Hepatotoxicity Associated With the New Antidepressants

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Background: Safety profiles of classical and new antidepressants are well established. Hepatotoxicity is known to occur. Recently, several cases of severe hepatic injury associated with the new antidepressants have been reported, prompting us to quantify this risk.

Method: To estimate the cumulative incidence of hepatic adverse reactions associated with antidepressants, we used cases of hepatic damage collected via spontaneous reporting and included in the Spanish Pharmacovigilance System database; for exposure, we have used data from drug sales to the Spanish National Health System.

Results: The estimated reported incidence did not show major differences for the antidepressants studied, ranging from 1.28 cases per 100,000 patient-years for sertraline to 4.00 for clomipramine, except for nefazodone, which was the agent that had the highest incidence with 28.96 cases per 100,000 patient-years.

Conclusion: The reported incidence of hepatic adverse reactions to nefazodone seems to be higher than that estimated so far. Given the high prevalence of depression and the widespread use of antidepressants, physicians should be alert to the possibility that these medications cause hepatitis and consider early discontinuation of an antidepressant if the condition is suspected.

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Depression is one of the most prevalent illnesses, and the use of antidepressant medication is increasing accordingly.[1] Modern pharmacotherapy is the cornerstone of effective treatment of depression. In recent years, the introduction of several new antidepressants with different pharmacologic properties into the market[2] has expanded the options open to physicians for depression treatment.

Currently, the use of the classical antidepressants is limited because of their anticholinergic and sedative effects, their cardiovascular toxicity, and their potential interaction with alcohol. The newer selective serotonin reuptake inhibitor antidepressants (SSRIs) are devoid of these effects, although they share others.[3] For both types of antidepressants, hepatotoxicity has been described to occur.[4] Antidepressants have been associated with a low incidence of idiosyncratic hepatic injury and, with a few exceptions, lead to a uniform and characteristic form of injury, either cholestatic or hepatocellular.[5] Some recently reported cases of severe hepatic injury associated with the new antidepressants[6–14] have prompted us to quantify the risk of such an adverse effect.

METHOD

In this study, cases of hepatic damage associated with antidepressants, collected by the Spanish Pharmacovigilance System,[15] via "yellow card," have been used. Briefly, this is a decentralized system with regional centers to which physicians and hospital pharmacists send spontaneous reports of suspected adverse drug reactions. Events associated with the previous use of recently marketed drugs are specifically requested. Reports are classified as fatal (the drug has or may have contributed to the fatal outcome), serious (life-threatening), moderate (adverse drug reactions led to admission to hospital or absence from work or school, without being directly life-threatening), or mild (adverse drug reactions with little importance and short duration) and are included on-line into a common database, accessible from both regional centers and the coordinating center. Adverse drug reactions are classified in organ-system categories according to the World Health Organization terminology.[16]

Table 1. Reported Rate of Hepatic Injury Associated With Antidepressants[a]

Antidepressant	Number of Cases[b]	Number of DDDs[c]	Reporting Rate per 100,000 Patient-Years (95% CI)
Classical			
Clomipramine	16	146,267,025	4.00 (2.28 to 6.49)
Imipramine	6	76,138,490	2.88 (1.06 to 6.26)
Maprotiline	4	102,825,732	1.42 (0.39 to 3.64)
Amitriptyline	7	172,325,315	1.48 (0.60 to 3.06)
Mianserin	6	69,101,597	3.17 (1.16 to 6.90)
Trazodone	1	14,356,467	2.54 (0.06 to 14.18)
New			
Fluvoxamine	6	60,502,795	3.62 (1.33 to 7.88)
Venlafaxine	3	43,088,205	2.54 (0.52 to 7.43)
Paroxetine	14	281,849,974	1.81 (0.99 to 3.04)
Citalopram	2	50,508,598	1.45 (0.18 to 5.22)
Fluoxetine	26	531,180,860	1.79 (1.17 to 2.61)
Sertraline	5	142,201,020	1.28 (0.42 to 3.00)
Nefazodone	3	3,783,355	28.96 (5.97 to 84.64)

[a]Abbreviations: CI = confidence interval, DDD = defined daily dose.
[b]Period considered, 1989–1999 for all but: venlafaxine, 1995–1999; paroxetine, 1992–1999; citalopram, 1996–1999; sertraline, 1993–1999, and nefazodone, 1997–1999.
[c]DDD values in mg: clomipramine, 100; imipramine, 100; maprotiline, 100; amitriptyline, 75; mianserin, 60; trazodone, 300; fluvoxamine, 100; venlafaxine, 100; paroxetine, 20; citalopram, 20; fluoxetine, 20; sertraline, 50; nefazodone, 400.

Exposure information was gathered from the ECOM (Especialidades Consumo de Medicamentos) database of the Ministry of Health. This database contains information of the community drug consumption done through the Spanish National Health System, which covers virtually the whole population (99%). Drug consumption data were converted into defined daily doses (DDD)[17] and then into treated patients: a consumption of 365 DDD accounting for 1 patient treated in a year. DDD values were those proposed by the World Health Organization.[18] In this manner, reporting rate can be estimated as the quotient between the number of reported cases and the number of person-years.[19] The estimation of the reporting rate was based on the assumption that the exposed population was large and the cases scarce[20]; accordingly, the reporting of suspected adverse reactions associated with these drugs would follow a Poisson distribution and, based on its relation to the chi-square distribution, confidence limits could be obtained.[21]

RESULTS

The reporting rate of hepatic injury cases associated with the use of antidepressants was similar, ranging from 1.28 cases per 100,000 patient-years for sertraline to 4.00 for clomipramine, except for nefazodone, which was the agent that had the highest incidence with 28.96 cases per 100,000 patient-years (Table 1). Table 2 displays some details of all the cases with suspected hepatic injury related to nefazodone.

With regard to severity, 13 of 99 reported cases of hepatotoxicity presumably associated with antidepressants were considered as serious or fatal: 12.5% for classical antidepressants and 13.6% for the new antidepressants.

DISCUSSION

The main finding of the present study is the abnormally high incidence of hepatic damage reported for nefazodone. Nefazodone is a phenylpiperazine derivative that inhibits the reuptake of both norepinephrine and serotonin and antagonizes the 5-HT_2 and α_1-adrenergic receptors. Premarketing evaluation of nefazodone showed the drug to be an extremely safe and effective treatment for depression, although it found infrequent abnormal liver function tests.[6] In 1997, the Swedish Medical Products Agency stated that new adverse reactions to nefazodone included hepatitis,[22] and recently, some serious cases of nefazodone hepatocellular injury have also been described.[6,8,13,14]

Some biases could account for our findings. First, it is theoretically possible that spontaneous reporting accounts for some differences between drugs if adverse drug reactions are reported in different ways. Also, the various antidepressants might be used by different types of patients or for different durations. Since there has been no interaction between the pharmacovigilance centers and doctors in this regard and there is no reason to explain a preferential use of whatever antidepressant in patients prone to develop hepatic damage or for different durations, we firmly believe that these biases do not influence our present results. Moreover, in our estimation, it has been assumed that all antidepressants prescribed were taken by patients; otherwise, incidences would increase and the risk would be higher. Finally, although the incidence figures for nefazodone seem to be low (3 cases in 10,000 patients treated per year), it should be taken into account that these figures are affected by underreporting, which has recently been estimated in Spain to the order of one thousandth—i.e., 1 case out of 1000 (severe reactions are less affected by underreporting).[23] Thus, it is plausible to presume that the real incidence is higher. On the other hand, asymptomatic or subclinical hepatic reactions may not be detected, and subsequently not reported, despite the fact that these reactions could evolve into chronic liver diseases. Small numbers, as is the case with nefazodone, are always a problem in spontaneous reporting. This problem should be dealt with by using comparable denominators when possible and by using appropriate statistical methods. At any rate, the scarcity of cases does not preclude using these data for signal generation or for strengthening previous signals.

For the 3 cases related to nefazodone, a probable causal relationship between the use of nefazodone and hepatic injury can be established according to Karch-Lasagna's algorithm[24] since there was a temporal relationship between the administration of the drug and the onset of the patients' signs and symptoms and because alternative explanations were ruled out. In these patients, nefazodone

Table 2. Main Features of Cases With Suspected Hepatic Injury Related to Nefazodone[a]

Patient[b]	Age (y)/ Gender	Treatment Duration (days)	Bilirubin[c] (μmol/L)	ALT[c] (U/L)	AP (U/L)	Type of Damage	Severity (outcome)
1[13]	73/F	49	292.4	834	115	Hepatocellular necrosis (zone 3)	Fatal (death)
2[14]	38/F	195	321.5	ND	ND	ND	Moderate (no recovery in 3 months)
3	44/F	74	21.0	116	ND	Hepatocellular	Moderate (recovery)

[a]Abbreviations: ALT = alanine aminotransferase (normal < 40 U/L), AP = alkaline phosphatase (normal < 279 U/L), bilirubin (normal < 1.0 mg/dL), ND = no data.
[b]In all 3 cases, nefazodone was administered at 400 mg/day for depression; cases 1 and 2 also took lorazepam.
[c]The ALT values are those at presentation, whereas bilirubin values are the highest recorded.

was the only suspected drug. Withdrawal of the drug was followed by an abatement of liver dysfunction except in the patient who died. In this case, the findings in the liver biopsy specimen showed marked centrozonal necrosis, which is consistent with a toxic etiology, as zone 3 contains higher cytochrome P450 activity. All cases exhibited a hepatocellular pattern of injury with high serum aminotransferase levels and increases in serum total bilirubin. The absence of clinical hallmarks of hypersensitivity suggests that a toxic metabolite, rather than drug allergy, is probably responsible (metabolic idiosyncrasy).

In conclusion, we think that our results further emphasize the importance of hepatic injury associated with nefazodone. The fact that nefazodone, in contrast to tricyclic and other SSRI antidepressants, is being promoted as devoid of sexual effects in either men or women could account for an increase in its use and the appearance of a great number of cases of hepatic damage. Physicians should be alert to the possibility of antidepressant-associated hepatitis, particularly when nefazodone is used, and consider early discontinuation of the drug if this condition is suspected. It seems reasonable to avoid the use of this drug in patients with preexisting liver disease. Routine liver chemistries should be performed before nefazodone therapy begins, and patients should be monitored regularly.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lorazepam (Ativan and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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