A Critical Review of Selective Serotonin Reuptake Inhibitor–Associated Bleeding: Balancing the Risk of Treating Hepatitis C–Infected Patients

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Background: Selective serotonin reuptake inhibitors (SSRIs) are increasingly being used to treat interferon-associated side effects in patients receiving hepatitis C virus (HCV) therapy. Because there is an increased risk of bleeding in HCV-infected patients who have developed cirrhosis and either portal hypertension or hepatic failure or both, we critically reviewed the literature on SSRI-associated bleeding.

Data Sources and Study Selection: We performed a MEDLINE search of literature from 1966 to the present using *hemorrhage*, *SSRI*, and *antidepressants* as search terms and followed up on relevant citations. We reviewed 6 retrospective studies, 5 of which were case-control studies, and 18 case reports of bleeding in 37 people. Our review is supplemented with a case report of a possible connection between SSRI treatment and a fatal gastrointestinal bleed in an HCV-infected man.

Data Synthesis: Bleeding events in 12/18 reports (67%) describing 19/24 people (79%) were closely associated with the use of SSRIs.

Conclusion: Combining aspirin or nonsteroidal anti-inflammatory drugs with SSRIs for the treatment of interferon-associated neuropsychiatric side effects increases the risks of hemorrhage in patients with HCV who have developed cirrhosis and either portal hypertension or hepatic failure or both. We recommend that clinicians exercise caution when prescribing medications that can promote spontaneous bleeding to patients with multiple risk factors for internal hemorrhage.

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Approximately 4 million people in the United States are infected with the hepatitis C virus (HCV), a highly mutable, hepatotropic RNA virus causing acute and chronic hepatitis that can progress to end-stage liver disease and liver cancer.[1–3] The prevalence of HCV is estimated to be 1.8%, making HCV the most common bloodborne infection in the United States.[4] Because of the propensity for persistent infection, it is estimated that the prevalence of HCV infection will increase 4-fold between 1990 and 2015.[4] The standard for treatment of chronic HCV infection is once-weekly pegylated interferon alfa-2b plus daily ribavirin. This combination provides greater efficacy than the previous standard combination of thrice-weekly interferon and ribavirin in achieving sustained virological clearance.[5–7] The sustained virological response with up to 48 weeks of the pegylated interferon alfa-2b and ribavirin combination is up to 46% for genotype 1 infection and 82% for genotypes 2 or 3.[4]

Unfortunately, interferon alfa is associated with neuropsychiatric and somatic side effects that can interfere with adherence to the drug in some patients. These adverse

events include flu-like symptoms (fatigue, headache, fever, myalgia) in ~60% of patients, gastrointestinal symptoms (anorexia, diarrhea, nausea) in ~30%, and a neuropsychiatric syndrome called "depression or sickness behavior" characterized by anhedonia, malaise, impaired concentration, irritability, insomnia, and anxiety in up to 44%.[8–11] As a result of these symptoms, treatment cessation has been found to occur in 20% of patients, while dose reduction significantly diminishes effectiveness in 30% to 40% of patients.[4,6] Interferon-induced neuropsychiatric symptoms have been associated with relapse to substance use and even suicides.[12] Therefore, it is common practice for many clinicians to attempt to ameliorate the side effects of interferon by treating patients with selective serotonin reuptake inhibitor antidepressants (SSRIs) after psychiatric symptoms emerge.[8] In fact, the most recent HCV treatment guidelines endorse the potential usefulness of SSRIs in managing interferon-associated depression.[4] Results from one, albeit preliminary, study showed that 84% of patients whose depression was treated with SSRIs were able to complete interferon treatment.[13]

SSRIs are widely prescribed for a variety of psychiatric disorders because of their effectiveness, ease of administration, mild side effect profile, and, importantly, record of safety. However, SSRIs have been linked to instances of spontaneous bleeding in some patients. Given that HCV patients who have developed cirrhosis and either portal hypertension or hepatic failure or both are inherently at risk of bleeding from complications of HCV infection and that SSRIs are being used more frequently for the treatment of interferon-associated side effects, we recognized a need to critically examine the relevant literature. The objective of this article was to assess the strength of the purported association between bleeding and the use of SSRIs and, in particular, how it might apply to the subgroup of HCV-infected patients who are at greatest risk of hemorrhage. In addition to our literature review on SSRI-associated bleeding, we describe a case of an HCV-infected man who developed fatal gastrointestinal bleeding during prophylactic SSRI therapy for interferon-associated neuropsychiatric side effects. This case report underscores a number of risk factors that can increase the chance of bleeding, including SSRIs. Finally, we discuss why combining over-the-counter analgesics and other commonly prescribed medications may increase the risks of a bleeding event, and we discuss the need for caution when using medications that may promote spontaneous bleeding, particularly in those patients receiving treatment for HCV infection who are at greatest risk for hemorrhage.

METHOD

We performed a literature search using MEDLINE from 1966 to the present using *hemorrhage*, *SSRI*, and *antidepressants* as search terms and followed up on relevant citations from the literature we searched (sources were excluded if multiple causes of bleeding did not allow discernment of a meaningful relationship between SSRIs and bleeding, or if the information given was insufficient to allow any conclusions).

RESULTS

Retrospective Case-Control Studies

We identified 6 retrospective studies, 5 of which were case-control studies, that evaluated the link between bleeding and the use of SSRIs, 1 in a cohort of elderly patients[14] and 5 in general practice[15–19] (Table 1). The study of elderly patients sought to determine the association between inhibition of serotonin by SSRIs and upper gastrointestinal bleeds from a large population-based database.[14] The primary outcome measure was admission to the hospital for upper gastrointestinal bleeding. The overall risk of bleeding was found to be 7.3/1000 person-years. When the authors controlled for age, the risk increased by 10.7% for each increase in serotonin inhibition. For example, for octogenarians, the risk for bleeding increased from 10.6/1000 person-years in the lowest serotonin inhibition group to 14.7/1000 person-years in the highest serotonin inhibition group. The authors calculated that for every 244 patients treated with an SSRI with high rather than low serotonin inhibition, 1 extra upper gastrointestinal bleed could be expected. Important omissions noted by the authors were that they could not capture over-the-counter use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin, both known to promote bleeding in susceptible individuals, and that they missed patients whose bleeds resulted in death prior to admission to the hospital. Although the authors concluded that there was a significant association between upper gastrointestinal bleeding in octogenarians and patients with a prior history of upper gastrointestinal bleeds and SSRIs that possess higher serotonin inhibition, they stratified patients by inhibition of serotonin uptake based on equilibrium dissociation constants in human cell cultures. Because this method of measuring potency does not consider differences in dose, blood drug level, protein binding, or the activity of metabolites, it is not a strong reflection of clinical use. Therefore, the strength of their conclusions must be questioned.

Two studies evaluated the association between gastrointestinal bleeding and the use of SSRIs. The first study assessed adult general practice patients from the United Kingdom General Practice Research Database.[17] A cohort of 1651 patients aged 40 to 79 years with incidents of gastrointestinal bleeding was compared with 10,000 randomly chosen controls matched for age, sex, and time of study. Patients with cancer, esophageal varices, Mallory-Weiss disease, alcoholism, liver disease, or coagulopathies were excluded. Fifty-two (3.1%) of the

Table 1. Retrospective Studies of Antidepressant-Associated Bleeding

Study	Study Design	Primary Outcomes Studied	Subjects (N)		Age of Subjects (y)	Patients With Bleeding		Bleeding Rates
			AD Users	Non-AD Users		AD Users	Non-AD Users	
Any bleeding								
Layton et al, 2001[19]	Population-based observational cohort	Any abnormal bleeding	50,150[a]	36,116/50,488[b]	49–60[c]	486	234–509[b]	SSRIs, 2.77; other psychiatric drugs, 2.41; non-CNS drugs, 2.26[d]
Gastrointestinal bleeding								
Dalton et al, 2003[16]	Retrospective cohort of current and former users and nonusers of SSRIs	Admission to hospital for acute upper GI bleed	26,005[a]	Unspecified	17–105	55	15.3 expected	3.1/1000 treatment-years
Van Walraven et al, 2001[14]	Retrospective, cohort	Admission to hospital for acute upper GI bleed	317,824	None	Over 65	974	None	7.3/1000 person-years
			Subjects (N)			SSRI Users (N)		
			Patients w/Bleeding	Controls w/No Bleeding		Patients w/ Bleeding	Controls w/No Bleeding	
de Abajo et al, 1999[17]	Population-based, case-control	Upper GI bleed or perforated ulcer	1651	10,000	40–79	52[e]	95	1/1300 SSRI users
Intracranial bleeding								
Bak et al, 2002[15]	Case-control nested in Danish population	Hemorrhagic and ischemic stroke	4765	40,000[f]	> 20	Hemorrhagic, 21 ischemic, 100[g]	742	Hemorrhagic, 0.6 (0.1 to 4.4); ischemic, 1.1 (0.9 to 1.4)[h]
de Abajo et al, 2000[18]	Case-control nested in AD users	Intracranial hemorrhage	65	247	18–79	7	24	Not given

[a]The antidepressants received were SSRIs. [b]Study included 2 control groups; shown as other psychiatric drugs/non-CNS drugs. [c]Standard deviation = 17.4. [d]Per 1000 months of treatment, adjusted for age and gender. [e]The 52 cases of bleeding arose from a cohort of 69,593 patients who received antidepressant prescriptions. [f]Control population also included 4411 twins. [g]Of the total sample of stroke patients, 659 patients had hemorrhagic stroke, and 2717 had ischemic stroke. [h]Values shown as adjusted odds ratio (95% CI).
Abbreviations: AD = antidepressant, CNS = central nervous system, GI = gastrointestinal, SSRI = selective serotonin reuptake inhibitor.

patients with upper gastrointestinal bleeds were taking SSRIs versus 95 (1.0%) of the controls. The study indicated that SSRIs increased the risk of upper gastrointestinal bleeding 3-fold, but not the risk of perforated ulcers. No association was found with antidepressants that have no action on the serotonin uptake system. The 52 incident cases of upper gastrointestinal bleeding arose from a cohort of 69,593 patients who received a total of 435,021 prescriptions for any of the SSRIs. The crude incidence rate of upper gastrointestinal bleeding was estimated as 1 case per 1300 users, about the same as for low-dose ibuprofen. The adjusted rate ratio for bleeding associated with SSRI use was 3.0 (2.1–4.4) compared with 1.4 (1.1–1.9) for other antidepressant use. Despite small numbers, the authors of this study concluded that concomitant use of NSAIDs with SSRIs was associated with the greatest risk of bleeding compared with controls (N = 16; 1.0% vs. N = 9; 0.1%, respectively; relative risk = 15.6). Three letters to the editor subsequently questioned the validity of the author's conclusions based on various possible confounds; however, in each instance, the authors' replies adequately defended their conclusions.[20–23] Nonetheless, de Abajo et al.[17] emphasized the need for further studies.

A more recent study compared hospitalizations for upper gastrointestinal bleeding among 26,005 users of antidepressants and those who never received antidepressants in a Danish county.[16] Subjects were tracked by a prescription database consisting of information from every pharmacy in the county, including most patients who took NSAIDs. This information was linked to a comprehensive registry of hospitalizations and deaths. Patients who had medical conditions or were taking prescriptions that were associated with an increased risk of upper gastrointestinal bleeding were excluded. The risk of upper gastrointestinal bleeding among current users of SSRIs was 3.6 times greater than in persons of similar age and sex for whom these medicines were not prescribed. Use of SSRIs with NSAIDs increased the risk of upper gastrointestinal bleeding by more than 12. Increased risk of bleeding in SSRI users was confined to periods of SSRI use compared with risk estimates for non-SSRI users, in whom the risk remained similar for periods of use and nonuse. Given that the Danish system of health care allowed for such completeness of data acquisition, the authors' assertion of a causal relationship between SSRI use and risk of upper gastrointestinal bleeding seems justified.

An observational cohort study investigated 50,150 SSRI users and compared their risk of abnormal bleeding of any kind with that of patients receiving non-SSRI psychiatric drugs and those receiving non-central nervous system (CNS) medications in England over a 6-month period of time.[19] Data were retrieved from forms that were routinely mailed to general practitioners 6 months after they wrote a new prescription. Only 51% of general practitioners responded to the forms, identifying a total of 1240 patients who experienced bleeding. Incidence densities per 1000 patient-months of treatment adjusted for age and sex were as follows: SSRIs = 2.77 (95% CI = 2.53 to 3.04), other psychiatric drugs = 2.41 (95% CI = 2.12 to 2.76), and non-CNS drugs = 2.26 (95% CI = 2.07 to 2.48). Limitations specified by the authors included the inability to sample nearly half of the population and to track NSAID, corticosteroid, anticoagulant, or aspirin use. Preexisting diseases were not reported, and the influence of smoking or alcohol use could not be taken into account. Still, the population studied was quite large, and, despite the study's limitations, evidence suggested that SSRI users carried nearly twice the risk of spontaneous bleeding as those who took nonpsychiatric drugs within 1 month of starting SSRIs. The investigators concluded that their data demonstrated a weak link between SSRI use and bleeding and stressed the need for a nested case-control study to better evaluate preexisting disease and concomitant medications.

Two case-control studies[15,18] reported on intracranial bleeds in antidepressant-using patients. One study[18] culled from the same data used in an aforementioned study[17] by the same lead author (Table 1). Patients were followed from the start of the study until they suffered an intracranial hemorrhage, reached 80 years of age, or died or the study concluded. Subjects were excluded if they had a prior intracranial hemorrhage or a diagnosis of ischemic cerebrovascular disease, heart failure, cardiac dysrhythmia, epilepsy, cancer, coagulopathy, chronic liver disease, connective tissue disorders, hyperthyroidism, diabetes, or alcohol abuse. Patients on anticoagulant therapy and pregnant women were also excluded. Sixty-five incident cases of intracranial bleeding were compared with a matched sample of 247 subjects. Current SSRI use was found in 7 patients with intracranial bleeding (10.8%) compared with 24 controls (9.7%). The authors reported the adjusted odds ratio for bleeding associated with no antidepressant use as 1.0; for SSRI use, as 0.80 (95% CI = 0.3 to 2.3); and for other non-SSRI antidepressant use, as 1.0 (95% CI = 0.2 to 4.9). Thus, no association of SSRI use with rates of intracranial hemorrhage was found.

Another Danish study evaluated whether SSRI use either reduced the risk of new-onset ischemic stroke (N = 2717) or increased the risk of new-onset hemorrhagic stroke (N = 659) in a large population-based cohort[15] (Table 1). The relative risk of intracerebral hemorrhage in current users of SSRIs was 1.0 (95% CI = 0.6 to 1.6) compared with never-users after adjustments for the effects of age, sex, date of bleeding event, and use of other confounding medications. For ischemic stroke, the adjusted relative risk in current SSRI users was 1.1 (95% CI = 0.9 to 1.4) versus never-users. The authors even surveyed twins who were current SSRI users and nonusers and found a similar lack of association of current exposure to SSRIs and decreased risk of ischemic stroke. Although the number of subjects in this study was larger than in the de Abajo et al. study,[18] the authors point out that confounding factors such as the effects of alcohol intake and smoking could have resulted in overestimation of both hemorrhagic and ischemic stroke in SSRI users versus nonusers. Still, the overall conclusions corresponded with those of de Abajo and colleagues in that the investigators found no association of SSRI use and increased risk of intracerebral hemorrhage.

Case Reports

We found 18 reports describing bleeding in 37 people taking SSRIs (Table 2). Seven reports described an "A-B-A" design in which 7 patients bled at their first exposure to an SSRI, then the bleeding stopped when the SSRI was discontinued, but returned once the SSRI was reintroduced.[25–27,36–38,41] One report described heavy menstruation and bruising in a 33-year-old woman taking paroxetine for panic with no prior bleeding tendencies.[30] Interestingly, her physician successfully treated the bleeding with vitamin C after reading a case report describing the use of vitamin C to treat a case of SSRI-associated bleeding. The author indicated that when the vitamin C was stopped, the bleeding resumed. Paroxetine was then discontinued and replaced with fluvoxamine, after which the bleeding returned, but was successfully treated by reintroducing vitamin C. Apparently, the treatment of scurvy with citrus fruit in the Dutch navy long ago provided the impetus for this novel approach, postulated to work by reducing capillary fragility.

Another report provided a detailed description of a 49-year-old man with anorexia nervosa who was treated with haloperidol, benztropine, and desipramine who did not bleed, but developed thrombocytopenia, presumably from desipramine.[42] Desipramine was replaced with fluoxetine, which resulted in normalization of the patient's platelet count, and no evidence of desipramine-related antiplatelet antibodies was found. The investigators went on to perform platelet aggregation studies and discovered a release-type defect in platelet aggregation that corrected after fluoxetine treatment was stopped. One of 2 patients in a report by Ottervanger et al.[36] also had abnormal platelet aggregation without bleeding time abnormalities that disappeared after withdrawal of the SSRI. In contrast, a 44-year-old postmenopausal woman with a lifelong history of easy bruising was reported to have prolonged

Table 2. Case Reports of SSRI-Associated Bleeding

Study	Rechallenge With Drug?	N	Subject Age (y)/Sex	Drug Name and Dose	Bleeding Site
Smith and Robinson, 2002[24]	–	1	67/F	Sertraline, 25 mg/d	Vagina
Vandel et al, 2001[25]	+	2	19/F	Sertraline, 50 mg/d then fluoxetine, 5 mg/d	Menorrhagia
			53/M	Fluoxetine, 20 mg/d	Bloody sputum
Nelva et al, 2000[26]	+ in 1/7 cases	7	Mean = 49.7/7 F	Fluoxetine, 20 mg/d; paroxetine, 20 mg/d (2 cases); fluoxetine or paroxetine (? dose in 4 cases)	Lower extremities, menorrhagia, arm/fingers, epistaxis
Lake et al, 2000[27]	+ in 1/5 cases	5	8–15/1 F, 4 M	Sertraline, 25–100 mg/d	Epistaxis in boys, lower extremity bruising in girl
Shen et al, 1999[28]	–	1	45/M	Sertraline, 50 mg/d	Gums
Cooper et al, 1998[29]	–	1	47/F	Paroxetine, 20 mg/d	Arm, leg, hip bruises
Tielens, 1997[30]	+ and rechallenge with vitamin C	1	33/F	Paroxetine, 40 mg/d, then fluvoxamine, 150 mg/d	Arm, leg bruises, menorrhagia
Kohn and Labbate, 1997[31]	–	1	19/F	Venlafaxine, 100 mg/d	Arm bruises
Wilmshurst and Kumar, 1996[32]	–	1	51/F	Fluoxetine, 20 mg/d	Eye (subhyaloid hemorrhage)
Pai and Kelly, 1996[33]	–	1	31/F	Fluoxetine, 20 mg/d	Upper arm, thigh, and popliteal fossa
Calhoun and Calhoun, 1996[34]	–	1	16/F	Sertraline, 50 mg/d	Bilateral arm, leg
Leung and Shore, 1996[35]	–	1	38/M	Fluvoxamine, 200 mg/d	Epistaxis, arm
Ottervanger et al, 1994[36]	+	2	27/F	Fluoxetine, 20 mg/d, then paroxetine, 20 mg/d	Legs
	–		47/F	Paroxetine, 20 mg/d	Legs
Gunzberger and Martinez, 1992[37]	+	1	38/M	Fluoxetine, 40 mg/d	Epistaxis, bilateral great toes
Aranth and Lindberg, 1992[38]	+	1	40/F	Fluoxetine, 60 mg/d	Knee to hip, menorrhagia
Evans et al, 1991[39]	–	1	33/M	Fluoxetine, 20 mg/d	Prior subdural hematoma, which worsened, leading to patient's death
Yaryura-Tobias et al, 1991[40]	–	8	16–75 (mean = 35.1)/ sex not published	Fluoxetine, 20–80 mg/d	Epistaxis, arms, legs, hemorrhoids
Humphries et al, 1990[41]	+	1	64/F	Fluoxetine, 20 mg every other day	Inner arm petechiae

Abbreviations: F = female, M = male, SSRI = selective serotonin reuptake inhibitor. Symbols: – = no, + = yes.

bleeding times with normal platelet aggregation studies despite exhibiting the A-B-A rebleeding design.[41]

All but 3 reports[24,28,40] provided some information indicating whether other common causes of bleeding besides SSRIs might have contributed to instances of bleeding in the cases we reviewed. Examples included abnormal complete blood counts, concomitant medications including NSAIDs or aspirin, coagulopathies, recent trauma, multiple systemic illnesses, or recent alcohol or drug use. Thus, bleeding events in 12/18 reports (67%) describing 19/24 people (79%) were closely associated with the use of SSRIs with few or no confounding variables that could otherwise have explained the bleeding.[25–27,30–32,34–38]

We found 2 reports that we could not evaluate because of multiple possible causes of bleeding or insufficient information.[29,33] Only 1 report described a death in a patient with human immunodeficiency virus infection (a 33-year-old man).[39] Multiple potential confounds in addition to fluoxetine may have contributed to this patient's death from bilateral subdural hematomas. Musselman et al.[43] published a study of paroxetine for the prevention of interferon-associated neuropsychiatric side effects in patients with malignant melanoma in which 1 irreversible and 2 reversible retinal hemorrhages were described in 3 (17%) of 18 patients receiving paroxetine versus 0 of 20 patients in the placebo group. Although the aims of their study did not include evaluating SSRI-associated bleeding and the authors stated that other risk factors may have contributed to the hemorrhages, the potential for an association of SSRIs and retinal bleeding in this population is worthy of further exploration.

Literature Reviews

We found 3 reviews of the literature on SSRI-associated bleeding published prior to the Van Walraven et al.[14] and de Abajo et al.[17] articles cited above. One was

published in a French journal by Nelva et al.[26] and described each of the cases we reviewed plus 7 adults and 2 infants exposed to SSRIs in utero that were reported to the French Monitoring Agency for Medication Related Side Effects. Physicians from hospital- or office-based practices spontaneously report these episodes of bleeding to the French Monitoring Agency, which then investigates the validity and degree of certainty of the incidents. Details were not provided as to the methods used to assess the validity and certainty of those reports.

The second review, by Skop and Brown,[44] provided very brief descriptions for 15 of the reports of SSRI-associated bleeding complications we reviewed. The authors found no abnormalities in platelet counts, prothrombin, or partial thromboplastin times in patients who bled, but in some cases prolonged bleeding times were found.

The third review provided a general evaluation of a variety of possible hematologic side effects from each of the major classes of psychotropic drugs.[45] In addition to the information we reviewed, they described a report in which fluvoxamine administered for 12 weeks at 100 to 130 mg/day reduced platelet serotonin to 11% of pretreatment concentrations.[46] A few case studies reporting an association of tricyclic antidepressant use with bleeding were also identified in our literature search.[47,48]

In the following section, we present a case report of an HCV-infected man with multiple medical problems who had a fatal bleed while taking SSRIs for the prevention of interferon-associated neuropsychiatric side effects. The purpose of this case report is to provide an example of research-to-practice that illustrates the difficulty in predicting whether an SSRI-associated bleed may occur and whether the bleeding event is associated with use of the SSRI.

CASE REPORT

Mr. A, a 52-year-old white man, had volunteered as a subject in an institutional review board–approved, randomized, open-label, flexible-dose pilot study of the safety and feasibility of prophylactically administered SSRIs in the treatment of interferon alfa-2b–associated neuropsychiatric side effects.

Approximately 1 month prior to starting the study, the patient underwent a thorough history and physical examination. He denied bleeding tendencies, increased abdominal girth, leg swelling, easy bruising, or changes in weight or bowel habits including bloody or dark stool. He had multiple spider angiomas and a firm nodular liver with a prominent left lobe and a palpable spleen tip.

Mr. A had Child's class A cirrhosis secondary to hepatitis C (genotype 2b) and alcohol consumption. Other comorbid conditions included non–insulin dependent diabetes mellitus, alcohol dependence in early sustained remission (last reported alcohol consumption was 6 months prior to examination), and opioid dependence treated with stable methadone maintenance therapy. His past medical history was unremarkable, and his psychiatric history included 30 years of intravenous opiate dependence, his last use being 12 years ago, and a 10-year history of amphetamine and benzodiazepine dependence, ceasing nearly 20 years ago. He also carried the diagnosis of posttraumatic stress disorder, but had been asymptomatic for 5 years at the time of study initiation.

Medication at Initiation of Trial

Mr. A was receiving glipizide, 5 mg/day, and methadone, 80 mg/day. He had not yet started interferon/ribavirin therapy.

Pertinent Prestudy Laboratory Values

Two months prior to the patient's death, his prothrombin time was 15.5 s (normal range, 11.7–14.6 s), and his international normalized ratio was 1.23 (normal range, 2–3).

One month prior to death, the patient's white blood cell count, hemoglobin, hematocrit, serum albumin, and serum alkaline phosphatase findings were all within normal range. Laboratory findings were as follows: platelets, $75\times10^3/\mu L$ (normal range, $140–415\times10^3/\mu L$); total bilirubin, 1.6 mg/dL (normal range, 0.1–1.2 mg/dL); aspartate aminotransferase, 267 IU/L (normal range, 0–40 IU/L); alanine aminotransferase, 210 IU/L (normal range, 0–40 IU/L).

Although Mr. A had cirrhosis, thrombocytopenia, and a complex psychosocial history, we offered him a course of interferon/ribavirin therapy based on careful consideration of the following facts: he expressed a strong desire to be treated for HCV, he had 6 months of documented alcohol abstinence and over 10 years of abstinence from illicit drug use, and he had the potential for a high likelihood of treatment success with only 6 months of therapy (70%–80% predicted sustained virological response) because he was infected with HCV genotype 2b.

Critical Incident

On day 1 of the study, the patient began taking paroxetine, 10 mg in the morning. By day 8 of the study, he agreed to increase his dose to 20 mg. The following day, a family member witnessed him vomiting blood on multiple occasions, yet he refused to go to the hospital. After bleeding most of the night, Mr. A had a seizure and his family had him transported to the hospital by ambulance. On arrival, he was unresponsive and bleeding, markedly hypotensive, and anemic. Upper endoscopy identified grade 3–4 esophageal varices. Abdominal ultrasound demonstrated extensive ascites. Despite intensive management including a transjugular intrahepatic portosystemic shunt (TIPS) insertion to reduce the portal pressure, his bleeding continued. The following day, the

patient succumbed due to disseminated intravascular coagulopathy, profound shock, and acidosis. An autopsy was not performed.

In subsequent conversations with a relative of the patient, we learned Mr. A was taking amoxicillin and daily aspirin for an unknown period of time for an ear infection. The family member said the patient never increased his dose of paroxetine, nor had he started interferon. Unfortunately, despite our twice-weekly probing, this patient repeatedly denied having concomitant medical problems or taking additional medications. In the following section, we return to this case and review factors that may have led to his bleed in addition to treatment considerations in similar cases.

DISCUSSION

The existence of neuropsychiatric side effects, particularly depression, due to interferon alfa-2b is well documented.[13,49] However, we are aware of only 1 controlled study describing the safety and effectiveness of an SSRI (paroxetine) for the prevention of depression induced by high-dose interferon alfa.[43] Patients in that study were treated with high-dose intravenous interferon for malignant melanoma, and therefore results may not generalize to the care of HCV-infected patients treated with typically lower doses of interferon. Open-label studies and case reports using citalopram, paroxetine, stimulants, and opioid receptor antagonists[8,10,50] have been reported to reduce interferon's side effects. It is also possible that antidepressants in other classes with no association to bleeding, such as bupropion, may be helpful in ameliorating interferon-associated neuropsychiatric symptoms, but no studies currently exist to support this. Nonetheless, it is common clinical practice to treat the psychiatric side effects of interferon therapy for hepatitis C with SSRIs despite the lack of controlled studies to support its efficacy.

It is significant that the rationale behind the use of SSRIs for this off-label indication (reduction of depression produced by interferon among those treated for HCV) is based primarily on case reports and some animal studies,[51,52] but not a wealth of clinical trials. Moreover, it is also true that the basis for the association between SSRIs and bleeding is a logical connection, i.e., the result of the actions of SSRIs on reducing platelet serotonin, a necessary component of platelet plug formation,[53,54] but, again, there are no well-controlled clinical trials among those in treatment for HCV. For these reasons, the practitioner is urged to exert caution in both prescribing SSRIs for relief of interferon-associated depression (since these medications have not been demonstrated effective under these circumstances) and attributing resultant bleeding to the SSRIs, since the evidence for this as a causal agent is not conclusive.

The practitioner is urged to monitor carefully for evidence of bleeding in all patients receiving treatment for HCV, but special attention should be paid to those with cirrhosis, portal hypertension, or hepatic failure. Indeed, in our case study, we identified 3 major factors that could have independently initiated or worsened our patient's bleed, but more likely did so synergistically. These factors were (1) ingestion of aspirin, an established thrombolytic agent[55,56]; (2) the presence of end-stage liver disease with esophageal varices, thrombocytopenia, and portal hypertension; and (3) ingestion of the SSRI paroxetine. One caveat is that because an autopsy was not performed, it is not possible to say that the major source of bleeding in our patient was due to esophageal varices and not peptic ulcer disease or portal hypertensive gastritis, especially since he did not respond to TIPS. Another theory is that inhibition of serotonin reuptake altered the vascular tone in the splanchnic bed, thereby increasing portal blood pressure. This hypothesis is plausible because it is known that variceal bleeding is triggered when blood flow in the portal bed sufficiently increases the trans-sinusoidal gradient. A final, but less likely, contributor to his bleeding may have been his ingestion of antibiotics. This is because patients on treatment with warfarin taking antibiotics have been shown to have increased anticoagulation due to decreased production of vitamin K by colonic bacteria.[57] Thus, in a cirrhotic patient with impaired vitamin K synthesis in the liver, one could see the same effect.

While it cannot be said that SSRIs are conclusively linked with gastrointestinal bleeding, we and others[45,54,58,59] believe there is enough evidence to be cautious when prescribing SSRIs in vulnerable populations. We believe our article is the first to thoroughly examine the issue of a need for careful medication management when treating HCV-infected patients. If the results described in the Dalton et al.[16] and de Abajo et al.[17] studies are valid, then the risks of bleeding when SSRIs are taken with NSAIDs are increased between 3- and 12-fold. Patients with a bleeding diathesis, like those with hepatitis C–related cirrhosis and liver failure or portal hypertension or both, appear to be at the greatest risk of bleeding. Given that interferon alfa-2b is independently associated with thrombocytopenia and patients may be tempted or even instructed to use NSAIDs to control interferon's "flu-like" symptoms, prescribers should be aware of the increased risk of bleeding under these conditions.

As the rates of HCV infection in the United States increase, so does awareness of the potential benefits of treating the neuropsychiatric side effects of interferon with SSRIs. It is therefore essential that well-designed, randomized, controlled trials of SSRIs and other antidepressant classes be conducted in HCV-infected persons to evaluate the efficacy of these agents in the treatment of

interferon-associated neuropsychiatric side effects. Until then, our review and case study suggest the need for caution in assuming that SSRIs will be effective for relief of depression or other psychiatric sequelae—and caution in monitoring all patients receiving SSRI therapy, particularly those with cirrhosis and multiple risk factors for bleeding and those taking NSAIDs.

Drug names: amoxicillin (Amoxil, Trimox, and others), benztropine (Cogentin and others), bupropion (Wellbutrin and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others), glipizide (Glucotrol XL and others), haloperidol (Haldol and others), ibuprofen (Motrin and others), methadone (Methadose, Dolophine, and others), paroxetine (Paxil), ribavirin and interferon alfa-2b combination (Rebetron), warfarin (Coumadin).

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