Patients with MRI lesions characteristic of MS, but without associated signs or symptoms, are at increased risk for multiple sclerosis and are described as having a "radiologically-isolated syndrome" (RIS).

**Background:** Asymptomatic white-matter lesions are commonly found on T2-weighted MRI imaging of the adult brain. Most are attributed to small vessel disease accompanying hypertension, diabetes, cocaine abuse, or other vasculopathy. Some lesions, however, have a topography and morphology highly suggestive of multiple sclerosis (MS): periventricular distribution; involvement of the corpus callosum; and an ovoid, homogeneous, well-circumscribed appearance. Similar profiles in optic neuritis and clinically isolated syndrome (CIS) are associated with high conversion rates to clinically definite MS. What happens to individuals in whom such lesions are discovered incidentally is uncertain.

**Objective:** To characterize the clinical and radiological course of asymptomatic patients with MRI lesions otherwise consistent with MS.

**Methods:** Incidental hyperintense T2-weighted white matter lesions detected by MRI (1.5 to 3.0 Tesla) had to be ≥3 mm, have a morphology and anatomical distribution highly suggestive of MS, and satisfy at least 3 of 4 Barkhof criteria for dissemination in space. Lesions with vascular patterns were excluded. Reasons for ordering MRI included migraine, head trauma, spells of uncertain origin, panic attacks, screening for aneurysms, curiosity, and other reasons. A detailed clinical history, examination, and serological and cerebrospinal fluid (CSF) testing excluded other disorders that can cause white matter lesions including vasculitis, blood dyscrasias, drug abuse, and toxic exposure. The MRI lesions had to be asymptomatic and could not account for any social, occupational, or overt mental dysfunction. Outcome measures included the time to the first clinical event (CIS) and the time to detection of a new, enlarging, or newly contrast-enhancing lesion on MRI.

**Results:** Among 44 subjects (41 females; median age, 38 years), 41 had longitudinal clinical follow-up and 41 had longitudinal MRI follow-up. The neurological examination was essentially normal at initial MRI. MRI lesions progressed in 59% of cases over a median 3-year period, but only 10 patients converted to either CIS or definite MS. The median time to CIS was 5 years. The presence of contrast-enhancing lesions on the initial MRI tripled the likelihood for developing new lesions on repeat MRI. Over more than a decade of observation, no disorder other than MS, was ever identified to account for the white matter lesions.

**Conclusions:** Individuals with incidental MRI findings highly suspicious for demyelinating lesions are at increased risk for developing MS. More studies are needed to fully characterize this risk. The authors propose the term "radiologically isolated syndrome" (RIS) to describe such patients.

**Reviewer's Comments:** An accompanying editorial examines whether RIS patients should receive treatment for very early MS. Bourdette and Simon argue "no" pending further research, unless it were shown that asymptomatic RIS patients were actually cognitively impaired or destined to progress to future disability, something current technology cannot predict. (Reviewer-Michael Jacewicz, MD).

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Keywords: MRI Anomalies

Print Tag: Refer to original journal article
RS May Be Alternative to Open Surgery for MTLE

A Multicenter, Prospective Pilot Study of Gamma Knife Radiosurgery for Mesial Temporal Lobe Epilepsy: Seizure Response, Adverse Events, and Verbal Memory.

Barbaro NM, Quigg M, et al:
Ann Neurol 2009; 65 (February): 167-175

Following gamma knife radiosurgery for unilateral mesial temporal lobe epilepsy, patients frequently experience a transient increase in auras.

Background: Temporal lobectomy is the most common surgery for intractable epilepsy. One randomized controlled trial reported a 1-year seizure-free rate of 65% after temporal lobectomy. Adverse events can include verbal memory deficits, mood disorders, psychosis (rarely) after this costly open surgery.

Objective: To investigate the efficacy and safety of gamma knife radiosurgery (RS) for unilateral mesial temporal lobe epilepsy (MTLE).

Design: Pilot prospective study.

Participants: Adults from 7 epilepsy centers with intractable temporal lobe seizures arising from a single temporal lobe, as documented by video-electroencephalogram (EEG) and MRI were included. Exclusion criteria were other neuroradiologic abnormalities, psychological diagnoses that would make it difficult to accurately assess seizures, significant medical comorbidities, noncompliance, and drug abuse. All subjects experienced an average of at least 3 complex partial seizures per month over a 3-month pretreatment observation phase, despite best medical care.

Methods: 30 subjects were randomized to treatment with either a 20 or 24 Gy dose of RS to an area including the amygdala, the anterior 2 cm of the hippocampus, and parahippocampal gyrus. Seizure frequency was documented prior to treatment. The primary outcome measure was seizure frequency at follow-up. Neuropsychological testing was performed at baseline and at 12 and 24 months after RS. There were 13 high-dose and 17 low-dose subjects. Three subjects did not complete the 36 month study: 1 was lost to follow-up, 1 required urgent temporal lobe surgery because of massive brain edema, and another underwent temporal lobectomy at 24 months. The 2 treatment groups were comparable with respect to gender and mean baseline seizure frequency. Statistical analysis was on an intention-to-treat basis.

Results: Both groups had significant reductions in seizures by 1 year after treatment. At the 36-month follow-up evaluation, 67% of subjects were seizure-free for the prior 12 months (77% in the high-dose group and 59% in the low-dose group). The prevalence of verbal memory impairment was 15%; 12% of subjects had verbal memory improvement. Subjects often experienced a transient increase in auras. This effect receded as seizures came under better control. Higher RS dose resulted in increased steroid prescribing, new headaches, and visual field defects.

Conclusions: RS for unilateral MTLE provides seizure remission rates comparable with those reported previously for open surgery, with minimal safety concerns.

Reviewer's Comments: This well-done study demonstrates that gamma knife RS may eventually be a viable alternative treatment to temporal lobectomy for patients with unilateral MTLE. The advantage of this treatment over temporal lobectomy would be less expense and avoidance of craniotomy. The disadvantage of this treatment would be that seizure control might be delayed for up to 1 year, whereas it is typically immediate after temporal lobectomy. (Reviewer-W. Steven Metzer, MD).

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Keywords: Mesial Temporal Lobe Epilepsy

Print Tag: Refer to original journal article
DNET in children is commonly associated with refractory partial onset seizures. Removal of the lesion and surrounding epileptogenic zone, when applicable, commonly results in complete resolution of seizures.

**Background:** Dysembryoplastic neuroepithelial tumors (DNET) in children are characteristically cortically based and frequently cause seizures. The presenting symptom is typically partial onset seizures that are commonly difficult to control with medication. MRI typically reveals a well demarcated lesion that usually does not enhance significantly following contrast administration. Pathological classification is usually World Health Organization (WHO) grade 1, with only rare reports of malignant transformation. Complete surgical resection alone is usually curative.

**Objective:** To examine the outcome following resection of DNET from children with epilepsy.

**Methods:** A retrospective review at a children's hospital in Turkey identified 29 consecutive patients who had DNET between 1994 and 2007. Age at seizure onset, age at time of surgery, electroencephalogram (EEG) findings, MRI findings, medical treatment, surgical procedure, seizure outcome, and pathological findings were all documented.

**Results:** The number of males and females was essentially equal. All patients had presented with seizures, including 27 with complex partial, 1 with simple partial seizures, and 1 with generalized seizures. Interictal epileptiform abnormalities were present in just over 80% of patients. Almost 70% of the tumors were localized to the temporal lobes on MRI. Tumor location was extratemporal in 9 patients or about 30%. Of the 20 patients with DNET within the temporal lobe, 16 underwent temporal lobectomy. This included amygdalohippocampectomy in 13 patients due to the close proximity of the lesion to the mesial temporal structures. Three patients had anterior temporal lobectomy without resection of the mesial structures. Lesionectomy was performed in 13 patients, with location in the temporal lobe in 4, intraventricular in 3, frontal in 2, parietal in 2, and frontoparietal and parietooccipital in 1 each. Postoperative follow-up ranged from 3 months to 10 years. Outcome was complete seizure freedom or Engel Class IA in 27 (>90%) and Engel Class IB in the remaining 2 patients. Recurrence of seizures occurred in 8 patients with residual tumor, and a second surgery, with resection of the residual tumor resulted in seizure-freedom in all 8.

**Reviewer’s Comments:** This study documents that DNET in children is almost always associated with medically-refractory seizures. Removal of the lesion and surrounding epileptogenic zone when applicable, most commonly results in a good outcome with resolution of seizures. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Dysembryoplastic Neuroepithelial Tumor

Print Tag: Refer to original journal article
Incidence/Prognosis

**Objective:** To ascertain the prevalence of ≥50% stenosis of large vessels of the posterior circulation in patients with a recent stroke or transient ischaemic attack (TIA) in that distribution.

**Design:** Substudy of the Oxford Vascular Study, an ongoing population-based study of vascular events in approximately 90,000 residents of 1 area in the United Kingdom.

**Participants:** Consecutive patients with a vertebrobasilar (VB) TIA or stroke in a 3-year period.

**Methods:** Patients with minor strokes or TIAs during the study were identified by routine surveillance, and then seen by study physicians who obtained a history and neurologic examination, as well as information on stroke risk factors. Patients with VB symptoms had contrast-enhanced magnetic resonance angiography (MRA) or computed tomography angiography (CTA) in cases where MRI was not possible. Stenoses of the vertebral artery (VA) or basilar artery (BA) ≥50% were deemed "symptomatic" if they were felt reasonably likely to be responsible for recent symptoms. All patients were treated with aspirin ± clopidogrel and a statin and followed up to 90 days.

**Results:** TIA or minor stroke occurred in 151 patients with a VB distribution. Of these, 141 had MRA or CTA, which revealed a 26% incidence of ≥50% stenosis in the VB circulation. This was higher than the incidence of ≥50% internal carotid artery (ICA) stenosis in patients with carotid distribution TIAs (only 12%). The sole clinical feature predicting the finding of a ≥50% VB stenosis was the occurrence of multiple TIAs prior to the first clinic or emergency department visit. Of the 37 VB stenoses, 23 were in the extracranial VA, 11 in the intracranial VA, and 3 in the basilar artery (BA). The majority of the extracranial VA stenoses were at or near the origin. Of the 37 patients with symptomatic VB stenoses, 18 had infarcts on MRI, reasonably well distributed among the occipital lobes, cerebellum, thalamus, and brainstem. The risk of recurrent VB TIA or ischemic stroke was higher for patients with a stenosis than for patients with a recent VB event without VB stenosis.

**Conclusions:** The frequency of ≥50% stenosis in at least 1 vessel in the VB circulation in patients with a TIA or minor stroke in that territory was greater than that of a stenosis of the internal carotid artery in patients with recent anterior circulation symptoms. Symptomatic VB stenosis was associated with a high risk of recurrent events, including stroke.

**Reviewer's Comments:** Conventional wisdom has, for many years, held that the prognosis of posterior circulation TIAs was better than that for carotid TIAs. Recent clinical studies contradict this, as does the current study. The issue of atheromata at or near the VB take-off, where it is accessible to either angioplasty/stenting or endarterectomy, will probably need to be revisited, perhaps in a randomized controlled trial. (Reviewer-James W. Schmidley, MD).

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Keywords: Vertebral/Basilar Artery Stenosis

Print Tag: Refer to original journal article
Increased Risk of Epilepsy After TBI Persists Over 10 Yrs

Long-Term Risk of Epilepsy After Traumatic Brain Injury in Children and Young Adults: A Population-Based Cohort Study.

Christensen J, Pedersen MG, et al:

Lancet 2009; (February 23): epub ahead of print

Relative risk for epilepsy after TBI increases with increasing age, female gender, and a positive family history of epilepsy.

**Background:** The risk of epilepsy is known to be increased after traumatic brain injury (TBI), but the duration of this increased risk has been poorly defined.

**Objective:** To investigate long-term risk of epilepsy after TBI.

**Design:** Retrospective, population-based, cohort review.

**Participants:** 1,605,216 people born in Denmark over a 25-year period (1977 to 2002).

**Methods:** Medical follow-up data for this cohort were analyzed for a total of 19,527,337 person-years.

**Results:** During this period, a total of 78,572 people were identified as having at least 1 TBI; in the same period, 17,470 people developed epilepsy. Of these, 1017 had a preceding TBI. Relative to no brain injury, the overall average risk of epilepsy over time was 2 times higher after a mild brain injury (RR, 2.22), 7 times higher after severe brain injury (RR, 7.4), and 2 times higher after skull fracture (RR, 2.17) (all statistically significant). The relative risk of epilepsy after mild and severe brain injury was highest during the first 6 months following the injury (5.46 and 21.26, respectively), but remained significantly higher for >10 years after TBIs, compared to people without a history of head injury. TBI was associated with a significantly increased risk of epilepsy in all age groups, although the risk increased significantly with age for mild and severe TBI, and was highest among people aged >15 years at injury. The relative risk of epilepsy after mild TBI was higher among women than among men, and a family history of epilepsy further significantly increased the relative risk of developing epilepsy after TBI.

**Conclusions:** An increased relative risk of epilepsy can persist for >10 years after TBI. The investigators emphasize that these data suggest a long time interval for potential preventive treatment of high-risk patients.

**Reviewer’s Comments:** This study provides interesting information about the long-term risk of epilepsy after even mild TBI, and this risk increases with increasing age, female gender, and a positive family history of epilepsy. Unfortunately, we have no established prophylactic therapy at this time for the prevention of epilepsy in these patients. (Reviewer-W. Steven Metzer, MD).

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Keywords: Epilepsy

Print Tag: Refer to original journal article
In semantic dementia, whole-word reading of exceptional item-specific word forms is lost and such words are read using subword processing circuits in the inferior parietal region.

**Objective:** To determine the anatomical substrates for whole-word and subword processing by testing patients with semantic dementia (SD) and surface dyslexia.

**Participants/Methods:** 5 patients with SD based on published criteria read orthographically regular words and orthographically regular pseudowords better than exception words (orthographically irregular). Patients were compared to a control group as they underwent functional MRI (fMRI) scanning while reading aloud different regular words, exception words, and pseudowords. Regular words and exception words were either high frequency or low frequency. Pseudowords were generated by changing 1 or 2 letters in the regular words, thereby maintaining orthographic regularity. Patients and controls also underwent MRI scanning and voxel-based morphometry; regions of interest included occipital cortex, fusiform gyrus, sensorimotor cortex, and superior temporal gyrus, regions activated in prior studies of single word reading.

**Results:** All SD patients made numerous over-regularization errors on low-frequency exception words, for example, reading "plaid" as "played." Patients were also worse than controls in reading low-frequency regular words and pseudowords, but these difficulties were much less severe than with low-frequency exception words. During fMRI in control subjects, all 5 word types produced bilateral activation in the occipital cortex, fusiform gyrus, sensorimotor cortex, and superior temporal gyrus. Pseudowords and low frequency regular words produced additional activation in the left intraparietal sulcus. In the SD patients, all 5 word types produced bilateral activation in occipital and sensorimotor cortex but none in the fusiform gyrus or the superior temporal gyrus. As with the controls, pseudowords and low-frequency regular words produced additional activation in the left intraparietal sulcus. Unlike the controls, however, the intraparietal sulcus was also activated by low-frequency exception words. In the SD patients, voxel-based morphometry revealed reduced grey matter volumes bilaterally, greatest on the left, involving the temporal poles, fusiform gyrus, and anterior superior temporal gyrus; the left intraparietal sulcus was spared.

**Conclusions:** The left intraparietal sulcus is involved in subword reading processes. In SD with surface dyslexia, loss of anterior temporal lobe structures necessary for whole-word (nonphonological) reading processes results in recruitment of the left intraparietal sulcus for reading orthographically irregular exception words, and accounts for over-regularization errors. This study thus provides an anatomical explanation for the difference between surface dyslexia and phonological dyslexia and why surface dyslexia is a feature of semantic dementia.

**Reviewer's Comments:** This study provides an anatomical explanation for the difference between surface dyslexia and phonological dyslexia. Although tough sledding for the non-specialist, it is worth the effort.

(Reviewer- John C. Brust, MD).

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Keywords: Semantic Dementia

Print Tag: Refer to original journal article
Clopidogrel is a prodrug; it is converted to an active drug by the cytochrome P450 system, especially CYP2C19.

Objective: Patients taking clopidogrel who carry alleles of the CYP2C19 gene that are associated with lower enzymatic activity have an increased risk of cardiovascular events, mainly MIs, but including stroke. Some proton pump inhibitors (PPIs) inhibit CYP2C19, thus potentially compromising the effectiveness of clopidogrel, as well.

Design: Population-based, nested, case-controlled study.

Participants: Residents of a Canadian province, aged >65 years, who had had suffered a recent myocardial infarction (MI), but survived to be discharged from hospital.

Methods: National databases were used to track prescriptions and to identify clinical end point events. The cohort was defined as all patients aged >65 years who had been hospitalized for an MI and filled a prescription for clopidogrel within 3 days of discharge. This cohort was followed until they had another MI, died, or survived for 90 days after the index hospital discharge. Cases were defined as patients from the cohort who died or had a second MI during follow-up. Controls were selected from patients in the cohort who survived and were not readmitted for MI during follow-up; they were matched for age, whether or not they had received percutaneous coronary intervention, discharge date, and probability of death using a validated predictive model. PPI use within the 30 days immediately before the end of the follow-up period (whether defined by a recurrent MI or death or completion of the 90 days) was considered "current." "Previous" use was defined as within 31 to 90 days of the end of the follow-up period; "remote" use was essentially before the index MI. Logistic regression was used to generate an odds ratio for the association between reinfarction/death and use of a PPI. The reference group was patients who had no prescription for a PPI. (Recall that all patients had filled a prescription for clopidogrel.) Odds ratios were adjusted for multiple factors known to affect prognosis following MI. Use of other cardiovascular medications, including CYP 450 inhibitors and inducers, was also taken into account.

Results: There were approximately 750 cases and >2000 controls. Only "current" PPI use was associated with increased risk of recurrent MI/death. This relationship was significant for the PPIs as a class, but not for pantoprazole as an individual drug.

Conclusions: Use of most PPIs was associated with increased risk of recurrent MI and death in older patients treated with clopidogrel following an MI.

Reviewer's Comments: It would be very interesting to re-examine the results of the recent randomized controlled trial (PROFESS) comparing aspirin/extended-release dipyridamole with clopidogrel for secondary stroke prevention, with separate analysis of patients using PPIs, if possible, by individual drug. (Reviewer-James W. Schmidley, MD).

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Keywords: Clopidogrel

Print Tag: Refer to original journal article
**BoNT Should Be First-Line Tx for Upper Limb Spasticity**

**Botulinum Neurotoxin Versus Tizanidine in Upper Limb Spasticity: A Placebo-Controlled Study.**

Simpson DM, Gracies JM, et al:

J Neurol Neurosurg Psychiatry 2009; 80 (April): 380-385

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**BoNT injections should be considered early for the treatment of upper extremity spasticity.**

**Design/Objective:** This randomized, controlled, parallel-group, double-blind, multicenter study compared the efficacy, safety, and tolerability of botulinum neurotoxin (BoNT) with oral tizanidine (TZD) in the treatment of upper limb spasticity.

**Participants/Methods:** Participants were 18 to 85 years of age with a stroke or traumatic brain injury (TBI) at least 3 months earlier and spasticity of the wrist (score ≥3 for wrist flexor tone on the modified Ashworth Scale [MAS]). This had to cause difficulty with hygiene or dressing, pain, or malposition of the wrist (score of ≥2 on the Disability Assessment Scale [DAS]). Exclusion criteria were the inability to passively move the wrist >10°, prior phenol/alcohol block, or tendon transfer of the affected extremity, BoNT injection in the last 4 months, prior casting of the limb within 2 weeks, severe muscle atrophy or infection of the limb, orthostatic hypotension or an oral antispasticity agent within 14 days, impaired renal or hepatic function, pregnancy, or plan for pregnancy. Patients were randomly assigned to 1 of 3 groups: (1) intramuscular BoNT-A (Botox, Allergan, Irvine, California) plus oral placebo; (2) intramuscular placebo plus oral TZD; or (3) intramuscular placebo plus oral placebo. The oral medication (placebo or TZD) was initiated at 2 mg and slowly increased as tolerated to as much as 36 mg a day in 2 divided doses. The study lasted 22 to 24 weeks with a screening visit, a second visit to initiate oral medications and give injections, and follow-up assessments at 3, 6, 12, and 18 weeks. The primary efficacy measure was the difference in change from baseline in the wrist MAS between treatment groups at 6 weeks after treatment initiation. Secondary outcome variables included differences in change from baseline in the following measures: DAS, Modified Frenchay Scale, 10 m walking speed, grip strength, finger tap test, Epworth Sleepiness Scale, and various cognitive evaluations. Adverse events, vital signs, physical examination, and liver function tests were assessed.

**Results:** 60 patients were randomized equally to the 3 groups. Fifty-six patients remained through the 6-week primary end point and 41 patients remained at 22 weeks. BoNT yielded greater tone reduction in finger and wrist flexors at 3 and 6 weeks than TZD or placebo. BoNT showed greater improvement in the cosmosis domain of the DAS at 6 weeks. TZD was no better than placebo in tone reduction and had more adverse effects than the other groups, while BoNT had no more side effects than placebo.

**Conclusions:** BoNT is safer and more effective for reducing spasticity of the upper extremity than TZD and should be considered a first-line therapy.

**Reviewer’s Comments:** This study supports the use of BoNT for spasticity early in treatment, a time when it should work well with a physical therapy program. (Reviewer-John Schwankhaus, MD).

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Keywords: Spasticity

Print Tag: Refer to original journal article
In Parkinson's disease, high-frequency stimulation of the SNr improves balance during locomotion, but not step length and velocity.

**Objective:** To determine the effects of high-frequency substantia nigra pars reticulata (SNr) stimulation on locomotion and balance in Parkinson's disease (PD).

**Participants/Methods:** Of the 204 patients with bilaterally implanted electrodes for subthalamic nucleus (STN) stimulation, 7 had at least 1 contact electrode within SNr. Patient ranged in age from 50 years to 68 years. Disease duration was 13 to 20 years, the duration of STN stimulation was 20 to 72 months, and all patients were taking levodopa. Patients were compared to 7 controls. Subjects were tested in 5 conditions: ON STN stimulation/OFF drug; ON SNr stimulation/OFF drug; OFF stimulation/OFF drug; OFF stimulation/ON drug; and ON STN stimulation/ON drug. Patients received disability scores reflecting both axial and distal symptoms. Specific testing involved gait initiation and walking either "naturally" or "fast" for several meters. Quantitative measures were taken of step length, peak progression velocity of the first step, and vertical velocity of the center of gravity, with the latter reflecting "braking capacity" and control of balance. Electromyography (EMG) recorded activity in the soleus muscle.

**Results:** Whereas levodopa and STN stimulation (alone or together) improved both axial and distal symptoms, SNr stimulation improved only axial symptoms. On tests of gait initiation, levodopa and STN stimulation (alone or together) improved step length and velocity, but SNr stimulation did not. On the other hand, during fast walking, levodopa had no effect on braking, whereas both STN and SNr stimulation improved braking, with increased activity in the stance leg soleus muscle.

**Conclusions:** Locomotion, as reflected in anteroposterior (length and velocity) measures, and balance, as reflected in vertical (braking capacity) measures, are controlled by 2 distinct systems within the basal ganglia. The system controlling balance appears to be levodopa-independent and to involve the SNr and its inhibitory projections to pontomesencephalic structures, including the pedunculopontine and cuneiform nuclei. High-frequency stimulation is thought to reduce neuronal activity, whereas low-frequency stimulation is thought to activate neuronal activity. Thus, improved postural control during high-frequency stimulation of the SNr is consistent with similar improvement during low-frequency stimulation of the pedunculopontine nuclei.

**Reviewer's Comments:** Clinical investigation thus continues to increase our understanding of basic neurophysiological mechanisms. (Reviewer-John C. Brust, MD).
Contrary to previous beliefs, the frequent use of analgesic/narcotic medications may not block the effect of prophylactic medications for medication overuse headaches.

**Objective:** To evaluate the effect of early introduction of prophylactic treatment compared with abrupt withdrawal and with a control group, in patients with medication overuse headache (MOH).

**Design:** Open-label, randomized, multicenter trial.

**Methods:** Patients with suspected MOH completed a headache diary for at least 3 months before the first visit. Inclusion criteria were age 18 years to 70 years, headache ≥15 days/month for at least 3 months with combined intake of ergots, triptans, opioids, and/or combination medication (simple analgesics with caffeine) for ≥10 days/month, or simple analgesics ≥15 days/month. Patients were excluded if there were contraindications for all types of prophylactic drugs, no improvement of headache at previous trials to stop overused medications, a history of hemicrania continua, chronic paroxysmal hemicrania or cluster headache, frequent use of analgesics for complaints other than headache, pregnancy, breastfeeding, or not using effective contraception. Patients were randomly assigned to 1 of 3 groups. In the withdrawal group, patients were advised to withdraw medications abruptly, allowed to use rescue medication up to 2 days per week, offered inpatient detox or up to 2 weeks sick leave, and offered to start prophylactic medication after 3 months. In the prophylaxis group, preventive medication started on day 1, and patients were not explicitly advised to withdraw overused medications. In the control group, no preventive medication was used and patients were not advised to stop analgesics. Follow-up visits were at 1, 3, 5, and 12 months, with anxiety, depression, and quality-of-life questionnaires performed at baseline and months 5 and 12. In the headache diary, information on the presence, duration, severity, and associated symptoms of headache was recorded. The major primary outcome measure was change in the number of headache days at month 3 compared to baseline.

**Results:** The primary outcome measure, change in headache days per month, did not differ among groups. The prophylaxis group had the greatest decrease in headache days compared to baseline, as well as a significantly more pronounced reduction in headache index (headache days/month x headache intensity x headache hours) at 3 and 12 months compared with the withdrawal group. Fifty-three percent of those in the prophylaxis group compared to 25% in the withdrawal group had a ≥50% reduction in headache days at 12 months.

**Conclusions:** Total headache suffering was reduced more effectively by starting prophylactic medications without previous detoxification as compared to abrupt withdrawal of overused medications without associated administration of prophylactic drugs.

**Reviewer's Comments:** It is important to know that early introduction of prophylactic medications is effective in treating MOH, even without stopping the offending agents, especially in patients who need these medications for other nonheadache pain. (Reviewer-John Schwankhaus, MD).

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Keywords: Medication Overuse Headaches

Print Tag: Refer to original journal article
100 mg/day Topiramate for Tx of Adolescent Migraines

Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Topiramate for Migraine Prevention in Pediatric Subjects 12 to 17 Years of Age.

Lewis D, Winner P, et al:

Pediatrics 2009; 123 (March): 924-934

A dose of 100 mg/day of topiramate for migraine prevention in adolescents is more effective than 50 mg/day, which is essentially no better than placebo.

Background: The onset of migraine commonly occurs during childhood or adolescence. Approximately 10% of children between the age of 5 years and 15 years and >25% of individuals between 15 years and 19 years of age experience migraine. There are actually no medications approved by the Food and Drug Administration for prophylaxis against migraine in the pediatric age group.

Objective: To evaluate the safety and efficacy of topiramate in the prevention of migraine in adolescents between 12 and 17 years of age.

Design/Methods: A randomized, double-blind, parallel-group, placebo-controlled trial was performed to evaluate topiramate as therapy for adolescents with at least a 6-month history of migraine. These patients were required to have an average of 3 to 12 migraine episodes per month and no more than 14 headache days per month. There was a pretreatment phase of 9 weeks that included a 1-week evaluation phase, 4 weeks to taper off other medications used for migraine prevention, and a 4-week baseline phase. Subjects were then randomized to receive topiramate with an ultimate dose of 50 mg/day or 100 mg/day, or to receive placebo. The treatment phase included a 4-week titration phase and a 12-week period on the target dose. This was followed by a 2-week period during which the study medication was tapered and discontinued, and a 4-week period off medication. Headache and medication records were maintained by each subject throughout the study. The primary outcome measure was the percent reduction in monthly migraine attacks comparing the number at baseline to that during the last 12 weeks of the treatment phase. Secondary measures were the percent decrease in the number of migraine days per month and the 50% responder rate. Safety and tolerability were also evaluated.

Results: A statistically significant decrease in the number of migraine attacks per month occurred in the 100-mg/day group, with a median decrease of 72% compared to 44% in the placebo group. The reduction in migraine attacks in the 50-mg/day group was essentially equal to that in the placebo group. Likewise, the 100-mg/day dose resulted in a statistically significant decrease in migraine days per month compared to placebo and the 50-mg/day dose did not. A >50% reduction in migraines occurred in 83% of patients in the 100-mg/day group compared to 45% in the placebo group. Side effects that were more common in the treatment groups compared to placebo were paresthesia and dizziness. Serious adverse reactions were not reported.

Reviewer's Comments: Topiramate has become a commonly used medication for the prevention of migraines in children and adolescents. This study indicates that a dose of 100 mg/day is needed to likely reduce migraine frequency in adolescents. A 50-mg/day dose was no more effective than placebo. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Topiramate

Print Tag: Refer to original journal article
More than 90% of patients with IIH are women, but men are twice as likely to suffer severe loss of vision.

**Background:** Idiopathic intracranial hypertension (IIH) is much less common in men than women.

**Objective:** To compare the characteristics of IIH in men versus women.

**Design:** Retrospective study.

**Participants:** All patients with IIH treated at 3 academic neuro-ophthalmology clinics from 1989 to 2007.

**Methods:** The diagnosis of IIH was made according to the modified Dandy criteria: the presence of binocular papilledema; the absence of focal neurological signs except abducens nerve palsy; cerebrospinal fluid (CSF) opening pressure ≥25 cm; normal CSF composition; normal imaging of the brain; and no dural venous sinus thrombosis.

**Results:** Of the 721 patients, 655 (91%) were women and 66 (9%) were men. Women were significantly more likely than men to present with headache, and men were more likely than women to present with visual symptoms. Men had worse visual acuity and visual-field loss than women, at both presentation and final evaluation. The relative risk of visual loss for men compared to women was 2.1 (95% CI; 1.4 to 3.3; \( P = 0.002 \)) for 1 eye and 2.1 (95% CI; 1.1 to 3.7; \( P = 0.03 \)) for both eyes. Men were more likely to have sleep apnea than women (24% vs 4%; \( P < 0.001 \)). Men did not differ from women in age or degree of obesity.

**Conclusions:** This is the largest series of patients and of men with IIH ever reported. Men are twice as likely as women to suffer severe loss of vision; therefore, they require more frequent examination and more aggressive treatment.

**Reviewer’s Comments:** Obstructive sleep apnea (OSA) causes hypoxemia and hypercarbia, which can, in turn, cause intracranial hypertension through cerebral vasodilatation. In their accompanying editorial, Wall and Purvin consider what relationship OSA (which is more common in men than women with IIH) might have with IIH. Is OSA a comorbidity with obesity or a cause of intracranial hypertension that persists throughout the day? Does OSA and not gender account for the worse visual outcome in men? Because the study was retrospective, it cannot answer these questions, but it seems reasonable to evaluate men with IIH for OSA. (Reviewer-Marc D. Winkelman, MD).

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**Keywords:** Idiopathic Intracranial Hypertension

**Print Tag:** Refer to original journal article
Oral Methotrexate May Be Ineffective Steroid-Sparing Agent in CIDP

Randomised Controlled Trial of Methotrexate for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (RMC Trial): A Pilot, Multicentre Study.

RMC Trial Group:

Lancet Neurol 2009; 8 (February): 158-164

Oral methotrexate may not prove to be effective in chronic inflammatory demyelinating polyradiculoneuropathy.

Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated polyneuropathy, often responsive to corticosteroids or intravenous immunoglobulin (IVIG). Immunosuppressive agents are often used as steroid-sparing agents or to decrease the dosing of pulse IVIG therapy.

Objective: To test whether methotrexate is effective in CIDP and, particularly, in achieving this goal.

Design: Pilot, multicenter, randomized, placebo-controlled study in 26 European centers.

Participants: Patients with CIDP, confirmed by neurologists and based on accepted clinical and electrodiagnostic criteria, who responded to IVIG, corticosteroids or both, were included. Patients had a modest disability based on the overall neuropathy limitations score (ONLS; range, 0 to 12) and a medical research council (MRC) sum score (range, 0 to 80). Most patients (82%) were receiving IVIG.

Methods: Patients were randomized to receive oral methotrexate (15 mg weekly) or equivalent placebo over 40 weeks. After the mid-trial visit (usually week 16), the dose of IVIG or corticosteroid for patients who were improving or stable was decreased by 20% every 4 weeks until discontinued by week 32. The primary outcome was the proportion of change in mean weekly dose per kilogram of body weight of IVIG or corticosteroids in the last 4 weeks compared to the first 4 weeks. Secondary outcomes included changes in ONLS and MRC sum score.

Results: 59 of 60 randomized patients completed the study with no differences in disability between either group at entry. Fourteen of 27 patients (52%) receiving methotrexate compared to 14 of 32 (44%) of the placebo group were able to reduce their dosage by 20% (adjusted OR, 1.21; 95% CI, 0.40 to 3.70). There were no differences in any of the secondary outcomes. The drug was well tolerated with lymphopenia in 37% of patients receiving methotrexate vs 18% with placebo.

Conclusions: Oral methotrexate (15 mg weekly) does not seem to benefit patients with CIDP and does not offer a steroid-sparing effect or assist in reducing IVIG dosage.

Reviewer's Comments: This study was plagued by a higher-than-expected response to placebo, similar to a recent study on the efficacy of another immunosuppressive (mycophenolate mofetil) in a different neuromuscular autoimmune disorder (myasthenia gravis) (Neurology 2008; 71: 400-406; reviewed October 2008). It is possible that patients were "over-treated" with higher IVIG and steroid dosages than necessary, which made it possible to taper the placebo group too. Although many U.S. neuromuscular specialists do not use methotrexate as a first-line immunosuppressant agent, this was a disappointing pilot trial. However, a larger study and a different design are necessary for confirmation and before methotrexate is considered definitely ineffective in CIDP. (Reviewer-Bashar Kadirji, MD).

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Keywords: Chronic Inflammatory Demyelinating Polyneuropathy

Print Tag: Refer to original journal article
Orthostatic headache can occur without evidence of CSF leak, intracranial hypotension, or postural orthostatic tachycardia syndrome. The pathophysiology is unknown.

**Background:** Orthostatic headache (OH) is present in the upright posture and is relieved by lying down. It can be a symptom of intracranial hypotension, caused by a cerebrospinal fluid (CSF) leak, either spontaneous or iatrogenic (lumbar puncture or spinal surgery) or a symptom of postural orthostatic tachycardia syndrome (POTS).

**Objective:** To report patients with OH not caused by those mechanisms.

**Design:** Retrospective case series.

**Participants:** From 2001 to 2006, 125 patients were referred to the senior author at the Mayo Clinic for OH. Six patients (4.8%) proved not to have intracranial hypotension, CSF leak, or POTS.

**Methods:** Evidence of intracranial hypotension consisted of CSF opening pressure <65 mm H$_2$O on recumbent lumbar puncture and several head MRI findings (subdural fluid collection, abnormal pachymeningeal enhancement, pituitary enlargement, descent of cerebellar tonsils, crowding of the posterior fossa, obliteration of perichiasmatic or preponopt cistern, and flattening of the pons or optic chiasm. In order to exclude a CSF leak, patients underwent MRI with and without contrast and CT myelography of the spine, as well as indium-111 radioisotope cisternography. In patients with orthostatic intolerance, POTS was excluded by “autonomic reflex screen testing” (tests not specified).

**Results:** 4 of the 6 patients were men. The mean age of the patients was 40 years (range, 20 to 65 years). The median duration of symptoms was 2 years (range, 0.5 to 16 years). The location of headache varied, but was bilateral. The headache was described as a steady pressure. Relief with recumbency was complete in 4 patients and partial in 2. Cochleovestibular symptoms (tinnitus, sensation of fullness in the ears, dizziness or vertigo) were present in 4 patients; and photophobia and phonophobia in 3. The median CSF pressure was 140 mm H$_2$O (range, 86 to 186 mm H$_2$O). Analgesic medications were ineffective. Epidural blood patch helped for at most 2 weeks. Three patients could not work because of their headaches. The mean duration of follow-up was 4 years (range, 2.5 to 5.5 years), during which only 1 patient recovered spontaneously.

**Conclusions:** OH can occur without evidence of CSF leak, intracranial hypotension, or POTS.

**Reviewer’s Comments:** Although the pathophysiology is unknown, the authors offer 2 possible mechanisms for their findings: (1) an intermittent CSF leak or one that is too slow to be detected; and (2) an overly compliant lumbar cistern into which CSF from the head shifts when the patient is upright.

(Reviewer-Marc D. Winkelman, MD)
The incidence of CTS has significantly increased in the last 2 decades.

**Background:** Carpal tunnel syndrome (CTS) is one of the most common entrapment neuropathies seen in clinical practice. The incidence of CTS and its surgical treatment has not been investigated, partly because there is no gold standard for diagnosis.

**Objective:** To investigate the trends in CTS over 2.5 decades in Olmsted County, MN.

**Design:** Retrospective analysis of the records of patients with CTS diagnosed between 1981 and 2005 and filed in the Rochester Epidemiology Project medical record system.

**Methods:** 10,069 patients were diagnosed with CTS in this period. Due to the large number of cases, one of the authors reviewed 194 sample charts. Of these, 156 cases met criteria for CTS: 131 met symptom criteria for classic/probable CTS (defined as numbness, tingling, burning, or pain in at least 2 of digits 1, 2, or 3), and 25 met criteria for possible CTS (defined as numbness, tingling, burning, or pain in at least 1 of these digits). Of these patients, 113 (58%) had an electrodiagnostic study, and 88 (45% of the whole sample and 78% of those tested) had findings consistent with CTS.

**Results:** The female-to-male ratio was 2.2:1, which did not change significantly over time. The incidence of CTS diagnosis increased from an overall incidence of 258 per 100,000 person-years in 1981-1985 to 424 per 100,000 in 2001-2005 (P <0.0001). This was more pronounced in older patients. CTS surgery decreased slightly (but not significantly) throughout the period from 108 per 100,000 person-years in 1981-1985 to 94 per 100,000 person-years in 1995-2000, but increased sharply in 2001-2005 to 134 per 100,000 person-years, mostly to increased rates of surgery in patients >50 years old. The incidence of work-related CTS increased dramatically in the 1980s, declined in 1990s, and has remained relatively stable ever since.

**Conclusions:** The incidence of medically diagnosed CTS increased almost 2-fold between 1981-1985 and 2000-2005. The incidence of CTS surgery increased recently, primarily in the elderly with more severe disease.

**Reviewer's Comments:** This study is unique since it followed the incidence of CTS and CTS surgery over 2.5 decades. The incidence was much higher than in other international studies, but this could be related to timing, different health systems, and access to health care. The study was retrospective and may have included many patients with an incorrect diagnosis, since only approximately 75% of patients who had electrodiagnostic studies showed evidence of CTS. This could be in part due to the fact that sensitive internal comparison studies (such as median/ulnar sensory comparison to the ring finger, median/radial sensory comparison to the thumb, and median-ulnar motor comparison to the second lumbrical-interossei) or Kimura's inching technique were not done. (Reviewer-Bashar Katirji, MD).

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Keywords: Carpal Tunnel Syndrome

Print Tag: Refer to original journal article
No Significant Benefit to Combining MTX and/or IVMP With IFNb-1a in RRMS

Results of the Avonex Combination Trial (ACT) in Relapsing-Remitting MS.

Cohen JA, Imrey PB, et al:

Neurology 2009; 72 (February 10): 535-541

Combination treatment of IFNb-1a and MTX and/or IVMP is not superior to IFNb-1a alone in RRMS.

Background: Multiple sclerosis (MS) has many disease mechanisms that can vary between patients and over time in the same patient. This allows for the possibility of multiple therapies working synergistically or additively. Clinical experience and preliminary studies showed some benefits of these combinations, although no large scale study has been undertaken previously.

Objective: To report on the results of the Avonex Combination Trial (ACT, which assessed methotrexate (MTX), IV methylprednisolone [IVMP] or both) in patients with active relapsing-remitting MS [RRMS]) who were on interferon beta-1a (IFNb-1a) alone.

Methods: Inclusion criteria were age 18 to 55 years, RRMS diagnosis, Expanded Disability Status Scale of 0.0 to 5.5, IFNb-1a for ≥6 months, active disease in previous 12 months (≥1 relapse or ≥ gadolinium-enhancing [GdE] lesion on cranial or spinal MRI). Eligible subjects continued IFNb-1a 30 μg IM weekly and were randomized to weekly placebo or MTX 20 mg by mouth, with or without bimonthly IVMP 1000 mg/day for 3 days. The primary end point was new or enhanced (N/E) T2 lesion number at month 12 versus baseline. Secondary outcome measures included GdE number, relapse rate, and MS Functional Scale change.

Results: The initial target enrolment of 900 subjects was scaled down to 300 to 350 due to slow enrolment; 313 subjects were available for analysis. Baseline characteristics were comparable across groups. Combination therapies were well tolerated in all patient groups. Some trends were noted supporting modest benefits with IVMP, but none reached statistical significance. No data suggested a benefit of combining MTX and IFNb-1a. The patients who received IVMP had reduced anti-IFNb neutralizing antibody titers.

Conclusions: This large study did not show any statistically significant benefit of combining MTX and IVMP with IFNb-1a in RRMS.

Reviewer's Comments: Yet another study of a combination of immunomodulating agents for RRMS fails to come to fruition, albeit for different reasons this time (no efficacy). Other studies (IFNb-1a plus natalizumab and glatiramer acetate plus natalizumab) had to be discontinued, due to the development of progressive multifocal leukoencephalopathy in some patients in the former study. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Relapsing-Remitting MS

Print Tag: Refer to original journal article
Is Combination GA Plus Natalizumab Safe and Efficacious?

GLANCE: Results of a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study.
Goodman AD, Rossman H, et al:

Neurology 2009; 72 (March 3): 806-812

Combination treatment of glatiramer acetate and natalizumab is safe and effective in this 6-month study in patients with relapsing MS; however, currently, such a combination is not recommended.

**Background:** In view of significant beneficial effects of natalizumab on the relapse rate and progression of disability in multiple sclerosis (MS), it was believed that it may be used as an add-on therapy with glatiramer acetate (GA). However, concerns were raised that the combination may reduce the efficacy of GA (due to α4-integrin blockade by natalizumab, thereby possibly preventing GA cellular entry into the brain) and produce higher immunogenicity to natalizumab (due to modification of immune response by GA).

**Objective:** The Glatiramer Acetate and Natalizumab Combination Evaluation (GLANCE) study was planned to assess the safety and tolerability of the combination therapy.

**Design:** GLANCE was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 25 centers in the United States between June 2003 and March 2004.

**Participants:** Patients were aged 18 to 55 years, with relapsing MS, an Expanded Disability Status Scale (EDSS) score of 0 to 5.0, and were on GA for 12 months, with at least 1 relapse during that time.

**Methods:** Patients randomly received IV natalizumab 300 mg or placebo every 4 weeks in addition to GA 20 mg subcutaneously once a day for 24 weeks. Cranial MRIs were performed at 0, 4, 8, 12, 16, 20, and 24 weeks. The primary end point was the rate of development of new lesions. The secondary end point was the incidence and severity of adverse events (AEs).

**Results:** 110 patients were enrolled. Median duration of GA treatment was 33.9 months. In the 12 months prior, 1.4 ± 0.6 relapses were recorded. Mean number of gadolinium-enhancing (Gd+) lesions was 0.6 ± 1.5. Combination therapy versus GA alone produced the following: a lower mean rate of development of new lesions (0.03 vs 0.11; \( P = 0.031 \)); fewer new Gd+ lesions (0.6 vs 2.3; \( P = 0.020 \)); and fewer new/newly enlarging T2-hyperintense lesions (0.5 vs 1.5; \( P = 0.029 \)). No hypersensitivity reactions were seen, and the frequency of AEs was similar in both groups. Persistent antinatalizumab antibodies were seen in 13% receiving combination treatment versus 6% in the phase 3 trial with natalizumab alone. No cases of progressive multifocal leukoencephalopathy (PML) were seen during the GLANCE study or the subsequent safety-extension study.

**Conclusions:** Combination therapy of GA and natalizumab is safe and efficacious over a 6-month period.

**Reviewer's Comments:** While it appears that the combination treatment is superior to GA alone, in the absence of comparison with a natalizumab-alone cohort, it is not clear whether the combination is better than natalizumab alone. While the study demonstrates a short-term safety of the combination, at the current time, combining natalizumab with any other immunomodulatory agent is not recommended in view of ongoing concerns regarding PML in such a setting. In fact, the GLANCE study was discontinued due to development of PML in another study (SENTINEL) using a combination of interferon-β and natalizumab. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Natalizumab & Glatiramer Acetate

Print Tag: Refer to original journal article
A diffuse bilateral pattern of lesions on MRI supports a diagnosis of ADEM, and the presence of black holes and ≥2 periventricular lesions support a probable first attack of MS in children.

**Background:** Acute disseminated encephalomyelitis (ADEM) is typically viewed as a monophasic, postinfectious, demyelinating disorder affecting the central nervous system. In children, it can sometimes be difficult to differentiate ADEM from an initial episode of demyelination due to multiple sclerosis (MS).

**Objective:** To determine if quantitative analysis of MRI images of the brain in children can be used to reliably differentiate between ADEM and an initial attack of MS.

**Participants/Methods:** MRI scans from 20 children with a diagnosis of ADEM were retrospectively analyzed and compared with scans from 28 children with an initial attack of MS based on progression to definite MS over time. All patients were <18 years of age at the time of initial presentation. The children with ADEM were followed clinically for at least 2 years after diagnosis with no evidence of clinical deterioration with at least 1 follow-up MRI scan obtained >6 months after diagnosis with the absence of new demyelinating lesions. A diagnosis of MS was made based on at least 2 separate attacks of demyelination separated by a period of >30 days. Hyperintense lesions on T2/fluid attenuated inversion recovery images were quantified and categorized based on location, description, and size. The presence of black holes and positive enhancement with gadolinium on T1-weighted sequences were likewise documented. Mean lesion counts, other features, and statistical analysis were used to devise a quantitative method for a proposed diagnostic model.

**Results:** The total number of lesions did not correlate with or differentiate between ADEM and MS. Periventricular lesions were much more prevalent in children with MS, with a mean lesion count of approximately 7 compared to just over 1 in children with ADEM. Diffuse bilateral distribution of lesions was more common in ADEM. So-called "black holes" on T1-weighted images were present in almost 60% of children with MS compared to only 5% of those with ADEM. A combination of quantitative and qualitative analysis led to the following criteria to differentiate between the diagnosis of MS and ADEM: (1) absence of a diffuse bilateral pattern; (2) presence of black holes; and (3) presence of ≥2 periventricular lesions. If 2 of these 3 criteria were present, a first attack of MS in children could be distinguished from ADEM with a sensitivity of approximately 80% and a specificity of 95%.

**Reviewer's Comments:** These simple criteria can potentially be used to determine a first episode of MS versus ADEM in children, which should be very useful clinically. (Reviewer-Gregory B. Sharp, MD).

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Keywords: ADEM vs MS

Print Tag: Refer to original journal article
Weight Gain in response to valproate in children may tend to be more dramatic early during therapy but may diminish over time with extended therapy.

**Background:** It is well known that many patients treated with valproate experience significant weight gain. While this tendency seems to be more consistent in adults, reports in children have been more variable.

**Objective:** To evaluate the impact of valproate therapy on weight gain in children, and to determine if there are clinical predictors of weight gain.

**Design/Methods:** A retrospective chart review within a general pediatric neurology practice was performed to identify children with epilepsy between the ages of 2 to 20 years who had been treated with valproate. Children who had their weight and height documented at baseline and during follow-up and who were treated with valproate for at least 4 months were included. Patients with severe mental retardation that might affect eating habits, those who were on the ketogenic diet or were fed via gastrostomy, and those who were on other medications that were felt to potentially affect appetite or weight gain (positively or negatively) were excluded. Data were recorded at baseline and at each follow-up visit.

**Results:** A group of 94 children treated with valproate were identified who met study criteria. The mean age at the onset of treatment with valproate was approximately 9 years. There were 49 females and 45 males. Approximately 45% were white, 40% were Hispanic, 10% were black, and 5% were considered “other.” About one-third of subjects had primary generalized epilepsy, and two-thirds had partial-onset or mixed epilepsy. The duration of follow-up on valproate therapy ranged from 4 to 89 months, with a mean of 30 months. The mean dose over time ranged from about 5 to 40 mg/kg per day. Extended-release formulations used included sprinkles for 42 patients, and extended-release preparations were used in 16. Only 2 patients were on once-daily dosing. Standard-release formulations including liquid were used for 36 patients. Serum concentrations of valproate ranged from 29 to 137 μg/mL. At baseline, just over 35% were above the 85th percentile, 30% were over the 90th percentile, and 25% were over the 95th percentile for weight. Approximately 25% of patients experienced an increase in z score for weight of >0.25 SD/year, and 13% experienced a change in z score of >0.5 SD/year. Longer duration of therapy with valproate was associated with a lesser impact on change in z score for weight. No other significant clinical identifiers predicted a tendency for increased weight gain on valproate.

**Reviewer’s Comments:** Adult studies have indicated that up to 70% of patients gain weight on valproate. In this pediatric study, about one-fourth of patients experienced significant weight gain. There were no strong indicators that overweight patients were more likely to experience excessive weight gain. Increased weight gain also tended to occur early and was less prominent with long-term therapy. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Valproate

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