Current research suggests that risperidone acts in a fashion similar to a class III antiarrhythmic, causing concentration-dependent blockage of the rapid component of the delayed rectifier K^+ current (I_{Kr}) in ventricular monocytes and possibly explaining the QTc prolongation in some patients (2). As an atypical antipsychotic, risperidone is an attractive agent because of the relatively low side effect profile and decreased extrapyramidal effects. However, it is important to note that death secondary to risperidone overdose and symptomatic cardiac side effects have been noted but at moderate to high levels of risperidone (6–24 mg/day) (3). Geriatric patients may be more susceptible to the cardiac side effects of risperidone, perhaps because of cardiac comorbidities or metabolic differences. Although our patient reported no symptoms of syncope or palpitations, it was difficult to assess his ability to report such symptoms because he was demented. We emphasize that elderly patients like our own, with coronary artery and cerebrovascular disease, require more careful monitoring. Since QTc prolongation and ventricular arrhythmias can potentially result in fatal cardiac processes, we suggest that risperidone use should be monitored with ECG, especially with the elderly, who are more susceptible to decompensation.

References

1. Goyal RS, Goyal SB: Symptomatic bradyarrhythmia secondary to risperidone (letter). Am J Psychiatry 2003; 160:2243
2. Magyar J, Banyasz T, Bagi Z, Pacher P, Szentandrassy N, Fulop L, Kecskemeti V, Nanasi PP: Electrophysiological effects of risperidone in mammalian cardiac cells. Naunyn Schmiedebergs Arch Pharmacol 2002; 366:350–356
3. Kopala LC, Day C, Dillman B, Gardner D: A case of risperidone overdose in early schizophrenia: a review of potential complications. J Psychiatry Neurosci 1998; 23:305–308

KIEN T. TRAN, PH.D.
PETER GOLDMAN, M.D.
TRACY LARK, P.A.-C.
N.J. JACOB, M.D.
Pittsburgh, Pa.

Withdrawal Syndrome After Delayed Tramadol Intake

TO THE EDITOR: Tramadol is a centrally active synthetic analgesic drug with opioid and nonopioid properties (norepinephrine and serotonin reuptake inhibition). Its widespread use in benign and malignant painful conditions is due to the following: 1) tramadol is a nonscheduled medication, 2) most people are unaware of its opioid nature, 3) its name does not produce "opiophobia" like morphine does, and 4) it is not considered a drug that produces severe adverse effects, dependence, or abuse. However, some studies have reported tramadol abuse, respiratory depression in patients with renal failure, cerebral depression, and even a fatal outcome in association with a benzodiazepine (1, 2).

In patients with or without a history of drug abuse who were treated with tramadol for chronic benign pain, also in therapeutic doses (up until 400 mg/day), dependence and withdrawal syndrome after abrupt discontinuation have been reported (3, 4). Tramadol is the third active principle most frequently involved in withdrawal syndromes (5). We could not locate in the literature any case of withdrawal in cancer patients taking tramadol.

Ms. A was a 51-year-old nonsmoking woman with breast cancer, lung metastases, and brachial plexopathy, with no history of chemical or alcohol dependence. She was referred to the outpatient clinic because of severe pain. She had been taking tramadol for 2 years: 50 mg t.i.d. increasing to 100 mg t.i.d., plus 50 mg intramuscularly as needed. Switching to a strong opioid was proposed, but Ms. A refused for 2 months, notwithstanding her uncontrolled pain, because she said she became very agitated when delaying or skipping the tramadol administration, and she had learned to recognize the onset and then fear this nervousness, which reversed only by taking tramadol.

One day she did not take tramadol twice in a row. After a few hours of having missed the first administration, she became very nervous. Upon missing the second dose, she began to have anxiety, anguish, a feeling of pins and needles all over her body, sweating, and palpitations. She knelt down and rolled on the floor, pressing her hands against her head so as "not to feel and not to understand what was happening" and begged her husband to take her back home immediately so she could have her tramadol dose. When we asked about her pain on that occasion, she replied, "I do not know because I felt too bad." She described what happened very clearly and with great preoccupation because she felt like a "drug addict," and when we suggested changing the opioid, she agreed so as not to undergo another similar experience. We stopped tramadol and prescribed oral methadone, 5 mg t.i.d., reducing it to 3 mg t.i.d. after a week, which resulted in analgesic benefit and no adverse effects.

"Physical dependence" is the term used to describe the phenomenon of withdrawal when an opioid is abruptly discontinued. The severity of withdrawal is a function of the patient's prior opioid exposure. Here we have a case of withdrawal due to physical dependence on tramadol even if no tolerance had developed over 2 years. The patient became nervous and agitated if the tramadol intake was merely delayed. When the patient missed the dose twice in a row, her withdrawal symptoms became severe, with an overwhelming need to take the drug that could appear as psychological dependence.

We believe that 1) patients must be advised to take tramadol regularly and to stop gradually especially after long treatment periods, 2) physicians should consider the potential physical dependence when they prescribe tramadol for pain, and 3) any form of "dependence" of cancer patients taking tramadol, however, needs to be further explored. In fact, we are observing some patients who continue to take tramadol in order "to achieve a feeling of well-being," even though their pain is controlled after disease regression or switching to strong opioids. This may be related to the inhibition of serotonin reuptake of tramadol.

References

1. Lee CR, McTavish D, Sorkin EM: Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs 1993; 46:313–340
2. Freye E, Levy J: Acute abstinence syndrome following abrupt cessation of long-term use of tramadol: a case study. Eur J Pain 2000; 4:307–311
3. La Farmacovigilanza. http//:www.farmacovigilanza.org
4. Withdrawal syndrome and dependence: tramadol too. Prescrire Int 2003; 12:99–100

5. Raine JM: Seroxat and withdrawal reactions (letter to Mr Medawar). Medicines Control Agency, July 3, 2002. http://www.socialaudit.org.uk/43800046.htm

CARLA RIPAMONTI, M.D.
ELENA FAGNONI, M.D.
FRANCO DE CONNO, M.D.
Milan, Italy

Publication Bias Against Eating Disorders?

TO THE EDITOR: Susie Frost, M.Sc., et al. (1) have reported that the number of articles on eating disorders published in the top psychiatric, psychological, and medical journals between 1996 and 2001 was consistently lower than that of articles published about panic disorder and agoraphobia in the same journals. The authors acknowledged that they were unable to demonstrate the existence of a publication bias against eating disorders but, nevertheless, suggested that negative attitudes (including sexist and clinical prejudices) from editors and reviewers (although many of them are women and/or experts on eating disorders) toward this group of disorders might explain their observations.

In their Discussion section, the authors preliminarily dismissed the possibility that the lower rate of publication might result from a poorer quality of the eating disorder articles. A recent study (2), however, found a positive association between the methodological quality of clinical research articles and several journal quality indicators, such as the impact factor. We decided, therefore, to compare the quality of the studies on panic disorder and agoraphobia and on eating disorders, using the number of published randomized controlled trials, the gold standard for scientific evidence, as a surrogate for the excellence of the scientific production on the subject.

Our search was restricted to MEDLINE since we found that, except for one, all 534 articles identified by the authors in their study could be located through MEDLINE alone. We used the search terms delineated by Ms. Frost et al. (1) to determine total publication rates for panic disorder/agoraphobia and for eating disorders. The "randomized controlled trials" option of the "type of publication" search limit of MEDLINE was employed to track down the randomized controlled trials. We discovered that between 1996 and 2001, although the total figures for publications on eating disorders and on panic disorder/agoraphobia were roughly equivalent (N=2,361 and N=2,128, respectively), panic disorder/agoraphobia far outnumbered eating disorders in terms of published randomized controlled trials (N=209 versus N=90, respectively).

A cross-tabulation (panic disorder and agoraphobia versus eating disorders; randomized controlled trials versus other types of publications) showed that panic disorder/agoraphobia publications exhibited a significantly higher proportion of randomized controlled trials than eating disorders publications (χ^2=64.05, df=1, p<0.001, with Yate's correction). These high-quality studies are presumably more likely to get accepted in the top journals. In fact, we found that 51 randomized controlled trials on panic disorder and agoraphobia were published in the top journals between 1996 and 2001 compared to only 19 randomized controlled trials on eating disorders. It is also conceivable that the data generated by these randomized controlled trials will be employed in secondary analyses, thus resulting in additional high-quality publications.

In summary, we agree with the conclusion of Ms. Frost and co-workers that articles about eating disorders may have a lower chance of getting published in the top journals. However, our findings suggest that the possibility of a higher quality of the publications on panic disorder/agoraphobia may account at least for part of this trend cannot be dismissed at this point.

References

1. Frost S, Murphy R, Webster P, Schmidt U: Are top journals biased against eating disorders topics? Am J Psychiatry 2003; 160:363–365
2. Lee KP, Schotland M, Bacchetti P, Bero LA: Association of journal quality indicators with methodological quality of clinical research articles. JAMA 2002; 287:2805–2808

MAURO V. MENDLOWICZ, M.D.
IVAN FIGUEIRA, M.D.
WANDERSON F. SOUZA, B.S.
Rio de Janeiro, Brazil

Catatonia in Psychiatric Classification

TO THE EDITOR: We support the view of Michael Alan Taylor, M.D., and Max Fink, M.D. (1), that catatonia should be considered as an individual category in psychiatric diagnostic systems.

First, we would like to comment on the proposed categories for the diagnostic classification of catatonia. The category "delirious catatonia" is confusing, since it is difficult to distinguish catatonic excitement from the excited states of bipolar disorder. As a consequence, the category "delirious catatonia" shows an important overlap with the DSM category of the manic episode. An alternative classification could be composed of two categories, "nonmalignant catatonia" and "malignant catatonia," with an additional specifier of "retarded" or "excited." In this classification, the Kahlbaum syndrome would be regarded as a retarded form of nonmalignant catatonia, and delirious mania would be classified as an excited form of nonmalignant catatonia. The classic description of "lethal catatonia" would correspond with the excited malignant catatonia, whereas neuroleptic malignant syndrome could be considered a retarded variant.

Second, the authors argued that exposure to an atypical antipsychotic drug usually worsens catatonia, but the scientific evidence to which they refer for this statement is poor. Several cases in which exposure to an atypical antipsychotic drug led to an improvement or to the remission of nonmalignant catatonia have been reported. In some of these cases, a causal relationship is probable. For instance, in the case studies by Cook et al. (2) and by Hesslinger et al. (3), a decrease in the dose of risperidone was followed by a recurrence of symptoms and the subsequent increase in dose by remission.

Third, we would like to nuance the therapeutic effects of benzodiazepines in catatonia. According to Rosebush and Masurek (4), patients with schizophrenia are the least likely to respond to benzodiazepines; the response rates range from 40% to 50%.

Finally, Drs. Taylor and Fink (1) use a broad definition of catatonia, stating that neuroleptic malignant syndrome and the toxic serotonin syndrome are most likely severe forms of catatonia. Their evidence for this statement is based on the clinical similarities and on the responses to similar treatment