Simple Cooling Methods Render Improved Outcomes After Cardiac Arrest

Hypothermia for Neuroprotection in Adults After Cardiopulmonary Resuscitation.
Arrich J, Holzer M, et al:
Cochrane Database Syst Rev 2009; October 7 (Issue 4): CD004128

Mild hypothermia induced by simple cooling methods improves neurological outcome and survival after cardiac arrest.

Background: Neurological outcome after cardiac arrest is often poor. Only 10% to 30% of patients who are resuscitated from cardiac arrest survive to live an independent life. However, both animal and clinical studies suggest that induced hypothermia can improve neurological outcome.

Objective: To review the medical literature and assess the efficacy of therapeutic hypothermia after cardiac arrest.

Methods: The medical literature was searched for randomized controlled trials using hypothermia after cardiac arrest in adults up through January 2007. Any cooling method was acceptable if it was applied within 6 hours of cardiac arrest, brought body temperature <35°C, and was maintained for 24 hours. Nearly 500 patients from 4 trials and 1 abstract were included in the systematic review. In 3 comparable studies, conventional cooling methods (eg, cooling blankets, ice packs) were used, and individual patient data (195 cases, 188 controls) were pooled for meta-analysis. Patients were grouped into 5 categories of cerebral performance: category 1, no or very minor neurological deficits; category 2, moderate disability but independent in activities of daily living; category 3, dependent on others; category 4, vegetative; and category 5, dead. The primary outcome measure was neurological recovery reaching category 1 or 2 during hospitalization. The secondary outcome parameter was survival to hospital discharge. Adverse events with hypothermia were assessed.

Results: More hypothermia-treated patients reached a best cerebral performance category 1 or 2 (risk ratio [RR], 1.55; 95% CI, 1.22 to 1.96) and more survived to be discharged from the hospital (RR, 1.35; 95% CI, 1.10 to 1.65) when compared to controls. Adverse events were indistinguishable in the 2 groups. One study using hemofiltration to cool patients could not be used in the meta-analysis. It showed no difference in outcome. Another study that did not report its cooling method showed better survival in the hypothermia group. There were no data on 6-month neurological outcome, quality of life, or survival.

Conclusions: Conventional cooling methods that induce mild hypothermia after cardiac arrest improve survival and neurologic outcome without adverse effects. The analysis supports the best medical practice recommended by the International Resuscitation Guidelines in 2003 and by the American Heart Association.

Reviewer's Comments: The conclusion is certainly "heartening" for patients and for ICU physicians who are likely to expand their use of hypothermia because of this meta-analysis. For neurologists, it means new challenges. The prognostic information gained by the neurological exam and ancillary testing, such as the somatosensory evoked potential, will not necessarily apply to the hypothermic patient, even after rewarming, so prognostication will not be straightforward. The Practice Parameters guidelines issued in 2006 by the American Academy of Neurology regarding prognosis in hypoxic coma will have to be revalidated or revised with new studies that include hypothermia in the treatment paradigm. (Reviewer-Michael Jacewicz, MD).

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Keywords: Cardiac Arrest, Anoxic Coma, Cardiopulmonary Resuscitation, Hypothermia

Print Tag: Refer to original journal article
Infants and children with severe infections and respiratory compromise due to respiratory syncytial virus are at increased risk for seizures and other neurologic complications.

**Background:** Especially in young infants and high-risk children, respiratory syncytial virus (RSV) can be severe, and intensive care hospitalization may be necessary. The focus of care is placed on the respiratory illness, and attention may not be paid to potential neurologic complications that have been reported to include central apnea, seizures, and encephalopathy.

**Objective:** To document potential neurologic complications in children with severe illness due to RSV infection.

**Design/Methods:** A retrospective review was performed to identify clinical and neurologic findings from a case series of 9 children with RSV who were admitted to the pediatric ICU at a single institution; a neurologic consultation was requested for these children. A diagnosis of RSV was confirmed by rapid testing of nasal secretions.

**Results:** 8 patients were infants aged 5 to 16 weeks, and 1 child was aged 3 years. There were 5 boys and 4 girls. There was no significant past medical history or risk factors in 6 patients. One child had hypothyroidism, 1 had a history of prematurity but was healthy, and the 3-year-old had a history of prematurity, bronchopulmonary dysplasia, and static encephalopathy. There was no history of prior seizures in any of these children. Intubation and mechanical ventilation were required for 7 patients, and 2 were placed on ECMO. Indications for neurologic consultation included cardiac arrest that had occurred in 4 children, seizures in 4, and hypertonia in 1. Cerebrospinal fluid examination was performed in 4 patients, with the only abnormality of increased protein concentration in 1. EEGs were performed on 8 patients and revealed an abnormality in 7 that included electrographic seizures in 1, focal spikes in 1, multifocal spikes in 2, focal slowing in 1, focal attenuation in 1, and diffuse attenuation in 1. MRI of the brain was performed on 5 patients and was abnormal in 1 with evidence of acute ischemic injury with restricted diffusion in the posterior globus pallidus bilaterally. Both patients treated with ECMO died during the acute illness. Follow-up information was available on all but 1 patient. The only surviving patient with residual deficits was the one with the abnormal MRI who was hypertonic at follow-up. None of the children who experienced seizures developed recurrent seizures following recovery from the acute illness, and they were not treated with long-term antiepileptic drug therapy.

**Reviewer's Comments:** RSV is a common cause of respiratory illness in children. It can produce severe respiratory compromise in young infants and high-risk children. Care providers should be aware of the potential for neurologic complications and, specifically, seizures in children with severe illness due to RSV. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Respiratory Syncytial Virus Infection, Neurologic Complications, Children

Print Tag: Refer to original journal article
Objective: To determine if particular psychotic symptoms in dementia with Lewy bodies are associated with particular regional abnormalities of cerebral blood flow.
Methods: Diagnosis of dementia with Lewy bodies was based on published consensus clinical criteria. Patients whose dementia developed 12 months or later after onset of Parkinson disease were excluded, as were those with a Mini-Mental State Examination Score of <11 and those who showed moderate-to-severe ischemic changes on brain imaging. Therefore, 100 patients and 21 controls without dementia underwent single photon emission CT. Seventeen psychotic symptoms that appeared in at least 5 different patients were grouped by factor analysis into 4 domains.
Results: Compared to controls, patients with dementia with Lewy bodies had significant hypoperfusion bilaterally in frontal, temporal, parietal, and occipital cortex, thalamus, and lenticular nuclei. Factor 1 symptoms (misidentifications) were associated with significant hypoperfusion in the left hippocampus, insula, frontal operculum, and ventral striatum/accumbens. Factor 3 symptoms (visual hallucinations of person) were associated with significant hypoperfusion in the angular gyri bilaterally, the right supramarginal gyrus, and the left ventral occipital gyrus. Persecutory delusions were associated with significant hyperperfusion in the right rostral medial frontal cortex, bilateral middle frontal gyrus, right inferior frontal gyrus, and left middle frontopolar gyrus. There were no significant cerebral blood flow differences associated with factor 2 or factor 4 symptoms.
Conclusions: Different psychotic symptoms in dementia with Lewy bodies are associated with dysfunction of particular cerebral networks. Hallucinations of person are associated with brain regions involved in face or object recognition and location, and misidentifications are associated with brain regions involved in emotional accompaniments of sensory and mnemonic images. The prefrontal hyperperfusion associated with persecutory delusions is the opposite of what has been reported in Alzheimer disease, in which such delusions are associated with prefrontal hypoperfusion but is consistent with schizophrenia, in which positive symptoms are associated with prefrontal hyperperfusion.
Reviewer’s Comments: The findings of this study, while not surprising, have functional implications beyond the symptomatic variability of dementia with Lewy bodies. (Reviewer-John C. Brust, MD).
Can Infarct Risk Distal to Asymptomatic ICA Stenosis Really Be That Low?

Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment. A Prospective, Population-Based Study.

Marquardt L, Geraghty OC, et al:

Stroke 2010; November 19 (): epub ahead of print

The risk of stroke in patients on intensive medical therapy with asymptomatic internal carotid artery stenosis is lower than the published risks associated with carotid endarterectomy or angioplasty/stenting.

Background/Objective: Recently, some have suggested that the risk of stroke in patients with asymptomatic internal carotid artery (ICA) stenosis is less than the widely quoted 2% to 3% per year. This decrease, if real, is presumed to be secondary to better/more aggressive risk factor management.

Design: Prospective cohort substudy.

Participants: Consecutive patients from the Oxford Vascular Study, a population-based ongoing study of cardiovascular disease in some 91,000 individuals, with asymptomatic (≥50%) stenosis of an ICA, detected following a recent mild stroke (NIHSS ≤5) or transient ischemic attack (TIA) that occurred in another vascular territory.

Interventions: Patients were treated with antithrombotic therapy, nearly always antiplatelet agents, and a statin, unless contraindicated. Antihypertensives were given for blood pressure readings of >130/80. Blood glucose was treated "as appropriate." All patients were also given lifestyle advice, particularly, being urged to stop smoking.

Methods: ICA stenosis was determined and quantified by ultrasound and/or MR angiography. Stenoses in the cervical portion of the ICA were deemed asymptomatic if they were >50% and not responsible for any cerebrovascular symptoms in the ipsilateral brain or eye. Follow-up was a maximum of 5 years. The primary end point was recurrent ischemic stroke or TIA, especially in the territory of the asymptomatic ICA under study. Strokes associated with carotid intervention (carotid endarterectomy or angioplasty/stenting) were included. Diagnosis of stroke and assignment of vascular territory were done by study neurologists.

Results: Of 1153 patients with TIA or mild ischemic stroke who underwent carotid imaging, 101 had asymptomatic stenosis >50% of an ICA. (The majority of these were contralateral to a symptomatic ICA.) At baseline, the cohort had an average age of 75 years, 61% were male, and 68% were hypertensive. Diabetes and previous myocardial infarctions were present in about 15% each, 60% were former and 15% were current smokers, and 12% had atrial fibrillation. About half of the group presented with a stroke, the other half as TIA. Mean follow-up was 3 years. Medical interventions were widely used. Only 6 events occurred distal to an asymptomatic (≥50%) ICA stenosis: 1 was a stroke, and the other 5 were TIAs. Annual risk for ipsilateral ICA territory ischemic infarct was 0.34%. This was actually less than the risk for stroke elsewhere, which was 8%, and also lower for risk of myocardial infarction (5%) and vascular death (8%).

Conclusions: The risk of stroke in patients on intensive medical therapy with asymptomatic ICA stenosis is lower than previously thought and lower than the published risks associated with carotid endarterectomy or angioplasty/stenting. Obviously, larger trials are needed to confirm these encouraging findings.

Reviewer’s Comments: This study was small, but nonetheless encouraging. It would have been interesting to have more information on whether other interventions, such as smoking cessation and glucose control, actually worked. (Reviewer-James W. Schmidley, MD).

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Keywords: Asymptomatic Carotid Stenosis, Ipsilateral Stroke

Print Tag: Refer to original journal article
Use of extended-release niacin results in a significant reduction of carotid intima–media thickness when added to statin therapy.

**Background:** Statins (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors) reduce LDL cholesterol levels and result in clinically significant reductions of major cardiovascular events. There is enthusiasm for using a second agent to further lower LDL or raise HDL cholesterol for additional protection.

**Objective:** To compare the effect of extended-release niacin versus ezetimibe, added to statin, on atherosclerosis and atherosclerotic events.

**Design:** Prospective, randomized, parallel-group open-label study with blinded end point evaluation.

**Participants:** 363 subjects were enrolled. There were about equal numbers of men and women. Subjects were aged ≥30 years and had known atherosclerotic coronary/vascular disease or a coronary heart disease risk equivalent. All subjects had been treated with statin monotherapy at a consistent dose, with LDL cholesterol <100 mg% and HDL cholesterol <50 mg% (men) and <55 mg% (women).

**Methods:** Subjects were randomized to receive extended-release niacin (target dose, 2000 mg/day) or ezetimibe (10 mg/day) in addition to their statin. There were no significant differences between the 2 groups with respect to baseline demographic data, comorbid vascular risk factors, or medications. The primary end point for the study was the between-group difference in the change of (and mean) carotid intima–media thickness after 14 months, a surrogate marker for atherosclerosis. Secondary end points included changes in lipid values, major adverse cardiovascular events, and discontinuation of the study drug due to adverse effects.

**Results:** This study was terminated early after 208 subjects had completed a 14-month study period, due to the superiority of niacin over ezetimibe. The mean HDL cholesterol in the niacin group increased by 18.4% and LDL cholesterol in the ezetimibe group decreased by 19.2%; both of these findings were statistically significant. Niacin therapy significantly reduced LDL cholesterol and triglyceride levels. Ezetimibe reduced HDL cholesterol and triglyceride levels. Compared with ezetimibe, niacin had significantly greater efficacy regarding the change in carotid intima–media thickness over 14 months, resulting in a significant reduction of both mean and maximal carotid intima–media thickness. A paradoxical significant increase in mean carotid intima–media thickness was noted with greater reductions in LDL cholesterol levels with ezetimibe treatment. The incidence of major cardiovascular events was significantly lower in the niacin group than in the ezetimibe group.

**Conclusions:** The use of extended-release niacin results in a significant reduction of carotid intima–media thickness when added to statin therapy, and niacin is superior to ezetimibe. The authors opine that prudent clinical practice currently favors the avoidance of ezetimibe.

**Reviewer's Comments:** Two informative editorials accompany this article. Both of the editorialists agree that the addition of niacin to statin therapy appears to be beneficial, and both are critical of early termination of this study. The editorialists state that the investigators' condemnation of ezetimibe is probably premature and excessively harsh. The conclusion that the addition of extended-release niacin to statin therapy may help reverse atherosclerosis and its complications appears to be well founded. (Reviewer-W. Steven Metzer, MD).

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Keywords: Atherosclerosis, Carotic Artery Disease, Hyperlipidemia, Niacin, Ezetimibe

Print Tag: Refer to original journal article
Distinguishing Somatoparaphrenia From Simple Asomatognosia

The Neuroanatomy of Asomatognosia and Somatoparaphrenia.
Feinberg TE, Venneri A, et al:
J Neurol Neurosurg Psychiatry 2009; September 24 (): epub ahead of print

Right orbitofrontal damage is key to the development of somatoparaphrenia.

Background: Asomatognosia means lack of recognition of the body. In its most frequent form, a patient denies ownership of the left arm in the setting of a right hemispheric lesion associated with left hemiplegia, left hemisensory deficit, and hemineglect. Somatoparaphrenia involves misidentification of the arm and delusions that it belongs to someone else. Studies have linked these syndromes to various anatomical areas of the brain.

Objective: To determine the neuroanatomic substrate of these syndromes.

Methods: Patients with right hemispheric strokes and left hemiplegia were separated into 3 groups: G1, asomatognosia + neglect; G2, non-asomatognosia + neglect; and G3, hemiplegia only. All patients underwent evaluation for hemispatial neglect via the line cancellation task and brain imaging within 1 week of acute hospitalization. To determine the presence of asomatognosia, the examiner approaches the patient from the right, raises the patient's right arm, and asks "What is this?" If the patient correctly identified the right arm, the examiner then brings the left arm into the right hemispace and repeats the question. Based on the response, patients are identified as asomatognosic or non-asomatognosic. Any patient responses of extended beliefs, delusions, or confabulations were recorded. The asomatognosia group was further subdivided into those with somatoparaphrenia (G1-SP) or without somatoparaphrenia (G1-SA). Lesions on CT scans were fitted into a standard template space and were identified using Brodmann's areas.

Results: Of 13 G1 cases, 7 were G1-SP. There were 7 cases of G2 and 6 cases of G3. Patients with asomatognosia had larger lesions than those without. G1 subjects had more lesion involvement of the medial frontal lobe but not the lateral or orbitofrontal lobe. For the asomatognosia groups, G1-SP showed more lesion involvement than G2 in the frontal and temporal lobes, but not the parietal lobes. G1-SP had more involvement in all lobes than G3. G1-SP showed more involvement than G1-SA in the medial, lateral, and orbital frontal lobe. Both G1-SP and G1-SA had more involvement in the medial frontal areas than G2 and G3. There was greater orbitofrontal damage in G1-SP compared to G1-SA. Lateral frontal involvement, alone or in combination with parietal damage, did not distinguish asomatognosic from non-asomatognosic patients.

Conclusions: Asomatognosia occurs most commonly in the setting of temporoparietal damage, hemispatial neglect, and medial frontal damage. The combination of right temporoparietal, mediofrontal, and orbitofrontal dysfunction may distinguish somatoparaphrenia from simple asomatognosia.

Reviewer's Comments: It is interesting that while right parietal damage is necessary for both of these syndromes, other areas are also key: the right frontomedial area for asomatognosia and the right orbitofrontal area for somatoparaphrenia. The numbers in this study are small, and further studies are needed to confirm these results. (Reviewer-John Schwankhaus, MD).

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Keywords: Asomatognosia, Somatoparaphrenia, Frontal Lobes, Confabulation

Print Tag: Refer to original journal article
Background: Restless legs syndrome (RLS) is believed to have a prevalence of approximately 10% in the general Caucasian population. The prevalence of RLS in Parkinson's disease (PD) has been somewhat controversial, although it has reportedly increased compared to the general population.

Objective: (1) To investigate the lifetime prevalence of RLS in PD using essential diagnostic criteria, and (2) to explore potential RLS associations with PD clinical features, especially motor fluctuations.

Design: Cross-sectional outpatient observational study.

Participants: Subjects included 113 consecutive outpatients of a movement disorders clinic with a diagnosis of PD (male-to-female ratio, 82:31; mean age, 67.4 ± 9.2 years; mean disease duration, 9.4 ± 5.6 years; mean UPDRS motor score, 28.9 ± 12.1; and mean Hoehn and Yahr stage, 2.7 ± 0.9). Motor fluctuations were present in 66% of patients, most commonly "wearing off" (58%). Dyskinesia was present in 42% of patients, and off-dystonia was present in 41%. More than half of subjects fulfilled DSM-IV criteria for major or minor depressive disorder or dysthymia, and 43% had chronic pain.

Methods: Subjects completed a structured questionnaire addressing the 4 essential diagnostic criteria for RLS.

Results: 28 of the 113 subjects (25%) met diagnostic criteria for RLS. Mean age at onset of RLS symptoms was 58.2 ± 10.4 years, with mean age of onset of PD of 54.1 ± 9.5 years. RLS symptoms began after the onset of PD in the majority of cases (82%) with a mean interval of 4.5 ± 3.7 years. PD subjects with RLS were significantly younger, had a significantly earlier onset of PD, and received significantly lower levodopa (L-dopa)-equivalent dosages than subjects who did not fulfill RLS criteria. Seventeen of 28 subjects with PD and RLS (61%) reported that the urge to move the legs and unpleasant sensations were associated with wearing off.

Conclusions: There is a consistently reported higher prevalence of RLS symptoms in patients with PD compared to that in the general population, but the explanation for this remains uncertain. This study suggests that RLS symptoms are part of the sensorimotor spectrum of wearing-off in L-dopa-treated PD, and the potential of L-dopa to induce RLS needs further investigation.

Reviewer's Comments: This is a useful study, but it would have been better had it been controlled. It provides further evidence of a possible association between PD and RLS, and indicates that it may tend to be associated with wearing off in patients with PD. Clinicians should be cognizant of this in treating PD patients. The common denominator relating these 2 disorders could be iron metabolism in the CNS. It would have been useful had these investigators compared serum ferritin levels for PD subjects with and without RLS. (Reviewer-W. Steven Metzer, MD).

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Keywords: Restless Legs Syndrome, Parkinson's Disease, Motor Fluctuations

Print Tag: Refer to original journal article
Can AEDs Be Discontinued in Patients With JME?

Juvenile Myoclonic Epilepsy 25 Years After Seizure Onset: A Population-Based Study.

Camfield CS, Camfield PR:

Neurology 2009; 73 (September 29): 1041-1045

Resolution of seizures and discontinuation of antiepileptic drug therapy may be eventually possible in some patients with juvenile myoclonic epilepsy.

**Background:** Juvenile myoclonic epilepsy (JME) is a common form of idiopathic generalized epilepsy. Seizure onset is usually during late childhood or adolescence. All patients have myoclonus, most experience generalized tonic-clonic (GTC) seizures, and about one third have absence seizures. It has typically been believed that most, if not all, patients with JME will have lifelong epilepsy, and discontinuation of antiepileptic drug (AED) therapy should not be recommended.

**Objective:** To assess the long-term evolution of seizure occurrence and control in a population-based cohort.

**Participants/Methods:** All patients who developed epilepsy with a diagnosis of JME in Nova Scotia between 1977 and 1985 were subsequently contacted between 2006 and 2008, providing 25 years of follow-up after seizure onset. A diagnosis of JME was based on the following: (1) occurrence of myoclonic seizures and at least one GTC seizure, with onset during late childhood or adolescence and before age 16 years; or (2) in children who have otherwise been normal with EEG findings of generalized spike wave of ≥3 Hz frequency or polyspike. Follow-up 25 years later was performed via review of medical records and telephone or face-to-face interviews.

**Results:** 24 patients were identified who developed JME approximately 25 years previously. This accounted for 3.5% of all cases of childhood-onset epilepsy in Nova Scotia during that time period. There were 17 females and 7 males who experienced a first seizure at a mean age of slightly >10 years. All patients had a history of myoclonic and GTC seizures, and 60% had a history suggestive of at least some absence seizures. Contact was made with 23 patients at a mean age of 36 years. All patients had initially been treated with AEDs. At the time of follow-up, AED therapy had been discontinued in almost one half of patients (11 of 23). Six patients had been seizure-free off AEDs for periods ranging from 5 to 23 years. Three patients still had myoclonic seizures, and 2 still had rare convulsive seizures but were off AED therapy. Episodes of convulsive status epilepticus had occurred in approximately one third of subjects, and 3 patients had medically refractory epilepsy. Quality of life was reported as good by 70% who said they were satisfied with their health, work, friendships, and social life. Approximately 90% of subjects had graduated from high school, but about one third were unemployed. About 40% of patients were on antidepressant medications. There appeared to be relatively high rates of social isolation and social impulsiveness.

**Reviewer's Comments:** The relatively novel finding of this study is that JME may not result in lifelong epilepsy in some patients. Approximately one third of patients in this long-term study either had complete resolution of seizures or only myoclonus, and AED therapy had been discontinued. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Juvenile Myoclonic Epilepsy, Antiepileptic Drugs, Follow-Up

Print Tag: Refer to original journal article
Preventing Stroke--ARB, ACEI, or CCB?

A Systematic Review of Angiotensin Receptor Blockers in Preventing Stroke.


Stroke 2009; 40 (December): 3876-3878

Angiotensin receptor blockers have no specific protective effect, compared with angiotensin-converting enzyme inhibitors or calcium channel blockers, in the prevention of stroke.

**Background:** Theoretically, angiotensin receptor blockers (ARBs) might protect against stroke beyond their blood pressure-lowering effects. This might be possible because, while they competitively inhibit the binding of angiotensin II (AT) to AT type 1 (AT1) receptors, they allow unopposed stimulation of AT type 2 (AT2) receptors. Blockade of AT1 receptors leads to an increase in angiotensin II levels, and AT2 receptors, which are not blocked by ARBs, are increasingly stimulated. Stimulation of AT2 receptors is hypothesized to be vasoprotective and to attenuate thrombosis, inflammation, and endothelial dysfunction.

**Objective:** To assess the effect of ARBs on primary and secondary prevention of all types of stroke.

**Design:** Meta-analysis of randomized, controlled trials involving patients at high cardiovascular risk who were treated with ARBs.

**Methods:** Stroke was identified as an end point. Separate overviews were done of ARBs versus placebo (n=11), ARBs versus angiotensin-converting enzyme inhibitors (ACEIs; n=6), and ARBs versus calcium channel blockers (CCBs; n=4). Patients entered into these trials had various combinations of congestive heart failure, diabetes with nephropathy, stroke, peripheral vascular disease, hypertension, and/or myocardial infarction.

**Results:** 20 randomized, controlled trials were identified, involving >108,000 patients. For studies of ARB versus ACEI and ARB versus placebo, funnel plots revealed no publication bias. ARBs decreased the risk of stroke compared with placebo. Interestingly, the trial in which ARBs resulted in no change in blood pressure had a greater effect in stroke prevention than the 2 trials in which ARBs actually lowered blood pressure compared to placebo. In trials of ARB versus ACEI, there was no difference in stroke outcomes. There was a trend favoring trials in which ARBs produced a greater decrease in blood pressure than did ACEIs. There was also no difference in trials of ARBs versus CCBs, although there was a trend for a benefit in stroke prevention in the 2 trials in which CCBs lowered blood pressure more than ARBs. In subgroup analyses, baseline disease had no effect on outcomes produced by ARBs.

**Conclusions:** ARBs have no specific protective effect, compared with ACEIs or CCBs, in the prevention of stroke. Not surprisingly, they are superior to placebo for stroke prevention. There was a suggestion that a lower blood pressure, regardless of the drug used to achieve it, was beneficial. This trend was seen in trials of ARBs versus ACEIs in which the ARBs produced lower blood pressure, and in trials of CCBs versus ARBs in which the CCBs produced a lower blood pressure. The authors suggested further trials of ARBs in normotensive patients at risk for stroke and other cardiovascular events.

**Reviewer's Comments:** As is usually the case with meta-analyses, no attempt was made to distinguish between intracranial hemorrhage and ischemia. This is the largest meta-analysis yet published concerning this issue. (Reviewer-James W. Schmidley, MD).

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Keywords: Angiotensin Receptor Blockers, Stroke Prevention, Angiotensin Converting Enzyme Inhibitors, Calcium Channel Blockers

Print Tag: Refer to original journal article
Frontotemporal dementias can be caused by a variety of biochemical abnormalities.

**Background:** Frontotemporal dementia (FTD) is a clinical syndrome that affects behavior, personality, and language with relative preservation of memory. The neuropathology is varied, with about half of cases showing hyperphosphorylated tau in neurons and glia (FTD-tau). Other FTD cases are ubiquitin positive and contain neuronal inclusions with the transactive response (TAR) DNA-binding protein (TDP-43), also seen in some cases of amyotrophic lateral sclerosis (ALS). This variety does not, however, explain all the cases of FTD with ubiquitin inclusions (FTD-U) and ALS. Recent studies have identified mutations in the fused in sarcoma (FUS) protein as a cause of familial ALS.

**Objective:** To determine whether FUS is the pathological protein in some cases of tau/TDP-43 negative FTD.

**Methods:** 15 cases of tau/TDP-43 negative, FTD-U were evaluated for FUS pathology. These cases were also negative for neuronal intermediate filaments and α-synuclein. A polyclonal antibody to FUS was used for immunohistochemical studies. Immunoblot analysis of protein extracted from post-mortem FTD-U as well as genetic analysis was performed.

**Results:** The 15 subjects fulfilled criteria for FTD with mean age of onset at 38 years. Symptoms were mainly progressive personality and behavioral changes with later frontal language impairments and relative sparing of memory. In all 15 cases, FUS immunochemistry labeled all the neuronal inclusions and also identified previously unrecognized glial pathology. The amount of FUS pathology was greatest in the hippocampal dentate fascia and moderate in the frontal and temporal neocortex and striatum. Normal and neurological controls, with only one exception, did not show any FUS pathology. Specifically, senile plaques, neurofibrillary tangles, Lewy bodies, Pick bodies, ballooned neurons, neuronal inclusions in ALS or FTD-TDP-43 pathology, or glial inclusions in tauopathies or multiple system atrophy did not stain. Immunoblot analysis of extracted protein showed increased levels of insoluble FUS. None of the cases had mutations of the FUS gene.

**Conclusions:** The findings strongly suggest that the FUS protein is the pathological protein in a subset of FTD patients. This provides a further biochemical link of FTDs to ALS.

**Reviewer’s Comments:** There are now 3 distinct pathological processes that can cause frontotemporal dementia. Unfortunately, any of these can cause any of the clinical subtypes. A specific clinical syndrome does not identify the underlying pathology. (Reviewer-John Schwankhaus, MD).

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Keywords: Frontotemporal Lobar Dementia, Frontotemporal Dementia Fused in Sarcoma

Print Tag: Refer to original journal article
Cigarette smoking has an adverse effect on the progression of multiple sclerosis and hastens conversion from a relapsing-remitting course to a progressive course.

**Background:** 2 past studies tried to determine whether smoking cigarettes worsens the course of multiple sclerosis (MS) but reached opposite conclusions (*Brain* 2005; 128:1461-1465; *Neurology* 2007; 69:1515-1520).

**Objective:** To study the same question in a larger cohort of patients.

**Design:** This was an observational study. In a cross-sectional survey at baseline and in a second survey after prospective follow-up of 0 to 8 years (mean, 3 years; standard deviation, 2 years), the authors examined whether the smoking history at baseline was related to the severity of MS.

**Participants:** 1465 patients with MS, including 1020 with a relapsing-remitting (RRMS) course at baseline, 212 with a secondary progressive (SPMS) course at baseline, and 63 with a primary progressive course at baseline. At baseline, 257 patients were smokers, 428 were ex-smokers, and 780 had never smoked (never-smokers). The clinical severity of MS was assessed by the Expanded Disability Status Scale (EDSS), and the MRI severity, by volume of T2-weighted hyperintense lesions and brain parenchymal fraction (BPF), a measure of brain atrophy.

**Methods:** Smokers were divided into light smokers (<3 pack-years), medium smokers (3 to 20 pack-years), and heavy smokers (>20 pack-years). The statistical analyses were adjusted for appropriate potential confounders, including baseline age, sex, disease duration, and MS course and treatment.

**Results:** At baseline, the EDSS was significantly worse in smokers than never-smokers (adjusted \( P < 0.001 \)). Furthermore, there was a dose-response relationship, in that the EDSS was worse in heavy smokers than moderate and light smokers. The EDSS of ex-smokers was no worse than that of never-smokers; therefore, the adverse effects of smoking may be reversible. Current smokers had significantly more brain atrophy than never-smokers (adjusted \( P = 0.004 \)) and ex-smokers. In the longitudinal analysis, conversion from RRMS to SPMS occurred significantly faster in smokers than ex-smokers and never-smokers (Hazard Ratio for smokers vs never-smokers, 2.5; 95% confidence interval, 1.4 to 4.4), and T2-weighted lesion volume and brain atrophy increased significantly more (\( P = 0.02 \)).

**Conclusions:** Cigarette smoking has an adverse effect on the progression of MS and hastens conversion of RRMS to SPMS. The adverse effects of smoking may be at least partly reversed by cessation.

**Reviewer’s Comments:** The results of this study prompt us to encourage our patients with MS not to smoke cigarettes or to quit smoking. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Cigarette Smoking, Secondary Progressive

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Facial Diplegia With Distal Limb Paresthesias May Tell the Tale of GBS

A Guillain-Barré Syndrome Variant With Prominent Facial Diplegia.

Susuki K, Koga M, et al:

J Neurol 2009; 256 (November): 1899-1905

A Guillain-Barré syndrome variant, characterized by facial diplegia only, is often associated with distal limb paresthesias, abnormal limb nerve conduction studies, and positive serology for a recent cytomegalovirus infection.

**Background:** Guillain-Barré syndrome (GBS) is associated with facial diplegia in up to 60% of cases. Also, GBS may be "descending" or strictly regional, as in the pharyngeal-cervical-brachial form. Isolated facial diplegia as manifestation of GBS has rarely been described.

**Objective:** To examine patients with isolated facial diplegia without limb weakness or ataxia who underwent serological evaluations in a tertiary referral laboratory in Japan.

**Design:** Retrospective analysis.

**Participants/Methods:** 22 patients with subacute facial diplegia without limb weakness or ataxia were included in this study. Patients with distal limb paresthesias or depressed/absent muscle stretch reflexes were included, while those with significant cerebrospinal fluid pleocytosis (>10 cells) were excluded in an effort not to include patients with infections such as neuroborreliosis. Sera for cytomegalovirus (CMV), Epstein-Barr virus, *Mycoplasma pneumonia*, and *Campylobacter jejuni* were analyzed and compared to 50 patients with typical GBS, 20 patients with Bell's palsy, and 30 healthy controls.

**Results:** A preceding infectious illness occurred in 18 of 22 patients (82%) and the majority (59%) had an upper respiratory infection. CMV infection, diagnosed based on elevated CMV IgM titers, accounted for 35% of these infections in patients with facial diplegia compared with 4% of patients with typical GBS (*P* =0.002), and none of the patients with Bell's palsy (*P* =0.008) or healthy controls (*P* =0.001). The frequency of other infections was not statistically different among these groups. Distal limb numbness was present in 20 patients (91%) and preceded the facial weakness by 3 to 10 days in the majority of patients (86%). Anti-GM2 IgM antibodies were detected in 5 patients only. Abnormal limb motor and sensory nerve conduction studies occurred in 14 of 22 (64%) and 6 of 22 patients (27%), respectively. Favorable outcome occurred in 12 patients, while 10 had residual severe facial weakness 10 months later.

**Conclusions:** A GBS variant, characterized by facial diplegia only, is often associated with distal limb paresthesias, abnormal limb nerve conduction studies, and positive serology for a recent CMV infection.

**Reviewer's Comments:** Facial diplegia, an ominous sign, is often a diagnostic challenge due to its wide variety of causes. The authors ascribed their selected cases to GBS because of a high incidence of associated limb paresthesias, cerebrospinal albuminocytologic association, CMV-positive serology, and demyelinating changes on nerve conduction studies of limbs. It remains difficult to attribute facial diplegia to GBS when none of these other associated findings are present. (Reviewer-Bashar Katirji, MD).

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**Keywords:** Guillain-Barré Syndrome, Facial Nerve Palsy

**Print Tag:** Refer to original journal article
Repeater (identical) F-waves are common and useful in patients with suspected L5 or S1 radiculopathies.

**Background:** F-waves are the results of discharges of a low percentage of anterior horn cells (<5%) in responses to motor axon antidromic stimulations. F-waves have variable amplitudes and latencies and rarely recur. Repeater (or identical) F-waves have the same latency, amplitude, and morphology.

**Objective:** To assess F-wave parameters in patients with unilateral lumbosacral radiculopathy (ULSR) with emphasis on the utility of repeater waves.

**Participants/Methods:** 22 patients (13 men and 9 women) with L5 or S1 ULSR were studied and compared to 13 healthy controls. ULSR was confirmed by fibrillation potentials and neurogenic changes in motor unit action potentials in 2 muscles innervated by the affected root and by different peripheral nerves with normal sural and superficial peroneal sensory responses. The peroneal and tibial nerves were stimulated 30 times each at the ankles bilaterally. Side-to-side comparison and comparison with the healthy controls was made. The authors excluded patients with bilateral radiculopathies and patients with polyneuropathy, motor neuron disease, plexopathy, and peroneal or tibial mononeuropathy.

**Results:** The percentage of peroneal repeater F-waves was 69% ± 18% of symptomatic limbs while it was present in 24% ± 20% of asymptomatic limbs ($P < 0.001$) and 18% ± 15% of healthy controls. Similarly, tibial repeater F-waves occurred in 52% ± 31% of symptomatic limbs, while it was present in 7% ± 10% of asymptomatic limbs ($P < 0.05$) and 4% ± 6% of healthy controls. The pooled relative value of peroneal and tibial repeater F-waves was also higher on the symptomatic side (4.19 with respect to 1.00; $P < 0.001$). The minimum and mean F-wave latencies were also higher on the symptomatic side but less significant (1.05 and 1.04 with respect to 1.00; $P < 0.01$).

**Conclusions:** An increase in the number of repeater F-waves is a useful finding in unilateral L5 and S1 radiculopathies.

**Reviewer's Comments:** Enthusiasm about the utility of F-waves in the diagnosis of radiculopathy has waxed and waned over the last 3 decades. This is, in part, due to the long list of parameters that could be analyzed including F-wave minimal, mean, or median latencies; persistence, chronodispersion; conduction velocity; and absolute and relative F-wave amplitude. This study emphasizes the role of repeater F-waves in the diagnosis of lumbosacral radiculopathy. Several points make this finding somewhat impractical. First, both lower limbs need to be studied in all patients with ULSR. Second, the authors stimulated the peroneal and tibial nerves each 30 times looking for repeater F-waves. To prevent excessive discomfort, most EMG laboratories apply 8 to 10 stimulations only. (Reviewer-Bashar Katirji, MD).

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Keywords: Lumbosacral Radiculopathy, Repeater Waves, F-Wave Parameters

Print Tag: Refer to original journal article
On fMRI, stimulants appear to cause changes in brain regions that are involved in decreasing mind-wandering, better matching attention-deficit/hyperactivity disorder patients to healthy children.

**Background:** Functional imaging studies have demonstrated with fair consistency that the striatum, the anterior cingulate cortex, the prefrontal cortex, and the inferior frontal gyrus have decreased activation in children with attention-deficit/hyperactivity disorder (ADHD) compared with healthy controls, during tasks that require attention and inhibitory control.

**Objective:** To determine whether stimulants in children/adolescents with stimulant-responsive ADHD result in activation of the above brain regions that more closely approximates the activation of healthy controls during a task that requires selective attention and inhibitory control.

**Participants:** 16 children, aged 7 to 18 years, who were documented robust responders to ADHD medications, and 20 healthy comparison subjects were studied. All participants in the ADHD group met criteria for ADHD combined type.

**Methods:** ADHD subjects were scanned twice with functional MRI: once while medicated with stimulants (methylphenidate or dextroamphetamine) and once unmedicated. Healthy comparator subjects were scanned once. Scanning was conducted while all participants were administered the Stroop Color and Word Test, which tests for inhibitory control (eg, correctly pressing a button whenever one sees the word blue, in whichever color ink, and not pressing it when another color’s name, such as red appears in blue ink).

**Results:** Participants in the ADHD and comparison groups both activated prefrontal, anterior cingulate, and parietal cortices; basal ganglia; and the thalamus. Comparing brain activation in unmedicated children with ADHD and comparison subjects revealed significantly less prominent deactivation in the ADHD group than in the comparison group in the ventral anterior cingulate gyrus. These abnormalities were not detected in the ADHD group when they were on stimulants.

**Conclusions:** In children with ADHD, stimulants appear to normalize activation in brain regions, particularly the ventral anterior cingulate cortex, associated with suppression of mind-wandering in tasks requiring sustained attention.

**Reviewer’s Comments:** The ventral anterior cingulate cortex interconnects the orbitofrontal cortex, temporal pole, amygdala, ventral striatum, and hypothalamus. It is an anatomic crossroads that contributes to motivational processes for goal-directed behaviors. It is encouraging to see that stimulants appear to normalize aspects of these pathways, particularly the lateral prefrontal cortex. It would be interesting to test whether nonstimulant ADHD medications, such as atomoxetine, have similar fMRI activity profiles. (Reviewer-John G. Koutras, MD).

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Keywords: Attention-Deficit/Hyperactivity Disorder, Stimulants

Print Tag: Refer to original journal article
Effects of Conservative Tx on Vestibular Schwannomas


Godefroy WP, Kaptein AA, et al:

Otol Neurotol 2009; 30 (September 2): 968-974

Almost 50% of patients managed conservatively experience a decrease in hearing during a 4-year follow-up period after a diagnosis of vestibular schwannoma.

Background: Decades ago, removal of a vestibular schwannoma (VS) could be a life-saving surgery that was also associated with considerable morbidity and even perioperative mortality. In the modern era of MRI, VSs are discovered earlier and at a smaller size than in the past. Often, these smaller tumors will not have significant growth, so they can be simply observed with periodic MRIs. Even when large, these tumors are now almost never fatal.

Objective: To determine quality of life (QOL) following long-term conservative management of a VS.

Design: Prospective study.

Participants: 70 patients, who were found to have a VS and were candidates for conservative management, were included. Patients were excluded for neurofibromatosis type 2, prior surgical or radiation therapy, or if they had only a single MRI as were those who were low to follow-up. Patients were diagnosed in 2002 and 2003 and followed until 2008. Average tumor was 10 mm. Patients were considered for active treatment if they had significant tumor growth, hearing deterioration, or if it was the patient’s preference. Patients who had treatment received either stereotactic radiation or surgery.

Methods: Patients underwent gadolinium-enhanced MRI that was generally conducted yearly for the first 4 years after diagnosis. Audiometry was also periodically performed. QOL was measured using the Short Form 36 Health Survey (SF-36) at the time of diagnosis and at the end of the study period.

Interventions: SF-36, MRI, and surgery or radiation if warranted.

Results: Unilateral hearing loss was almost a universal presenting symptom. In 63% of patients, no tumor growth was observed during the follow-up period. Tumors that grew did so at an average rate of 1.5 mm/year. A total of 39% of patients failed conservative management. Two patients died during follow-up of causes unrelated to their VS. Of patients who remained in the conservative treatment group, 49% had worsening of hearing. SF-36 scores did not significantly differ from those at diagnosis at the end of the follow-up period.

Conclusions: Conservative management of VS does not affect SF-36 scores.

Reviewer’s Comments: The authors concluded that QOL does not deteriorate during conservative management of VS, even though 50% of these patients had deterioration in hearing during the follow-up period. The study is limited because QOL was not reported in those who had surgery. Also, SF-36 is a very general instrument that has no questions that are directly related to communication. Other studies that have used the SF-36 to gauge the effect of hearing loss (such as in hearing aid patients) have also failed to show an effect. Thus, it is likely that the SF-36 is not the best QOL measure in this population. (Reviewer-Benjamin T. Crane, MD).

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Keywords: Acoustic Neuroma, Quality of Life, Hearing Loss, Vestibular Schwannoma

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Most Children Are Seizure-Free After First AED

Effectiveness of the First Antiepileptic Drug in the Treatment of Pediatric Epilepsy.
Ma M-S, Ding Y-X, et al:
Pediatr Neurol 2009; 41 (July): 22-26

In this retrospective study of the effectiveness of the first antiepileptic drug for seizure disorders, tolerability was nearly as important as efficacy in the overall effectiveness of a single medication.

**Background:** Studies of the effectiveness of the initial antiepileptic drug (AED) are limited in children.

**Objective:** To investigate the interaction among efficacy, tolerability, and overall effectiveness of the first AED in children with newly diagnosed seizures.

**Design:** Retrospective review of records of patients seen at Beijing Children's Hospital from 2000 to 2004 with follow-up until 2007.

**Participants:** 520 children with seizure disorders who had not previously been on therapy and who followed a treatment regimen for at least 1 year were included.

**Methods:** Classification of seizure types was performed using criteria of the International League Against Epilepsy and involved primarily 3 types: idiopathic, cryptogenic, and remotely symptomatic. Choice of AED was at the discretion of the treating neurologist. Patients were monitored at an epilepsy clinic every 4 to 6 weeks during the first 6 months and 3 to 4 months thereafter. Dosing of medication was adjusted based on response. Response to the first medication was classified as (1) seizure free, (2) lack of efficacy, (3) lack of tolerability, or (4) change in treatment for reasons unrelated to efficacy or tolerability.

**Results:** 95% of prescribed medications were sodium valproate, topiramate, or carbamazepine. Of 520 children, 344 (66%) became seizure-free with the first AED, ranging from 60% with symptomatic epilepsy to 74% with idiopathic epilepsy. In patients who tolerated the medication, inadequate seizure control occurred with each medication at a rate of approximately 17%. Of those taking carbamazepine, 17% discontinued the medication, usually due to rash; 12% stopped topiramate, usually due to hyperthermia.

**Conclusions:** Nearly two thirds of patients who are placed on a first medication for a seizure disorder will become seizure-free with that therapy alone. Slightly fewer than 1 in 5 will not respond to the medication. Depending on the treatment, 4% to 17% will have to discontinue the medication due to adverse events.

**Reviewer's Comments:** The retrospective nature of the study and the broad range of seizure disorders covered are both limiting factors. The selection of medication solely by the clinician could involve bias. However, the data indicate a generally good prognosis after treatment and demonstrate the importance of tolerability. The latter would be part of the rubric of compliance. If a patient does not take a medication, it cannot be effective. (Reviewer-Mark F. Ditmar, MD).

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Keywords: Pediatric Epilepsy, Antiepileptic Drug

Print Tag: Refer to original journal article
How Common Are Seizures After Regional Block in Patients With Seizure History?

Regional Blockade in Patients With a History of a Seizure Disorder.

Kopp SL, Wynd KP, et al:
Anesth Analg 2009; 109 (July): 272-278

Perioperative seizures after a regional block are not associated with a pre-existing history of seizures in the majority of cases.

**Background:** Low blood levels of local anesthetics (LAs) decrease brain electrical activity and are potent anticonvulsants, whereas high levels of LAs may lower the seizure threshold. It is not known if patients with a seizure disorder are at higher risk of central nervous system (CNS) toxicity from LAs.

**Objective:** To determine the frequency of seizure activity following a regional block in patients with a history of seizure disorder.

**Design:** Retrospective cohort study.

**Methods:** Medical records of 335 patients who underwent epidural, caudal, or peripheral nerve block and who had a known seizure disorder were reviewed during a 14-year period (1988 to 2001). Data collection included patient demographics, seizure disorder history, details of the regional block, type of procedure, adjuvant drugs, and presence of any CNS activity. The main end point was any seizure activity documented during hospitalization.

**Results:** 411 regional procedures were performed in 335 patients with a seizure disorder. Twenty-four patients had at least 1 episode of seizure activity in the perioperative period. Of these patients, 16 had a single injection of local anesthetic, and 8 had a continuous infusion of an LA. No patient experienced seizures during or immediately after administration of an LA initial bolus (<50 minutes). Patients with recent preoperative seizures were more likely to experience a seizure during the perioperative period. In 19 of 24 patients, no causal association between the regional block and the seizure activity was found because of the extended time interval between the seizure and the block. However, in 5 patients, the LA may have contributed to the seizure activity because it occurred during LA infusion. Based on these data, the overall incidence of seizures was 5.8%, of which 1.2% (95% CI, 0.4% to 2.8%) may have been attributed to LA CNS toxicity.

**Conclusions:** The etiology of perioperative seizures in patients with a pre-existing seizure disorder is multifactorial and includes stress, fatigue, sleep deprivation, antiepileptic medication drug level fluctuation, perioperative medications, and altered drug absorption. LA toxicity may contribute to perioperative seizures in a small percentage of patients. The authors recommend being prepared to treat seizure activity in patients with a recent seizure, regardless of the anesthetic and analgesic technique.

**Reviewer's Comments:** The incidence of seizures after regional anesthesia is quite sparse. It is reported to be between 0.01% after an epidural block and up to 0.8% following a supraclavicular brachial plexus block. These rates are much lower than those reported in this study. It would have been valuable if the authors compared the incidence of seizures in general and regional anesthesia in patients with pre-existing seizure disorder. Since there is no comparison group, the authors should not make inferences about the association between regional block and perioperative seizure activity in this patient group. (Reviewer-Ioanna Apostolidou, MD).

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Keywords: Seizure History, Regional Block, Central Nervous System Toxicity

Print Tag: Refer to original journal article
Cannabis is the most commonly used illicit drug among people with schizophrenia. Progression to daily use of cannabis and tobacco increases the relative risk of onset of psychosis.

**Background:** In first-episode psychotic patients, cannabis abuse rates range from 15% to 65%, alcohol abuse rates range from 27% to 43%, and daily cigarette smoking rates range from 50% to 75%. Drug abuse typically begins prior to onset of psychotic symptoms, and there is evidence that cannabis abuse may be associated with an earlier onset of psychosis. A less richly explored topic is whether cannabis abuse is associated with an earlier age of onset of prodromal symptoms.

**Objective:** To identify whether cannabis, tobacco, and alcohol use prior to psychotic or prodromal symptoms is associated with earlier onset of those symptoms in an urban minority population.

**Participants/Methods:** 109 patients were recruited from 2 inpatient units at an urban public hospital and a psychiatric crisis center in Georgia. All patients had first-episode nonaffective psychoses (most were diagnosed with schizophrenia). Substance use data and information about age of onset of prodromal and psychotic symptoms was also collected. For the analysis, patients were grouped according to their substance use and progression to increasing severity.

**Results:** Prior to psychosis onset, 40.6% of the sample used cannabis daily, 44.1% smoked tobacco daily, and 7.9% drank alcohol daily. Although there was no significant effect of cannabis or tobacco on the risk of onset of psychosis, those who drank alcohol weekly or daily had a later age of onset of psychosis. However, progression to daily use of cannabis and tobacco was significantly associated with onset of psychosis, and even more strongly significant with onset of prodromal symptoms. This relationship was stronger for female patients than for males.

**Conclusions:** Rapid progression to daily use of cannabis and tobacco is associated with a higher risk of initiation of psychotic and prodromal symptoms. However, because the association does not determine causality, it is also possible that approaching psychosis triggers increased cannabis or tobacco use.

**Reviewer’s Comments:** This study highlights what I have found in clinical practice, working in an urban public-sector hospital -- a large percentage of first-break psychotic patients smoke cannabis. The mechanism is not clearly known, but it likely relates to the effect of cannabinoids on neurotransmitters, such as dopamine and glutamate, in areas of the brain associated with schizophrenia. The explanation for the increased risk of onset of symptoms with nicotine is not as evident, although there is some evidence of a connection between nicotinic neurotransmitters and schizophrenia. (Reviewer-Elizabeth Ford, MD).

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Keywords: Psychosis, Substance Abuse

Print Tag: Refer to original journal article