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Paroxetine Use in Medically Ill Patients

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ABSTRACT ~ Depression is a highly prevalent disorder in the adult population and often worsens the prognosis of comorbid medical illnesses. Recent research has illuminated biological mechanisms by which psychiatric and medical illnesses, as well as their treatments, may affect each other. The relationship between depression and ischemic heart disease is particularly well studied in this regard. The efficacy and safety of antidepressants in the treatment of depression in medically ill patients is an area of increasing interest. The selective serotonin reuptake inhibitors (SSRIs) are often considered the treatment of choice in this clinical setting because of their demonstrated efficacy and safety. This article reviews published studies of SSRIs in the treatment of depression in patients with medical illnesses, with a focus on the contributions of paroxetine. *Psychopharmacology Bulletin*. 2003;37(Suppl 1): 108-122.

INTRODUCTION

An outgrowth of the increasing interest in mind-body interactions is the ongoing and intense scrutiny of central nervous system dysfunction and health outcomes in patients with major medical disorders. Major depression affects 2%-4% of people in the community, 5%-10% of patients in outpatient clinics, and 10%-14% of medical inpatients.¹ Certain medical illnesses are associated with a particularly high rate of major depression (Table 1). Severity of a physical illness is one of the most important variables associated with depression, and rates of depression clearly increase as the health of the patient population declines.^{1,3,4} Conversely, depression leads to greater use of health care resources, inhibits compliance with

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health-promoting behaviors, and adversely impacts the quality of life and survival of the medically ill.⁵

As the bidirectional influences between depression and medical illness have been increasingly documented,^{5,6} another synergy has occurred between the rapidly accumulating understanding of the neurobiology of major mental disorders and the explosion of information about the pathophysiology of diseases such as atherosclerosis, diabetes, and cancer. The notion that psychiatric interventions, in serving to ameliorate the mental stressors associated with declining health and enhance coping strategies, may also inhibit and decelerate disease progression has yet to be proven. At present, antidepressant treatment of depressive disorders may normalize intermediate markers (ie, putative factors associated with a medical disorder) and may or may not diminish disease-related long-term outcomes of morbidity and mortality. Meanwhile, the neurobehavioral alterations that accompany medical illnesses and their treatments afford an opportunity to understand the pathophysiology underlying the so-called "mental disorders," thereby stimulating a more sophisticated phenomenology based on neurobiologic perturbations.

Since their introduction to the market more than 10 years ago, the selective serotonin reuptake inhibitors (SSRIs) have become widely used in the treatment of a broad range of mood and anxiety disorders. Although the use of SSRIs in patients with concomitant medical illnesses has increased over time, some clinicians may be hesitant to use these antidepressants or may be reluctant to use full-dose treatment. Skillful psychopharmacologic treatment of the medically ill patient requires continued efforts to familiarize oneself with medications outside of one's usual pharmacopeia, and vigilance to drug-drug interactions, adverse-event profiles, and drug pharmacokinetics.⁷ A thorough understanding of the therapeutic impact of the SSRI antidepressants in the

TABLE 1

PREVALENCE OF MAJOR DEPRESSION IN SUBGROUPS
OF MEDICALLY ILL PATIENTS²

PATIENT SUBGROUP	RATE OF MAJOR DEPRESSION (%)
Outpatient	2-15
Inpatient	12
Cancer	18-39
Myocardial infarction	15-19
Rheumatoid arthritis	13
Parkinson's disease	10-37
Stroke	22-50
Diabetes	9-27

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context of medical illness is necessary for optimal therapeutic outcome. In accordance with the theme of this supplement, the use of the SSRI antidepressants, and paroxetine in particular, is reviewed herein.

CARDIOVASCULAR DISEASE

An extensive literature has accumulated demonstrating that major depression is an independent risk factor, after controlling for smoking and sedentary lifestyle, for the development of coronary atherosclerotic disease (CAD),⁸ and a significant predictor of early mortality in patients after index myocardial infarction.^{9,10} The pathophysiologic mechanisms contributing to this association are thought to include (1) decreased heart rate variability reflecting imbalance of parasympathetic and sympathetic modulation of heart rate, with resulting predisposition to ventricular arrhythmias,^{11,12} and (2) increased platelet activation.^{13,14} In a 6-week, randomized, double-blind trial comparing nortriptyline and paroxetine for the treatment of depression in 81 patients with CAD, paroxetine and nortriptyline were equally effective antidepressants, but paroxetine was better tolerated.¹⁵ Consistent with the minimal antimuscarinic action of paroxetine at therapeutic doses,^{16,17} paroxetine had no detrimental vagolytic actions on heart-rate variability. In contrast to the cardiovascular effects of tricyclic antidepressants (TCAs), paroxetine and other SSRIs do not have clinically significant effects on heart rate, blood pressure, or the electrocardiogram (Table 2).

Two studies have demonstrated that paroxetine treatment reduces abnormally increased platelet reactivity in depressed patients without¹⁸ and with¹⁹ CAD (Figure 1). Fluoxetine²⁰ and sertraline²¹ also have been shown to inhibit platelet aggregation. The mechanisms responsible for these changes following SSRI treatment have yet to be clearly elucidated, but may involve depletion of intraplatelet serotonin, changes in cell

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TABLE 2

CARDIOVASCULAR EFFECTS OF TRICYCLIC/TETRACYCLIC ANTIDEPRESSANTS AND SSRIS⁸

	TCAS	SSRIS
Overdose	Lethal	Safe
Effects on blood pressure	Orthostatic hypotension	None
Effects on heart rate	Tachycardia	Rare sinus node slowing
Effects on cardiac contractility	None	None
Effects on cardiac conduction	Slowing	None
Antiarrhythmic effects	Type IA antiarrhythmics	None

SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

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surface expression of serotonin transporters and receptors, and/or inhibition of nitric oxide production.^{8,22}

Retrospective examinations of prescription databases have been conducted comparing the safety and efficacy of SSRI versus non-SSRI antidepressants with regard to cardiovascular outcomes.^{23,24} The findings of a double-blind, randomized trial of sertraline versus placebo in patients with recurrent depression who were hospitalized for acute coronary syndromes (N = 369) demonstrated the safety and efficacy of this agent, especially in patients whose depression was of moderate or greater severity.²⁵

In summary, paroxetine and other SSRIs appear to be safe and effective agents in patients with CAD. Plans are currently underway to examine whether effective antidepressant treatment reduces morbidity and mortality in these patients.

NEUROLOGIC DISEASE

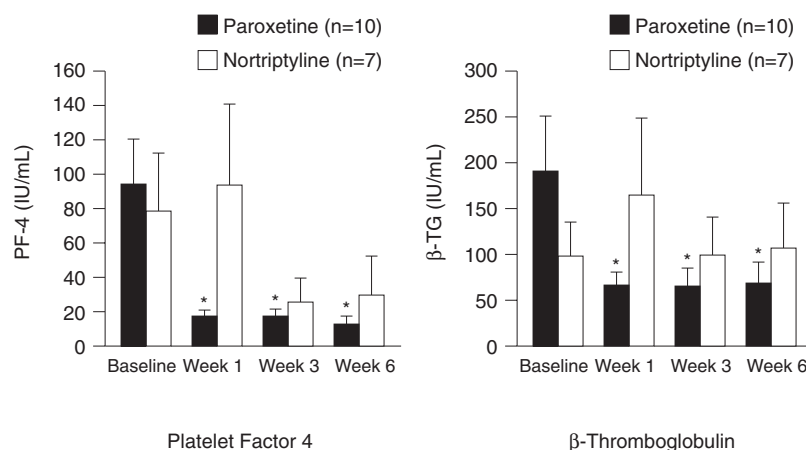
The incidence of depression in patients with neurologic disorders such as stroke or Parkinson's disease has been often attributed to disruption of neurocircuitry critical to maintenance of mood. However, a recent meta-analysis of this literature did not find any consistent association between brain territory of the stroke lesion and vulnerability to depression.²⁶

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FIGURE 1

EFFECT OF PAROXETINE AND NORTRIPTYLINE ON PF-4 AND β TG PLASMA LEVELS IN DEPRESSED PATIENTS WITH ISCHEMIC HEART DISEASE



* $P < .05$ vs baseline.

PF-4=platelet factor; β TG= β -thromboglobulin.

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Randomized, double-blind, placebo-controlled trials have demonstrated the efficacy of nortriptyline²⁷⁻²⁹ and citalopram³⁰ in the treatment of post-stroke depression, and sertraline in the treatment of post-stroke emotional lability.³¹ The findings of double-blind trials of fluoxetine are largely positive, showing efficacy in treatment of post-stroke depression³² or mood lability,³³ although a discordant report exists.²⁹ To date, there are no published trials of paroxetine treatment in post-stroke patients.

Other investigators have queried whether SSRI administration is associated with exacerbation of underlying neurologic disease. Case-control series have demonstrated no association between the use of SSRIs and an increased risk of ischemic³⁴ or hemorrhagic^{34,35} stroke. The SSRIs have been associated with sporadic extrapyramidal symptoms, including Parkinsonian signs,³⁶ and there are case reports of exacerbation of Parkinson's disease during treatment with paroxetine or other SSRIs.³⁷ Two open-label trials of paroxetine (10-20 mg/d) for 3 to 6 months in a total of 98 patients with comorbid depression and Parkinson's disease revealed worsening of motor symptoms in only 3 patients.^{38,39} Conclusive demonstration of the safety and tolerability of paroxetine and other SSRIs in depressed patients with Parkinson's disease will require well-controlled, prospective studies.

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HIV AND AIDS

Depression should be viewed as a major health risk for persons who are HIV-positive because it has been linked with disability, lower quality of life, neurocognitive impairment, declining immune function, accelerated disease progression, and increased mortality.^{40,41} Aside from open-label trials of SSRIs⁴² and nefazodone,⁴³ we are aware of only 2 randomized, double-blind, placebo-controlled trials of antidepressants in HIV patients. A trial of 75 predominantly white, male, HIV-positive outpatients randomized to a 12-week treatment with paroxetine (mean dose, 34 mg/d), imipramine (mean dose, 163 mg/d), or placebo revealed comparable efficacy of paroxetine and imipramine as measured by the Hamilton Rating Scale for Depression and Hamilton Rating Scale for Anxiety (Figure 2).⁴⁰ However, paroxetine was better tolerated, with a dropout rate of 20% compared with that of 48% among imipramine-treated patients and 24% among patients in the placebo group. Dropouts in the imipramine group were frequently the result of such side effects as dry mouth, dizziness/postural hypotension, and palpitations. A second study demonstrated the efficacy and tolerability of fluoxetine in a similar, HIV-positive population.⁴⁴

Further investigation of antidepressant treatment in minority, female, and low-income populations is certainly needed. Remaining to be determined is whether antidepressant treatment of HIV/AIDS patients will improve long-term survival.

Clinicians should be mindful of potential drug-drug interactions between antidepressants and HIV medications. In particular, the protease inhibitors are metabolized by the cytochrome P450 (CYP450) system and are potent inhibitors of CYP3A4 and CYP2D6. Coadministration of paroxetine or other antidepressants along with protease inhibitors may lead to higher plasma concentrations of both medications, resulting in greater propensity for gastrointestinal and other adverse effects.⁴⁵

CANCER

In addition to extraordinary psychosocial challenges and losses, patients with cancer may be especially susceptible to the induction of depressive syndromes secondary to release of proinflammatory cytokines in response to tumor load, tissue damage and destruction, and/or antineoplastic therapies.⁴⁶ Cytokines directly stimulate the hypothalamic-pituitary-adrenal (HPA) axis;⁴⁶⁻⁴⁸ abnormal HPA axis function in depressed patients, in turn, may exert untoward effects on immune system function and reduce long-term survival.⁴⁹

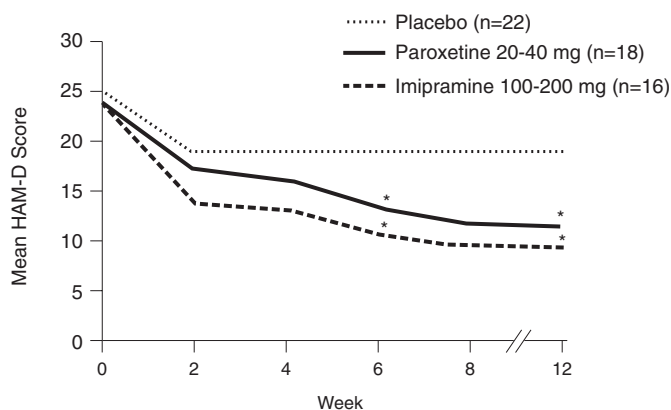
Relatively few well-designed antidepressant trials have been performed in patients with cancer. A multicenter, double-blind, parallel-group study of 179 women with breast cancer randomized to paroxetine (20-40 mg/d) or amitriptyline (75-150 mg/d) found marked improvement in both groups' depressive symptomatology after 8 weeks of treatment.⁵⁰ There

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FIGURE 2

TREATMENT RESPONSE IN HIV-POSITIVE PATIENTS WITH MAJOR DEPRESSION



* $P < .01$ vs placebo

HAM-D=Hamilton Rating Scale for Depression.

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was no difference in efficacy between the 2 agents, whereas paroxetine was better tolerated than amitriptyline. Only mianserin, which is an atypical antidepressant similar in structure to mirtazapine and unavailable in the United States, has been shown to be effective in comparison with placebo in the treatment of depression in patients with cancer.^{51,52} Interestingly, randomized, double-blind, placebo-controlled trials have demonstrated that fluoxetine and venlafaxine are effective in reducing hot flashes in women with estrogen/progesterone receptor-positive breast tumors.^{53,54} In 2 other, open-label trials of paroxetine (20 mg/d for 5-6 weeks) in women with breast cancer (n=13; n=30), the majority of women (62%-73%) reported improvement in hot flash severity and associated fatigue and sleep disturbance.^{55,56}

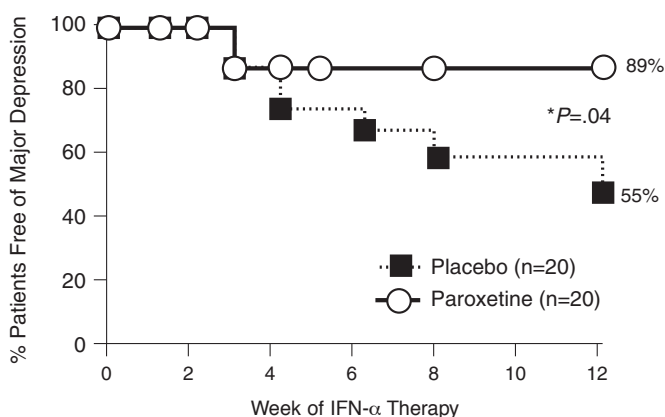
Given the debilitating depressive symptoms suffered by patients receiving immunotherapy, we recently conducted a randomized, double-blind, placebo-controlled trial to determine whether pretreatment with paroxetine would effectively block induction of depressive symptoms by high doses of the cytokine interferon alpha (IFN- α) in nondepressed patients with malignant melanoma.⁵⁷ Patients began receiving paroxetine or placebo 2 weeks prior to initiation of IFN- α administration and continued paroxetine treatment during the first 3 months of IFN- α therapy (mean paroxetine dose, 30 mg/d). Nearly half (45%) of the malignant melanoma patients treated with placebo developed symptoms

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FIGURE 3

PREVENTION OF MAJOR DEPRESSION BY PAROXETINE TREATMENT PRIOR TO AND DURING IFN- α THERAPY IN PATIENTS WITH MALIGNANT MELANOMA



Treatment with paroxetine 20-40 mg/day; IFN- α =interferon- α ; relative risk=0.24 (95% confidence interval, 0.08-0.85).

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sufficient to meet the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*) criteria for major depression in the first 3 months of IFN- α therapy, in comparison to only 11% of the patients treated with paroxetine (Figure 3). The paroxetine-treated patients experienced significantly reduced severity of both anxiety ($P<.001$) and neurotoxicity ($P<.001$) symptoms; these symptoms were reduced by 50% or more in comparison with the placebo-treated patients. Paroxetine treatment also significantly decreased the likelihood that IFN- α had to be discontinued because of severe depression or neurotoxicity (Figure 4).

Further studies are required to determine whether antidepressant treatment in cancer patients influences neoplastic progression.

OBESITY AND DIABETES

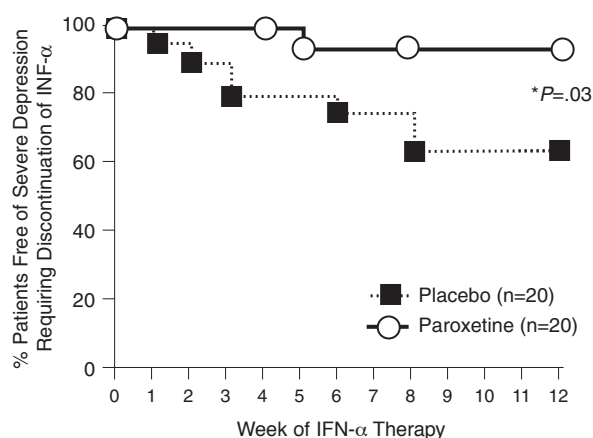
Depression is also associated with abnormalities in metabolically significant pathways. Indeed, patients with major depression without other risk factors for diabetes exhibit evidence of insulin resistance (precursor state to type II diabetes, characterized by impaired glucose metabolism with hyperinsulinemia).⁵⁸⁻⁶² Although the underlying mechanisms are poorly understood, potential biologic pathways by which major depression may act as an independent risk factor for type II diabetes⁶³ include

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FIGURE 4

RATES OF DISCONTINUATION OF IFN- α THERAPY IN PATIENTS WITH MALIGNANT MELANOMA: EFFECT OF PAROXETINE TREATMENT



Treatment with paroxetine 20-40 mg/day; relative risk=0.14 (95% confidence interval, 0.05- 0.85).

IFN- α =interferon- α .

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increased release of counter-regulatory hormones (glucocorticoids, growth hormone, catecholamines, glucagon), alterations in central glucose transporter function, and increased immunoinflammatory activation.⁶⁴

Whereas the TCAs and mirtazapine have been associated with clinically significant weight gain,⁶⁵⁻⁶⁷ the SSRIs have not been consistently associated with significant weight change nor have reproducible differences among SSRIs been demonstrated.^{68,69} Interestingly, when administered for 4 weeks to obese, nondepressed patients with type II diabetes, fluoxetine (60 mg/d) was associated with improved insulin sensitivity without a corresponding weight loss or decrement in glycosylated hemoglobin (HbA1c).^{70,71} In patients with type II diabetes, fluoxetine at this same dosage level has also been documented to be associated with weight loss and clinically significant reductions in HbA1c by 6 months,^{72,73} but not by 12 months.⁷³ Whether these beneficial changes are the result of improved dietary compliance,⁷⁰ increased glycogen synthase activity in skeletal muscle,⁷² or direct effect on glucose transport mechanisms, remains unknown. Paroxetine has not been well studied in patients with diabetes mellitus.

Because of the metabolism of certain oral hypoglycemics by the CYP3A4 isoenzyme (ie, the thiazolidinedione pioglitazone, and the meglitinides, repaglinide and nateglinide), hypoglycemia may be induced if patients are coprescribed SSRI inhibitors of this isoenzyme

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TABLE 3

STUDIES OF SSRI AND OTHER PRESCRIPTION MEDICATION USE AND RISK OF HOSPITALIZATION FOR UPPER GI BLEEDING, SELECTED DATA

Authors	Study Type	Sample Population
de Abajo et al. ^{77*}	Case-control	1651 cases of upper GI bleeding and 10,000 controls in UK general practice database, 1993-1997
Dalton et al. ⁷⁸	Retrospective cohort	Cohort of 490,000 Danish residents, including 26,005 patients receiving antidepressants, excluding patients with history of upper GI bleed or predisposing conditions (alcoholism, esophageal varices, etc), 1991-1995

* Adjusted for sex, age, year, antecedents of upper GI disorders, smoking status, and use of NSAIDs, aspirin, anticoagulants, or steroids.
NSAID=nonsteroidal anti-inflammatory drug; SRI=serotonin reuptake inhibitor;
SSRI=selective serotonin reuptake inhibitor; GI=gastrointestinal.

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(nefazodone, fluoxetine, fluvoxamine). Likewise, inhibition of the CYP2C9 isoenzyme by fluoxetine, fluvoxamine, or sertraline may also potentially interfere with the CYP2C9 metabolism of sulfonureas tolbutamide and glimepride.⁷⁴ Paroxetine is a potent inhibitor of CYP2D6, but has little or no effect on the CYP3A4 and CYP2C9 enzymes;^{75,76} thus, it has minimal potential to inhibit metabolism of currently available hypoglycemic agents.⁷⁴

SPECIAL CONSIDERATIONS FOR USE OF SSRIs IN MEDICALLY ILL PATIENTS

Gastrointestinal Bleeding

Because the SSRIs as a class decrease platelet activation, treatment with these agents may increase the risk of gastrointestinal (GI) bleeding in some patients. Selected results from a case-control study and a retrospective cohort study of upper GI bleeding in relation to antidepressant use recorded in public health databases are presented in Table 3. In both studies, antidepressant agents were assigned to classes based on degree or specificity of serotonin transporter inhibition (eg, clomipramine was included in the SSRI group, as well as trazodone in the case-control study). Comparisons between drug classes were made, in part, to negate confounding variables between depressed and nondepressed patients.

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Subgroup	Risk Ratios (95% confidence interval)
SSRI (current) *	3.0 (2.1 – 4.4)
Nonselective SRI	1.4 (1.1 – 1.9)
Other antidepressant	0.8 (0.2 – 2.4)
SSRI vs no NSAIDs	2.6 (1.7 – 3.8)
NSAID	3.7 (3.2 – 4.4)
SSRI + NSAID	15.6 (6.6 – 36.6)
SSRI (current)	3.6 (2.7 – 4.7)
Nonselective SRI	2.3 (1.5 – 3.4)
Other antidepressant	1.7 (0.8 – 3.1)
SSRI + NSAID	12.2 (7.1 – 19.5)
SSRI + high-dose aspirin, vitamin K antagonist, or corticosteroid	11.6 (7.5 – 16.6)

Ongoing use of SSRIs was associated with the greatest statistically significant increase in risk of bleeding, nonselective serotonin reuptake inhibitors with an intermediate relative risk, and nonserotonin reuptake inhibitors with no statistically significant increase. Concomitant SSRI and nonsteroidal anti-inflammatory drug (NSAID) use (dosages not provided) increased the risk by approximately 4- to 5-fold compared to the risk with SSRI use alone. A third, retrospective cohort study of 317,824 residents of Ontario, aged 65 years and older, who were prescribed an antidepressant agent between 1992 and 1998, compared upper GI bleeding rates according to degree of serotonin transporter inhibition (divided into 3 classes, with paroxetine in the high and trazodone in the low group).⁷⁹ There was no overall association between serotonin transporter inhibition and GI bleeding, but subgroup analysis revealed that a greater degree of serotonin transporter inhibition was associated with a higher risk in patients who were older than 80 years, or had a previous occurrence of gastrointestinal bleeding. There was no statistically significant interaction between any antidepressant class and NSAID use in this study. Taken together, these studies suggest that clinicians should be cautious when using antidepressant agents that are potent inhibitors of serotonin reuptake, particularly in patients who are elderly, have a history of GI bleeding, or are taking high-dose NSAID medication.

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USE OF SSRIS IN PATIENTS WITH LIVER DISEASE

In comparison to liver toxicity associated with use of the atypical antidepressant nefazodone,⁸⁰ there have been very few reports of hepatotoxicity attributed to use of paroxetine or other SSRIs. Eight cases of allergic or idiosyncratic reversible hepatotoxicity attributed to paroxetine use have been reported.⁸¹ Given the widespread use of paroxetine, routine monitoring of liver function tests is not warranted. The elimination half-life of paroxetine is increased in patients with alcoholic cirrhosis; cirrhotic patients may therefore require lower therapeutic doses or be more prone to side effects (eg, nausea) at higher doses.⁸²

DRUG-DRUG INTERACTIONS

The SSRIs are, to variable degrees, associated with inhibition of hepatic drug metabolism involving the CYP450 enzyme system. Paroxetine and fluoxetine are potent inhibitors of the CYP2D6 enzyme, which metabolizes most β -blockers and type I antiarrhythmic drugs, as well as many psychotropic medications. Also, the SSRIs may potentiate the effects of warfarin (eg, in patients taking this agent for atrial fibrillation), because of displacement of the anticoagulant from protein-binding sites.⁷⁵ The pharmacokinetic properties of paroxetine are reviewed elsewhere in this supplement.⁸³

CONCLUSION

Antidepressant treatment in the medically ill patient requires special attention to drug-disease and drug-drug interactions. In the case of paroxetine, particular attention should be paid to potential interactions with other medications metabolized by the CYP2D6 enzyme, and to the possibility that paroxetine and other SSRIs may increase the risk of GI bleeding. This risk appears to be negligible in most patients, but is of particular clinical significance in patients with a history of prior GI bleeding, or in patients who take both an SSRI and high-dose NSAIDs or aspirin.

In addition to the important benefit of relieving emotional suffering, antidepressant treatment may provide benefit in other areas not directly related to the alleviation of core depressive symptoms. For example, paroxetine treatment has been shown to alleviate cognitive dysfunction and pain in patients with malignant melanoma undergoing IFN- α therapy,⁸⁴ improve compliance with immunotherapy and health-related quality of life in HIV patients,^{42,85} and improve hot flashes in patients with breast cancer.^{55,56} Platelet-inhibitory effects of paroxetine may also provide some cardioprotective benefit in patients with ischemic heart disease, but clinical trials are required to test this hypothesis. Compared with the TCAs, which among other liabilities have unfavorable cardiovascular effects, anticholinergic side effects, and high dropout rates in clinical trials, paroxetine and other SSRIs are safe and well tolerated in most groups of medically ill patients. ❀

DISCLOSURE

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