Letters
Correspondance

Addictive evidence

In his clinical review of zopiclone, Dr Cimolai concludes that, "Zopiclone has the potential for being an agent of abuse and addiction."[1] We agree that zopiclone—like any psychoactive compound—can and will be abused; however, we disagree that Dr Cimolai's review provides any evidence of a noteworthy risk for addiction, which, by definition, requires that the user is periodically or chronically intoxicated, shows a compulsion to take zopiclone, has great difficulty in voluntarily ceasing or modifying zopiclone use, and exhibits determination to obtain zopiclone by almost any means.[2] It is unfortunate that the Editor has chosen to leave open, in the Editor's Key Points, the question of addiction potential when the main articles cited in the paper (for example, reference 52[3]) clearly state that addiction is "quite rare."

In our experience, whenever an apparent authority makes statements about hypnotic use that are unnecessarily alarmist, clinicians respond by switching from medications that are widely acknowledged to be the safest hypnotics—the benzodiazepines and their receptor agonists (eg, zopiclone)—and using the sedative side effects of "off-label" compounds that have their own abuse, dependency, and withdrawal liabilities, and far worse side effect and safety profiles.

Had Dr Cimolai applied his own research methodology to the 2 drugs he recommends (amitriptyline and trazodone) he would have found several case reports of amitriptyline abuse,[4,5] which, unlike benzodiazepine abuse or misuse, can be fatal.[6] He also would have noted that even after short-term use, both drugs have a withdrawal syndrome indicating physiologic dependence.[7,8] Clearly, once again, benzodiazepines and their receptor agonists are being treated prejudicially.[9]

It is surprising that the usual standards for reporting clinical cases have not been applied to Dr Cimolai's opening case report. The reviewers and Editor appear satisfied that the patient's admission of addiction is a sufficient diagnosis and that a quantification of the sleep complaint, its differential diagnosis, and actual outcome are not required.

We wonder if more common, alternative explanations to addiction might explain this particular misuse of zopiclone. For example, patients with obsessive-compulsive disorder are often extremely distressed throughout the night by obsessions and associated compulsions, and seek "rapid unconsciousness" as a way of coping.[10] Additionally, they might have a circadian disruption of the sleep process[11] or have a concurrent sleep disorder, such as paradoxical insomnia or sleep-state misperception.[12] In these conditions, patients often inappropriately escalate their hypnotic dose with the sole goal of symptom relief, as opposed to the goal of the addict, which is intoxication.

Of course, patients often confuse the precise and specific medical meaning of addiction[2,13] and might misidentify misuse, abuse, tolerance, physiologic and psychological dependence, and rebound phenomena as addiction. These distinctions, which Dr Cimolai confuses ("some even believe zopiclone is not addictive at all… many respondents were unaware of its dependence potential"), are important. Even if the treatment is evidence-based, patients and their physicians are unlikely to use medications that are perceived to be addictive.

Citing another case report,[14] Dr Cimolai stated that the "use of zopiclone appeared to instigate a relapse into narcotic use." Given the facts of the case, we do not believe that this serious allegation is supported; other nonbiological, psychosocial factors likely played a prominent role. The patient was a 29-year-old physician in "stable recovery from pethidine addiction for 12 months."[14] He had stopped attending his recovery program some time before taking a single dose of zopiclone, 7.5 mg, "following a busy period of broken sleep due to a busy on call roster." He experienced a "rapid and powerful reemergence of physical symptoms of craving for narcotics after an absence of 12 months … which led, within 24 hours, to a 48-hour relapse on narcotics." In the original case report, no information is provided about why the patient ceased to attend his recovery program, his status with his licensing authority, testing for other medications or substances of abuse, or—most importantly—the proposed mechanism through which a short-acting benzodiazepine receptor agonist might cause a relapse of pethidine addiction 24 hours after ingestion.

Dr Cimolai correctly notes that some argue that misuse of "Z" drugs (zopiclone, zolpidem, zaleplon) must be low given the frequency of prescriptions, and then points out that there are cases of reported dependency. Dependency, both psychological and physiologic, is to be expected with all centrally acting medications, is not an absolute indication of addiction, and, if required, can be easily managed by behavioural interventions and a slow taper.[15]

Most hypnotic users take stable, low dosages of their medications with demonstrable benefit to their waking lives. Although the old maxim of "the lowest dose for the shortest time" is sensible, it is important to note that the previous recommendation, promoted by regulators and other authorities,[16] was not evidence-based and is now considered by the National Institute of Health to be obsolete.[17] Long-term hypnotic use can be appropriate[17] and effective.[18] Regardless of duration of use, if a patient's usage escalates, a rapid exploration of all the

possible reasons is required before prematurely and inappropriately labeling the patient as an addict.

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Competing interests

Dr Fleming *has no current competing interests. In the 1980s he had a grant from Rhone-Poulenc to complete 2 studies of zopiclone and he sat on 2 of their physician advisory groups. He also presented at local and national rounds on insomnia at conferences sponsored by Rhone-Poulenc, and later Rhone-Poulenc Rorer, for which he received honoraria.* **Dr Samuels** *is the co-chair of the national steering committee for the development of clinical practice guidelines for insomnia and the chair of the Alberta provincial committee (Toward Optimized Practice/AMA) that has developed a provincial clinical practice guideline on insomnia. The national committee was originally funded by industry (Servier Canada, 2001 to 2002). Between 2001 and 2002 he presented continuing medical education (CME) programs on behalf of the Department of CME at the University of Calgary, which received funding from Servier to develop the CME programs. He does not receive pharmaceutical industry funding for any insomnia-related research or education at this time. He is currently involved in an initiative to develop programming for shift-work sleep disorder funded by Shire Canada.* **Dr MacFarlane** *has no current competing interests. When zopiclone was first available (in the 1990s), he sat on 2 of their medical advisory groups. More than 10 years ago, he presented at local and national rounds on insomnia at conferences sponsored by Rhone-Poulenc, later Rhone-Poulenc Rorer, and ICN Pharmaceuticals, for which he received honoraria.* **Dr Morehouse** *has no current competing interests. She currently has grants with Lundbeck and Sanofi Aventis. She had speaking engagements with Rhone-Poulenc Rorer, Draxis, and Orphan (now Valeant) in the 1990s.*

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Response

I welcome the positive comments from Fleming et al, and I thank the Editor for the opportunity to further an open discussion on these very important issues. The topic of psychotropic pharmacotherapy has a history of impassioned debate in Canada,[1] and whether pedagogic or merely academic, such discussions will hopefully lead to an improvement in patient care.

The definitions of abuse, dependence, and addiction are certainly shaped by the eye of the beholder. One need only examine the varying definitions published by Fleming et al in their letter, described by the Centre for Addiction and Mental Health,[2] and noted in a reference cited by Fleming et al.[3] Perhaps those on the street who suffer such maladies might add to the controversy and critique those definitions further.

Fleming et al indicate that amitriptyline abuse can be fatal, unlike benzodiazepine abuse. It is too bad that those who have died after a benzodiazepine overdose are not available to speak for themselves.[4]

Fleming et al rightfully examine the alternative explanations for zopiclone misuse, such as in patients with obsessive-compulsive disorder.[5] This reference, however, details a large group of pediatric patients. The latter have little similarity to the older patients who typically request zopiclone and who admittedly abuse prescription medications. In addition, it is generally futile to overly speculate, particularly retrospectively, about the few details that are offered by case reports.