Reviewer's report

Title: A Fatal Case of Bupropion (Zyban) Hepatotoxicity with Autoimmune Features

Version: 4 Date: 9 May 2007

Reviewer: Steven Schenker

I am familiar with the literature and believe that this case meets one of the 7 criteria for evaluation in the journal: Unreported or unusual side effects or adverse interactions involving medications

Has the case been reported coherently?: No

Is the case report authentic?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Comments to authors:

General
The paper by Humayun, et al, entitled "A fatal case of bupropion (Zyban) hepatotoxicity with autoimmune features: case report", is a reasonable analysis of this rare event.

The authors marshall evidence for Zyban causation. However, their discounting of the possible paroxetine effect, based on prior tolerance of this drug, is not fully persuasive to this reviewer. Paroxetine is also known to cause idiosyncratic (rare) hepatotoxicity, and one could argue that the initial exposure may have been a sensitizer to the second insult. This is certainly reported with other agents, ie, furadantin. So the argument that this is Zyban and not paroxetine toxicity is debatable. While I, too, would favor Zyban, I cannot rule out the other drug. I understand that both drugs were stopped with the onset of jaundice.

There is less chance that this is drug-unrelated autoimmune disease. This was a male, there was no prior liver disease, there were few plasma cells in the biopsy, and the gamma globulin was not high (what were normal units for this?). The response to steroids likely represents attenuation of the drug-induced autoimmune process. It is an impressive effect in my experience and requires more mechanistic discussion. The bottom line is that I cannot exclude a paroxetine effect.

There are some difficulties for me with the description of the case.

1. The PT course in the case is not given beyond the initial value, somewhat confounded by the anticoagulant used. One needs to know how the PT INR responded to steroids and what it was during the second admission.

2. No CBC data are given.

3. Why was the second liver biopsy done and what are the findings?

4. I am frankly surprised that the patient was apparently not receiving antibacterial and antifungal coverage. With a 30% incidence of sepsis with liver failure, without steroids, such a possibility would be magnified WITH steroid use. We need to know more about the autopsy. How extensive was the sepsis? Did he die of it?

In my view, revisions should address the general and more specific concerns raised here.

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Revisions necessary for publication

**What next?:** Revise and resubmit

**Quality of written English:** Acceptable