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## Effects of Midazolam and/or Butorphanol: I

*To the Editor:*—In their comparison of the sedation and amnesia provided by three different dosages of butorphanol and midazolam as well as three combinations of these drugs, Dershwitz *et al.*<sup>1</sup> showed each subject two playing cards before and 5 min after intravenous administration of the study drug(s). On the first postoperative day, the patients were asked to recall the cards they were shown. They were given 1 point for remembering the suit of the card and 1 point for recalling its number. Thus, the maximum score was 4. Dershwitz *et al.* noted that "most" subjects recalled the names and suits of the cards shown prior to the drug administration (score =  $3.4 \pm 0.4$ ), but that recall of the cards shown afterward was statistically significantly impaired by both drugs. They also reported that 11 of 14 subjects receiving midazolam 42.9  $\mu\text{g}/\text{kg}$  were able correctly to recall the cards shown before the drug was given. Since the subjects did not achieve a perfect score of 4 for retrograde amnesia and since 3 of 14 could not remember the cards shown before the treatment drug was administered, it seems surprising that the authors state emphatically that "there was no evidence that any treatment produced retrograde amnesia."<sup>1</sup> It certainly is possible that the frequency of retrograde amnesia seen

might be no greater than the frequency that might have occurred in a group of patients receiving a placebo. However, since there was no control group, the occurrence of some retrograde amnesia with midazolam cannot be ruled out.

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## Effects of Midazolam and/or Butorphanol: II

*To the Editor:*—The question addressed by Dershwitz and colleagues<sup>1</sup> as to whether combinations of sedative drugs have synergistic or additive effects is an important one. If sedative drugs are synergistic, then low-dose combinations of drugs should enable the same sedative effect to be obtained but with faster recovery times compared with the use of single drugs. However, the conclusion of Dershwitz and colleagues<sup>1</sup> that butorphanol and midazolam are supraadditive cannot be accepted using their methods. Their definition of supraadditivity and the method used to test its significance were not supported by reference to other studies, and the degrees of freedom used to assess significance were stated. Their method assessed the sedative effect of midazolam, butorphanol, and a combination of half the dose of midazolam and butorphanol. Their definition of supraadditivity is correct only if the dose-response curves are linear. If more than half the drug effect is obtained from half the dose of the individual drugs, then combinations may appear to be supraadditive when compared with the average of the effect of the individual drugs. As an extreme example of this: if the effects of both the full and half doses were on the upper flat parts of two sigmoid dose-response curves, the effect of the combination might be the higher maximum effect, whereas the average effect for the individual drugs will be halfway between the two maximum effects, and therefore less.

According to the method of Dershwitz and colleagues, the combination is supraadditive, whereas in fact, the combination has no more additional effect than the more potent drug used alone.

The authors did their test only for supraadditivity using the high-dose combinations, even though the effect outlined above is more likely. It would be equally valid for the authors to do this test for the medium-

and low-dose combinations. Was this done, and what were the results? Valid statistical methods of distinguishing additivity from synergy include isobolographic techniques,<sup>2</sup> algebraic fractional analysis,<sup>3</sup> or the method described by Plummer and Short.<sup>4</sup>

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