Allergic Reaction to Depot Risperidone but Not to Oral Risperidone

Sir: Oral risperidone is an effective and well-tolerated atypical antipsychotic[1] that has been in widespread clinical usage for over 10 years. In recent years, a long-acting injectable form of depot risperidone with a delivery system different from other depot antipsychotics became available in the United States following several years of marketing in other countries. This formulation consists of risperidone microencapsulated in 7525 polylactide-co-glycolide (PLG) at a concentration of 381 mg of risperidone per gram of microspheres[2]; the PLG slowly hydrolyzes to release risperidone, allowing administration every 2 weeks. Depot risperidone has been shown to be therapeutically equivalent to oral risperidone and is also well tolerated.[3,4] We describe a patient who developed a severe allergic reaction concomitant with administration of depot risperidone, although he had taken oral risperidone with no side effects.

Case report. Mr. A, a 46-year-old man with a long history of schizophrenia, was hospitalized in January 2005 with paranoia and disorganization of thought processes after stopping his medication (ziprasidone, 80 mg b.i.d.) and using cocaine. Review of his records revealed that he had been taking several different antipsychotics, including risperidone, 4 mg at bedtime, from August 2002 to July 2003. In July 2003, his treatment was switched to ziprasidone, 80 mg b.i.d., in an attempt to better control his symptoms. However, he eventually stopped taking the medication, leading to his hospitalization. He had no history of any drug allergies or hypersensitivity reactions.

Because of Mr. A's history of noncompliance, plans were made to initiate treatment with depot risperidone. He was given oral risperidone, 3 mg daily, for 3 days without problems and was then given depot risperidone, 25 mg IM. Within 4 to 6 hours of the injection, he developed urticaria with an erythematous, raised pruritic rash covering large areas of his body. He was administered oral diphenhydramine, 50 mg t.i.d., and topical hydrocortisone cream (1%). The next day, the rash had worsened and faint expiratory wheezing was present bilaterally. He was given dexamethasone, 4 mg IM, and the rash began to improve over the next 48 hours, resolving after about 5 days. Mr. A was then treated with ziprasidone and was ultimately discharged on a dosage of 80 mg b.i.d.

A MEDLINE search and review of published articles on depot risperidone revealed no reports of allergic reactions to the formulation. A study using doses as high as 75 mg did not report the occurrence of rash or similar reactions.[5] In the present case, the rapid onset of rash concomitant with depot risperidone injection after no such problem was encountered with oral risperidone suggests that the patient had a reaction to the copolymer complex of the formulation and not to risperidone itself. Clinicians prescribing depot risperidone should be aware that such a reaction can occur.

Drs. Reeves and Mack report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Grant S, Fitton A. Risperidone: a review of its pharmacology and therapeutic potential in the treatment of schizophrenia. Drugs 1994; 48:253–273
2. Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2003
3. Chue P, Eerdekens M, Augustyns I, et al. Efficacy and safety of long acting risperidone microspheres and risperidone oral tablets. Schizophr Res 2002;53(3, suppl 1):174–175
4. Taylor DM, Young CL, Mace S, et al. Early clinical experience with risperidone long-acting injection: a prospective, 6-month follow-up of 100 patients. J Clin Psychiatry 2004;65:1076–1083
5. Kane JM, Eerdekens M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 2003;160:1125–1132

Roy R. Reeves, D.O., Ph.D.
James E. Mack, Ph.D.
G.V. (Sonny) Montgomery VA Medical Center
Department of Psychiatry
University of Mississippi School of Medicine
Jackson, Mississippi

Relapsing Paranoid Psychosis as the First Manifestation of Pheochromocytoma

Sir: Psychiatric manifestations of pheochromocytoma—a rare disease in which a tumor causes the adrenal medulla to overproduce epinephrine and norepinephrine hormones—are usually limited to anxiety states. We report a patient who presented with paranoid psychosis as the only manifestation of pheochromocytoma long before pheochromocytoma was diagnosed.

Case report. Mr. A, a 35-year-old man, developed psychotic symptoms of 2 months' duration in March 1999. He had no previous psychiatric disorders or toxic intake and reported no relevant familial psychiatric or medical history. Mr. A had no hallucinations or disturbance in his consciousness level but specifically believed that many people considered him responsible for the death of a friend. Scores on a personality evaluation test (the Minnesota Multiphasic Personality Inventory[1]) ranked high for paranoia and schizoid personality features. Psychotic disorder not otherwise specified was diagnosed according to DSM-IV criteria.[2] Antipsychotic treatment was begun with olanzapine (30 mg/day), which led to remission of symptoms. However, several relapses were observed from the beginning of treatment, which always coincided with increasing anxiety and disappeared when the dose of olanzapine was increased. Mr. A was instructed on how to recognize the stress-inducing circumstances that could lead to relapse and how to detect psychotic symptoms early.

Twenty-five months after consultation, after 8 psychotic episodes, Mr. A had a hypertensive crisis accompanied by palpitations, anxiety, sweating, and chest pain. At that time, he was diagnosed with chronic delusional disorder (DSM-IV criteria). He had not been psychiatrically hospitalized at any point during the previous 2 years, and results of his routine medical evaluations, including physical examination and laboratory analysis, were normal. Olanzapine had been maintained during the entirety of Mr. A's disease course at a daily dose of 10 to 30 mg. At the time of his hypertensive crisis, high urinary levels of catecholamines were found. Abdominal computed tomography displayed a left suprarenal mass (diameter, 4 cm). Mr. A underwent a surgical resection of the mass at 26 months after consultation. Pathologic study confirmed a diagnosis of

pheochromocytoma. Following surgery, he had no further psychotic symptoms, and olanzapine was progressively discontinued during the next 6 weeks. Three and a half years after stopping olanzapine treatment, he is symptom free. Further personality evaluation using the MMPI no longer revealed paranoia or schizoid personality features.

Presenting features of pheochromocytoma include intermittent sweating, headache, palpitations, and hypertension. Since Medvei first observed the association of pheochromocytoma with psychiatric disturbances,[3] the association has been reported by several authors.[4–9] In 1955, Sulamaa and Wallgren[6] described the case of a 10-year-old boy, subsequently shown to have a pheochromocytoma, who had presented with headache, vomiting, restlessness, nervousness, and "fits" of 9 months' duration; the boy had first been referred to a psychiatrist. Thomas and associates,[7] in a review of 100 patients with proven pheochromocytoma who were seen at the Mayo Clinic between July 1945 and June 1965, reported 22 as having had anxiety states with agitation, tremulousness, palpitation, nausea, and sweating. In 1969, Sack[8] reported that 12 of 33 patients with pheochromocytoma presented with neurologic and psychiatric symptoms. Perhaps the most dramatic was the case reported by el-Matri et al.[9] of a 27-year-old woman who had had severe psychiatric disturbances, including 3 suicide attempts, prior to a diagnosis of pheochromocytoma. Her psychiatric problems disappeared completely after removal of the tumor. In our patient, pheochromocytoma manifested as a relapsing psychotic state that did not exhibit typical features of an organic psychosis.

Norepinephrine is suspected to play a role in schizophrenia and psychotic symptoms.[10,11] In compensated patients with schizophrenia who are receiving haloperidol therapy, an increased noradrenergic activity can predict a relapse of psychosis within 6 weeks following haloperidol discontinuation.[9] Our patient's psychosis was susceptible to stress-inducing environmental situations that were most likely associated with increased catecholaminergic activity.

Norepinephrine and epinephrine are synthesized via dopamine in the chromaffin tissue of the adrenal medulla.[11] An increase in dopaminergic activity may be related to the eclosion of paranoid symptoms. Pheochromocytoma could become a natural example explaining the catecholaminergic pathophysiology involved in such a psychosis. Our case's exceptionality stems from the fact that psychosis not only was the unique initial feature of pheochromocytoma but heralded typical presenting features for a long time.

Drs. Bosch, Benabarre, Plana, Lecube, Vieta, Cirera, and Valdés report no financial or other relationships relevant to the subject of this letter.

REFERENCES

1. Hathaway SR, McKinley JC. Minnesota Multiphasic Personality Inventory Manual [revised edition]. New York, NY: Psychological Corp; 1967
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
3. Medvei VC. Endocrine disorders and the mind. Practitioner 1949;162:139–147
4. Starkman MN, Cameron OG, Nesse RM, et al. Peripheral catecholamine levels and the symptoms of anxiety: studies in patients with and without pheochromocytoma. Psychosom Med 1990;52:129–142
5. Starkman MN, Zelnik TC, Nesse RM, et al. Anxiety in patients with pheochromocytomas. Arch Intern Med 1985;145:248–252
6. Sulamaa M, Wallgren GR. On topical diagnosis and treatment of pheochromocytoma: report of a case. Acta Chir Scand 1955;108: 478–483
7. Thomas JE, Rooke ED, Kvale WF. The neurologist's experience with pheochromocytoma: a review of 100 cases. JAMA 1966;197: 754–758
8. Sack H. Neurologic symptoms in patients with pheochromocytoma [in German]. Munch Med Wochenschr 1969;111:535–541
9. el-Matri A, Slim R, Zmerli S, et al. Phaeochromocytoma with psychiatric disturbances: one case [in French]. Nouv Presse Med 1978;7:1467–1470
10. Van Kammen DP, Agren H, Yao JK, et al. Noradrenergic activity and prediction of psychotic relapse following haloperidol withdrawal in schizophrenia. Am J Psychiatry 1994;151:379–384
11. Trifaro JM. Molecular biology of the chromaffin cell. Ann N Y Acad Sci 2002; 971:11–18

Antoni Benabarre, M.D.
Department of Psychiatry
Hospital Clínic, University of Barcelona
Xavier Bosch, M.D.
Department of Internal Medicine
Maria T. Plana, M.D.
Department of Psychiatry
Hospital Clínic, University of Barcelona
Albert Lecube, M.D.
Department of Endocrinology
Hospital General Vall d'Hebrón
Eduard Vieta, M.D., Ph.D.
Esteve Cirera, M.D.
Manuel Valdés, M.D.
Department of Psychiatry
Hospital Clínic, University of Barcelona
Barcelona, Spain

Weight Gain and Antipsychotics

Sir: The recent (November 2004) Commentary by Kane et al.[1] provides readers with a comprehensive overview of the current situation with regard to the controversy surrounding the association of adverse metabolic effects with atypical antipsychotic drugs. The discussion reported in the Commentary was a response to a recently published consensus statement,[2] as well as the U.S. Food and Drug Administration's suggested changes to labeling, and was intended to advise clinicians how these recommendations may affect their clinical practice.

The panel of experts correctly identify the important areas of uncertainty related to this topic, and they highlight the need for further rigorous studies designed to examine the differential effects of individual atypical agents. This is particularly important given the controversy surrounding issues such as weight gain and its attendant metabolic complications. Pharmaceutical companies are eager to present clinicians with data on weight gain that show their own product in a favorable light, and often clinicians are left floundering amidst the plethora of conflicting information. Articles such as the Commentary by Kane et al.[1] are often useful for objective analyses of the current data, but it is with regret that I note an important misrepresentation of the data in Figure 1. This figure ("reprinted with permission from Allison et al. Am J Psychiatry 1999;156:1686–1696") reports mean weight change during short-term (10-week) treatment with antipsychotics. The figure shows quetiapine ranking third behind clozapine and olanzapine, suggesting a mean weight gain of around 8 lb at 10 weeks. Quetiapine does not feature at all in the corresponding figure in the article by Allison et al.[3] and appears to have been

added at a later stage. Indeed, the conclusion is clearly stated that "insufficient data were available to evaluate quetiapine at 10 weeks."[3(p1686)] As such, the data presented in this Commentary regarding weight gain are clearly misleading and add another layer of complexity for the practicing clinician attempting to make sense of this complex area.

Dr. Mackin has participated in speakers or advisory boards for Eli Lilly, Janssen-Cilag, AstraZeneca, and Bristol-Myers Squibb.

REFERENCES

1. Kane JM, Barrett EJ, Casey DE, et al. Metabolic effects of treatment with atypical antipsychotics. J Clin Psychiatry 2004:65:1447–1455
2. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. J Clin Psychiatry 2004;65:267–272
3. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696

Paul Mackin, M.D., Ph.D., M.R.C.Psych.
School of Neurology, Neurobiology and Psychiatry
University of Newcastle upon Tyne
Newcastle upon Tyne, United Kingdom

Dr. Kane Replies

Sir: My colleagues and I thank Dr. Mackin for pointing out this inconsistency. The quetiapine data that have often been added to discussions and presentations of the Allison et al.[1] meta-analysis, and that were added to the figure we used, are derived from 6-week data from pooled quetiapine clinical trials described in a poster by Jones et al.[2] These 6-week data are similar to longer-term pooled weight gain data for quetiapine from that same poster. That poster's description of pooled clinical trial data for quetiapine-associated weight gain has been the only available source of data for quetiapine that would be comparable to those presented by Allison et al. in their original analysis,[1] and as such has been valuable to clinicians and researchers working in this area. We would prefer that such data were available in a peer-reviewed article. We agree that our figure should have been described as an "adaptation from" the original figure used in the article by Allison et al.[1] and that the explanation and citation for this adaptation should have been given. We apologize for this oversight.

Dr. Kane has been a consultant for and has participated in speakers or advisory boards for Abbott, Bristol-Myers Squibb, Janssen, Eli Lilly, and Pfizer.

REFERENCES

1. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
2. Jones AM, Rak IW, Raniwalla J, et al. Weight changes in patients treated with Seroquel (quetiapine) [poster]. Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1999; Acapulco, Mexico

John M. Kane, M.D.
Department of Psychiatry
The Zucker Hillside Hospital
Glen Oaks, New York

Increasing Energy Expenditure Is Important to Enhance Management of Antipsychotic-Associated Weight Gain

Sir: As clinicians and researchers we were delighted to read the 2 recent articles that described weight management strategies for people taking atypical antipsychotic medications.[1,2] Despite weight loss that was relatively modest in those studies, it is important to realize that the long-term success rate for weight management in the wider population is low.[3] Most importantly, strategies used to date could be significantly enhanced by more effective approaches to increase energy expenditure.

Traditionally, weight management approaches have been biased toward reducing energy intake.[3] However, long-term success is contingent upon a combination of sensible dietary modification and increases in energy expenditure. Notwithstanding the link between increased appetite and food intake among those taking atypical antipsychotic medication,[4] weight loss will result when energy expenditure exceeds energy intake. Therefore, when overfeeding occurs, individuals who do not increase their physical activity to compensate will gain weight.[5] In short, increasing physical activity is an essential component of both weight loss and weight maintenance.[6,7]

The primary focus of the weight management program described by Brar et al.[1] is weight reduction through calorie restriction (18 of the 20 behavioral therapy sessions focus on this aspect). Other programs support a more prominent role for increasing energy expenditure,[2,8] with formal exercise the strategy of choice. However, simply providing opportunities to exercise is not effective in this population.[9] Hills and Byrne[10] identify the most suitable form of "exercise" for the obese as "physical activity as part of daily life." Lifestyle programs are as effective as structured programs in achieving weight loss.[11] Indeed, sedentary people who comply with formal exercise programs may not increase their total daily energy expenditure due to compensatory reductions in energy expenditure during the day.[12]

An alternative and effective strategy to the promotion of physical activity is to focus on reducing sedentary behavior.[13] By replacing a sedentary 6-hour period (2 hours lying down, 4 hours sitting watching television) with activity (1 hour of housework, 1 hour of shopping, 1 hour of cooking, 1 hour of playing billiards, and 2 hours of seated activity such as playing cards), a 98-kg person would use approximately 550 kcal more per day than if he or she remained sedentary but went for a 30-minute brisk walk. With no change in energy intake, the additional energy deficit achieved in the second scenario would result in a 0.5-kg weight loss per week.

In summary, we suggest that programs designed to manage atypical antipsychotic weight gain should give equal emphasis to nutrition and physical activity components. Efforts to reduce sedentary behaviors and increase activity levels should not be viewed as an optional extra. A comprehensive behavioral program similar to that used by Brar et al.[1] will improve the chance for success. From our clinical experience, the addition of motivational interviewing may further increase energy expenditure, reduce body weight, and improve quality of life.

Drs. Stedman and Byrne, Prof. Hills, and Ms. Sharpe report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Brar JS, Ganguli R, Pandina G, et al. Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry 2005;66:205–212

2. Menza M, Vreeland B, Minsky S, et al. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. J Clin Psychiatry 2004;65:471–477
3. Ayyad C, Andersen T. Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obes Rev 2000;1:113–119
4. McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. J Clin Psychiatry 2001;62(suppl 23):23–29
5. Levine JA. Nonexercise activity thermogenesis (NEAT): environment and biology [Erratum in Am J Physiol Endocrinol Metab 2005;288:E285]. Am J Physiol Endocrinol Metab 2004;286: E675–E685
6. Weinsier RL, Hunter GR, Desmond RA, et al. Free-living activity energy expenditure in women successful and unsuccessful at maintaining a normal body weight. Am J Clin Nutr 2002;75:499–504
7. McGuire MT, Wing RR, Klem ML, et al. Behavioral strategies of individuals who maintained long-term weight losses. Obes Res 1999;7:334–341
8. Littrell KH, Hilligoss NM, Kirshner CD, et al. The effects of an educational intervention on antipsychotic-induced weight gain. J Nurs Scholarsh 2003;35:237–241
9. Archie S, Wilson JH, Osborne S, et al. Pilot study: access to fitness facility and exercise levels in olanzapine-treated patients. Can J Psychiatry 2003;48:628–632
10. Hills AP, Byrne NM. Exercise prescription for weight management. Proc Nutr Soc 1998;57:93–103
11. Andersen RE, Wadden TA, Bartlett SJ, et al. Effects of lifestyle activity vs structured aerobic exercise in obese women: a randomized trial. JAMA 1999;281:335–340
12. Goran MI, Poehlman E. Endurance training does not enhance total energy expenditure in healthy older persons. Am J Physiol 1992;263: E950–E957
13. Epstein LH, Valoski AM, Vara LS. Effects of decreasing sedentary behavior and increasing activity on weight change in obese children. Health Psychol 1995;14:109–115

Jenny-Kay Sharpe, M.H.Sc.
Terry J. Stedman, F.R.A.N.Z.C.P.
The Park—Centre for Mental Health
Brisbane, Australia
Nuala M. Byrne, Ph.D.
Andrew P. Hills, Ph.D.
Queensland University of Technology
Brisbane, Australia

Drs. Ganguli and Brar Reply

Sir: We thank the editors for the opportunity to respond to the letter by Sharpe and colleagues. We would like to start by stating that we are in complete agreement with them that, theoretically, increasing energy expenditure is important in the management of weight gain, whether induced by antipsychotics or not. Furthermore, on the basis of studies in non–psychiatrically ill populations, increased energy expenditure might be predicted to be even more important in the maintenance of weight loss.[1] Sharpe and colleagues appear to take us to task for the program reported in Brar et al.,[2] for introducing exercise only in the latter stages of our 14-week intervention. Let us also say that we now not only agree with their viewpoint, but have in the latest iteration of our intervention added increased energy expenditure (mainly increased walking) at the very beginning of the program. However, it is also worth pointing out that Sharpe and colleagues base their recommendations on studies that did not involve people suffering from schizophrenia and that in fact reported interventions predominantly involving subjects with no psychiatric disorder whatsoever. Thus, some caution is appropriate in extrapolating to individuals with severe mental illness.

We would like to take this opportunity to explain how we developed the program described in the publication[2] in more detail than we were able to, due to space constraints, in the article. We initially adapted some of the components of our intervention from the only earlier randomized clinical trial of weight reduction in schizophrenia patients.[3] The interventions were updated, based on our best reading of published intervention studies from other populations. We then piloted the intervention in 33 overweight schizophrenia patients and made further modifications, based on feedback from the participants as well as the clinicians administering the intervention. The advice from the majority of the above was that, given the extremely sedentary lifestyle of our chronic patients, it was advisable to introduce increased activity only after the subjects had become comfortable in the groups and, preferably, after they had also experienced some success in losing weight. This is why we emphasized reduction in food (and calorie) intake as the initial steps and added techniques for energy expenditure only toward the latter stages of the intervention in the study previously reported.[2]

In the study reported in the *Journal*,[2] in addition to the emphasis on walking, the program also recommended subtle energy expenditure ("wasting") techniques that could be incorporated in one's daily activities, i.e., "doing everyday activities the long and hard way," for example, taking the stairs instead of the elevator, standing in line instead of sitting, and getting off the bus one stop early. Recent research has borne out that even small but sustained changes in one's daily activities can profoundly affect energy balance and body weight.[4] Since then, with increasing experience in working specifically with individuals suffering from schizophrenia, we have been pleasantly surprised that most patients are able to incorporate increased energy expenditure into early phases of the intervention. Consequently, we are currently studying an intervention in which we provide subjects with pedometers and weighing machines, along with diaries for recording both food intake and energy expenditure, as the first step. We also develop goals with the subjects for both reductions in food intake and increases in energy expenditure from the beginning.

Thus, while we agree with the principles voiced by Sharpe and colleagues, we do feel that the actual interventions need to be rigorously tested in the specific patient populations for whom they are intended before we can make statements about their efficacy.

Drs. Ganguli and Brar report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Wing RR. Behavioral treatment of obesity. In: Wadden TA, Stunkard AJ, eds. Obesity Handbook. New York, NY: Guilford Press; 2001: 455–462
2. Brar JS, Ganguli R, Pandina G, et al. Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry 2005;66:205–212
3. Rotatori AF, Fox R, Wicks A. Weight loss with psychiatric residents in a behavioral self control program. Psychol Rep 1980;46:483–486
4. Levine JA, Lannigham-Foster LM, McCrady SK, et al. Interindividual variation in posture allocation: possible role in human obesity. Science 2005;307:584–586

Rohan Ganguli, M.D.
Jaspreet S. Brar, M.D., M.P.H.
Western Psychiatric Institute and Clinic
University of Pittsburgh
Pittsburgh, Pennsylvania