We understand that true hereditary or acquired angioedema is resistant to antihistamines and corticosteroids. Chodirker is correct to point out that our treatment was based upon the emergent approach to undiagnosed angioedema that does include antihistamines, steroids and epinephrine. Our empirical regimen appears to work in angioedema associated with tissue plasminogen activator but of course we have no control group with which to properly assess efficacy. Given our experience with our first patient, who ultimately died, we remain committed to treating alteplase-associated angioedema because the regimen is generally safe.

Finally, although we agree that epidemiological evidence (i.e., a good case–control study) is needed to assess the true risk of angioedema with thrombolytic stroke treatment in patients on angiotensin-converting-enzyme inhibitors, we would challenge Chodirker to assess the proposed mechanism for biological plausibility because it is all we have at the moment.

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Treatment of primary insomnia

A major problem with the meta-analysis by Anne Holbrook and colleagues of benzodiazepine use in the treatment of insomnia[1] is that benzodiazepines were considered as a single medication; this class of drugs in fact consists of several compounds with marked differences in pharmacokinetics and side-effect profiles. Patients may be prescribed short-, intermediate- or long-acting compounds. Among other side effects, short-acting benzodiazepines cause daytime anxiety, amnesia and rebound insomnia upon withdrawal, whereas long-acting compounds cause residual sleepiness and cognitive impairments. Because the side effects differ so much from one compound to the next, those of benzodiazepines were not found to differ significantly from those of either a placebo or other insomnia treatments in the meta-analysis, which pooled studies investigating different benzodiazepines. They are nevertheless of prime importance for the clinician who has to choose a single hypnotic.

These side effects, especially the residual sleepiness and cognitive impairments, considerably limit the clinical use of benzodiazepines. As a result, several controlled studies have concluded that zopiclone should be recommended in ambulant or out-patient populations.[2,3] The effects of hypnotics on breathing during sleep should also be considered. There are several indications that benzodiazepines depress respiration during sleep whereas zopiclone does not.[4–7] This is important, especially in patients with chronic obstructive pulmonary disease, sleep apnea syndrome and upper airway resistance and, to a certain extent, in people who snore. Another clinical indication of zopiclone is its usefulness in the treatment of benzodiazepine dependency.[8–10] Finally, a major advantage of zopiclone is that, unlike most benzodiazepines, it does not modify sleep architecture (most benzodiazepines reduce both slow-wave and REM sleep).[6,11]

I agree with Anne Holbrook and colleagues that nonpharmacological treatments are the treatment of choice for chronic primary insomnia.[1] However, when comparing hypnotics, I believe that zopiclone has several advantages over each benzodiazepine taken separately.

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[The authors respond:]

Although Jacques Montplaisir may be correct in his assertion that shorter and longer acting benzodiazepines differ in their profiles of adverse effects on the central nervous system, this was not evident in our systematic review.[1] Many of the studies published on amnesia and rebound insomnia have involved triazolam, a potent benzodiazepine with one of the shortest half-lives of the group. However, these and other cognitive impairment effects have been ascribed to all benzodiazepines.[2,3] We remind readers that no benzodiazepine is reliably short acting in terms of sedation in elderly patients with comorbidity, particularly if doses are not adjusted downward.[4–6] There has been virtually no research on therapeutic strategies for insomnia involving this group of patients, who are arguably the highest per capita users of benzodiazepines and alternatives.

Zopiclone is an interesting nonbenzodiazepine sedative. Unlike Montplaisir, we are not convinced that it is superior in efficacy or safety to all benzodiazepines. Studies involving zopiclone tend to be disabled by the use of suboptimal benzodiazepines for comparison (very-long-acting benzodiazepines are used instead of shorter acting drugs similar to zopiclone), small patient numbers and concerns regarding dose equivalence. Our systematic review of 9 randomized controlled trials including 3

appropriate for meta-analysis did not suggest that zopiclone is superior for sleep.[1] A separate meta-analysis of sleep laboratory studies also noted the paucity of high-quality studies involving zopiclone, but the available studies suggest that it is similar to shorter acting benzodiazepines in efficacy, tolerance and rebound.[7] Several studies have noted that zopiclone has adverse effects on human performance similar to those seen with benzodiazepines.[8–11] Finally, although it represents a lower quality of evidence according to our criteria, we are highly persuaded by the zopiclone manufacturer's own product monograph (monographs are often based on information not available for public scrutiny) that "the pharmacological profile of zopiclone is similar to that of the benzodiazepines."[12]

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