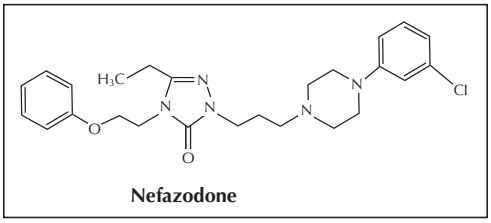
# Nefazodone (Serzone) withdrawn because of hepatotoxicity

***Reason for posting:*** Because of concerns of hepatotoxicity, the sale of the antidepressant nefazodone hydrochloride (Serzone) will be discontinued by the manufacturer effective Nov. 27, 2003. Since the drug's introduction in 1994, there have been 51 Canadian reports of adverse hepatic events, including jaundice, hepatitis and hepatocellular necrosis. In 2 of these cases the patients subsequently underwent liver transplantation. Also, an article published earlier this year found an unexpectedly high number of reports of hepatic injury associated with nefazodone in the World Health Organization's database of adverse drug reactions.[1]

***The drug:*** Nefazodone is an antidepressant structurally distinct from selective serotonin reuptake inhibitors (SSRIs), tricyclics, tetracyclics and monoamine oxidase inhibitors. It achieves its clinical effects by inhibiting the reuptake of primarily serotonin but also norepinephrine and by antagonizing the postsynaptic 5-$HT_2$ receptor and $\alpha_1$-adrenergic receptors. Nefazodone is metabolized by the cytochrome p450 isoenzyme, CYP 3A4, but it is also an inhibitor of this enzyme, which results in potential interactions with numerous drugs, including HMG–CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase inhibitors, carbamazepine and macrolide antibiotics.

***What to do:*** If you have patients who are currently taking nefazodone, then you should switch the treatment to an alternative therapy before Nov. 27, 2003, taking into account the patient's past response to antidepressants, risk of overdose, side effects, drug interactions and cost.[2] SSRIs remain the most popular class of antidepressants; however, if your patient has responded well to nefazodone, other drugs are available that have similar mechanisms of action, specifically those inhibiting both serotonin and norepinephrine reuptake.[3] Should you choose a monoamine oxidase inhibitor, a washout period of 1 week is recommended after discontinuing nefazodone.

If patients who are taking nefazodone show signs or symptoms of hepatic dysfunction, then the drug should be stopped immediately and the patient investigated for other potential causes. In addition, these patients should be closely followed for progression of hepatic problems. The majority of reported cases of hepatotoxicity associated with nefazodone occurred within the first 4 months of starting the drug. In one report, only 17 (53%) of 32 patients who had nefazodone-induced liver dysfunction recovered without sequelae.[4]



Nefazodone

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## References

1. Spigset O, Hagg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug reactions. *Int Clin Psychopharmacol* 2003;18:157-61.
2. Remick RA. Diagnosis and management of depression in primary care: a clinical update and review. *CMAJ* 2002;167(11):1253-60.
3. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression [published erratum in *Lancet* 2000;355:2000]. *Lancet* 2000;355:911-8.
4. Stewart DE. Hepatic adverse reactions associated with nefazodone. *Can J Psychiatry* 2002;47:375-7.