

Dr. Ananth Replies to Drs. Carroll and Lee “Catatonia Is a Risk Factor for Neuroleptic Malignant Syndrome”

Sir: I thank Drs. Carroll and Lee for their excellent comments¹ and for providing additional viewpoints through which to analyze the case reports and subtype neuroleptic malignant syndrome (NMS). They have clearly described the additional risk factors for NMS to be considered.

As we focused on NMS only and the cases reviewed were already diagnosed as NMS, we did not go into the details of differential diagnosis. However, many of the reports indicated an absence of extrapyramidal symptoms (EPS) prior to NMS, indicating that EPS occurred after NMS. I fully agree with the authors that the other risk factors for NMS need to be assessed in a clinical setting. Much of the information that they would like to analyze was not available in the case reports.

Carroll and Lee's letter highlights the importance of non-response to benzodiazepines and nonresponse of EPS to anticholinergic medications as clinical indicators of NMS. These are clinically very useful.

Dr. Ananth reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Jambur Ananth, M.D.

University of California, Los Angeles
Los Angeles, California

Interactions of Cyclobenzaprine and Tricyclic Antidepressants

Sir: Cyclobenzaprine, a tricyclic compound, is closely related to the tricyclic antidepressants. Structurally, it differs from amitriptyline only by 1 double bond. It is classified as a muscle relaxant and is used frequently in primary care settings to treat musculoskeletal pain, sometimes in combination with tricyclic antidepressants. As illustrated in the case below, it may interact both clinically and in laboratory tests with tricyclic antidepressants and appears to possess risks similar to those agents.

Case report. Mr. A, a 54-year-old man with a remote history of alcohol abuse, hypertension, lumbosacral disc degeneration, migraines, and depression, underwent a comprehensive evaluation for presyncope/syncope of unknown etiology. Descriptions of his episodes varied. In one episode, he awoke on the floor of his kitchen, having spilled food all around himself. He denied any associated visual, olfactory, or auditory sensations preceding the event or coughing, incontinence, light-headedness, or tachycardia at any point surrounding the event. In one presyncopal episode, he described feeling light-headed and collapsing against a nearby wall. No symptoms were noted leading up to this event; however, he did complain of nonradiating chest pain 5 minutes later, described as feeling like reflux symptoms. Another presyncopal episode was associated with immediate chest discomfort.

Mr. A's medications included, for migraines, divalproex sodium 500 to 750 mg/day (levels of 33.5-48.9 mg/L except for 1

value of 81.9 mg/L, most likely measured right after dosing), sumatriptan as needed, gabapentin up to 1200 mg 3 times per day, and meclizine 25 mg every 6 hours as needed (meclizine was discontinued during the syncope workup); for hypertension, furosemide 20 to 40 mg/day and atenolol up to 100 mg/day, both discontinued during the syncope workup; for back pain, oxycodone (with acetaminophen) up to 10 mg 3 times per day as needed; and for depression, citalopram 40 mg/day.

In addition, Mr. A was given nortriptyline 100 mg at bedtime to target pain, depression, and insomnia and cyclobenzaprine 60 to 80 mg/day for pain. An extensive workup including electrocardiogram, dipyridamole-thallium cardiac exercise tolerance test, magnetic resonance imaging of the brain, magnetic resonance angiography of the circle of Willis, and cardiac electrophysiology studies was negative. Video/electroencephalographic telemetry captured episodes of dizziness, but no loss of consciousness. Sinus tachycardia up to 130 beats per minute was noted, but no seizure activity was recorded, and the patient's blood pressure remained stable. Multiple urine toxicology screens were negative for substances other than prescribed medication, except for 1 positive result for cocaine, which the patient embarrassedly admitted to having used.

Mr. A's nortriptyline level was noted to be 406 ng/mL (therapeutic range, 50-150 ng/mL), and his dose was first decreased to 50 mg/day and then discontinued. Follow-up levels 3 and 4 weeks later were 631 and 400 ng/mL, respectively. Four months later, when the patient was off nortriptyline treatment and on cyclobenzaprine treatment (70 mg/day), his serum nortriptyline level was reported as 156 ng/mL, and another 5 months later, with the same dose, as 378 ng/mL. A reevaluation of this final sample, utilizing a high-performance liquid chromatographic (HPLC) assay, revealed the patient's nortriptyline level to be 0.

The patient presented a complex picture, and his various physicians considered many possible causes for his episodes, including orthostasis, seizures, cardiac arrhythmia, bilateral basilar insufficiency, cardiac ischemia, carotid hypersensitivity, anxiety/panic, and somatization, as well as factitious illness or malingering. A note was also made that "syncopal spells of his in the past have also been associated with misuse of prescription drugs" (apparently referring to nortriptyline), and surreptitious use was considered. This was ultimately thought to be unlikely, as the patient was receiving all of his care through the Veterans Affairs system, which allows tracking of all medications prescribed, and he had meager financial resources with which to obtain outside care. The wildly fluctuating "nortriptyline" levels were most likely due to varying intervals between cyclobenzaprine dosing and blood draw, as the patient's dose remained quite stable. Although numerous diagnoses were considered in the preceding case, cyclobenzaprine's contribution to the high reported levels of nortriptyline, as well as its possible involvement in clinical symptoms, was overlooked for almost a year. A definitive diagnosis was never made, but his syncopal and near-syncopal episodes disappeared on discontinuation of cyclobenzaprine.

Cyclobenzaprine was originally found to be an effective antidepressant, equivalent in efficacy to imipramine, with common side effects of dry mouth, sleepiness, tachycardia, and disturbances in visual accommodation.¹ When used as an antidepressant, it is dosed similarly to imipramine and amitriptyline, with doses of 150 to 250 mg/day being typical, but up to 400 mg/day utilized.¹ It has been reported to induce both mania and delirium.² In overdose, it appears to have risks similar to those of other tricyclics.³ One study⁴ appears to show that cyclobenzaprine is quite safe in overdose by itself; however, the mean ingestion in that chart review was 133 mg, with the largest

being 1 g. The more commonly used tricyclic antidepressants would also not be expected to cause frequent complications with single-agent ingestions similar to those in this study. Therefore, as with other tricyclic antidepressants used in the treatment of pain, low-dose ingestions of cyclobenzaprine appear quite safe.

Cyclobenzaprine is metabolized to desmethylcyclobenzaprine primarily by cytochrome P450 3A4 and 1A2,⁵ but it is unclear if this metabolite is clinically active and what its further metabolic fate is, making prediction of its interaction with other drugs difficult. It is known to interfere with laboratory assays for amitriptyline and nortriptyline, sometimes requiring sophisticated extraction and gas chromatography analysis to differentiate.⁶ However, as the above example illustrates, modern HPLC assays appear to differentiate at least between nortriptyline and cyclobenzaprine.

Cyclobenzaprine is generally described as being closely related to the tricyclic antidepressants. As the above discussion suggests, it would be more accurate to regard it as belonging to that class, both clinically and toxicologically.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Nicholas Z. Rosenlicht, M.D.
Kristin P. Riley-Lazo, M.D.
 Department of Psychiatry
 University of California, San Francisco
 San Francisco, California

Extrapyramidal Side Effects Associated With Aripiprazole Coprescription in 2 Patients

Sir: Aripiprazole, a novel atypical antipsychotic with a unique mechanism of action,¹⁻³ appears to be effective and well tolerated in most schizophrenic patients.² However, there has been little systematic investigation of aripiprazole's pharmacodynamic properties and side effect profile in the presence of other psychotropic agents, particularly in nonschizophrenic individuals. We report 2 cases in which aripiprazole, coprescribed with serotonergic agents, was associated with significant extrapyramidal side effects (EPS).

Case 1. Ms. A, a 29-year-old woman, had an 18-month history of progressively worsening depressive symptoms and hy-

pochondriasis with poor insight. She reported having "chronic fatigue syndrome," although numerous medical workups could not confirm this. Over the course of several months, she had 3 hospital admissions for depression and suicidal ideation. During the last hospitalization, Ms. A was started on treatment with venlafaxine extended-release, titrated to 225 mg q.a.m., as well as trazodone 50 mg q.h.s. and clonazepam 1.0 mg b.i.d. p.r.n. This regimen appeared to be well tolerated. Owing to the delusional quality of her somatic preoccupations, aripiprazole (15 mg/day) was added just prior to discharge.

Two days after discharge, the patient's mother reported that the patient had "developed Parkinson's disease," which had been diagnosed in the patient's grandmother. When evaluated the next day, Ms. A presented with new onset of shuffling gait, mask-like facies, cogwheeling, anxiety, and restlessness. Aripiprazole was discontinued, and over the next week, the patient's parkinsonian symptoms completely resolved.

Case 2. Mr. B, a 24-year-old graduate student, presented with depressive and obsessive-compulsive symptoms that responded well to sertraline. He also showed a persistent slow response time to questions, even after improvement in his depression. Over subsequent months, the patient began to show increasing psychomotor retardation, hypersomnia, and a continued, prolonged "lag" in his response to questions. This delay seemed to be autonomous, raising the suspicion that the patient was responding to internal stimuli; however, neuropsychological testing did not confirm a psychotic process. Nevertheless, Mr. B was begun on treatment with aripiprazole, up to 10 mg/day, concomitantly with sertraline, up to 200 mg/day.

The patient showed a marked reduction in his hypersomnia, and both his mood and academic functioning improved considerably. However, at 10 mg/day of aripiprazole, Mr. B developed severe akathisia. Addition of benzotropine (2 mg/day) had only a modest effect, and reduction of the aripiprazole dose to 5 mg/day also failed to resolve the akathisia. Ultimately, the aripiprazole was discontinued, and discontinuation was associated with deterioration in the patient's sleep and some recurrence of depressive and obsessive ideation. The akathisia gradually resolved after discontinuation of aripiprazole.

Aripiprazole is classified as a partial agonist at D₂ receptors, an antagonist at 5-HT_{2A} receptors, and a partial agonist at 5-HT_{1A} receptors.^{1,2} Aripiprazole appears to be effective and well tolerated in schizophrenic populations, with a low incidence of EPS.² In contrast, several anecdotal, postmarketing reports of aripiprazole-associated EPS have appeared,⁴ usually involving patients taking serotonergic medications with modest noradrenergic activity,⁵ e.g., paroxetine, fluoxetine, or nefazodone.⁴ One report of exacerbation of Parkinson's disease associated with aripiprazole—without reduction in psychotic symptoms—has also appeared.⁶ It is possible that our first patient's EPS was related, in part, to a genetic propensity for parkinsonism.

Neither of our patients clearly suffered from schizophrenia. Moreover, coprescribed antidepressants may have modified aripiprazole's neurochemical effects; e.g., sertraline has both serotonergic and dopaminergic effects, whereas venlafaxine is predominantly serotonergic in doses less than about 250 to 300 mg/day.⁵ The precise role of serotonergic, noradrenergic, and dopaminergic mechanisms in the cases reported must therefore remain speculative. Furthermore, it is possible that sertraline may have elevated blood aripiprazole levels in case 2.⁷ Similar pharmacokinetic interactions cannot be excluded in case 1.

There are virtually no published data regarding the neurochemical effects of aripiprazole in combination with antidepressants, nor does aripiprazole product labeling recommend such

concomitant treatment.⁸ Until these issues are clarified, it may be prudent to start some patients on low doses of aripiprazole (2.5–5 mg/day), while monitoring closely for EPS. Finally, although a “dose-time” relationship to EPS has not been confirmed with aripiprazole, slow titration to target dose may reduce the risk of EPS and akathisia with this agent.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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S. Tziporah Cohen, M.D.

Department of Psychiatry
Harvard Medical School
Boston, Massachusetts

Daphne Rulf, M.D.

Private Practice
Cambridge, Massachusetts

Ronald Pies, M.D.

Department of Psychiatry
Tufts University School of Medicine
Boston, Massachusetts

The second crucial question follows a positive answer to the first: “Was it *hearing* or some other experience (e.g., humming, remembering)?” This question may not suffice to discriminate hallucinations from obsessive imagery of music. The experience that a tune “keeps running through your head” is not uncommon and can be considered to be an (often mild) obsessive symptom. A high prevalence of this phenomenon in OCD patients is to be expected, and this may have inflated the prevalence of hallucinations in the study. Hermesh and colleagues acknowledged this problem, but their suggestion that in daily clinical practice musical hallucinations could be renamed “musical obsessions” is not satisfactory. Musical hallucinations and obsessive musical imagery are clearly different phenomena. A hallucination has the compelling sense of reality of a true perception,² whereas imagery, intrusive as it may be in its obsessive form, is merely its pale shadow. To ensure the truly hallucinatory nature of the phenomena, patients with spontaneous musical experiences could be asked whether the music they perceive sounds as vivid and real as music of external origin (e.g., the radio).

Dr. Teunisse reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Robert J. Teunisse, Ph.D.

Department of Geriatric Psychiatry
Adhesie GGZ Midden Overijssel
Deventer, the Netherlands

Dr. Hermesh and Colleagues Reply

Sir: We thank Dr. Teunisse for his comments regarding our article on musical hallucinations (MH)/musical obsessions (MO).

His first concern was that the 2 questions we used to assess MH may have caused a biased rate of MH in different mental diagnoses, due to more false-negative responses among psychotic patients. However, as mentioned in the Method section, following the 2 direct questions on MH/MO, the patients should also have been able to provide many more details on their past MH experience. These details either confirmed or refuted the occurrence of MH/MO and are currently under final analysis, with the aim of disentangling the MH/MO dilemma. The Geha Short Interview for Musical Hallucinations is an interview with patients, so explanations such as “music that others could not hear” and “where there was no radio, CD player, or record player in the room” were usually added.

In addition, our clinical experience with MH patients does not support the prejudiced idea that psychotic patients will hide and underreport their MH. On the contrary, while some of the schizophrenic patients did “de-simulate” their paranoid delusions and hallucinations, they were usually frank and reliable about their MH. They provided the explanation that based on their experience over time, people around them usually criticized them about regular hallucinations but not MH. Moreover, as mentioned in the Discussion section of our article (p. 194), we formed the impression that underreporting of MH is common among OCD patients who are ashamed of such a proof of their “insanity.”

Problems in Assessing Musical Hallucinations

Sir: Hermesh and colleagues¹ recently introduced a questionnaire for assessing musical hallucinations (the Geha Short Interview for Musical Hallucinations [GSIMH]) and reported a high prevalence of these phenomena in psychiatric outpatients and even a prevalence of 41.4% in those with obsessive-compulsive disorder (OCD). Discussing these interesting and surprising results, the authors stated that only further studies, using the GSIMH with other designated tools for assessing musical hallucinations, will clarify the issue of whether their instrument is reliable. However, upon examining the 2 questions they used to assess musical hallucinations, some suggestions to improve their questionnaire could be made already.

The first question in the GSIMH is, “Have you ever *heard* music that was not of external origin?” A lack of insight might lead psychotic patients to a (false) negative answer. To overcome this problem, patients could be asked whether they heard music without being able to locate the source, or music that other people in their surroundings did not hear.

Regarding the second debate of how to differentiate true MH from pseudo-MH, namely MO, it makes clinical sense to adhere to the tradition of assessing the degree of vigor, vividness, and ego-dystonicity. Along this line, we are currently analyzing our series of over 51 MH/MO cases, hoping to provide empirical data to support the rather theoretical ideas presented in our article.

Interestingly, similar parallel analysis is required for differentiating pathologic MH/MO from normal MH/MO, which is called *internal hearing*. Such normal hearing is a mandatory skill and aptitude of musicians and is not part of any psychopathology and, hence, should usually be excluded from the process of differential diagnosis.

We hope this letter satisfactorily replies to all points raised by Dr. Teunisse.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

Haggai Hermesh, M.D.
Ruth Gross-Isseroff, D.Sc.
Shai Konas, M.D.
Roni Shiloh, M.D.
Abraham Weizman, M.D.
Sofi Marom, Ph.D.
 Sackler Faculty of Medicine
Reuven Dar, Ph.D.
 Department of Psychology
 Tel Aviv University
 Tel Aviv, Israel

Development of an Atherogenic Metabolic Risk Factor Profile Associated With the Use of Atypical Antipsychotics

Sir: We read with interest the article by Alm eras et al.¹ reporting a worse metabolic risk profile in olanzapine-treated patients compared with risperidone-treated patients and a control group. While we agree with the authors on the need for research on this important topic, we believe the serious limitations to the methodology employed in this study significantly limit the interpretation and generalizability of their findings.

First, the nonrandomized, cross-sectional design introduces likely bias in the selection of patients assigned to risperidone and olanzapine. Additional factors biasing this study include the exclusion of patients receiving treatment for hypertension, dyslipidemias, endocrine disorders, or obesity, as well as those who had recently stopped smoking. The allowed patients therefore may have been in poorer health, as is commonly seen in schizophrenia^{2,3}; have had abnormal metabolic parameters; or otherwise have had poor health habits. The exclusion of these patients and any female patients limits the generalization of the results to more clinically relevant samples. Moreover, the substantial differences between the patient groups and the non-clinical control group, which consisted of nondiabetic and non-schizophrenic men, preclude meaningful comparisons.

Measurements were conducted in a cross-sectional manner, and no baseline data were collected for any of the variables of interest. Therefore, abnormal results on parameters may have been present even before patients had begun receiving risperidone or olanzapine. It is therefore inappropriate to conclude that olanzapine-treated patients had a "deterioration" in their metabolic risk profile, since this implies their profile was known to be better at baseline, which was clearly not the case. The fasting

measurements are also confounded by the potential for patients to surreptitiously break their fast. It is not clear from the description of the methodology in the article what safeguards were in place to ensure an adequate fast duration prior to blood draws.

In their analysis of the data, the authors report a total of 48 statistical comparisons. It is not clear from the article which analyses were driven by a priori hypotheses versus post hoc data analyses. There were no adjustments for multiplicity; with significance set at a level of $p < .05$, there is a high likelihood of chance (type I) errors.⁴

The clinical implications of weight gain remain a topic of considerable debate in the field. Contrary to what Alm eras et al. state in the introduction, weight gain is not always associated with noncompliance and in fact may be associated with therapeutic benefit in the case of clozapine^{5,6}; further understanding of this correlation is needed. When tolerability considerations impact compliance, other important risk factors that should also be taken into account include neuroleptic dysphoria,⁷ extrapyramidal symptoms,⁶ and tardive dyskinesia, which may be seen with other antipsychotics more than with olanzapine or risperidone. As stated by Meltzer,⁶ physicians should consider metabolic side effects as well as other risks and benefits of atypical antipsychotics. Twenty years ago, psychiatrists were satisfied with mere relief of positive symptoms, tardive dyskinesia was common, and returning to work or school was virtually unheard of. The benefits of atypical antipsychotic treatment include improved quality of life and, in some cases, improvement in social and work-related activities, which should be part of the risk-benefit considerations involved in treatment selection. We agree with the authors in that prospective, adequately controlled research is needed to improve clinicians' ability to choose the best interventions for each of their patients and assist them in managing concerns that may arise with the different therapies available while heeding the need for all patients to have routine metabolic screening.

Dr. Karagianis has received grant/research support in the past from Janssen.

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James L. Karagianis, M.D., F.R.C.P.C.
 Eli Lilly Canada, Inc.
 Scarborough, Ontario, Canada
Eduardo Dunayevich, M.D.
 Eli Lilly and Co.
 Indianapolis, Indiana

Dr. Alméras and Colleagues Reply

Sir: We are grateful to have been given the opportunity to reply to the letter by Karagianis and Dunayevich. We by all means agree that a cross-sectional study has limitations in its design. Our study should be considered as a first attempt to document the metabolic risk profile of patients who had been exposed for the same period of time to 2 atypical antipsychotics: olanzapine and risperidone. However, we disagree that our study has serious limitations for the following reasons.

First, patients treated with medications known to have a significant impact on the metabolic parameters studied (such as medications for hypertension and dyslipidemia) as well as individuals treated with any concomitant medications affecting the central nervous system were excluded. Including those patients would have added considerable noise in the interpretation of the data. We also disagree that, as a consequence, patients included in our study were in poorer health; in fact, the contrary is more likely. Including patients with complications requiring medical treatment would have generated a higher-risk sample.

In addition, the inclusion of a control group was actually an attempt to obtain a more balanced evaluation of the effect of this class of drugs on the metabolic risk profile. Our exclusion of women is justified by the well-documented gender difference in metabolic risk variables and in body fat distribution. On the other hand, we agree that metabolic disorders may have been present before patients began taking the medications studied; however, this point can be applied to both the olanzapine and risperidone groups. Moreover, regarding the possible nonfasting measurements in some subjects, this could occur in any study requiring an overnight fast. Again, there is no reason to believe that there would have been a consistent bias in subjects' allocation to the 2 groups.

Regarding the issue of multiple comparisons, our laboratory has studied obesity and metabolic risk factors for 20 years, and we have contributed to documenting the associations between metabolic parameters and indices of obesity and of abdominal fat accumulation.¹⁻⁵ Therefore, there is a large amount of literature documenting the relationships. Our analyses were planned in the protocol and were not a random explanatory exercise. Our metabolic markers (insulin, apolipoprotein B, low-density lipoprotein particle size, etc.) have been shown to provide more precise measurements of the risk of diabetes and coronary heart disease than traditional risk factors used in clinical practice.⁶ Our results emphasize the need to perform additional studies to further explore the metabolic impact of antipsychotics in this population of patients. We would welcome collaborations with Karagianis and Dunayevich to address these clinically important issues.

Finally, the introduction of atypical antipsychotics in clinical practice has without a doubt been a remarkable advance, and the clinical benefits are overwhelmingly clear. However, if, as claimed by Karagianis and Dunayevich, the clinical benefits of some antipsychotics are related to weight gain,⁷ this issue needs to be seriously examined to properly quantify the risk-benefit ratio. The deleterious effects of weight gain and of abdominal obesity are well known in the cardiovascular field and are now an area of focus for psychiatrists concerned with the overall general health of their patients. Our study was a first attempt to explore the potential effects of antipsychotics on parameters that were until recently ignored in clinical practice: metabolic markers of diabetes and coronary heart disease risk. We welcome Karagianis and Dunayevich's comments and invite them to join forces to properly document, through a series of care-

fully designed studies, the metabolic effects of antipsychotic drugs in a context in which we should not lose track of the tremendous clinical benefits associated with their use.

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Natalie Alméras, Ph.D.

Jean-Pierre Després, Ph.D., F.A.H.A.

Laval Hospital Research Center

Ste-Foy, Québec, Canada

Julie Villeneuve, B.Pharm.

Marie-France Demers, M.Sc., B.Pharm.

Roch-Hugo Bouchard, M.D.

Centre de recherche Université Laval Robert-Giffard

Québec City, Québec, Canada

Corrections

In the letter "A Case of Venous Thromboembolism Probably Associated With Hyperprolactinemia After the Addition of Olanzapine to Typical Antipsychotics" by Shigeru Toki, M.D., et al. (November 2004 issue, pp. 1576-1577), the departmental affiliation should be Department of Psychiatry and Neurosciences.

In the article "Topiramate in the Long-Term Treatment of Binge-Eating Disorder Associated With Obesity" by Susan L. McElroy, M.D., et al. (November 2004 issue, pp. 1463-1469), the corrected values for pounds are as follow: 6.7 kg (14.7 lb) and 14.1 kg (31.0 lb) on page 1467 (right column, lines 12 and 13); 6.4 kg (14.1 lb) and 14.5 kg (31.9 lb) on page 1468 (left column, lines 5 and 6).

The online versions of the letter and the article have been corrected. The staff regrets the errors.