PANEL DISCUSSIONS

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DISCUSSION I

Dr. Holmes: Dr. Greenblatt, since tolerance is such a serious problem, does it make sense to administer clonazepam every other day or to use clonazepam with nitrazepam on alternate days?

Dr. Greenblatt: If you define tolerance as a diminished adverse drug effect caused by reduced drug presence, then administering clonazepam every other day instead of every day will, of course, diminish net exposure to the drug. At the end of each 48-hour interval the plasma and brain concentrations decline, resulting in reduced drug exposure and uncovering of the receptor. This may prevent the development of tolerance. This approach has some anecdotal support from clinical experience, but we need controlled data on varying administration schedules before we can recommend a regimen to decrease tolerance.

The second suggestion, alternating clonazepam with nitrazepam, doesn't make sense. Nitrazepam and clonazepam are structurally very similar—although nitrazepam's half-life of 24 hours is shorter than clonazepam's 48 to 72 hours—so I cannot see that administering the drugs on alternate days would make much difference.

Dr. Wyllie: Would you comment on withdrawal symptoms after discontinuation of benzodiazepines?

Dr. Greenblatt: When a benzodiazepine is prescribed for a while—for anxiety, insomnia, or seizures—and then stopped, most patients experience what I like to call drug discontinuation syndromes. These may take the following forms:

(1) Recurrence, that is, reappearance of the underlying disease for which the drug was taken. Recurrence is expected because none of these drugs is a cure any more than aspirin cures arthritis or insulin cures diabetes;

(2) Rebound, in which the underlying disease comes back but is transiently worse than initially. This is most commonly seen when short-half-life benzodiazepines, such as triazolam, are used to treat insomnia. For example, on the first night after discontinuation, because of the rapid uncovering of the receptor and other changes, patients sleep worse for a night or two than they did before they ever got the drug; and

(3) Withdrawal, which is relatively unusual. Some patients, however, have typical autonomic symptoms of withdrawal similar to a mild case of delirium tremens—sensitivity to light and sound, tachycardia, restlessness, sweating, tremors—implying a degree of physical dependence.

If the syndrome is recurrent, then there will not be recovery from recurrence. The underlying disease will persist as long as there is no drug therapy. A withdrawal syndrome should be self-limited and usually last for a few days or a week or two. I have seen reports of withdrawal syndromes lasting for months or even years but there's no clinical, biochemical or experimental evidence that this is a new syndrome attributable to drug discontinuation. There's no evidence that benzodiazepines produce any structural CNS damage of any kind that could account for a prolonged withdrawal syndrome.

While I don't dispute the validity of the observations, I think they may be either a reappearance of another syndrome that has nothing to do with drug therapy or simply a progression of the underlying disease.

Dr. Leppik: Some people with severe, long-standing multifocal epilepsy can be started on 3 or 4 mg of

Klonopin (clonazepam) per day with very little sedation, and eventually require 15 or 20 mg a day. Might such patients have some deficiency in benzodiazepine receptors due to their epilepsy?

Dr. Greenblatt: I don't know whether the underlying disease accentuates the development of tolerance, but with chronic benzodiazepine administration, there is unquestionable development of tolerance. The kind of patients you describe are not typical, however.

By the way, tolerance is not a pharmacokinetic phenomenon. Tolerance is a receptor phenomenon. There is no evidence that benzodiazepines either induce or impair their own metabolism; so as long as you don't add carbamazepine, for example, the clearance of clonazepam will be the same after one dose as it is during multiple-dose therapy.

Dr. Tesar: Dr. Schenck, although you demonstrated no association of psychiatric disorders with your nocturnal *pugilistica*, did psychometric testing show any trends toward certain personality styles?

Dr. Schenck: Not really. We are starting to use the Multidimensional Personality Questionnaire, the MPQ, by Dr. Telligan at the University of Minnesota—not just for the REM behavior disorder but also for the adults suffering from night terrors and sleepwalking—to try to determine if there are certain personality profiles. Interestingly, almost all the family members, particularly the wives, have mentioned that these are men who have generally been quite mellow throughout their lifetimes. What we don't know is whether they have been suppressing anger. I didn't get a feel for that.

There are a couple of cases of men with intermittent explosive disorder whose daytime anger states diminished when their explosive disorder developed.

Dr. Andermann: Some of these people get out of bed and display directed, aggressive behavior. Is this the same or a different entity?

Dr. Schenck: That happens uncommonly. We believe such people may have an abrupt arousal while they are in the dream state. Because this is a dissociated state, they are able to use what is at hand in the environment. The mechanism may be the same as with postobstructive apnea violence. There's a whole range from totally within-sleep behaviors to dissociated arousal and sleep behaviors.

Dr. Ryan: Is the onset of night terrors in non-REM sleep a consistent finding?

Dr. Schenck: Yes, although with adults there is nothing sacred about delta-wave sleep. Quite a few adults come out of stage 2 sleep—very rarely out of REM sleep. We consider night terrors more of a non-REM sleep phenomenon and not just a slow-wave sleep phenomenon. It can occur in stage 2 sleep.

Dr. Ryan: What role do benzodiazepines have in the treatment of night terrors?

Dr. Schenck: Quite a number of people activate themselves in a variety of ways, by drinking too much alcohol or caffeine at night, and then wonder why they have a sleep disorder. Behavior modification is a useful technique in this situation. If, however, sleep hygiene is under control and they aren't injuring themselves, then hypnosis is fairly effective. For people who do injure themselves or others, we turn to clonazepam, based on our experience with the drug in our REM behavior disorder.

Dr. Rosenbaum in Boston suggested that high doses of other benzodiazepines might be as effective as clonazepam. We have had people on a variety of other benzodiazepines, in low to moderate, at times high, doses, and they did not respond; so we suspect that clonazepam probably is special. We haven't tested high-dose diazepam or other benzodiazepines for this indication, partially for ethical reasons. We have demonstrated how effective clonazepam is.

Dr. Pollak: The classic night-terror syndrome of childhood is described as occurring from stage 4, deep non-REM sleep. Some young adults, however, combine sleepwalking with night terrors. Sometimes they show more motor activity, other times more autonomic arousal. This is not a REM-related phenomenon and is clearly distinct from the REM behavior disorder that Dr. Schenck described.

We and other researchers have observed that this syndrome is not as specifically related to stage 4 as is the childhood sleep disturbance. People who suffer from the combined syndrome often have major psychiatric syndromes of various kinds, which respond well to benzodiazepines. We have used diazepam, 10 to 15 mg at bedtime, in an adult to suppress the episodes.

Of course, with benzodiazepine treatment there's a tradeoff with daytime side effects, especially morning hangover; but if the nocturnal behavior disorder is causing risk to the subject or to a bed partner, it may be worth treating on a long-term basis.

Dr. Schenck: Even our patients who need medication for night terrors do not automatically get treatment indefinitely. We use medication to settle the problem down for a number of months; then we try hypnosis and attempt to taper the medication. We don't necessarily want to commit them to long-term medication when it may not be necessary.

Dr. Ryan: Is it possible that an interictal burst of

epileptiform discharges might trigger a sudden awakening from stage 4 sleep, causing a night terror?

Dr. Pollak: We usually get a complete EEG when the question of seizures arises, both in children and adults who have repetitive, highly stereotyped events that do not respond to treatment with medication.

Over the years, we have seen only a few examples of sleep-related seizures that truly looked like sleep terrors. However, we have seen many examples of sleep terrors with no associated EEG epileptiform activity. Of course, that doesn't mean there may not be some epileptiform activity we aren't detecting.

Dr. Schenck: In the mid-1960s, Gastaut and Broughton studied children with epilepsy who had night terrors. They demonstrated that the episodes were sudden arousal from stage 4 sleep, without epileptiform activity. We assume, then, that most children with night terrors have a stage 4 phenomenon.

Dr. Andermann: There is a possibility that night terrors are migraine-related, and migraine is the major source of epileptiform "red herrings" on EEG.

Is nocturnal paroxysmal dystonia an epileptic phenomenon?

Dr. Schenck: Mahwald and Lugarisi recently reported that certain patients with paroxysmal nocturnal dystonia, which is a syndrome without any EEG abnormality, responded beautifully to carbamazepine. On long-term follow up, a few of them developed definite epileptic seizures. These results seemed to confirm the suspicion that if you wait long enough, a subgroup of patients with paroxysmal nocturnal dystonia will manifest an overt seizure disorder.

Dr. Andermann: Some of these patients with nocturnal paroxysmal dystonia may have had toxic seizures arising from the mesial frontal area.

Dr. Wyllie: Making the diagnosis of mesial frontal area epilepsy can be difficult. The epileptic discharge is buried in the inner hemispheric fissure, so that scalp EEG can be normal even during clinical attacks. Some of these patients may progress to have generalized tonic-clonic seizures as well as tonic attacks.

Dr. Leppik: Even though clonazepam works well for REM-sleep behavior disorder, a double-blind trial will be needed for the drug to get orphan status for this indication. There aren't many cases of sleep behavior disorder, so clinical trials would involve fewer patients than the usual.

Dr. Schenck: People with REM behavior disorder have episodes at least two or three times a week, if not many times per night, so it would not take long to show results. Patients would have to be confined in a sleep lab every night for their own safety, if they were to receive placebo or some agent other than clonazepam.

Dr. Wyllie: What is the mortality of REM-sleep behavior disorder?

Dr. Schenck: We don't know, but I wonder, for example, about older men with no history of depression who are found dead after jumping through a window at night. I'm sure there is a certain amount of mortality; there is undeniably a high morbidity.

DISCUSSION II

Dr. Schenck: Dr. Leppik, are new epileptic foci induced by status epilepticus so that new seizure types develop?

Dr. Leppik: We don't know the answer to that question. Hauser's data show that about 8 to 10 percent of people with epilepsy originally presented with status epilepticus. Dodrill's recent unpublished data showed that epileptic patients with neuropsychologic degeneration tend to be those who have had bouts of status epilepticus, and that even one bout of status epilepticus can be associated with a significant drop in I.Q.

Dr. Andermann: One specific type of patient is relevant to this issue—the child with a prolonged febrile convulsion who later develops temporal-lobe epilepsy. There is evidence to suggest that prolonged convulsions lead to mesial temporal sclerosis. This association is not clear from population studies of children with febrile convulsions, but it is clear in studies of patients who present later in life with temporal-lobe epilepsy.

Dr. Tesar: What is atypical alcohol withdrawal, and how do you treat it?

Dr. Leppik: We used the term "atypical alcohol withdrawal" for patients with a history of alcohol abuse who presented with serial seizures or status epilepticus. In retrospect, the only identifying factor was alcohol use, but perhaps they had fallen and the blow to the head precipitated the seizure. The exact role of alcohol withdrawal is still controversial.

We don't treat standard alcohol withdrawal. If such a patient has a single seizure, we may treat briefly with benzodiazepines but we would not begin chronic antiepileptic medication.

Dr. Pollak: As of a few years ago, the literature identified sleep disturbances as one of the leading precipitants of status epilepticus. Can you comment on this?

Dr. Leppik: We haven't seen that association in our

series. However, sleep deprivation is very epileptogenic. Some patients whose seizures we listed as idiopathic may well have had a trigger of some kind. College students who have seizures after staying awake for three or four days and nights in a row and using excitatory transmitter agents usually have a single seizure, but occasionally they do have status epilepticus.

Dr. Schenck: Dr. Greene, what types of tardive dystonias have you seen in patients on antipsychotic medications?

Dr. Greene: Most people we see with tardive dystonia have retrocollis. Some patients with tardive dystonia look similar to those with idiopathic dystonia, but the movements tend to be concentrated in the same place as other tardive movements are concentrated—in the shoulders and up. Some patients with tardive dystonia have a jerky in-turning of the arms, but blepharospasm, jaw clenching or jaw opening and arching of the back are not uncommon. Dystonia of the legs is uncommon. Several clinical clues point to tardive dystonia: these patients tend to have rapid, myoclonic, jerky dystonia, which is less common in idiopathic form. Many have akathisia or tardive dyskinesias, which are never seen in idiopathic dystonias. Finally, most patients with dystonia get worse when they walk around and improve when they lie down. In a large minority with tardive dystonia, the opposite is true: they are forced to walk around all day, because when lying down they are practically in a two-point position, resting on the crown of the head and on their bottom.

Dr. Leppik: Dr. Greene, I always thought blepharospasm was a tic rather than a dystonia.

Dr. Greene: Unlike people with tics, those with hereditary dystonia have no preceding urge, no inner anxiety, they cannot suppress the blepharospasm, and except for occasional pain, they rarely have a physical sensation. Tics are probably the single most common movement disorder and therefore the most common cause for blepharospasm, but it is easy, in fact, to distinguish people with blepharospasm caused by tics from people with blepharospasm caused by typical dystonia whose mean age of onset is 60.

Dr. Wyllie: Dr. Andermann, will you describe your experience with clobazam?

Dr. Andermann: Clobazam is a benzodiazepine available in Europe under a variety of trade names. For a number of years it has not been available in Canada, except under compassionate release, because it induces thyroid cancer in old male, but not old female, rats.

Last spring, however, the drug was released to 1,277 patients and the company has collected information on approximately 800 of these patients treated by about 40 neurologists across the country.

Basically, two groups of patients benefited most: those with focal temporal-lobe epilepsy and those with secondary generalized epilepsy. Both groups included patients who did extremely well, but after three or four months the rate of recurrence of the epilepsy was high. We don't yet know which patients will have a sustained effect and which will have recurrence. The drug has a long half-life and is very well tolerated with few side effects, but tolerance is a problem.

Dr. Wyllie: Dr. Holmes, have your patients experienced seizure exacerbations during intermittent therapy with clonazepam?

Dr. Holmes: My experience has been very limited. Some of my patients have had seizures on the off days, some have not. I have found, though, that if a patient develops tolerance to clonazepam, restarting the dose after a few months' layoff rarely works.

Dr. Leppik: Dr. Andermann, will you comment on the statement in the *PDR* that the combination of clonazepam and valproic acid can cause seizures?

Dr. Andermann: This is a perfect example of the kind of canard that creeps into the literature and, once there, is impossible to remove. Dr. Jeavons had written that the combination induces absence status, but later retracted the statement. Unfortunately, the retraction never had the same impact as the original statement.

Dr. Leppik: On my review of the literature, there is very little evidence of the teratogenicity of benzodiazepines. Yet given the incidence of birth defects, the issue could be problematic. Is there good scientific evidence, either pro or con, about the use of benzodiazepines during pregnancy?

Dr. Schenck: I would be very reluctant to treat a pregnant woman with a benzodiazepine.

Dr. Leppik: But the real problem, I think, is that women are undertreated in this country, probably because of excessive concern about teratogenicity. That's not fair.

Dr. Tesar: The majority of our panic patients are women in their 20s and 30s, and this problem comes up often. Lacking hard data one way or the other, we counsel them to reduce and possibly discontinue the benzodiazepine because of concerns not only about teratogenicity, but also long-term behavioral effects on the child, which have not yet been described, but hypothetically possible. On the other hand, we don't know how dangerous it may be for a fetus to be exposed

to frequent panic attacks during the first trimester, so many of our patients do stay on benzodiazepines.

Dr. Greene: With a disorder like the REM sleep disorder, the risks of running around in the middle of the night and falling down a flight of stairs seem greater than the risks of treatment with benzodiazepines.

Dr. Andermann: We also face this question in the treatment of epilepsy. All the anticonvulsants are potentially teratogenic to a greater or lesser extent. Some patients can reasonably be treated with a drug such as valproic acid during pregnancy, whereas others should more reasonably have the drug withdrawn. The decision whether or not to treat depends on the seizure pattern and the risks from the seizures.

Dr. Schenck: What effect does pregnancy have on epilepsy?

Dr. Leppik: Seventy-five percent of women do not have an increase in severity of seizures during pregnancy. Those who do have worsening are generally uncontrolled prior to the pregnancy. The increase may have to do more with changes in drug pharmacokinetics, such as dropping blood levels, than with any intrinsic epileptogenic phenomenon during pregnancy. It has been clearly shown that phenytoin, carbamazepine, phenobarbital and valproic acid serum levels are decreased during pregnancy unless doses are increased, and this may account for the 25 percent of patients who have more seizures.

DISCUSSION III

Dr. Leppik: What are the most recent data on benzodiazepines as antianxiety agents?

Dr. Tesar: Chlordiazepoxide, brand name Librium, of course, is effective as an antianxiety and antipanic agent, but other benzodiazepines, such as diazepam and lorazepam, also are effective in equipotent doses. For example, one study showed that about 40 mg of diazepam was as effective as 1 mg of alprazolam.

Dr. Leppik: How do you choose the optimal drug for individual patients?

Dr. Tesar: It depends largely on patient acceptance. Side effects may be more intense with lower-potency agents that require higher doses. But when we compare clonazepam and alprazolam, for example, the longer half-life and slower onset of action of clonazepam make it a more favorable agent in certain patients. Alprazolam is a good drug for a number of patients with panic attacks, but in those who develop interdose symptom recurrence and rebound, clonazepam is superior. In short, there is no single best agent for panic disorder, but some patients respond better to one drug or another.

Dr. Ryan: I recall a report from Spain a few years ago, published in the *Annals of Neurology*, about sporadic and familial hyperexplexia. The sporadic patients were treated with clonazepam and failed, and the familial patients were not treated. Would you comment on the sporadic form of the disease and the efficacy of clonazepam in hyperexplexia?

Dr. Andermann: I wrote to the editor of the *Annals* because the article didn't make clear exactly what these people had. The familial disorder in the four or five reported siblings was clearly startle disease. The family may have been hyperstartlers, as Simons called them. In any case, they were not well studied, and it's difficult to know what kind of treatment they received.

I have seen one sporadic case, and his responses were typical in every respect—quite similar to the familial cases. I studied his family carefully, and no one else was affected.

Dr. Ryan: Are you aware of any experience in treating infants with startle disease with clonazepam?

Dr. Andermann: No. The stiff baby syndrome evolved as a separate entity and only later did physicians realize that this was really a manifestation of startle disease. As you know, the startle reaction is not the major feature in infancy; rigidity and apnea are.

Some people still persist in regarding stiff baby syndrome as being related to stiff man syndrome, or continuous muscle activity—but really the stiff baby syndrome is a different condition. People remain unconvinced that the stiffness in these infants is a manifestation of startle disease.

The posture of the stiff baby is characteristic: when the baby is on his back, his head is flexed forward and his legs are extended. The posture is unlike that in the spastic child.

When a family with hyperexplexia is identified, we must monitor the pregnancies and the deliveries and follow these children carefully. How they will respond as neonates to clonazepam is an open question.

Dr. Ryan: It seems that so often families with this syndrome live in a remote rural area, and tend to deny their symptoms.

Dr. Pollak: Do patients with hyperexplexia have lower intelligence than normal?

Dr. Andermann: In the Spanish family described in the *Annals of Neurology*, there were four children. The two affected ones were definitely less bright; one had low-average intelligence, and the other had an IQ of 85

or 90. The two normal children had higher intelligence. The one sporadic case in my own practice has behavioral problems and was a delinquent in his teens, but his sister is a very bright, able young woman. Bruyn wrote about the association between hyperexplexia and low IQ in the first pedigree. However, in the family from Cape Breton and in Dr. Ryan's patients, there was no low intelligence. There is clearly some degree of variability.

Dr. Schenck: Dr. Andermann, there seems to be an opposite condition from startle disease, namely, cataplexy, characterized by a sudden hypotonia or atonia without loss of consciousness after a novel stimulus. Do you have any thoughts about the contrast between these two conditions?

Dr. Andermann: One point of similarity is that in startle disease a stimulus produces rigidity and a fall; it is not a loss of tone but rather an increase in tone to maintain posture. I don't know the neurophysiology of this or how to explain it.

Dr. Greene: I don't know what the physiology is, either, but in startle disease the initial response is inhibition—the first thing you see is the tonic jaw reflex—followed by a rebound excitation.

Dr. Schenck: How short is the inhibition?

Dr. Greene: Well below a second. Some people find two phases of inhibition, both very brief.

Dr. Leppik: It might be useful to study those patients with very rapid video EEG.

Dr. Andermann: We have done that. These patients have a centripetal spread of the response. If you give them clonazepam, the response is much attenuated, but the latency period is not prolonged, just as Hallett had predicted.

Dr. Greene: My only suggestion is to try L-dopa, because we know from patients with Parkinson's disease and abnormal persistence that the electrophysiologic correlate disappears after treatment with dopa or dopamine agonists.

Dr. Pollak: Is there anything to indicate an increase in arousal or anxiety in people with hyperexplexia? They are very sensitive to sensory stimuli and one would think that perhaps arousal might also be a manifestation of that response.

Dr. Andermann: One cause of anxiety in startle disease is the uncertainty of gait after medication is discontinued. Patients tend to walk around holding onto people or onto the wall, with a broad-based gait, ready to fall at any time. It is a striking and typical manifestation in patients with startle disorder.

Dr. Ryan: One of our patients was a woman in her 70s who had walked with a cane all her adult life. When she was put on clonazepam, she threw the cane away.

One question about the EEG findings in hyperexplexia. Were the epileptiform abnormalities interictal?

Dr. Andermann: Yes. One of the girls I treated had spike and wave discharges when she was startled that were certainly not epileptic. The boy had vertex spikes. Bruyn mentioned that some of these patients had epileptiform discharges, with a CNS maturational defect, of which startle disease is only one expression. What surprises me is that benzodiazepines do not lose their effectiveness in this condition.