There is growing evidence that a low serum level of vitamin D increases the risk for developing multiple sclerosis.

**Background:** The pathophysiology of multiple sclerosis (MS) is a mystery yet to be unraveled. Genetic factors, auto-immune mechanisms, and viruses such as Epstein-Barr virus are believed to be central players. However, a growing body of evidence suggests that sun exposure and serum vitamin D levels may play key roles as well.

**Objective:** To persuade the reader that sufficient evidence exists to link low serum levels of vitamin D to an increased risk for the development and progression of MS.

**Design:** Literature review.

**Methods:** The author cites experimental, immunological, epidemiological, and early treatment studies with special attention to the effects of latitude and sun exposure on serum vitamin D levels and the prevalence of MS.

**Results:** Apart from its well-known role in calcium and phosphorous metabolism, vitamin D is involved in multiple other bodily functions including modulation of the immune system. In murine experimental autoimmune encephalitis (EAE), vitamin D prevents the induction of EAE if given before the disease is triggered. If administered afterward, vitamin D attenuates the disease. Multiple hypotheses have been advanced to explain this protection, but the best evidence suggests that vitamin D has immunomodulatory effects on T lymphocytes similar to interferon-beta. Geographic prevalence of MS falls with decreasing latitude, coincident with increasing sun exposure and higher serum vitamin D levels in populations living closer to the equator. A case-control study in Tasmania that estimated sun exposure by questionnaire and by solar skin damage found that higher sun exposure in childhood and adolescence was associated with a lower risk of developing MS. A study of 79 monozygotic twins in North America reported that the twin with MS had less sun exposure than the unaffected twin, suggesting a protective effect of sunshine independent of genetic susceptibility. In a prospective, nested, case-control study of 7 million U.S. military personnel over 12 years, vitamin D levels were measured in sera collected before any neurological symptoms appeared. A total of 257 soldiers developed MS. When compared to 514 control subjects, those with MS had significantly lower serum vitamin D levels. In addition, 3 separate studies have shown significantly lower vitamin D levels during MS relapses than at other times. Preliminary phase I and II studies, although lacking controls and limited in patient numbers, suggest that vitamin D supplementation can reduce the relapse rate in MS without inducing hypercalcemia or other toxicity from vitamin D.

**Conclusions:** Vitamin D supplementation may prevent the development of MS and/or attenuate its progression.

**Reviewer’s Comments:** One prominent MS investigator estimates that three-fourths of MS cases could be prevented if vitamin D levels in childhood and adolescence were maintained at physiologically normal levels through sun exposure or supplementation. That seems too good to be true, but large carefully controlled clinical studies appear to be warranted. (Reviewer-Michael Jacewicz, MD).
The risk of rebleeding from coiled aneurysms is slightly higher than from those that are clipped, but mortality is less.

**Background:** The International Subarachnoid Aneurysm Trial (ISAT) randomly assigned 2143 patients with ruptured intracranial aneurysm to neurosurgical clipping or coiling. The primary outcome of death or dependency at 1 year occurred in 24% of the coiled group and 31% of the clipping group. The long-term benefit of coiling is unknown, with concern for rebleeding over time.

**Objective:** Long-term follow-up of patients in the ISAT study to determine benefit of the 2 procedures over time.

**Participants/Methods:** 2004 of the 2143 original patients were included and seen annually for 5 to 8 years. Patients received annual questionnaires regarding dependency, quality of life, further hospitalizations, and further treatment related to their subarachnoid hemorrhage (SAH) or aneurysm. All information was reviewed by an experienced neurosurgeon and neuroradiologist. Survival analyses were performed for time to rebleeding and time to death measured from the time of original SAH.

**Results:** Follow-up data were reported for a minimum of 6 years and a maximum of 14 years. Overall, 24 rebleeds were confirmed in 24 patients (13 from the same aneurysm or in the same location as the previously treated aneurysm). A new or pre-existing aneurysm that was previously unruptured was the source of hemorrhage in 10 cases (4 from another aneurysm seen at original presentation, 6 from a de novo aneurysm). The last patient had a hemorrhage from an unknown source. In the endovascular cohort, 10 patients had rebleeds from the treated aneurysm; 3 had rebleeding from another known aneurysm, 3 rebled from a new aneurysm, and in 1 patient, the source of rebleeding was unknown. In the neurosurgical group, 3 patients had SAH from a treated aneurysm, and all died within 30 days; 1 bled from another known aneurysm and 3 bled from a new aneurysm. There was a nonsignificant increased risk of rebleeding from the treated aneurysm in the endovascular group. No difference was found in the mortality rate of rebleeding between groups. The time to recurrent hemorrhage from pre-existing aneurysms was between 2 and 4 years and from new aneurysms, between 4 and 9 years.

**Conclusions:** There was an increased risk of recurrent bleeding from the coiled group, but risks were small. The risk of death at 5 years was significantly lower in the coiled group.

**Reviewer’s Comments:** In patients who are candidates for both procedures, coiling has benefits over clipping. This difference decreases over time with an increased recurrent risk of rebleeding in the coiled group. These patients are best managed at a center that provides both options with decisions for which treatment to use made on an individual basis. (Reviewer-John Schwankhaus, MD).

© 2009, Oakstone Medical Publishing

Keywords: Neurosurgical Clipping/Coiling

Print Tag: Refer to original journal article
**ALDH7A1 Mutations in Neonatal-Onset PDS**

*Prevalence of ALDH7A1 Mutations in 18 North American Pyridoxine-Dependent Seizure (PDS) Patients.*

Bennett CL, Chen Y, et al:

Epilepsia 2009; 50 (May): 1167-1175

---

When pyridoxine-dependent seizures are considered in infants with refractory seizures, start a trial of pyridoxine. If a positive response occurs, proceed with *ALDH7A1* mutation analysis.

---

**Background:** Pyridoxine-dependent seizure (PDS) is a rare disorder that typically presents with seizures during the neonatal period that are refractory to antiepileptic drug therapy. Seizures less commonly begin later, usually during the first year or as late as the third year of life. Previously, the diagnosis was made when a trial of pyridoxine or vitamin B6 therapy in neonates and young children with refractory seizures resulted in cessation of seizures that subsequently recurred when pyridoxine was stopped. Ongoing pyridoxine supplementation typically results in complete seizure prevention, or at least marked improvement. Elevation of plasma pipecolic acid (PA) has been noted in cases of PDS. Recently, mutations of the antiquitin gene or *ALDH7A1* have been detected, primarily in neonatal-onset cases. When antiquitin function is defective, piperidine-6-carboxylic acid accumulates and reacts with pyridoxal-5 phosphate (PLP), resulting in its depletion. The exact mechanism that results in seizures is not completely understood, but evidently PLP serves as a coenzyme in neurotransmitter synthesis.

**Objective:** To determine the prevalence of *ALDH7A1* mutations in patients with neonatal-onset compared to late-onset PDS.

**Participants:** A total of 25 patients with PDS were identified and included 14 boys, 11 girls, and 7 sibling pairs with 17 neonatal-onset and 8 late-onset subjects. For genetic analysis purposes, sibling pairs were considered as single cases. Thus, there were 12 neonatal-onset and 6 late-onset cases. One sibling pair included a child with neonatal-onset and a child with late-onset seizures at 9 months of age. This pair was considered in the analysis as a neonatal-onset case. Late onset of seizures began between 2 and 9 months of age. Seizure types included partial, generalized convulsive, myoclonic, and infantile spasms.

**Methods:** Testing included bidirectional DNA sequence analysis of *ALDH7A1* and measurement of plasma PA.

**Results:** In the neonatal-onset PDS group, compound heterozygous or homozygous *ALDH7A1* mutations were found in 10 of 12 cases, and a single mutation was present in 2 cases. *ALDH7A1* mutations were detected in 3 of 6 late-onset cases. In total, 13 novel *ALDH7A1* mutations were identified. PA was elevated in 11, normal in 3, and not tested in 4 cases. In 2 late-onset cases with infantile spasms that responded to pyridoxine therapy, no *ALDH7A1* mutations were detected and plasma PA was normal. One neonatal-onset case with confirmed *ALDH7A1* mutation had a normal PA level.

**Reviewer’s Comments:** When a diagnosis of PDS is considered in neonates and young children with refractory seizures, serum and/or urine levels of PA can be measured, then a therapeutic trial of pyridoxine can be started. If there appears to be a positive response to pyridoxine, proceed with *ALDH7A1* mutation analysis to confirm the diagnosis. (Reviewer-Gregory B. Sharp, MD).

© 2009, Oakstone Medical Publishing

Keywords: *ALDH7A1*Mutations

Print Tag: Refer to original journal article
What Is CARASIL, and What Is Its Cause?

Association of HTRA1 Mutations and Familial Ischemic Cerebral Small-Vessel Disease.

Hara K, Shiga A, et al: N Engl J Med 2009; 360 (April 23): 1729-1739

Mutation of gene encoding serine protease 1 causes CARASIL, perhaps as a result of repressed inhibition of transforming growth factor-β signaling.

**Objective:** To determine whether mutations in *HTRA1*, a gene encoding HtrA serine protease 1, cause cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), in which cerebral small vessel pathological changes resemble what is seen in nonhereditary ischemic small vessel disease. Patients with CARASIL also have alopecia and spondylosis.

**Methods:** 6 probands from 6 affected families plus some family members were studied using linkage analysis, fine mapping of the region implicated in the disease, and sequence analysis of the candidate gene. *HTRA1*, the gene encoding HtrA serine protease 1, was selected as a candidate gene because it is expressed in blood vessels, bone, and skin. Functional analyses then compared the ability of mutated and wild-type HtrA serine protease to inhibit transforming growth factor-β (TGF-β) signaling.

**Results:** Linkage of the disease was found to a 2.4-megabase region on chromosome 10q, which contains the HtrA serine protease (*HTRA1*) gene. Found in the 5 families were 2 nonsense mutations and 2 missense mutations in *HTRA1*. Three of the mutations resulted in low levels of protease activity, which failed to inhibit TGF-β signaling. The other mutation caused total loss of HtrA serine protease by decay of messenger RNA. In 2 patients, neuropathological examination and immunohistological staining revealed increased expression of TGF-β in tunica media of cerebral small arteries. The thickened tunica intrina showed increased expression of fibronectin and versican, which are extracellular matrix proteins, the synthesis of which is increased by TGF-β signaling.

**Conclusions:** CARASIL is associated with mutations of the gene encoding HtrA1 serine protease, with arteriopathy probably resulting from decreased inhibition of TGF-β signaling and accumulation of matrix proteins within vessel walls, resulting in fibrosis. The molecular basis for regulation of TGF-β signaling by HtrA serine protease is, as yet, unclear.

**Reviewer's Comments:** Is it possible that hypertension causes cerebral small vessel disease by increasing TGF-β signaling? (Reviewer-John C. Brust, MD).

© 2009, Oakstone Medical Publishing

Keywords: Small Vessel

Print Tag: Refer to original journal article
Idiopathic RBD Risk Factor for Neurodegenerative Disorder

Quantifying the Risk of Neurodegenerative Disease in Idiopathic REM Sleep Behavior Disorder.

Postuma RB, Gagnon JF, et al:

Neurology 2009; 72 (April 14): 1296-1300

Those with idiopathic RBD should be observed closely for evidence of a neurodegenerative disorder.

Objective: To determine the risk of developing Parkinson disease or other neurodegenerative disorders in patients with idiopathic rapid eye movement (REM) sleep behavior disorder (RBD).

Methods: All patients diagnosed with RBD at the Hôpital du Sacré Cœur in Montreal, Canada, between 1989 and 2006 were included in the study. Minimal inclusion criteria were: (1) polysomnogram-confirmed cases; (2) absence of signs of neurological disease; and (3) at least 1 follow-up exam ≥1 year after the baseline examination. Follow-up evaluations included, at minimum, a complete medical history and neurological examination, assessment of the Unified Parkinson's Disease Rating Scale Part III, and cognitive testing (at minimum, the Folstein Mini-Mental Status Examination). Neuropsychological evaluation and extensive evaluation of nonmotor symptoms was offered to all patients but not required for inclusion. For a subset of patients unable to attend an in-person evaluation, a telephone interview was conducted by a neurologist. Strict guidelines were employed to diagnose the type of parkinsonism or dementia. The primary outcome measure was defined as the risk of developing parkinsonism or dementia. Linear regression analysis of disease risk over time was performed.

Results: Of 113 patients initially diagnosed with RBD, 93 met inclusion criteria. Of these, 78 met the strictest inclusion criteria, which included a full research evaluation follow-up examination. The mean age was 65.4 years, and 80% of patients were men. Twenty-six patients developed a neurodegenerative disorder, 15 had parkinsonism (14 with idiopathic Parkinson disease, 1 with multiple systems atrophy) and 11 had dementia (7 with Lewy body disease and 4 with Alzheimer disease). The estimated 5-year risk of developing a neurodegenerative disorder was 17.7% with estimated 10- and 12-year risks of 40.6% and 52.4%, respectively.

Conclusions: In idiopathic RBD, the risk of developing a neurodegenerative disorder is substantial.

Reviewer's Comments: This study demonstrates a definite risk of developing a neurodegenerative disorder in those with RBD. Longer-term follow-up and pathological examinations are needed to more accurately identify the risk and the specific disorders involved. (Reviewer-John Schwankhaus, MD).

© 2009, Oakstone Medical Publishing

Keywords: REM Sleep Behavior Disorder

Print Tag: Refer to original journal article
Genomewide Association Studies of Stroke

Ikram MA, Seshadri S, et al:
N Engl J Med 2009; 360 (April 23): 1718-1728

A genetic locus on chromosome 12p13 is associated with an increased risk of stroke.

Objective: To identify haplotypes associated with an increased risk of stroke.
Methods: 19,602 white individuals were pooled from 4 prospective population-based cohorts: the Atherosclerosis Risk in Communities cohort, the Cardiovascular Health Study cohort, the Framingham Heart Study cohort, and the Rotterdam Study cohort. Replication studies were then performed on smaller black and Dutch cohorts. Stroke-free on entry, subjects were followed up for incident stroke. Subarachnoid hemorrhage was excluded, and ischemic stroke was subdivided into atherothrombotic and cardioembolic subtypes. Genotyping was performed using chip-based commercial products. Analyses of ischemic stroke were adjusted for age, sex, blood pressure, diabetes, and atrial fibrillation. More than 2 million single nucleotide polymorphisms were analyzed, and, because of frequent false positives, a target threshold of 5 x 10^{-8} was chosen to indicate "highly significant association."
Results: During an average 11-year follow-up, 1544 strokes (1164 ischemic) were observed. Two single nucleotide polymorphisms on chromosome 12p13 surpassed the threshold for total stroke and ischemic stroke. Each copy of a minor allele at these 2 loci appeared to increase the hazard ratio for ischemic stroke by 1.39 to 1.41, corresponding to a population-attributable risk of 14% to 17%. There was no association of either allele with nonischemic stroke. The risk of atherothrombotic stroke was greater than that for all ischemic strokes. Comparable associations were found in the replicative studies on blacks and Dutch whites.
Conclusions: 2 loci on chromosome 12p13 are associated with an increased risk of ischemic stroke. Both single nucleotide polymorphisms are in close proximity to the gene \textit{NINJ2}, which encodes ninjurin2, 1 of 2 transmembrane proteins in the ninjurin (or "nerve injury-induced protein") family. In rats, ninjurin is induced in Schwann cells and dorsal root ganglia by nerve injury, and it promotes nerve regeneration. In the CNS, ninjurin is present in glia, and it is possible that it affects how the brain tolerates ischemia. The second closest gene to the polymorphisms is \textit{WNK1}, which encodes a protein kinase present in mouse vasculature that has been related to blood pressure levels and the severity of hypertension. However, adjusting for hypertension in the present study did not change the strength of association between the 12p13 locus and ischemic stroke.
Reviewer's Comments: In the same issue of this journal is a review article by John Hardy and Andrew Singleton describing genome-wide association studies, including a useful glossary. (Reviewer-John C. Brust, MD).

© 2009, Oakstone Medical Publishing

Keywords: Stroke

Print Tag: Refer to original journal article
How Often Do Triptans Cause Organ Ischemia?

Acute Myocardial Infarction With Sumatriptan: A Case Report and Review of the Literature.

Chalaupka FD:

Headache 2009; 49 (May): 762-765

Prudence is in order when considering triptan use for patients with cardiovascular risk factors or in those aged >40 years, especially men.

**Background:** Triptan drugs cause vasoconstriction by way of agonist actions at the 5-HT1B serotonin receptor. Although this action is more prominent for the cerebral circulation, it affects the coronary arteries as well. Triptans are, accordingly, labeled as contraindicated in patients with coronary artery disease (CAD).

**Objective:** To describe a case of myocardial infarction (MI) associated with sumatriptan use, and to critically review the literature concerning this association.

**Methods:** In addition to the case presented, the author identified and analyzed 32 reported cases of cardiovascular events associated with triptan use. **Case Report:** A 54-year-old woman with a history of migraine since her 20s had an uncomplicated non-Q-wave MI after using sumatriptan subcutaneously. She had used the same drug for many years. Investigations revealed hypercholesterolemia and hypertension. After discharge, she continued to treat her migraine with reduced oral doses of sumatriptan.

**Results:** Of the 32 other cases analyzed, 25 were women. The mean age was 45 years, although the range was 16 to 68 years. Sumatriptan was implicated in 26 cases, zolmitriptan in 5, and rizatriptan in 1. The sumatriptan was given by various routes and in various doses, but with no intentional or inadvertent reports of overdose. Surprisingly, adverse events occurred after months or years of triptan use in approximately half the cases and were documented to occur after first use in only 5 cases. The most frequent adverse event was MI. There were 6 CNS events, 5 involving the brain and 1 involving the spinal cord. The remaining cases involved other viscera, such as the spleen, colon, and kidney. In some cases, it was difficult to accept a cause-and-effect relationship between triptan use and the event, which occurred 7 to 10 half-lives after triptan use (Proofer: does this make sense?). Fourteen cases had ≥2 cardiovascular risk factors. Nine cases actually had angiographically documented CAD at the time of triptan administration. The use of drugs at least theoretically capable of increasing the risk of an adverse cardiovascular event, most notably ergots, was recorded in 9 cases. After exclusion of patients with confounding factors and obvious cardiovascular risk factors, the author ultimately considered only 4 cases to be valid examples of adverse cardiovascular events caused solely by triptans when administered to patients with low cardiovascular risk.

**Conclusions:** Most of the cases of serious cardiovascular adverse events attributable to triptans involved patients with obvious cardiovascular disease or who were using other vasoactive drugs.

**Reviewer's Comments:** The author does a good job of discussing factors that confound the potential association between triptan use and cardiovascular events. He shows that, in some cases, a cause-and-effect relationship is extremely questionable. Nonetheless, prudence is in order when considering triptans for patients with cardiovascular risk factors or in those aged >40 years, especially men. Obviously, patients who develop chest pain or other symptoms suggesting possible ischemia should be investigated carefully. (Reviewer: James W. Schmidley, MD).

© 2009, Oakstone Medical Publishing

Keywords: Triptan Drugs

Print Tag: Refer to original journal article
If seizure frequency is reduced in children treated with vagus nerve stimulation, expect a decrease in seizure severity and an increase in mental alertness.

Background: Vagus nerve stimulation (VNS) is used as adjunctive therapy for children with medically refractory epilepsy. Response to VNS has primarily focused on a decrease in seizure frequency. Objective: To evaluate the impact of VNS therapy on seizure severity in children with refractory seizures. Participants/Methods: A retrospective review was performed that included 26 consecutive children with epilepsy treated with VNS who were followed for a minimum of 18 months. Attention was paid to clinical characteristics, seizure type and frequency, epilepsy syndrome, and the impact of VNS on seizure frequency and severity. Those who experienced ≥50% reduction in seizure frequency were considered responders. Standard VNS settings included an on-time of 30 seconds, off-time of 3 minutes, and frequency of 30 Hz. The current was titrated gradually to a target of 1.75 mA. A rapid cycling protocol with an on-time of 7 seconds and off-time of 12 seconds was used in 7 patients who did not respond to the standard stimulation protocol. Age at implantation of VNS ranged from 5 to 16 years and follow-up ranged from 1.5 to just over 8 years (mean, 3 years). Epilepsy syndromes included Lennox-Gastaut syndrome (LGS) in 9 children, symptomatic partial epilepsy in 12, symptomatic generalized epilepsy other than LGS in 3, and Dravet syndrome in 2. The underlying etiology was considered cryptogenic in 10 children, a brain malformation in 5, encephalitis in 5, sodium channel mutation in 2, tuberous sclerosis in 2, neonatal encephalopathy in 1, and congenital B12 deficiency in 1 patient. Approximately 80% of these children experienced multiple seizure types. Intellectual disabilities were prevalent and present in 85% and were considered severe in 70%.

Results: Just over 50% of the patients were responders, and approximately 33% experienced a >75% reduction in seizure frequency. The best responder rate was seen in children with LGS at just over 75%. This group experienced a marked decrease in tonic seizures and drop attacks. There were 4 children with a history of recurrent episodes of status epilepticus (SE) who all improved, with cessation of SE in 2 and a marked decrease in 2. Longer periods of seizure freedom, from days to weeks, occurred in 5 patients with a history of daily seizures prior to VNS. Rapid stimulation was effective in only 1 patient. All responders experienced a significant decrease in seizure severity, duration, and recovery time. Improved alertness was also reported in all responders and 3 nonresponders. A decrease in dosage and/or number of antiepileptic drugs was achieved in approximately 33% of the patients.

Reviewer's Comments: VNS can be an effective treatment for refractory seizures in children. In addition to decreased seizure frequency, seizure severity and quality of life are also commonly improved. (Reviewer-Gregory B. Sharp, MD).
Background: >15 years ago, autopsy studies first implicated aortic atheroma in the pathogenesis of cerebral infarction. Since then, the concept has risen and fallen with results of further studies, but therapy remains empirical and not directed by good clinical trial evidence.

Objective: To define the risk of ischemic stroke in patients with or without aortic arch atheroma randomly assigned to aspirin (ASA) or warfarin (W).

Design: The current study is a substudy of the Warfarin Aspirin Recurrent Stroke Study (WARSS), a double-blind, controlled trial comparing ASA and W in ischemic stroke patients without strong indications or contraindications to either drug and who were not scheduled to have carotid endarterectomy.

Participants: 630 of the 2206 patients participating in WARSS who had transesophageal echocardiography (TEE) participated in this study.

Methods: Patients were randomized to ASA 325 mg/day or to W, with a target international normalized ratio (INR) of 1.4 to 2.8. To keep patients unaware of treatment, a "double dummy" design was used. Methods: Follow-up was for at least 2 years, with scheduled visits every 3 months. Echocardiographic tapes were assessed by reviewers unaware of treatment. Aortic arch atheroma were graded as small (<4 mm) or large (≥4 mm). Plaques with ulceration or mobile components were designated "complex." The primary end points were recurrent ischemic infarct and death, plus hemorrhages, especially intracerebral hemorrhage.

Results: 630 patients were enrolled. Of these, 516 had adequate visualization of the aortic arch on TEE; 35% had no aortic arch atheroma, 20% had large plaques, and 45% had small plaques. Approximately 9% had "complex" features. As expected, the frequencies of various plaque types and of no aortic arch atheroma were equal in the W and ASA groups. Mean INR in the W group was barely 2.0 and was the same for patients with no, small, and large plaques. Although ischemic stroke risk increased with size and complexity of aortic arch atheroma, stroke rates were not favorably influenced by W therapy as opposed to ASA.

Conclusions: Large and complex aortic plaques are associated with an increased risk of recurrent cerebral infarction, regardless of antithrombotic therapy.

Reviewer's Comments: Recruitment for the study started in 1993 and ended in 2000, thus, there were probably very few patients on statins. The entire study was supposed to focus on patients with "cryptogenic" strokes, but 60% were eventually considered to have a known cause. Complex aortic arch atheroma may be 1 of the few indications for combined antiplatelet therapy, or anti-platelet therapy plus warfarin. Were the INRs high enough? Is aortic arch atheroma an indication for INRs closer to 3 than to 2? (Reviewer-James W. Schmidley, MD).

© 2009, Oakstone Medical Publishing

Keywords: Aortic Arch Atheroma

Print Tag: Refer to original journal article
Neurotoxicity From Abuse of Common Household Product

Mothball Mayhem: Relapsing Toxic Leukoencephalopathy Due to p-Dichlorobenzene Neurotoxicity.

Kumar N, Dale LC, et al:

Ann Intern Med 2009; 150 (March 3): 362-363

The fluctuating clinical course resulting from sporadic abuse of mothballs might, along with the MRI appearance, lead one to consider a diagnosis of multiple sclerosis.

Background: Aromatic inhalants are relatively unusual substances of abuse. The advantages to their abuse include ubiquity, low price, legality, and ease of administration (meaning they require no special paraphernalia).

Objective: To call listeners' attention to a rare, potentially reversible cause of neurotoxicity that is the result of abuse of a common household product. Case Report: A 33-year-old woman was evaluated for recurrent episodes of dysarthria, ataxia, and cognitive loss, associated with scaling skin. Examination showed dementia, 4-limb spasticity and weakness, hyperreflexia, ataxia, and dysarthria. She was bradykinetic and unable to walk. Bariatric surgery had been done 5 years previously, but no evidence of nutritional deficiency was noted. Additional extensive investigations revealed no diagnosis. MRI showed diffuse high T2 signal in the white matter of the cerebellum and cerebral hemispheres. She improved, but was later readmitted from a skilled nursing facility after again deteriorating. Further questioning disclosed a long history of chronic mothball sniffing, and eventually, ingestion. Resumption of this habit following prior hospitalizations accounted for the fluctuating course. Plasma p-dichlorobenzene (PDB) levels were detected on 2 occasions by gas chromatography.

Results: PDB may also cause methemoglobinemia with hemolytic anemia, and sometimes a skin rash, as well as neurotoxicity. It is rapidly cleared by the liver, but its metabolite 2, 5-dichlorophenol accumulates in fat and may contribute to neurotoxicity. The skin lesions caused by PDB are bilateral and ichthyotic, hyperpigmented, keratotic plaques with geographic borders on the extremities. PBD is also found in insect repellents, air fresheners, toilet-bowl and diaper-pail deodorizers, and fungicides. It replaced naphthalene in mothballs because it is less toxic than the former agent.

Conclusions: Chronic inhalational abuse of mothballs can cause a severe encephalopathy. This may occasionally explain otherwise obscure cases of fluctuating cerebrospinal fluid dysfunction with widespread white matter signal changes.

Reviewer’s Comments: This presentation is similar to toluene toxicity, which was common in the city where I last practiced neurology. Toluene, like mothballs, is cheap, legal, easy to obtain, and produces a similar neurological picture. The fluctuating clinical course resulting from sporadic abuse of mothballs or toluene might, along with the MRI appearance, lead one to consider a diagnosis of multiple sclerosis. The skin lesions caused by PDB abuse are nicely illustrated in the New England Journal of Medicine (2006; 55 [July 27]: 423-424). (Reviewer-James W. Schmidley, MD).

© 2009, Oakstone Medical Publishing

Keywords: Toxic Leukoencephalopathy

Print Tag: Refer to original journal article
Management of the neurogenic bladder in multiple sclerosis patients can be based on simple data (urinalysis and bladder post-void residual volume), and accomplished with antimuscarinic medications and, if necessary, clean intermittent self-catheterization.

**Background:** Approximately 75% of patients with multiple sclerosis (MS) have symptoms of disordered micturition.

**Objective:** To create guidelines for managing the neurogenic bladder in MS patients.

**Methods:** Experts from the British professional societies of neurology, urology, primary care, and nursing reviewed the literature and expressed their opinions. They graded their guidelines as follows: A, if based on randomized controlled studies; B, if based on controlled studies without randomization; C, if based on descriptive studies; and D, if based on opinion.

**Results:** Treatment is aimed at urinary tract infections (UTIs) and disordered storage and emptying of urine by the bladder, but not at detrusor sphincter dyssynergia (grade D). Only 2 diagnostic tests are needed for MS patients with lower urinary tract symptoms: a urinalysis, to detect UTI, and measurement of post-void bladder residual volume (PVR) to detect incomplete bladder emptying (grade D). For the latter, the noninvasive abdominal ultrasound is preferred over invasive, in-out bladder catheterization (grade D). Cystometry and bladder-sphincter electromyography (EMG) are unnecessary, unless a condition unrelated to MS, such as stress incontinence, is suspected (grade D). If the bladder PVR is >100 mL, patients should use clean intermittent self-catheterization (grade D). If a patient is too disabled to carry this out, a long-term indwelling catheter should be used. It should be suprapubic, to avoid damage to the urethra. Symptoms of an overactive detrusor (urinary frequency, urgency, and urge incontinence) should be treated with an oral antimuscarinic drug (grade A). Often a combination of intermittent self-catheterization and an antimuscarinic drug is most effective. If it is ineffective or the antimuscarinic drug causes unacceptable side effects, such as confusion, the injection of botulinum toxin A into the detrusor should be the next step (grade A). Almost always, it greatly elevates the bladder PVR; therefore, intermittent self-catheterization will also be needed. Desmopressin (DDAVP 100 to 400 μg orally or 10 to 40 μg intranasally every 24 hours) is effective for treating daytime urinary frequency and nocturia (grade A). Another treatment of nocturia, especially effective in patients with dependent edema, is a diuretic taken in the afternoon (grade D). Cranberry extract tablets reduce the likelihood of UTI, but prophylactic antibiotics should not be given (grade A).

**Conclusions:** Management of the neurogenic bladder in MS can be based on simple data (urinalysis and bladder PVR) and accomplished with antimuscarinic medications and, if necessary, clean intermittent self-catheterization.

**Reviewer's Comments:** Most neurologists have little knowledge of urology; so, these guidelines, which are simple enough for most of us to apply to our patients with MS, are most welcome. (Reviewer-Marc D. Winkelman, MD.)
Diagnosing and Treating Muscle Channelopathies

Diagnosis and New Treatment in Muscle Channelopathies.
Meola G, Hanna MG, Fontaine B:

J Neurol Neurosurg Psychiatry 2009; 80 (April): 360-365

Recent advances in molecular genetics and functional EMG can help diagnose muscle channelopathies in patients who present with periodic paralysis or myotonia.

(Proofer, pls check my italics) Background: The action potential and contraction of muscle depends on ions flowing through specific channels in the sarcolemma.

Objective: To review diseases caused by malfunction of the channels (ie, muscle channelopathies).

Results: Muscle channelopathies cause periodic paralysis and some myotonias. Myotonia congenita (MC) is due to abnormality of the chloride channel, caused by mutation of the gene CLCN1, on chromosome 7q35. Symptoms begin in the first 2 decades of life. Myotonia is worse in the cold and after rest, and it improves with exercise (warm-up phenomenon). Paramyotonia congenita (PC) is due to defective sodium channels, caused by mutation of the SCN4A gene, on chromosome 17q23.1. Symptoms begin earlier than in MC. The myotonia is worse with exercise (paradoxical myotonia, paramyotonia). Patients are prone to periodic attacks of limb paralysis, brought on by exercise, and cold temperatures. Hypokalemic periodic paralysis (hypoPP) is due to abnormal calcium channels, caused by mutations in the CACNA1 gene, on chromosome 1q32. Symptoms begin in the first 2 decades of life. Attacks occur seldom to weekly, last several hours, and are precipitated by rest after exertion or heavy intake of carbohydrates. Hyperkalemic periodic paralysis (hyperPP) is due to malfunctioning sodium channels, caused by a mutation of the SCN4A gene, different from the one that causes PC. Attacks appear in the first decade of life. Compared to those of hypoPP, they occur more often, but are shorter and milder. Common triggers include rest after exercise, fasting, and cold exposure. Exercise once an attack has begun can alleviate or abort it. Serum potassium may be high or normal. Mild myotonia may be present, if only on electromyography (EMG). Andersen-Tawil syndrome (ATS) is a potassium channelopathy caused by mutation of the KCNJ2 gene, near the SCN4A gene on chromosome 17q23.1. Periodic paralysis occurs with hyperkalemia or hypokalemia. The disorder also includes cardiac arrhythmia and dysmorphism (short stature, broad-based nose, broad forehead, hypertelorism, low-set ears, micrognathia, cleft palate, clinodactyly, syndactyly, and scoliosis). Surface and needle EMG performed after exercise or cooling (functional EMG) can help diagnose the muscle channelopathies. Patients with hypoPP should avoid high-carbohydrate meals, and those with hyperPP should avoid potassium-rich foods and fasting. Salbutamol, inhaled at the beginning of an attack of hyperPP, may shorten or abort the attack. Chronic use of acetazolamide can reduce the frequency of attacks in the periodic paralyses and ATS. Mexiletine and, to a lesser extent, carbamazepine, flecainide, and tocainide, can reduce myotonia.

Reviewer's Comments: Functional EMG and molecular genetic testing can help diagnose muscle channelopathies in patients who present with periodic paralysis or myotonia. (Reviewer-Marc D. Winkelman, MD).

© 2009, Oakstone Medical Publishing

Keywords: Myotonia

Print Tag: Refer to original journal article
The levetiracetam dose used in this study for adjunctive therapy in children with refractory partial onset seizures was 40 mg/kg per day in the 1- to 6-month-old group, and 50 mg/kg per day in the 6 month to <4-year-old group.

**Objective:** To evaluate the efficacy, safety, and tolerability of levetiracetam (LEV) as adjunctive therapy for refractory partial-onset seizures in infants and young children from 1 month to <4 years of age.

**Design:** Multicenter, double-blind, randomized, placebo-controlled trial.

**Participants:** All participants had partial-onset seizures that were not adequately controlled in response to 1 or 2 antiepileptic drugs (AEDs).

**Methods:** An initial inpatient baseline 48-hour video-electroencephalography (EEG) was performed, and subjects who experienced at least 2 partial-onset seizures were then randomized to treatment with LEV or placebo. LEV was initiated with a 1-day up-titration followed by a stable dose for the next 4 days. The initial dose for 1 day was 20 mg/kg in 2 divided doses followed by 40 mg/kg per day in 2 divided doses for subjects from 1 to 6 months of age, and 25 mg/kg for the first day followed by 50 mg/kg/day in 2 divided doses for those between 6 months and 4 years of age. An evaluation 48-hour video EEG was performed during the last 2 treatment days. Subjects were then allowed to enter a long-term follow-up study. Exclusion criteria included weight <4 kg, prior treatment with LEV, treatable seizure etiology, febrile seizures, status epilepticus during the prior month, a diagnosis of Lennox-Gastaut syndrome, a progressive cerebral or neurodegenerative disorder, or a serious medical condition. The primary outcome measure for efficacy was responder to therapy with a ≥50% reduction in seizure frequency during the evaluation compared to the baseline 48-hour video-EEGs.

**Results:** A total of 175 subjects were screened, and 116 met criteria for randomization, with 60 randomized to LEV and 56 to placebo. Two subjects in the LEV group and 1 in the placebo group experienced adverse events and discontinued participation prior to completion. Just over two-thirds of the patients in each group were taking 2 AEDs at study entry. The ≥50% responder rate was achieved in just over 40% in the LEV group compared to approximately 20% in the placebo group with no significant differences based on age. Subjects in the LEV group experienced a median percent reduction in average daily partial onset seizure frequency of >40% compared to 7% in the placebo group. LEV was well tolerated in general. The most frequently reported adverse events in the LEV group were somnolence in 13% and irritability in 12% compared to 2% and 0%, respectively, in the placebo group.

**Reviewer's Comments:** Therapeutic trials are difficult to accomplish in very young children in this age group, and the authors are to be commended for their efforts. LEV does appear safe and effective for adjunctive treatment of partial onset seizures in children between 1 month and 4 years of age. (Reviewer-Gregory B. Sharp, MD).

© 2009, Oakstone Medical Publishing

Keywords: Levetiracetam

Print Tag: Refer to original journal article
When treating children with epilepsy with levetiracetam, achieve a starting dose of approximately 20 mg/kg per day in 2 divided doses, and then titrate the dosage upward as indicated based on resultant seizure control and tolerability.

**Background:** The official recommended, FDA-approved dosage of levetiracetam (LEV) in children for adjunctive therapy for partial onset seizures down to age 4 years is 60 mg/kg per day. In clinical practice, many clinicians have recognized that LEV therapy at lower doses in children is often effective and the dose is commonly titrated to effect tolerability. Better dosing guidelines are needed for LEV therapy in children.

**Objective:** To develop a population pharmacokinetic model to evaluate the pharmacokinetics of LEV in children and to suggest appropriate recommended dosages.

**Methods:** A prospective open trial was performed that included 170 concentration-time records and covariate information from 44 children between 4 and 16 years of age using a population approach and a Nonlinear Mixed Effects Model. Variables evaluated for possible associations with pharmacokinetic parameters included age, gender, weight, creatinine clearance, and concomitant therapy with other antiepileptic drugs (AEDs.) A final model was used to perform Monte Carlo simulations in order to determine dosing regimens in children that would result in similar serum concentrations compared with those achieved with standard adult doses of LEV.

**Results:** The study group of 44 children included 22 girls and 22 boys. The most frequently used concomitant AEDs were valproic acid, lamotrigine, carbamazepine, and vigabatrin. LEV pharmacokinetics in children appeared relatively straightforward. A classical one-compartment model with an absorption lag-time, first-order absorption, and linear elimination was most consistent with the data. The apparent clearance of LEV and the volume of distribution were primarily related to body weight. No significant pharmacokinetic interactions with other AEDs were observed. Analysis indicated that a dosage regimen of 20 mg/kg per day in 2 divided doses will result in a plasma LEV concentration similar to that obtained in adults treated with the standard adult starting-dose of 500 mg twice daily. Likewise, dosage regimens of 30 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day in 2 divided doses in children appear comparable to 1000 mg twice a day, 1500 mg twice a day, and 2000 mg twice a day dosing regimens in adults respectively. The regimen of 40 mg/kg/day in 2 divided doses will typically achieve a trough plasma concentration within the suggested target range of 6 to 20 mg/L.

**Reviewer’s Comments:** It is typically not a necessity to quickly achieve a total daily dose of 60 mg/kg of LEV in the treatment of children with epilepsy. A more rational approach is to achieve a starting dose of about 20 mg/kg/day and subsequently titrate the dose, based on achieved seizure control and tolerability, in a stepwise fashion to a maximum daily dose if necessary of about 60 mg/kg/day. In order to minimize potential adverse effects, maintenance of the smallest effective dose is logical. (Reviewer-Gregory B. Sharp, MD.)
Patients with peripheral polyneuropathy do not have a higher risk of restless legs syndrome.

**Background:** Restless legs syndrome (RLS) is a common disorder affecting approximately 10% of the population in western countries. An association between peripheral polyneuropathy and RLS is commonly quoted. This study was set to address whether there is a higher risk of RLS in patients with peripheral polyneuropathy compared to controls.

**Design:** Analysis of patients seen in a tertiary Canadian peripheral polyneuropathy clinic.

**Methods:** Patients with peripheral polyneuropathy seen over a decade participated in a telephone screening questionnaire that included the international RLS diagnostic criteria. Controls included patient spouses and friends as well as general neurology clinic patients. Subjects who screened positive for RLS were further evaluated in the clinic or by phone by a movement disorder specialist. The primary outcome was the prevalence of RLS in peripheral polyneuropathy subtypes, the mean RLS score in patients with peripheral polyneuropathy versus controls, and the positive predictive value (PPV) and specificity of the screening questionnaire in patients with peripheral polyneuropathy versus controls.

**Results:** Among the 275 patients contacted, 245 were screened and compared to the 245 controls. The initial questionnaire yielded RLS in 68 patients (27%) and 26 controls (10%), a statistically significant difference ($P < 0.0001$). However, after being interviewed by a movement disorder specialist, 30 patients (12%) with peripheral polyneuropathy were confirmed to have RLS, while 20 controls (8%) had RLS (a statistically insignificant difference; $P = 0.14$). False-positive screens were due to cramps, paresthesias, lack of rest exacerbation, or lack of diurnal variation. Patients with hereditary neuropathy had a more prevalent RLS than those with acquired neuropathy ($P = 0.033$) and controls ($P = 0.016$). The PPV and specificity of the telephone screening questionnaire was lower in peripheral polyneuropathy versus controls (PPV, 46% vs 87%; specificity, 82% to 91% vs 98% to 99%, respectively).

**Conclusions:** RLS is not more prevalent in patients with peripheral polyneuropathy than in the general population. RLS is, however, slightly more prevalent among patients with hereditary neuropathy, but not those with acquired neuropathy.

**Reviewer’s Comments:** I have been long impressed by the lack of RLS symptoms in patients with peripheral polyneuropathy, though prior literature suggested that 5% to 50% of such patients have RLS. This study supported my clinical inclination and clearer distinction between the painful and burning legs in patients with peripheral polyneuropathy and the uncomfortable legs with the need to move or walk around in patients with RLS. Because of the significant clinical overlap, caution should be taken in using RLS questionnaires in patients with peripheral polyneuropathy. A thorough history with detailed description of the symptoms is important since the work-up and pharmacologic treatment of RLS versus neuropathic pain is quite different. (Reviewer-Bashar Katirji, MD).

© 2009, Oakstone Medical Publishing

Keywords: Peripheral Neuropathy

Print Tag: Refer to original journal article
FA and FL syndromes are distinct ALS variants with much better survival rates.

**Background:** Amyotrophic lateral sclerosis (ALS) is classified into limb-onset ALS, progressive bulbar palsy, primary lateral sclerosis, and progressive muscular atrophy (PMA). The flail arm (FA) and the flail leg (FL) syndromes are uncommon variants of ALS, sometimes lumped under PMA. FA is characterized by progressive upper limb weakness and wasting resulting in a "man-in-the-barrel" phenotype. FL is characterized by progressive lower limb weakness and atrophy resulting in flaccid paraplegia.

**Design:** Retrospective analysis of patients in 2 tertiary ALS clinics in London, England, and Melbourne, Australia.

**Methods:** ALS Patients from both institutions (1,188 in London; 432 in Melbourne) seen over 12 to 14 years were analyzed. Patients were classified into limb-onset ALS, bulbar-onset ALS, FA, FL or PMA. FA and FL were defined as disorders in which weakness and atrophy remained confined to the flail limbs (arms or legs) for at least 12 months after onset of symptoms. PMA was diagnosed when the characteristic pattern of wasting did not follow the FA or FL phenotypes. Patients with other motor neuron disorders were excluded. Survival times were analyzed using the Kaplan-Meier method and the Cox proportional hazards model.

**Results:** FA and FL represented 11% and 6% of all ALS patients in the London ALS cohort, and 5% and 3% in the Melbourne cohort. The median survival (months) for limb-onset ALS, bulbar-onset ALS, FA, and FL was 35 months, 27 months, 61 months ($P<0.001$), and 69 months ($P<0.001$) in London, and 31 months, 27 months, 66 months ($P<0.001$), and 71 months ($P<0.001$) in Melbourne. PMA cases falling outside FA and FL definitions had a survival probability identical to limb-onset ALS. The 5-year survival rates were higher in FA and FL (52% and 64%, respectively) compared to limb-onset and bulbar-onset ALS (20% and 9%, respectively). Median time to spread to a second region of the neuraxis was longer in FA and FL (29 and 33 months, respectively) compared to limb-onset ALS, bulbar-onset ALS, and PMA (8, 12, and 14 months, respectively; $P<0.001$). Weakness remained confined to upper limbs in FA or lower limbs in FL at 18 months in 56% and 63%, respectively, and at 36 months in 27% and 28%, respectively. Median time from symptom onset to diagnosis was longer in FA (17 months) and FL (25 months) compared to limb-onset ALS (10 months; $P<0.001$).

**Conclusions:** FA and FL syndromes are distinct ALS variants and carry significantly better survival than limb-onset ALS and PMA.

**Reviewer's Comments:** This study confirms the distinction between limb-onset ALS and PMA versus FA and FL variants. Patients with weakness and atrophy confined to upper or lower limbs for >1 year from onset of symptoms suffer from these variants, and have a comparatively slower progression. These patients will continue to be excluded from ALS trials because of their relatively benign natural course. (Reviewer-Bashar Katirji, MD).

© 2009, Oakstone Medical Publishing

Keywords: ALS Variants

Print Tag: Refer to original journal article
Antithrombotic Agents and Cerebral Microbleeds

Use of Antithrombotic Drugs and the Presence of Cerebral Microbleeds: The Rotterdam Scan Study.

Vernooij MW, Haag MDM, et al:
Arch Neurol 2009; 66 (epub ahead of print):

Antiplatelet agents increase the risk of cerebral microbleeds.

**Background:** Lacunar infarcts and white matter lesions, and more recently cerebral microbleeds (CMB), are considered markers for cerebral small vessel disease. CMBs are recognized as small areas of hypointensity on T2-weighted gradient-recalled echo (GRE) MRI, and consist of hemosiderin deposits in macrophages. Generally, microbleeds occurring strictly in the lobar areas are due to cerebral amyloid angiopathy (CAA), and those occurring in deep or infratentorial locations are due to hypertension or arteriosclerotic microangiopathy. In CAA, anticoagulants and anti-platelet agents are associated with symptomatic hemorrhage. Therefore, it is possible that strictly lobar microbleeds occur more often in patients on antithrombotic drugs.

**Objective:** To evaluate the association between the use of antithrombotic agents and CMBs.

**Design/Methods:** This was a population-based, cross-sectional analysis of data from the Rotterdam Scan Study, which evaluated a general elderly community in the Netherlands. The subjects underwent MRI between August 2005 and November 2006. Information regarding the use of antithrombotic agents was obtained from the automated pharmacy records. CMBs were defined as areas of low-signal intensity on T2-weighted GRE MRI images.

**Results:** Of the 1062 patients, 543 were women (51.1%); 363 patients were on antithrombotic drugs, and 245 were on anti-platelet agents (including 67 on aspirin and 141 on carbasalate calcium). Sixty-one patients were on anticoagulants, including vitamin K antagonists and heparin. CMBs were seen 250 subjects (23.5%); these CMBs were strictly lobar in 146 (13.7%) and deep or infratentorial in 104 (9.8%). CMBs were more common in patients on antiplatelet agents compared to subjects on no antithrombotic agents (adjusted OR, 1.71; 95% CI, 1.21 to 2.41). No significant association was found between CMBs and anticoagulant use. Strictly lobar cerebral microbleeds were more prevalent among those on aspirin (adjusted OR, 2.70) compared to those on carbasalate calcium (adjusted OR, 1.16). The difference was even more pronounced when similar doses (in terms of aspirin equivalence) of both drugs were used.

**Conclusions:** CMBs were more common in those using antiplatelet agents. Aspirin users had a higher risk of developing strictly lobar CMBs than carbasalate calcium users.

**Reviewer's Comments:** This is an interesting study showing an increased risk of CMBs in antiplatelet users. It is well known that the benefits of antiplatelet therapy outweigh the risks of bleeding. What is not known, however, is whether the presence of cerebral microbleeds increases the risk of symptomatic hemorrhages. If future studies show that this is indeed true, a case may be made for using carbasalate calcium instead of aspirin in patients with CAA, although few of us in the United States have any experience with this medication. (Reviewer-Chitharanjan Rao, MD).

© 2009, Oakstone Medical Publishing

Keywords: Cerebral Microbleeds

Print Tag: Refer to original journal article
Initial treatment of Parkinson disease patients with either levodopa or dopamine agonists results in similar long-term disability.

**Background:** Several studies have shown that initial treatment with dopamine agonists delays the development of dopaminergic side effects, whereas initial treatment with levodopa results in better symptom control. Dopamine agonists are often preferred to levodopa in early Parkinson disease (PD) with the belief that delaying dopaminergic events results in lower long-term disability and better quality of life. However, there are no major longitudinal studies comparing initial treatment with these 2 treatment options in early PD.

**Objective:** To report the results of the CALM Cohort study, an extended follow-up of the Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) trial participants.

**Methods:** The CALM-PD study enrolled PD patients between 1996 and 1997 at 22 sites in North America. At the conclusion of the CALM-PD study, consenting participants were enrolled in the CALM Cohort study from 2002 to 2004. Patients were followed up for 2 years. The primary outcome measure was the disability score on the Schwab and England Activities of Daily Living (S/E ADL) Scale. Secondary outcome measures were Unified Parkinson's Disease Rating Scale (UPDRS) score, the Lang-Fahn ADL dyskinesia scale score, the quality-of-life scale score, and the Epworth Sleepiness Scale (ESS) score.

**Results:** In the initial CALM-PD trial, 301 patients were randomized (151 to the pramipexole arm and 150 to the levodopa arm). Of these patients, 222 (108 and 114 from the respective arms) were recruited into the CALM Cohort study. Mean follow-up was 6 years. At the end of the study, most patients were on combination therapy regardless of their initial medication. More than 90% of subjects in both groups were on levodopa, >80% of the patients in the initial pramipexole arm were still on the pramipexole, and 16.7% in the initial pramipexole group and 30% in the initial levodopa group were on amantadine. The mean S/E ADL scores were similar in both groups, 79.9 and 82.5, respectively. Dopaminergic motor events (dyskinesias, wearing off) were more common in the initial levodopa group (68.4%) than in the initial pramipexole group (50.0%); however, disabling dyskinesias were uncommon and were equally likely in either group. The mean ESS score was significantly higher in the initial pramipexole group (11.3) compared to the initial levodopa group (8.6). Mean changes from baseline in UPDRS scores were similar in both groups.

**Conclusions:** Although the initial levodopa treatment group had more dopaminergic motor events and the initial pramipexole group had more somnolence, self-reported disability was similar in both groups.

**Reviewer's Comments:** This is an important study showing that, contrary to our belief, initial treatment with either levodopa or dopamine-agonists has similar benefits and treatment-associated disabilities. However, a higher proportion of the initial levodopa group were on amantadine (30% vs 16.7%), possibly confounding the data on disabling dyskinesias in that group. (Reviewer-Chitharanjan Rao, MD).