Correspondence

Autism's home in the brain

To the Editor: Thank you for the interesting articles on autism by Rapin,[1] DeLong,[2] Minshew et al.,[3] and Courchesne et al.[4] I would like to bring up for discussion the possibility that dysgenesis of temporal and frontal lobes, abnormalities of the cerebellar vermis, oculomotor signs, and a disorder of serotonergic neurotransmission could result from perinatal disruption of aerobic metabolism. Anoxia, infections, or exposure to toxic substances during gestation or early postnatal development may impair brainstem nuclei of high metabolic rate in a Wernicke encephalopathy–type symmetric bilateral pattern, whether visible damage is apparent.[5] Reports of brainstem damage in infants who died during the perinatal period demonstrate that this kind of pathology occurs.[6] Less severe submicroscopic involvement of brainstem nuclei could alter the biochemical processes required for normal development of later maturing areas of the cerebral cortex.

It might be worth considering whether autism spectrum disorders including Asperger's syndrome and antisocial personality disorder could be caused by maldevelopment due to loss of trophic influences from caudal to rostral brain centers. Growth of the human cerebral cortex continues past the second decade, but brainstem nuclei mature much earlier.[7] The inferior colliculus is the earliest structure myelinated in the human brain, and the auditory system is functional by the 30th week of gestation.[8] Early maturation and intactness of the brainstem auditory system may be important for growth and development of the temporal lobes. Activity of serotonin-sensitive adenylate cyclase is especially high in the inferior and superior colliculi of immature rats and may stimulate synaptic proliferation.[9]

The brainstem structures damaged in Wernicke's encephalopathy are among the brain areas of highest metabolic rate as measured by the deoxyglucose method of Sokoloff.[5] The mamillary bodies, inferior olives, and cerebellar vermis are affected in Wernicke's encephalopathy—structures all reported to be affected in individuals with autism.[10] However, the inferior colliculi in the auditory pathway are also frequently involved in Wernicke's encephalopathy,[11] and the deoxyglucose method has shown that the inferior colliculus is the structure of highest metabolic rate in the brain.[5] High metabolic activity plus early maturation could influence growth and development of the temporal lobes and early language learning. Rapin's proposal that verbal auditory agnosia (VAA) may be the cause of the language disorder in autism[12] suggests impairment of function within the auditory system.

Wernicke's encephalopathy is often accompanied by cerebellar damage associated with damage of the inferior olives.[13] Abnormalities of the cerebellar vermis in some children with autism might be the only visible sign of a Wernicke-type encephalopathy. Oculomotor signs are also prominent in Wernicke's encephalopathy. Poor eye contact and lack of facial expression in children with autism perhaps signifies a minimal involvement of oculomotor and facial nuclei. An investigation of oculomotor and blink responses to acoustic stimuli might provide information on intactness of connections between auditory and facial and oculomotor nerve circuits.

There is much more to discuss, but allotted space has run out.

Nicole Simon, PhD, *Lexington, MA*

Reply from the Authors: Dr. Simon speculates that a subtle prenatal, perinatal, or postnatal anoxic or toxic insult to highly metabolically active brainstem and diencephalic nuclei might account for (some cases of) autism. Experiments in asphyxiated neonatal monkeys damaged brainstem nuclei with the highest metabolic rate,[14] but whether the animals would have had autistic symptoms is unknown, and the relevance of these experiments to Leigh's disease, let alone autism, is tenuous. Involvement of brainstem nuclei in autism was raised by three observations: an autopsy study by Rodier on a classically autistic woman who had been exposed to alcohol in utero and had cellular abnormalities of the facial and other brain stem nuclei;[15] thalidomide embryopathy, which was associated with cranial nerve involvement and, in 4 of 100 cases, autism;[16] and the report of an occasional child with Moebius syndrome said to have been autistic.[17] In my experience, unstigmatized autistic children have no clinical signs of cranial nerve involvement. Furthermore, there is ample evidence that many genetic and nongenetic conditions affecting the immature brain may be associated with autism, which, like dementia or mental retardation, is a behaviorally defined syndrome. Perinatal factors are not among frequent nongenetic causes of autism.[18,19]

I would like to correct a statement in Dr. Simon's letter: VAA is not *the* language deficit of autism, but *a* language disorder, and not the most prevalent.[20] It is the most frequent language deficit in acquired epileptic aphasia (Landau-Kleffner syndrome [LKS]), and, although more frequent in nonepileptic children with autism than in those with developmental language disorders;[21] it is rare. At least in LKS, the evidence points to pathology in temporal auditory cortices, not the brainstem.[22] Drs. Michelle Dunn, Judith Gravel, and colleagues are currently conducting a systematic clinical and electrophysiologic exploration of each relay of the auditory system. Thus far, preliminary data do not point to a subcortical cause for the language disorders of verbal autistic children, including those who fulfill criteria for Asperger syndrome (personal communication, 1999).

Isabelle Rapin, MD, *Bronx, NY*

Reply from the Authors: Dr. Simon makes a case for Wernicke-type encephalopathy as a cause of autism; that is, that the substrate for autism could result from perinatal disruption of aerobic metabolism.[23] This type of hypoxic-ischemic injury is indeed common in the perinatal period and has been well recognized and studied. However, to my knowledge, no significant correlation has been established between such perinatal hypoxic injury and autism. Where it has been studied carefully, little or no correlation has been found between perinatal risk factors and autism.[19,24-29]

G. Robert DeLong, MD, *Durham, NC*

Reply from the Authors: Dr. Simon hypothesizes that perinatal disruption of aerobic metabolism might produce a brainstem injury that then interferes with the development of the forebrain, thus causing autism. This theory is reminiscent of the early "Whisper of the Bang" theory proposed by Tanguay and Edwards[30] to explain how abnormalities detected with brainstem-evoked potential studies might adversely influence forebrain development. There is no clinical or empiric neurologic evidence to support such a pathophysiologic model in autism.

Disruption of aerobic metabolism in the brainstem is a common consequence of neonatal hypoxic-ischemic injury, and the empiric evidence does not support a connection to the development of autism. It is my experience that children with autism very rarely have clinical evidence of cranial nerve VI or VII involvement. Rather, the paucity of facial expression seen in autism is of the type seen in PD. That is, facial expression is masked during social communication, i.e., is not used during communication but becomes animated when the autistic individual thinks of something funny or experiences emotion internally. Secondly, the study that we reported on saccadic eye movements demonstrates that there is no evidence of abnormalities in the function of the oculomotor nuclei in the brain stem.[3] We have additional reflexive saccade and oculovestibular data on a separate group of 78 autistic individuals and 78 controls, and again there is no evidence of dysfunction of the oculomotor nuclei or of their brainstem connections with the vestibular system.

A separate issue raised by Dr. Simon at the beginning of her letter is the possible mechanisms that underlie the development of neocortex and neocortical systems. These mechanisms and the genetic control over them are largely unknown and are exciting areas of ongoing neuroscience research. The importance of defining these mechanisms and their genetic basis is the reason that developmental disorders with a strong family genetic component like autism have become of such great general interest to neuroscience.

Nancy Minshew, MD, *Pittsburgh, PA*

Reply from the Authors: We agree with Dr. Simon that the effects of intrauterine neurodevelopmental disturbances, such as hypoxia or exposure to neurotoxins, may share certain features with autism. Simon describes some interesting potential parallels between autism and Wernicke-type encephalopathy in terms of neurostructural abnormality and perceptuomotor deficit. However, we do not believe that autism can be explained in terms of a unique etiology. It is likely that in some instances, neurotoxic exposure can affect the developing CNS in ways that will result in an individual fulfilling the diagnostic criteria for autism, as in the case presented by Rodier.[15] Yet, one of the established etiologic findings in autism is the importance of *genetic* factors.[31-33] This is hard to reconcile with Simon's proposal that autism may be typically or even exclusively explained by lack of trophic substances owing to, e.g., maternal alcoholism.

Furthermore, explanatory models based on a single sensorimotor deficit are attractive in view of their simplicity. We do indeed believe that some of the "higher cognitive" deficits in autism, such as the so-called "theory of mind" deficit,[34] may be explained in terms of quite elementary perceptuomotor and attentional impairments.[35] Nonetheless, it should be noted that auditory agnosia or oculomotor abnormalities, although they may be often observed in autistic individuals, are by no means *necessarily linked* to autism. Most individuals with auditory agnosia or oculomotor impairments are not autistic. It remains theoretically possible, though, that *specific types* of auditory agnosia or oculomotor abnormalities could play some role in autistic etiology.

Given the current behavioral, imaging, genetic, biochemical, and postmortem evidence, it appears unlikely that autism can be explained as a single disorder resulting from a single etiologic path and affecting a single brain structure or region.[36] Instead, we believe that the spectrum of disorders classified as autistic includes a wide range of different potential behavioral and cognitive deficits, which are outcomes of a number of different potential etiologies.

Ralph-Axel Müller, PhD, Eric Courchesne, PhD, *San Diego, CA*

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Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults

To the Editor: We read with interest the report on the cognitive effects of topiramate (TPM), gabapentin, and lamotrigine on healthy young adults by Martin et al.[1] The authors used an impressive battery of cognitive tests to determine that, in the acute and "steady state" settings, TPM was more likely to cause serious cognitive side effects than either lamotrigine or gabapentin.

The clinical impact of this study is limited, and the authors have noted the rather restricted scope of the findings. The entire study population consisted of 17 adults, 3 of whom dropped out, and the study itself was over a short period of time (4 weeks). They also acknowledge that in the case of topiramate, the initial dose for the "acute" phase of the study was rather large (almost 200 mg for a 70-kg adult and 8 times the dose one would start within clinical practice). Similarly, in the second phase of the tests, dose titration was at least four times as rapid for TPM as one would normally undertake in clinical practice. Double-blind, placebo-controlled trials[2] have already made it clear that nervous system side effects are common and in trials were seen in 74% of patients (34% in placebo).[3] It has also been shown that patients appear to tolerate the drug much better when given smaller initial doses and then dose titrated slowly to maintenance doses.[4] In reality, patients are unlikely to be prescribed TPM in the same

way as in the study, thereby lessening the occurrence of serious cognitive side effects.

A major factor mentioned by the authors as not having been considered in this study is drug efficacy in seizure control because none of the test subjects had epilepsy. This is of vital importance and further dilutes clinical impact as patients with chronic epilepsy (the population most likely to be prescribed these drugs) often judge acceptability of a drug's side effects in the context of its effectiveness in controlling seizures. We recently conducted an audit of the long-term retention rates of gabapentin, lamotrigine, and TPM in patients with chronic epilepsy in a tertiary referral clinic. A higher percentage of patients stopped TPM because of adverse events than they did any other drug, and in the majority of cases, cognitive side effects were responsible. However, at 3 years after initiation of therapy, patients were significantly more likely to be on TPM than either lamotrigine or gabapentin. This suggests that adverse events constitute just one of several variables that decide whether a patient continues therapy on a particular drug. Other factors in addition to lack of efficacy that are likely to be important are concomitant medication, severity of epilepsy, and prior medication.

Disclosure. Our unit has received travel, research, and training grants from Glaxo Wellcome, Ltd., Janssen Cilag, Ltd., and Parke Davis, Ltd., the manufacturers of lamotrigine, topiramate, and gabapentin. Dr. Sander has been on the Speaker's Bureau of all four companies.

S.D. Lhatoo, MRCP, J.W.A.S. Sander, PhD, *London, UK,*
I.C.K. Wong, PhD, *Bradford, UK*

To the Editor: I read with interest the article by Martin et al.[1] reporting the cognitive effects of TPM, gabapentin, and lamotrigine in six healthy volunteers, particularly because the authors used a dose-escalation rate very reminiscent of that in initial randomized clinical trials of TPM: 100 mg/day TPM starting dose increased weekly in 100 to 200-mg increments.[5-9] Escalating the TPM dose to 200 or 400 mg/day within just 2 to 3 weeks was associated with somnolence, psychomotor slowing, speech disorders, and concentration and memory difficulties.[5,7] Martin et al. show neuropsychometric changes commensurate with these CNS effects.

However, current clinical practice is to start TPM more gradually to improve tolerability, as demonstrated in a randomized, controlled trial comparing rapid escalation of TPM with a starting dose of 50 mg/day TPM increased 50 mg weekly.[4] Interruptions and discontinuations of therapy were significantly reduced with gradual initiation of TPM. In a neuropsychometric substudy of this titration study,[10] Meador reported a much more limited effect of TPM on cognitive function. From a test battery of 23 variables, 4 variables measuring attention, vigilance, and word naming, displayed only mild to moderate changes. The sample size of the Meador study adds to its validity: 155 patients with epilepsy.

In both studies, but particularly in that of Martin et al., neuropsychometric testing was conducted before subjects could have become habituated to the effects of TPM therapy. CNS effects associated with the initiation of antiepileptic drugs (AEDs) tend to lessen over time, even as AED doses increase.[11] Martin et al. conducted neuropsychometric testing during dose escalation and 1 week after the last dosage increase to 400 mg/day (after 4 weeks of TPM). Meador conducted neuropsychometric testing 4 to 8 weeks after the last TPM dosage increase (after 12 weeks of TPM). Thus, the much more limited effects of TPM on cognitive function as reported by Meador may have reflected the longer habituation period as well as the more gradual rate at which TPM therapy was initiated.

My colleagues and I will report the final results of a study comparing cognitive effects of TPM and valproate (VPA) added to therapeutic dosages of carbamazepine in patients with epilepsy.[12] In contrast to the above studies, we used a starting dose of 25 mg/day TPM, increased weekly in 25-mg increments; neuropsychometric testing was conducted 8 weeks after the last dosage increase (20 weeks after the start of TPM therapy). Preliminary analyses of our data show no difference between VPA and TPM on the major cognitive variables after 20 weeks' treatment.

In concert with the different rates of initiating TPM in the studies cited here, the cognitive effects ranged from the 30% to 50% reductions in neurocognitive parameters recorded by Martin et al. (rapid dose escalation), to the modest effects (15% to 20% reductions) reported by Meador in only a limited number of cognitive parameters (intermediate dose escalation), to the minimal effects that we have observed with gradual dose escalation. Thus, the results of neuropsychometric testing complement clinical observations that the cognitive effects of TPM may be, at least in part, a function of the rate at which TPM is introduced. Although 50 mg/day TPM as a starting dose increased in 50-mg increments was recommended when TPM first became available, more recent experience with the drug would suggest that even more gradual initiation (e.g., starting dose 25 mg/day TPM increased weekly in 25-mg increments, at least for a period of 4 to 6 weeks) may minimize the cognitive effects of TPM even further. More gradual initiation offers the added advantage of achieving the optimal TPM dose without overshooting it.

Albert P. Aldenkamp, PhD, *Amsterdam, the Netherlands*

Reply from the Authors: We appreciate the comments of Lhatoo et al. and Dr. Aldenkamp regarding our data concerning the cognitive effects of three newer AEDs. We agree completely with their comments that the severity of cognitive side effects were probably greater in our subjects than would be expected in clinical practice. However, our study highlighted the nature and quality of the cognitive effects of TPM. Clinicians need to recognize and be vigilant for these specific effects in patients.

A second issue raised by Lhatto et al. regards drug efficacy and trade-offs that are made between drug side effects and seizure control. Many factors contribute to the continuation of a particular AED, and we agree with the author's point. The current study was unable to address drug efficacy issues. However, the central point of our study was the investigation of potential cognitive effects of TPM, gabapentin, and lamotrigine in a group of healthy young adults. It still remains to be demonstrated whether any of the newer antiepileptic medications, taken over an extended period of time and within standard clinical dosage range would affect day-to-day cognitive functioning (e.g., job performance), especially in those patients that are higher functioning. This issue is still not adequately understood, although the research presented by Dr. Aldenkamp indicates that slower "habituating" dosing produces much less untoward cognitive effects than those reported in our study. Such studies are encouraging and warrant replication. Another point is that by studying healthy adult populations the confounding effects of seizures can be controlled for and the potential cognitive effects of AEDs can be more readily examined.[13] Finally, further research is needed evaluating the potential for amelioration or continuation of cognitive effects in the long-term (i.e., several months) clinical trial with TPM monotherapy in both patient and control groups.

R. Martin, PhD, R. Kuzniecky, MD, S. Hu, H. Hetherington, J. Pen, K. Sinclair, F. Gilliam, MD, E. Fraught, *Birmingham, AL*

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The cerebellar seizures of Hughlings Jackson

To the Editor: As a follow-up to the Historical Note by McCrory et al.,[1] I would like to report a well-studied patient with the "cerebellar seizures of Hughlings Jackson" occurring consequent to intermittent cerebellar tonsillar herniation. This observation supports the contention of Kinnier Wilson that these paroxysmal events are caused by brainstem compression.[2]

The 48-year-old man was admitted to the hospital on June 7, 1979, with malaise, headache, and fever. He had been treated for cryptococcal meningitis in November 1977. Physical examination was remarkable for a temperature of 101 °F and a soft systolic murmur. The neurologic examination was remarkable for the absence of spontaneous venous pulsations on funduscopy and a mild decrease furrowing of the right nasal labial fold. CT of the head showed only mild ventricular dilatation. Lumbar puncture revealed an opening pressure of >500 mL water, white blood cells 16/mm^3 (100% mononuclear), protein 80 mg/dL, glucose 4 mg/dL with a peripheral glucose of 139 mg/dL, and a positive India ink.

Treatment with amphotericin B was reinitiated. During the course of his hospitalization, he developed a stereotypic paroxysmal loss of consciousness. Initially, he would complain of increasing headache accompanied by visual obscuration and dysarthria. Within 1 minute of onset, he would lose consciousness and display opisthotonic posturing of his head and neck, decerebrate posturing of the limbs, and either an irregular respiratory pattern or hyperventilation. At times, various ophthalmologic abnormalities were noted to accompany the episodes of loss of consciousness. These included transient rightward gaze, right internuclear ophthalmoplegia, skew deviation, and right Horner's syndrome. The altered consciousness, posturing, and abnormal respiratory pattern resolved within 1 to 2 minutes of their onset. During these events, which occurred several times per day without any recognized precipitant, an EEG showed generalized slowing. After 7 weeks of therapy and without change in his head CT, a repeat lumbar puncture showed an opening pressure of 240 mL water, no cells but abundant yeast, protein 107 mg/dL, and glucose 1 mg/dL with peripheral glucose of 111 mg/dL. After one of his fits later that day, he became apneic and hypotensive. Resuscitation was unsuccessful.

An autopsy showed active cryptococcal meningitis characterized by a diffuse meningitic exudate most prominent at the base of the brain. Inflammation was minimal. *Cryptococcus neoformans* yeasts were abundant. The cerebellar tonsils were impacted in the foramen magnum with hemorrhagic necrosis of their tips and distortion of the medulla.

I posit that the "cerebellar seizures of Hughlings Jackson," typically associated with mass lesions in the posterior fossa or increased intracranial pressure,[1] are the consequence of transient impaction of the cerebellar tonsils in the foramen magnum with resultant brainstem compression. Resolution follows their spontaneous disimpaction. The placement of a ventricular drain should be strongly considered in any such person. Additionally, I think that the term "tonic fits" as proposed by Kinnier Wilson[2] is more appropriate than "cerebellar seizures." First, the events are not likely to be the consequence of abnormal cortical neuronal activity as suggested by the term "seizure." Second, they occur independent of pathology of the cerebellum.

Joseph R. Berger, MD, *Lexington, KY*

Reply from the Authors: Dr. Berger highlights a number of issues in relation to this interesting condition. First, "Jacksonian cerebellar seizures" are extremely rare in contemporary practice. In part, this may be caused by a reduction in infective causes of basal meningitis, such as tuberculosis, which was the etiology of Jackson's original case. Second, he addresses the underlying etiology of the episodes. Although Dr. Berger posits intermittent cerebellar tonsillar herniation with brainstem compression as the basis for these episodes, it is equally likely that obstruction to the CSF pathways with resultant raised intracranial pressure may be the cause. In Dr. Berger's case, the intracranial pressure was significantly elevated throughout the terminal illness. The role of ventricular CSF drainage in this setting is not new and was the standard management in the pre–CT scan era.

Dr. Berger's case also has a number of clinical differences to the original case, namely the occurrence of loss of consciousness with the tonic episodes, as well as the presence of focal brainstem signs. These may reflect a different pathophysiologic mechanism from Jackson's case.

The characterization of these episodes as "tonic fits" as suggested by Dr. Berger is complex. Although Kinnier Wilson did in fact use this rubric to describe a broad range of conditions such as decerebrate posturing, Jacksonian cerebellar seizures, and tonic epileptic seizures, it is clear from his later writings that he did not resolve the etiologic issues in this regard.[3] We have used the term "cerebellar seizures of Hughlings Jackson" to emphasize both the accuracy of the original clinical description as well as its place in neurologic history, given that this concept is now largely forgotten by modern neurologists.

Paul McCrory, FRACP, Peter Bladin, MD, FRACP, Samuel Berkovic, MD, FRACP, *Victoria, Australia*

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Simultaneous repetitive transcranial magnetic stimulation does not speed fine movement in PD

To the Editor: I read with interest the paper of Ghabra et al.[1] Using the Grooved Pegboard Test, the authors reevaluated the effect of simultaneous subthreshold 5-Hz repetitive transcranial magnetic stimulation (rTMS) over the primary motor hand area (M1) on fine hand movement in PD. In contrast to a previous study,[2] Ghabra et al.[1] found no improvement of motor performance during simultaneous 5-Hz rTMS over the contralateral M1 applied at an intensity just below active motor threshold. The data of Ghabra et al.[1] confirm our previous study, which demonstrated no beneficial effects of simultaneous subthreshold 5-Hz rTMS on handwriting in unmedicated PD patients.[3]

Ghabra et al.[1] investigated the immediate effects of subthreshold rTMS on concurrent fine manual movements to define the potential therapeutic role of rTMS in PD. However, the authors provide no evidence that the immediate effects of simultaneous rTMS on manual skills predict the therapeutic potential of rTMS in PD. Because rTMS is likely to impair the function of the stimulated cortical target during the time of magnetic stimulation,[4,5] there is no reason why simultaneous rTMS over M1 should improve skilled motor tasks in PD patients. On the contrary, it seems more likely that rTMS just below active motor threshold might disturb the fine tuning of intracortical neuronal activity in M1, which generates the appropriate motor commands during highly skilled movements.[5] Considering that studies on fine manual movements during simultaneous rTMS of M1 are dealing with the interference between externally (i.e., transcranially) induced neuronal activity and intrinsic neuronal activity, this experimental approach is suitable to explore the role of M1 in motor control.[5] However, I like to make the point that studies on fine movements during simultaneous rTMS provide no clues to the therapeutic potential of rTMS in PD. Because rTMS can induce a lasting modulation of intrinsic cortical neuronal activity,[6,7] potential therapeutic effects of rTMS are likely to be mediated by an outlasting modulation of the excitability of cortical circuitry. Therefore, studies on therapeutic effects of rTMS in patients with movement disorders should assess motor performance before and after rTMS instead of focusing on movements before and during rTMS.[7,8]

Hartwig R. Siebner, MD, *Munich, Germany*

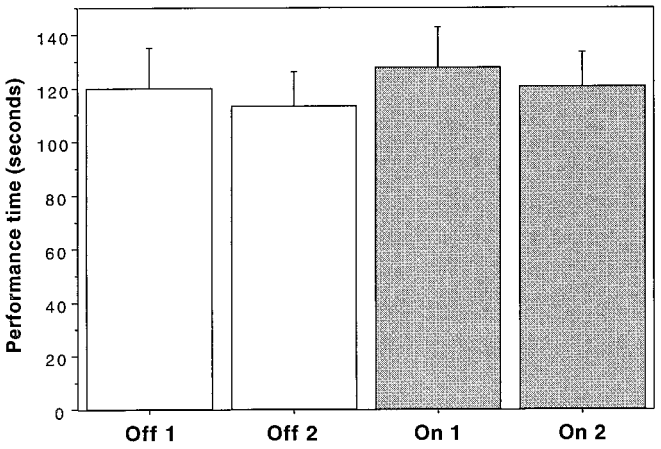

Figure. Graph showing mean performance times (± standard error) for the groups receiving stimulation off-head (open bars) and on-head (shaded bars) as the first testing condition. The two times for each group are from before and after performance under the alternate condition.

Reply from the Authors: We appreciate Dr. Siebner's interest in our article where we describe our unsuccessful attempt to replicate an earlier finding of a beneficial effect of rTMS on the Grooved Pegboard task in PD. We intentionally restricted our discussion to the therapeutic potential of rTMS delivered during task performance and left the possibility of effects after treatment open, citing Dr. Siebner's work. However, our article contains data that suggest that there is no lasting benefit of rTMS delivered at these settings.

Six of our patients performed the task with the coil held off the head before receiving any rTMS. These individuals then received continuous on-head stimulation for an average of 115 seconds while performing the task and were retested under the off-head condition. They showed only an incremental improvement in performance between the two off-head sets, similar to the improvement seen between the two on-head sets in the group who received on-head stimulation first (figure) and attributable to the effect of practice. In addition, while all patients performed the task twice under the on and off-head conditions and only these data were reported in the paper, six of the patients performed the task under both conditions several more times with no evidence of a cumulative effect. Although results may differ with other experimental conditions, we have seen no evidence of lasting beneficial effects in PD.

The notion of rTMS as therapy for brain disorders has diffused rapidly into the clinical and general media in the last few years,[9] but the effects have generally been weak and have not always been reproducible. We believe that the situation calls for particular caution and attention to reproducibility.

Eric M. Wassermann, MD, Mark Hallet, MD, *Bethesda, MD*

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Phenotypic variability in rippling muscle disease

To the Editor: Vorgerd et al. are to be commended for their description of phenotypic variability in two previously unreported kindreds with autosomal dominant rippling muscle disease (RMD).[1]

Accurate description of the clinical manifestations of rippling muscle disorders is important because of the potential basic science ramifications. Because these disorders are typified by stretch or percussion-induced contractions that are "electrically silent" (i.e., without myotonia), we have suggested that these disorders represent the first clinical evidence for the existence of stretch-activated or mechanosensitive channels in humans.[2,3]

Our case of rippling muscles associated with MG[4] was cited along with sporadic cases of rippling muscles. The other sporadic cases cited by the authors were in abstract form only, with the exception of our case and the 1980 case of Alberca et al,[5] which was lost to follow-up (personal communication, 1997).

We have suggested that our case of rippling muscles associated with MG was autoimmune in etiology.[2-4,6] Since our original description, two additional cases of rippling muscles with MG[7] responding to treatment with azathioprine have been reported.[8] There have also been three additional cases mentioned as part of a poster presentation at a recent meeting.[9]

Therefore, in addition to the well-characterized autosomal dominant form of RMD, there is ample evidence for an autoimmune form of rippling muscles associated with MG (with or without thymoma). Although the latter may represent a rippling muscle "syndrome," we believe that further study of these disorders (both inherited and autoimmune) may yield important insights into stretch-activated or mechanosensitive channels in human skeletal muscle.

Carl F. Ansevin, MD, *Cleveland, OH*

Reply from the Authors: We appreciate Dr. Ansevin's letter pointing out that among sporadic cases with rippling muscles an autoimmune form associated with MG can be delineated. Indeed, in symptomatic as well as hereditary RMD the underlying molecular pathomechanisms may in part be similar and may involve stretch-activated or mechanosensitive channels of the human skeletal muscle. Percussion and rapid palpation of muscle may liberate calcium from the sarcoplasmic reticulum. Hence, free calcium may activate the contractile system to produce local mounding, percussion-induced rapid muscle contraction, and muscle rippling. However, the precise pathophysiologic mechanism in RMD remains to be elucidated. The most straightforward way might be the identification of RMD genes by positional cloning.[1,10,11] Further analyses of the predicted gene products in hereditary monogenic RMD may aid in the understanding of calcium release in muscle sarcoplasmic reticulum and the mechanics of this disorder. This will probably shed light on the pathomechanism in symptomatic RMD as well.

Matthias Vorgerd, MD, Jean-Pierre Malin, MD, Wilhelm Mortier, MD, *Bochum, Germany,* Christian Kubisch, MD, *Bonn, Germany*

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Falling asleep at the wheel: Motor vehicle mishaps in people taking pramipexole and ropinirole

To the Editor: We read with interest the article by Frucht et al. describing episodes of falling asleep while driving in Parkinson's disease (PD) patients, which they termed "sleep attacks".[1] We question the concept of a "sleep attack" and suggest that these patients likely fell asleep at the wheel because of medication-induced drowsiness on a background of the excessive daytime sleepiness that is frequently seen in PD patients. The term "sleep attack" may be misleading because it implies that attacks are unavoidable. This term was used historically in patients with narcolepsy but was abandoned because of lack of evidence that the phenomenon of irresistible attack of sleep actually exists. Current evidence indicates that narcoleptics fall asleep because they are continuously sleepy and are put in situations where resistance to sleep is decreased.[2] They may not, however, be aware that they are drowsy because of the amnesia associated with falling asleep and a tendency for the awareness of drowsiness to attenuate.[2] Sleep-monitoring studies demonstrate that patients frequently fall asleep without recalling that they were somnolent beforehand, despite clinical and electrophysiologic evidence to the contrary.[2,3] This somnolence is often not detected by simply asking the patient whether he or she is drowsy but can be identified by sleep instruments such as the Epworth scale that inquire about tendencies to fall asleep in inappropriate conditions as well as subjective sleepiness.

Sleep questionnaires were not used in the Frucht study, although it is noted that four patients had prior episodes of inappropriately falling asleep during business meetings and telephone calls. Sleep studies were not performed, so it is not known whether any of the patients had a sleep disorder and excessive daytime sleepiness that are found in the majority of PD patients.[4] However, they were receiving a variety of medications that can induce drowsiness. Dose-related sedation and drowsiness have been described with virtually all dopaminergic agents.[5–7] The patients received an average daily dose of 2.9 mg of pramipexole, a dose that has been shown to be associated with excess sedation in clinical trials.[5] Two patients were also receiving cimetadine, which inhibits pramipexole metabolism and increases plasma levels of the drug. The one patient who had a sleep episode on ropinirole was receiving 16 mg per day, a relatively high dose. In addition, all patients received other dopaminergic agents and some took clonazepam, clonidine, and paroxetine that could also have contributed to sleepiness.[2]

These observations suggest that sedation likely played a role in the episodes that were described. These episodes may have been observed more frequently with pramipexole because the drug tends to be widely used, titrated rapidly, and used in relatively high doses. Patients are typically titrated to 1.5 mg over 4 to 6 weeks, a dose that provides maximal clinical benefit for most patients.[5] Higher doses are used by many physicians and are associated with excess sedation. In contrast, other dopamine agonists such as ropinirole, pergolide, and bromocriptine are generally used in doses that are considerably below those that provide maximal clinical benefit and may thus have relatively less propensity to induce sleepiness at routinely used doses. Since the time of the Frucht report, we have observed this same phenomenon in several patients receiving relatively high doses of other dopaminergic agents including pergolide and levodopa/carbidopa, suggesting that this is a class effect and not related to just one or two dopamine agonists.

Falling asleep while driving is a serious problem, but it is well known to occur with sedative medications and excess sleepiness.[8] There is nothing to indicate that the episodes described in PD patients represent a new phenomenon. Further, we suggest that there are several steps that physicians can take to identify at-risk patients with PD and to reduce the risk that these events will occur:

1. Physicians treating patients with PD should routinely use sleep questionnaires such as the Epworth Sleepiness Scale or the Sleep Wake Inventory, which can detect sedation even when patients are not themselves aware of the problem. It is not enough to just ask patients whether they are drowsy or sedated.
2. Prior episodes of falling asleep in inappropriate situations such as while reading, talking, or watching television almost always precede their occurrence in dangerous situations and must be sought.
3. Dopaminergic agents should be used at the lowest dose that controls PD features to avoid unnecessary sedation.
4. Patients with PD must be informed of the dangers of driving if they feel drowsy or if they have unwanted episodes of falling asleep in other situations.
5. If these episodes occur, the dose of dopaminergic medications should be reduced and driving should be temporarily restricted in patients.
6. Other sedating medications should be avoided if possible.
7. The possibility of sleep disorders should be considered.

C.W. Olanow, MD, FRCPC, *New York, NY;* A.H.V. Schapira, MD, DSc, FRCP, *London, UK;* T. Roth, PhD, *Detroit, MI*

To the Editor: The report by Frucht et al.[1] that describes eight patients from three different movement disorder centers who experienced motor vehicle accidents while taking either pramipexole or ropinirole is of great interest. It is well known that levodopa and all of the dopamine receptor agonists, including bromocriptine, pergolide, pramipexole, and ropinirole, induce somnolence. The degree of somnolence in different patients varies highly and sometimes the degree of somnolence induced by these drugs is either dose limiting or so severe that the drug must be discontinued. In my experience of treating patients with PD with dopamine agonists I have not encountered uncontrollable falling asleep in the context of absolutely no history of drug-induced somnolence or complaints of increasing somnolence before episodes of falling asleep. The induction of irresistible episodes of uncontrollable sleep is quite unusual and not at all in keeping with the prior literature of agonist-induced somnolence and sleepiness.

Several questions regarding the methodology employed in this report should be addressed. It appears from the authors' table 1 that four patients had "sleep attacks" during other activities and that four patients had "sleep attacks" only while driving. How do the authors account for "sleep attacks" that occur only during the specific setting of driving a motor vehicle and not during other activities of daily living? With regard to the four patients who had "sleep attacks" during other activities, how was this distinguished from somnolence and simply falling asleep? If the patients were having excessive somnolence and sleepiness, why were they still driving? In the structured phone interviews that were described, how was somnolence judged so that we may know more clearly that patients were not having drug-induced somnolence of the type previously well documented? In addition, the structured interviews took place after the patients' motor vehicle accidents—how was reverse recall bias avoided. In other words, patients who were involved in a motor vehicle accident and acknowledged that they fell asleep at the wheel might not wish to recall that they were having excessive somnolence prior to beginning their operation of the motor vehicle. Frucht et al.'s[1] patients seem quite unusual, as all of them with stage II PD and an average disease duration of 6.4 years were reported as having *no* sleep distur-

bance. What is the prevalence of motor vehicle accidents in patients taking bromocriptine, pergolide, levodopa, or, for that matter, pramipexole or ropinirole? What is the prevalence of motor vehicle accidents related to sleepiness in aged matched nondiseased subjects? What is the prevalence of sleepiness-related motor vehicle accidents in patients with other chronic medical illnesses?

Whether the sleep disturbance reported in this article is different from drug-induced somnolence and excessive sleepiness remains to be determined. This is an extremely important issue and further study of this question must be undertaken.

William J. Weiner, MD

To the Editor: I was extremely pleased to read the excellent report by Frucht et al. concerning patients' falling asleep while taking pramipexole for PD.

This phenomenon has been of concern since 1994. Patients fall asleep without warning, drowsiness, sleep deprivation, or circumstances particularly conducive to sleep, and often at inappropriate and even dangerous times. These episodes last seconds, perhaps a few minutes, but documentation of exact duration has been difficult. After the episode, patients are aware that a lapse of consciousness has occurred.

Terminology has been a difficult problem. Although usually reported as "somnolence," this is misleading. Clinically, the term "narcolepsy" is the most recognizable, but probably should be reserved until the pathophysiology of both conditions is determined. The authors' term "sleep attacks" seems appropriate.

I would like to report nine such episodes in my own patients. They have resulted in contusions, "fender benders," loss of employment, and considerable social embarrassment. There were six men and three women, ages 48–79, with idiopathic PD for 2–8 years; all except one, who was at stage III, were stage II. At the time of the first report of the "sleep attacks," patients were taking between 0.75 mg and 4.5 mg pramipexole daily, and had been taking it between 2 weeks and 5 years. Five patients discontinued pramipexole, and "sleep attacks" ceased immediately. Two patients decreased the dosage, and "sleep attacks" ceased, but at the sacrifice of motor function. Because of antiparkinson benefits, two patients have elected to remain on 4.5 mg daily, but have markedly limited their personal activities to avoid dangerous situations.

I commend Drs. Frucht et al. for bringing this significant adverse effect of pramipexole to our attention.

Margaret M. Hoehn, MD, *Denver, CO*

To the Editor: In a recently published report, Frucht et al.[1] called to attention the occurrence of sleep attacks associated with pramipexole and ropinirole treatment. The authors described eight patients treated with pramipexole who were involved in automobile accidents as a result of sleep attacks. Patients described their symptoms as "sudden, irresistible, overwhelming sleepiness without awareness of falling asleep that in most cases occurred acutely and without warning." In one patient, pramipexole was replaced by ropinirole and the patient experienced a further sleep attack. The authors concluded that pramipexole and ropinirole were causally related to the sleep attacks in the eight patients discussed.

Sleep attacks similar to the ones described in the case series have not been reported with PD, even if other sleep disturbances have been described in PD as being related to both the disease itself and to antiparkinsonian treatment.[9]

Various pivotal large, double-blind, placebo-controlled studies using dopamine agonists as monotherapy and as adjunct therapy in PD have been published. A summary of the incidence of somnolence reported in these studies with pergolide, ropinirole, and pramipexole are shown in the table.[10-14]

Table *Reported somnolence*[3-8]

Therapy	Pergolide	Ropinirole	Pramipexole
Monotherapy	12.7	36.2	18.3
Adjunct therapy	10.0	20.0	9.0

Values are percentages.

Whereas somnolence is a commonly reported adverse event with all dopamine agonists, we are not aware of any reports in the medical literature of sleep attacks, catalepsy, or narcolepsy with pergolide.

A review of the pergolide spontaneous adverse event data, stored on Eli Lilly and Company's worldwide safety database, was conducted to identify any adverse event reports to date suggestive of sleep attacks like those described by Frucht et al. This safety database has been collecting safety data on pergolide, the world's most frequently prescribed dopamine agonist, for more than 10 years. The review did not yield any reports where pergolide was related to sleep attacks, narcolepsy, hypersomnia, or catalepsy as either an actual adverse event term or as a term included in the summary text of the report.

Alberto Lledó, MD, PhD, Julie Nash, BSc (Hon), *Surrey, UK*

To the Editor: Frucht et al. review, an individual physician series of patients reporting the side effect of "sleep attacks" associated with PD patients taking pramipexole and ropinerole. While perhaps an important clinical signal, these anecdotal series await confirmation and must be considered in the spectrum of scientific evidence to support the causal association between a drug and a symptom.

The separation of the symptom from the underlying disease complex, which has sleep disturbance among its symptomatic manifestations, is essential. Regardless of drug use, patients with PD suffer from disturbances in sleep architecture related to the patients' age and the disease itself. To complicate matters further, the vast majority of PD treatments induce somnolence, and most patients receive concomitant drugs with the similar side effects. The term used to describe the findings ("sleep attack") suggests that the subjects, who fall asleep, do so without previous awareness. Sleep experts describe the term "sleep attack" as outmoded and prefer characterization of these episodes as an extreme manifestation in the spectrum of sedation.

A systematic review of this spectrum of sedation associated with any drug requires awareness of this complexity and requires multiple approaches. Although reviews of spontaneous report databases are invaluable for signal generation, they seldom provide evidence for establishing a causal relationship due to uncertainties in both the numerator (because of underreporting and reporting biases) and the denominator (an estimate at best). Further, reviews of adverse events collected from controlled clinical trial data, while having the advantage of a known sample, suffer from reporting bias. In this particular example, symptoms such as "sleep attacks" are unlikely to have been captured through standard adverse event reporting systems, or might be "hidden" under a number of other "proxies" (e.g., drowsiness, somnolence).

The gold standard of evidence is the randomized, controlled clinical trial, but it can rarely be used retrospectively to address phenomena that arise in the post-marketing pharmacovigilance environment. We have performed and continue conducting a systematic, multidisciplinary review of our databases on pramipexole. In addition, complex epidemiologic approaches that might help to determine whether a causal relationship might exist. However, for a condition beset by as many multifactorial determinants as "sleep attacks" in the setting of PD, nothing short of a carefully conducted sleep laboratory trial will confirm the effects of pramipexole, or indeed any dopamine agonist on sleep in patients with PD.

Felix M. Arellano, MD, Mark Corrigan, MD, *Peapack, NJ*

To the Editor: Pramipexole has recently been reported to elicit sudden onset of sleep at the wheel.[1] Changing the dopaminergic therapy to the second nonergot agonist ropinirole did not resolve the problem in all cases. The authors concluded that nonergot dopamine agonists are at higher risk for sudden onset of sleep. We report a patient who noticed the same problem after increasing the daily dose of pergolide, an ergot-derived dopamine agonist.

A 61-year-old man developed an akinetic and rigid syndrome in 1994, which was diagnosed as idiopathic PD a few months later. The patient reported a clear improvement of his symptoms with levodopa, 100 mg TID. Pergolide was added and slowly increased over the next 3 years, resulting in a final dose of 3 mg per day. In addition, levodopa was changed to a slow release formulation and increased to 500 mg. During this period, the patient was

nearly without symptoms except for micrography and continued working as a salesman. When a daily dosage of 3 mg was reached, the patient reported daytime tiredness. We added selegiline 5 mg once a day to further improve Parkinsonian symptoms and to use the stimulating potential of this substance. Three months later, he reported a slight deterioration of the Parkinsonian symptoms, especially his speech, his handwriting, and an increased drooling. Furthermore, he noticed slight dystonia and reported to be nervous during the daytime. To improve his Parkinsonian symptoms, we decided to further increase the daily dosage of pergolide to 5 mg. We attributed his nervousness to selegiline and stopped this drug. Three months later, the patient reported a good effect of the pergolide dosage on the Parkinsonian symptoms, especially on his speech and the drooling, but he noticed further increased tiredness and reported for the first time that he fell almost asleep at the wheel. A precise question elicited that his falling asleep occurred within seconds. He changed his driving habits, introducing more pauses, and never had an accident. As a consequence of his report, we reduced pergolide to the previous level and introduced selegiline again. Three weeks later, he noticed a deterioration of his Parkinsonian symptoms but did not suddenly fall asleep. After increasing the daily pergolide dose to 5 mg again, his Parkinsonian symptoms improved again accompanied by sudden onset of sleep.

Sudden onset of sleep at the wheel induced by an ergot-derived dopamine agonist has not yet been published. According to the criteria of Karch and Lasagna,[15] the relationship to pergolide in our case must be rated as "definite" because decreasing the substance and re-introducing the substance decreased and increased frequency of the adverse event. Different from the patients in the report of Frucht et al.,[1] our patient did not cause an accident. He reported tiredness during a mid-range dose of pergolide that increased with high doses and lead to sudden onset of sleep.

The manufacturer of pergolide has no reports of sudden onset of sleep in its data file (personal communication). This might be a result of the fact that neurologists did not precisely ask for sudden onset of sleep but for tiredness and somnolence in Parkinsonian patients. Further investigations are necessary to identify patients at risk for tiredness and sudden onset of sleep because a combination therapy with levodopa and dopamine agonists is mandatory to reduce fluctuations in Parkinsonian patients.

Guy Arnold, MD, *Berlin, Germany*

To the Editor: A recent communication in *Neurology* reports precipitation of sleep attacks in PD patients by the D2/D3 dopamine receptor agonists pramipexole and ropinirole.[1] Press accounts generated concern in patients prescribed these agents for PD and for amelioration of restless legs syndrome (RLS) and periodic leg movements of sleep (PLMs) and fueled discussion about dopamine's modulation of wakefulness and sleep at the recent Association of Professional Sleep Societies meeting. We therefore felt compelled to comment here on the prevalence, risk factors, and pathophysiology of such sleep attacks in PD and sleep attack risk in nonparkinsonian patients prescribed dopamine agonists. Our experience derives from a tertiary-based sleep center where many PD and RLS/PLMs patients are referred as well as experiments in nonhuman parkinsonian primates.

Caution should be exercised in concluding that D2/D3 agonists are solely responsible for sleepiness and sleep attacks in PD. Sleepiness might signal one or a combination of alternate pathophysiologies. Unmedicated parkinsonian states such as juvenile PD[16] and the nonhuman MPTP primate model of PD[17] themselves are characterized by pathologically short daytime sleep latencies (i.e., < 5 minutes) and intrusion of REM sleep into daytime naps (viz., a narcolepsy-like phenotype). Approximately 15% of PD patients referred to us express a similar phenotype, and it is more likely to manifest in patients with longer disease courses and superior quality and quantity of the prior night's sleep,[18] but is not associated with use of the D2-like agonist pergolide. Recognizing a narcolepsy-like phenotype is challenging, as PD patients and their caregivers do not often volunteer complaints of excessive sleepiness, and if they can be prompted to, the severity of sleepiness is typically underestimated. Moreover, many physicians too often attribute sleepiness to depression or a metabolic disorder.

Parallels between parkinsonian sleep attacks and those seen in narcolepsy are therefore justified and suggest a common pathophysiology in dopamine sensitive basal ganglia circuits as discussed by Frucht et al. The proposal that dopamine agonists precipitate sleep attacks via presynaptic inhibitory autoreceptors on dopaminergic ventral tegmental area neurons is consistent with most experimental data. However, we are unaware of any experience or objective data that dopamine agonists interfere similarly with wakefulness or precipitate sleep outside of the PD population. In the treatment of RLS/PLMs, for example, pramipexole has been noted to produce only occasional "fatigue" and mild REM-sleep suppression.[19] A compromised arousal mechanism intrinsic to parkinsonism therefore appears to be a necessary substrate for the precipitation of sleep attacks by D2/D3 agonists.

Physicians need to be vigilant in assessing PD patients for daytime sleepiness. Proper treatment can dramatically enhance quality of life and prevent the significant morbidity and mortality that attends pathologic sleepiness. When confident that dopamine agonists are the sole precipitant of sleepiness, we would advocate discontinuation, as do Frucht et al. Because primary sleep disorders can coexist with PD, these potential contributors to daytime sleepiness should be carefully assessed with polysomnography and treated appropriately. Identification of a narcolepsy-like phenotype in PD may necessitate treatment with wake-promoting agents such as bupropion, modafinil, or traditional psychostimulants.

David B. Rye, MD, PhD, Donald L. Bliwise, PhD, *Atlanta, GA*

Reply from the Authors: In the 6 months after publication of our report, physicians and patients have raised many important comments regarding this controversial issue. The letters that precede this reply are representative of the spectrum of opinions we have encountered.

Drs. Weiner, Olanow, Schapira, and Roth raise several important questions in their commentaries. Both letters address the important distinction between somnolence and sleep attacks. In our article,[1] we defined sleep attacks as sudden, irresistible episodes of sleep. Patients were unaware that they fell asleep until awakened by a motor vehicle accident or by some other event. The critical factor distinguishing these events from ordinary somnolence is the *time* elapsed between a state of normal arousal and sleep. As Drs. Weiner and Olanow, Schapira, and Roth state, levodopa and all of the dopamine receptor agonists, including bromocriptine, pergolide, pramipexole, and ropinirole, can produce somnolence, defined as the sensation of sleepiness. Olanow et al. agree with Weiner's statement that "induction of irresistible episodes of uncontrollable sleep is quite unusual and not at all in keeping with the prior literature of agonist-induced somnolence and sleepiness." In fact, this is the reason that we reported these patients.

Of our eight patients who experienced these events, four experienced their first attack of sudden sleep while driving and four had sleep attacks during other activities. Dr. Weiner asks how we can account for the time at which these events occurred in our patients. We are unable to do so, and because they occurred at various times of the day and after widely varying lengths of exposure to drug, we suspect they are stochastic in nature. Unfortunately, we were not made aware of sleep attacks until after patients experienced their accidents.

Based on interviews of our patients in the office and on the telephone, we specifically separated drug-induced somnolence from attacks of sudden sleep. In their letters, Drs. Olanow and Arellano question the wisdom of calling these events "sleep attacks." We realize that the American Sleep Disorders Association does not classify this term as a sleep disorder. However, we purposely chose to use this term because it best described our patients' accounts of their experiences. It makes little difference to the patient whether he falls asleep suddenly without warning or falls asleep after a brief period of unrecognized somnolence. In either case, the patient who experiences this event while driving has insufficient time to recognize that he is in danger to pull off the road.

We readily acknowledge the difficulty in eliminating recall bias from historical data. This does not change the fact that these patients experienced these events and that they narrowly escaped serious injury. It was not our experience that patients were reluctant to admit these events. Rather, similar to Dr. Hoehn's experi-

ence, they were extremely concerned about them, for the obvious risks of personal injury and injury to the public.

Dr. Weiner comments that he has not encountered this phenomenon in his practice. Unfortunately, in the 6 months since presentation of our data at the 51st meeting of the American Academy of Neurology, we have been informed by other neurologists of at least 16 additional examples of sudden attacks of sleep in patients taking pramipexole, resulting in actual or near automobile accidents. Nine of these additional cases are reported in Dr. Hoehn's letter. Although all of our patients were men, this phenomenon is not restricted to this sex, as three of Dr. Hoehn's patients were women. Attacks have also occurred during other activities, including while talking on the telephone, riding an escalator, and in one case, while a patient held a grandchild. Two of these events occurred in patients with restless legs syndrome who did not have PD. Two attacks were witnessed by family members who reported that patients fell asleep during active conversation—in one case in mid-sentence. Although we only reported one patient who experienced a sleep attack on ropinirole, SmithKline Beecham subsequently reported 17 PD patients who experienced sudden onset of sleep on ropinirole, in a letter sent to healthcare professionals of the European Union. We agree with Drs. Arellano and Corrigan that these events are underreported by patients and often unrecognized by neurologists.

In our article, we drew an analogy between these events and attacks of sudden sleep occurring in narcolepsy. Recent work, some published since submission of our article, is particularly germane to this issue. Using a well-established canine model of narcolepsy, Nishino et al. showed that systemic administration of small doses of D2-type receptor agonists aggravated cataplexy, suggesting an effect at presynaptic autoreceptors.[20] Local infusion of D3-specific receptor agonists into the ventral tegmental area and lateral globus pallidus/putamen produced identical effects in these animals.[21] These effects can be selectively blocked by D3-specific antagonists.[22] We suggest the possibility that the biologic effect in our patients may derive from pramipexole and ropinirole's enhanced affinity for the D3 receptor. The average dose of pramipexole at which these events occurred was 2.9 mg/day in our patients; however, four of the patients took 2 mg or less, consistent with the possibility of a presynaptic mechanism.

The review by Drs. Lledo and Nash of the worldwide safety database in patients taking pergolide, a drug less active at the D3 receptor at therapeutic doses, did not reveal any examples of events that could be interpreted as sleep attacks. This is not surprising, as we were unaware of any similar events occurring with pergolide despite two decades of routine use. We question the wisdom of drawing conclusions from an informal survey of movement disorders experts about the relative sedating effect of dopaminergic drugs. We would classify the experience of Dr. Arnold's patient as sedation rather than a sleep attack.

Neurologists who care for patients with PD face a difficult decision when deciding to treat patients with the new dopamine agonists. Drs. Olanow, Schapira, and Roth outline the importance of sleep in contributing to automobile accidents. Given the magnitude of this problem and its impact on public health, we were surprised by their recommendations for guidelines for the safe use of pramipexole in patients who drive. They state that prior episodes of falling asleep almost always precede the occurrence of sleep attacks behind the wheel. The data simply do not support this conclusion: four of our eight patients experienced their first event behind the wheel, and subsequent patients encountered after our paper was published had similar experiences. Further, these events can occur at doses of pramipexole less than 1 mg/day. We are not aware of any data to support their recommendation that doses of 1.5 mg per day will safeguard against these events. A prospective survey of the prevalence of sedation and sleep attacks in patients with PD who are taking dopamine agonists would provide data to help answer these questions.

At present, it remains unresolved whether pramipexole and ropinirole can be used safely in patients who drive. It is also not known whether all patients with PD are susceptible to this side effect or whether there are specific risk factors that increase the chance of these events. Fortunately the majority of patients using these agonists do not encounter this side effect. Subsequent to our report, the Food and Drug Administration changed the warning label on pramipexole, and the European Medicines Evaluation Agency has amended its warning label to strongly urge patients not to drive while taking pramipexole. Similar steps are in progress with the warning label for ropinirole. We agree with our colleagues that this is an extremely important issue warranting further study.

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Correction

In the article "Viual field constriction in children treated with vigabatrin" (*Neurology* 1999;52:1713–1714) by Vanhatalo et al, the name of coauthor Dr. I. Nousiainen was erroneously omitted. Dr. Nousiainen, a consultant ophthalmologist from the Department of Ophthalmology, University Hospital of Kuopio, Finand, performed all ophthalmologic examinations, including Goldmann's visual field tests and interpretation of these. The authors apologize for the error.