Heuristics are very useful diagnostic shortcuts for experienced clinicians, if errors are avoided, but this method of diagnosis should not be taught to medical students and junior residents.

**Background:** Physicians use shortcuts in decision making to help them efficiently manage complex information involved in formulating a diagnosis. These shortcuts often involve heuristics. A heuristic is defined as a somewhat speculative thought process serving as a guide in the investigation or solution of a problem. The difficulty is that heuristic reasoning can be flawed, resulting in misdiagnosis.

**Objective:** To describe heuristics commonly used in neurologic diagnosis, present case examples, and provide recommendations for avoiding pitfalls.

**Design:** Case reports.

**Participants:** 5 patients with neurologic problems misdiagnosed because of errors in using heuristic thinking.

**Results:** The 5 heuristics described include framing effects, anchoring, availability, representativeness, blind obedience and over-reliance on test results. Cases that are representative of misuse of all 5 of these heuristics are presented. With framing effects, the clinician is swayed by the leading aspects of the initial information presented to him. This can result in erroneous initiation of the process by focusing on certain aspects of the case in preference to others. The anchoring heuristic refers to formulation of an initial diagnosis based on information without adjusting the probability of this diagnosis when new information comes to light. The availability heuristic is the practice of allowing the likelihood of a diagnosis to be influenced by the ease of recall of similar examples. The representativeness heuristic uses the process of arriving at a diagnosis based primarily on how well the clinical presentation resembles other patients with a well characterized disease, with a tendency to ignore prior probabilities or base rates of the disease. The blind obedience and over-reliance on test results heuristic can be faulty in that clinicians may focus on a particular diagnosis, based on a diagnostic test result, without considering the test's sensitivity or specificity or base a decision on undue deference to authority figures. As noted, the authors provide case examples of errors in thinking utilizing all 5 of these heuristic methods, as well as tips on ways to eliminate errors in the utilization of these heuristics.

**Conclusions:** Physicians use heuristics by necessity to help them sort through complex clinical information and formulate diagnoses and treatment strategies. The important thing is for physicians to recognize the potential for pitfalls with the use of heuristics and to avoid these pitfalls.

**Reviewer's Comments:** I first heard this information presented at the American Neurological Association Meeting in 2008 and found it to be extremely interesting. I have seen these errors in thinking committed by myself and others in arriving at diagnoses. Heuristic reasoning can be used by experienced clinicians to efficiently make diagnoses, but this diagnostic method should not be taught to medical students and junior residents. This is a very interesting article that can be recommended for all neurologists and other physicians. (Reviewer-W. Steven Metzer, MD).

Keywords: Cognitive Psychology, Diagnostic Errors, Neurological Diagnosis

Print Tag: Refer to original journal article
The gradient-recalled echo MRI is best for identifying microbleeds.

**Background/Objective:** I am frequently called by internists caring for patients with atrial fibrillation who are pondering an MRI report that describes cerebral microbleeds (MBs). They want to know whether this finding means they cannot administer warfarin for stroke prevention. My answer for this question usually is not satisfactory, as it is informed neither by good data nor even reasonable expert opinion. The authors of this study tried to do what they could with the available data on this question.

**Design:** Systematic review.

**Methods:** 2 types of studies were reviewed. Most were retrospective, identifying patients who presented with an acute stroke or transient ischemic attack (TIA) and examining the relationship between prior antithrombotic drug use and the presence of MBs on MRI at the time of the event. Far fewer were prospective, examining the subsequent course of patients who presented with a cerebrovascular event, had a gradient-recalled echo (GRE) MRI, and were then placed on antithrombotic drugs. The studies were somewhat heterogeneous as to the definition of MB and MRI technique, although all used the GRE sequence.

**Results:** The pooled retrospective analysis included >5000 patients. Among 63 warfarin users who presented with intracerebral hemorrhage (ICH), 44 (approximately two-thirds) had MBs, while among 164 warfarin users with ischemic stroke/TIA, only 54 (approximately one-third) had MBs. Among 115 antiplatelet drug users with ICH, 83 (over two-thirds) had MBs, and among 695 antiplatelet drug users with ischemic stroke/TIA, 194 had MBs (<30%). Among 595 patients on no antithrombotic medication before an ICH, approximately 60% had MBs, while among 1595 patients on no antithrombotic medication before a cerebral infarct/TIA, 428 (slightly >25%) had MBs. Thus, MBs are significantly more common in all patients who present with ICH compared to those presenting with ischemia, with this tendency more marked in patients on antithrombotic drugs. In the prospective cohort, the numbers were much smaller (n=approximately 750), but the presence of MB on GRE was strongly associated with subsequent cerebrovascular events in those patients being ICHs as opposed to ischemic; numbers were insufficient to distinguish between the effects of warfarin versus antiplatelet medications.

**Conclusions:** The authors stop short of advising that antithrombotic drugs may be contraindicated in some patients with MBs and encourage better prospective data. They acknowledged that all potential confounders were not accounted for.

**Reviewer's Comments:** Ultimately, there is nothing in these studies to guide current practice, but this paper sets out what imperfect data do exist. (Reviewer-James W. Schmidley, MD).

**Keywords:** Microbleeds, Gradient-Recalled Echo MRI, Antithrombotic Drugs

**Print Tag:** Refer to original journal article
Once dyskinesia appears during levodopa therapy, it is triggered at the same levodopa blood level threshold that initiates the antiparkinsonian response.

**Background:** Dyskinesia rarely complicates levodopa therapy for Parkinson disease (PD) when it is first initiated, but after 2 years of treatment, approximately 33% of subjects develop some dyskinesia. There is a widespread belief that the plasma threshold for levodopa inducing dyskinesia is initially much higher than that for antiparkinsonian relief. In other words, PD symptoms respond to plasma levodopa levels well below those causing dyskinesia. Over many years of therapy, this therapeutic window gradually narrows, and in advanced PD, dyskinesia and the antiparkinsonian response appear together at the same levodopa plasma levels. Just how these threshold differences change during long-term levodopa therapy has not been systematically investigated.

**Objective:** To examine the temporal relationship between dyskinesia and the antiparkinsonian response when dyskinesia first appears in long-term levodopa therapy for PD.

**Design/Participants:** Retrospective analysis of 20 subjects with early PD previously recruited into a longitudinal, 4-year study of the levodopa response.

**Methods:** Before starting oral levodopa, patients were infused with levodopa (1 mg/kg per minute) for 2 hours and assessed for improvement in bradykinesia (rapid finger tapping test) and/or tremor and monitored for dyskinesia. Similar testing was repeated at intervals over the next 4 years. Once dyskinesia appeared, its onset and disappearance (offset) were compared to the onset and offset of the antiparkinsonian response. The findings were then compared with 20 PD patients who had received levodopa therapy for an average of 8 years and had developed severe dyskinesias and motor fluctuations.

**Results:** Given their first-ever dose of levodopa, the patients demonstrated an antiparkinsonian response approximately 2 hours after beginning the infusion. The effect lasted approximately 3 hours. No dyskinesias were observed. With interval re-testing, levodopa infusions triggered dyskinesia in 8 subjects after 6 months of levodopa therapy, in 12 subjects after 12 months, in 15 subjects at 2 years, and in 16 subjects at 4 years. The dyskinesia and antiparkinsonian response appeared together about 1.5 hours after the start of infusion and disappeared together 2.5 hours later. In the long-term levodopa group, the onset of dyskinesia and the antiparkinsonian response began 1 hour after the start of infusion and disappeared an average of 3 hours later.

**Conclusions:** Once dyskinesia emerges during levodopa therapy, its appearance and disappearance coincide closely with the onset and offset of the antiparkinsonian response. This is true for both early and advanced PD. These observations do not support the often postulated therapeutic window between the antiparkinsonian response and dyskinesia.

**Reviewer's Comments:** As the authors point out, many therapeutic strategies attempt to dissociate dyskinesia from the antiparkinsonian response to levodopa believing that they are driven by 2 different mechanisms. The authors suggest it is time to "think outside the box" and look for other pharmacologic or physiologic methods to correct the disordered basal ganglia circuitry. (Reviewer-Michael Jacewicz, MD).

**Keywords:** Levodopa, Dyskinesia, Parkinson Disease

**Print Tag:** Refer to original journal article
Shorter Survival Seen in PSP Patients Than in FTD Patients

Survival in Progressive Supranuclear Palsy and Frontotemporal Dementia.

Chiu WZ, Kaat LD, et al:
J Neurol Neurosurg Psychiatry 2010; 81 (April): 441-445

Frontotemporal dementia patients with motor neuron disease tend to have a very short survival.

**Background:** Progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) are neurodegenerative disorders with clinical, genetic, and pathologic overlap.

**Objective:** To prospectively investigate the survival of patients with these 2 disorders (PSP and FTD) in relationship to clinical and demographic features.

**Methods:** A detailed clinical history was obtained from patients, their family, and their medical records. Family history was deemed positive if at least 1 first-degree relative suffered from parkinsonism, dementia, or motor neuron disease. Neuroimaging was reviewed to exclude other structural causes of symptoms. PSP patients had clinical symptoms quantified with the Mini-Mental Status Examination, Frontal Assessment Battery, Unified Parkinson's Disease Rating Scale III, and the PSP Rating Scale (PSPRS). FTD patients underwent neurological examination, neuropsychological examination, and neuroimaging. The clinical diagnoses were established according to the National Institutes of Neurological Diseases and Stroke Society for PSP and the Lund and Manchester criteria for FTD. Genes were sequenced for \( MAPT \), \( CHMP2B \), and \( GRN \) in all familial cases. On those with neuropathological examination immunohistochemistry was performed for AT8, ubiquitin, both 3 and 4 repeat tau, TDP-43, B-amyloid, and alpha-synuclein. The neuropathological diagnosis of FTD was classified as FTD-tau or FTD-ubiquitin (with or without TDP-43). FTD-motor neuron patients were excluded from the study. The neuropathologic diagnosis of PSP was made with a semiquantitative assessment of neurofibrillary tangles, tufted astrocytes, oligodendroglial coiled bodies, and thread pathology. Statistical analyses were performed.

**Results:** The mean age of onset and death were significantly higher in the PSP patients as compared to the FTD patients. Of the 197 patients with PSP, 133 died at a mean disease duration of 7.2 ± 2.6 years, and 242 of 354 FTD patients died at a mean disease duration of 9.2 ± 4.1 years. This poorer prognosis for PSP patients remained significant after adjustment for gender, age-onset, and family history. A Cox proportional hazards regression model of PSP patients revealed male gender, older age at onset (>72 years), and a higher PSPRS score to be independent predictors of disease duration. For FTD patients, a positive family history and age at onset of >64 years were significantly associated with poor survival. Pathological examination was carried out on 24 PSP and 61 FTD patients. The FTD group showed a higher percentage with a positive family history (57.6%) and younger age of onset (55.3 years).

**Conclusions:** Survival of PSP patients is shorter than that of FTD patients.

**Reviewer's Comments:** This study shows the prognostic value of the PSPRS, with a rise in the probability of death associated with a score >60. Although there were only 7 patients with the PSP Parkinson phenotype, these patients had a much longer survival (11.6 years). In patients with familial FTD, those with \( GRN \) mutations had a shorter survival than those with \( MAPT \) mutations. (Reviewer-John Schwankhaus, MD).

**Keywords:** Parkinsonism, Progressive Supranuclear Palsy, Frontotemporal Dementia

**Print Tag:** Refer to original journal article
What Is Abnormal in Forebrain White Matter Tracts in Schizophrenia?

Diffusion Tensor Tractography Findings in Schizophrenia Across the Adult Lifespan.

Voineskos AN, Lobaugh NJ, et al:

Brain 2010; 133 (May): 1494-1504

Young schizophrenics have reduced fractional anisotropy in the left uncinate fasciculus and the right cingulum bundle.

**Background/Objective:** A variety of electron microscopic, genetic, and animal studies point to oligodendrocyte dysfunction in schizophrenia. The current study examined the microstructural integrity of frontotemporal and interhemispheric white matter tracts in schizophrenia across the adult lifespan.

**Participants/Methods:** Diffusion tensor imaging was performed in 25 schizophrenic patients \( \leq 55 \) years of age, 25 schizophrenic patients \( \geq 56 \) years of age, 25 younger control subjects, and 25 older control subjects. Whole-brain tractography and a clustering segmentation technique was used to isolate white matter tracts, namely left and right uncinate fasciculus, inferior occipito-frontal fasciculus, cingulum bundle, inferior longitudinal fasciculus, arcuate fasciculus, and genu and splenium of the corpus callosum.

**Results:** Significantly decreased microstructural integrity (reduced fractional anisotropy [FA]) was identified in the left uncinate fasciculus and right cingulum bundle in younger schizophrenics compared with young controls, but no differences in FA were observed between older patients and controls. Age-related decline in FA occurred in both patients and controls but was not accelerated in patients.

**Conclusions:** The left uncinate fasciculus and right cingulum bundle are disrupted in young schizophrenic patients, consistent with prior studies suggesting frontotemporal disconnectivity in schizophrenia. Disruption of the uncinate fasciculus might be related to impaired self-regulation, self-awareness, goal-directed behavior, and social cognition. Disruption of the cingulum bundle might be related to negative symptoms and impaired executive function. The lack of difference between older patients and controls in these measures might be related to these older patients having mild enough disease to be community dwellers, reflecting resilience to white matter disruption.

**Reviewer’s Comments:** This study adds to a growing literature documenting frontal and temporal lobe morphological abnormalities in schizophrenia; the fact that only 2 of 7 white matter tracts showed abnormal FA is consistent with specific regional vulnerability. It is not clear why oligodendrocytes would be dysfunctional only in the selected tracts. The lack of difference in older patients suggests that the deficits are acquired early in life and do not progress with aging. (Reviewer-John C. Brust, MD).

**Keywords:** Schizophrenia, Diffusion Tensor, Ageing, White Matter Fibre Pathways

Print Tag: Refer to original journal article
What Is Neurophysiological Evidence That DLPFC Is Disrupted in Schizophrenia?

Evidence for Gamma Inhibition Deficits in the Dorsolateral Prefrontal Cortex of Patients With Schizophrenia.

Farzan F, Barr MS, et al:

Brain 2010; 133 (May): 1505-1514

In schizophrenia, gamma-aminobutyric acid-mediated cortical inhibition is impaired in the dorsolateral prefrontal cortex but not in the motor cortex.

**Objective:** To evaluate the effect of gamma-aminobutyric acid-type B (GABA_B) receptor mediated inhibitory neurotransmission on gamma oscillations in the dorsolateral prefrontal cortex (DLPFC) and motor cortex of patients with schizophrenia compared to patients with bipolar disorder and healthy subjects.

**Participants/Methods:** 14 subjects, matched for age and sex, were in each group; the severity of symptoms was comparable in those with schizophrenia and bipolar disorder. Transcranial magnetic stimulation (TMS) was administered over the left DLPFC and left motor cortex, and cortical inhibition was measured using EMG and EEG. (Cortical inhibition occurs when a transcranial magnetic conditioning stimulus, followed by a test stimulus, reduces the size of the evoked cortical potential produced by the test stimulus.) Cortical inhibition in the motor cortex was examined using EEG and EMG and in the dorsolateral prefrontal cortex by using EEG only. Cortical potentials evoked by TMS were decomposed into delta, theta, alpha, and gamma frequency components using an impulse response filter.

**Results:** Patients with schizophrenia had significantly lower cortical inhibition of gamma frequency in the DLPFC compared to patients with bipolar disorder and healthy subjects. There was no significant difference between groups in cortical inhibition of gamma frequency in the motor cortex, and there was no difference between groups in inhibition of other oscillatory frequencies in the DLPFC or the motor cortex.

**Conclusions:** GABA_B suppression of gamma oscillations in the DLPFC is impaired in schizophrenia. This region has been implicated in the cognitive deficits encountered in schizophrenia, including problems with working memory. Notably, in contrast to schizophrenia, working memory is normal in bipolar disorder, which in the present study was not associated with impaired DLPFC gamma oscillatory inhibition. The authors of this study speculate that "the functional role of this inhibition may be to shape the temporal profile of incoming information during different phases of cognitive tasks such as working memory."

**Reviewer’s Comments:** This report adds to ever-growing evidence that DLPFC abnormalities play a fundamental role in the cognitive abnormalities of schizophrenia. (Reviewer-John C. Brust, MD).

Keywords: Schizophrenia, Gamma Inhibition Deficits, Dorsolateral Prefrontal Cortex, Bipolar Disorder

Print Tag: Refer to original journal article
Valproate appears to be effective in many refractory cases of epilepsy in older adults.

**Background:** Previous randomized controlled trials comparing the efficacy of antiepileptic drugs (AEDs) in older adults appear to have included only 2 or 3 AEDs, typically lamotrigine, gabapentin, and carbamazepine.

**Objective:** To determine the efficacy and tolerability of several AEDs in elderly adults.

**Design:** Retrospective chart review.

**Participants:** 417 outpatients, who were ≥55 years old and took any of the most commonly prescribed AEDs during a 5-year period, were identified. Of these 417 patients, 293 had initially begun to take an AED during this time, involving 15 different AEDs. Five of these were rarely used, so the analysis was of 247 patients taking ≥1 of 10 commonly prescribed AEDs.

**Methods:** The main outcome measure was ≥12 months of continuing to take an AED (12-month retention). The investigators also measured efficacy (12-month seizure freedom) and adverse effects leading to dose change.

**Results:** Overall, approximately 79% of these patients continued to take 1 AED for at least 1 year. There were no significant nondrug predictors of retention of treatment. Lamotrigine had the highest 12-month drug retention treatment rate (79%), significantly better than carbamazepine (48%), gabapentin (59%), oxcarbazepine (24%), phenytoin (59%), and topiramate (56%). The drug retention treatment rate for levetiracetam was 73%. This was second highest and significantly higher than for carbamazepine and oxcarbazepine. Oxcarbazepine had the lowest drug treatment retention rate, and this was significantly lower than all other AEDs. Lamotrigine had the highest 12-month seizure freedom rate (54%), followed by levetiracetam (43%). The most common intolerable adverse effects from AEDs were imbalance, drowsiness, and gastrointestinal symptoms.

**Conclusions:** Lamotrigine was the most effective AED as measured by 12-month drug retention rate and seizure freedom, with levetiracetam almost as good. Oxcarbazepine was consistently less effective than most other AEDs. The authors also noted that valproate appears to be effective in many refractory cases.

**Reviewer’s Comments:** Although this is an uncontrolled retrospective study, it reinforces my impression that levetiracetam and lamotrigine are effective and well tolerated AEDs for elderly adults. This study suggests that oxcarbazepine should not be used routinely to treat seizures in elderly adults. (Reviewer-W. Steven Metzer, MD).

**Keywords:** Antiepileptic Drugs, Epilepsy, Geriatrics, Medical Therapy, Treatment

**Print Tag:** Refer to original journal article
Generic AED Tx for Epilepsy Results in Increased Medical Utilization

Generic Antiepileptic Drugs and Associated Medical Resource Utilization in the United States.

Labiner DM, Paradis PE, et al:

Neurology 2010; 74 (May 18): 1566-1574

The use of generic antiepileptic drugs in the treatment of patients with epilepsy results in increased medical utilization and risk of associated injury.

Background: The debate continues concerning the proper use of generic medications in the treatment of epilepsy. The Food and Drug Administration (FDA) defines a generic substitution as bioequivalent to the brand name drug, but the FDA's bioequivalence limits range from 80% to 125%. Since antiepileptic drugs (AEDs) are used chronically, generic prescribing will commonly result in substitution with multiple generic products for a given drug over an extended period of time, likely increasing the chance that at some point, the patient will receive a product that approaches the 80% margin, with potentially increased seizure frequency or severity. The alternative (125% bioavailability) increases risk of toxicity.

Objective: To determine if generic substitution of 5 commonly used AEDs for epilepsy in the United States results in increased medical resource utilization.

Methods: An analysis of a health insurance claims database (that included approximately 90 health care plans) between 2000 and 2007 was performed, with selection of adult epileptic patients treated chronically with carbamazepine, gabapentin, phenytoin, primidone, or zonisamide. Using a retrospective open-cohort design, patients were classified into mutually exclusive periods of time when they were treated with brand versus generic AEDs. A comparison of these 2 periods was performed using multivariate regression analyses. Incidence rates of health care utilization were calculated with attention to prescriptions for other AEDs and non-AEDs, hospitalizations, length of hospital stay, and outpatient clinic and emergency department visits. Results were also stratified for groups of patients with stable versus unstable epilepsy.

Results: The stable epilepsy group included 18,125 patients and the unstable group included 15,500 patients. After adjustments for covariates were made, it was determined that additional use of other AEDs and non-AEDs were significantly increased during the period of generic AED use compared to brand use. Medical utilization was also increased during periods of generic AED therapy, with significant increases in hospitalizations, outpatient visits, and length of hospital stays. Generic AED therapy resulted in increased medical utilization in both epilepsy groups (stable and unstable). Generic AED therapy was associated with a 20% increase in risk of injury compared to brand name AED therapy.

Conclusions: The use of generic AEDs in adult patients with epilepsy resulted in increased medical utilization and increased risk for epilepsy-related events and injury. This held true in patients with unstable and stable epilepsy.

Reviewer's Comments: It is obvious that the primary purpose for using generic AEDs is lower cost. Health care plans are increasingly dictating generic substitution, and for patients with epilepsy, more attention should be paid to what is in the patient's best interest in this regard. Further studies should evaluate the cost savings with generics versus the costs of increased medical utilization. (Reviewer-Gregory B. Sharp, MD).

Keywords: Epilepsy, Generic Antiepileptic Drugs, Medical Utilization, United States

Print Tag: Refer to original journal article
The treatment of post-stroke spasticity with botulinum toxin can improve the function of an upper extremity.

**Background:** Botulinum toxin has become the standard of care for spasticity after stroke. Studies have demonstrated improvement in spasticity using static scales, such as the Ashworth scale. Functional improvement has been more difficult to demonstrate.

**Objective:** To show functional improvement with Botulinum Toxin Type-A (BoNT-A) using upper-limb kinematics.

**Participants:** The 8 subjects had a clinical stroke <1 year prior to the study and were initially hemiplegic but experienced motor improvement to strength graded 3+ or more on the Medical Research Council scale. They were felt to have gained maximum improvement from standard physical and occupational therapy. The patients had flexor spasticity compromising the elbow, wrist, and fingers, yet had full passive range of motion, selective motor control of finger extensors when tested at maximal wrist flexion, adequate finger flexor strength, and a partial limitation of finger extensors due to the spastic flexor pattern, plus the ability to perform the reaching, grasping, and transport task at baseline. Patients were excluded if they had moderate to severe sensory loss.

**Methods:** For kinematic studies, the subjects sat comfortably in the chair with their elbow at 90° flexion and their shoulder in the neutral position. The task involved locating an object 35 cm from the body, grabbing the object, and transporting it to a spot in the middle of the desk. An auditory signal acted as the "go" instruction, and patients were asked to perform the task as accurately as possible at the most comfortable speed. Five trials were performed both before BoNT-A and 1 month after. Peak velocity, displayed distance, and the phase duration were recorded for each trial in the reaching phase, grasping phase, and transport phase. BoNT-A was given at the specialist's discretion, not to exceed 400 units. Injections were placed using anatomic landmarks and EMG guidance. All patients also received 1 hour of physical/occupational therapy twice weekly.

**Results:** Patients with a stroke had slower mean peak velocity both before and after BoNT-A compared to normal controls. A significant reduction was found in the duration of each phase of the movement (reaching, grasping, and transporting) 1 month after BoNT-A injection.

**Conclusions:** Focal treatment of spasticity with BoNT-A leads to an adaptive change in the upper limb of patients with spastic stroke.

**Reviewer's Comments:** This is one of the first studies to demonstrate real improvement of active motor function after botulinum toxin treatment of spasticity in moderate hemiplegia. (Reviewer-John Schwankhaus, MD).

**Keywords:** Stroke, Upper-Limb Spasticity, Botulinum Toxin

**Print Tag:** Refer to original journal article
Knowledge Does Not Always Translate Into Action

Lack of Association Between Stroke Symptom Knowledge and Intent to Call 911: A Population-Based Survey.

Fussman C, Rafferty AP, et al:

Stroke 2010; 41 (July 1): 1501-1507

The public is unaware of the advantages of emergency medical service transport, and better education is needed to overcome obstacles to activating it by calling 911.

**Background:** Despite a decade of public education about acute ischemic stroke, rates of tissue plasminogen activator (tPA) use in the U.S. remain discouragingly low.

**Objective:** To ascertain what fraction of the adult population of Michigan would call 911 when confronted with stroke warning signs and how this response is influenced by the knowledge of stroke.

**Design:** Population-based, telephone survey.

**Participants:** Adults participating in the Michigan Behavioral Risk Factor Surveillance System, a project funded by the Centers for Disease Control and Prevention to assess health behaviors and awareness, were included.

**Methods:** Respondents were asked what they would do in 5 hypothetical situations involving acute symptoms in a family member. Three vignettes involved stroke symptoms (essentially, aphasia, lateralized weakness/numbness, loss of vision in 1 or both eyes), and the other 2 vignettes involved fever and leg injury. Possible responses were: administer first-aid or medication; call physician; call 911; take patient to emergency room; and do nothing. An adequate response was defined as calling 911 for all 3 stroke scenarios, and an inadequate response was not calling 911 for any of the scenarios. After this, respondents were also asked to name 3 warning signs of stroke, with adequate knowledge defined as an ability to produce 3 correct answers.

**Results:** The response rate was 48%. Rates of "call 911" were slightly >50% for the aphasia scenario and slightly >40% for the lateralized numbness and weakness. Only 20% of respondents would call 911 for the visual loss vignette, about the same as for leg injury (25%). African Americans consistently had the highest rates of calling 911 for stroke symptoms. Only 14% of respondents had "adequate intent to call 911" (ie, they would have called 911 for all 3 of the stroke scenarios); 37% would not have called 911 for any of them. Percentage of patients with adequate intent increased with age. Surprisingly, knowledge that a specific symptom was a warning sign of stroke was not strongly associated with intent to call 911 for the scenario describing that specific symptom. For example, only 55% of respondents who knew that aphasia was a stroke warning sign would have called 911, but 48% of those who did not know this would have done the same thing. Comparable figures for the visual loss scenario were 24% versus 19%, and for the lateralized symptoms scenario, 43% and 39%.

**Conclusions:** The public is unaware of the advantages of emergency medical service transport, and better education is needed to overcome obstacles to activating it by calling 911.

**Reviewer's Comments:** The age of the person in the scenario was not given; surely the response to symptoms in a 70-year-old patient would be different than in a 20 year old. In fairness, when the "call 911" response was combined with "take the person to the emergency room," >70% of patients with acute stroke symptoms would have been rapidly delivered to emergency care. (Reviewer-James W. Schmidley, MD).

**Keywords:** Emergencies, Emergency Medical Services Activation, Acute Stroke

**Print Tag:** Refer to original journal article
When children with Tourette syndrome are treated with antipsychotic medication, weight gain and lipid profiles should be followed closely.

**Background:** Treatment with medications to control tics in children with Tourette syndrome is generally used when the tics become a significant problem for the child. Antipsychotic medications are commonly used in children with Tourette syndrome, but associated side effects can be significant.

**Objective:** To assess metabolic and neurologic side effects associated with antipsychotic medications used in the treatment of children with Tourette syndrome.

**Participants/Methods:** All children at a single center with Tourette syndrome treated with antipsychotic medications were evaluated for metabolic and neurologic side effects every 6 months. Monitoring included height and weight measurements, calculations of body mass index (BMI) percentiles, performance on a standard assessment of extrapyramidal signs, and laboratory evaluations of cholesterol and glucose metabolism.

**Results:** The mean duration of follow-up was approximately 40 months for 73 children. The average age at commencement of monitoring was just over 10 years, and 88% of the patients were boys. Primary therapy was with an atypical antipsychotic in all but 2 patients. The primary medication used was risperidone in 49 children, quetiapine in 17, olanzapine in 5, and pimozide and haloperidol in 1 child each. Lipid abnormalities developed in 45% of patients. Compared to normative population-based mean lipid levels for boys, there were significant elevations in total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels. The girls had lower high-density lipoprotein levels. BMI percentiles were abnormally high in 50% of the patients, and two-thirds with elevated BMI also had lipid elevations. Three children developed neurologic abnormalities. One child developed akathisia in response to haloperidol, and 2 children experienced an acute dystonic reaction in response to an increase in the dose of haloperidol in one and risperidone in the other. There were no observed cases of tardive dyskinesia, tremor, or Parkinsonism.

**Conclusions:** Metabolic complications, including elevated lipid profiles and weight gain, are common in children with Tourette syndrome treated with antipsychotics. Neurologic complications are uncommon.

**Reviewer’s Comments:** As always, when considering treatment of any disorder, the benefit of therapy is weighed against the risk. This principle is applied to the treatment of children with Tourette syndrome, and the risks and benefits should be discussed with the parents or caregivers prior to initiating therapy. When atypical antipsychotics are used, attention should be paid to weight gain, and lipid profiles should be monitored. (Reviewer-Gregory B. Sharp, MD).

Keywords: Antipsychotic Drugs, Tourette Syndrome

Print Tag: Refer to original journal article
Patients With PD Should Have Regular Melanoma Screening

*Increased Melanoma Risk in Parkinson Disease: A Prospective Clinicopathological Study.*

Bertoni JM, Arlette JP, et al:

Arch Neurol 2010; 67 (March): 347-352

Keywords: Parkinson Disease, Melanoma Risk

Print Tag: Refer to original journal article

Parkinson disease patients are at a higher risk for melanoma than the general population, and it is the disease itself, not treatment with levodopa, that confers the risk.

**Objective:** To determine whether melanoma occurs more frequently in patients with Parkinson disease (PD) than in the general population and, if it does, whether the association is with the disease itself or treatment with levodopa.

**Design:** Prospective study involving 31 centers in the United States and Canada.

**Participants:** Adults with idiopathic PD were enrolled during 8 months in 2003. There were 2 groups of controls, both historical. One was a 5-year, limited-duration estimate of the prevalence of invasive melanoma (the U.S. Surveillance Epidemiology and End Results [SEER] cancer database), and the other was the American Academy of Dermatology (AAD) screening program for in situ and invasive melanoma.

**Methods:** At visit 1, a neurologist enrolled the patient. At visit 2, a dermatologist recorded any past history of melanoma and tried to get pathological verification and biopsied any suspicious skin lesions found on examination.

**Results:** The study enrolled 2106 patients from 31 to 100 years of age (mean age, 69 years). Dermatologists found 24 new cases of melanoma (4 invasive, 20 in situ), for a prevalence of 1.1% among the PD patients. In the AAD screening program, there were 3.8 cases of melanoma in an age- and sex-matched population of the same size, for a prevalence of 0.01%. Thus, the relative risk of melanoma was 6.2 times higher (95% CI, 4.2 to 9.5) for a patient with PD than for someone in the general population. The dermatologists also found another 68 PD patients with a past history of melanoma. Six of them had had melanoma in the previous 5 years, but the diagnosis could be pathologically verified in only 3. Comparing the 10 cases (4 new ones and 6 past ones) of invasive melanoma among the PD patients to the 5.5 cases in an age- and sex-matched population of the same size from the SEER database yielded a relative risk of invasive melanoma 1.8 times higher (95% CI, 1.0 to 3.4) in PD than in the general population. The use of levodopa did not differ significantly between PD patients with and without melanoma.

**Conclusions:** Patients with PD are at a higher risk for melanoma than the general population, and it is the disease itself, not treatment with levodopa, that confers the risk.

**Reviewer's Comments:** The weaknesses of the study are its use of historical controls and the lack of pathological verification of 30% of the cases of invasive melanoma in the PD subjects. The authors do, however, cite several other recent studies that arrived at the same conclusion; so it seems reasonable to accept it. (Reviewer-Marc D. Winkelman, MD).
The American Academy of Neurology practice parameter for neurologic prognosis of coma after cardiac arrest is less reliable in patients who are treated with therapeutic hypothermia. In particular, the motor response to deep pain on day 3 has no independent predictive power.

**Background:** According to the practice parameter from the American Academy of Neurology (AAN), a patient in coma after cardiac arrest (CA) has no chance (false positive rate [FPR] = 0) of a good neurologic outcome if the following conditions are met: (1) there is status myoclonus on day 1; (2) the patient has absent pupillary or corneal reflex during days 1 to 3; (3) there is absent or extensor motor response on day 3, and/or (4) there is bilateral absence of the N20 response on median-nerve somatosensory-evoked potentials (SSEP) during days 1 to 3 (Neurology 2006; 67: 203-210). In 2002, a randomized clinical trial showed that therapeutic hypothermia (TH) improves neurologic outcome in comatose survivors of CA (N Engl J Med 2002; 346: 557-563).

**Objective:** To determine whether the same prognostic rules apply to comatose patients given TH after CA.

**Design:** Prospective observational study.

**Participants:** Consecutive adults (n=111) who were treated with TH for coma after CA and were not brain dead within 2 days.

**Interventions:** TH to 33 ± 1°C was started after cardiac resuscitation and continued for 1 day.

**Methods:** Neurologic examination on days 2 and 3 and EEG and bilateral median-nerve SSEP on days 2 or 3 were performed. The brainstem reflexes tested were pupillary, oculocephalic, and corneal. Motor response to pain was categorized as no movement or extensor posture versus flexor posture or better. "Early myoclonus" was that which appeared within 1 day of stopping hypothermia, but the authors did not say whether it had to be status myoclonus. EEG reactivity was defined as a change in background frequency and amplitude after auditory or noxious stimulation. A poor outcome was defined as dementia, vegetative state, or death.

**Results:** No single clinical variable had an FPR of 0 for a poor outcome, but the presence of ≥2 variables among absent cortical SSEP, unreactive EEG background, early myoclonus, and ≥1 absent brainstem reflex did have an FPR of 0. Motor response worse than flexion did not contribute to an FPR of 0.

**Conclusions:** The AAN practice parameter for neurologic prognosis of coma after CA is less reliable in patients who are treated with TH; in particular, the motor response to deep pain on day 3 has no independent predictive power. The EEG background reactivity is strongly associated with outcome.

**Reviewer's Comments:** As the authors say, it is not clear whether TH alters or temporally displaces the prognostic value of the neurologic examination in patients with anoxic encephalopathy after CA. (Reviewer-Marc D. Winkelman, MD).

Keywords: Anoxic Encephalopathy, Prognosis, Coma, Cardiac Arrest

Print Tag: Refer to original journal article
In patients with late-onset Pompe’s disease, enzyme replacement therapy with recombinant human alglucosidase alpha is safe and effective.

**Background:** Pompe’s disease (glycogenosis type II, acid maltase deficiency) is an autosomal recessive disorder caused by a deficiency of acid alpha glucosidase (GAA) that degrades lysosomal glycogen. Its severe infantile form, characterized by cardiomyopathy and myopathy, responds to recombinant human alglucosidase alpha (HAA).

**Objective:** To test whether the same enzyme therapy is effective in late-onset Pompe’s disease (LOPD), characterized by progressive proximal myopathy with predilection to early respiratory failure.

**Design:** Randomized, placebo-controlled, multicenter trial in the United States and Europe.

**Participants:** Patients with LOPD, confirmed by GAA deficiency and positive gene mutations, were recruited. Patients in the study could walk >40 m on a 6-minute walk test, had predicted forced vital capacity (FVC) of 30% to 80%, and had muscle weakness in the legs (defined as <80% of predicted on quantitative muscle testing [QMT]). Patients on respirators or noninvasive ventilators while awake and upright were excluded.

**Methods:** Patients were randomized on a 2:1 ratio to receive biweekly infusions of HAA (20 mg/kg) or placebo. The primary outcomes were meters walked on the 6-minute walk test and the percentage of the predicted FVC in the upright position. Secondary outcomes included changes in the predicted QMT scores for the arm and leg, and maximum inspiratory and expiratory pressures. Serum IgG antibodies to alglucosidase alpha were measured throughout the study.

**Results:** 90 patients aged 10 to 70 years were included. Of these, 60 patients received HAA and 30 received placebo, with 81 patients completing the study. There were no baseline differences between both groups except that the placebo group patients were younger (mean, 23.9 vs 30.3 years; \( P = 0.02 \)). By 78 weeks, the HAA-treated group had significant changes in both primary outcomes: The 6-minute walk test increased by 25 m in the treatment group but decreased by 3 m in the placebo group (differential effect of 28 m; \( P = 0.03 \)), and the predicted FVC increased by 1.2% in the treatment group but decreased by 2.2% in the placebo group (differential effect of 3.4%; \( P = 0.006 \)). The change in QMT scores for the arm and leg were not significant (\( P = 0.11 \) and 0.19), while the improvements in maximum inspiratory and expiratory pressures were significant (\( P = 0.04 \) and 0.09). Infusion-associated reactions, including anaphylaxis, occurred in 5% to 8% of the treated patients. Antibodies developed in all treated patients, with no associations between the titer and the primary outcomes or the incidence of adverse effects.

**Conclusions:** Enzyme replacement therapy with recombinant HAA stabilizes pulmonary function and improves walking distance in LOPD.

**Reviewer’s Comments:** This is the second seminal study on HAA (Myozyme) replacement therapy, now convincingly effective and safe in teens and adults. It is a matter of time before the only FDA-approved agent for myopathies becomes a standard treatment for LOPD. (Reviewer-Bashar Katirji, MD).

**Keywords:** Pompe’s Disease, Alglucosidase Alpha

**Print Tag:** Refer to original journal article
Charcot–Marie–Tooth disease 1A is caused by overexpression of peripheral myelin protein 22.

**Background:** Charcot–Marie–Tooth disease 1A (CMT1A) is the most common hereditary neuropathy and is caused by overexpression of peripheral myelin protein 22 (PMP22). Ascorbic acid can inhibit cAMP-dependent PMP22 expression, possibly leading to phenotypic correction. Studies of the transgenic mouse model of CMT1A showed that ascorbic acid improves its neuropathic manifestations.

**Objective:** To test the safety and efficacy of ascorbic acid in adults with CMT1A.

**Design:** Multicenter, double-blind, randomized, placebo-controlled trial from 3 hospitals in France.

**Methods:** All 179 treated patients had CMT1A confirmed by duplication in 17p11.2. Patients were randomized on a 1:1:1 ratio to receive either ascorbic acid (1 g or 3 g per day) or placebo for 1 year. Patients were followed using the CMT neuropathy score (CMTNS), which includes the electrodiagnostic studies as well as the CMT examination score (CMTES) but does not include electrodiagnostic studies. The primary outcome was the CMTNS at 1 year.

**Results:** The median change in CMTNS over 1 year was not significant between the 3 groups: 0.5 points for the placebo group (95% CI; -0.3 to 1.4), 0.7 points (95% CI; 0.0 to 1.4) for the 1-g ascorbic acid group, and -0.4 (95% CI; -1.2 to 0.4) for the 3-g ascorbic acid group. However, there was a significant difference ($P =0.02$) in the CMTES (CMTNS minus electrophysiology) over 1 year between groups: CMTES worsened in the placebo group (0.9 points; 95% CI; 0.1 to 1.7) and the 1-g per day group (0.7 points; 95% CI; 0.1 to 1.3 ) but was unchanged in the 3-g per day group (-0.1; 95% CI; -0.8 to 0.6). The dropout rate was low, and ascorbic acid was well tolerated.

**Conclusions:** Ascorbic acid is safe and well tolerated in CMT1A patients. However, there was no significant difference between ascorbic acid and placebo over 1 year.

**Reviewer's Comments:** This study was underpowered because the authors’ estimation of sample size was based on the overoptimistic assumption of a 5-point difference in CMTNS between groups, while it is now known that the expected worsening in CMTNS over time is 0.7 points per year. Additionally, post-hoc analysis showed that changes in the CMTES are significant for the 3-g ascorbic acid group. A longer treatment period is likely required to detect treatment effects due to the slow progression of neurological disability in patients with CMT1A. (Reviewer-Bashar Katirji, MD).

**Keywords:** Charcot–Marie–Tooth Disease, Ascorbic Acid

**Print Tag:** Refer to original journal article
Levetiracetam Is Safe in Adjunctive Tx in Young Children With Epilepsy

Efficacy and Safety of Levetiracetam as an Add-On Therapy in Children Aged Less Than 4 Years With Refractory Epilepsy.

Li S, Cao J, et al:

J Child Neurol 2010; 25 (May): 609-613

Levetiracetam appears to be effective for multiple seizure types and is well tolerated in children <4 years of age with refractory epilepsy.

**Background:** Levetiracetam is FDA approved for use in children >4 years of age as adjunctive therapy for partial-onset seizures. It has a low side effect profile, is not metabolized by the liver, does not interact significantly with other drugs, and is well tolerated in children. There are limited published data concerning the use of levetiracetam in children <4 years of age.

**Objective:** To evaluate the efficacy and tolerability of levetiracetam as adjunctive therapy in children <4 years of age with refractory epilepsy.

**Methods:** A retrospective chart review was performed at a single center in China to identify children <4 years of age with refractory epilepsy who had been unsuccessfully treated with ≥2 antiepileptic drugs (AEDs) and had at least 2 seizures per month who had then received levetiracetam as add-on therapy. Data recorded included demographic information, seizure type, seizure frequency before and during levetiracetam therapy, and levetiracetam dose, side effects, and discontinuation due to any reason.

**Results:** A group of 24 children <4 years of age with refractory epilepsy who had been treated with levetiracetam as adjunctive therapy were identified. Age at initiation of levetiracetam ranged from 5 to 47 months. Approximately 40% of children had generalized epilepsy, 55% had partial-onset epilepsy, 45% had experienced infantile spasms, 1 patient had Lennox-Gastaut syndrome, and 1 had Dravet syndrome. One-third of patients had >1 seizure type. An average of 4 AEDs had been previously tried on each child. AEDS used were topiramate, valproic acid, clonazepam, prednisone for patients with infantile spasms, lamotrigine, phenobarbital, nitrazepam, carbamazepine, and oxcarbazepine. Levetiracetam was initiated at 10 mg/kg per day divided twice daily and titrated up to 65 mg/kg per day based on response and tolerability. At the time of the last follow-up visit, a ≥50% reduction in seizure frequency had been achieved and maintained in approximately 60% of patients, and 20% were seizure-free. The mean daily dose of levetiracetam in the group with significant improvement was approximately 40 mg/kg. Adverse effects were reported in slightly more than one-third of patients; however, these were typically mild and self-limited, with the most common being irritability (in 25%), followed by fatigue, decreased appetite, and aggression. Only 2 patients discontinued levetiracetam due to adverse effects of decreased speech and diplopia. An increase in seizures resulted in discontinuation in 2 additional patients.

**Conclusions:** Levetiracetam appears to be beneficial for multiple seizure types and is safe as adjunctive therapy for refractory epilepsy in children <4 years of age.

**Reviewer’s Comments:** In clinical practice, levetiracetam is being used with increasing frequency in young children, including neonates. This study supports the efficacy and safety of levetiracetam in young children and infants. (Reviewer-Gregory B. Sharp, MD).

Keywords: Levetiracetam, Refractory Epilepsy, Children

Print Tag: Refer to original journal article
Epilepsy in Children -- Consider Vitamin D Deficiency

Prevalence and Risk Factors for Vitamin D Insufficiency Among Children With Epilepsy.

Shellhaas RA, Barks AK, Joshi SM:

Pediatr Neurol 2010; 42 (June): 422-426

Although bone health in children is determined by more than vitamin D levels alone, the latter is important in bone mineralization. A deficit can be associated with problems such as increased fractures, particularly in patients with epilepsy.

Background: There has been a recent focus on the importance of vitamin D and the common deficiency of vitamin D in the general population. Seizures pose a risk for injury, including fractures, reiterating the importance of vitamin D in the pediatric epilepsy population.

Objective: To identify the incidence of, and risk factors for, vitamin D deficiency in children with epilepsy.

Design: Cross-sectional study.

Participants: 78 children aged 3 to 17 years with epilepsy treated at a single general pediatric neurology clinic over a 7-month period during the fall and winter months were chosen to decrease the variability of sun exposure among patients. More than 80% of children were of European origin, and approximately 60% were girls. Exclusion criteria included children with underlying metabolic bone disease, significant renal impairment, and endocrine disorders.

Methods: All participants were screened on a clinical basis for hypovitaminosis via measurement of vitamin D levels. A multiple logistic regression model was used based on a dichotomous outcome with 25-hydroxyvitamin D (25OHD) levels of <25 or >25 ng/mL. In actuality, the recent literature suggests a normal value of >32 ng/mL; however, few patients had levels this high, so this study did not have sufficient power to analyze the data at this value. Potential risk factors for low vitamin D levels were also examined.

Results: The mean level of 25OHD was 28 ng/mL. The bottom quartile of patients had levels <20 ng/mL, while only the top quartile had levels typically considered normal. All participants had normal serum calcium, magnesium, and phosphorus levels. Analysis revealed significantly increased odds of low 25OHD levels associated with female sex, localization-related epilepsy, and increased body mass index (BMI). The increased risk with localization-related epilepsy in this study was thought to be related to the higher BMI in the group with partial-onset epilepsy. Remaining variables that included seizure frequency, duration of therapy, and type of AED did not contribute to an increased risk of low levels of 25OHD.

Reviewer's Comments: Although the rate of vitamin D deficiency in this study was similar to the rate of the general population, it showed that potential risk factors including specific AED therapy did not contribute significantly to the risk of low vitamin levels. However, the study was limited by the small population size. Regardless, clinicians should remember that although bone health in children is determined by more than vitamin D levels alone, the latter is important in bone mineralization, and a deficit can be associated with problems such as increased fractures, particularly in patients with epilepsy. (Reviewer-Gregory B. Sharp, MD).

Keywords: Vitamin D Deficiency, Epilepsy, Children

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