

Of course, the excellent study done at the Lexington Center has proved that this drug is addicting when given in the high dose for even a relatively short period of time. Obviously, Dr. McHardy had not proved that there was no possibility of addiction to R1132. If he had, why is the firm adding atropine sulfate to the drug to prevent it being used for overdose and addiction.

On page 10 the statement under the heading "Chemistry", "Lomotil consists of this substance to which a sub-therapeutic amount of atropine sulfate is added deliberately to discourage overdosage."

*Comment*

As I stated before, "I don't understand how atropine sulfate is going to discourage overdosage, and I don't agree that it is a sub-therapeutic amount of atropine sulfate when under the recommended dose you can get 1/300 of a grain in one 24 hour period."

On page 11 under the heading "Addicting Liability" the following quote: "Lomotil prevented withdrawal symptoms when it was administered to monkeys addicted to morphine. Thus, the drug can be said to have addicting liability."

*Comment*

It seems unusual that they would cite the monkey studies and not the human studies in the NOA which clearly indicated that the drug could be addicting in humans.

Also, page 11 the following quote: "When measured on a milligram-per-milligram basis, the addicting liability of Lomotil was approximately equal or slightly less than that of meperidine. However, meperidine is used clinically as an analgesic in doses of 100 or 150 milligrams three or four times daily while Lomotil is effective in adults as an anti-diarrheal agent in oral doses of 5 milligrams three times daily."

*Comment*

I do not recall seeing this work with meperidine in the NDA. I do recall seeing the work done comparing it with codeine and morphine illustrating that 60 milligrams of this drug has the effect of producing the equivalent euphoria of about 30 milligrams of morphine or 90 milligrams of codeine. It was considered one half as potent as morphine and one and one half times as potent as codeine in this respect. The final quote in this paragraph on addicting liability is "This low dosage of Lomotil carries little or no risk of addiction as clinical evaluation has not revealed any evidence of dependency."

*Comment*

This statement is patently untrue because Fraser and Isbell in their study at Lexington showed that this drug could produce addiction in humans. Obviously this entire paragraph is very misleading and should be revised completely.

On page 12 under the heading "Mydriatic Activity" with regard to a study in mice, the following: "Doses of 10, 20, 40 and 80 milligrams per kilogram of body weight failed to produce significant mydriasis."

*Comment*

However, the human studies done by Fraser and Isbell demonstrated definite mydriasis in humans when used.

On page 12 under the heading "Human Pharmacology" the following quote: "In these studies it was observed that Lomotil was capable of preventing withdrawal symptoms in known narcotic addicts. Because of this observation Lomotil must be legally classified as a narcotic, although there is little or no evidence in clinical use of any tendency for it to cause either dependency or analgesia."

*Comment*

Again the studies done at Lexington by Fraser and Isbell prove that this is a narcotic, that it produces euphoria in humans, that it produces mydriasis, that it produces nausea, that it produces constipation. Furthermore, it also produces euphoria and is more potent in this respect than codeine.

Obviously, then, this statement could serve to mislead the practicing physician and should be completely rewritten.

On page 12 under the heading "Addiction Potential" the authors referred to the study done by Fraser and Isbell and on page 13 under the same heading they write: "As a result of their studies they conclude, in general, that the abuse liability is less than that of morphine and more comparable to codeine."