high-pass filtered at 0.02 Hz [17]. Figure 3 of the review paper by Vanhatalo et al. on "Full-band EEG" [26], which is also reproduced in the textbook chapter, provides a typical example. It is essentially indistinguishable from our results as will be shown later.

In contrast to the negative observations by Gross et al. several authors have thereafter confirmed Ikeda's findings in patients implanted with subdural grid/strip and/or depth-electrodes. Bragin et al. noted that 75 seizures onsets in 19 patients with temporal lobe epilepsy when recorded with depth electrodes, had a low voltage fast activity onset, Ikeda's electrodecremental pattern. It was associated with an ictal onset slow wave in 89 per cent. An EEG system with a low frequency cutoff of 0.1 Hz was used and the wave lasted between 0.5 and 6 seconds (mean 2.3). The authors commented that with a low filter setting of 0.5 Hz the mentioned slow wave had previously been seen, but was disregarded as a delta wave. Hypersynchronous onset failed to show the initial slow shift and it was postulated that different generators are at work. Furthermore, since depth electrodes did not show phase reversals and maximum amplitude was in white matter or at the border of a deep temporal structure a possible non-neuronal mechanism was suggested [27].

Mader et al. reported on five patients with depth and grid/strip electrodes. The former were inserted stereotactically bilaterally from a burr hole in the occipital area and its most anterior contact reached the anterior inferior amygdala. The electrodes were lateral to the hippocampus and slightly inferior to its plane. The EEG system also had a 0.1 Hz lower frequency limit. An ictal shift was regarded as >1.5 seconds in duration and an amplitude of >100 µV. It was present in 84% of all seizures and the polarity was positive at its maximum. Since the slow wave was more discretely localized than the conventional EEG frequencies, although at times at neighboring electrodes rather than at the maximum as seen on conventional frequencies, the authors regarded it as a useful aid in determining seizure onset [28].

This study can be compared with that of Shih et al. who had likewise used the occipital approach for bilateral hippocampal depth-electrode insertion [29]. But radiographs showed that the left electrode, the side of ictal onset, had ended up in ventricular fluid rather than brain parenchyma. The anterior three contacts were located in the atrium of the inferior horn adjacent to white matter, while the subsequent five were in contact with the hippocampal formation. This allowed a determination of the extent infraslow ictal baseline shifts can be recorded under these circumstances. Although the data showed attenuation of the signal in all left sided contacts compared with the right, even in the interictal state, left sided seizure onset, accompanied by negative baseline shifts, was clearly present. The maximum amplitude of the left sided shift on a Pz referential montage was 1.9 mV at electrode contact 4. This contact also showed phase reversal on a bipolar montage and was located adjacent to the alveus of

the mid-hippocampal gyrus. The progression of the left sided partial seizure onset with spread to the right side and the ensuing tonic-clonic seizure was clearly seen in the infraslow data and reached during that time, an amplitude of 4.6 mV in contact 4 on the right (XLTEK system with LF of 0.05 Hz). It likewise showed phase reversal at that electrode contact which was located in the same a-p location as on the left side but situated in the depth of the collateral sulcus. After a standard left anterior temporal lobectomy which included: amygdala, anterior hippocampus, hippocampal gyrus and inferior temporal gyrus up to a distance of 3 cm, the patient was rendered seizure free at the time of the report (16 months). One additional point needs to be emphasized. In the immediate postictal period a highly regular 0.1 Hz rhythm was seen, which persisted throughout the rest of the 17 minute file.

Ren et al. noted in three patients with intracranial recordings, that intermittent periodic shifts were observed from 8-22 minutes prior to clinical onset [30]. Modur and Scherg published a single case report comparing the onset of the baseline shift with high frequency oscillations >70 Hz (HFO) [31] and Modur et al. then expanded the study to 11 seizures from 6 patients with neocortical seizures obtained from subdural electrodes on an NK System. Baseline shifts were positive or negative in polarity and lasted up to 16.8 seconds with amplitudes of up to 3.3 mV. High gamma activity closely preceded or followed the baseline shift by < 300 ms [32]. Modur subsequently published a review of the relationship of HFO to baseline shifts [33].

Another study by Wu et al. of temporal lobe seizures and depth-electrode recordings, likewise with a NK system, showed ictal onset baseline shifts in 91% of seizures and concomitant high gamma activity in 81%. All baseline shifts overlapped the ictal onset zone while this was found for high gamma activity in 70% of seizures. Shifts lasted from five to 180 s and polarity at onset could be positive or negative. The amplitude was between 300 µV and 3.4 mV, with a mean of 1.7 mV [34].

These data can now be compared with what seems to be the only report of intracranial recorded seizures with a DC system [23]. Eighty-two seizures were recorded from 11 patients with a bandwidth of 0-100 Hz from subdural grids. Ictal slow shifts were observed in 10 of the 11 patients. These preceded in some instances clinical onset by 2-29 seconds. The shifts were localized to the ictal onset zone in 7 patients. Shift polarity could either be positive or negative in a given seizure. The amplitudes ranged from 800-10,000 µV, but the latter was an exception and occurred only once. Generally, amplitudes ranged between 800-4,000 µV. This information is important because it shows that the AC amplifiers of the NK and XLTEK system had not appreciably reduced the signal amplitude. Although Kim et al. had not mentioned the average duration of shifts, they were reported as 5-10 seconds for one case, which is also in keeping with AC amplifier results.

Apart from Ikeda et al.'s original work and our studies there seem to be only two publications which deal with infraslow scalp recordings. Hughes et al. demonstrated the "initial ictal slow shift" in two patients with subdural grid electrodes and one with scalp recordings, on an EEG system with a low filter setting of 0.1 Hz [35]. The scalp recorded patient suffered from absence seizures with 3 per second spike-wave (SW) episodes. The intracranial findings were in conformity with previous reports. The scalp recording of the third patient showed in two seizures a brief positive slow wave prior to the first SW and a sustained positive shift, within 1-4 seconds after onset of the ictal pattern was seen in all. It was maximal in Fp1/2 and reached to F3/4. An asymmetry between the hemispheres also was observed. While occasionally a brief negative shift appeared, the end of the ictal pattern was always associated with a marked positive swing in the prefrontal/frontal areas lasting for up to five seconds. The authors commented that the differences from previous DC studies were that those had shown a negative displacement from the baseline and there were no preictal as well as postictal changes.

The other report by Miller at al. dealt with scalp recordings obtained on a DC system [24]. Twenty seizures from 11 patients were analyzed and the BESA software package which allows for "source montages" was used [36, 37]. Their benefit will be discussed in relation to our studies. A comparison of activity for <0.5 Hz, 0.5-2 Hz and >2 Hz was then carried out and an ictal onset shift was defined as lasting a minimum of 2 seconds. Infraslow signals occurred with all seizures and were frequently substantially higher than the conventional frequencies. In 5 of 8 patients who came to surgery infraslow activity correctly localized the ictal onset, while this was the case in only 3 of the 5 for conventional frequencies. All 5 patients had substantial improvement of seizures after surgery. Source montages combined with infraslow recordings were recommended because better localization can readily be achieved.

Personal publications

During the period of the late 1960s through the 1970s our experimental scientific work dealt with the problem of the relationship between the brain's electrical activity and the behavior of cats when seizures were induced by chemical means. I am mentioning these studies because of their relevance to the plethora of high frequencies investigations which are currently being carried out. It was immediately apparent that no moment-moment correlation with behavior existed in the conventional frequency band for metrazol induced seizures. But since Buchwald et al. [38, 39] had shown that extreme high frequencies could be recorded from cerebral structures we decided to study in detail activity above 100 Hz. Through the courtesy of Mr. Albert

Grass, a 16 channel model78 instrument was provided to us, which had a frequency range of 0.1-10,000 Hz, in addition to a DC channel. Since DC was being actively investigated by others at the time, and the amplifier required frequent resetting of the baseline, we stopped using it after a few trials. For the AC channels we compared the frequency range of 0.1-100 Hz and 30-3,000 Hz (filter settings were fixed by the system). A computer generated time code allowed comparison with the clinical behavior of the cat, which was recorded on film. A variety of cortical and deep structures were sampled with stereotactically implanted semi-micro depth-electrodes and several main findings emerged. Pre-ictal myoclonic jerks were accompanied by bursts of high frequency activity in the low brainstem and when these bursts fused into a continuum the tonic-clonic seizure ensued. This relationship was highly reproducible and unequivocal. It corresponded to the attenuation of the conventional frequencies which preceded rhythmic ictal activity and was similar to an "arousal response" resulting from reticular formation stimulation experiments. It was also shown that the high frequency discharges (frequencies varied between brain structures; in the thousands of Hz in the low brainstem, in the hundreds in cortex) were extremely localized. When the two contacts of the semi-microelectrode (spaced 0.5 mm apart) where led separately to a screw in the frontal bone of the cat, different wave forms could at times be seen. In addition, slow shifts were observed at times in close association with the high frequency discharges in the low brainstem at seizure onset, but we ignored them at the time as artifact from cable movement. In retrospect it is, however, clear that they were genuine and Figure 1 of a recent summary of the findings shows the phenomenon [40]. An earlier summary, but without reference to infraslow, was published in the German literature [41]. Since the methodology was cumbersome the study of extreme high frequency activity was not widely taken up by other laboratories, but digital technology led to a resurgence of interest and there is a steady increase in publications of high gamma as well as still higher frequencies, only a few of which are cited here [42-46].

The infraslow investigations reported here resulted from an opportunity to compare MEG with co-registered EEG data. Since the MEG system's frequency range extended well below 0.1 Hz it was of obvious interest, after having earlier explored the high frequencies, to look at the slow end with the BESA software. The previously mentioned source montages have not only the advantage of reducing the 256 gradiometer channels from 128 brain locations into an easily viewable format of 19 source channels but also allow a direct comparison of MEG gradiometer data in terms of amplitudes with EEG. While gradiometer data are reported in ft/cm and EEG in µV, both types of activity are shown in nanoAmpères. When the low filter was opened to 0.01 Hz (removing the low filter altogether led to channel offsets) it was immediately apparent that a very regular 0.2-0.3 Hz rhythm dominated several channels. When it was also noted that the rhythm increased at times and then stopped for several seconds to recur thereafter, and this event repeated at intervals, it became clear that we were dealing with respiration artifact and intermittent sleep apneas since all patients were sedated with chloral hydrate to achieve a minimum of movement artifact.

Although this phenomenon was less well seen in the EEG, we then decided to have our own electrical activity recorded at the department's sleep laboratory where respirations could be monitored. The EEG system had a low frequency filter of 0.1 Hz and since the MEG had shown the rhythmic activity predominantly in the occipital area only 6 electrodes were used: bilateral occipital and Oz as well as bilateral Cb and the inion. Hyperventilation (HV), the time of which was left to the subject's discretion, led to an unexpected phenomenon. In a one minute window out of pre-existing infraslow activity a higher amplitude rhythm of slightly shorter than 0.1 Hz appeared approximately seven seconds prior to HV and persisted during it. The record was not contaminated by movement artifact and corresponded to the time when HV was considered to be performed. The phenomenon is shown in Figure 3 of the publication on "Subdelta Activity" [47]. For technical reasons we were unable to repeat the experiment on a subsequent occasion and prominent colleagues with whom I discussed the phenomenon regarded it as artifact because the readiness potential and EEG event synchronization/desynchronization, do not extend over such a relatively long time period. To the best of my knowledge the question of artifact versus genuine phenomenon has so far not been investigated by other laboratories. Yet an indirect potential validation of the observation appeared in a 2008 publication based on fMRI. Changes in prefrontal and parietal cortex were noted up to ten seconds prior to a voluntary motor act [48]. The authors were unaware of our publication and did not refer to it. Since the finding is potentially of considerable psychophysiological interest, I have referred to it here in the hope that other investigators may pursue this subject with the 10-20 system of electrode placement including the cerebellar locations.

Having established that the existence of subdelta (0.1-0.9 Hz) and even slower frequencies can be seen by commercial EEG/MEG systems without DC amplifiers, we subsequently investigated archived routine EEG data from 5 different laboratories. Scalp as well as intracranial recordings were studied and infraslow activity was present in all instances. With Dr. Wong's intracranial recordings we could also establish the relationship of high frequency gamma activity to ictal infraslow changes. The overall purpose of this publication was to acquaint the clinical EEG community with the vast amount of information which can be obtained from archived recordings when optimally evaluated [49].

The study was then extended to a comparison of absence and partial seizures [50]. The absence findings largely agreed with those of Hughes et al.'s patient but the partial seizure patients showed a potential clinically important phenomenon. While in some instances ISA was restricted to one temporal lobe with only reduced amplitude in the contralateral one, in others an additional more wide-spread, especially bi-frontal, element was seen similar to that of absence seizures. It was suggested that in some patients with partial seizures a more generalized seizure tendency may, in addition, be present.

These investigations had also pointed to the problem of precise assessment of seizure onset, which led to a subsequent publication [51]. It was apparent that depending on filter settings different results were obtained. The most reliable determination appeared to be when infraslow shifts coincided with high frequency activity and ictal changes in the conventional frequency band. In scalp recordings high frequency activity is, however, not necessarily trustworthy because of inevitable admixture of muscle activity. Since infraslow and high frequency activity have a very restricted electrical field they are likely to be useful in distinguishing locally generated from conducted events even in the interictal state.

For most of these studies EEG systems with a low frequency filter of 0.1 Hz had been available, except for Dr. McIntyre's routine scalp recordings which were obtained on XLTEK system. But Dr. Modur's data, obtained on a NK system, subsequently allowed us to duplicate Ikeda et al.'s original findings on intracranial recorded seizures [52]. In as much as longer preictal data were at times available, we noted that the ictal baseline shifts usually did not arise suddenly but consisted of a gradual buildup of pre-existing infraslow activity, albeit not necessarily in the electrodes that had shown major ictal onset activity in the conventional frequency band. The most dramatic amplitude increase occurred at the transition from partial to tonic-clonic seizures when negative wave forms of several mV were reached. In addition, it was noted that in these instances ISA persisted unabated through the postictal EEG attenuation phase and beyond, for about 2 minutes. It could then be followed in some channels by the 0.1 Hz rhythm which was mentioned in the discussion of the hippocampal seizures, although only neocortical seizures were involved in these patients. Subsequent investigations showed that this rhythm could occur in any cortical area. It could last up to one half hour in the interictal state and was also seen in the scalp recording of a normal control person.

In 2012 the American Clinical Neurophysiology Society held a symposium on cerebral electromagnetic activity [53]. Rampp and Stefan presented intracranial data obtained from an EEG system with a LF of 0.1 Hz and emphasized that even this limited frequency range validated Ikeda et al.'s conclusions [54]. Constantino and Rodin provided a preliminary report on interictal scalp and intracranial data from continuous 24 hour recordings on 5 patients. Epochs of several minutes, up to one and a half hours, of spontaneous marked interictal increase in ISA, at times reaching ictal amplitudes, were noted although not necessarily in the area of ictal onset. Shorter epochs could also be detected in scalp recordings, but the latter showed considerably more movement artifact, which made interpretation difficult [55]. Modur et al. then presented the above discussed information on the relationship of high frequency activity to ictal baseline shifts [32]. Ictal MEG data were presented by Bowyer et al. from 12 patients who were recorded on a DC system. It was noted that in the minutes preceding the seizure "large ISA waveforms were detected, signaling the onset of the seizure" [56]. When the Constantino-Rodin data were prepared for publication it was noted that 2 of the 5 patients had marked diminution of amplitudes and somewhat faster ISA than the other 3. Since we did not know the cause at the time, we simply reported the fact. After further studies, we became aware that these 2 patients had not been recorded on the 128 channel XLTEK system with a low frequency filter of 0.05 Hz as was usually the case, but on a 40 channel system which had a low frequency filter of 0.1 Hz. This explained the finding.

During the following year further 24 hour data were collected from consecutive patients. The findings of 12 patients with intracranial recordings and 3 additional ones with scalp records were presented. The previously seen waxing and waning ISA interictal increase was confirmed and it should be emphasized that in contrast to Ren et al.'s observations [30] was not tied to seizure onset, but occurred in an apparently random manner especially during nocturnal sleep. The difference in ISA amplitude between the waking and sleep state, reported in the earlier publication, was also confirmed. It was increased when the patients were awake and decreased in nocturnal sleep. Although this seems counterintuitive in view of increased slow activity in the conventional frequencies during sleep, it might not be unexpected when one considers that the same phenomenon was seen in the cat experiments with high frequency recordings. In regard to scalp recordings, 2 patients showed a regular buildup of rhythmic ISA during the spindle-K complex stages of sleep, lasting 20 and 30 minutes respectively. In both instances it was terminated by a body movement [57].

Conclusions, additional unpublished observations and recommendations

From the above information it is apparent that ISA in the peri-ictal and interictal state can provide additional useful clinical information about the "epileptogenic zone." Furthermore, there is beginning evidence for informational content in the interictal state, above

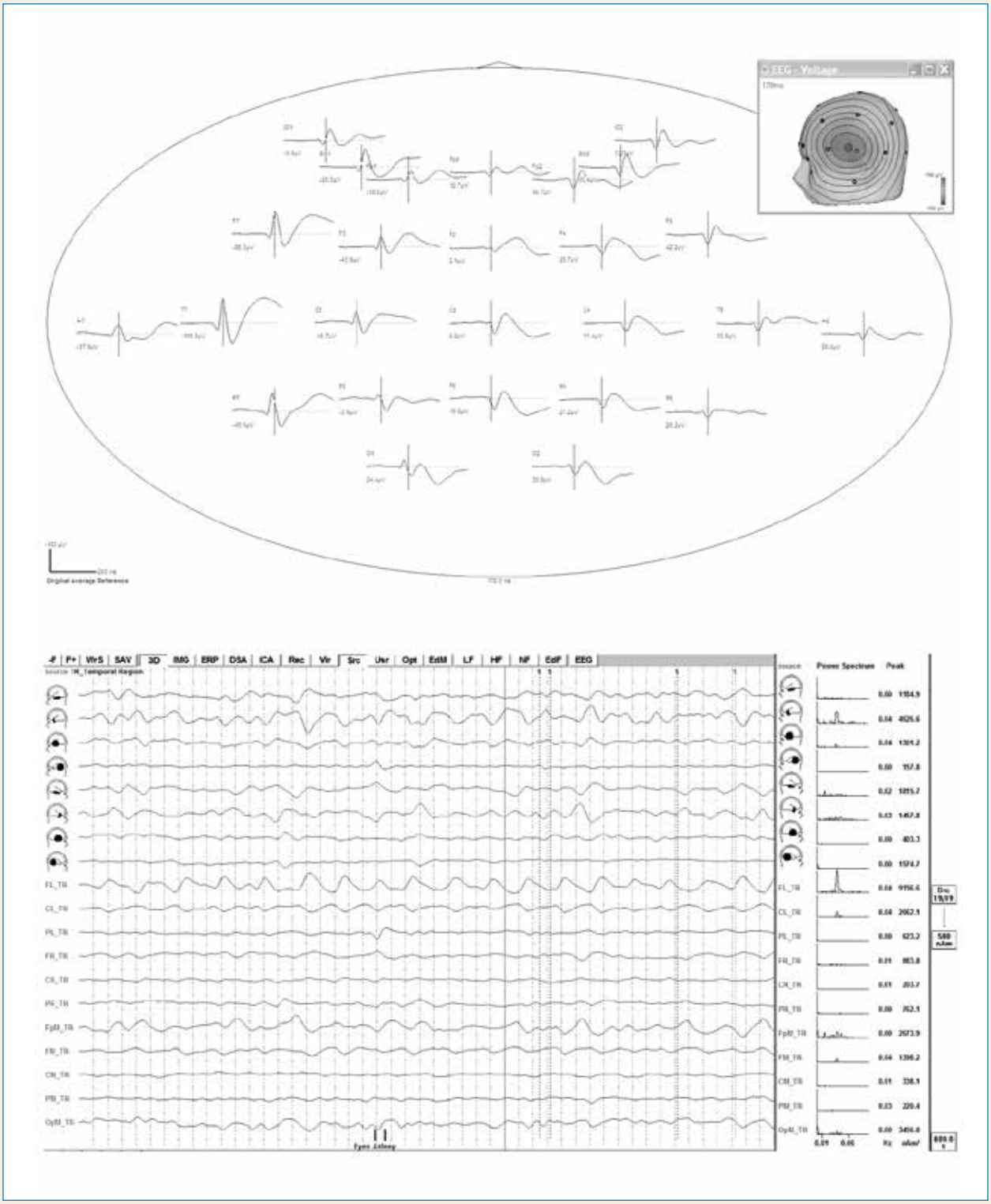

Figure 1: Relationship of interictal spikes in a routine clinical EEG to ISA. Top portion shows on topographic display 25 spikes averaged from the left midtemporal area. The inserted map shows a radial orientation. Inspection of spike latencies indicates onset in the posterior temporal area which proceeds anteriorly. The bottom portion shows 10 minutes of the drowsy/sleep state, on a temporal source montage, filtered for ISA between 0.01-0.1 Hz. The major activity, around 0.04 Hz (FFT spectrum on the right), is in the left temporal polar and frontal areas. The number 1 on top of the tracings indicates individual spikes used in the average. Their preponderance on the ascending phase and on top of the temporal polar wave is coincidental and no phase relationship existed in other samples. Vertical lines denote 10 second intervals. The first comment on the bottom is truncated for Eyes Closed.

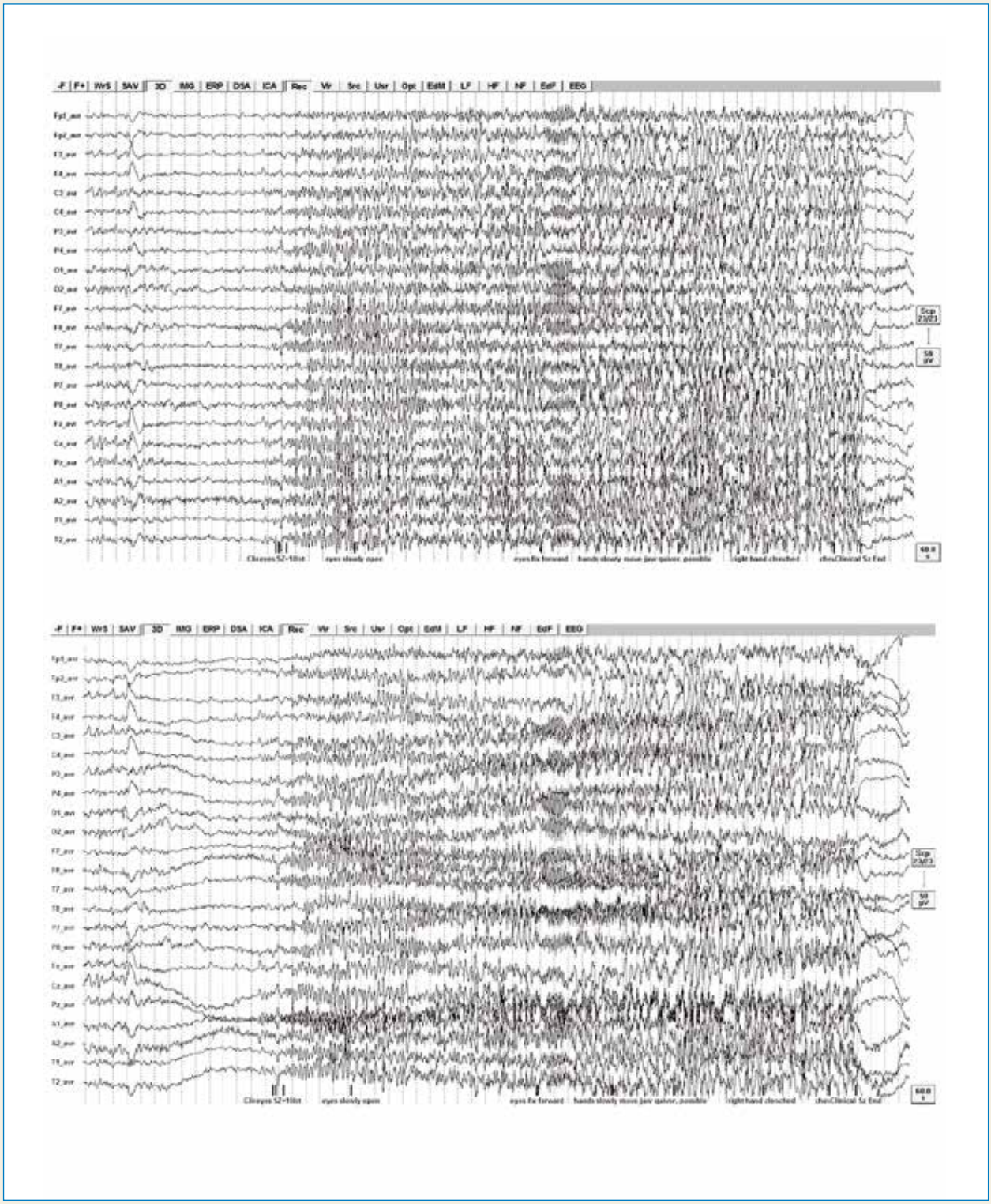

Figure 2: Example of electrodecremental seizure onset and baseline shifts. The patient was asleep and there was no movement artifact. The top portion shows a 55 second partial seizure on filter settings 1-70 Hz. It is initiated by a relatively wide-spread 1 second discharge, which might represent momentary arousal. It is followed by attenuation of electrical activity and subsequent rhythmic frequencies. Lateralization of seizure onset cannot be reliably determined.
The bottom portion shows the same data but with the low filter changed to 0.01 Hz. Several ictal onset baseline shifts are apparent. They start after the initial discharge and continue throughout the seizure into the postictal phase, with varying polarity in different channels. The shifts involve at onset both hemispheres and a definitive lateralization is likewise not possible. Vertical lines delineate 1 second intervals.

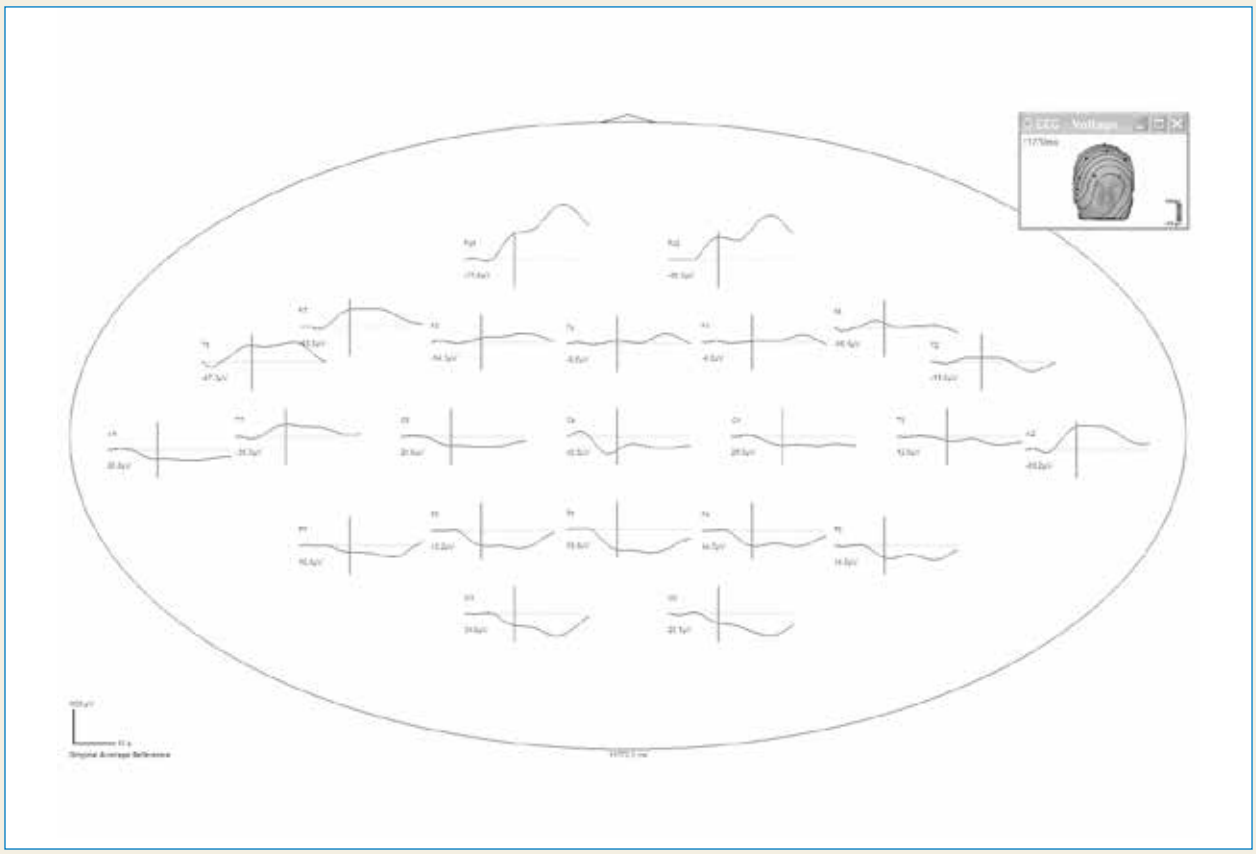

Figure 2a: shows the 30 second ictal onset baseline shift prior to rhythmic activity on a topographic display. Initial negativity is most marked in the left anterior temporal and frontopolar areas. The inserted map shows the frontopolar distribution at the time of the earliest F7/Fp1 peak. In addition there is a negative event at A2, suggesting independent right sided involvement at seizure onset. Past experience suggests that patients with a complex picture of this type tend to have a poorer surgical prognosis.

and beyond what is seen in the conventional frequency band, but its clinical relevance requires further study.

The peri-ictal ISA investigations not only add to our information about electrophysiological processes, but since they are non-neuronal in nature, they may provide information on the metabolic processes underlying the electrical phenomena. Among those, the ones associated with glia functions are probably the most important. In this connection animal work has shown that in metrazol kindling experiments astrocytic swelling and compression of capillaries, preceded neuronal changes at a time when the animal (rat) showed only whisker twitching accompanied by the rat's equivalent of SW discharges [58]. Early glia changes were also reported in measles infected mice prior to seizures [59]. Furthermore, it is important to point out that astrocyte oscillations have been reported for a frequency range of 0.003-0.1 Hz [3].

In as much as only patients with "partial seizures" are evaluated with intracranial recordings it has become apparent that the current distinction between "partial" and "generalized" is not as sharp as the names imply. As the published figures show, ictal onset ISA shifts are sometimes, in spite of their limited electrical field, rather wide-spread and can be seen in a regional and multi-lobar distribution, suggesting a considerably wider process than a discrete focal one. This may well have implications for the post-surgical prognosis. The other extreme, namely absence of ictal onset shifts, could also be interpreted not simply as a failure of the method [20], but that the areas sampled by the available intracranial electrodes only show conducted activity rather than what was locally generated. This is best seen when foramen ovale electrodes are added to the 10-20 system. These can not only show ictal onset, that is not seen in the conventional montage even when inferior temporal electrodes are added, but also ictal onset shifts as first reported by Wieser et al. [60] and confirmed by us [51].

Since the placement of intracranial electrodes is dependent on scalp recordings, at times supplemented by MEG, the optimal evaluation of these data is crucial. But assessment of ISA in interictal and peri-ictal recordings exists currently only in isolated case reports and systematic work-up of the data, correlated with long-term surgical results, still needs to be performed. In as much as it is well known that seizures may recur several years after surgery, 5-10 year follow-up studies, correlated with existing archived ISA data, should be performed.

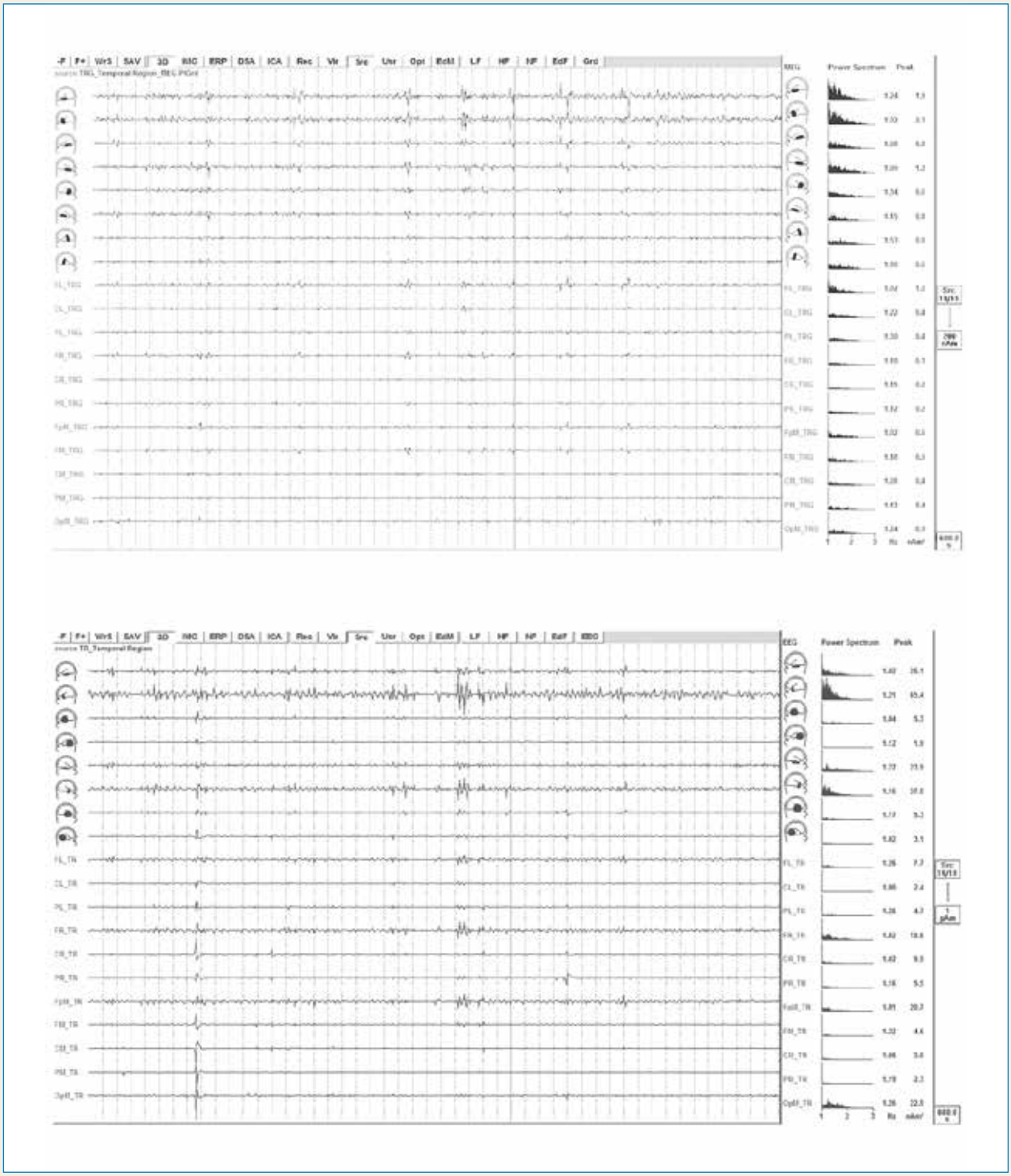

Figure 3: presents a co-registration of MEG with EEG for delta activity and ISA during sedated sleep. The top portion shows the MEG on a 10 minute window for delta and the bottom portion for EEG with the power spectrum inserted. In both instances maximum power is in the left temporal polar area and the data are artifact free.

The following set of figures, which have not been previously published, deals exclusively with surface recordings obtained from four different laboratories. The first two confirm that ISA can be extracted from routine recordings and show that ictal as well as interictal activity can have localizing value. **Figure 1** demonstrates the relationship between 25 averaged left mid-temporal spikes obtained during a routine clinical recording on an XLTEK system in Dr. McIntyre's laboratory (Torrance CA). The top portion demonstrates that, in spite of the mid-temporal peak with radial orientation (map insert), the spikes appear earliest in the posterior temporal region and subsequently move anteriorly. Mirror activity with markedly diminished amplitudes is pre-

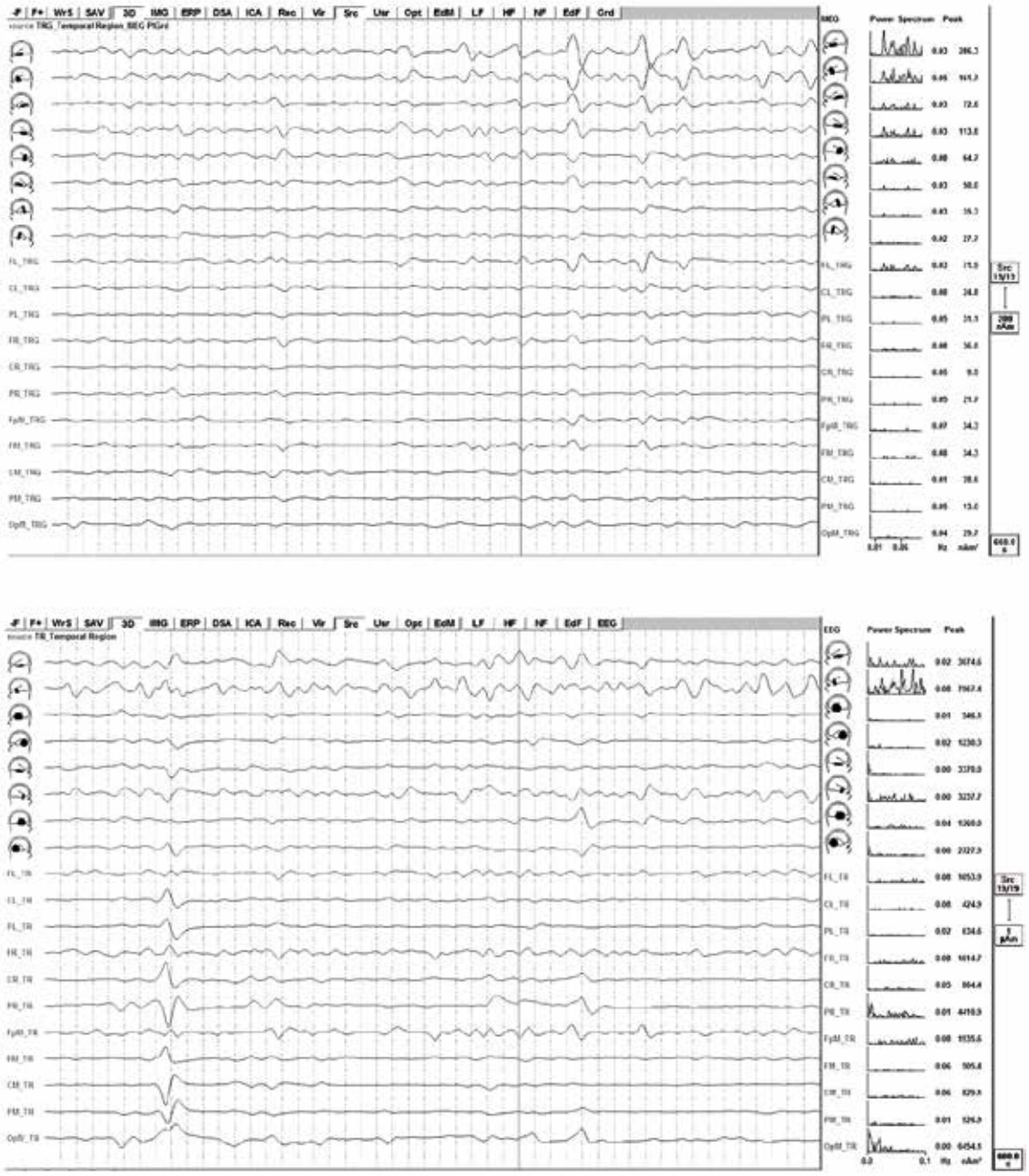

Figure 3a: shows the same data for a filter setting of 0.01-0.1 Hz, with MEG again on top. Similar wave forms are seen for the two modalities. Although the left temporal area shows again maximal power it is highest in the baso-temporal, rather than temporopolar region, in the MEG, while the opposite is the case for the EEG. The phase reversals within the left temporal regions are also more marked in the MEG. The early higher amplitude transient in the EEG, which is not seen in the MEG, may represent a K-complex. Vertical lines delineate 10 second intervals. Please note that, for both frequency ranges, amplifications of the wave forms are 5 times higher for the MEG (200 nAm vs. 1µAm).

sent on the right. The bottom portion shows 10 minutes ISA during drowsiness/sleep on a source montage and the corresponding power spectrum. Maximum activity is in the left frontal and temporal polar region.

The file for **Figure 2** was sent by Dr. Hasegawa (Kalamazoo MI) for a second opinion. The figure shows on top a one minute epoch of a partial seizure on a filter setting of 1-70 Hz. The tracings are artifact free and the seizure is initiated by a one second higher amplitude

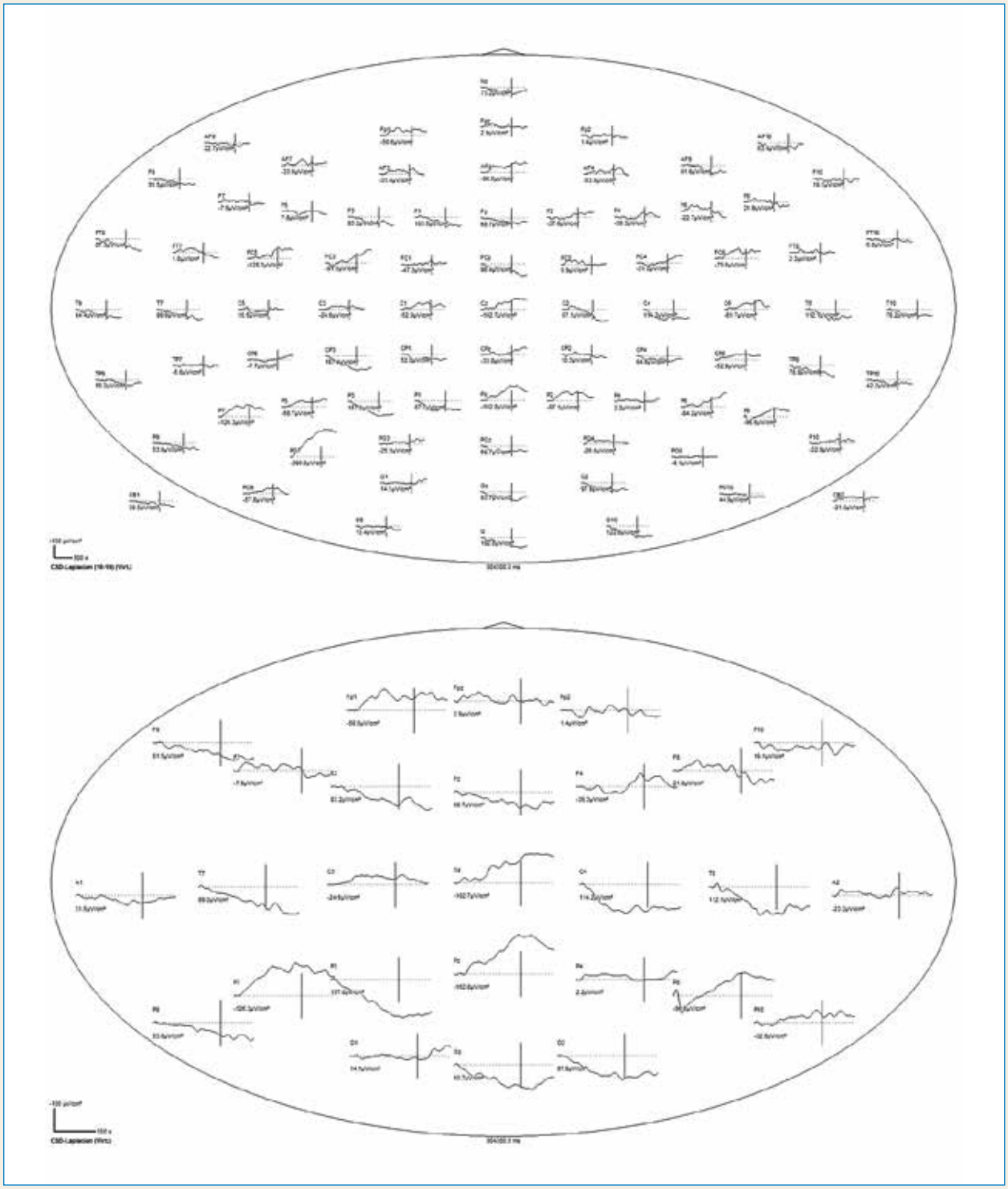

Figure 4. Twenty minute ISA during a P300 discrimination task obtained on an ANT DC system on a Laplacian (CSD) montage in a normal person. In order to establish a baseline and allow slower wave forms to emerge the data are filtered between 0.0002-0.01 Hz. 128 channels were recorded. BESA coordinates were only available for the corresponding 10-10 international montage and the result is shown in the top portion. Since the picture is rather condensed, the same data are shown on an expanded 10-20 montage with some inferior temporal channels added. It is apparent that in some channels the wave forms do not return to the baseline within this 20 minute limit. While the 10-10 montage shows maximum negativity at PO7 it is maximal at P7 for the 10-20 montage. The marker, for amplitude determination, is placed at the peak of the highest slow wave. Although a somewhat complex pattern can be discerned, a statement about the clinical validity of the data requires further study. The picture is only shown to demonstrate what is seen with DC amplifiers and a relatively long time window.

discharge followed by attenuation of activity and subsequent rhythmic discharges. A determination of lateralization is difficult. In the bottom section the low filter was changed to 0.01 Hz and ictal onset shifts during the electrodecremental phase of the seizure are immediately apparent. But since they are rather widespread and of different polarities, lateralization is still difficult. **Figure 2a** demonstrates the 30 second shift onset on a topographic display and it seems that there are two separate distributions. One involves the left anterior quadrant, but this leaves the A2 activity unexplained. It suggests independent involvement that should probably be taken into account if intracranial electrodes were to be placed.

These figures were shown to emphasize that, especially during drowsiness and sleep, adequate scalp ISA assessment is feasible and that even partial seizures can have at onset quite complex configurations. **Figure 3** demonstrates ISA relationships between MEG and EEG. In Dr. Funke's laboratory at our University a Neuromag/Elekta system with 256 gradiometer and 128 magnetometer sensors was used; 60 EEG channels were co-recorded. In view of the large number of channels the data are shown on a BESA source montage with inserts for frequency spectra. The figure shows in the top portion the MEG for a 10 minute epoch and the co-registered EEG on the bottom for delta activity. The wave forms as well as power values are shown and the data are artifact free. **Figure 3a** shows the corresponding ISA values in the same layout. Please note that MEG amplitudes and corresponding power values are lower for MEG in the raw data as well as the frequency spectra. Good correspondence regardless of frequencies studied can be noted. The early higher amplitude transient in the EEG, which is not seen in the MEG, may represent a K complex. The MRI was negative, and interictal spikes were seen on MEG in the area of left insular cortex as well as left inferior and middle frontal gyrus. The entire available case material is currently under study and the findings will be reported at a later date.

The current BESA limit for frequency spectra is 0.01 Hz and still slower activity is displayed as 0.00. In as much as this can frequently be seen in records of 10 and 20 minute duration (maximum BESA limit), the question arises to what extent still slower wave forms can be demonstrated. The Department of Psychiatry of our University has recently acquired a 128 channel ANT system for psychophysiological investigations and Dr. Johnson kindly sent me some files. The electrode cap has sintered Ag/AgCl electrodes and DC amplifiers are used. **Figure 4** shows an initial observation on a normal person during the P300 discrimination task. Although 128 electrodes were used for recording, BESA currently can only display those with 10-10 system labels. But since even this display is quite compressed for easy viewing, the bottom portion shows the same information on an expanded 10-20 montage which has some inferior temporal electrodes added. Both data sets are on a Laplacian (CSD) montage with filter settings of 0.0002-0.01 Hz. This is the lowest filter provided by BESA and at 0.0001 Hz the data revert to default (0.5 Hz). Removing the LF altogether led to channel offsets. The figure suggests that what we record as ISA activity may ride in part on still slower "swells," which extend beyond 20 minutes. This would validate some of Aladjahova's work, although technical problems such as possible amplifier drift, electrode polarization, skin potential contamination and other factors, will have to be taken into consideration in the interpretation of the results. The figure is only shown because to date no such picture seems to exist in the modern literature and to emphasize the need for ISA study also of <0.01 Hz. Theoretically MEG might lend itself well to these investigations because contamination by electrodes and skin potentials is absent. But MEG has different technical problems most of which relate to amplifier performance at extremely long wave durations and environmental noise can become a significant contaminant. Nevertheless it should not deter attempts to determine what the longest wave forms are that can be reliably recorded with current technology.

In conclusion, it is apparent that since ISA, including what is seen with DC amplifiers, is a highly promising field for the study of normal as well as pathological cerebral electromagnetic activity, it should be actively pursued with the most up to date hardware as well as signal analysis techniques.

Disclosure:
The author had no financial support and is happy to express his sincere gratitude to the physicians who had provided the data, as well as to their technologists who anonymized the information. Special thanks are also due to Dr. Michael Scherg and his team at BESA who helped with technical details.

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Die Epilepsie-Liga hat zuletzt 2006 die Richtlinien zur Kraftfahreignung bei Epilepsie überarbeitet. Erfahrungen bei der praktischen Anwendung, neue Richtlinien auf europäischer Ebene sowie eine neue Epilepsiedefinition durch die Internationale Liga gegen Epilepsie waren Anlass für eine Aktualisierung.

Der neue Flyer „Führerschein und Epilepsie“ enthält die revidierten Richtlinien sowie ein nicht-obligatorisches Beispiel für ein fachärztlich-neurologisches Zeugnis zu Händen des Strassenverkehrsamtes.

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Erhältlich bei der Epilepsie-Liga, info@epi.ch, Tel. 043 488 67 77

Sari ist eine begabte Literaturstudentin, die äusserlich beherrscht und selbstbewusst wirkt. Ihr Leben ist jedoch durch eine gewisse Zurückgezogenheit geprägt. Die Kolleginnen beneiden sie um ihre Intelligenz und Schönheit, die männlichen Komilitonen bewundern sie aus der Ferne aus denselben Gründen. Aber in Saris Innerem lauert eine Bestie, die sie vom Rest der Welt isoliert: die junge Frau hat Epilepsie, eine gefürchtete und geheimnisvolle Krankheit, und die Angst vor Anfällen macht sie vorsichtig. Sie achtet auf eine gewisse Distanz zu anderen Menschen. Als Sari dem älteren Literaturdozenten Mikko Groman begegnet, erkennt sie in ihm ein ähnliches Element von Reserviertheit. Mikko, der sich in seiner ganz eigenen, komplizierten Gedankenwelt bewegt, fühlt sich nur in der Dichtkunst des 19. Jahrhunderts so richtig zuhause. In der leistungsorientierten modernen Welt der Computer und Iphones ist er ein Sonderling. In Mikko findet Sari einen Seelenverwandten, doch in den Augen der anderen scheinen die beiden überhaupt nicht zueinander zu passen.

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www.swissneuro.ch/Young_Neurologists

2.-7.8.2015 | Sigulda, Lettland
9th Baltic Sea Summer School on Epilepsy
Information: petra.novotny@wolfstiftung.org,
www.epilepsiestiftung-wolf.de

20.08.2015 | Basel, Hotel Hilton, 9.30 Uhr
Basler Epilepsietag 2015:
„Epilepsie, Psyche und Kognition“
Information: Stephan.Rueegg@usb.ch

4.-5.9.2015 | Bielefeld-Bethel, Deutschland
2nd International Epilepsy Symposium
Information: http://bbs2015@mara.de

5.-9.9.2015 | Istanbul, Türkei
31th International Epilepsy Congress
Information: Congress Secretariat,
7 Priory Hall Stillorgan Road, Dublin, Irland,
Tel. 00353 / 1 / 2056720,
e-mail: istanbul@epilepsycongress.org

9.-13.9.2015 | München, Deutschland
Annual Conference on Clinical Neurophysiology and NeuroImaging 2015 – Joint Meeting of ECNS (EEG & Clinical Neuroscience Society), ISNIP (International Society for Neuroimaging in Psychiatry) & ISBET (International Society for Brain Electromagnetic Tomography)
Information: Prof Dr. Oliver Pogarell, Dr. Daniel Keeser, PD Dr. Dipl. Psych. Susanne Karch, Klinische Neurophysiologie, Klinik für Psychiatrie und Psychotherapie der Ludwig- Maximilians-Universität München,
Nussbaumstr. 7, 80336 München, Deutschland,
Tel. 0049 / 89 / 4400 / 55541,
Fax 0049 / 89 / 4400 / 55542,
www.eeg-munich.com

10.-11.9.2015 | Luzern
Gemeinsame Jahrestagung 2015 Schweizerische Gesellschaft für Neurochirurgie, Schweizerische Gesellschaft für Neuroradiologie mit Interessengruppe Neurochirurgisches Operationspersonal Schweiz
Information:
http://kongress.imk.ch/ssns2015preview/Intro

23.-26.9.2015 | Düsseldorf, Deutschland
88. Kongress der Deutschen Gesellschaft für Neurologie
Information: www.dgn.org/-kongress-kalender.html

1.10.2015 | Zürich, EPI-Parksaal, 19 Uhr
Tag der Epilepsie
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

11.-16.10.2015 | Jerusalem, Israel
6th Eilat International Educational Course on the Pharmacological Treatment of Epilepsy (6thEilat Edu)
Information: 6th Eilat International Educational Course: Target Conferences, 65 Derech Menachem Begin, P.O. Box 51227, Tel Aviv, 6713818 Israel,
Tel. 00972/ 3 / 5175150,
Fax 00972 / 3 / 5175155,
e-mail: eilatedu@target-conferencess.com
www.eilatedu2015.com/

29.-30.10.2015 | Bern, BernExpo
Jahrestagung 2015 Schweizerische Neurologische Gesellschaft (SNG)
Gastgesellschaften: Schweizerische Gesellschaft für Verhaltensneurologie, Schweizerische Gesellschaft für Neurorehabilitation, Schweizerische Kopfwehgesellschaft in Zusammenarbeit mit dem Ärztlichen Beirat der Schweizerischen Multiple Sklerose Gesellschaft
Information: http://kongress.imk.ch/sng2015preview/Intro

31.10.-5.11.2015 | Santiago, Chile
XXII World Congress of Neurology (WCN)
Information: Kenes International,
1-3 Rue de Chantepoulet, P.O. Box 1726, 1211,
Genf 1, Tel. 0041 / 22 / 9080488,
Fax 0041 / 22 / 9069140,
www.wcn-neurology.com/congress-information

7.11.2014 | Zürich
Patiententag
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

3.12.2015 | Biel/Bienne, 17 Uhr
Fachveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

3.12.2015 | Biel/Bienne, 19.30 Uhr
Publikumsveranstaltung der Epilepsie-Liga
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Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

4.-8.12.2015 | Philadelphia, Pennsylvania, USA
69th Annual Meeting of the American Epilepsy Society
Information: American Epilepsy Society, 342 North Main Street, West Hartford, CT 06117-2507 USA,
Tel. 001 / 860 / 5867505,
Fax 001 / 860 / 5867550,
e-mail: info@aesnet.org, http://www.aesnet.org/
Information: Conventus Congressmanagement & Marketing GmbH, Carl-Pulfrich-Strasse 1,
D 07745 Jena, Deutschland, Mandy Wagner

Impressum

Herausgeber | Administration | Schlussredaktion
Schweizerische Liga gegen Epilepsie
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Konzeption | Gestaltung | Reinzeichnung
screenblue Büro für Design | Birgit Depping
Gazellenkamp 99, D-22529 Hamburg
bd@screenblue.de, www.screenblue.de

Titelbild
www.istockphoto.com, Fotograf: haydenbird

Belichtung | Druck
Bruns Druckwelt GmbH & Co. KG
D-32423 Minden, www.bruns-druckwelt.de

Auflage
1.200 Exemplare

Versand
Eingliederungs- und Dauerwerkstätte
des Schweiz. Epilepsie-Zentrums
Bleulerstrasse 72, 8008 Zürich