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INSIDE



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# Levetiracetam Is Not Better than Older Antiepileptic Drugs as Initial Monotherapy for Newly Diagnosed Epilepsy

ABSTRACT & COMMENTARY

***By Elayna Rubens, MD***

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*Dr. Rubens reports no financial relationships relevant to this field of study.*

***Synopsis:*** *In patients with newly diagnosed epilepsy, levetiracetam monotherapy was not superior to monotherapy with controlled-release carbamazepine or extended-release sodium valproate.*

**Source:** Trinka E, et al. KOMET: An unblinded, randomized, two parallel-group, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy. *J Neurol Neurosurg Psychiatry* 2013;84:1138-1147.

THE DEVELOPMENT OF NEWER ANTIEPILEPTIC DRUGS (AEDS) HAS RESULTED IN many new treatment options for patients with epilepsy. Despite the increasing number of choices, however, there is limited information to guide clinical selection of an AED, particularly in the common scenario of selecting a drug for initial monotherapy. The limitations of existing clinical trials of newer AEDs (small sample size, short follow-up duration, dose variation, adjunctive treatments, and limited patient population) make their results difficult to apply to everyday clinical practice. While many studies have shown that newer AEDs are efficacious in the treatment of seizures, their effectiveness as monotherapy compared to older AEDs is not well established. KOMET (Keppra against Older Monotherapy in Epilepsy Trial) attempts to compare, head-to-head, the effectiveness of levetiracetam (LEV) to that of controlled-release carbamazepine (CBZ) and extended-release sodium valproate (VPA). The study was designed to evaluate whether initial monotherapy with LEV is superior to treatment with either CBZ or VPA with the primary outcome measure of time to withdrawal of treatment (a measure of effectiveness reflecting both effi-

cacy and tolerability).

KOMET is an industry-sponsored (UCB), unblinded, randomized, parallel-group, 52-week follow-up study that was conducted between February 2005 and October 2007 in 269 centers in Europe and Australia. Patients were aged 16 years and older, had two or more unprovoked seizures in the previous 2 years, and had at least one seizure in the previous 6 months. Exclusion criteria were prior treatment with LEV, CBZ or VPA, or any AED in the past 6 months. At the initial screening, clinicians decided whether a given patient would receive VPA or CBZ as the standard first-line treatment. Within each stratum (VPA or CBZ), the patients were randomized to receive either the standard AED or LEV. Initially, patients entered a 2-week titration period during which they received LEV 500 mg/day, VPA 500 mg/day, or CBZ 200 mg/day at first with uptitration to initial target doses LEV 1000 mg/day, VPA 1000 mg/day, and CBZ 600 mg/day. Further dose increases were permitted up to a predetermined maximum dose at the clinician's discretion. Patients underwent an evaluation period of 52 weeks during which time seizures and adverse events were tracked and quality of life and health status questionnaires were completed. The primary outcome measure, time to withdrawal from study medication, was calculated from the time of randomization. Secondary outcome measures were time to first seizure as well as treatment withdrawal and seizure freedom rates at 6 and 12 months.

A total of 1688 patients were included in the study. For the primary outcome measure, time to withdrawal from study medication, there was no significant difference between LEV and standard AEDs when treatment strata were combined or analyzed separately. The time to first seizure was significantly longer for patients receiving standard AEDs than in those receiving LEV (hazard ratio 1.2; 95% confidence interval, 1.03-1.39). Analysis of the time to first seizure within each treatment stratum also favored the older AEDs, but the differences were not statistically significant. Seizure freedom rates at 6 and 12 months showed no difference between LEV and the older AEDs. The authors conclude from these findings that LEV is non-superior to both VPA and CBZ for monotherapy in patients with newly diagnosed epilepsy.

## ■ COMMENTARY

Clinical trials of most of the newer-generation AEDs are adjunctive therapy trials wherein the newer medications were shown, against placebo, to be effective when added to existing AED treatment. Thus, many of the second-generation AEDs, including LEV, are approved in the United States only as add-on therapy. LEV is approved for use in the United States as an adjunctive treatment for partial-onset seizures in adults and children, myoclonic seizures in adolescents and adults with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in adults and children with idiopathic generalized epilepsy. However, in clinical practice, LEV is increasingly being used as monotherapy. The increasing off-label use is due to accumulated clinical experience, broad-spectrum efficacy, ease of use, tolerability, availability in IV formulation, few drug-drug interactions, and successful marketing of the drug by the pharmaceutical industry to doctors and patients. It has been assumed that LEV, given its adjunctive efficacy, will also work as monotherapy. This assumption needs to be systematically examined in long-term clinical monotherapy trials. KOMET attempts to do so, but falls short of providing a definitive answer regarding the effectiveness of LEV in monotherapy compared to older AEDs.

In order for an AED to obtain an indication for monotherapy in the United States, the FDA requires that the drug is determined to be superior to a placebo control. The placebo can take the form of an inactive placebo, suboptimal drug dose (also known as a "pseudoplacebo"), or, in some cases, historical controls. However, in the treatment of epilepsy, the gold standard placebo-controlled trial is ethically unacceptable since one group of patients would receive no or suboptimal treatment. To circumvent this ethical dilemma, active-control (head-to-head) comparison trials (like KOMET) that compare a new drug to an accepted treatment have been used to establish non-inferiority or superiority of the new drug. In other words, non-inferiority trials are designed to establish that the new drug is at least not worse than the old one, while superiority trials aim to show that one drug is better than

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another. Non-inferiority trials are used to establish monotherapy indications by regulatory bodies in Europe, but are not acceptable to the FDA due to questions of validity of comparing two active drugs that could be equally ineffective. Prior head-to-head comparison studies of older and newer AEDs have not shown significant differences in efficacy and typically have shown equal or slightly better tolerability of the newer AEDs.[1] One previous randomized, double-blind, non-inferiority trial of LEV compared to CBZ in adults with newly diagnosed epilepsy showed that LEV was non-inferior to CBZ.[2] This trial resulted in a monotherapy indication for LEV in Europe and offered reassurance to doctors and patients using LEV as off-label monotherapy.

KOMET, however, was not designed as a non-inferiority trial. KOMET is an active-control superiority trial. This distinction is important when interpreting the results of KOMET. Because there was no significant difference between LEV and the older AEDs, in this study the results can only be used to make the claim that Keppra is not better than the old AEDs. One cannot, on the other hand, use the results of KOMET to claim that LEV is the same or equally as good as the older AEDs. This conclusion would require a different data analysis and larger sample size. Unfortunately, the misinterpretation of a nonsignificant superiority trial such as KOMET to mean evidence of no difference between treatments is common.[3] If LEV is non-inferior to the older AEDs, KOMET does not prove it. Therefore, further long-term monotherapy trials of the newer AEDs, including LEV, are necessary to better define their use in the clinical scenario of choosing an initial monotherapy for newly diagnosed epilepsy. ■

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# Maternal Hypothyroxinemia and Autism

ABSTRACT & COMMENTARY


***By Sotirios Keros, MD, PhD***

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*Dr. Keros reports no financial relationships relevant to this field of study.*


***Synopsis:*** *Very low levels of early-maternal free thyroxine are associated with a 4-fold increased risk of parental reports of autism symptoms in their offspring.*


**Source:** Román GC, et al. Association of gestational maternal hypothyroxinemia and increased autism risk. *Ann Neurol* 2013 Aug 13; doi: 10.1002/ana.23976. [Epub ahead of print].


AUTISM SPECTRUM DISORDER (ASD) REPRESENTS A SOMEWHAT diverse set of conditions that are linked by key clinical features. Currently, more than 100 genes have been identified that cause or are otherwise potential risk factors for autism. In addition, it is clear that there are many environmental factors that affect ASD risk. It has long been known that congenital hypothyroidism and maternal hypothyroidism result in cognitive disabilities. Relatively recently, it has been suggested that maternal hypothyroxinemia during the first trimester negatively affects cognitive development in humans, and that transient maternal hypothyroxinemia in animal models leads to alterations in brain structure and function that resemble those seen in human ASD.

In this study, the authors evaluated maternal thyroid function during pregnancy and parental report of autism symptoms taken from the Netherlands-based Generation R Study. The study enrolled 8870 pregnant women who delivered between 2002 and 2006. Of these, 4039 maternal-child pairs met the study inclusion criteria of: consent for the study; maternal thyroid measurements consisting of free thyroxine ($fT_4$), serum thyroptropin (TSH), and thyroid peroxidase antibodies before 18 weeks of gestation; and information about autistic symptoms in the child through age 6. Mild hypothyroxinemia was defined as an $fT_4$ level less than 10th percentile (n = 295; $fT_4$ < 11.82 pmol/L) with an otherwise normal TSH, and severe hypothyroxinemia was defined as less than the fifth percentile (n = 136; $fT_4$ < 10.99 pmol/L). In addition, the subset of women who fell between the 5th and 10th percentile were labeled as *only mild hypothyroxinemia* (n = 159; 10.99 < $fT_4$ < 11.82 pmol/L). Autistic symptoms in children were assessed by the parents as reported on the Pervasive Developmental Problems (PDP) subset of the Child Behavioral Checklist for Toddlers as well as the Social Responsiveness Scale (SRS). Children with a PDP score above the 93rd percentile were classified as having *borderline* PDP, while those above the 98th percentile were labeled as *clinical* PDP. Children who had a PDP score of greater than 98th percentile as well as an SRS score in the top 5% were classified as a *probable autistic child*. Statistical models were adjusted for sex, ethnicity, gestational age at birth, birth weight, education, smoking history, parental age, thyroid medication during pregnancy, and pregnancy folate and CRP.

The study found that early maternal severe hypothyroxinemia was associated with a four-fold risk (odds ratio [OR], 3.89; 95% confidence interval [CI], 1.83-8.20) of

# Stroke Alert: A Review of Current Clinical Stroke Literature

***By Matthew E. Fink, MD,*** *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

## Surgical Decompression for Large Ischemic Strokes May Have Long-Term Benefit

**Source:** Geurts M, et al. Surgical decompression for space-occupying cerebral infarction. Outcomes at 3 years in the randomized HAMLET trial. *Stroke* 2013;44:2506-2508.

In a pooled analysis of three European randomized trials of hemicraniectomy for large hemispheric infarctions (*Lancet Neurology* 2009;8:326) within 48 hours, there was a dramatic improvement in survival at 1 year. However, this large reduction in case fatality came at the risk of severe disability in the survivors. The HAMLET investigators (Netherlands) followed up their patients at 3 years to assess functional outcome and quality of life. Poor outcome was defined as a modified Rankin Scale > 3.

Of 64 patients, 32 were randomized to surgery and 32 to best medical treatment. Just as reported at 1 year, at 3 years, surgery had no effect on the risk of poor functional outcome, but it reduced case fatality (absolute risk reduction, 37%; 95% confidence interval, 14-60). Sixteen surgical patients and eight medical controls lived at home (relative risk = 27%), and quality of life improved between 1 and 3 years in the surgical group. In conclusion, the survival benefits and disability noted at 1 year were sustained at 3 years. ■

having a probable autistic child. When looking solely at PDP scores, severe hypothyroxinemia conferred an OR of 2.02 (95% CI, 1.16-3.51) and 2.6 (95% CI, 1.30-5.18) on the development of borderline and clinical PDP, respectively. Severe hypothyroxinemia was also associated with increased SRS scores. Outcomes were similar when comparing the mild hypothyroxinemia group with the only mild hypothyroxinemia group and, thus, the authors did not find a statistically significant dose-response relationship, as assessed by the risk of developing borderline PDP or clinical PDP. In addition, there was no dose-response relationship between hypothyroxinemia and scores on the PDP subtest and SRS as measured by linear regression. TSH levels and TPO antibodies during pregnancy were not correlated with autistic features.

**■ COMMENTARY**

This study provides strong evidence for an association between low $fT_4$ levels in pregnancy and autism. Although this study cannot prove causation, it strengthens the link to this modifiable risk factor and gives support to a potential policy of testing and treatment of otherwise euthyroid maternal hypothyroxinemia during early pregnancy. One limitation of the study is that the children did not have clinically diagnosed autism. But the parental reporting scales used are well validated and highly sensitive and specific for a clinical diagnosis. Also, more than half of the original enrollees in the study were not ultimately included due to loss to follow-up or lack of autism reports and, thus, these results are subject to selection bias. However, the large sample size and population-based birth cohort design otherwise help to provide additional evidence to the hypothesis that thyroxine is critical for normal fetal brain development early in gestation. ■

## Headaches – A Hidden Disability Associated with Seizures

ABSTRACT & COMMENTARY

***By Dara Jamieson, MD***

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*Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim and Bayer, and is on the speakers bureau for Boehringer Ingelheim.*

***Synopsis:*** *Periictal headaches are frequent, severe, and undertreated, and can be predicted by younger age at epilepsy onset, drug polytherapy, and tonic-clonic generalized seizures.*

**Source:** Duchaczek B, et al. Interictal and periictal headache in patients with epilepsy. *Eur J Neurol* 2013;20:1360-1366.

All patients aged 18 years or older with epilepsy or one unprovoked epileptic seizure, who were seen in the tertiary epilepsy outpatient clinic of the Charité University Hospital between October 2006 and December 2007, underwent a semi-structured interview to determine

## New Devices for Mechanical Thrombectomy Show Promise

**Source:** Pereira VM, et al. Prospective, multicenter, single arm study of mechanical thrombectomy using solitaire flow restoration in acute ischemic stroke. *Stroke* 2013;44:2802-2807.

In the May 2012 issue of *NEUROLOGY ALERT*, we reviewed three published studies of intracranial thrombectomy (*New Engl J Med*, 2012) for acute ischemic stroke, and noted that there was no benefit compared to intravenous thrombolysis alone. However, these studies were performed with the first generation of thrombectomy devices, and the expectation was always that newer devices would show better results. Now, investigators using one of the newer devices, a stent-retriever named "Solitaire," have reported on their results in 202 patients with anterior circulation ischemic strokes treated within 8 hours of symptom onset. The primary endpoint was revascularization of the occluded artery, and the secondary endpoint was the rate of good functional outcome (defined as Rankin Scale 0-2 at 90 days).

The median age of the patients was 72 years, and 60% were females. The median NIH Stroke Scale was 17. Intracranial occlusions occurred at the internal carotid artery in 18% and middle cerebral artery in 82%. Successful revascularization was achieved in 79.2% of patients and procedure-related adverse events occurred in 7.4%. Favorable neurological outcomes were found in 57.9% and mortality was 6.9%. Symptomatic intracranial hemorrhage occurred in 1.5%. Although this was a single-arm study without a control group, the results are highly suggestive of a dramatic benefit from use of this device, and a randomized, controlled trial is needed to confirm these results. ■

the prevalence of interictal (IIH) and periictal (PIH) headache. Headaches that occurred within 1 year before or after an epileptic seizure were defined as IIH. PIHs were temporally divided into preictal (occurring until the onset of a seizure or beginning at least 24 hours before seizure), ictal (during a seizure without loss of consciousness), and postictal (occurring with the end of the seizure) headaches. IIH was considered to be migraine, tension-type headache, and "other" headache. PIHs were migrainous or tension-type headaches.

A total of 201 patients (median, 42 years; range, 18-83 years), including 95 (47.3%) female patients, were interviewed. Headaches were reported by 113 patients (56.2%) with migraine in 10.9% and tension-type headache in 19.4%. There were 69 patients (34.3%) suffering from IIH, 71 (35.3%) from PIH, and 27 (13.4%) from both headache types. Out of 69 patients with IIH, 22 (31.9%) suffered from migraine, 39 (56.5%) from tension-type headaches, and 10 (14.5%) from other types, with two patients reporting both migraine and tension-type headache. The vast majority of PIHs occurred postictally with either migrainous or tension-type headache. Analgesic treatment of IIH was more common than acute treatment of PIH. Multivariate analysis identified female sex as the only independent predictor of IIH, and low age at epilepsy onset and antiepileptic polytherapy as independent predictors of PIH. PIH was significantly associated with generalized tonic-clonic seizures. The vast majority of PIH occurred postictally and had either migrainous or tension-type headache-like characteristics. This study found that while IIH, and in particular migraine, did not occur more often in patients with epilepsy than expected in the general population, PIH occurred in more than a third of patients with epilepsy.

**■ COMMENTARY**

With headache being a virtually universal experience, an overlap between primary headaches (migraine and tension-type headaches) and other neurological diseases is to be expected. Determining whether there is an increased prevalence of headache in patients with a neurological disease, especially when the neurological disease and headaches occur in populations of predominantly the same age and gender, can be problematic. In this study of IIH in patients with epilepsy, the prevalence of tension-type headache (19%) and migraine (11%) was less than the prevalence predicted from epidemiological studies performed on the general population. More information is needed to analyze this finding, including whether the choice of antiepileptic drug (AED) could impact the prevalence of migraine headaches in an epileptic population.

PIH was frequently reported by patients with multiple seizures and was infrequently treated, even with over-the-counter analgesic medication. The disability associated with the actual seizure is often overt, but the head pain around the ictal event, while less evident to the health care provider, may be equally debilitating. The use of acute pain medications after a seizure should be encouraged in those with PIH. The impact of headaches associated with a seizure may dictate the choice of AED, with the possibility of dual therapeutic benefit. ■

# Seizure Characteristics in Early-stage AD

ABSTRACT & COMMENTARY

***By Padmaja Kandula, MD***

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*Dr. Kandula reports no financial relationships relevant to this field of study.*

***Synopsis:*** *This 5-year retrospective observational study describes the epilepsy encountered in patients with amnestic mild cognitive impairment and early Alzheimer's disease.*

**Source:** Vossel K, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol* 2013;70:1158-1166.

It has long been known that epilepsy may coexist with neurodegenerative illnesses such as Alzheimer's disease (AD). However, the timing of either clinical or subclinical epileptic activity with regards to cognitive decline has not been well established. These authors systematically studied the clinical and neurophysiologic characteristics of patients with early AD and amnestic mild cognitive impairment (aMCI) who had epilepsy vs control patients without epilepsy.

The investigators retrospectively searched the 5-year database (2007-2012) of the Memory and Aging Center at the University of California for those patients who met criteria for aMI and probable AD based on the International Working Group research criteria for aMCI or National Institute of Neurological and Communicative Disorders and Stroke — Alzheimer's Disease and Related Disorder Association criteria.

Among these candidates, patients with either a clinical diagnosis of epilepsy (two or more unprovoked seizures or first unprovoked seizure plus epileptiform electroencephalogram [EEG]) or subclinical epileptiform activity were then identified. Those patients with early-life onset of seizures or other possible epilepsy risk factors were excluded. Eventually, 12 cases of aMCI epilepsy, 35 cases of AD epilepsy, and seven cases of AD subclinical epileptiform activity were included in the study.

Date of onset of cognitive decline was obtained by caregiver retrospective assessment of behavioral baseline change that eventually developed into an obvious aMCI or AD feature. Seizure onset was also obtained by caregivers as first spell suggestive of later habitual seizures. The date of neurodegenerative disease diagnosis was the first visit fulfilling all research criteria for aMCI or probable AD. Cognitive function was assessed with the standard Mini-Mental State Examination. All EEGs were performed with 10-20 electrode placement. Antiepileptic drug response was assessed over a minimum of 3 months and categorized as either seizure-free, partial response (seizures reduced in severity and or frequency), neutral (no change in seizures), or paradoxical worsening (increase in seizure frequency or severity).

In those patients with aMCI and epilepsy, cognitive decline occurred 6.8 years earlier at 64.3 years vs 71.1 years in those without epilepsy. Patients with probable AD and epilepsy presented with cognitive decline 5.5 years earlier (64.8 years) vs those without epilepsy (70.3 years). Patients with AD and subclinical epileptiform activity showed an earlier cognitive decline at 58.9 years vs those without epilepsy (70.3 years).

Overall, seizure onset preceded or was simultaneous with aMCI or AD diagnosis in 83% of patients. Not surprisingly, the most common seizure type (47%) was complex partial and 55% were nonconvulsive seizures. EEG testing revealed epileptiform activity in 62% of patients with aMCI or AD. Epileptiform activity was predominantly unilateral and temporal. Of the four antiepileptic drug regiments (valproic acid, phenytoin, lamotrigine, levetiracetam), lamotrigine and levetiracetam had the best tolerability and efficacy (55% and 44% seizure free, respectively).

## ■ COMMENTARY

The findings of this study — that the incidence of seizures is independent of disease stage and can occur early or coincide with onset of cognitive decline — has potentially important clinical implications. In addition, the finding that more than half of the epilepsy cases were nonconvulsive also highlights the importance of early detection of seizures in this patient cohort. However, what remains unanswered is whether aggressive clinical treatment with an appropriate antiepileptic drug regimen can ultimately improve cognitive outcome or even disease course in this group. A clinical trial to answer that question would be important. ■

# Botulinum Toxin for Postherpetic Neuralgia

ABSTRACT & COMMENATARY

***By Michael Rubin, MD***

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*Dr. Rubin reports no financial relationships relevant to this field of study.*

***Synopsis:*** *In a small, placebo-controlled trial, botulinum toxin treatment showed a significant benefit for postherpetic neuralgia.*

**Source:** Apalla Z, et al. Botulinum toxin A in postherpetic neuralgia: A parallel, randomized, double-blind, single-dose, placebo-controlled trial. *Clin J Pain* 2013;29:857-864.

RARE IN CHILDREN AND THOSE UNDER 60 YEARS OF AGE, postherpetic neuralgia (PHN) causes persistent pain for months to years following resolution of the acute zoster rash, occurring in 6.9% of patients 60-69 years of age and in 18.5% of those 70 years or older, with increasing severity and persistence of PHN associated with advancing age. Current treatment options include tricyclic antidepressants, anticonvulsants, opioids, topical creams such as capsaicin or lidocaine, and intrathecal glucocorticoids. Botulinum toxin appears to be another, less invasive and reasonable, option.

Between April and November 2009, 30 adults, aged ≥ 18 years, with PHN of more than 3 months' duration, were enrolled in a 4-week, randomized, double-blinded, two-arm, single-dose, placebo-controlled study examining the safety, efficacy, and tolerability of botulinum toxin A (BTX-A) for PHN. Complete responders were subsequently maintained in an open-label, 20-week follow-up phase to evaluate continued pain control. Study enrollment required a baseline pain score of at least 7, as measured by a visual analogue scale (VAS), and patients were excluded if they demonstrated cranial nerve involvement, skin disorders that might interfere with BTX-A injection, or severe non-PHN pain disorders that could interfere with pain measurements. Dose of BTX-A totaled 100 IU, and was injected over the affected area in a checkerboard fashion, with each patient receiving a total of 40 injections. Patients assessed their pain severity daily for 2 weeks on waking in the morning, using a VAS (0-10), and then every 2 weeks for 12 weeks, followed by every 4 weeks for 10 weeks. Quality of sleep was assessed using a five-item questionnaire, encompassing overall sleep quality, number of nights unable to sleep due to pain, number of times sleep was interrupted at night by pain, number of continuous hours of nightly sleep, and length of time until falling asleep. VAS score reduction was the primary outcome measure, and secondary outcome measures included sleep score improvement and maintenance of > 50% improvement of VAS score after treatment. Statistical analysis encompassed Fisher exact test and, where appropriate, Mann-Whitney U test or the Pearson X2 test.

Thirty PHN patients were enrolled, mean age was 73.2 years, with 15 enrolled in each arm. Of those receiving BTX-A, 13 patients (87%) experienced at least 50% reduction in VAS pain score, compared to none of the placebo patients, with improvement achieved within the first 2 weeks and maintained over a median of 16 weeks. Sleep

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score similarly improved within 2 weeks among BTX-A recipients and continued until week 16. BTX-A was well tolerated, with no patient discontinuing treatment or experiencing systemic side effects. Pain during injection was seen equally in both the BTX-A and placebo arms, was transient, and resolved within 24 hours. BTX-A is safe and effective for PHN.

**■ COMMENTARY**

Initially introduced in the late 1970s for focal dystonias and strabismus, botulinum toxin presently enjoys widespread use for everything from anal spasm to vaginismus, including autonomic disorders such as hyperhidrosis, cosmetically troubling "crows-feet" and other troublesome facial lines, and even pain syndromes such as migraine and tension headaches. Best known for inhibiting acetylcholine release at the neuromuscular junction by interfering with calcium regulated synaptic vesicle exocytosis, its pain-modulating qualities appear to be independent of its effect on muscle contraction, suggesting alternate mechanisms for its analgesic capabilities. Evidence suggests that it both reduces Ia afferent fiber traffic and inhibits release of substance P, a neuropeptide with a significant role in pain perception and neurogenic inflammation. Formalin-induced pain in experimental animals, which results from direct stimulation of nociceptors followed by inflammation, rather than through muscle tension, is also reduced by botulinum toxin, supporting a direct effect on the nociceptor system, in addition to its neuromuscular junctional effect. ■

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## CME Questions

**1. Levetiracetam is approved by the FDA for all of the following *except*:**
   a. adjunctive treatment for idiopathic generalized epilepsy.
   b. monotherapy for juvenile myoclonic epilepsy.
   c. adjunctive treatment of partial onset seizures.
   d. adjunctive treatment of myoclonic seizures in juvenile myoclonic epilepsy.

**2. Maternal thyroxine levels between the 5th and 10th percentiles confer an increased risk for the development of autism.**
   a. True
   b. False

**3. Periictal headache is associated with which of the following?**
   a. Male gender
   b, Recent onset of seizures
   c. Tonic-clonic seizures
   d. Antiepileptic drug monotherapy
   e. Increased seizure frequency

**4. Which of the following was not a primary outcome measures of this retrospective observational study regarding seizure characteristics and Alzheimer's disease?**
   a. Response to antiepileptic drug treatment
   b. Seizure onset in relation to cognitive decline
   c. Medication adherence
   d. Epileptiform activity detection and location

**5. Which of the following is a treatment option for postherpetic neuralgia?**
   a. Antidepressants
   b. Topical creams such as capsaicin or lidocaine
   c. Intrathecal glucocorticoids
   d. Botulinum toxin A injections
   e. All the above

**6. Hemicraniectomy for large hemispheric infarcts results in a reduction in mortality, compared to medically treated patients.**
   a. True
   b. False

**7. Intracranial thrombectomy with the Solitaire stent-retriever results in good functional outcomes at 90 days in the majority of treated patients.**
   a. True
   b. False

**In Future Issues:** Neurodegenerative Disorders

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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## Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

**Source:** Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

## Addressing Diabetic Neuropathy

**Source:** Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

## When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

**Source:** Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

## Wedge Insoles for Knee Osteoarthritis: Probably Not

**Source:** Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

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## Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

**Source:** The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

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## Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

**Source:** Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

# Medications for Risk Reduction of Breast Cancer in Women

***In this issue:*** USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

## Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

## Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

## Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

## FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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