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Fluoxetine

A Review of its Therapeutic Potential in the Treatment of Depression Associated with Physical Illness

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Data Selection

Sources: Medical literature published in any language since 1966 on Fluoxetine, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'Fluoxetine' or 'LY 110140' and ('cardiovascular-diseases' or 'neoplasms' or 'HIV' or 'acquired-immunodeficiency-syndrome' or 'diabetes-mellitus' or 'hypotension-orthostatic'). EMBASE search terms were 'Fluoxetine' or 'LY 110140' and ('stroke' or 'cardiovascular-disease' or 'cancer' or 'human-immunodeficiency-virus' or 'acquired-immune-deficiency-syndrome' or 'diabetes-mellitus' or 'heart-infarction' or 'orthostatic-hypotension'). AdisBase search terms were 'Fluoxetine' or 'LY 110140' and ('stroke' or 'cardiovascular-disease' or 'cardiovascular-disorders' or 'cancer' or 'HIV' or 'acquired-immunodeficiency-syndrome' or 'diabetes-mellitus' or 'orthostatic-hypotension'. Searches were last updated 24 Oct 2000.

Selection: Studies in patients with depression and HIV/AIDS, diabetes mellitus, stroke or cancer who received fluoxetine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: fluoxetine, comorbid physical illness, depression, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Fluoxetine is a potent and selective inhibitor of neuronal serotonin (5-hydroxytryptamine) reuptake. Fluoxetine reduces food, energy and carbohydrate intake and increases resting energy expenditure, which may account for the moderate and transient bodyweight loss observed with its use. Glucose tolerance and/or hypoglycaemia in patients with type 2 diabetes mellitus improve with fluoxetine therapy.

The ability of fluoxetine to inhibit cytochrome P450 (CYP) isoenzymes (CYP2D6, CYP2C and CYP3A4), is potentially important for patients with physical illness who may be taking multiple concomitant medications.

Fluoxetine was more effective than placebo in 2 double-blind, randomised trials, and according to limited data appears to be equally effective compared with other SSRIs and tricyclic antidepressants (TCAs), in the treatment of depression in patients with HIV/AIDS. The efficacy of fluoxetine is also superior to that of placebo in the treatment of depression in patients with diabetes mellitus and stroke as shown in double-blind randomised trials, although its efficacy relative to that of nortriptyline in stroke is uncertain. Fluoxetine had similar efficacy to that of desipramine in patients with cancer, with improved Hamilton Depression Rating Scale and quality-of-life scores from baseline; however, the drug was not more effective than placebo in a double-blind randomised trial.

Medically healthy individuals tolerate fluoxetine well. Like other SSRIs, fluoxetine lacks the anticholinergic, cardiovascular, sedative and weight-increasing properties of TCAs, and is safer in overdose than TCAs and monoamine

oxidase inhibitors. Rates of sexual dysfunction and suicidal ideation with fluoxetine appear similar to those seen with other SSRIs.

Conclusion: Fluoxetine has shown superior efficacy compared with placebo in the treatment of depression in patients with HIV/AIDS, diabetes mellitus or stroke; however, it has not significantly improved depressive symptoms versus placebo in patients with cancer. The efficacy of fluoxetine appears similar to that of desipramine in patients with stroke, cancer or HIV, and is similar to that of sertraline or paroxetine in patients with HIV/AIDS; comparisons with nortriptyline give equivocal results. The potential for drug interactions with fluoxetine use should be carefully considered because most patients with comorbid physical illness will be receiving multiple comedications. Although fluoxetine has proved effective as an antidepressant in this population in several clinical trials, its drug interaction profile and long half-life are a potential limitation, and these properties should be carefully considered in relation to the status of each patient.

Pharmacodynamic Properties

Fluoxetine and its major metabolite, norfluoxetine, are potent and selective inhibitors of neuronal serotonin (5-hydroxytryptamine; 5HT) reuptake. In comparative *in vitro* studies, fluoxetine shows less selectivity in its effects on serotonin reuptake than most other serotonin reuptake inhibitors (SSRIs), including sertraline and paroxetine. Fluoxetine has little or no affinity for α_1-, α_2- and β-adrenoceptors, muscarinic, serotonin 5-HT_1, 5-HT_2, histamine H_1, opioid, dopamine and γ-aminobutyric acid B receptors.

Total daily food intake in healthy volunteers with normal bodyweight, and energy and carbohydrate intake in patients with type 2 diabetes mellitus are reduced with fluoxetine treatment, whereas resting energy expenditure in patients with moderate obesity is increased; these effects may result in bodyweight loss. Treatment with fluoxetine improves glucose tolerance and/or hypoglycaemia in patients with type 2 diabetes mellitus irrespective of the bodyweight-lowering effects of the drug. Discontinuation of fluoxetine treatment may result in hyperglycaemia. Unlike tricyclic antidepressants (TCAs), fluoxetine has no significant clinical effects on cognitive or psychomotor abilities. Fluoxetine treatment does not significantly alter CD4+ counts in patients with HIV/AIDS.

Case reports indicate that fluoxetine can decrease the antiemetic efficacy of ondansetron, a 5-HT_3 antagonist; this effect probably results from the accumulation of serotonin, which competes with ondansetron at the receptor.

Pharmacokinetic Properties

Fluoxetine is well absorbed following oral administration, with mean peak plasma concentrations (C_{max}) of 15 to 55 μg/L after a single dose of 30 or 40mg. The time to C_{max} (t_{max}) is 6 to 8 hours. Coadministration of fluoxetine with food increases the t_{max} by 3 to 5 hours but does not alter the area under the plasma concentration-time curve or C_{max}. Steady-state plasma concentrations are reached after 2 to 4 weeks of fluoxetine treatment. The volume of distribution of fluoxetine ranges from 12 to 43 L/kg after single or multiple doses and the drug is highly protein bound.

Transformation of fluoxetine into norfluoxetine (the primary active metabolite) occurs after extensive first-pass hepatic metabolism involving cytochrome P450 (CYP) 2C and 2D6 isoenzymes. As a potent inhibitor of CYP2D6, fluoxetine is capable of inhibiting its own metabolism, which results in nonlinear pharmacokinetics and high interindividual pharmacokinetic variability. The elimination half-life ($t_{½\beta}$) of fluoxetine is 2 to 7 (mean 4) days after multiple doses; norfluoxetine has a $t_{½\beta}$ of 7 to 15 days.

The clearance of fluoxetine is reduced and $t_{1/2}\beta$ increased in patients with hepatic impairment. In contrast, the pharmacokinetics of fluoxetine and norfluoxetine are not significantly altered in patients with renal failure. The $t_{1/2}\beta$ values of fluoxetine (40 mg/day for 43 days) and norfluoxetine were increased by 28 and 35%, respectively, in healthy elderly volunteers in a multiple-dose study.

Fluoxetine inhibits CYP2D6, CYP2C and CYP3A4, which are involved in the metabolism of a wide range of drugs (including TCAs, some antiarrhythmics, antipsychotics and β-blockers). Caution is advised when coadministering fluoxetine with drugs metabolised by these pathways. In patients with diabetes mellitus, fluoxetine may enhance or prolong the hypoglycaemic response to sulphonylureas.

Therapeutic Efficacy

Fluoxetine has been compared with placebo and other antidepressants in patients with depression and various comorbid physical illnesses. Trials were double-blind and randomised except where stated.

Patients with Depression and HIV/AIDS: Fluoxetine (20 to 60 mg/day for 7 or 8 weeks) with or without group therapy significantly improved symptoms of depression (in multiple assessment scales) compared with placebo in patients who were HIV-seropositive in 2 trials, although results were significant only in an evaluable-patients analysis in 1 of these studies; there were no statistically significant differences from placebo in a third smaller trial. The response to fluoxetine was maintained over an extended 26-week period (including 18 weeks that were noncomparative) in 1 trial.

Fluoxetine 20 to 40 mg/day appeared to have similar efficacy to desipramine (target dose 75 to 100 mg/day), sertraline (50 to 150 mg/day) or paroxetine (20 to 40 mg/day) in small (n = 12 to 24), 6-week trials.

Patients with Depression and Diabetes Mellitus: Significantly more fluoxetine (20 to 40 mg/day) than placebo recipients were classified as responders [a decrease in Beck Depression Inventory (BDI) scores of ≥50%] in an intent-to-treat analysis (n = 60) of an 8-week trial; however, significant differences did not occur between treatment groups in response rates assessed using the Hamilton Depression Rating Scale (HDRS) or in the percentage of patients achieving remission of depression. In an analysis of evaluable patients, fluoxetine significantly improved symptoms of depression from baseline (HDRS and BDI) to a greater extent than placebo. Patients had either type 1 or type 2 diabetes mellitus.

Patients with Post-Stroke Depression: Fluoxetine (20 mg/day for up to 45 days) improved symptoms of depression from baseline [Montgomery and Åsberg Depression Rating Scale (MÅDRS)] to a significantly greater extent than placebo in an intent-to-treat analysis of 31 patients with post-stroke depression. In addition, fluoxetine (20 mg/day) and nortriptyline (25 to 75 mg/day) were equally more effective than placebo (change in HDRS scores from baseline; $p < 0.001$ combined drug treatments) in patients with post-stroke depression (n = 48) in a 6-week study, albeit of nonrandomised design.

In contrast, the efficacy of fluoxetine (10 to 40 mg/day for 12 weeks) was no different from that of placebo and significantly lower than that of nortriptyline (25 to 100 mg/day) [$p = 0.002$] in the treatment of mild to moderate depression in an intent-to-treat analysis (n = 40) in elderly patients recovering from stroke (measured as a >50% reduction in HDRS scores). The lack of efficacy of fluoxetine may have resulted from lower than steady-state concentrations in some

patients and/or the heterogeneous population sample with respect to type of depression.

There were no statistically significant differences in percentage change in HDRS scores from baseline among fluoxetine (10 to 20 mg/day), desipramine (50 to 100 mg/day) or trazodone (50 to 100 mg/day) recipients in the treatment of post-stroke depression in 24 patients in a double-blind randomised trial.

Patients with Depression and Cancer: There was no significant difference in the efficacy of fluoxetine (20 mg/day) versus placebo in the treatment of depression and anxiety in 91 patients with cancer [measured as Hospital Anxiety and Depression Scale (HADS) scores of <8, and improvement of ≥50% in HADS or MÅDRS]. However, fluoxetine (20 to 60 mg/day) and desipramine (25 to 100 mg/day) had similar efficacy in the treatment of 38 women with cancer, with HDRS improved by 43% from baseline in both groups ($p < 0.001$ for both treatments).

Tolerability

Because of the limited nature of the tolerability data in patients with physical illness, this summary focuses on the general tolerability profile of fluoxetine in otherwise healthy individuals with depression. These data may underestimate the adverse effects of fluoxetine in patients with other medical illnesses.

In a survey of 12 692 fluoxetine recipients, adverse events which occurred at a frequency of ≥5% during the first month of treatment included nausea (16.2%), malaise (10.5%), headache (9.4%), insomnia (7.9%), anxiety (7.4%), drowsiness/sedation (6.7%), diarrhoea (5.8%), dizziness (5.4%), vomiting (5.4%) and agitation (5.0%). In a smaller survey of 19 randomised, placebo-controlled trials, adverse events which were reported by ≥5% of respondents and occurred at a higher frequency ($p \leq 0.05$) in patients receiving fluoxetine (20 to 80 mg/day; $n = 1322$) than placebo ($n = 569$) included nausea, insomnia, nervousness, somnolence, anxiety, anorexia, diarrhoea, tremor, dizziness, sweating, asthenia and dyspepsia. Many adverse events experienced with fluoxetine occur early in treatment, with some abating with continued use.

Fluoxetine, like other SSRIs, lacks TCA-like anticholinergic, cardiovascular, sedative and bodyweight-increasing properties, as well as lethality in overdose. In contrast, fluoxetine was associated with higher frequencies of nausea, insomnia, anxiety, diarrhoea, anorexia and rhinitis than TCAs in a survey of 19 randomised clinical trials in patients with major depression. Adverse effects associated with fluoxetine caused fewer premature treatment terminations than adverse effects associated with TCAs ($p < 0.001$).

The incidence of sexual dysfunction with fluoxetine use varies considerably; sexual dysfunction was reported by 5.2% and 58% of fluoxetine recipients in 2 separate analyses. In each study, the level of sexual dysfunction reported with fluoxetine use was similar to that reported with the use of other SSRIs (analyses included 1256 and 693 patients; data for both studies were published in abstracts with no statistical analysis).

Treatment with fluoxetine has been associated with a moderate and transient bodyweight loss in otherwise healthy individuals with depression. Significant bodyweight loss was reported for patients (including some with type 2 diabetes mellitus) treated with fluoxetine (60 mg/day for 36 or 60 weeks) compared with placebo in a retrospective analysis of 950 patients from 3 double-blind, placebo-controlled trials (analysis published as an abstract). Elderly patients (>75 years of age) who were medically ill were also reported to have lost significantly more

bodyweight (average 4.6kg, p = 0.0062) than other groups in a retrospective analysis. In addition, significantly more fluoxetine recipients with post-stroke depression lost ≥8% of initial bodyweight compared with nortriptyline-treated patients (p = 0.0004; analysis of 25 patients).

The overall picture from large cohort and prospective studies and retrospective analyses indicates that the incidence of suicide or suicidal acts in patients using fluoxetine is similar to that for patients using other SSRIs or TCAs.

Fluoxetine alone does not appear to induce serotonin syndrome; however, this event has been reported with the coadministration of fluoxetine and monoamine oxidase inhibitors (MAOIs).

Dosage and Administration

In patients with depression, the initial recommended fluoxetine dosage is 20 mg/day, with additional increases to a maximum of 80 mg/day if patients do not exhibit clinical improvement after several weeks of treatment. Dosage should be reduced for patients with hepatic impairment; reductions in dosage should also be considered for elderly patients and patients using multiple concomitant medications or those with concurrent disease. Fluoxetine may alter glycaemic control in patients with diabetes mellitus; this may require an adjustment in insulin and/or oral hypoglycaemic dosage when fluoxetine therapy is instituted or discontinued.

To reduce the risk of serotonin syndrome, fluoxetine should not be used in combination with an MAOI, and there should be ≥14 days between discontinuing treatment with an MAOI and starting fluoxetine therapy and ≥5 weeks between stopping fluoxetine and starting an MAOI. Caution is advised when coadministering fluoxetine and drugs that are active in the CNS, and/or drugs metabolised by CYP2D6 or CYP3A.

1. Introduction

The prevalence of depressive illness has been estimated at approximately 5% of the general population of the United States.[1] However, approximately 25 to 50% of patients with chronic medical conditions are clinically depressed.[1] The rates, aetiology and course of depression in these patients vary from illness to illness.

Depression occurs in 4 to 22% of patients with HIV/AIDS,[2,3] with rates of depression remaining constant with advancing HIV illness.[4] Depression associated with HIV/AIDS probably results from a complex interaction of psychological and neurological factors;[5] it may be reactive secondary to learning of HIV infection, organic in origin or related to higher rates of preinfection depression.[3,6,7] Lifetime rates of depression are elevated in patients with HIV and approximately 80% of patients with HIV and depression have had depressive episodes prior to infection.[8] There is no consistent evidence that antiretroviral medications are risk factors for depression,[5] and the literature does not support the hypothesis that HIV causes mood changes or that AIDS-related dementia manifests as depression.[5]

The prevalence of major depressive disorder is approximately 9 to 27% in patients with diabetes mellitus (data from structured diagnostic interviews from 4 controlled studies; reviewed by Goodnick et al.[9]), with relapse rates being 8 times greater in these patients than in medically healthy individuals.[10] Depression severity directly interacts with the incidence of complaints and level of hyperglycaemia in patients with type 1 diabetes mellitus.[9] In addition, depression has been associated with an increased rate of diabetic complications in patients with type 2 diabetes mellitus.[11] Furthermore, in elderly patients with diabetes mellitus, major depression adversely affects cognitive

functioning,[12] and the relative severity of depression correlates with worsened glucose control.[13]

Up to 50% of patients with stroke may develop depression (major or minor) during the acute post-stroke period (reviewed by Starkstein and Robinson[14]). Patients with major depression experience spontaneous remission 1 to 2 years post-stroke, whereas the majority of those with minor depression remain depressed 2 years after stroke.[14] Depression associated with stroke may, in part, be related to the areas of the brain affected by the stroke.[15-17] The severity of major depression was greater in patients with left hemisphere brain injury than in those with right hemisphere or brain stem infarctions in a study of 103 patients attending a stroke clinic,[15] and was related to the proximity of the lesion to the left frontal pole in a study of 36 patients (evaluated with computerised tomography).[16] Research indicates that post-stroke depression is involved in a complex interactive relationship with physical impairment and is associated with cognitive deficits. This reduced physical and cognitive functioning impairs social functioning (reviewed by Starkstein and Robinson[14]).

Prevalence rates for depression in patients with cancer range widely, from as low as 4.5% to as high as 58% (reviewed by Massie and Holland[18]); variations are due to differences in the indices used to measure depression, patient populations, hospitalisation status, and cancer stage and type.[19] The prevalence of depression in hospitalised patients with cancer is 20 to 25%.[18] The incidence of depression in patients with cancer appears to be related to the stage of cancer, the level of patient disability,[19] the degree of pain experienced, and a history of affective illness or alcoholism.[18,20] In addition, depression may result from cancer medications.[18]

The diagnosis of depression in patients with physical illness is often difficult and may be complicated by somatic symptoms (such as anorexia, bodyweight loss, fatigue and insomnia) that are common to both depression and the comorbid illness.[4,20] Furthermore, depressive symptoms may be accepted as a natural or inevitable part of the original disease and thus go untreated.[1] As a consequence, depression is diagnosed in fewer than half of those with depressive disorders and physical illness, and appropriately treated in only 30% of patients who are correctly diagnosed.[1]

Antidepressant treatment in patients with physical illness has included serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), amfebutamone (bupropion)[20,21] and venlafaxine,[22] although there has been little systematic study on the efficacy of antidepressants in the treatment of this patient group.[23] This review specifically examines the use of the SSRI fluoxetine in the treatment of depression in patients with HIV/AIDS, diabetes mellitus, stroke or cancer. There are no comparative or placebo-controlled trials of fluoxetine treatment for depression in patients with cardiovascular disease (CVD); thus this patient group has not been included in the review.

2. Pharmacodynamic Properties

It is not within the scope of this article to provide a detailed review of the pharmacodynamic properties of fluoxetine in medically healthy populations; comprehensive reviews have been presented in detail in other publications.[24-27] This section includes a brief overview of the general pharmacodynamic profile of fluoxetine but highlights the pharmacodynamic effects of the drug that may affect the progression of physical disease in patients with comorbid depression.

2.1 General Pharmacodynamic Profile

Fluoxetine and its active metabolite norfluoxetine (section 3.2) are potent and selective inhibitors of *in vitro* and *in vivo* neuronal serotonin reuptake.[25,26] The resultant increased synaptic level of serotonin facilitates serotonergic neurotransmission.[24]

Fluoxetine is less selective in its effects on serotonin reuptake than most other SSRIs. The selectivity ratio for serotonin uptake [the concentration

required to inhibit 50% of uptake sites (IC_{50}) for noradrenaline (norepinephrine)/IC_{50} for serotonin] for fluoxetine (54) was lower than that for citalopram (3400), sertraline (840), paroxetine (280) and fluvoxamine (160) but higher than that for clomipramine (14).[28] Using single photon emission computerised tomography, researchers showed a >40% blockade of selective serotonin transporters in the human brain in 1 patient treated with fluoxetine (up to 60 mg/day; the duration of treatment was not clearly indicated).[29]

In vitro, fluoxetine has little or no affinity for α_1-, α_2- and β-adrenoceptors, muscarinic, serotonin 5-HT_1, 5-HT_2, histamine H_1, opioid, dopamine and γ-aminobutyric acid (GABA) B receptors.[26,28,30] In contrast with TCAs, the lower affinity of fluoxetine for muscarinic receptors results in a relatively low incidence of anticholinergic-type adverse effects (section 5.1).[26]

Fluoxetine treatment may produce a slight and transient drop in bodyweight (section 5.2.2). Fluoxetine 40 mg/day for 16 days decreased the total daily intake of regular and high-fat diets by 18.5 and 14.3% compared with placebo ($p < 0.0001$ and $p < 0.003$) in a single-blind crossover study ($n = 11$).[31] All participants were healthy volunteers with normal bodyweight. The median reduction in energy intake from baseline was significantly greater at 3 and 6 months in fluoxetine (–212 and –279 kcal) than in placebo (+45 and –80 kcal) treatment groups ($p < 0.05$ for both periods) in a 12-month, randomised, double-blind trial in patients with obesity and type 2 diabetes mellitus.[32] In addition, median carbohydrate intake was significantly reduced for fluoxetine versus placebo treatment groups, both as daily intake after 3 and 6 months (3 months, –34 *vs* +4 g/day; 6 months, –26 *vs* +3 g/day; $p < 0.05$) and percentage of daily energy intake at 3, 6 and 9 months (3 months, –6.4 *vs* –0.5%; 6 months, –5.9 *vs* +0.2%; 9 months, –2.2 *vs* +1.8%; $p < 0.05$ for all 3 periods). However, at 12 months there were no significant differences for any parameter. Data were analysed for 7 patients receiving fluoxetine 60 mg/day and 9 patients receiving placebo.[32]

In a randomised, double-blind, placebo-controlled trial, fluoxetine 60 mg/day increased the resting energy expenditure of 10 patients with moderate obesity by 4.4% ($p < 0.005$) from baseline within 3 days of treatment initiation despite restriction of energy intake.[33] This delayed the expected reduction in resting energy expenditure that usually accompanies severe energy restriction; resting energy expenditure fell below normal after a mean of 9.8 days for fluoxetine recipients. In contrast, resting energy expenditure decreased from baseline after a mean of 5.6 days for 10 participants receiving placebo.[33]

Unlike TCAs, fluoxetine (in single 40mg doses or 20 mg/day for 22 days) does not significantly affect cognitive or psychomotor performance (including driving ability) in healthy volunteers.[34-36] In addition, fluoxetine (10 to 20 mg/day for 6 weeks) did not significantly affect mood in volunteers not experiencing significant anxiety or depression.[37]

An association between fluoxetine treatment and disorders of haemostasis has been documented in case reports; however, results from several small studies ($n = 5$ to 10) do not provide any evidence of significant or marked impairment of haemostatic function in healthy volunteers and patients with depression receiving fluoxetine 20 or 40 mg/day.[38-40] Parameters assessed included thrombin time, partial thromboplastin time, platelet aggregation and plasma levels of fibrinogen and coagulation factors.

2.2 In Patients with Depression and Comorbid Physical Illness

This section is focused on additional pharmacodynamic effects of fluoxetine that may have a beneficial or adverse effect on disease progression in patients with depression and comorbid physical illness (see also section 7).

2.2.1 Glucose Control in Patients with Diabetes Mellitus

Case reports indicate that patients with diabetes mellitus may experience improved glucose tolerance and/or hypoglycaemia with fluoxetine use and hyperglycaemia with treatment discontinuation.[41,42]

These effects are more common in patients with type 2 diabetes mellitus; in a study of 7 adolescents with type 1 diabetes mellitus there were no significant changes in blood glucose levels or daily insulin requirements after fluoxetine 20 mg/day for 2 weeks.[43]

Fluoxetine (60 mg/day for 2 or 4 weeks), however, improves insulin sensitivity in patients with type 2 diabetes mellitus;[44,45] these effects occur irrespective of the bodyweight-lowering effect of the drug. For example, in a randomised, double-blind, placebo-controlled trial, fluoxetine (60 mg/day for 4 weeks) improved insulin sensitivity measured with the euglycaemic hyperinsulinaemic clamp (see DeFronzo et al.[46]) in 12 patients with obesity (body mass index over 27 kg/m^2) and type 2 diabetes mellitus.[45] At lower insulin infusion concentrations (40 mU/m^2/min), there were significant differences in the percentage change from baseline for fluoxetine versus placebo in the amount of glucose infused, the insulin sensitivity index and the glucose metabolic clearance rate (fig. 1). At higher insulin infusion concentrations (400 mU/m^2/min), the percentage change from baseline in the insulin sensitivity index was significantly different for fluoxetine versus placebo treatment groups (fig. 1). There was no loss in bodyweight throughout the treatment period.

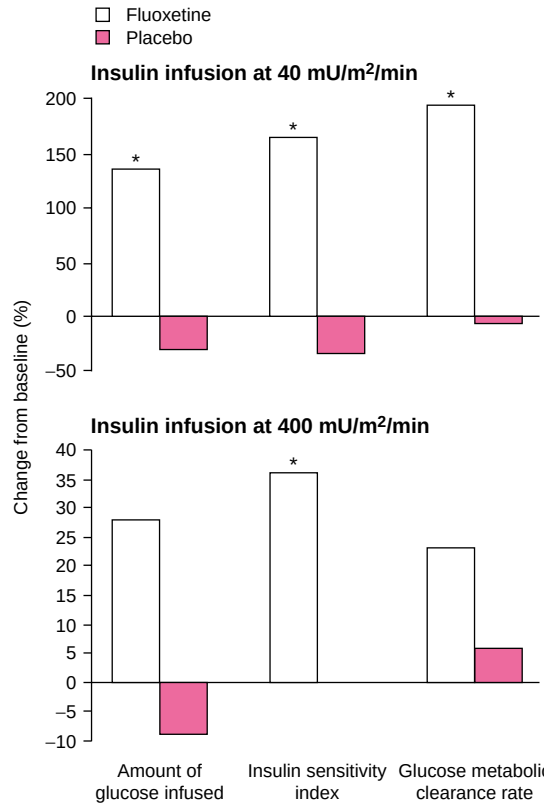

Fig. 1. Insulin sensitivity results of the euglycaemic hyperinsulinaemic clamp after fluoxetine (60 mg/day for 4 weeks) or placebo.[45] Data for 12 patients with obesity (body mass index >27 kg/m^2) and type 2 diabetes mellitus. Amount of glucose infused = the glucose disposal rate; insulin sensitivity index = glucose disposal rate divided by steady-state plasma insulin level; glucose metabolic clearance rate = glucose disposal rate divided by steady-state plasma glucose level. * $p \leq 0.05$ *vs* placebo.

2.2.2 CD4+ Status in Patients with HIV/AIDS

Depression has been associated with immunosuppression and more rapid progression of HIV illness,[47] although this relationship has not been consistently demonstrated,[48] with some studies failing to find an effect (e.g. Rabkin et al.[49]). Pharmacological treatment could potentially improve immune status secondary to improvement in depressive symptoms; however, medication could also adversely affect patients with already compromised immune systems.[23] The effect of fluoxetine on immune status secondary to the treatment of depression has been investigated in 2 clinical trials in patients with HIV/AIDS.[23,50]

Fluoxetine treatment did not significantly alter CD4+ counts from baseline in a double-blind, randomised, placebo-controlled trial in patients with depression comorbid with HIV/AIDS.[23] At trial completion [an average of 18 and 12 weeks for fluoxetine (20 to 60 mg/day) and placebo recipients, respectively], the CD4+ count had not significantly changed from baseline for 57 patients receiving fluoxetine (baseline mean = 306 cells/mm^3, end-point mean = 277 cells/mm^3) or 30 patients receiving placebo (baseline mean = 248 cells/mm^3, end-point mean = 250 cells/mm^3).[23] A

similar nonsignificant decrease in CD4+ counts from baseline was reported in a noncomparative trial of 18 fluoxetine recipients and 12 patients treated with coadministered fluoxetine and dexamphetamine.[50] All patients were HIV-seropositive; mean treatment duration was 26 weeks for patients treated with fluoxetine (10 to 60 mg/day) and 30 weeks for those receiving fluoxetine (dosage unclear) plus dexamphetamine (dosage beginning at 2.5 mg/day).

2.3 Pharmacodynamic Drug Interactions

At a pharmacodynamic level, SSRIs can interact with other central serotonin agonists.[51] Coadministration of fluoxetine has been reported to decrease the antiemetic effects of ondansetron (observed as increased vomiting; data were from 3 case reports).[52] Ondansetron is a 5-HT_3 antagonist; when fluoxetine and ondansetron are used concomitantly, it is likely that the accumulation of serotonin (resulting from fluoxetine use) competes with ondansetron at the 5-HT_3 receptors.[52]

3. Pharmacokinetic Properties

There are no studies on the pharmacokinetic properties of fluoxetine in patients with depression and comorbid physical illness; therefore the data reviewed in this section are from healthy volunteers or patients with depression. The general pharmacokinetic properties of fluoxetine have been comprehensively reviewed in previous publications[26,53-56] and therefore are only briefly reviewed here.

3.1 Absorption and Distribution

Fluoxetine is well absorbed following oral administration, with an oral bioavailability of 72% (in beagle dogs).[26,54] Mean peak plasma concentrations (C_{max}) were 15 to 55 μg/L in healthy volunteers after a single dose of fluoxetine 30 or 40mg; time to C_{max} (t_{max}) was 6 to 8 hours.[54] Although t_{max} was increased by 3 to 5 hours when fluoxetine was coadministered with food, the extent of absorption [area under the plasma concentration-time curve (AUC)] and C_{max} were not altered, which suggests that the consumption of food slows the rate but does not affect the overall extent of absorption of fluoxetine.[57] C_{max} values were dose proportional for fluoxetine 20 to 80mg;[57] however, interindividual variability was high.[58]

Steady-state plasma concentrations (C^{ss}) are reached after 2 to 4 weeks of fluoxetine treatment with no further accumulation during long term administration (up to 3 years).[26] The volume of distribution of fluoxetine, which ranges from 12 to 43 L/kg after single or multiple doses, is high because of extensive tissue distribution.[26,54,59] There is also extensive (94%) plasma protein binding.[26,54]

3.2 Metabolism and Elimination

Fluoxetine undergoes extensive first-pass metabolism in the liver. The primary metabolite, norfluoxetine, has similar activity to fluoxetine.[53,54] The formation of norfluoxetine from fluoxetine appears to involve cytochrome P450 (CYP) 2C[60,61] and 2D6 isoenzymes.[62]

Fluoxetine is also a potent inhibitor of the isoenzyme CYP2D6[53,54,63] (see also section 3.4) and thus can inhibit its own metabolism.[24] Consequently, nonlinear pharmacokinetics and high interindividual pharmacokinetic variability are observed with fluoxetine administration.[54,63] In addition, no consistent relationship has been described between plasma fluoxetine concentrations and clinical response.[63]

The elimination half-life ($t_{½β}$) of fluoxetine is 1 to 4 (mean 2) days after a single dose and 2 to 7 (mean 4) days after multiple doses.[53,54] Norfluoxetine has a $t_{½β}$ of 7 to 15 days.[53]

3.3 Special Patient Groups

Values for fluoxetine $t_{½β}$ were significantly increased in 13 patients with hepatic impairment (cirrhotic changes on biopsy and/or liver isotope scan) compared with 12 healthy volunteers (6.6 *vs* 2.2 days, $p = 0.008$).[64] This reflected a significant reduction in plasma clearance (17.8 *vs* 44.8 L/h, $p = 0.01$). In contrast, the pharmacokinetics of fluoxetine and norfluoxetine were not significantly dif-

ferent for 7 patients with renal failure requiring haemodialysis (creatinine clearance not stated) compared with 9 patients with normal renal function.[65] Mean fluoxetine C^{ss} values were similar in both groups after 8 weeks of treatment with fluoxetine 20 mg/day (218 *vs* 253 μg/L).

Fluoxetine is excreted in breast milk; however, there are no recorded abnormalities in breast-fed babies during treatment or follow-up (mean duration of 64.8 days).[66]

The effect of age on the elimination of fluoxetine remains unclear.[58] In a single-dose study of fluoxetine 40mg there were no significant pharmacokinetic differences for fluoxetine and norfluoxetine in elderly (aged 65 to 77 years) compared with young healthy volunteers.[67] However, the possibility of altered pharmacokinetics in elderly patients can not be eliminated on the basis of single-dose studies because fluoxetine has a relatively long $t_{½β}$ and nonlinear disposition after multiple-dose administration. This may be of particular importance in elderly patients with systemic disease and/or in those receiving multiple medications concomitantly.[58] In a multiple-dose study (40 mg/day, for 43 days), $t_{½β}$ values for fluoxetine and norfluoxetine were increased by 28 and 35%, respectively, in 16 healthy elderly volunteers (aged 65 to 82 years; 5 and 20.3 days, respectively) than in 14 healthy adult volunteers (3.9 and 15 days);[68] however, the difference did not reach statistical significance.[69] C_{max} and AUC_{0-24} of fluoxetine and norfluoxetine were lower in elderly than in adult volunteers (fluoxetine, 268 *vs* 276 μg/L and 5573 *vs* 5730 μg/L · h, respectively; norfluoxetine, 241 *vs* 336 μg/L and 5131 *vs* 7177 μg/L · h); the differences with age in C_{max} and AUC_{0-24} were significant for norfluoxetine ($p < 0.01$ for both measures).[69]

3.4 Pharmacokinetic Drug Interactions

Fluoxetine and norfluoxetine concentration-dependently inhibit a range of CYP isoenzymes.[70] At the usual effective dose, fluoxetine potently inhibits CYP2D6,[53,71,72] and CYP2C9/10,[72,73] moderately inhibits CYP2C19[73] and mildly inhibits CYP3A3/4,[53,72] but has no clinically meaningful effects on CYP1A2.[53] Norfluoxetine, the primary metabolite of fluoxetine, is more potent than the parent drug in its *in vitro* inhibition of CYP2C19, 2D6 and 3A3/4 (reviewed by Shad and Preskorn[73]). This is clinically relevant given that, under steady-state conditions, the plasma concentrations of norfluoxetine exceed those of fluoxetine, and norfluoxetine has an extended $t_{½β}$ (section 3.2).[73]

The CYP isoenzymes are involved in the metabolism of a wide range of drugs, including TCAs, some antiarrhythmics, antipsychotics and β-blockers.[24] Potential drug interactions with fluoxetine have been presented elsewhere.[24,70,74] This section is primarily focused on potential interactions between fluoxetine and other medications taken by patients with HIV/AIDS, diabetes mellitus, stroke or cancer.

As discussed, both fluoxetine and norfluoxetine are potent inhibitors of CYP2D6.[53] Drugs, such as the antineoplastic agent vinblastine, which are predominantly metabolised by this isoenzyme and have relatively narrow therapeutic indices could potentially reach toxic concentrations if coadministered with fluoxetine.[53,71,75]

Plasma concentrations of fluoxetine and norfluoxetine may be increased with coadministration of drugs that are substantial inhibitors of CYP3A isoenzymes (including protease inhibitors, especially ritonavir[76]). Coadministration of fluoxetine and ritonavir appears to result in an increase in serum fluoxetine concentrations[76] and is associated with cardiac and neurological events which may result from a drug-drug interaction.[77] In 1 study, coadministration of fluoxetine increased the AUC of ritonavir (by 19%), which is metabolised primarily by CYP3A4 and, to a lesser extent, by CYP2D6, although this was not of sufficient magnitude to be clinically significant.[78] Dosage adjustments have not been recommended for either drug based on this evidence.[76] This study has been criticised for not achieving steady-state concentrations of fluoxetine, which are necessary when as-

sessing a pharmacokinetic interaction between 2 drugs.[79]

Coadministration of fluoxetine with sulphonylurea drugs may enhance or prolong the hypoglycaemic response to sulphonylureas in patients with diabetes mellitus.[74]

Because of the prolonged elimination of both fluoxetine and norfluoxetine (section 3.2), drug interactions may occur with medication administered several weeks after fluoxetine treatment has been discontinued.[58] If such interactions are known or suspected, management options include monitoring for clinical signs of drug toxicity, monitoring plasma drug concentrations and adjusting the dosage when appropriate, or avoiding the drug combination.[53]

4. Therapeutic Efficacy

Comparative clinical trials evaluating the efficacy of fluoxetine versus placebo, TCAs or heterocyclic antidepressants, or other SSRIs for the treatment of depression (including major depression, dysthymia and minor depression) comorbid with physical illness have been conducted in patients with HIV/AIDS,[23,80-84] diabetes mellitus,[85] stroke[86-89] or cancer.[90,91] The majority of studies had small sample sizes, with the number of patients enrolled ranging from 14 to 120. Most comparative trials were double-blind and randomised,[23,80-82,85-88,90,91] although 1 trial[89] of fluoxetine versus nortriptyline and 2 studies[83,84] of fluoxetine versus other SSRIs were nonblind and nonrandomised. Some trials included a placebo washout period of 1 or 2 weeks to either exclude early placebo responders or wash out previous psychotropic medications.[80,82,90]

The efficacy of fluoxetine (20mg twice weekly to 60 mg/day) for the treatment of depression comorbid with physical illness has also been evaluated in several small (n = 8 to 32) noncomparative trials of 4 to 12 weeks' duration;[50,92-96] fluoxetine dosage and trial length were unclear in a trial in elderly patients.[97]

Evaluation of the efficacy of fluoxetine for the treatment of depression in patients with physical illness is complicated by the diverse range of efficacy measures used in clinical trials. The Hamilton Rating Scale for Depression (HDRS), the Clinical Global Impression (CGI) scale and the Beck Depression Inventory (BDI) were the most common measures used in comparative trials. Primary efficacy measures included changes from baseline in mean HDRS and/or BDI or CGI scores,[23,80,84,88,89,91] mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MÅDRS),[86] percentage of patients responding (a decrease in HDRS scores of ≥50%, or CGI scores of either 1 or 2)[23,80] or success rates [Hospital Anxiety and Depression Scale (HADS) < 8].[90] The primary efficacy measure was not clearly indicated in 5 trials;[81-83,85,87] all these trials used several of the measures indicated above.

In most clinical trials, DSM-III-R or DSM-IV criteria were used to diagnose depression and determine patient inclusion;[23,80,82-85,87,88,90,91] however, diagnostic criteria were not clearly stated in 1 trial.[81] In 1 trial in patients recovering from stroke, depression was assessed using Research Diagnostic Criteria,[89] and in another study in patients with stroke, depression was determined using the International Classification of Diseases 10th Revision and MÅDRS score.[86] Additional inclusion criteria based on HDRS, BDI or HADS scores were used in some trials.[81-83,85,87,89,90] Across studies, the depressive characteristics of patients were heterogeneous; some studies included patients with major depressive disorder only,[80,82-86,93,94,96] whereas others also included patients with other disorders (e.g. adjustment disorder with depressed mood[81,91] or mixed features,[90] organic mood disorder with depression,[88] dysthymia,[23,50] and minor depressive disorder[90]). The type of depressive disorder was difficult to determine in 4 studies.[87,89,92,97]

Baseline scores ranged from 17.5 to 23.5 for HDRS,[23,80,81,83,87-89] 13.7 to 33.6 for BDI,[80,83-85] 22.7 to 23.5 for HADS[90] and 25.2 to 28.5 for MÅDRS.[86,90] The mean baseline score was not reported in 1 study, although a score of >14 on the first 17 items on the HDRS scale was required for

inclusion.[89] There were no significant differences in baseline scores for fluoxetine versus placebo treatment groups in any of the placebo-controlled trials.[23,80,81,85,86,90] In most randomised comparative trials there were no differences at baseline between fluoxetine and the comparator antidepressants;[83,87-89] however, baseline scores were not reported in a study in patients with cancer,[91] and statistical analysis of baseline scores was not reported in 2 studies in patients with HIV.[82,84]

4.1 Comparison with Placebo

4.1.1 Patients with Depression and HIV/AIDS

Intent-to-treat analyses demonstrated a significant improvement in symptoms of depression (evaluated in multiple assessment scales) in patients who were HIV-seropositive (some had an AIDS-defining condition) receiving fluoxetine (20 to 60 mg/day) compared with placebo in 1[80] of 3 trials (table I).[23,80,81] Significantly more patients receiving fluoxetine than placebo were classified as responders using the HDRS (≥50% decrease in HDRS scores).[80] The change in HDRS and BDI scores from baseline was also significantly greater for fluoxetine than placebo recipients in this trial.[80] There were significant improvements in depression (percentage of patients responding using HDRS and CGI) in an analysis of evaluable patients in 1 trial (table I).[23] However, a third trial did not show a significant improvement in favour of fluoxetine (20 mg/day) [using HDRS and Profile of Mood States-depression];[81] the small sample size (n = 18) in this trial may have contributed to the lack of statistical power. In 2 trials (1 with significant[80] and the other nonsignificant[81] results), all patients received concurrent group therapy. There were no significant differences in dropout rates for fluoxetine- versus placebo-treated patients in the 2 largest studies;[23,80] statistical analysis was not reported in the smallest trial.[81] Reasons for discontinuation included loss to follow-up, development of adverse events, nontreatment-related illness, worsening of mood symptoms, substance abuse and lack of efficacy.[23,80]

Two studies evaluated whether depression severity was related to treatment outcome.[23,80] In 1 trial, significantly more patients with severe (baseline HDRS ≥24) but not mild to moderate (baseline HDRS <24) depression responded (CGI score of 1 or 2) to fluoxetine versus placebo (severe depression: 83 *vs* 33%, $p = 0.03$; mild to moderate depression: 63 *vs* 50%, not significant).[80] In the second trial, there were no differences in mean baseline HDRS scores or chronicity between responders and nonresponders in either treatment group (patients with chronic disease had dysthymia with or without major depression or major depression with recurring episodes, whereas patients with nonchronic disease were experiencing their first episode of major depression).[23] The dropout rate was 27.5% (33 patients, of whom 24 had been assigned to fluoxetine);[23] patients who completed the study were more likely to have more chronic or recurrent ($p < 0.05$) and more severe (HDRS; $p < 0.01$) depressive illness than noncompleters.[23]

Evaluation of fluoxetine was extended over a 26-week period (which included the 8-week placebo-controlled period and an 18-week noncontrolled period) in 1 trial.[23] The 28 fluoxetine responders from the blind phase who continued to take fluoxetine all maintained their response. Four of 6 patients who had a partial response (not defined) to fluoxetine in the initial phase responded by week 16 of treatment, although 1 also took adjunctive amphetamine and 2 had fluctuating mood courses. Seven of 10 patients unresponsive to placebo responded to fluoxetine treatment in the long term study (measured at week 16), and 5 of 6 placebo responders who started fluoxetine had additional benefit.[23]

4.1.2 Patients with Depression and Diabetes Mellitus

Significantly more patients with type 1 or 2 diabetes mellitus receiving fluoxetine (20 to 40 mg/day for 8 weeks) than placebo were classified as responders using the BDI scale (≥50% decrease in BDI scores) in an intent-to-treat analysis of 60 patients (table I).[85] However, there were no significant differences between treatment groups in

Table I. Efficacy of fluoxetine (FLU) in patients with depression comorbid with physical illness in double-blind, randomised, placebo (PL)-controlled trials. Efficacy was measured as percentage of patients responding and/or percentage change from baseline using various scales; the most common included HDRS,[23,80,81,85] CGI[23,80] and BDI,[80,97] although MÅDRS[86,90] and HADS were also used[90]

Reference	No. of patients randomised (evaluable)	Duration of study (wk)	Treatment/dosage (mg/day)	Results: ITT (evaluable patients) analysis[a]			
				patients responding[b] (%)		change from baseline (%)	
				HDRS	other	HDRS[c]	other[d]
HIV/AIDS							
Rabkin et al.[23]	81 (57)	8	FLU 20-60	(79*)	51 (74**) CGI	67	NR
	39 (30)		PL	(57)	36 (47) CGI	56	NR
Targ et al.[81]	(9)[e]	12	FLU 20 + structured group therapy	NR	NR	68	NR
	(9)[e]		PL + structured group therapy	NR	NR	68	NR
Zisook et al.[80]	25 (21)	7	FLU 20-60 + group psychotherapy	64**	64 CGI	59*	42* BDI
	22 (16)		PL + group psychotherapy	23	50 CGI	33	9 BDI
Diabetes mellitus							
Lustman et al.[85]	30 (27)	8	FLU 20-40	53 (59)	60* (67*) BDI	(53**)	(59*) BDI
	30 (27)		PL	37 (41)	33 (37) BDI	(27)	(39) BDI
Stroke							
Wiart et al.[86]	16 (14)	≤45d	FLU 20	NR	63 MÅDRS	NR	59* MÅDRS
	15 (15)		PL	NR	33 MÅDRS	NR	31 MÅDRS
Cancer							
Razavi et al.[90]	45 (30)	5	FLU 20	NR	31 MÅDRS; 18 HADS	NR	(48) MÅDRS; (34) HADS
	46 (39)		PL	NR	33 MÅDRS; 20 HADS	NR	(41) MÅDRS; (26) HADS

a Results from both ITT (unbracketed) and evaluable patients (bracketed) analyses have been presented.

b Definitions of patient response varied amongst the trials and included a decrease in HDRS scores of ≥50%,[23,80,85] CGI scores of either 1 or 2 (indicating very much or much improved),[23,80] a decrease in BDI scores of ≥50%,[85] and an improvement in HADS and MÅDRS scores of ≥50%[90] or >50%.[86]

c Baseline scores ranged from 18.6 to 20.8.[23,80,81]

d Baseline scores ranged from 13.7 to 23.6 for BDI,[80,85] and 25.2 to 28.5 for MÅDRS,[86,90] and were 22.7 to 23.5 for HADS.[90]

e 18 patients completed this trial (9 in fluoxetine and 9 in placebo treatment groups); however 20 patients were randomised. The distribution of these patients in treatment groups is unclear.

BDI = Beck Depression Inventory; **CGI** = Clinical Global Impression; **HADS** = Hospital Anxiety and Depression Scale; **HDRS** = Hamilton Rating Scale for Depression; **ITT** = intent-to-treat; **MÅDRS** = Montgomery-Åsberg Depression Rating Scale; **NR** = not reported; * $p < 0.05$, ** $p \leq 0.01$ *vs* PL.

response rates assessed using HDRS (≥50% reduction in HDRS score) [table I] or in the proportion of patients achieving remission of depression (BDI score ≤9, HDRS score ≤7).[85] In an analysis of evaluable patients in this study, there was a significantly greater reduction from baseline in both BDI and HDRS scores in the fluoxetine versus placebo treatment groups (table I). Six of 60 patients discontinued treatment early, 3 in the fluoxetine and 3 in the placebo treatment groups. Four patients withdrew without explanation, 1 patient experienced fluoxetine-associated adverse effects and 1 patient receiving placebo had a cardiac event.[85]

4.1.3 Patients with Post-Stroke Depression

In an intent-to-treat analysis, there was a significantly greater percentage change in MÅDRS scores from baseline with fluoxetine (20 mg/day for up to 45 days) than with placebo in 31 elderly patients who had had a single ischaemic or haemor-

rhagic stroke within the last 3 months (mean ages were 66.3 and 68.9 years for fluoxetine- and placebo-treated patients) [table I].[86] There was a nonsignificant trend toward a difference between treatment groups in the percentage of patients responding (improvement in MÅDRS >50%). Two patients receiving fluoxetine discontinued treatment early; 1 patient developed increased hepatic alanine aminotransferase and aspartate aminotransferase levels and the other did not comply with the treatment regimen.[86]

4.1.4 Patients with Depression and Cancer

Fluoxetine (20 mg/day for 5 weeks) was not significantly better than placebo in the treatment of depression and anxiety in patients with cancer.[90] 11% of patients (5 of 45) receiving fluoxetine and 7% of those taking placebo (3 of 46) had HADS scores of <8 (primary end-point) in an intent-to-treat analysis. The difference between treatment groups was not significant for this variable or for HADS or MÅDRS response rates (table I).[90] There were no significant changes from baseline in HADS or MÅDRS scores in an analysis of evaluable patients (table I).[90] Significantly more patients dropped out of the fluoxetine than placebo treatment groups ($p = 0.04$).[90] The main reason for patients discontinuing fluoxetine treatment was the development of adverse events. Other reasons included alcohol abuse, and non-compliance with the protocol.[90]

4.2 Comparison with Other Antidepressants

4.2.1 Comparison with Tricyclic and Heterocyclic Antidepressants

Patients with Post-Stroke Depression

Fluoxetine was either less effective than[87] or equally effective as[89] nortriptyline in 2 trials comprising different trial designs and study groups. Fluoxetine (10 to 40 mg/day for 12 weeks) was significantly less effective than nortriptyline (25 to 100 mg/day) [$p = 0.002$] and no different from placebo in patients with mild to moderate depression, measured as a >50% reduction in HDRS scores (table II), in an intent-to-treat analysis in a double-blind, randomised, crossover, placebo-controlled trial in elderly patients recovering from stroke (mean ages were 65, 64 and 73 years for patients treated with fluoxetine, nortriptyline and placebo).[87] In addition, the percentage change in HDRS score from baseline was smaller in the fluoxetine (9%) versus the nortriptyline (60%) and placebo (30%) treatment groups in an analysis of evaluable patients (table II). The p-values for fluoxetine versus nortriptyline or placebo were not reported for this variable.[87] Patients with and without depression were included in this study to determine whether any observed improvement was related to recovery from depression or a depression-independent neurochemical effect.[87] These results are surprising given that fluoxetine has shown efficacy greater than placebo in elderly patients with post-stroke depression (section 4.1.3). Possible reasons for the lack of efficacy in this study are discussed in section 7.3.

On the other hand, fluoxetine (20 mg/day) and nortriptyline (25 to 75 mg/day) were equally effective in the treatment of depression in patients (n = 48) recovering from stroke in a 6-week study, albeit of nonrandomised design (although patients were randomised to the placebo group, patients in the fluoxetine and nortriptyline groups were non-randomly selected based on their cardiac profile; blinding was not stated).[89] Fluoxetine produced a 66% and nortriptyline a 65% change from baseline in HDRS scores compared with 4% for placebo ($p < 0.001$ combined fluoxetine and nortriptyline *vs* placebo; values estimated from a graph). At the end of 6 weeks, patients treated with fluoxetine or nortriptyline had mean HDRS values similar to those for untreated patients (n = 82) without depression [8 and 7.5 *vs* 7, respectively (values taken from a graph)].[89]

Symptoms of depression improved from baseline (percentage change in HDRS) to a similar extent in patients receiving fluoxetine (10 to 20 mg/day), desipramine (50 to 150 mg/day) or trazodone (50 to 100 mg/day) for 4 weeks in a small (n = 24), double-blind, randomised clinical trial (table II).[88]

Table II. Efficacy of fluoxetine (FLU) compared with tricyclic and heterocyclic antidepressants in patients with depression comorbid with physical illness in double-blind, randomised, parallel-group[82,88,91] or crossover[87] trials

Reference	No. of patients randomised (evaluable)	Duration of study (wk)	Treatment (mg/day)	Results: ITT (evaluable-patients) analysis[a]	
				no. patients responding (HDRS)[b]	change from baseline in HDRS score (%)
HIV					
Schwartz & McDaniel[82]	8 (8)	6	FLU 20-40	3 (partial)[c] 2 (full)[c,d]	43[c]
	6 (2)		DES 75-100	2 (partial) 1 (full)	33
Stroke					
Miyai & Reding[88]	5 (4)	4	FLU 10-20	NR	14
	13 (9)		DES 50-100	NR	17
	6 (6)		TRA 50-100	NR	35
Robinson et al.[87]	23 (14)[e]	12	FLU 10-40	2	(9)
	16 (13)[e]		NOR 25-100	10[†]	(60)[f]
	17 (13)[e]		PL	4	(30)[f]
Cancer					
Holland et al.[91]	21 (15)	6	FLU 20-60	NR	43
	17 (10)		DES 25-150	NR	43

a Results from both ITT analysis (unbracketed) and analysis of evaluable patients (bracketed) have been presented.

b ≥50% reduction in HDRS score. Additional requirements included no longer fulfilling diagnostic criteria for major depression in 1 study.[87]

c Sample sizes were too small to analyse statistical significance for fluoxetine *vs* desipramine.

d A full response was defined as partial response (≥50% reduction in HDRS score from baseline) plus HDRS scores falling below 8.

e This trial included 56 patients with and 48 patients without depression, making a total sample size of 104. Data for patients with depression only are presented in this table.

f p-values for mean change or percentage change in HDRS scores from baseline were not presented for fluoxetine *vs* nortriptyline or placebo groups. Mean HDRS scores at 12 weeks were significantly lower in the nortriptyline *vs* fluoxetine group (Duncan statistic, $p < 0.05$) and the placebo *vs* fluoxetine group (Duncan statistic, $p < 0.05$).

DES = desipramine; **HDRS** Hamilton Rating Scale for Depression; **ITT** = intent-to-treat; **NOR** = nortriptyline; **NR** = not reported; **PL** = placebo; **TRA** = trazodone; † $p = 0.002$ for nortriptyline *vs* fluoxetine, $p = 0.05$ for nortriptyline *vs* placebo.

Patients with Depression and HIV or Cancer

Fluoxetine (20 to 60 mg/day) and desipramine (25 to 150 mg/day) have been compared in similar small studies in patients with HIV (n = 14)[82] or women with cancer (n = 38).[91] The percentage change from baseline after 6 weeks was 43% for both fluoxetine and desipramine ($p < 0.001$ *vs* baseline) in patients with cancer (table II).[91] Quality of life (evaluated in multiple assessment scales) was also improved with fluoxetine or desipramine use in this patient group. Fluoxetine- but not desipramine-treated patients showed statistically significant improvements from baseline in Memorial Pain Assessment Card Mood scale ($p < 0.001$) and Pain Intensity scale ($p = 0.005$) scores after adjusting for investigator effects.[91] Both fluoxetine and desipramine recipients showed significant improvements from baseline in adjusted Functional Living Index for Cancer sum scores ($p = 0.008$ and $p = 0.025$) and in SF-36 Health Survey transformed mean scores for 'Role Emotional', 'Social Functioning', 'Mental Health' and 'Vitality' (p-values were not reported).[91]

Improvements in symptoms of depression after 6 weeks tended to be greater in the fluoxetine (43% change from baseline HDRS) than in the desipramine (33%) treatment group in an intent-to-treat analysis in the small trial in patients with HIV infection (table II).[82] The number of responders on HDRS (table II; partial response, ≥50% reduction in score from baseline; full response, partial response and final HDRS scores <8) and CGI (rating

of 1 or 2) scales appeared similar.[82] The small sample sizes in this trial prevented any meaningful statistical analysis.

4.2.2 Comparison with Other Serotonin Reuptake Inhibitors in Patients with Depression and HIV/AIDS

Fluoxetine (20 mg/day) and paroxetine (20 mg/day) improved symptoms of depression from baseline (mean baseline scores, 28.4 and 33.6, respectively), measured using BDI, by 69 and 79% in a small nonblind, nonrandomised 6-week clinical trial in patients with HIV infection (evaluable n = 12; treatment groups were combined for statistical analysis, $p < 0.001$).[84]

Similarly, 9 of 10 patients treated with fluoxetine (20 to 40 mg/day) were classified as responders (CGI scores of 1 or 2) versus 5 of 7 patients receiving sertraline (50 to 150 mg/day) and 6 of 7 who were administered paroxetine (20 to 40 mg/day) in a small, nonblind, nonrandomised 6-week trial in patients with HIV/AIDS (n = 24).[83] There were also reductions from baseline in HDRS and BDI scores for all treatment groups, although supporting data were not presented.[83]

4.3 Noncomparative Trials

An improvement in symptoms of depression [measured as change from baseline HDRS, BDI or CGI scores, response according to CGI (score of 9 or 10 with no existing major depressive disorder), Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) depression score <3, or improvement on BDI], was demonstrated with fluoxetine treatment (20mg twice weekly to 60 mg/day) in small (n = 8 to 32) noncomparative trials in patients with HIV/AIDS,[50,92-95] patients recovering from stroke,[96] or elderly patients with a wide range of comorbid physical illnesses.[97] The changes in HDRS scores from baseline were statistically significant in 2 trials in patients with HIV ($p < 0.0001$;[50] the p-value was not reported in 1 trial[93]), and similar for seronegative and seropositive patients in a third trial.[94]

5. Tolerability

Tolerability data for fluoxetine in patients with physical illness are limited. Most clinical trials are small, which prevents meaningful analysis of adverse effects. Of all the clinical trials in patients with concurrent depression and physical illness, comparative statistical analysis of adverse effects has been carried out in only one – a trial in 38 patients with cancer receiving either fluoxetine (20 to 60 mg/day) or desipramine (25 to 150 mg/day).[91] However, results from this trial were confounded by adverse events which probably resulted from concurrent therapeutic regimens.[91]

Given the lack of tolerability data in patients with physical illness, this section briefly reviews the general tolerability profile of fluoxetine in otherwise healthy patients with depression; these data may underestimate the adverse effects of fluoxetine in patients with physical illness. Where possible, any issues significant for patients with depression comorbid with HIV/AIDS, cancer, stroke or diabetes mellitus are highlighted. More comprehensive reviews of the tolerability profile of fluoxetine are available in other publications.[24,98-100]

5.1 General Tolerability Profile

In a large survey of 12 692 fluoxetine recipients, the most commonly reported adverse events were nausea (16.2%), malaise (10.5%), headache (9.4%), insomnia (7.9%), anxiety (7.4%), drowsiness/sedation (6.7%), diarrhoea (5.8%), dizziness (5.4%), vomiting (5.4%) and agitation (5.0%).[101] All these events occurred at a frequency of ≥>5% during the first month of fluoxetine treatment; 89.4% of patients received fluoxetine 20 mg/day, and the remainder received daily doses of up to 120mg.[101] All adverse events that occurred at a frequency of ≥5% in a smaller survey of 19 randomised placebo-controlled trials are presented in figure 2.[102] Most adverse events, except headache, dry mouth, rhinitis and constipation, were reported at a significantly higher frequency ($p \leq 0.05$) by patients receiving fluoxetine [20 to 80 mg/day (trial durations were not reported); n =

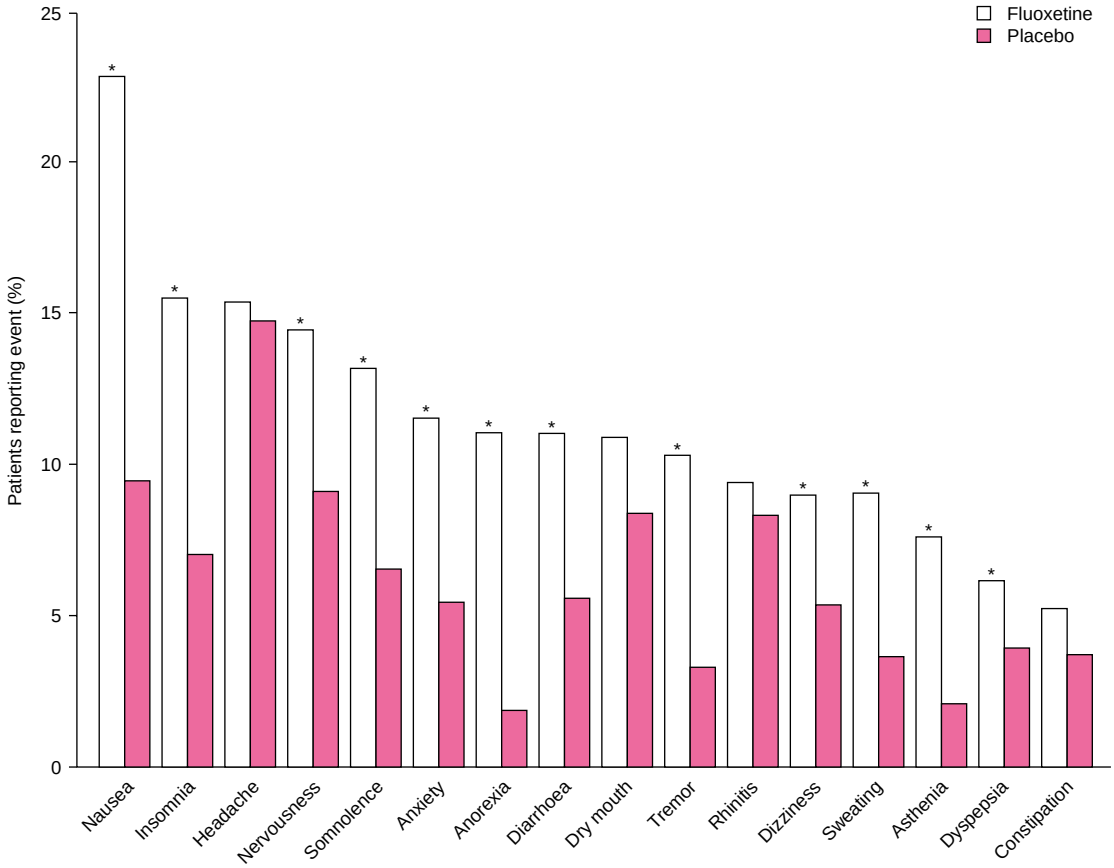

Fig. 2. Treatment-emergent adverse events occurring in ≥5% of patients with depression after fluoxetine or placebo treatment.[102] Data for 1891 patients (1322 receiving fluoxetine 20 to 80 mg/day and 569 receiving placebo) from a meta-analysis of 19 randomised trials (trial durations were not given). * $p \leq 0.05$ *vs* placebo.

1322] than those receiving placebo (n = 569) [fig. 2].[102]

Infrequent (1/100 to 1/1000 patients) or rare (<1/1000 patients) adverse effects associated with fluoxetine treatment include hypotension, atrial fibrillation, bradycardia, extrapyramidal symptoms, akathisia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), skin rashes, hallucinations, paranoid reactions and altered liver function tests.[75] Mania has been reported with fluoxetine use in patients with post-stroke depression, although data are from only a small number of case reports.[103,104] Cases of hyponatraemia, which may result from SIADH, have been reported in elderly patients. However, there were no statistically significant differences in the prevalence of hyponatraemia in elderly patients (≥60 years of age) receiving fluoxetine versus placebo (3 *vs* 2%) in two 6-week controlled studies.[105]

Many adverse effects experienced with fluoxetine occur early in treatment and some – including nausea, insomnia and headache – abate with continued use.[98,106] In a survey of 299 patients, the frequency of all adverse events reported by ≥5% of

fluoxetine (20 mg/day) recipients in the first 4 weeks of treatment significantly declined with continued fluoxetine use over a 6-month period (p values ranged from 0.032 to < 0.001).[106]

Fluoxetine, like other SSRIs, has a different tolerability profile from that of the TCAs. It lacks TCA-like anticholinergic, cardiovascular, sedative and bodyweight-increasing properties, as well as lethality in overdose.[98] In the survey of 19 randomised clinical trials in patients with major depression, significantly more patients ($p \leq 0.05$) in the fluoxetine (20 to 80 mg/day; n = 781) than the TCA (n = 788) treatment group reported nausea (24 *vs* 16%), insomnia (14 *vs* 7%), anxiety (11 *vs* 7%), diarrhoea (9.2 *vs* 4%), anorexia (7 *vs* 3%) or rhinitis (6 *vs* 4%), whereas significantly more patients ($p \leq 0.05$) receiving TCAs had dry mouth (62.6 *vs* 19.7%), somnolence (29.1 *vs* 19.2%), dizziness (28.4 *vs* 12.2%), constipation (26.0 *vs* 9.3%), abnormal vision (11.2 *vs* 6.3%) or paraesthesia (6.9 *vs* 3.3%).[102] Fluoxetine-associated adverse effects caused fewer premature treatment terminations than adverse effects associated with TCAs (16.6 *vs* 30.6%, $p < 0.001$).[102]

5.2 Other Effects

Other effects of fluoxetine (e.g. sexual dysfunction, bodyweight change and suicidal ideation) may be exacerbated by symptoms of pre-existing disease in patients with physical illness and, thus, these effects may be of particular importance in the treatment of depression in this group. Decreased libido and bodyweight loss (each <5%) were reported more often ($p \leq 0.05$) by patients receiving fluoxetine than placebo in a survey of 19 randomised trials.[102] However, with the exception of analyses of bodyweight changes in patients treated with fluoxetine for depression comorbid with diabetes mellitus[107] or stroke[87] and elderly patients with comorbid physical illness,[108] there is no research on these events in patients with physical illness. The association of sexual dysfunction, bodyweight change, suicidal ideation or serotonin syndrome with fluoxetine use in otherwise healthy patients with depression has been comprehensively reviewed or evaluated in other publications.[24,109,110] These events will therefore be only briefly reviewed in this article.

5.2.1 Sexual Dysfunction

There are numerous reports of the type and incidence of sexual dysfunction in patients receiving fluoxetine.[111-116] The incidence of sexual dysfunction with fluoxetine use varies considerably. This can be illustrated by 2 large multicentre prospective studies.[114,115] In an analysis of 1256 patients receiving SSRIs for the first time, 5.2% of those treated with fluoxetine had sexual dysfunction compared with 6.9, 9.4 and 12.6% of patients treated with fluvoxamine, sertraline and paroxetine, respectively, with sexual dysfunction more common in men than women (16.2 *vs* 6.2%, $p < 0.001$).[114] In contrast, in an analysis of 693 patients, 58% of patients receiving fluoxetine compared with 61, 64, 67 and 80% of those treated with sertraline, fluvoxamine, paroxetine and citalopram, respectively, had sexual dysfunction.[115] All of the SSRIs produced a higher incidence of sexual dysfunction than other drugs such as nefazodone, mirtazapine and amineptine.[115] Both studies were published as abstracts; no statistical data were provided.

5.2.2 Bodyweight Change

In otherwise healthy patients with depression, treatment with fluoxetine has been associated with a moderate and transient bodyweight loss,[117-120] although bodyweight gain and hyperphagia have been observed in some patients.[121,122] Moderate bodyweight losses (<0.5kg) were observed in all patients (n = 832) during fluoxetine treatment (20 mg/day) in the initial nonblind phase (12 weeks) of a long term trial; bodyweight loss occurred primarily in the first 4 weeks of treatment.[117] However, during the randomised, double-blind, placebo-controlled phase (an additional 14, 26 or 38 weeks), in which 395 patients were enrolled, there were no significant differences in bodyweight loss for patients receiving fluoxetine (20 mg/day) versus placebo; in fact, bodyweight gain was observed overall in both treatment groups during this period.[117]

In a retrospective analysis of data from 3 double-blind, placebo-controlled trials (36 or 60 weeks' duration) of 950 patients (some with type 2 diabetes mellitus), patients treated with fluoxetine (60 mg/day) lost significantly more bodyweight ($p < 0.05$) than patients receiving placebo.[107] There were no differences in bodyweight loss between patients with or without diabetes mellitus (analysis published as an abstract).[107]

In a retrospective review of 103 medical charts, patients who were medically ill and >75 years old experienced significantly greater bodyweight loss (average 4.6kg, $p = 0.0062$) compared with patients of the same age group who were not taking medication or who were using TCAs, and younger patients (60 to 71 years) receiving fluoxetine.[108] Bodyweight loss was greater than 5% of baseline bodyweight in 7 of 15 patients in this group.[108] Similarly, 10 of 12 fluoxetine-treated patients with post-stroke depression lost ≥8% of initial bodyweight compared with only 2 of 13 nortriptyline-treated patients ($p = 0.0004$).[87] This analysis included only patients for whom bodyweight data were available (25 of 104 patients).

5.2.3 Suicidal Ideation

Attention was focused on fluoxetine in relation to suicide after case reports emerged of patients who developed increased suicidal ideation after starting treatment with fluoxetine.[109] However, a large cohort study (12 692 fluoxetine recipients),[123] a large retrospective analysis of data from double-blind clinical trials (1765 fluoxetine recipients)[124] and a small prospective study (185 fluoxetine recipients)[125] have not shown any statistical differences in the incidence of suicide in patients using fluoxetine compared with those using other SSRIs, or any association between fluoxetine and suicidal behaviour. A meta-analysis of data from 17 double-blind trials involving a total of 3065 patients revealed no statistically significant differences in the incidence of suicidal acts or the worsening of suicidal ideation between patients receiving fluoxetine and those receiving placebo or TCAs.[124] The pooled incidence of the emergence of substantial suicidal ideation was significantly lower with fluoxetine (1.2%) than with placebo (2.6%, $p = 0.042$) or TCAs (3.6%, $p = 0.001$). In addition, there was significantly more improvement of suicidal ideation for fluoxetine (72.2%) versus placebo (54.8%, $p < 0.001$) in a pooled analysis; improvement was similar with fluoxetine and TCAs (69.8%). Worsening of suicidal ideation was similar in all groups (15.3, 16.3 and 17.9% for fluoxetine, TCAs and placebo).[124]

5.2.4 Serotonin Syndrome

Serotonin syndrome, which results from excessive serotonergic activity, is rare but potentially fatal. Symptoms, which include changes in mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination and fever, occur after the initiation or dosage increase of a serotonergic agent.[110] Fluoxetine alone does not appear to induce serotonin syndrome; however, fluoxetine coadministered with MAOIs, tryptophan or sertraline can provoke this syndrome.[110] Thus coadministration of fluoxetine and MAOIs is contraindicated and caution is advised during concomitant administration of fluoxetine with other serotonergic agents (section 6).

6. Dosage and Administration

Fluoxetine is recommended at an initial daily dose of 20mg administered in the morning. The dosage can be increased if patients do not exhibit clinical improvement after several weeks of treatment; however, it should not exceed a maximum of 80 mg/day.[105]

Caution is advised, and a lower or less frequent dose should be considered, when fluoxetine is administered to patients using multiple concomitant medications or with concurrent disease.[105] Fluoxetine should be given at lower or less frequent doses to patients with hepatic impairment (including cirrhosis of the liver) because the systemic clearances of both fluoxetine and its metabolite norfluoxetine are decreased and $t_{½\beta}$ increased in this patient group (section 3.3).[105] Dosage adjustments are not routinely necessary for patients with renal impairment; there is no evidence of excessive

accumulation of fluoxetine or norfluoxetine in plasma in patients on dialysis (section 3.3).[105]

Fluoxetine treatment may alter glycaemic control in patients with diabetes mellitus; hypoglycaemia has been observed with fluoxetine use and hyperglycaemia has occurred following fluoxetine discontinuation (section 2.2.1). Therefore, insulin and/or oral hypoglycaemic dosages may need to be adjusted when fluoxetine therapy is instituted or discontinued.[105] Bodyweight loss may be an undesirable result of treatment with fluoxetine (section 5.2.2),[105] especially in patients with advanced cancer who may already be underweight or anorexic (section 7); thus, lower or less frequent doses should be considered. However, bodyweight loss may be desirable in patients with diabetes mellitus (section 7.2).

Lower or less frequent doses of fluoxetine should be considered in elderly patients; after multiple doses, $t_{½\beta}$ values for fluoxetine and norfluoxetine were longer in elderly volunteers (section 3.3).[105] Breast feeding during fluoxetine treatment is not recommended.[105]

The risk of serotonin syndrome (section 5.2.4) means that fluoxetine should not be used in combination with an MAOI.[105] Furthermore, ≥14 days should be allowed to elapse between discontinuing treatment with an MAOI and starting fluoxetine therapy, and ≥5 weeks should be allowed between stopping fluoxetine and starting an MAOI because of the long $t_{½\beta}$ values of fluoxetine and norfluoxetine.[105] Caution is advised when coadministering fluoxetine and drugs that are active in the CNS, and/or drugs metabolised by CYP2D6 (especially those with a narrow therapeutic index, such as vinblastine) or CYP3A [section 3.4].[105]

7. Place of Fluoxetine in the Management of Depression in Patients with Physical Illness

Fluoxetine, along with other SSRIs (sertraline and paroxetine), TCAs, MAOIs, amfebutamone and venlafaxine, has been used for the treatment of depression in patients with physical illness.[20,21] When prescribing an antidepressant for this patient group, in addition to typical considerations, a physician must also consider the patient's medical diagnosis and any complications, the potential for drug interactions between the antidepressant and concomitant medications (sections 3.4 and 7.6), and the tolerability profile of the antidepressant in association with the patient's disease symptoms.[20]

There has been little systematic study of the efficacy of antidepressant treatment in patients with physical illness.[23] Comparative and/or placebo-controlled trials have been conducted in patients with HIV infection and AIDS, diabetes mellitus, stroke or cancer (section 4) but not CVD. Most trials are small and have high placebo response rates, which may result in only a modest or no difference in efficacy between the treatments. In addition, disease factors (e.g. spontaneous neurological improvement after stroke) or rehabilitation care may have increased placebo response rates in some trials.[86] Comparison across trials is often complicated by differences in both inclusion criteria for depression and efficacy measures (section 4).

7.1 Patients with Depression and HIV/AIDS

Fluoxetine was more effective than placebo in the treatment of depression in patients who were HIV-seropositive in 2 of 3 randomised, double-blind clinical trials (section 4.1.1);[23,80] however, in 1 trial,[23] improvement in symptoms was significant only in an of evaluable patients. Furthermore, the placebo response rate in both trials was relatively high and thus the difference between the 2 treatments was modest. In 1 trial[80] all participants received concurrent group therapy; thus absolute fluoxetine and placebo responses may not have been assessed. The lack of efficacy of fluoxetine versus placebo (over and above group therapy) in a third trial may be the result of the small sample size, large placebo effect and sample heterogeneity (not all patients met the criteria for a major depressive disorder).[81]

The efficacy of fluoxetine for the treatment of depression in patients with HIV/AIDS appears similar to that of other SSRIs (paroxetine and

sertraline) [section 4.2.2] and TCAs (desipramine) [section 4.2.1] in a small number of clinical trials, although group comparisons were not statistically analysed because of small sample sizes. The full therapeutic effects of fluoxetine may not have been established because of short trial durations (6 weeks for all trials).[126] Despite these limitations, fluoxetine response was comparable to responses reported for SSRIs (sertraline[4] and paroxetine[127]) and TCAs (imipramine[127-130]) in other double-blind studies not involving fluoxetine in patients who were HIV-seropositive.

SSRIs (including fluoxetine) have several advantages over TCAs for the treatment of depression in patients with HIV/AIDS.[4] SSRIs do not have the anticholinergic or sedating adverse effects which are associated with TCA use (section 5.1).[4] TCAs with a higher incidence of anticholinergic adverse effects (e.g. amitriptyline) are generally not recommended for patients who are HIV-seropositive with cognitive impairment or dementia because of the potential for aggravated cognitive dysfunction or possible precipitation of delirium.[131] SSRIs have a simpler treatment regimen (e.g. 1 capsule of fluoxetine or 2 tablets of sertraline each day provide an effective therapeutic dosage for most patients compared with 5 or 6 tablets of various TCAs) and have a greater margin in overdose than TCAs (section 7.5).[4]

Adverse effects associated with SSRI treatment are fewer, milder and more transient than those occurring during TCA treatment.[4] However, the choice of antidepressant depends on the combination of the drug's tolerability profile and the patient's HIV-related symptoms.[130] For example, the sedating effects of TCAs (e.g. amitriptyline and imipramine) may be beneficial for patients experiencing restlessness, agitation or insomnia,[130,131] but are distressing for patients with fatigue and low energy.[130] Fluoxetine or sertraline (which are associated with diarrhoea) might be preferable for patients using high doses of opioid analgesics, which cause constipation.[130] However, they would not be suitable for patients with chronic diarrhoea caused by cryptosporidiosis.[130] TCAs may be preferred for the treatment of depression in patients with anorexia secondary to AIDS,[21] although bodyweight loss and anorexia associated with fluoxetine are generally transient (section 5.2).

Potential drug interactions between fluoxetine and protease inhibitors are discussed in sections 3.4 and 7.6.

7.2 Patients with Depression and Diabetes Mellitus

Overall, fluoxetine was more effective than placebo in the treatment of depression in patients with type 1 or 2 diabetes mellitus in a double-blind randomised trial (analysed using an intent-to-treat analysis of percentage of patients responding to BDI and evaluable-patient analysis of percentage change from baseline in BDI and HDRS) [section 4.1.2].[85] The efficacy of fluoxetine in these patients has not been compared with that of other antidepressants in clinical trials; however, response rates for fluoxetine were similar to those reported in a study of nortriptyline in patients with type 1 or 2 disease.[132]

Problematic adverse effects with MAOI and TCA treatment in patients with diabetes mellitus (below) have led some authors[133,134] to propose that SSRIs should be considered first-line therapy for the treatment of depression in this group. SSRIs, including fluoxetine, have been associated with hypoglycaemia and thus could potentially improve glucose control in patients with diabetes mellitus[9] – especially patients with type 2 disease (section 2.2.1). With fluoxetine use, insulin and/or oral hypoglycaemic dosage may need to be adjusted (section 6). The reduced food intake and bodyweight loss associated with SSRIs (sections 2.1 and 5.2.2)[9] may also be beneficial for patients with diabetes-associated obesity.

In contrast, TCAs should be used with caution[134] and MAOIs should be used only as a last-line therapy[133] for the treatment of depression in patients with diabetes mellitus. TCAs are associated with bodyweight gain[135,136] and cravings for sweets and carbohydrates,[137,138] which may be problematic for patients with calorie-controlled in-

take.[9,134] TCAs can worsen hyperglycaemia and glycaemic control during long term treatment,[132-134] and their anticholinergic, orthostatic hypotensive and cardiovascular adverse effects may exacerbate symptoms inherent to diabetes mellitus (e.g. constipation associated with diabetic gastroparesis).[134,139] MAOIs may exaggerate hypoglycaemia and delay recovery to normal glucose levels when used in combination with insulin or sulphonylureas.[140] In addition, MAOI treatment is associated with bodyweight gain and requires stringent dietary modification, which further complicates the dietary requirements of patients with diabetes mellitus.[134]

7.3 Patients with Post-Stroke Depression

Fluoxetine improved symptoms of depression in patients recovering from stroke to a significantly greater extent than placebo in a double-blind randomised trial (all patients had major depressive disorder; section 4.1.3).[86] However, the efficacy of fluoxetine was not significantly different from that of placebo and was less than that of nortriptyline in a double-blind, randomised trial in elderly patients with post-stroke depression (section 4.2.1).[87] The lack of efficacy for fluoxetine in this trial may have resulted, in part, from lower than steady-state fluoxetine concentrations in some patients; unfortunately, the authors did not monitor serum concentrations of fluoxetine and norfluoxetine. Efficacy may also have been affected by the inclusion of patients with minor as well as major depressive disorder;[87] however, the relationship between depression severity and response to fluoxetine has not been established for patients with post-stroke depression. Notably, the efficacy of fluoxetine was similar to that reported for nortriptyline in a different, albeit nonrandomised trial, and to that of desipramine and trazodone in a randomised comparative study (section 4.2.1).[88]

Many authors[89,96,141,142] advise the use of SSRIs (including fluoxetine) rather than TCAs for the treatment of patients with post-stroke depression; the anticholingeric, orthostatic hypotensive and cardiovascular adverse effects associated with TCA use may exacerbate symptoms associated with stroke. In contrast, fluoxetine may improve motor function[142] and cognitive performance[89] in patients with post-stroke depression. (Enhanced functional recovery has also been observed with administration of trazodone[88]).

Fluoxetine use has been associated with significant bodyweight loss in patients with stroke[87] and elderly patients with physical illness (section 5.2.2),[108] although fluoxetine-associated bodyweight loss and anorexia are often transient and disappear with long term administration in otherwise healthy individuals with depression (section 5.2.2).[9] The clinical relevance of bodyweight loss for patients recovering from stroke remains unclear.

7.4 Patients with Depression and Cancer

Fluoxetine improved symptoms of depression from baseline in patients with cancer in 2 double-blind, randomised trials,[90,91] with an efficacy comparable to that of desipramine in 1 trial (section 4.2.1).[91] In addition, fluoxetine significantly improved quality of life from baseline (evaluated in multiple scales) in the comparative study with desipramine (section 4.2.1).[91] However, in the placebo-controlled trial, improvement in depressive symptoms did not significantly differ for fluoxetine versus placebo (section 4.1.4).[90] In both studies, trial duration (5 and 6 weeks) may not have been long enough to establish the full therapeutic effect of fluoxetine, which has a relatively slow onset of action.[126]

The choice of antidepressant for the treatment of depression in patients with cancer depends largely on the agent's tolerability profile and potential for drug-drug interactions.[19] Nausea and vomiting, which have been reported with the use of fluoxetine, other SSRIs and venlafaxine may be problematic for patients with cancer undergoing emetic chemotherapy.[19] However, in medically healthy individuals nausea tends to emerge early during fluoxetine use, with many patients developing tolerance relatively rapidly (1 to 2 weeks) as a result of subsensitisation of 5-HT_3 receptors.[100]

In addition, fluoxetine has been reported to decrease the efficacy of the antiemetic ondansetron (section 2.3).[52] The occurrence of diarrhoea associated with fluoxetine may benefit patients with slow intestinal motility and constipation secondary to opioid pain medication.[19,143]

Although it is generally transient in otherwise healthy patients with depression (section 5.2.2), the bodyweight loss associated with fluoxetine use may be undesirable for patients with cancer who have lowered bodyweight associated with the cancer itself, or treatment or nutritional difficulties;[19] however, it may be preferable for patients with breast cancer who have bodyweight gain associated with adjuvant chemotherapy.[143]

Patients with stomatitis secondary to chemotherapy or radiotherapy require an antidepressant that is relatively free of anticholinergic effects.[19,144] Orthostatic hypotension associated with TCAs and trazodone may cause falls and fractures in patients with cancer who have skeletal weakness or bone metastases[19,143] and therefore these drugs may be unsuitable for these patients.

7.5 Overdose

Compared with the general population, patients with physical illness, especially advanced illness, are at greater risk for suicide.[144,145] Although fluoxetine use was linked with the emergence of suicidal ideation in initial case reports, this association has not been substantiated by results from a number of large studies (section 5.2.3).[123-125] In general, fluoxetine and other SSRIs are safer in overdose than TCAs or MAOIs.[51] SSRIs therefore may be more appropriate for the treatment of depression in patients at risk of serious suicide attempts or with suicidal ideation.[5] However, the actual relationship between antidepressant toxicity and mortality from overdose is controversial.[146] In a case-controlled cohort study, the risk of suicide was similar among 10 antidepressants (including fluoxetine and TCAs) when other correlates to suicide were controlled for.[147] Furthermore, patients are also likely to commit suicide by other methods.[148]

7.6 Pharmacological Considerations

Fluoxetine and its metabolite, norfluoxetine, have relatively long $t_{½\beta}$ values (section 3.2). It has been argued that this could be either advantageous[143] or disadvantageous[72,143] for the treatment of depression in patients with physical illness. After reaching steady-state concentrations, fluoxetine may be present in the plasma in detectable amounts for up to 5 weeks in healthy adults[139,143] and for more than 8 weeks in elderly patients[69] following drug discontinuation (compared with a minimum of 14 days for paroxetine and 7 days for sertraline in healthy adults).[139,143] This may be advantageous for very ill patients who are able to tolerate fluoxetine but are unable to comply with medication regimens; 1 or 2 missed doses should not significantly affect plasma concentrations of fluoxetine.[63,143]

However, the long $t_{½\beta}$ values of fluoxetine and its metabolite, norfluoxetine, may be disadvantageous for patients who do not tolerate the drug,[51] and potentially problematic in the case of drug-drug interactions,[72] or patient transfer to other antidepressant medications [especially MAOIs (section 6)];[139] adverse effects and drug interactions could potentially continue for weeks after fluoxetine discontinuation.[51,149] Furthermore, adverse effects and the effects of fluoxetine on CYP enzymes may last for an extended period after treatment discontinuation in patients with impaired liver function and elderly patients because of the extended $t_{½\beta}$ of both fluoxetine and norfluoxetine in these groups compared with healthy adults (section 3.3).[72,150] Considering these disadvantages associated with fluoxetine, some have argued that sertraline is the best choice of SSRI for elderly patients.[150] However, fluoxetine is not contraindicated in either elderly patients or those with impaired liver function, although the prescribing information recommends that fluoxetine should be given at lower and less frequent dosages in both these groups (section 6). Lower doses are also recommended with paroxetine but not sertraline in elderly patients.[139]

Patients with physical illness are often taking multiple medications and are thus at increased risk

of experiencing drug-drug interactions.[73] This will influence the choice of antidepressant medication in these patients.[139] In general, SSRIs have fewer clinically meaningful drug interactions than earlier antidepressants.[139] The risk of serotonin syndrome (section 5.2.4) is common to all SSRIs coadministered with MAOIs due to a pharmacodynamic drug interaction.[70] As a result, the combination of MAOIs and fluoxetine,[105] sertraline,[151] paroxetine[152] fluvoxamine[153] or citalopram[154] is contraindicated. Because of the long $t_{½\beta}$ of fluoxetine and norfluoxetine, ≥5 weeks should be allowed between stopping fluoxetine and starting an MAOI in adult patients (section 6).

The SSRIs differ in their potential for pharmacokinetic drug interactions because they differ in their effects on the CYP enzyme system. Fluoxetine is either a moderate or potent inhibitor of CYP2D6, 2C9/10 and 2C19 (section 3.4). Fluvoxamine and paroxetine also inhibit 1 or more CYP enzymes to a clinically significant degree but citalopram and sertraline do not.[72] Thus fluvoxamine, fluoxetine and paroxetine have a greater potential for clinically significant pharmacokinetic drug-drug interactions than citalopram or sertraline.[70] For this reason, some authors[9,70,155,156] suggest that sertraline is the preferred choice for the treatment of depression in patients receiving concurrent therapies metabolised by CYP enzymes.

Caution is advised when prescribing fluoxetine in combination with drugs that are active in the CNS, and/or drugs metabolised by CYP2D6 or CYP3A4 (section 6).[80] Both fluoxetine and its primary metabolite, norfluoxetine, are potent inhibitors of CYP2D6.[53] Drugs which are predominantly metabolised by this isoenzyme and have relatively narrow therapeutic indices (e.g the neoplastic agent vinblastine and TCAs) may reach toxic concentrations if coadministered with fluoxetine.[53,71,75] Increased plasma TCA concentrations have also been reported when given in conjunction with all other SSRIs except citalopram (data from case reports reviewed in Mitchell[70]). Therapeutic drug monitoring can be used to adapt the dosages of drugs metabolised by CYP2D6 when they are coprescribed with fluoxetine.[70]

Drugs that are substantial inhibitors of CYP3A (e.g. protease inhibitors, especially ritonavir) may increase the accumulation of fluoxetine and/or norfluoxetine by inhibiting their clearance (section 3.4). The inhibitory effect of SSRIs on CYP enzymes is concentration-dependent,[70] thus the accumulation of fluoxetine would also increase the degree of inhibition of other CYP isoenzymes (i.e. CYP2D6, 2C19, 2C9/10 and 3A3/4 in descending order of potency). Ritonavir, which is the most potent of all the protease inhibitors at inhibiting CYP3A4, may increase the serum concentrations of some TCAs and SSRIs [including fluoxetine (section 3.4)].[157] The prescribing information recommends that ritonavir should not be used concurrently with the antidepressants desipramine, imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine and sertraline without a careful assessment of the potential risks and benefits.[157] Fluoxetine has not been included in lists of drugs that are contraindicated with protease inhibitors or that cause interactions requiring dosage modifications or cautious use (with the exception of concomitant use with ritonavir) in review articles[76,158] or guidelines for the use of antiretroviral agents.[159,160] In addition, with the exception of vinblastine, review articles[70,74,161] have not included chemotherapeutic agents (e.g. tamoxifen, ifosfamide, paclitaxel and most vinca alkaloids) among the drugs having clinically important interactions with fluoxetine.

Physicians must be mindful of potential drug interactions when prescribing any antidepressant to patients with comorbid physical disease. If any interactions are known or suspected, management options include monitoring for clinical signs of drug toxicity, monitoring for plasma drug concentrations with dosage adjustments when appropriate, or avoidance of the drug combination.[53]

7.7 Conclusion

Fluoxetine has shown efficacy compared with placebo in the treatment of depression in patients

with HIV/AIDS, diabetes mellitus or stroke; however, significant improvement in depressive symptoms for fluoxetine over placebo has not been demonstrated in patients with cancer. Nonetheless, the efficacy of fluoxetine appears similar to that of desipramine in patients with stroke, cancer or HIV; comparisons with nortriptyline give equivocal results. In addition, fluoxetine has similar efficacy to that of sertraline or paroxetine in patients with HIV/AIDS. The potential for drug interactions in patients with comorbid depression needs to be carefully considered, as most patients will be receiving multiple comedications. Although fluoxetine has proved effective as an antidepressant in this population in several trials, and is a very well established antidepressant in general, its drug interaction profile and long half-life are a potential limitation in this particular population, and these properties should be carefully considered in relation to the status of each patient.

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