consultant to Corcept Therapeutics (October 2000 to March 2001) regarding the methodology of a clinical trial of mifepristone for the treatment of psychotic depression. In addition, I was an investigator at the University of Massachusetts Medical School for multisite clinical trials of mifepristone for the treatment of psychotic depression, a fact that is obvious from the relevant paragraph in the book.

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Dr. Rubin Replies

TO THE EDITOR: I appreciate the opportunity to reply to several issues raised by Dr. Rothschild. First is my taking him to task for nondisclosure of a financial conflict of interest. When I wrote my review of Dr. Rothschild's chapter, he had declared "a financial interest in Corcept Therapeutics" in a published article (1). Only recently did he clarify that "in the past, he has been a consultant to and received research grants from Corcept Therapeutics" (2). If Dr. Rothschild had provided a similar statement in the chapter in question, this issue would not have arisen.

Second is whether financial disclosures should be required in book chapters. I believe they should. Financial disclosure is a major issue now; e.g., following a recent exposé of the nondisclosure of several major financial conflicts in a review of depression treatments (3), the Nature Publishing Group extended its disclosure requirement to review articles (4). Other journals have expanded their disclosure policies to cover all published material, and public interest groups have lent their voice in support (5). Nevertheless, violations continue to surface; e.g., the controversy over nondisclosure in an article in the *Lancet* suggesting a link between measles-mumps-rubella vaccinations and pervasive developmental disorder in children (6). Even full disclosure, however, is not a panacea (7).

Third is the questionable efficacy of mifepristone in psychotic depression in contrast to Dr. Rothschild's statement of its use in "rapidly reversing psychotic major depression." In the two published studies on this issue, there was no significant drug effect (1, 8). In the first study (8), two placebo cells were eliminated because they were considered a drug carryover effect, and an independent-samples analysis apparently was performed, even though the data were paired (subjects were their own control subjects). My independent, paired-data analysis yielded a clearly nonsignificant difference. In the second study, no statistical analysis at all was presented. My analysis of those outcome data again yielded a clearly nonsignificant difference. As well, the April 2004 initial public offering filed with the Securities and Exchange Commission by Corcept Therapeutics (9) indicates that even in large double-blind trials, only a small number of patients became asymptomatic, with no significant difference between drug and placebo. Does this medication, then, warrant the paean of "ECT in a bottle" (10)?

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Potential for Misuse of Sedatives

TO THE EDITOR: The literature review by Ripu D. Jindal, M.D., et al. (1) highlighted important and timely issues concerning the public health problem of insomnia and the lack of literature on the maintenance treatment of insomnia. Although the authors discussed the ongoing debate on the long-term use of benzodiazepines, they cited a range of clinical and biological studies suggesting that "the liability of abuse of benzodiazepines is generally low." We would also stress the need to consider data on sedative abuse from large-scale community surveys that were not included in the review. The lifetime prevalence of sedative abuse/dependence was 1.2% in the Epidemiologic Catchment Area study (2). Recently, data from the National Comorbidity Survey suggested a lifetime prevalence of sedative dependence at 0.5%, as well as 7.1% of the U.S. population reporting the nonprescription use of sedatives (3). Respondents with sedative misuse and dependence had high levels of psychopathology and an increased risk of suicidal ideation/attempts (3).

To further examine this issue, we conducted analysis of a large community sample (N=8,116, ages 15–64) in Ontario, Canada, that had the same methodology as the National Comorbidity Survey (4). In the Ontario sample, 4.3% of the respondents reported nonprescription use of sedative/hypnotic medications, and 0.3% of the sample met DSM-III-R criteria for sedative abuse or dependence. Lifetime sedative misuse had a significant association with past-year suicidal ideation (odds ratio=2.34, 95% confidence interval [CI]=1.15–4.73), lifetime DSM-III-R major depression (odds ratio=4.47, 95% CI=3.00–6.66), and any lifetime anxiety disorder diagnosis (social phobia, simple phobia, generalized anxiety disorder, panic disorder, agoraphobia) (odds ratio=3.00, 95% CI=

2.11–4.30). All odds ratios presented are adjusted for age, gender, education, and low-income status.

In summary, data from community surveys in North American society suggest that misuse and abuse of sedative medications is prevalent in the community and is associated with significant psychiatric morbidity. Although the findings from the these community surveys are limited because of the cross-sectional design, we suggest that future longitudinal studies in clinical and community samples are required to delineate the risk factors associated with abuse of sedative medications. When treating individuals with insomnia, clinicians need to carefully weigh the risks and benefits of long-term sedative medications and to consider nonpharmacological treatments, such as cognitive behavior therapy (5).

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Dr. Jindal and Colleagues Reply

TO THE EDITOR: Dr. Sareen and colleagues raise several important points regarding the abuse liability of benzodiazepine receptor agonists and the relevance of this liability for the treatment of insomnia. We strongly agree with their call for longitudinal studies to assess the risk factors for benzodiazepine receptor agonist abuse and dependence and the need to carefully weigh the risks and benefits of long-term sedative medications in the treatment of insomnia patients. However, we think it is also important to point out the limitations of extrapolating from epidemiological data to clinical practice in this area. The data in the article by Goodwin and Hasin (2002) illustrate some of these problems.

First, the analyses confound different types of misuse. Thus, misuse was defined as either using a sedative without a prescription or using more than the amount prescribed by a physician. The prevalence of each type of misuse is not stated, but we would argue that these represent two different phenomena. Nonprescribed use of sedatives by some individuals bears little relevance to the risk of sedatives prescribed to another group of individuals. Second, the analyses do not consider the indication or diagnosis of individuals taking hypnotics. This is important because most patients with insomnia may have different risks than patients with anxiety or depressive disorders. Likewise, taking a benzodiazepine receptor agonist once per day (for insomnia) may carry different risks than taking such a drug multiple times per day (for anxiety or depression). Third, the definition of dependence (even in DSM) can confound truly maladaptive drug use with other phenomena, such as tolerance, rebound symptoms, withdrawal symptoms, and even recurrence of the original disorder. Physiological dependence can be observed with many types of drugs, including benzodiazepine receptor agonists and antidepressants, but is not necessarily an indicator of the real concern, which is maladaptive drug use. Fourth, the epidemiological data do not distinguish among different agents. In fact, there is some uncertainty regarding which drugs may be described as "sedative/hypnotics," given the widespread use of sedating antidepressants and antihistamines for insomnia. Within the class of benzodiazepine receptor agonists, there may be important differences among specific agents based on pharmacokinetics or receptor selectivity. Finally, as the authors point out, cross-sectional associations between sedative drugs and depression or suicidal ideation should not be taken as causal effects. Patients who are given prescriptions for psychotropic drugs are, by definition, at increased risk for these problems.

We do not dispute that misuse and dependence are important potential risks of benzodiazepine receptor agonists in the treatment of insomnia. However, to adequately evaluate this risk, we need different types of data. Specifically, we need longitudinal data that adequately characterize the conditions being treated, the specific agents and doses used, and the occurrence of carefully defined outcomes of misuse and dependence.

In clinical practice, we recommend the use of behavioral treatments for insomnia in virtually every case. We also recommend that benzodiazepine receptor agonists be used very cautiously, if at all, in patients with any history of substance abuse; that all patients taking benzodiazepine receptor agonists be monitored carefully during treatment; and that these drugs (like all drugs) be used only for as long as therapeutic benefits are realized. Epidemiological studies should inform our thinking, but we should be aware of their limitations as well. Finally, we should not deny reasonable treatment to individuals who have bona fide symptoms, who benefit from therapy, and who use medications in a responsible manner, as prescribed by their physicians.

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Heteromodal Association Cortex in Schizophrenia

TO THE EDITOR: In a recent issue, Robert W. Buchanan, M.D., and colleagues (1) reported a study based on volumetric magnetic resonance imaging of the heteromodal association cortex in schizophrenia. They "found evidence of disruption of heteromodal association cortical areas involved in the neuroanatomy of language in patients with schizophrenia." They found no differences in other "heteromodal" regions.

Although this is an interesting study, there appear to be inconsistencies regarding definitions of the region of interest,