## Pisa Syndrome and Atypical Antipsychotics

TO THE EDITOR: Pisa syndrome, or tonic flexion of the trunk, long considered a side effect of prolonged exposure to conventional antipsychotics, has recently been reported as occurring with atypical antipsychotics (1). It occurs mostly after changes in antipsychotic therapy. We report this syndrome appearing after the discontinuation of aripiprazole and the addition of clozapine.

**Ms. A, an 82-year-old woman, was admitted with major depressive disorder with psychotic features and demonstrated microangiopathic cerebrovascular disease upon neuroimaging. She had persecutory and referential delusions. At admission, she was taking venlafaxine, 375 mg/day, and lithium, 450 mg/day, in divided doses. Treatment with aripiprazole, 15 mg/day, was initiated with no improvement after 2 weeks of treatment. Ms. A had been given olanzapine, quetiapine, and risperidone before but had developed significant extrapyramidal symptoms, even at small doses. Since she had never been treated with clozapine, it was added at 12.5 mg/day and increased over 9 days to 150 mg/day while aripiprazole was discontinued without a taper. Two days after the increase in her clozapine dose from 100 to 150 mg/day, Ms. A was observed walking with a tilt toward the left. Her physical examination showed tonic flexion of the spine toward the left, along with a slight backward rotation. Her speech was slurred, and she had cogwheel rigidity and tremors. Her mental status was unchanged, and she had no focal neurological deficits. She had no history of scoliosis or idiopathic dystonic syndrome. Ms. A received lorazepam, 2 mg, parenterally once and was given 25 mg b.i.d. of diphenhydramine while her clozapine dose was held steady for the next 3 days and her lithium dose was tapered and stopped. Her dystonia and extrapyramidal symptoms resolved completely within 2 days. However, they reappeared when clozapine was initiated at 75 mg/day while she continued to take diphenhydramine. Clozapine was then discontinued with the resolution of her motor symptoms, and Ms. A was subsequently treated with ECT.**

A rechallenge with clozapine was associated with the reemergence of Pisa syndrome and thus can be implicated in this side effect. A PubMed search revealed only three previous reports of clozapine-associated Pisa syndrome (2–4). In most of these cases, the patients were elderly women exposed to typical antipsychotics and having an underlying disorder of the CNS, including brain atrophy on neuroimaging. However, to our knowledge, this is the first report of Pisa syndrome reemerging after reinitiation of clozapine. Risk factors for this syndrome include combined pharmacological treatment, old age, female gender, and the presence of an organic brain disorder (4), all of which were present in this patient. Aripiprazole, although discontinued about 11 days before Ms. A developed Pisa syndrome, cannot be ruled out as a potential cause of this side effect because of its long half-life of 60 hours. Moreover, Pisa syndrome has been described with antipsychotic discontinuation, which may be due to dopaminergic-cholinergic imbalance, the most accepted hypothesis for this syndrome (1, 5). Thus, caution is advised when changing atypical antipsychotic regimens in patients with risk factors for Pisa syndrome. As indicated by this and previous reports, reduction in dose or discontinuation of the antipsychotic drug remains the first-line treatment for Pisa syndrome. Besides this, about 40% of the patients with Pisa syndrome also show a therapeutic response to anticholinergics (1).

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## Aripiprazole and Parkinson's Disease Psychosis

TO THE EDITOR: Psychosis occurs in up to 30% of patients with Parkinson's disease, predominantly as a side effect of dopaminergic treatment (1). These patients do not generally tolerate classical antipsychotic drugs. Aripiprazole is a novel antipsychotic substance acting as a partial agonist at dopamine $D_2$ and serotonin 5-$HT_{1A}$ receptors and as an antagonist at 5-$HT_{2A}$ receptors (2). We report a severe exacerbation of Parkinson's disease without improvement of psychosis during treatment with aripiprazole.

**Mr. A was a 70-year-old Caucasian man with a 16-year history of Parkinson's disease who was admitted to our department for drug-induced psychosis. Clozapine had been successfully tried but was discontinued because of agranulocytosis. On admission, treatment consisted of 1200 mg/day of L-dopa/carbidopa, 375 mg/day of L-dopa/benserazide, 1200 mg/day of entacapone, and 800 mg/day of quetiapine. His physical examination revealed a slight hypomimia, a stooped posture, reduced automatic movements without major difficulty walking and turning around, and a slight resting tremor of the right hand. Mr. A's score on the Unified Parkinson's Disease Rating Scale (UPDRS) was 43, and his illness stage on the Hoehn and Yahr scale was 1.5. There were infrequent (two or three per week) off-episodes, with severe akinesia and rigidity lasting up to 1.5 hours. Otherwise, Mr. A's daily activities were only moderately affected; he was a professional artist, and he produced skillful watercolor paintings during his stay. He exhibited frank psychosis with vivid visual, auditory, and tactile hallucinations and fearful delusions of persecution with maximum severity at night. The results of laboratory tests and the findings of cranial magnetic resonance imaging, ECG, and electroencephalography were normal. L-Dopa/benserazide and quetiapine were discontinued with no apparent clinical change. On day 4, aripiprazole was started at 5 mg/day and increased by 5**

**mg every third day up to 10 mg t.i.d. Under this treatment, progressive hypokinesia and rigidity evolved into complete akinesia, including anarthria. By day 11, parenteral fluid substitution and gavage nutrition became necessary (UPDRS score=120, Hoehn and Yahr stage=5). Hallucinations and delusions, however, continued unmodified. L-Dopa/benserazide was reestablished and increased to 125 mg q.i.d. Mr. A's motor symptoms improved only marginally (UPDRS score=101). Nutrition was insufficient, and a weight loss of 8 kg occurred. On day 37, treatment failure was declared, and aripiprazole was replaced by ziprasidone, 40 mg/day, and increased up to 80 mg/day over 3 days. Within 2 weeks, the delusions and hallucinations had subsided completely. Motor impairment also improved to a large extent. Sitting, walking, and eating was possible, and Mr. A was able to successfully resume painting (UPDRS score=42).**

Dose reduction of dopaminergics and/or treatment with typical neuroleptics are known to improve drug-related psychosis in Parkinson's disease but may worsen parkinsonism. The remaining therapy options are quetiapine, clozapine, and ziprasidone, but clozapine use is limited by hematological side effects, quetiapine is not always effective, and experience is lacking regarding ziprasidone. Since drug-related psychosis in Parkinson's disease is a consequence of dopaminergic overstimulation combined with deficient dopaminergic transmission, partial agonism might be a promising approach. This hypothesis, however, is not supported by our observation of a massive deterioration of motor symptoms without improvement of psychotic symptoms under treatment with aripiprazole.

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## Suicide Attempt Due to a Misunderstood HIPAA Notice

TO THE EDITOR: The federally mandated Health Insurance Portability and Accountability Act (HIPAA) went into effect in April 2003 with the intent of providing standards for protection of patients' privacy. Attention has been given to the administrative burden that these requirements have placed upon health care providers and health care systems (1, 2). However, little focus has been placed on the potential negative impact that these new regulations will have on patients. We report a case in which HIPAA privacy notification was judged as a significant factor in precipitating a serious suicide attempt by an elderly woman due to a misunderstanding of the meaning of notification.

**Ms. A, a 79-year-old woman without a previous psychiatric history, was found in a pool of blood as a result of a self-inflicted gunshot wound to her left chest and the left upper quadrant of her abdomen. She was hospitalized, and a psychiatric consultation was obtained.**

**Ms. A's husband reported that she had recently received a letter from her insurance company regarding the new HIPAA policies. She misinterpreted the letter to mean that her insurance company was discontinuing her coverage. Ms. A reported that for several weeks she had planned to kill herself with a rifle because she feared that she had skin cancer (a physical examination did reveal a benign-appearing skin lesion on her chest) and believed she had no medical insurance to pay for treatment. She stated that she did not want to be a burden to her husband, physically or financially. She also admitted having a depressed mood, feelings of worthlessness, and loss of interest. She reported no other symptoms of major depression or previous episodes of depression.**

Legislative bodies need to be aware of the potential unanticipated negative impact of new laws. This case provides an example of such; others may follow. Patients with active medical, cognitive, or psychiatric illnesses may be more vulnerable to misinterpretation. Language in our patient's notice indicating who may have access to—and potential disclosure of—her protected health information may have contributed to her misunderstanding. Misinterpretation may also be related to the source of the notification (i.e., hospital, physician's office, or insurance company). In addition to patient confusion over the meaning of these new regulations, there is a potential for decreased communication between medical providers and families in the care of patients resulting from misunderstanding and fear of noncompliance with these complex regulations in a medical system already stressed by economic and regulatory pressures that are not conducive to effective communication. Ongoing evaluation of adverse events related to HIPAA notification should be part of future revisions of the act.

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## Worsening of Hyponatremia With Electrolyte-Containing Beverage

TO THE EDITOR: Many clinicians use electrolyte-containing beverages to try to improve electrolyte balance in schizophrenia patients with polydipsia-induced hyponatremia. Although oral sodium chloride tablets transiently appear to improve hyponatremia (1), there is little evidence of the efficacy of electrolyte-containing drinks for such patients (2). Recently, however, a man who had life-threatening episodes of hyponatremia-induced coma because of his inability to control his polydipsia was treated with some success with an electrolyte-balanced sports drink (3). Described here is a polydipsic patient whose electrolyte status was worsened by attempting to substitute the sports drink for water.

**Mr. A, a 47-year-old man with a history of schizophrenia of over 25 years' duration, was hospitalized when he became psychotic after losing his medication (risperidone, 4 mg/day, and fluoxetine, 20 mg/day, since 1999). The medication was resumed, but improvement occurred slowly. At admission, his sodium level was 126 mmol/liter, and a review of his records showed levels fluctuating from 125 to 133 mmol/liter during the previous 2 years. His past medical history was otherwise unremarkable, and there was no significant history of alcohol or drug abuse.**

**Frequent compulsive consumption of water was observed. Other causes of hyponatremia, including hypothyroidism, renal insufficiency, adrenal insufficiency, and the syndrome of inappropriate antidiuretic hormone secretion, were ruled out. Magnetic resonance imaging of the brain revealed mild ventricular enlargement and generalized atrophy.**

**Attempts to limit his fluid consumption were enacted but were difficult to enforce. He was encouraged to substitute an electrolyte-containing beverage when he could not control his urge to drink water. He liked the beverage and consumed large quantities of it. Within 2 weeks, his sodium level gradually decreased to 118 mmol/liter, and he became confused and lethargic. He was then placed on closely monitored fluid restriction, and his sodium level rose to 128–134 mmol/liter, thus improving his mental status. Mr. A later revealed that he had thought that the beverage was a suitable substitute for water because of its salt content and that he could safely drink as much of it as he wanted. Thus, he had made no attempt to limit his intake.**

Although the beverage he liked contains more electrolytes than other commercially available sports drinks, it still contains only 20 mmol/liter of sodium (110 mg per 8 fluid oz) (2). For the volume one would need to consume, drinking these beverages would appear to be a relatively inefficient method of increasing one's sodium level. In addition, freely allowing hyponatremic patients access to such beverages may tend to encourage rather than discourage fluid consumption in a population that is already polydipsic. Although electrolyte-containing beverages could help certain polydipsic hyponatremic patients, treatment in most cases might better focus on preventing or reversing deficits in water balance rather than trying to limit their impact with supplemental electrolytes.

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## γ-Hydroxybutyrate Dependence With Social Phobia

TO THE EDITOR: γ-Hydroxybutyrate (GHB), an endogenous γ-aminobutyric acid (GABA) metabolite with a short half-life, is a neurotransmitter and an emerging drug of abuse. First isolated in 1960, GHB was found to be a CNS depressant with similarities to classical sedatives/hypnotics, such as barbiturates and benzodiazepines. GHB binds reversibly to specific GHB receptors, although its mechanism of action is poorly understood (1). Clinically, it has been used as an anesthetic and to treat alcohol and opioid dependence (2), and it has been recently approved by the Food and Drug Administration for the treatment of narcolepsy. In the last decade, the use of GHB as a club drug (sold as "liquid X," "liquid ecstasy," "soap," "salty water," etc.) dramatically increased in the United States because of its mild euphoric and sedative effects. Case reports of physical dependence and of a severe withdrawal syndrome have been reported (1). We report on a patient who "successfully" self-treated his social phobia with GHB and became dependent.

**Mr. A was a 24-year-old highly educated European man who became psychiatrically ill with symptoms of social phobia at age 15 without having any other psychiatric disorder, according to DSM-IV. Because of his symptoms, he feared and avoided a variety of social and performance duties required during his university studies. During a practical course in China 4 years before, he followed the advice of a French physician and self-administered GHB, finally in a dose of 20 g/day.**

**GHB was obtained by means of the Internet and applied every 90–120 minutes. According to Mr. A, his symptoms of social phobia completely vanished under GHB treatment. However, sleep disturbances appeared, and finally, a single sleep period did not exceed 4 hours. Two hours after each drug administration, he experienced withdrawal symptoms, such as agitation, insomnia, sweating, trembling, tachycardia, and overheating. Six attempts at self-managed abstinence were unsuccessful. Finally, he applied to our institute and was admitted to the ward. GHB withdrawal with transient administration of diazepam (up to 40 mg/day) was successfully accomplished without complications. We started treatment with paroxetine and cognitive behavior therapy. We applied the Liebowitz Social Anxiety Scale before and after withdrawal and observed 70% less total social anxiety than during GHB intake. This is well above the 39.1% mean reduction in score after paroxetine treatment, as reported by Stein et al. (3).**

To our knowledge, this is the first report of a patient who self-treated his social phobia—the third most common psychiatric disorder—with GHB and who subsequently developed GHB dependency. GHB has been shown to possess anxiolytic effects in some animal models (1). However, anxiolytic properties in humans apparently have never been studied explicitly. Because of the potential anxiolytic properties of GHB, patients with anxiety disorders may be at a higher risk of abusing GHB and becoming dependent on this sedative drug. In addition, its anxiolytic properties, the therapeutic potential of GHB, and the exact mode of action deserve further research.

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## On Biology, Phenomenology, and Pharmacology in Schizophrenia

TO THE EDITOR: In a recent issue of the *Journal,* Shitij Kapur, M.D., Ph.D., F.R.C.P.C., described the linkage between biology, phenomenology, and pharmacology in schizophrenia (1). Two articles in the British literature from 1961 (2) and 1966 (3) seem to dovetail nicely with Dr. Kapur's elegantly crafted framework.

The British authors argued against Federn's 1953 theoretical model of psychosis (4) as an impairment of ego functions and suggested that the breakdown in interpersonal difficulties was a reaction to a primary cognitive disturbance in the field of attention and perception and that all schizophrenia symptom profiles could be interpreted as reactions to this basic disorder. Their methods consisted of meticulously recording clinical interviews with schizophrenia patients. They were not aware of the central role of dopamine in reward and reinforcement. Thus, they were not able to describe the reported abnormalities of perception in terms of aberrant salience rather than as phenomenological entities alone.

Dr. Kapur's convincing hypothesis presents strong experimental, pharmacological, and neurobiological data to help one understand the mass of schizophrenia phenomenology previously described and ascribed to varying, now presumably incorrect, hypotheses.

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TO THE EDITOR: I would argue that Dr. Kapur's model of psychosis as aberrant salience is important, not because he fingered dopamine as the culprit in psychosis, but because he emphasized that any meaningful neurobiological model must account for cross-sectional as well as longitudinal clinical observations. While it is implicit in his discussion, I wish he had stressed more that intimate knowledge of descriptive psychopathology and phenomenology is essential to building such clinically informed models. To illustrate this, I apply Dr. Kapur's model to a disease other than schizophrenia: alcoholic hallucinosis.

Our patient was admitted to an inpatient unit with a well-formed persecutory delusional system and auditory hallucinations following years of heavy drinking. He had attempted to make cassette tapes of the voices he heard saying derogatory things. No antipsychotics were given, and he made a *restitutio ad integrum*. Two weeks after admission, he sat down with me to listen to the tapes. After intently listening to an empty tape, he agreed with me that there was nothing recorded, but he could not explain why and stated, "I know that the voices are on there because I heard them and recorded them."

It is instructive to use this case to view the lack of insight into past psychosis and memories of delusions as opposed to delusional memories from within Dr. Kapur's framework. Memories of delusions can be defined as the accurate recollection of deluded thoughts and experiences that a person had while psychotic. These memories are not typically challenged once the person has recovered but can become integrated into the person's experience of himself. Memories of delusions are not to be confused with delusional memories (1): the latter are recollections of past events that either never happened or that happened but become meaningfully reinterpreted in the context of current psychosis. Delusional memories are evidence of ongoing psychosis and are potentially responsive to antipsychotics. If memories of delusions are not recognized and are confused with actively ongoing psychosis, patients are inappropriately diagnosed and treated.

Even though the patient in my case report was wrong in his conviction that there should be voices on the tape, it would be wrong to label him as currently psychotic. Rather, he had poor insight into his past psychosis. He did not recognize his previous psychotic state as a morbid change in himself. Most important, antipsychotic medication is not indicated since the pathological, meaning-imbuing mechanism is no longer present. Only psychological mechanisms will reinterpret past experience and lead to insight into past psychosis. Clinically, we know that this is difficult because there is continuity between the experience of psychosis and normality and because psychotic experiences are even more compelling than normal experiences since they are imbued with so much salience.

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TO THE EDITOR: Such an extravagantly comprehensive synthesis perhaps is permitted from Dr. Kapur, given his significant contribution to schizophrenia research. He appears to favor a simple linear relation between excess dopamine and abnormal salience, with antipsychotics "damping down" aberrant salience. This model of schizophrenia based on a quantitative change in dopamine function struggles to accommodate receptor imaging studies of antipsychotic drug action. Profound dopamine blockade produces little clinical benefit in up to 30% of schizophrenia patients. The most effective antipsychotic, clozapine, has only relatively modest dopamine $D_2$ antagonism. At issue is not *whether* but *how* dopamine function in schizophrenia is abnormal. These findings seem more

consistent with a more complex qualitative change in dopamine function. The efficacy of antipsychotics may depend on their dopaminergic antagonism but may be relatively independent of its magnitude.

The difficulties in accounting for the psychological mechanisms of psychosis are similar to those just presented in relation to the neurochemistry of schizophrenia. Actually, since the mechanism of normal belief formation remains unknown, it might appear premature, even presumptuous, to propose a mechanism for abnormal beliefs. Dr. Kapur adhered to a viewpoint common in modern cognitive psychology that supposes that psychotic beliefs reflect a quantitative change from normal belief mechanisms. Such an approach has led to the specific cognitive therapy of psychosis. But as with dopamine antagonism, cognitive therapy is not as effective as it should be if this view of psychosis is correct. The alternative is that psychosis involves a qualitatively distinct belief mechanism. While this does not immediately suggest novel therapeutic approaches, it has been previously suggested to account for the symptoms of schizophrenia (1).

What matters is not whether ideas are true but whether they are useful. The last decade has witnessed the introduction of a veritable cornucopia of new treatments. Such times probably needed a theoretical account that predicted the success of these treatments. In this respect, Dr. Kapur's thesis seems a good few years out of date. The inadequacy of current treatments and the persistence of resistant symptoms of schizophrenia suggest a need to reevaluate our current understanding of psychosis.

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TO THE EDITOR: Dr. Kapur provided an interesting review of "the emerging understanding regarding the role of dopamine as a mediator of motivational 'salience'" (p. 13). But can ideas that emerged well over a decade ago (1, 2) still be "emerging" today? It is, of course, possible that Dr. Kapur is unaware of these forerunners; at any rate, he does not cite them.

Dr. Kapur states his central proposal as follows: "In psychosis there is a dysregulated dopamine transmission that leads to stimulus-independent release of dopamine. This neurochemical aberration usurps the normal process of contextually driven salience attribution and leads to *aberrant assignment of salience to external objects and internal representations*" (italics in original) (p. 15). In considering the relationship of this proposal to "other models and ideas," he states further that none of them "specify how this dysregulation leads to symptoms" (p. 18). In contrast, he claims that his model "provides a heuristic for 'consilience'…between the neurochemical biology of psychosis and the…experience of psychosis" (p. 17).

My colleagues and I made a similar proposal in 1991, in greater anatomical and physiological detail and with similar claims for bridging the neural basis of psychosis to its symptoms. This article (2) appeared in a widely cited journal, *Behavioral and Brain Sciences,* whose exacting refereeing process ensured that we made proper reference to our own forerunners. It did not pass unnoticed. Over the period 1991–1999, it was the eighth most frequently cited article in schizophrenia research (http://esi-topics.com/schizophrenia/papers/a1.html). Its authors, including David Hemsley, Joram Feldon, and myself, have developed, applied, and reviewed these initial ideas in further publications (e.g., references 3–6). We also proposed a number of empirical tests of our hypotheses. One, a disruption of latent inhibition by augmented dopaminergic transmission in the nucleus accumbens, investigates just that process of "aberrant assignment of salience to external objects"—or "spurious novelty" (7)—that is central to Dr. Kapur's model. One might have expected him, therefore, to seek support in, or at least discuss, the abundant data concerning disrupted latent inhibition gathered since 1991 in numerous experiments with both animal and human subjects (4–7). Instead, in a lone mention, he dismisses latent inhibition as a "model of attentional habituation" (p. 18), a simplistic account that was considered and dismissed in our 1991 authors' response to multiple peer review in *Behavioral and Brain Sciences* (2). We stressed then, just as Dr. Kapur did, the critical role of *contextual* dependence of salience attribution, applying this concept in particular to latent inhibition and its disruption.

There is insufficient space in a brief letter to provide further details of these parallels (they are available upon request). It will no doubt seem to some (as it does in part to me) pettifogging to mention them, but science is a collective enterprise. We each place only a small brick in the wall—all the more reason that one should note carefully how much of the wall has been built already by others.

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## Dr. Kapur Replies

TO THE EDITOR: I thank Drs. Crane and Freudenreich for emphasizing that descriptive and empirical studies of psychopathology are as important as neuroscientific discoveries in any brain-mind syntheses and for drawing attention to the seminal work by Chapman and colleagues as an early example of careful attention to phenomenology and psychopathology. Dr. Freudenreich provides a good example of a subtle yet

remarkable difference between "delusional memories" versus "memory of a delusion." Unless neuroscientists play attention to such details, the powerful new sciences may end up chasing elusive targets.

Dr. Jones criticizes my article for providing a simple model of schizophrenia based on quantitative change in dopamine function. The target article is a model of psychosis, not schizophrenia (p. 18 in my article). While it argues for a prominent role for dopamine, it does not claim any exclusivity for it (p. 18). Dr. Jones points out that dopamine-based therapies do not work for nearly one-third of the patients, and therefore, these dopamine-related ideas may not have relevance to their psychosis. This is a fair critique. However, little is known about the biology of nonresponders that is reliable and replicable. There are no diagnostic or predictive markers of nonresponse. The only consensus is that some of them respond to clozapine, but then clozapine binds to over a dozen receptors, precluding any simple conclusions. Thus, the reason I did not attempt to explain the nonresponder issue is not that it is unimportant but because I found it difficult to synthesize the information into a coherent narrative.

Dr. Gray criticizes the article for omitting reference to earlier articles by him and his colleagues, most prominent among them the article in *Behavioral and Brain Sciences* (1991). The omission is regrettable, it was unintentional, and I missed that article just as it seems to have escaped the attention of MEDLINE. Regardless, the article by Dr. Gray and colleagues also tried to address how a neurobiological lesion might lead to symptoms by means of the disruption of a core psychological process. However, there are major differences. The focus of their claim is a putative neuroanatomical lesion (of the hippocampus or accumbens), not the clinical picture or phenomenology. The core psychological lesion in their model is a "failure…to integrate stored memories…with ongoing motor programs," as opposed to concepts of reward/salience, as in my article. Apart from the fact that antipsychotics are seen as dopamine blockers, little attention is paid to the nature and phenomenology of antipsychotic response and less still is said about the process of symptom resolution. As for the critique that I unfairly dismissed latent inhibition as a model of attentional abnormalities, some of the authors of the article by Dr. Gray et al. also see it as a model of attentional deficits (1), and others question whether it models attentional deficits at all (2, 3). Furthermore, the single largest clinical study of latent inhibition failed to find evidence for a disruption of latent inhibition or for the effects of treatment on latent inhibition (4). Nonetheless, I agree with their final point: that this discussion belonged in the original article, not here as an afterthought.

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