

**Indomethacin is inappropriate for use in the geriatric population**

TO THE EDITOR: We read with interest the case report by Mallet and Kuyumjian (*Ann Pharmacother* 1998;32:201-3), who described a case of indomethacin-induced behavioral changes in a 92-year-old man with Alzheimer's disease. Although it has been suggested that this is a rare adverse effect of indomethacin therapy, our experience and that of others suggest that it is not a rare event, but rather that it is unreported.<sup>1</sup> Indeed, it is well known that adverse drug reactions tend to be underreported for a variety of reasons.<sup>2</sup>

We agree that drug-induced psychosis may be unrecognized by some clinicians, possibly leading to inappropriate treatment of psychosis as a primary event. The literature contains various examples of potentially unrecognized drug-induced toxicity that are subsequently treated as a primary disorder. For example, Avorn et al.<sup>3</sup> reported an increased incidence of levodopa therapy following metoclopramide use in a case-control study of Medicaid enrollees aged 65 years and older. In this study, metoclopramide users were three times more likely to begin use of a levodopa-containing medication than were nonusers of metoclopramide.

However, we believe that the author's warning, "Healthcare providers should be aware that patients with dementia receiving indomethacin may be at risk of developing severe behavior problems along with gastrointestinal and renal adverse effects," may be far too conservative regarding the use of indomethacin in the older population. Indeed, Beers<sup>4</sup> published criteria for determining potentially inappropriate medication prescribing for the elderly that were published in revised format in 1997. These criteria were carefully developed by using a thorough literature review of medication use in the older population, and consensus methods with established expertise in clinical pharmacology, clinical pharmacy, geriatric medicine, pharmacoepidemiology, and psychopharmacology. These guidelines clearly state that indomethacin should not be used in the older population, as it "...produces the most central nervous system side effects...." Furthermore, indomethacin provides no clinical advantage over more easily tolerated agents such as ibuprofen, which could also be used to treat acute inflammatory arthropathies. Despite the fact that the use of indomethacin in the older population should be avoided, it remains a commonly prescribed antiinflammatory drug. In Nova Scotia, indomethacin was the third most commonly used antiinflammatory drug among patients aged 65 years and older from April 1, 1993, through March 31, 1994. If more clinicians are aware of such guidelines for appropriate medication use in older patients, perhaps drug-induced toxicity, which is an important and preventable cause of morbidity in this population, can be reduced.

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Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.—ED.

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## REFERENCES

- Hoppmann RA, Peden JG, Ober SK. Central nervous system side effects of nonsteroidal antiinflammatory drugs. Aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991;151:1309-13.
- Baum C, Kweder SL, Anello C. The spontaneous reporting system in the United States. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester, England: Wiley and Sons Ltd., 1994:549-80.
- Avorn J, Gurwitz JH, Bohn RL, Mogun H, Monane M, Walker A. Increased incidence of levodopa therapy following metoclopramide use. *JAMA* 1995;274:1780-2.
- Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. *Arch Intern Med* 1997;157:1531-6.

**Comment: use and abuse of flunitrazepam**

TO THE EDITOR: Simmons and Cupp (*Ann Pharmacother* 1998;32:117-9) do not mention that besides in South America, Asia, and Australia, flunitrazepam is also marketed in the majority of the European Union States (e.g., Austria, Belgium, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK). Although the date rape epidemic seems to be the most serious health problem derived from flunitrazepam misuse in the US, in those other countries where flunitrazepam is marketed, the abuse among opioid addicts constitutes a great threat to public health.

In reference to the reasons that explain flunitrazepam abuse liability, Simmons and Cupp state that "flunitrazepam is abused because of its ability to produce a relaxed feeling, similar to that in alcohol intoxication." Although this effect may contribute to its abuse, we think that is not the main reason for the abuse of flunitrazepam. The abuse potential of any psychoactive drug seems to be determined by its reinforcing properties, which depend on the ability to induce positive mood changes and pleasurable feelings (euphoria). Besides the relaxed feeling produced in opioid-dependent subjects, the abuse of benzodiazepines is motivated by the increase in the feelings of euphoria and well-being produced by opioids. Evidence from several epidemiologic studies in opioid-dependent subjects has shown that flunitrazepam is the most highly desired benzodiazepine because it is the strongest and gives a good "high."<sup>1-3</sup> Nevertheless, increases in drug-preference scales and drug-induced euphoria have been observed in experimental studies with opioid-dependent patients. In a sample of methadone-maintained patients, which is one target population for the abuse of benzodiazepines, it has been demonstrated

that flunitrazepam-induced increases in pleasurable effects and drug-induced euphoria were distinct from placebo and also from triazolam.<sup>4</sup>

We disagree with the authors' conclusion because after reviewing all epidemiologic and experimental evidence, it is clear that in Europe and other countries where flunitrazepam is marketed, the abuse of this drug among opioid addicts constitutes a greater public health risk than do other benzodiazepines in this specific population.

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#### REFERENCES

1. Navaratnam V, Foong K. Adjunctive drug use among opiate addicts. *Curr Med Res Opin* 1990;11:611-9.
2. Barnas C, Rossmann M, Roessler H, Reimer Y, Fleischacker WW. Benzodiazepines and other psychotropic drugs abused by patients in a methadone maintenance program: familiarity and preference. *J Clin Psychopharmacol* 1992;12:397-402.
3. Darke SG, Ross JE, Hall WD. Benzodiazepine use among injecting heroin users. *Med J Aust* 1995;162:645-7.
4. Farré M, Terán MT, Roset PN, Mas M, Torrens M, Camí J. Abuse liability of flunitrazepam among methadone-maintained patients. *Psychopharmacology* 1998 (in press).

**AUTHOR'S REPLY:** We agree that there is evidence from surveys of opiate users that flunitrazepam is desired more than other benzodiazepines by this population.<sup>1,2</sup> In addition, in our article we mention that users report that clonazepam does not produce the same degree of intoxication as does flunitrazepam.<sup>3</sup> However, there is also evidence that diazepam, which is more readily available than flunitrazepam in the US, is also preferred over other benzodiazepines by addicts,<sup>1,2,4</sup> and in one survey was similar to flunitrazepam in this respect.<sup>1</sup>

Surveys are not prospective, blind studies; the perception of heroin addicts that flunitrazepam is the "strongest" benzodiazepine and that it "gives a good high"<sup>2</sup> could be influenced by the drug's reputation on the street. In addition, it has been noted<sup>5</sup> that drug abusers do not necessarily distinguish flunitrazepam tablets from clonazepam, bromazepam, or diazepam tablets. Despite evidence that flunitrazepam may be the preferred benzodiazepine in opiate abusers, objective data<sup>5</sup> from animal and human studies do not suggest that flunitrazepam has a greater abuse potential than do other benzodiazepines. Currently, it is unclear whether flunitrazepam poses a greater public health risk than other benzodiazepines in the US.

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2. Darke SG, Ross JE, Hall WD. Benzodiazepine use among injecting heroin users. *Med J Aust* 1995;162:645-7.
3. Calhoun SR, Wesson DR, Galloway GP, Smith DE. Abuse of flunitrazepam (Rohypnol) and other benzodiazepines in Austin and South Texas. *J Psychoactive Drugs* 1996;28:1-7.
4. Griffiths RR, Wolf B. Relative abuse liability of different benzodiazepines in drug abusers. *J Clin Psychopharmacol* 1990;10:237-43.
5. Woods JH, Winger G. Abuse liability of flunitrazepam. *J Clin Psychopharmacol* 1997;17(suppl 2):1S-57S.

#### Comment: hyponatremia with venlafaxine

**TO THE EDITOR:** The recent report by Masood et al. (*Ann Pharmacother* 1998;32:49-51) described the occurrence of hyponatremia in a 92-year-old woman in association with venlafaxine. In Australia, venlafaxine has been marketed since mid-1996, and in that time, the Adverse Drug Reactions Advisory Committee (ADRAC) has received 234 reports of suspected adverse reactions in association with the drug. More commonly reported adverse effects include nausea (43 reports), headache (31), vomiting (22), increased sweating (22), dizziness (22), rashes (17), and withdrawal syndrome (14). Of particular interest is the fact that ADRAC has received 15 reports of hyponatremia with venlafaxine. The ages of the patients involved ranged from 34 to 89 years (median 78), although most (13) were aged 60 years or older, and 12 were women. Hyponatremia was detected between 3 and 20 days (median 9) after therapy commenced, with minimum values of serum sodium concentrations ranging from 116 to 130 mEq/L (median 124) (normal 135-145). Associated symptoms including confusion (3 cases), syncope, nausea, fatigue, hallucination, agitation, convulsions, delirium, and ataxia were reported in 7 cases. Two reports documented hyochloremia, with a mean minimum serum chloride concentration of 81 mEq/L (normal 95-108). The syndrome of inappropriate antidiuretic hormone secretion was suspected in 7 of the reports, but in the absence of urine osmolality measurements, this was only confirmed in 1.

Venlafaxine inhibits the uptake of both serotonin and norepinephrine and its adverse effect profile has some similarities to that of the selective serotonin-reuptake inhibitors (SSRIs).<sup>1</sup> As Masood et al. indicated, hyponatremia has been reported as an adverse effect of the SSRIs,<sup>2</sup> and the ADRAC has now received 35 such reports with fluoxetine, 26 with paroxetine, and 52 with sertraline. It seems likely that venlafaxine's effect on serotonin uptake is responsible for its association with hyponatremia.

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1. Adverse Drug Reactions Advisory Committee. Venlafaxine: not just an SSRI? *Aust Adv Drug React Bull* 1998;17:2.
2. Adverse Drug Reactions Advisory Committee. Selective serotonin reuptake inhibitors and SIADH. *Med J Aust* 1996;164:562.

**AUTHORS' REPLY:** The letter by Boyd reporting 12 cases of hyponatremia with venlafaxine supports our report of hyponatremia probably caused by venlafaxine. Since our initial report, we have had 3 more cases of hyponatremia closely associated with venlafaxine therapy. We did not perform detailed workup in these cases, but simply discontinued venlafaxine therapy. Sodium concentration was back to normal within a week of discontinuation of venlafaxine therapy.