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Paroxetine

An Update of its Pharmacology and Therapeutic Use in Depression and a Review of its Use in Other Disorders

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Synopsis

Paroxetine is a potent and selective inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine; 5-HT), which was previously reviewed as an antidepressant in Drugs in 1991. Since then, more comparative trials with other antidepressants have become available, and its use in the elderly and as long term maintenance therapy has been investigated. Paroxetine has also been studied in several other disorders with a presumed serotonergic component, primarily obsessive compulsive disorder (OCD) and panic disorder.

In short term clinical trials in patients with depression, paroxetine produced clinical improvements that were significantly greater than those with placebo and similar to those achieved with other agents, including tricyclic antidepressants (TCAs), maprotiline, nefazodone and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine and sertraline. Long term data suggest that paroxetine is effective in preventing relapse or recurrence of depression in patients treated for up to 1 year. In the elderly, the overall efficacy of paroxetine was at least as good as that of comparator agents.

In short term clinical trials involving patients with OCD or panic disorder, paroxetine was significantly more effective than placebo and of similar efficacy to clomipramine. Limited long term data show that paroxetine is effective in maintaining a therapeutic response over periods of 1 year (OCD) and up to 6 months (panic disorder). Preliminary data suggest that paroxetine has potential in the treatment of social phobia, premenstrual dysphoric disorder and chronic headache.

Like the other SSRIs, paroxetine is better tolerated than the TCAs, causing few anticholinergic adverse effects. The most commonly reported adverse event associated with paroxetine treatment is nausea, although this is generally mild and subsides with continued use. Fewer withdrawals from treatment due to adverse effects occurred with paroxetine treatment than with TCAs. The adverse events profile of paroxetine appears to be broadly similar to that of other SSRIs, although data from comparative trials are limited. Serious adverse effects associated with paroxetine are very rare.

In conclusion, paroxetine is effective and well tolerated, and suitable as first-line therapy for depression. It also appears to be a useful alternative to other available agents for the treatment of patients with OCD or panic disorder.

Pharmacodynamic Properties

Paroxetine potentiates serotonergic neurotransmission by the selective and potent inhibition of neuronal reuptake of serotonin. It possesses very weak inhibitory effects on noradrenaline (norepinephrine) and dopamine reuptake, and unlike the

tricyclic antidepressants (TCAs), has negligible affinity for various central neurotransmitter receptors except for displaying weak affinity for the muscarinic receptor.

Long term administration of paroxetine has not been associated with down-regulation of central β-adrenoceptors in rats; however, a decrease in the responsiveness of somatodendritic (5-HT_{1A}) and terminal (5-$HT_{1B/1D}$) serotonin autoreceptors has been observed after 2 to 3 weeks' paroxetine administration.

Various studies involving healthy volunteers and patients with depression have indicated that paroxetine is associated with a reduction in REM sleep time and prolongation of REM latency. In addition, although paroxetine has an alerting effect on sleep, particularly in terms of the number of awakenings, it improves the subjective quality of sleep in patients with depression.

When administered within the therapeutic range, paroxetine did not significantly impair psychomotor function in studies involving healthy volunteers, patients with depression and the elderly, and neither did it potentiate the CNS-depressant effects of alcohol. Paroxetine does not produce significant haemodynamic or electrophysiological cardiac effects in healthy volunteers or depressed patients with coexisting ischaemic heart disease.

Pharmacokinetic Properties

Paroxetine is almost completely absorbed after oral administration. There is considerable interindividual variation in plasma paroxetine concentrations, although no correlation between plasma drug concentration and clinical efficacy or tolerability has been demonstrated. Peak plasma paroxetine concentrations are reached about 5 hours after oral administration and steady-state plasma concentrations are reached after 7 to 14 days' administration. Plasma protein binding is approximately 95% and volume of distribution ranged from 3.1 to 28.0 L/kg.

Paroxetine is extensively metabolised by the cytochrome P450 (CYP) system in the liver, producing essentially inactive metabolites. Saturation of the CYP2D6 enzyme accounts for the nonlinear kinetics observed during repeated administration or after dosage increases. Paroxetine also inhibits the CYP2D6 enzyme. Only 1 to 2% of a paroxetine dose is excreted unchanged in the urine. The rest is excreted as metabolites in both the urine and the faeces. Paroxetine has an elimination half-life of approximately 21 hours.

In elderly individuals, plasma concentration, elimination half-life and the area under the plasma concentration-time curve for paroxetine are increased compared with values obtained in younger subjects. Increased plasma drug concentrations are also observed after single doses of paroxetine in patients with severe renal impairment (creatinine clearance <1.8 L/h) and after repeated administration in patients with hepatic impairment.

Therapeutic Efficacy

In patients with depression, paroxetine produced therapeutic responses that were approximately equivalent to those produced by tricyclic and related antidepressants. The proportion of paroxetine-treated patients who achieved ≥50% reduction from baseline Hamilton Depression Rating Scale (HDRS) scores after 6 to 12 weeks' treatment ranged from 60 to 74%, compared with 60 to 87% for patients receiving tricyclic and related antidepressants. Response rates according to other scales, such as the Montgomery Åsberg Depression Rating Scale and Clinical Global Impression (CGI) were similar between treatment groups. Paroxetine was also effective in relieving anxiety associated with depression. Similar reductions in Clinical Anxiety Scale were seen with paroxetine and clomipramine in patients with coexisting depression and anxiety. One study provided some evidence to

suggest a more rapid effect in improving depression and anxiety symptoms with paroxetine than imipramine.

Paroxetine also showed equivalent efficacy to fluoxetine, fluvoxamine and sertraline. One study suggested paroxetine has an earlier onset of action and may be more effective in relieving associated anxiety than fluoxetine. Paroxetine also had equivalent efficacy to nefazodone.

Paroxetine remains an effective maintenance treatment of depression for up to 1 year. The drug had comparable efficacy to imipramine in maintaining euthymia in patients who had responded to short term therapy.

Paroxetine is effective in the treatment of depression in the elderly. Comparative studies show that there is no difference in efficacy between paroxetine and amitriptyline in this group, although there is some evidence to suggest an earlier onset of action for paroxetine. Therapeutic equivalence with doxepin has also been reported. Paroxetine showed advantages over fluoxetine in 1 study in elderly patients, although response rates to both treatments were low.

Paroxetine has been used successfully in the treatment of patients with obsessive compulsive disorder (OCD). It was significantly more effective than placebo at dosages of 40 and 60 mg/day, but not at 20 mg/day. In a large comparative, placebo-controlled trial, paroxetine demonstrated similar efficacy to clomipramine. About 55% of patients in each active treatment group had a ≥25% reduction from baseline in Yale-Brown Obsessive-Compulsive Scale score at week 12. In a trial evaluating long term treatment of OCD, paroxetine was effective in maintaining a therapeutic response and preventing relapse over a period of 1 year.

Paroxetine 40 mg/day is significantly more effective than placebo in the short term treatment of panic disorder and at least as effective as clomipramine. Some evidence suggests an earlier onset of action for paroxetine than clomipramine. A long term trial found that fewer paroxetine-treated patients relapsed compared with placebo recipients.

Preliminary data have showed that paroxetine was significantly more effective than placebo in the treatment of social phobia. The drug has also been used successfully in the treatment of premenstrual dysphoric disorder and may be effective in treating chronic headache.

Tolerability

In general, paroxetine is well tolerated in the overall patient population and the elderly. Nausea, the most common adverse event during paroxetine treatment, occurs in 22% of patients compared with 14% of those receiving other antidepressants (mainly TCAs). The next most common adverse events include headache, somnolence, dry mouth, abnormal ejaculation, insomnia, asthenia, sweating, constipation and tremor. The anticholinergic adverse effects of dry mouth and constipation occurred at a much lower incidence with paroxetine (14 and 9%) than with other antidepressants (mainly TCAs) [32 and 13%] according to data from a clinical trial database. Overall, the tolerability profile of paroxetine resembles those of the other selective serotonin reuptake inhibitors, although data from comparative trials are limited.

Adverse events associated with paroxetine treatment tend to be mild and lead to fewer withdrawals from treatment than those associated with the TCAs. Furthermore, the incidence of nausea, the most common adverse event, decreases after a few weeks' treatment.

There is no evidence to suggest that paroxetine is associated with either physiological or psychological dependence. However, upon discontinuation of

paroxetine treatment, some patients may experience mild to moderate, self-limiting discontinuation symptoms such as dizziness, sweating, nausea, diarrhoea, insomnia, fatigue and headache. Slow tapering of the paroxetine dosage over several weeks minimises the extent of these symptoms.

Pharmacoeconomic Considerations

The pharmacoeconomics of paroxetine in depression have been assessed in 4 simulation models. Despite higher acquisition costs for paroxetine, 3 of these models showed that the total direct cost per successfully treated patient was slightly less for paroxetine than for TCAs (amitriptyline and imipramine). This was due to the higher treatment failure rates with TCAs and the consequent costs of additional physician visits, hospitalisation and alternative therapy. The other model found treatment costs for successfully treated patients to be slightly greater for paroxetine than those for imipramine or amitriptyline.

A retrospective cost analysis of prescription data suggests that the cost of paroxetine treatment may be less than that of fluoxetine or sertraline. Cost differences were attributed to fewer dosage adjustments required with paroxetine, and hence a reduction in associated physician and pharmacist labour costs. However, another retrospective cost analysis of data from patients in a health maintenance organisation found an increase in the direct healthcare costs of treatment with paroxetine compared with fluoxetine.

Drug Interactions

Paroxetine is both a substrate and an inhibitor of the hepatic enzyme CYP2D6. Consequently, it has the potential to interact with other drugs that either inhibit or are metabolised by CYP2D6.

Elevated plasma concentrations of desipramine and imipramine have been noted during the coadministration of paroxetine. Plasma concentrations of the anticonvulsant agents carbamazepine, phenytoin or valproic acid were not significantly affected by the coadministration of paroxetine to 20 patients with epilepsy. The bioavailability of paroxetine may be increased by cimetidine and decreased by phenytoin.

Although no significant pharmacokinetic interaction between paroxetine and warfarin has been demonstrated, 1 study found clinically significant bleeding occurred in 5 out of 27 individuals who received both drugs. Consequently, caution is required when these drugs are coadministered.

Development of the potentially fatal serotonin syndrome has been reported during concomitant use of paroxetine and other drugs including trazodone and nefazodone. Adverse effects indicative of potentiated serotonergic activity were also observed in a study involving the coadministration of paroxetine and moclobemide.

Dosage and Administration

The recommended starting dosage of paroxetine for the treatment of patients with depression is 20 mg/day taken orally as a single dose. This may also be the optimal dose for most patients. However, in those who do not show an adequate therapeutic response after 2 to 3 weeks, dosage increases of 10 mg/day at a minimum of weekly intervals to a maximum of 50 mg/day may be made.

The recommended starting dose for the treatment of patients with OCD is 20 mg/day, and the optimum target daily dose is 40 mg/day. For the treatment of patients with panic disorder, starting and target daily dosages are 10 and 40 mg/day, respectively. For both indications dosage increases are implemented in the same manner as for depressive illness to a maximum not exceeding 60 mg/day.

The dosage of paroxetine should not exceed 40 mg/day in elderly or debilitated

patients or those with severe renal or hepatic impairment, and should be initiated at 10 mg/day.

Concomitant use of monoamine oxidase inhibitors (MAOIs) and paroxetine is contraindicated, and a 2-week washout period is required before switching treatment between these agents.

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and was previously reviewed in *Drugs* in 1991.[1] At that time, depression was the sole clinical indication discussed. This review updates the use of paroxetine in depression and also includes its use in other indications. These primarily comprise obsessive compulsive disorder (OCD) and panic disorder, although results on its use in other disorders with a presumed serotonergic basis are briefly presented.

1. Overview of Pharmacodynamic Properties

The pharmacodynamic profile of paroxetine is well established (see original review for a more detailed discussion).[1] The following section presents a brief overview of its properties, with emphasis on recent clinically relevant data.

1.1 Inhibition of Neurotransmitter Reuptake

Paroxetine enhances serotonergic neurotransmission by the selective and potent inhibition of presynaptic serotonin (5-hydroxytryptamine; 5-HT) reuptake which results in prolonged activity of the neurotransmitter at its postsynaptic receptor sites.

In vitro potency and selectivity data for paroxetine, other SSRIs and tricyclic antidepressants (TCAs) are presented in table I. Paroxetine is a more potent inhibitor of serotonin uptake *in vitro* than the SSRIs citalopram, fluvoxamine and fluoxetine.[2-4] Paroxetine only weakly inhibits the uptake of noradrenaline (norepinephrine) and dopamine, and demonstrates greater selectivity for inhibition of serotonin versus noradrenaline uptake than fluvoxamine, fluoxetine or the TCAs, but less than that of citalopram.[2-4] Although the data presented in table I indicate that paroxetine has greater *in vitro* potency and selectivity for inhibition of serotonin reuptake than sertraline,[2,3] another study that compared the concentrations required to inhibit monoamine uptake by 50% found that paroxetine was less potent and selective than sertraline.[4]

The effects of paroxetine on serotonin reuptake are prolonged and are maintained upon repeat administration.[1]

Initial administration of paroxetine in rats is associated with inhibition of neuronal firing and reduced release of serotonin.[5-7] This effect is thought to arise from the blockade of serotonin reuptake in the raphé nuclei, which causes indirect activation of somatodendritic 5-HT_{1A} autoreceptors. This in turn counteracts the serotonin transmission-enhancing action of paroxetine. After approximately 2 weeks of paroxetine administration, the somatodendritic autoreceptors become desensitised and the firing rate of serotonergic neurons returns to normal. This effect is thought to account for the delayed onset of efficacy observed with paroxetine treatment (section 1.2).

1.2 Effects on Neurotransmitter Receptors

In contrast to the TCAs, paroxetine displays negligible affinity for α-adrenoceptors and dopamine D_2, histamine H_1 and 5-HT_2 receptors, and only weak affinity for the muscarinic cholinergic receptor.[2,4] The relative lack of affinity of paroxetine for these receptors is thought to account for its improved tolerability profile compared with TCAs (section 4). Although the affinity of paroxetine for the muscarinic cholinergic receptor is greater than that of other SSRIs (i.e. citalopram, sertraline, fluvoxamine or fluoxetine),[2,4] the clinical relevance of this is questionable.

Long term administration of paroxetine does not down-regulate central β-adrenoceptors in rats.[8,9] However, changes in synaptic serotonergic recep-

tors in rat brain tissue occur after 2 to 3 weeks' paroxetine administration. These include a decrease in the responsiveness of somatodendritic ($5\text{-}HT_{1A}$) and terminal ($5\text{-}HT_{1B/1D}$) serotonin autoreceptors, which leads to more serotonin being released with each action potential.[10] This adaptive change is thought to be central to the therapeutic efficacy of paroxetine.

1.3 Effects on the Electroencephalogram and Sleep Patterns

Sleep laboratory studies in healthy volunteers have consistently shown that paroxetine is associated with a reduction in REM sleep time and prolongation of REM latency, and that these changes appear to be dose related.[11-13] Similar findings have been noted previously.[1] A recent randomised double-blind trial in depressed inpatients that compared sleep EEG recordings in recipients of paroxetine 30 mg/day (n = 16) or amitriptyline 150 mg/day (n = 14) for 4 weeks found that paroxetine produced an initial large REM suppression that persisted for the treatment duration and was followed by a rebound after withdrawal. Similar, although less pronounced effects were observed in amitriptyline-treated patients.[14]

Table I. *In vitro* inhibition of [^{3}H]serotonin (5-hydroxytryptamine; 5-HT), [^{3}H]noradrenaline (norepinephrine; NA) and [^{3}H]dopamine (DA) uptake into rat brain tissue synaptosomes[2,3]

Agent	Mean uptake inhibition constant (K_i) [nmol/L]			5-HT selectivity (K_i NA/K_i 5-HT)
	5-HT	NA	DA	
Selective serotonin reuptake inhibitors				
Paroxetine	1.1	350	2 000	320
Citalopram	2.6	3900	NR	1500
Fluvoxamine	6.2	1100	>10 000	180
Sertraline	7.3	1400	230	190
Fluoxetine	25	500	4 200	20
Tricyclic antidepressant agents				
Clomipramine	7.4	96	9 100	13
Amitriptyline	87	79	4 300	0.91
Imipramine	100	65	8 500	0.65
Desipramine	1400	12	NR	0.0086

Abbreviation: NR = not reported.

Paroxetine administered to healthy volunteers increased the number of awakenings and decreased the total sleep time.[1,12,13] Subjective sleep quality was unchanged as assessed by self-rating scales.[13] In depressed inpatients, paroxetine was associated with an increase in the number of awakenings but no detrimental effects on total sleep time. Subjective sleep complaints, as reported on the Hamilton Depression Rating Scale (HDRS) improved during paroxetine treatment.[14]

Patients with depression who received paroxetine experienced better sleep quality and functioned better the next morning, than recipients of dothiepin[15] or mianserin.[16]

1.4 Effects on Psychomotor Function

It has been previously shown that paroxetine 30 mg/day is devoid of significant effects on objective measures of psychomotor function.[1] Recent data from studies involving healthy volunteers, elderly individuals and patients with depression confirm that psychomotor function is not significantly impaired by paroxetine at therapeutic dosages.[17-22] This is in marked contrast to the multiple psychomotor effects seen with other psychoactive agents such as amitriptyline, dothiepin, mianserin, lorazepam and doxepin.[19,20,23,24] In a crossover study involving 16 healthy volunteers, paroxetine 40 mg/day caused slight impairment of psychomotor function, but this effect was substantially less than that induced by amitriptyline 75 mg/day.[20] Interestingly, paroxetine produced slight enhancement of cognitive function, as indicated by the critical flicker fusion threshold in a recent study.[18] Paroxetine does not potentiate the CNS-depressant effects of alcohol.[25]

1.5 Cardiovascular Effects

Early data suggested that paroxetine has much weaker effects on the cardiovascular system than the TCAs, which can cause significant haemodynamic and cardiac function disturbance.[1] Subsequent studies have confirmed this finding.

In a crossover trial involving 14 healthy men, paroxetine 30 mg/day administered for 2 weeks did

not produce clinically significant haemodynamic or electrophysiological cardiac effects. This is in contrast to amitriptyline 150 mg/day, which significantly increased heart rate and had depressant effects on cardiac mechanical and electrical function as manifested by decreased left ventricular ejection time (LVET) index, increased pre-ejection period to LVET ratio, prolonged PR interval and reduced T-wave amplitude.[26]

In 32 patients with depression, paroxetine 20 mg/day or fluvoxamine 150 mg/day did not significantly affect cardiac autonomic function, as assessed by parameters of heart rate variability.[27] In contrast, amitriptyline 150 mg/day or doxepin 150 mg/day significantly suppressed heart rate variability, suggesting that these drugs have a greater effect on cardiac autonomic function than the SSRIs.

A recent randomised double-blind trial compared the cardiovascular effects of paroxetine (20 to 30 mg/day) with nortriptyline (25 to 125 mg/day) in 81 depressed patients with concomitant ischaemic heart disease over 6 weeks. Only 1 paroxetine-treated patient experienced a significant cardiac event (requiring intervention) compared with 7 nortriptyline recipients. In addition, paroxetine did not cause any significant changes in blood pressure, heart rate or ECG. In contrast, nortriptyline was associated with increases in heart rate of about 7 beats per minute, and prolonged PR and QTc intervals.[28,29]

The improved cardiovascular profile of paroxetine compared with the TCAs is thought to be due to its selectivity for the serotonergic system.

2. Overview of Pharmacokinetic Properties

This section draws upon the previous review in *Drugs*[1] and presents an overview of the pharmacokinetic properties of paroxetine, incorporating relevant data from more recent studies. The reader is referred to available reviews on the pharmacokinetics of SSRIs for further information.[30-33] In general, the pharmacokinetics of paroxetine in patients with depression are essentially the same as those in healthy subjects. There is considerable interindividual variability in the pharmacokinetics of this agent (table II).

Table II. Pharmacokinetic parameters of paroxetine in 15 healthy volunteers after oral administration of 30mg as a single dose and after 30 daily doses[34]

Parameter	Mean value (range)	
	after a single dose	after 30 daily doses
C_{max} (μg/L)	14 (1-39)	62 (9-105)
C_{min} (μg/L)	3 (0-8)	36 (9-70)
t_{max} (h)	5 (2-6)	5 (5-6)
$t_{½}$ (h)	10 (3-14)[a]	21 (9-30)
AUC_{∞} (μg/L • h)	191 (8-526)	1974 (100-4095)
AUC_{24h} (μg/L • h)	145 (7-415)	1020 (87-1911)

a Mean $t_{½}$ of paroxetine was approximately 21h after single doses of 20 or 30mg in 29 healthy volunteers.[32]

Abbreviations: AUC_{∞} = area under the plasma concentration-time curve extrapolated to infinity; AUC_{24h} = area under the plasma concentration-time curve over 24 hours; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration (measured 24 hours after dose); t_{max} = time to C_{max}; $t_{½}$ = terminal elimination half-life.

Paroxetine is almost completely absorbed from the GI tract following oral administration. Bioavailability is higher after repeated administration because of partial saturation of first-pass metabolism.[34] Absorption is not affected by the coadministration of food or antacids.[35]

Maximum plasma paroxetine concentrations (C_{max}) ranged between 0.8 and 65 μg/L in single dose (20 to 50mg) studies in healthy volunteers.[34] Mean time required to achieve C_{max} (t_{max}) was approximately 5 hours (range 0.5 to 11 hours).[34] In multiple dose studies (20mg daily for 15 days) in healthy volunteers, maximum plasma paroxetine concentrations ranged between 14.2 and 89.6 μg/L.[34] Steady-state plasma concentrations (C^{ss}) are reached after 7 to 14 days.[34] Studies have failed to demonstrate a relationship between plasma concentrations of paroxetine and clinical efficacy or tolerability.[36,37] However, this may partly be a reflection of the fact that paroxetine shows a relatively flat dose-response curve across the range of 20 to 40mg,[38] and that the studies attempting to correlate plasma paroxetine concen-

trations with efficacy or tolerability used dosages that were within this range.

Consistent with its lipophilic properties, paroxetine is extensively distributed into tissues, with volumes of distribution ranging from 3.1 to 28.0 L/kg after intravenous bolus and infusion administration in healthy volunteers.[34] Approximately 95% of paroxetine in the plasma is protein bound.[34]

Paroxetine is extensively metabolised in the liver by oxidation and methylation to produce glucuronide and sulphate metabolites. These metabolites have no significant inhibitory activity on either serotonin or noradrenaline uptake mechanisms.[39] Metabolism of paroxetine involves at least 2 enzymes in the hepatic cytochrome P450 (CYP) system.[40] CYP2D6 is a high-affinity, saturable enzyme, and is the primary enzyme involved in paroxetine metabolism in individuals classified as extensive metabolisers. The second enzyme (not yet identified) has a much lower affinity and is the primary enzyme of paroxetine metabolism in poor metabolisers. Nonlinear kinetics are observed during repeated paroxetine administration or after dosage increases; disproportionate increases in plasma drug concentration and terminal elimination half-life ($t_{1/2}$) may occur.[41,42] This is attributable to saturation of the CYP2D6 enzyme. However, in most patients treated with paroxetine 20 to 50 mg/day, the degree of pharmacokinetic nonlinearity is minimal.[34] In addition to being metabolised by CYP2D6, paroxetine inhibits this enzyme, thus creating the potential for interactions with other agents that are metabolised by CYP2D6 (see section 6). An intermediate metabolite of paroxetine (M2) has also been shown to have inhibitory activity against CYP2D6 *in vitro*.[43]

Only 1 to 2% of an administered dose of paroxetine is excreted unchanged in the urine. The rest is excreted as metabolites in both urine (about 64%) and faeces.[34] The mean $t_{1/2}$ of paroxetine was approximately 21 hours after single doses of 20 or 30mg in healthy volunteers, but this varied widely between individuals.[34]

In both healthy and depressed elderly individuals, steady-state plasma concentrations of paroxetine are generally increased compared with those in younger adults, and the $t_{1/2}$ is prolonged.[1] The mean minimum C^{ss} was 53 μg/L in 16 elderly healthy volunteers (aged 64 to 78 years) compared with 18 μg/L in 20 younger healthy volunteers (aged 21 to 34 years) after the drug was administered at a dosage of 20 mg/day for 15 days.[44] The mean maximum C^{ss} and the area under the plasma drug concentration-time curve (AUC) during the interval between doses were increased by approximately 2- and 3-fold, respectively, in the older, compared with the younger, volunteers.

Elevated plasma concentrations of paroxetine are seen in patients with severe renal impairment. In a single-dose study, in which paroxetine 30mg was administered to patients with varying degrees of renal impairment, those with creatinine clearance <1.8 L/h (30 ml/min) had a mean AUC to infinite time (AUC_∞) of 2046 μg/L · h and a mean $t_{1/2}$ of 29.7 hours. In contrast, values of 574 μg/L · h and 17.3 hours, respectively, were observed in healthy volunteers.[45]

In patients with hepatic cirrhosis, although no significant differences in pharmacokinetic parameters were observed after administration of a single dose of paroxetine (20mg),[46] repeated administration of paroxetine (20 to 30mg daily) over 14 days resulted in a doubling of C^{ss} and $t_{1/2}$ compared with values for healthy controls.[47]

Paroxetine dosages should be titrated carefully in patients who are elderly or have severe renal or hepatic impairment and should be kept at the lower end of the range recommended for the general population (see section 7).

3. Therapeutic Efficacy of Paroxetine

3.1 Depressive Illness

At the time of the previous review in *Drugs*,[1] paroxetine had been compared with placebo, imipramine, clomipramine, amitriptyline, dothiepin and mianserin. Subsequent double-blind randomised parallel-group studies have also compared the

Table III. Summary of comparative clinical trials with paroxetine (PAR) and tricyclic or tetracyclic antidepressants in patients with depression. All studies were of prospective randomised double-blind design and of 6wk duration in outpatients unless otherwise specified[a]

Reference	Treatment and dosage (mg/day)	No. of evaluable pts	Methods of assessment	HDRS scores			Overall efficacy[b]
				baseline	pts with ≥50% reduction from baseline (%)	mean decrease from baseline (%)	
Imipramine (IMI)							
Arminen et al.[37][c]	PAR 20-40	21	HDRS, MADRS, GA, BDI	24.0[d]	67[d]		PAR ≡ IMI
	IMI 100-200	29		24.2[d]	65[d]		
Feighner et al.[52]	PAR 10-50	240	HDRS, MADRS, CGI, CAS, PGE	26.4		37.9*	PAR ≡ IMI
	IMI 65-275	237		26.2		35.1*	
	PLA	240		26.6		21.8	
Öhrberg et al.[53][e]	PAR 10-50	65	HDRS, BRMS	22.9	70.8		PAR ≡ IMI
	IMI 50-250	65		22.2	60.0		
Amitriptyline (AMI)							
Bignamini & Rapisarda[54]	PAR 20-30	125	HDRS, CGI	30[d]	60.0		PAR ≡ AMI
	AMI 75-150	133		30[d]	65.4		
Christiansen et al.[55][f]	PAR 20-40	67	HDRS, CGI, VAS, FAE	23.8		66.0	PAR ≡ AMI
	AMI 50-150	67		24.2		71.5	
Möller et al.[56][g]	PAR 30	84	HDRS, CGI	30.2	74.0		PAR ≡ AMI
	AMI 150	76		29.7	87.0		
Stuppaeck et al.[57][g]	PAR 20-50	68	HDRS, MADRS, CGI	28.6	63		PAR ≡ AMI
	AMI 50-200	66		28.9	70		
Clomipramine (CLO)							
Ravindran et al.[58][h]	PAR 20-40	479	MADRS, CS, CGI	29.7[i]	68.5[i]	58.2[i]	PAR ≡ CLO
	CLO 75-150	474		29.1[i]	66.9[i]	56.7[i]	
Lofepramine (LOF)							
Moon & Vince[59]	PAR 20-30	60	MADRS, CGI	25[di]	63[i]		PAR ≡ LOF
	LOF 140-210	62		27[di]	54[i]		
Maprotiline (MAP)							
Schnyder & Koller-Leiser[60][j]	PAR 20-40	37	HDRS, MADRS, CGI, HSCL	25.6	60		PAR ≡ MAP
	MAP 50-150	34		25.6	62		
Szegedi et al.[61]	PAR 20-40	254	HDRS, MADRS, HARS, CGI, RDS, BRMS, CAS	18.8	72		PAR ≡ MAP
	MAP 100-150	258		19.1	70		
Kasas et al.[62][k]	PAR 20-40	65	HDRS, MADRS, CGI				PAR ≡ MAP
	MAP 50-150	66					

a All patients fulfilled DSM III-R criteria for major depression except in Szegedi et al.,[61] which included patients who met RDC criteria for either major or minor depression. Ravindran et al.[58] required patients to have coexisting anxiety (CS ≥ 11).

b Overall efficacy derived from all methods of assessment.

c Trial duration 12wk; inpatients.

d Values estimated from graph.

e 1y extension phase followed initial 6wk trial.

f Trial duration 8wk.

g Inpatients.

h Trial duration 12wk; efficacy data are given from assessment at week 8.

i Data are for MADRS scores.

j Inpatients and outpatients.

k This study was reported as an abstract. No efficacy data were presented although the authors claimed comparable antidepressant response was seen in both treatment groups as evidenced by HDRS, MADRS and CGI scores.

Abbreviations and symbols: BDI = Beck Depression Inventory; BRMS = Bech-Rafaelson Melancholia Scale; CAS = Covi Anxiety Scale; CGI = Clinical Global Impression; CS = Clinical Anxiety Scale; FAE = Final Assessment of Efficacy; GA = Global assessment; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; HSCL = Hopkins Symptom Checklist; MADRS = Montgomery Åsberg Depression Rating Scale; PGE = Patient Global Evaluation; PLA = placebo; pts = patients; RDC = Research Diagnostic Criteria; RDS = Raskin Depression Scale; VAS = visual analogue scale; * $p < 0.05$ *vs* placebo; ≡ indicates similar efficacy.

efficacy of paroxetine with that of placebo and tricyclic and tetracyclic antidepressants, as well as with that of nefazodone and several other SSRIs. Most clinical trials involved outpatients meeting DSM-III-R criteria[48] for major depression, although several studies in inpatients have also been performed. Initial minimum scores on the HDRS were required to be ≥18 in most cases and, in general, ranged between 20 and 30. Trial duration was typically 6 weeks, although some longer term studies are available. A dose-ranging study showed that 20mg once daily is the optimal starting dosage of paroxetine, and this should be increased gradually in 10mg increments if needed.[38] Consequently, paroxetine 20mg was the initial daily dose in most comparative trials. Thereafter, gradual dosage titration occurred within a range of 10 to 50 mg/day in some studies, according to clinical response and tolerability.

Responders were generally defined as patients who achieved ≥50% reduction in HDRS score at end-point compared with baseline. Alternatively, the mean change from baseline was presented. Other methods of assessment included Clinical Global Impressions (CGI), Montgomery Åsberg Depression Rating Scale (MADRS), Raskin Depression Rating Scale (RDS), Covi Anxiety Scale (CAS), and the Patient Global Evaluation (PGE). Analysis of efficacy included data from non-completers in most trials (last observation carried forward). Additional studies have addressed the use of paroxetine in the elderly, its efficacy in relapse prevention, ability to reduce suicidal ideation and its effect on anxiety associated with depression.

3.1.1 Comparisons with Placebo

Several early trials, reported in the previous review, have demonstrated that paroxetine in doses of 20 to 50 mg/day is more effective than placebo in reducing symptoms of depression.[1] A large recent study (n = 337) supports this finding.[49] End-point analysis showed a mean reduction in HDRS score of 47.8% for paroxetine-treated patients compared with 32.6% for those on placebo. Two other studies undertaken since the previous review failed to show a statistically significant difference in efficacy between paroxetine and placebo, although a trend favouring paroxetine was evident.[50,51] The small number of patients in these two trials (total of 107), however, suggests that the results should be interpreted with caution.

3.1.2 Comparisons with Tricyclic and Tetracyclic Antidepressants

Recent clinical trials which have compared paroxetine with tricyclic and related antidepressants demonstrate approximate therapeutic equivalence between treatment groups. This supports earlier findings.[1] The proportion of paroxetine recipients who achieved ≥50% reduction from baseline HDRS scores at the end of treatment ranged from 60 to 74%, compared with 60 to 87% for patients receiving tricyclic and related antidepressants (table III).

Three recent trials have confirmed that paroxetine has similar efficacy to imipramine.[37,52,53] In the largest study, which involved 717 outpatients with major depression, baseline HDRS scores were reduced at end-point by 37.9% in paroxetine recipients, 35.1% in imipramine recipients and 21.8% in placebo recipients.[52] (fig 1). In addition, paroxetine had an earlier onset of antidepressant action than imipramine (fig. 2). Significant improvements in paroxetine-treated patients compared with those on placebo occurred by week 1 on the MADRS and by week 2 on the HDRS.[52] Significant differences between imipramine- and placebo-treated patients emerged only after weeks 2 and 3 on these respective scales. Furthermore, results for both the anxiety-somatisation factor of the HDRS and the CAS showed that an earlier and greater beneficial effect in improving anxiety symptoms occurred with paroxetine than with imipramine.

Results from recent trials that have compared paroxetine with amitriptyline concur with previous findings[1] and indicate that these agents have equivalent therapeutic efficacy. This was evident for all measures of efficacy including the HDRS, MADRS and CGI. In a large 6-week trial comparing paroxetine (20 to 30 mg/day; n = 125) with

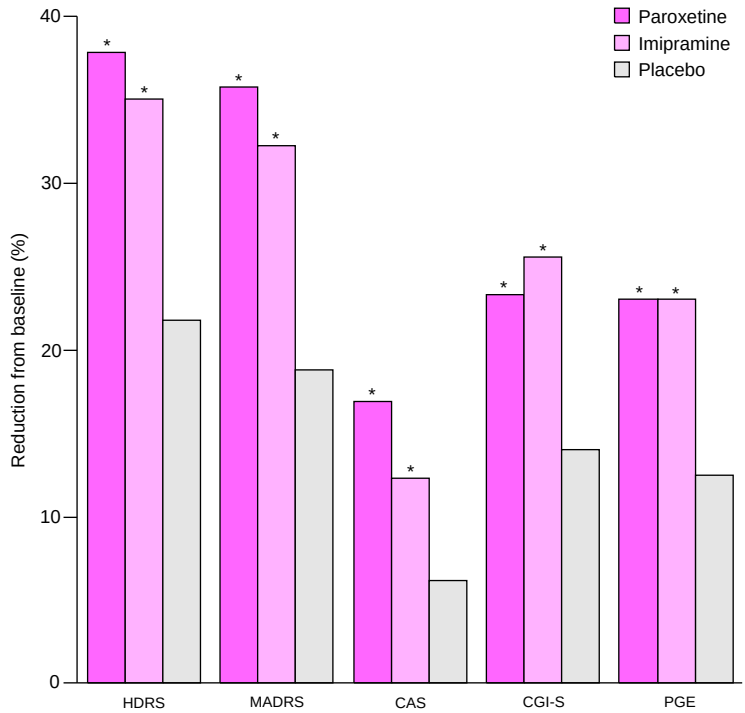

Fig. 1. Efficacy of paroxetine, imipramine and placebo in patients with major depression. Percentage reduction from baseline scores in various efficacy parameters at study end-point (6 weeks) in a randomised double-blind multicentre trial.[52] Treatment regimens: paroxetine 10-50 mg/day (n = 240); imipramine 65-275 mg/day (n = 237); placebo (n = 240). CAS = Covi Anxiety Scale; CGI-S = Clinical Global Impression – severity of illness; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; PGE = Patient Global Evaluation; * $p \leq 0.05$ *vs* placebo.

amitriptyline (75 to 150 mg/day; n = 133), the percentage of patients with ≥50% reduction from baseline in HDRS was 60.0% with paroxetine and 65.4% with amitriptyline.[54] Two similar studies compared the efficacy of these drugs in inpatients. The proportions of patients achieving ≥50% reduction from baseline in HDRS ranged from 63 to 74% with paroxetine and 70 to 87% with amitriptyline.[56,57]

In general, there was little difference between paroxetine and amitriptyline in terms of their time-course of action as assessed on a weekly or bi-weekly basis.[54,55] One study did show a significant superiority for amitriptyline over paroxetine at week 4 on the HDRS, although by week 6 this was no longer apparent.[57]

A large, 12-week, double-blind study compared the efficacy of paroxetine (20 to 40 mg/day; n = 479) with clomipramine (75 to 150 mg/day; n = 474) in patients specifically selected for coexisting depression and anxiety.[58] Both treatments reduced the MADRS and Clinical Anxiety Scale (CS) scores and there was no significant difference between treatment groups at any time point. In this study, end-point for assessment of efficacy was taken to be week 8, at which time at least 70% of patients remained in each treatment group. Mean reduction in MADRS score from baseline at this stage was 58.2% for paroxetine recipients and 56.7% for recipients of clomipramine. Corresponding values for the reduction in CS were 53.3 and 52.6%.

At present, there is only 1 published study comparing paroxetine with lofepramine. This involved 122 general practice patients with major depression, and showed that, at end-point, there was no significant difference in efficacy between paroxetine and lofepramine.[59] However, an apparent earlier onset of action with paroxetine was noted in the CGI severity of illness measure. At week 2, 20% of paroxetine recipients and 3% of lofepramine recipients had responded (score of 2 or less). By week 4, the proportion of responders had increased to 48% for paroxetine and 33% for lofepramine. At week 6, the proportions were 57% and 50%, respectively. The difference between treatment groups in this item was statistically significant at weeks 2 and 4 ($p \leq 0.01$).

Results from 3 recent studies comparing paroxetine with maprotiline are summarised in table III.[60-62] In a large 6-week study involving outpatients with major or minor depression (according to modified Research Diagnostic Criteria), 72% of paroxetine-treated patients (n = 254) had reduction of ≥50% from baseline in HDRS score compared with 70% of maprotiline recipients (n = 258).[61] Findings to suggest equivalent efficacy between treatments were also noted on other measures including the MADRS, CGI and Raskin Depression Scale. In addition, there was no difference between the treatment groups in the reduction of anxiety symptoms as indicated by Hamilton Anxiety Rating Scale (HARS) and CAS. Although there was a statistically significant difference in the percentage of patients with ≥50% reduction from baseline in HDRS at week 1 in favour of maprotiline, no significant differences between the treatment groups were observed at any other time.

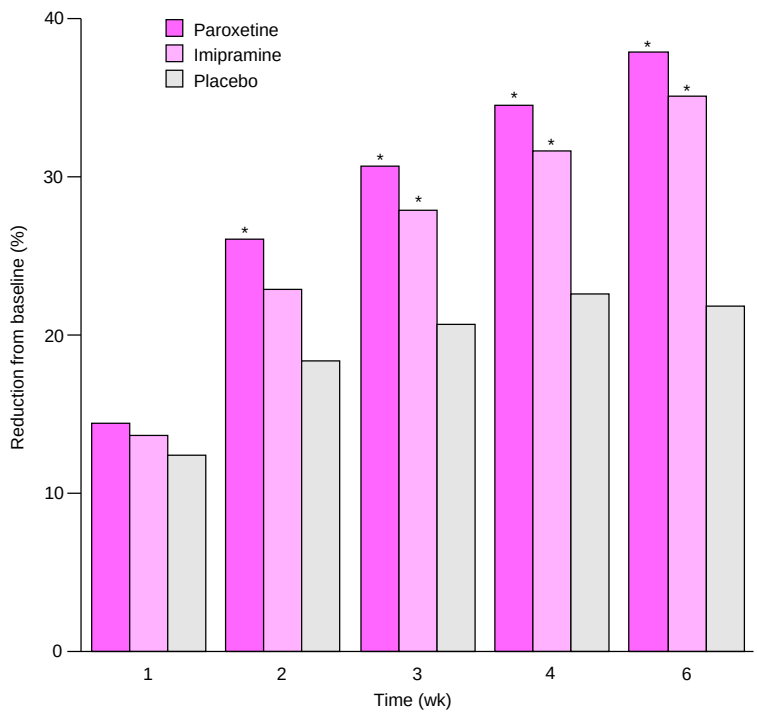

Fig. 2. Efficacy of paroxetine, imipramine and placebo in patients with major depression. Percentage reduction from baseline in Hamilton Depression Rating Scale (HDRS) scores at various time-points in a randomised double-blind multicentre trial[52] Treatment regimens: paroxetine 10-50 mg/day (n = 240); imipramine 65-275 mg/day (n = 237); placebo (n = 240); * $p \leq 0.05$ *vs* placebo.

Table IV. Summary of comparative trials with paroxetine (PAR) and other selective serotonin reuptake inhibitors in patients with depression. All studies were of prospective randomised double-blind design and of 6wk duration unless otherwise specified[a]

Reference	Treatment and dosage (mg/day)	No. of evaluable pts	Methods of assessment	HDRS scores			MADRS scores: pts with ≥50% reduction from baseline (%)	Overall efficacy[b]
				baseline	pts with ≥50% reduction from baseline (%)	mean decrease from baseline (%)		
Fluoxetine (FLX)								
De Wilde et al.[63]	PAR 20-40	37	HDRS, MADRS, HSCL, CGI	27.0	68	64	65	PAR ≡ FLX
	FLX 20-60	41		28.2	63	53	61	
Ontiveros & Garcia-Barriga[64]	PAR 20	60	HDRS, CGI	26.2	71	63		PAR ≡ FLX
	FLX 20	61		26.4	67	59		
Tignol[65]	PAR 20	89	MADRS, HARS, HADS, CGI, VAS				75[f]	PAR ≡ FLX
	FLX 20	87					78[f]	
Fluvoxamine (FLV)								
Ansseau et al.[66]	PAR 20-30	56	HDRS, HARS, CGI	26.0	53	49		PAR ≡ FLV
	FLV 50-200	64		26.5	50	46		
Kiev & Feiger[67][c]	PAR 20-50	29	HDRS, CGI, HARS, HSCL	24.9[d]		12.9[e]		PAR ≡ FLV
	FLV 50-150	29		26.0[d]		13.5[e]		
Sertraline (SER)								
Zanardi et al.[68]	PAR 20-50	13	HDRS, DDE					PAR ≡ SER
	SER 50-150	24						

a Studies involved only inpatients except in Kiev and Feiger,[67] which included only outpatients and Ansseau et al.,[66] which included both inpatients and outpatients. De Wilde et al.[63] did not specify patient status. All patients fulfilled DSM III-R criteria for major depression, except in Zanardi et al.,[68] in which patients met DSM III-R criteria for major depression with psychotic features.

b Overall efficacy derived from all methods of assessment.

c Trial duration 7wk.

d Values for baseline HDRS scores are for patients in centre 1 of a 2-centre study. Baseline HDRS scores for recipients of paroxetine and fluvoxamine in centre 2 were 23.7 and 22.6, respectively.

e Percentage not calculable: data are actual decrease from baseline.

f Baseline MADRS scores for recipients of paroxetine and fluoxetine in this study were 30.7 and 31.6, respectively.

Abbreviations and symbols: CGI = Clinical Global Impression; DDE = Dimensions of Delusional Experience; HADS = Hospital Anxiety and Depression Scale; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; HSCL = Hopkins Symptom Checklist; MADRS = Montgomery Åsberg Depression Rating Scale; pts = patients; VAS = visual analogue scale; ≡ indicates similar efficacy.

Paroxetine also appeared to have similar efficacy to maprotiline in the other 2 studies that have compared these agents.[60,62]

3.1.3 Comparisons with Other Selective Serotonin Reuptake Inhibitors

To date, there have been only a few studies comparing paroxetine with other members of its class (table IV). In general, paroxetine showed equivalent efficacy to other SSRIs, although in one instance an earlier onset of action was noted for paroxetine than for fluoxetine.[63]

In a 6-week randomised, double-blind study comparing titrated dosages of paroxetine and fluoxetine in 78 patients, there was no statistically significant difference in efficacy at end-point between the 2 groups.[63] 68% of paroxetine-treated patients achieved a ≥50% reduction from baseline HDRS score, compared with 63% of fluoxetine-treated patients. However, interesting differences did emerge between the two drugs regarding onset of antidepressant activity and effect on associated anxiety symptoms. At week 3, 36% of paroxetine recipients had HDRS scores reduced by 50% or more versus 16% of fluoxetine recipients ($p < 0.05$). This result was paralleled by similar effects on the MADRS at the same stage. In addition the

paroxetine group displayed a greater HDRS anxiety factor score reduction over the 6 weeks than the fluoxetine group. This was statistically significant at week 3; score reductions from baseline were 3.4 versus 2.1 ($p = 0.01$).

Similar antidepressant effects were reported in a trial that compared paroxetine with fluoxetine (both at 20 mg/day) in 176 hospitalised patients with major depression.[65] Associated anxiety was present in both groups at baseline. 75% of paroxetine-treated patients had a reduction of ≥50% in MADRS score after 6 weeks' treatment, compared with 78% in the fluoxetine group. However, in contrast to the previous trial, this study did not reveal any difference in the onset of action of the 2 drugs. Furthermore, both agents were equally effective in reducing symptoms of anxiety. By week 6, the proportion of patients achieving ≥50% reduction in HARS score was 70% in the paroxetine group, closely matching the 71% of patients in the fluoxetine group.

Further evidence to indicate equivalent antidepressant efficacy between paroxetine and fluoxetine is found in the most recent study to have compared these agents.[64] After 6 weeks of treatment, the mean decrease from baseline in HDRS score was 63% in paroxetine recipients (n = 60) compared with 59% in fluoxetine recipients (n = 61). The treatments were not significantly different at any point in time, although there was a significant treatment difference for the sleep disturbance subfactor at week 4 in favour of paroxetine.

In a 6-week trial in 120 in- or outpatients, the efficacy of paroxetine (20 to 30 mg/day) was similar to that of fluvoxamine (50 to 200 mg/day).[66] All methods of assessment found a consistent pattern of improvement in both treatment groups, and there was no significant difference at any stage of treatment to suggest a more rapid onset of action for either drug. At study end-point, 53% of paroxetine-treated patients and 50% of those treated with fluvoxamine had a ≥50% reduction from baseline HDRS score. Similar efficacy for the 2 SSRIs was also observed in terms of reduction in associated anxiety. Mean reduction in HARS from baseline was 43% in both treatment groups. A recent 7-week study also found that fluvoxamine (n = 29) and paroxetine (n = 29) were similarly effective in ameliorating depression, as demonstrated by mean reductions from baseline HDRS scores of 13.5 and 12.9, respectively.[67]

The only study comparing paroxetine with sertraline involved treatment of patients with delusional depression.[68] 46 hospitalised patients were treated with either paroxetine (20 to 50 mg/day) or sertraline (50 to 150 mg/day) for 6 weeks. Responders were identified as those with a score of less than 8 on the HDRS and 0 on the Dimensions of Delusional Experience Rating Scale (DDE) at the end of 6 weeks. According to these criteria, 75% (18 of 24) of sertraline-treated patients responded compared with 27% (6 of 22) in the paroxetine group ($p = 0.003$). The high percentage of withdrawals due to adverse effects in the paroxetine group (9 of 22) compared with none in the sertraline group means that the above response rates should be treated with caution. When only subjects who completed the study were considered (13 in the paroxetine group, 24 in the sertraline group), no significant difference between the drugs was found. Response rates to sertraline and paroxetine were 75% and 46%, respectively ($p = 0.16$), and the investigators concluded that sertraline and paroxetine are equally efficacious in patients with delusional depression. It should be noted, however, that a small number of patients participated in this study, which reduces its validity.

3.1.4 Comparison with Nefazodone

Nefazodone is an antidepressant with a pharmacological profile distinct from those of the TCAs and SSRIs.[69] Only 1 randomised, double-blind clinical trial comparing this agent with paroxetine is available. This involved administration of paroxetine (20 to 40 mg/day) or nefazodone (200 to 600 mg/day) to 196 outpatients over a period of 8 weeks.[70] Major efficacy measures included the HDRS, HARS, MADRS and CGI (both severity of illness and improvement). Results indicated that both treatments were equally efficacious, and no

significant difference was evident at any time. The proportion of patients achieving a reduction of ≥50% in HDRS at end-point was 42.3% in the paroxetine group versus 39.4% in the nefazodone group. Nefazodone and paroxetine were also equally effective in relieving associated symptoms of anxiety, as judged by improvements in the HARS score.

3.1.5 Long Term Treatment

It is important not to assume that an antidepressant medication shown to be effective in the short term treatment of acute depression will also provide adequate long term maintenance therapy.[71] Long term efficacy data for paroxetine have only recently become available and appear to indicate that paroxetine is an effective maintenance treatment for up to 1 year.[71,72]

An investigation of the long term efficacy of paroxetine in the prevention of relapse and recurrence of depression was undertaken in patients with a history of 2 or more previous episodes in the preceding 4 years.[71] Patients who responded to 8 weeks of nonblind treatment with paroxetine (20 to 40 mg/day) were eligible to enter the 1-year study and were randomised to receive paroxetine (20 to 30 mg/day, n = 68) or placebo (n = 67). The principal measure of outcome was the withdrawal of patients from the study because of the relapse or recurrence of depression.

Results were analysed separately for the first 16 weeks (relapse prevention period) and weeks 17 to 52 (recurrence prevention period). In the former period, 2 of 68 paroxetine-treated patients (2.9%) had a relapse of depression and were withdrawn from the study compared with 13 of 67 patients receiving placebo (19.4%). Between weeks 17 and 52, 9 of 66 patients receiving paroxetine (13.6%) experienced recurrence of depression and were withdrawn compared with 16 of 54 placebo recipients (29.6%). In both periods, this advantage for paroxetine over placebo was statistically significant ($p < 0.05$). Kaplan-Meier survival analysis also demonstrated superiority for paroxetine in terms of time to relapse and time to recurrence compared with placebo ($p < 0.005$).

Another study compared the long term efficacy of paroxetine with that of imipramine.[72] 219 depressed patients who had responded to short term therapy continued treatment with paroxetine (10 to 50 mg/day) or imipramine (65 to 275 mg/day) for 1 year. Results from the major efficacy variables (HDRS and CGI) were consistent in showing that both paroxetine and imipramine were effective in maintaining euthymia throughout the 1 year of maintenance treatment. 60 of 94 paroxetine-treated patients (63.8%) were considered treatment responders (HDRS score of 8 or less) compared with 53 of 79 imipramine recipients (67.0%) and 32 of 46 placebo recipients (69.6%). The high response rate in the placebo group is surprising, although significantly more responders in this group subsequently developed a relapse (25%). In comparison, relapse occurred in 15 and 4% of paroxetine and imipramine responders, respectively. Furthermore, a higher proportion of placebo-treated patients withdrew prematurely from the long term trial because of a lack of efficacy (22%) than did patients treated with either paroxetine (12%) or imipramine (4%).

3.1.6 Depression in the Elderly

Limited data available at the time of the previous review in *Drugs*[1] suggested that paroxetine had equivalent efficacy to clomipramine, amitriptyline and mianserin in elderly patients. Since then, 3 additional studies have become available,[73-75] and the results from 2 trials previously available only as abstracts have been published in full.[16,76] These studies were of similar design to those performed in the general patient population and the results are summarised in table V.

In a 6-week general practice study comparing paroxetine with amitriptyline in elderly patients with depression, there was no significant difference in efficacy between treatment groups at study end-point.[76] 76% of paroxetine recipients achieved a ≥50% reduction from baseline HDRS scores compared with 86% of amitriptyline recipients. However, paroxetine appeared to have an earlier onset of action than amitriptyline. After 1 week, 11% of paroxetine recipients had a ≥50%

reduction in HDRS scores, and by 2 weeks this had increased to 27% of patients. The corresponding results in the amitriptyline group were 3 and 17%, although it was not stated whether the differences were statistically significant.

A more recent study in elderly inpatients also found equivalent efficacy between paroxetine and amitriptyline; however, there was no evidence for an earlier onset of action with paroxetine.[75]

Paroxetine has been compared with doxepin in a 6-week double-blind trial in elderly outpatients with depression.[73] There was no significant difference between the 2 drugs according to the HDRS or the MADRS. Mean reduction from baseline HDRS score was 13.4 for paroxetine recipients and 11.9 for doxepin recipients. Paroxetine was significantly more effective than doxepin according to the CGI severity of illness scale at week 6 ($p = 0.01$).

The antidepressant efficacy of fluoxetine was compared with that of paroxetine in 106 elderly outpatients with depression. All reported results have been estimated from graphs. Paroxetine was superior to fluoxetine in some measures of efficacy, although overall response rates in both groups were quite low.[74] At week 6, about 38% of paroxetine-treated patients had a reduction of ≥50% in HDRS score, compared with 17% of fluoxetine recipients ($p = 0.03$). Furthermore, the authors reported a significant difference between

Table V. Summary of comparative trials with paroxetine (PAR) in elderly patients with major depression. All studies were of prospective randomised double-blind design and of 6wk duration in outpatients unless otherwise specified

Reference	Treatment and dosage (mg/day)	No. of evaluable pts	Age (y)	Methods of assessment	HDRS scores			Overall efficacy[a]
					baseline	pts with ≥50% reduction from baseline (%)	mean decrease from baseline (%)	
Fluoxetine (FLX)								
Schöne & Ludwig[74]	PAR 20-40	54	65-85	HDRS, MADRS, CGI, SCAG, MMSE	29[b]	38[b*]		PAR > FLX[c]
	FLX 20-60	52			28[b]	17[b]		
Amitriptyline (AMI)								
Hutchinson et al.[76]	PAR 20-30	58	≥65	HDRS, CGI, LSEQ	24.5[b]	76		PAR ≡ AMI
	AMI 50-100	32			23.0[b]	86		
Geretsegger et al.[75][d]	PAR 20-30	28	≥65	HDRS, MADRS, CGI	25.5[b]	64		PAR ≡ AMI
	AMI 50-150	31			27.5[b]	58		
Doxepin (DOX)								
Dunner et al.[73]	PAR 10-40	92	≥60	HDRS, MADRS, HSCL, CGI	25[b]		53.6	PAR ≡ DOX[e]
	DOX ≤200[f]	96			25[b]		47.6	
Mianserin (MIA)								
Dorman[16]	PAR 50-150	29	≥65	HDRS, CGI, LSEQ	23.0[b]	48*		PAR > MIA
	MIA 30-60	28			22.4[b]	18		

a Summary of efficacy applies to all methods of assessment unless otherwise stated.

b Values estimated from graph.

c Reflects findings based on patients achieving greater than 50% reduction in HDRS or MADRS scores from baseline. There were no statistically significant differences between treatment groups when the change in HDRS total score or CGI severity of illness scores were considered.

d Inpatients.

e Paroxetine was significantly superior to doxepin on the CGI severity of illness scale.

f Minimum dosage not stated.

Abbreviations and symbols: CGI = Clinical Global Impression; HDRS = Hamilton Depression Rating Scale; HSCL = Hopkins Symptom Checklist; LSEQ = Leeds Sleep Evaluation Questionnaire; MADRS = Montgomery Åsberg Depression Rating Scale; MMSE = Mini-Mental State Examination; pts = patients; SCAG = Sandoz Clinical Assessment Geriatric Scale; * $p = 0.03$ *vs* comparator; ≡ indicates similar efficacy; > indicates statistically significant greater effect.

the 2 treatment groups in favour of paroxetine at week 3, as measured by the change from baseline in total HDRS score ($p = 0.03$). HDRS scores at baseline and 3 weeks were about 29 and 22 for paroxetine recipients and approximately 28 and 25 for fluoxetine recipients. However, the 3-point difference between treatments at week 3 is of questionable clinical significance.[77]

The above study also assessed cognitive functioning.[74] While both drugs improved overall cognitive function as measured by the reduction in mean Sandoz Clinical Assessment Geriatric Scale (SCAG) total scores from baseline, paroxetine had an earlier onset of effect. By week 3, the SCAG total scores had fallen 10 points (from 62.5 to 52.5) in the paroxetine group and 4.5 points (from 60.5 to 56) in the fluoxetine group ($p < 0.05$). By week 6, SCAG total score had fallen to 47.5 in the paroxetine group and to 52.5 in the fluoxetine group.

In a trial comparing mianserin with paroxetine, significantly more patients receiving paroxetine (48%) had a ≥50% reduction in HDRS total score at week 6, compared with 18% of patients receiving mianserin ($p = 0.03$).[16] This study also assessed the effects of both drugs on sleep. Paroxetine recipients had a significant improvement in 6 of 10 Leeds Sleep Evaluation Questionnaire factors compared with only 1 of 10 factors for mianserin recipients.

3.1.7 Effect on Suicidality

A series of meta-analyses of clinical trial data were carried out to determine the effects of paroxetine on suicidality in patients with depression.[78] In general, patients receiving paroxetine showed a greater reduction in suicidal thoughts than placebo recipients. In addition, on the MADRS suicidal thoughts item (2423 patients), paroxetine also had a statistically significant advantage compared with active controls (largely TCAs) at various times. The change in MADRS suicide item from a baseline score of 1.8 (in all groups) was –1.3 for paroxetine versus –1.1 for active controls at 6 weeks ($p < 0.01$). The clinical significance of a difference of 0.2 on this scale, however, is less clear.

Emergence of suicidal thoughts during treatment was also assessed. There were significantly fewer emergent suicidal thoughts in paroxetine-treated patients than in those receiving placebo in all analyses and a significant advantage for paroxetine compared with active controls on the MADRS. At week 6, the proportions of patients with emergent suicidal thoughts on this scale were 14, 31 and 22%, respectively, for paroxetine, placebo and active control groups ($p < 0.01$ for paroxetine *vs* active control).

Evaluation of the number of suicides in each treatment group revealed that there were fewer suicides in recipients of paroxetine [0.005 cases per patient exposure year (PEY)] than in those receiving active controls (0.014 cases per PEY) or placebo (0.028 cases per PEY).[78]

3.2 Obsessive Compulsive Disorder

Clinical trials that have evaluated paroxetine in the treatment of patients with OCD suggest that it is more effective than placebo and at least as effective as clomipramine.

In a major efficacy study, 348 patients with OCD of at least 6 months' duration received either placebo or paroxetine at fixed doses of 20, 40 or 60mg daily for 12 weeks. The higher dosages were reached after gradual titration from 20 mg/day.[79] Paroxetine was effective in the treatment of OCD at doses of 40 and 60mg. At week 12, the mean reductions from baseline in Yale-Brown Obsessive-Compulsive Scale (YBOCS) total score were 3.4 for the placebo group and 4.2, 6.4 and 7.3 for the paroxetine 20, 40 and 60mg groups, respectively (values estimated from a graph). At the 2 higher doses, paroxetine was significantly superior to placebo ($p < 0.05$). Interestingly, the difference between paroxetine 20 and 60mg was also statistically significant ($p < 0.05$), suggesting a dose-response relationship.

Paroxetine [10 to 60 mg/day (mean 37.5 mg/day)] showed efficacy similar to that of clomipramine [25 to 250 mg/day (mean 113.1 mg/day)] in

a multicentre placebo-controlled study in 399 patients with OCD.[80] Inclusion criteria were at least 6 months duration of illness according to DSM-III-R criteria, baseline score ≥7 on the National Institute of Mental Health Obsessive-Compulsive Scale (NIMHOCS) and an initial YBOCS score of ≥16.

At week 12, 55.1% of paroxetine recipients, 55.3% of clomipramine recipients and 35.4% of placebo recipients had a ≥25% reduction in YBOCS total score from baseline. No statistically significant difference was evident between paroxetine and clomipramine at any stage in the trial. The superiority of both active drugs to placebo reached statistical significance by week 6 and was maintained throughout the remainder of the study. Similar results were observed in the analysis of the NIMHOCS; the reduction from baseline score was 2.5 in both paroxetine and clomipramine treatment groups, compared with a reduction of 1.4 in placebo recipients. The CGI efficacy index (representing a combination of both efficacy and safety) was, however, significantly higher in the paroxetine group than the clomipramine group at week 6 (0.3 *vs* 0.0, $p < 0.05$) and week 8 (0.3 *vs* 0.1, $p < 0.05$).

Only one published study evaluating the effectiveness of paroxetine in the long term treatment of OCD is available. This showed that paroxetine was effective in maintaining a therapeutic response and preventing relapse over 1 year.[81] The study included 263 patients who had completed a 12-week trial with paroxetine and who, in the opinion of the investigators, would benefit from continued treatment. A 6-month nonblind extension period (paroxetine 20 to 60 mg/day) was followed by a 6-month double-blind period in which patients who achieved a therapeutic response were randomised to receive either paroxetine or placebo.

After the 12-week trial, the mean improvement from baseline YBOCS in patients eligible to enter the extension phase was 5.7 points. Improvement in YBOCS continued during the nonblind period, and at month 6 the reduction was 10.8 points. 104 responders (as assessed by reduction in YBOCS of ≥25%) at 6 months were randomised to receive paroxetine (n = 53) or placebo (n = 51) for a further 6 months. During this period, the rate of relapse in the placebo group was significantly higher than in the paroxetine group (59 *vs* 38%, $p < 0.05$). The mean time to relapse was also significantly shorter in patients treated with placebo than in those receiving paroxetine (29 *vs* 63 days, $p = 0.01$).

3.3 Panic Disorder

3.3.1 Short Term Treatment

Three clinical trials have demonstrated the effectiveness of paroxetine in the short term treatment of patients with panic disorder (table VI).

Patients fulfilled DSM-III-R criteria for panic disorder and, in general, were required to have experienced at least 3 panic attacks in the 3 to 4 weeks prior to study entry. Except in the fixed-dose study,[82] daily doses of paroxetine were generally adjusted between 10 and 60mg according to efficacy and tolerability.[83,84] The primary efficacy indicator was the number of panic attacks. In general, clear superiority to placebo and equivalent efficacy to clomipramine were observed for paroxetine.[83-85] In addition, some evidence suggesting an earlier onset of action for paroxetine compared with clomipramine emerged.[83]

In a fixed-dose study comparing paroxetine 10, 20 or 40mg daily with placebo in 278 patients, 40mg was the minimum dose demonstrated to be more effective than placebo in the treatment of panic disorder, although some patients did respond to lower doses.[82] During the final 2 weeks of the study (weeks 9 and 10), 86% of patients in the paroxetine 40mg group were free of full panic attacks compared with 50% of placebo recipients ($p < 0.019$). Statistically significant differences were also observed between paroxetine 40mg and placebo for most other efficacy variables, including the reduction in full panic attacks and improvement in CGI-severity of illness.

Paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy in another study involving 120 patients with panic disorder.[84] Comparisons between the

Table VI. Efficacy of paroxetine (PAR) in the treatment of panic disorder, as compared with placebo (PLA) or clomipramine (CLO) in short term randomised, double-blind studies[a]

Reference	Treatment and dosage (mg/day)	No. of evaluable pts	Methods of assessment	No. of panic attacks at baseline	Results			Overall efficacy[b]
					pts with no panic attacks (%)	pts with ≥50% reduction in no. of panic attacks (%)	mean decrease in no. of panic attacks	
Ballenger et al.[82][c]	PAR 10	67	CGI-S, CGI-I, HARS, MSPS, MADRS	10.2	67		5.9	PAR 40 > PLA
	PAR 20	70		9.5	65		5.7	
	PAR 40	72		9.6	86*		8.6*	
	PLA	69		11.6	50		4.9	
Lecrubier et al.[83][d]	PAR 10-60	123	HARS, CGI-S, MSPS, PGE, SDS	18.6[e]	51*[†]	76*	11	PAR ≡ CLO > PLA
	CLO 10-150	121		14.6[e]	37	65	8	
	PLA	123		19.8[e]	32	60	8	
Oehrberg et al.[84][f]	PAR 10-60 + CT	60	HARS, CGI, ZSSA	21.2	36*[g]	82*	16	PAR > PLA
	PLA + CT	60		26.4	16[g]	50	9.8	

a Trial duration was 12wk, except in Ballenger et al.[82] (10wk). Efficacy data are on the basis of full panic attacks except in Oehrberg et al.[84] which measured the total number of all panic attacks.

b Overall efficacy derived from all measures of efficacy.

c In this study, panic attack frequency was assessed during weeks 9 and 10 of treatment and was compared with that during a 2wk placebo run-in period.

d In this study, panic attack frequency was assessed during weeks 7-9 of treatment and was compared with that during a 3wk placebo run-in period.

e Number of panic attacks at baseline in patients with agoraphobia. Numbers of panic attacks at baseline in patients without agoraphobia who received paroxetine, clomipramine or placebo were 14.9, 11.1 or 18.0, respectively.

f In this study, panic attack frequency was assessed during weeks 10-12 of treatment and was compared with that during a 3wk placebo run-in period.

g Percentage of patients who experienced no or 1 panic attack.

Abbreviations and symbols: CGI = Clinical Global Impression; CGI-I = Clinical Global Impression (improvement); CGI-S = Clinical Global Impression (severity of illness); CT = cognitive therapy; HARS = Hamilton Anxiety Rating Scale; MADRS = Montgomery Åsberg Depression Scale; MSPS = Marks-Sheehan Phobia Scale; PGE = Patient Global Evaluation; pts = patients; SDS = Sheehan Disability Scale; ZSSA = Zung Self-Rating Scale for Anxiety; * $p < 0.05$ vs placebo; [†] $p = 0.04$ *vs* clomipramine; > indicates statistically significant greater effect; ≡ indicates similar effect.

groups were based on findings at consecutive 3-week intervals for up to 12 weeks. At the end of the study, 82% of the paroxetine recipients had at least 50% reduction from baseline in the number of total panic attacks compared with 50% of the placebo recipients ($p = 0.001$). A statistically significant difference in favour of paroxetine was also seen in the number of patients with panic attacks reduced to 0 or 1. By week 12, 36% of paroxetine-treated patients had achieved this compared with 16% of those receiving placebo ($p = 0.024$). Significant improvement in the paroxetine recipients was also evident in the secondary measures of outcome: reduction by ≥50% in the HARS by week 12 occurred in 85% of paroxetine and 51% of placebo recipients ($p < 0.001$).

A recent multicentre randomised double-blind study compared paroxetine (10 to 60 mg/day, n = 123) with clomipramine (10 to 150 mg/day, n = 121) and placebo (n = 123) over 12 weeks.[83] Results were grouped into 3-week intervals. Although treatment was administered for 12 weeks, the study end-point for assessment of efficacy was taken to be the third 3-week interval (i.e. weeks 7 to 9), at which time at least 70% of patients remained in each treatment group.

In general, paroxetine was superior to placebo and equivalent to clomipramine. There was evidence, however, to suggest that the beneficial effects of paroxetine occurred before those of clomipramine (fig. 3).

At study end-point, 50.9% of paroxetine-treated patients experienced no full panic attacks compared with 36.7% of clomipramine-treated patients ($p = 0.041$) and 31.6% of placebo recipients ($p = 0.004$). The difference between clomipramine and placebo as measured according to this outcome did not reach statistical significance until the fourth 3-week period. Statistical significance in favour of paroxetine over placebo, and a trend in favour of paroxetine over clomipramine were observed in the percentage of patients with a ≥50% reduction from baseline in the total number of panic attacks at end-point. This occurred in 76.1% of the paroxetine group, 64.5% of the clomipramine group and 60% of the placebo group. Secondary measures of efficacy, such as the HARS and Marks Sheehan Phobia Scale (MSPS), demonstrated that both paroxetine and clomipramine were significantly superior to placebo at week 9, with no significant difference between active treatments.

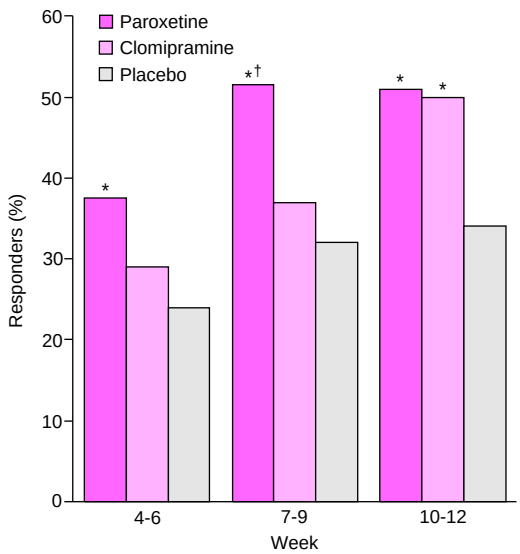

Fig. 3. Efficacy of paroxetine, clomipramine and placebo in patients with panic disorder. Percentage of patients with reduction in number of full panic attacks to zero in a randomised, double-blind, parallel group trial (some values estimated from a graph).[83] Treatment regimens: paroxetine 10-60 mg/day (n = 123); clomipramine 10-150 mg/day (n = 121); placebo (n = 123); * $p \leq 0.05$ *vs* placebo; † $p = 0.041$ *vs* clomipramine.

3.3.2 Long Term Treatment

Data from 2 trials which have evaluated the longer term efficacy of paroxetine in panic disorder suggest it is effective in maintaining a reduction in the number of panic attacks and in preventing relapse for up to 6 to 9 months.[86,87]

In a long term study by Lecrubier et al.[86] 176 patients who completed a 12-week trial[83] entered a 36-week extension phase. Inclusion was based on the willingness of patients to continue with their randomised treatment, and thus bias may have occurred.

Analysis of the mean reduction from baseline in the total number of panic attacks revealed statistically significant differences between paroxetine and placebo throughout the extension phase. No significant difference between paroxetine and clomipramine was observed on this parameter. At the eighth 3-week period (the defined study end-point by which at least 70% of patients remained in each group), the mean reductions in total number of panic attacks from baseline were 16.3, 14.3 and 10.2 for paroxetine, clomipramine and placebo recipients, respectively. At the end of the short term study, the corresponding values were 15.3, 12.1 and 10.2, indicating that continued improvement occurred with active treatment into the long term phase. An increase in the proportion of patients with no panic attacks was seen in all treatment groups during long term treatment. At the eighth 3-week period, 73.8% of paroxetine-treated patients had no panic attacks, as had 77.6% of those receiving clomipramine and 65.1% receiving placebo. Although there was no statistically significant difference between groups at this point, by the twelfth 3-week period, paroxetine was significantly more effective than placebo (84.6 *vs* 59.1% of patients, $p = 0.04$).

Results of another trial, designed specifically to assess the effectiveness of paroxetine in preventing relapse of panic disorder also support its long term efficacy.[87] 138 responders from a 10-week study entered a 6-month extension phase. This comprised an initial 3-month maintenance period (in which subjects continued their current medication)

followed by a subsequent 3-month period in which patients were re-randomised to either continue current treatment or switch to placebo. During the maintenance phase, the efficacy of paroxetine remained unchanged relative to the end of the initial 10-week study. During the subsequent 3-month phase, 30% of patients (11 of 37) who crossed over from paroxetine to placebo treatment groups relapsed, compared with 5% of those (2 of 43) who continued paroxetine therapy ($p = 0.002$).

3.4 Other Disorders

Paroxetine has been reported to be effective in the treatment of several other disorders with a presumed serotonergic basis. In some instances, well designed clinical trials have been conducted; however, in other cases, small nonblind studies or anecdotal evidence by way of case reports are all that are available.

3.4.1 Social Phobia

In addition to published case reports,[88] 3 clinical trials have documented the efficacy of paroxetine in this common, chronic and potentially debilitating condition.[89-91] All patients met DSM-III-R/DSM-IV criteria for social phobia (generalised type).

In the only available randomised, double-blind trial of paroxetine in the treatment of social phobia, patients received either paroxetine (20 to 50 mg/day, n = 94) or placebo (n = 93) for 12 weeks.[91] Primary indicators of efficacy included the Liebowitz Social Anxiety Scale (LSAS) and the proportion of patients with CGI global improvement scores ≤2. Significant differences in favour of paroxetine emerged from week 4 onwards. At end-point, mean reduction in the LSAS from baseline was 30.5 in paroxetine recipients compared with 14.5 in those receiving placebo ($p < 0.001$). Proportions of patients with CGI global improvement scores ≤2 were 55 and 24%, respectively, in the 2 treatment groups ($p < 0.001$). Similar findings were noted in the secondary efficacy measures, which included the Social Anxiety and Distress scale and Sheehan Disability Inventory.

In an 11-week nonblind study of paroxetine involving 36 patients with generalised social phobia, 23 of 30 patients who completed the study (77%) were responders in terms of a CGI scale rating of 'very much improved' or 'much improved'.[89] In addition, statistically significant reductions were observed in the Duke Social Phobia Scale (from 35.5 at baseline to 19.7 at week 11; $p < 0.0005$) and the LSAS (from 75.1 at baseline to 37.2 at week 11; $p < 0.0005$).

16 responders in this study participated in a double-blind, placebo-controlled discontinuation study.[89] Eight patients were randomised to continue taking paroxetine and 8 were randomised to placebo treatment. In the paroxetine group, 1 patient relapsed within 12 weeks compared with 5 in the placebo group. This difference was not statistically significant, probably because of the small sample size.

Another nonblind trial of paroxetine in the treatment of patients with social phobia (n = 18) produced similar results to those reported above.[90] 15 patients (83.3%) were considered responders in terms of having CGI-change scores of 1 (markedly improved) or 2 (moderately improved). Three patients (16.7%) were considered nonresponders with a CGI-change score of 4 (no change). Furthermore, statistically significant reductions in most other measures of social anxiety and avoidance were noted.

3.4.2 Premenstrual Dysphoric Disorder

Data from nonblind and double-blind clinical trials that have investigated the efficacy of paroxetine in patients with premenstrual dysphoric disorder (PMDD) provide some evidence to suggest it may be an effective treatment for this condition.

In a randomised double-blind trial, women with severe PMDD were treated daily for 3 menstrual cycles with paroxetine (10 to 30 mg/day, n = 22), maprotiline (25 to 150 mg/day, n = 21) or placebo (n = 22).[92] Symptom reduction in paroxetine-treated patients was superior to that in the placebo group for all measurements. In addition, with respect to irritability, bloating, increased appetite and breast tenderness, symptom reduction with

paroxetine was significantly superior to that with maprotiline.

A nonblind trial in which 14 women with PMDD were given placebo for 1 cycle and then paroxetine for 3 consecutive cycles produced results which support the efficacy of paroxetine.[93] The luteal phase HDRS showed a mean reduction from 14.9 during the placebo treatment cycle to 7.8 in the third paroxetine treatment cycle. A cluster of daily symptom ratings indicative of anger and irritability also decreased significantly with paroxetine treatment.

3.4.3 Chronic Headache

Current theories surrounding the pathogenesis of chronic headache include a possible serotonergic disturbance. This has provided the rationale to investigate paroxetine as a potential treatment for this condition, and results from the 2 available small trials suggest that it may be effective.[94,95]

In a nonblind study, 48 patients with chronic headache were treated with paroxetine (10 to 50 mg/day) for 3 to 9 months. The number of headaches during the final month of treatment was documented and compared with the month preceding the initiation of treatment with paroxetine. 92% of paroxetine-treated patients had ≥50% reduction in the number of headaches per month.[94]

In a double-blind crossover study of 50 nondepressed patients with chronic tension-type headache, treatment for 8 weeks with either paroxetine (20 to 30 mg/day) or sulpiride (200 to 400 mg/day) improved headache scores and reduced the need for analgesic intake compared with baseline.[95] However, patients gained better relief from sulpiride than paroxetine.

4. Tolerability

In general, patients receiving paroxetine for panic disorder or OCD experience a similar range of adverse events to those receiving the drug for depression. As most of the clinical experience with paroxetine relates to its use in the treatment of patients with major depression, tolerability data presented here are mainly from this setting. Since the first review in *Drugs*,[1] 2 new sources of data have become available: a postmarketing surveillance study conducted in Belgium (n = 4024)[96] and a prescription-event monitoring study conducted in England (n = 13 741).[97] In addition, the worldwide clinical trial database of patients receiving paroxetine (n = 6145), placebo (n = 1226) or active control treatment (amitriptyline, clomipramine, doxepin, dothiepin, imipramine, fluoxetine, maprotiline or mianserin; n = 3273) during comparative trials is considerably larger than at the time of the original review.[79]

4.1 General Adverse Event Profile

The most common adverse events occurring during paroxetine treatment and their frequency are illustrated in figure 4. Overall, nausea was the most frequent adverse event, occurring in 22% of patients in the clinical trial database[79] and in 14% of patients in the postmarketing surveillance study.[96] Headache, somnolence, dry mouth, insomnia, asthenia, sweating, abnormal ejaculation, constipation, dizziness and tremor occurred in ≥9% of paroxetine recipients during clinical trials,[79] and in 2 to 5% of patients during postmarketing surveillance.[96]

Anticholinergic effects (dry mouth and constipation) occurred much less frequently with paroxetine (14 and 9%) than with active controls (32 and 13%) during short term treatment.[79] This is similar to the findings from large single trials.[52,53,55,57,58] In a study comparing paroxetine (20 to 30 mg/day; n = 151) with amitriptyline (75 to 150 mg/day; n = 152) the frequency of dry mouth was 13% and constipation 9% in the paroxetine-treated group, compared with 35% and 18% in the amitriptyline group (values estimated from a graph).[54]

Overall, most of the adverse events experienced during paroxetine treatment tended to be mild. This applied particularly to nausea, the most frequent adverse event, which was rarely associated with vomiting. In a review of comparative trials,[98] adverse events led to withdrawal from treatment in 13% of paroxetine recipients (n = 2963) compared

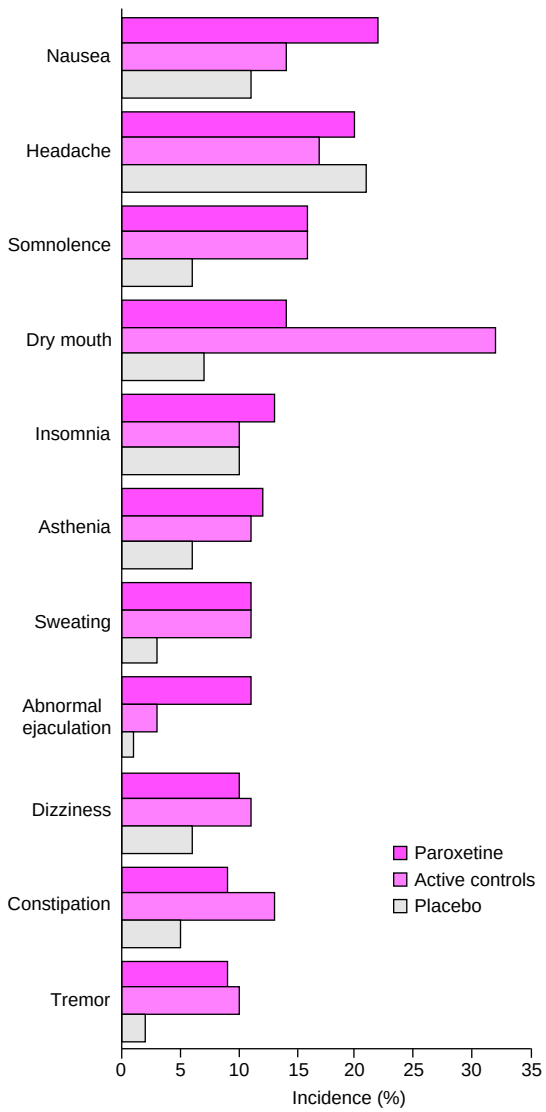

Fig. 4. Incidence of adverse events reported by 10% or more of patients with depression receiving either paroxetine (n = 6145), active control treatment (amitriptyline, clomipramine, doxepin, dothiepin, imipramine, fluoxetine, maprotiline or mianserin) [n = 3273], or placebo (n = 1226). Data are derived from a worldwide clinical trial database.[79]

with 19% of those receiving other antidepressants (mainly TCAs; n = 1151) and 5% of placebo recipients (n = 554).[98] The postmarketing study reported that 7% of paroxetine-treated patients discontinued treatment because of adverse events.[96]

A number of adverse effects (particularly nausea) which occur soon after commencing paroxetine appear to decrease in incidence after a few weeks of treatment. Although 14% of patients reported nausea in the first 3 weeks of treatment, this declined to just 3% between weeks 3 and 6.[96] In a worldwide dataset, the most common adverse events during long term paroxetine treatment (n = 934) were headache (19%), sweating (14%), asthenia (12%), insomnia (12%) and somnolence (12%).[98]

Sexual dysfunction with paroxetine is a clinically important issue. Differences in the various terms that have been used to assess its incidence with other SSRIs (e.g. ejaculatory disturbance with paroxetine, abnormal ejaculation with fluoxetine and ejaculatory failure with sertraline) make accurate comparisons between SSRIs difficult. In addition, the incidence of sexual dysfunction appears to be dose related, with a lower incidence reported with lower doses of SSRIs. This issue is important, since the dose of SSRI required to achieve a statistically significant clinical response in the treatment of OCD or panic disorder is 2 to 3 times the depression dose.

Prescribing information for paroxetine gives an incidence of ejaculatory disturbance (mostly ejaculatory delay) of 13% in males treated for depression.[99] Other male genital disorders (mostly anorgasmia, erectile difficulties, delayed ejaculation and impotence) were reported by 10%. It is not clear whether there is a degree of overlap between patients reporting ejaculatory disturbance and other male genital disorders. Female genital disorders (mostly anorgasmia and difficulty reaching orgasm) were reported by 2%. In the treatment of OCD, 23% of males reported abnormal ejaculation and 8% reported impotence; 3% of females reported genital disorder. In males receiving paroxetine for the treatment of panic disorder, 21% reported abnormal ejaculation and 5% reported impotence. Female genital disorder was reported by 9%. Decreased libido was reported by 3, 7 and 9% of patients receiving paroxetine for the treat-

ment of depression, OCD and panic disorder, respectively.[99]

Adverse effects with paroxetine in the prescription-event monitoring study were compared with those recorded in similar studies of other SSRIs. Overall, the tolerability profile of paroxetine was found to resemble that of other SSRIs. Although a greater frequency of male sexual dysfunction with paroxetine (7.1 per 1000 patients) than with fluvoxamine (0.3 per 1000 patients) or fluoxetine (0.5 per 1000 patients) was reported, prescription-event monitoring is not a credible source for obtaining data on sexual dysfunction and consequently, the validity of these data are questionable.

Tolerability data from clinical trials comparing paroxetine with other SSRIs are limited but in general appear to concur with those from the prescription-event study. In a trial comparing paroxetine 20 mg/day (n = 89) with fluoxetine 20 mg/day (n = 87),[65] there were no statistically significant differences in the number of adverse events between treatment groups. The most frequently reported adverse events for both agents involved the CNS and gastrointestinal systems, although there were fewer reports of nausea/vomiting in both groups (paroxetine 4%; fluoxetine 10%) than typically observed with SSRIs. The only notable difference between treatments was a significantly higher number of metabolic/nutritional adverse events reported in the fluoxetine group (11) than in the paroxetine group (3) [$p = 0.05$], primarily as a result of weight loss caused by fluoxetine.

A comparison of paroxetine 20 to 30 mg/day (n = 56) with fluvoxamine 50 to 200 mg/day (n = 64) also found no significant difference between treatment groups in the overall number of patients reporting adverse events.[66] Nausea, the most frequently reported adverse event, occurred in about 19% of both treatment groups. Interestingly, significantly fewer paroxetine than fluvoxamine recipients (7 *vs* 18; $p < 0.05$) rated adverse events as severe. Furthermore, adverse events caused 11 fluvoxamine-treated patients to drop out of the study compared with only 3 paroxetine recipients ($p = 0.05$).

Analysis of pooled clinical trial results shows that, in general, paroxetine is not associated with clinically significant changes in laboratory parameters.[100] The prescription-event monitoring study identified 7 cases of hyponatraemia associated with the use of paroxetine in more than 13 000 patients, suggesting that this is a rare event.[97]

4.2. Serious Adverse Events

There are very few reports of serious adverse events associated with paroxetine treatment. In the registration trial database, only 3 cases, 1 each of erythema nodosum, hepatitis, and pulmonary fibrosis, were identified as possibly being caused by paroxetine.[98] Furthermore, analysis of this database indicates that paroxetine has not been associated with the serotonergic syndrome.[98] However, instances of the serotonergic syndrome have been reported with the coadministration of paroxetine with certain other drugs (section 6). No deaths were attributed to paroxetine.

It is widely recognised that antidepressants may precipitate mania in patients with bipolar disorder. This appears to be more problematic with the TCAs than with paroxetine: 3 of 134 paroxetine recipients (2.2%) with known bipolar disorder experienced a manic episode compared with 10 of 86 who received comparator antidepressants (11.6%) [$p < 0.05$].[101]

Analysis of clinical trial data showed that the overall incidence of seizures associated with paroxetine was 0.1%. This compared with 0.5% with comparator antidepressants.[101] In addition, paroxetine did not precipitate seizures when given to patients with epilepsy who were receiving phenytoin, carbamazepine or valproic acid.[102]

4.3 Discontinuation Symptoms

A range of symptoms has been reported to appear within 1 to 10 days after discontinuation of paroxetine and other SSRIs. These include dizziness, sweating, influenza-like symptoms, nausea, diarrhoea, insomnia, tremor, fatigue, headache, agitation, visual phenomena and confusion.[103,104] In general, symptoms are mild to moderate and re-

solve spontaneously within 2 weeks. Gradual tapering of paroxetine dosage over several weeks is thought to help minimise discontinuation symptoms.[105-107]

In a comparison of the postmarketing safety profiles of 4 SSRIs, discontinuation symptoms were reported more often with paroxetine (0.3 reports per 1000 prescriptions) than with sertraline and fluvoxamine (each 0.03), and least often with fluoxetine (0.002).[108] Results of a retrospective chart review of supervised medication discontinuation in 171 outpatients tended to support these findings; discontinuation symptoms occurred significantly more frequently with paroxetine (20%), fluvoxamine (14%) or clomipramine (30.8%) than with fluoxetine (0%) or sertraline (2.2%).[109] However, in contrast, prescription-event monitoring did not show a difference in the frequency of discontinuation symptoms with paroxetine, fluoxetine or fluvoxamine.[97] Post-marketing studies, prescription-event monitoring and retrospective chart reviews do not substitute for prospective, randomised, placebo-controlled studies which compare the incidence of discontinuation symptoms with paroxetine and active control medications in the same type of patient population. Until these are available, the above data on discontinuation symptoms should be viewed as suggestive, rather than definitive.

Prescription-event monitoring found no evidence of physiological or psychological dependence in patients treated with paroxetine; there were no reports of tolerance, craving, drug-seeking behaviour or self-neglect.[97]

4.4 Adverse Events in the Elderly

The adverse events profile of paroxetine in the elderly is similar to that in patients aged less than 65 years.[98,100] Frequency or severity of adverse events in elderly patients does not appear to be increased.[98] In a meta-analysis of 10 studies in the elderly, adverse events occurred less frequently with paroxetine treatment (61%; n = 387) than with active controls (74%; amitriptyline, n = 110; clomipramine, n = 109; doxepin, n = 102; mianserin, n = 28) [$p \leq 0.05$].[110] Furthermore, significantly fewer anticholinergic events were observed with paroxetine treatment (19%) than with active control treatment (40%; $p \leq 0.05$). However, paroxetine-treated patients experienced nausea, decreased appetite and diarrhoea more frequently than those receiving active controls.

5. Pharmacoeconomic Considerations

Several recent pharmacoeconomic studies have shown that, despite the much higher acquisition costs for paroxetine compared with TCAs, improved tolerability resulted in overall cost savings.[111-113]

Most investigations measured the total direct cost of 1 year of treatment with paroxetine compared with alternative agents in patients with depression. They employed simulation models and used data on dropout and relapse rates from various clinical trials. The validity of the results from such methods of pharmacoeconomic analysis is dependent on the quality of the clinical data and soundness of the assumptions on which the model is based.

A Canadian investigation found that despite the much higher acquisition costs of paroxetine [$Can1.69 per day (1995 dollars)] compared with imipramine ($Can0.05 per day), the annual direct cost of paroxetine treatment per patient ($Can1679.00) was lower than that for imipramine ($Can1793.00).[111] This was due primarily to the higher rate of treatment failures with the tricyclic agent, which necessitated alternative therapy, additional physician visits and/or hospitalisation. Sensitivity analysis indicated that drug costs and the relapse rate after drug discontinuation had relatively little effect on the overall cost of care. Furthermore, paroxetine was cost-beneficial compared with imipramine if its continuation rate (patients responding to and tolerating treatment) was ≥47%.

Another investigation used similar methods to demonstrate that the total direct medical cost per patient over 1 year was slightly lower with paroxetine [$US2348.00 (1993 dollars)] than imipramine ($US2448.00), despite the higher acquisition cost

of paroxetine ($US1.51 per day compared with $US0.10 per day for imipramine).[112] Again, this was attributable to a higher rate of completion of the initial course of therapy and consequent reduced hospitalisation rates with paroxetine treatment. Results were sensitive to short term dropout rates but robust to changes in other variables.

Two other models comparing costs of paroxetine treatment with alternative antidepressants in the UK are available. In the first, the cost per successfully treated patient over 1 year (defined as no withdrawals due to adverse effects or lack of efficacy) was less for paroxetine [£824.00 (1993 pounds)] than imipramine (£1024.00).[113] However, this investigation has been criticised in the literature[114] over methodological issues and the high assumed dropout rate based on a study by Dunbar et al.[115] When the simulation was replicated by other investigators using revised key assumptions, imipramine was found to be at least as cost-effective than paroxetine, or more so.[116] The other model extended the comparison of treatment costs to include sertraline and amitriptyline.[117] Treatment costs were calculated for successfully treated patients (defined as those who tolerated and responded to treatment without relapse over 1 year) and were £547.65 (1993 pounds) for paroxetine, £491.25 for imipramine, £539.00 for amitriptyline and £581.46 for sertraline.

Results from a retrospective cost analysis of prescription data from 2096 patients who received at least 2 prescriptions for paroxetine, fluoxetine or sertraline in the US over 6 months suggest that paroxetine may be less costly than the other agents.[118] This was based on the finding that dosage adjustment was needed less frequently for patients treated with paroxetine (9.1% of recipients) than for fluoxetine and sertraline recipients (11.8 and 19.5%, respectively). Reduction in annual physician and pharmacist labour costs associated with dose adjustment would lead to annual cost savings in this group of patients of $US3840 by using paroxetine rather than fluoxetine and $US11 760 by using paroxetine rather than sertraline. When drug acquisition costs were incorporated, total savings of $US181 852 and $US44 690 could be achieved by using paroxetine rather than fluoxetine or sertraline, respectively. This study, however, has not been published, statistical analysis was not provided and only 7.6% of patients received paroxetine.

Contradictory findings to those discussed above have been reported in a retrospective analysis of 744 patients treated for depression in a health maintenance organisation.[119] In this study, dosage titration was required more often in patients who were prescribed paroxetine (28.1%) than in those treated with fluoxetine (16.1%), although less often than in those prescribed sertraline (40.3%). Multivariate regression analysis indicated that treatment with paroxetine resulted in an increase in total per capita health service expenditure of $US284.68 (1995 dollars) compared with fluoxetine treatment. However, there was no significant difference in expenditure between paroxetine and sertraline treatment.

6. Drug Interactions

Paroxetine is metabolised by hepatic enzymes (section 2). Hence, it is susceptible to pharmacokinetic interactions with drugs that either induce or inhibit these enzymes. Coadministration with cimetidine[120] or phenytoin,,[34] respectively, caused a 50% increase or a 28% decrease in the paroxetine AUC. In the context of wide interindividual variation in plasma concentration seen with paroxetine treatment, and the apparent lack of correlation between plasma paroxetine concentration and either efficacy or tolerability, the clinical significance of these interactions is unclear.

In addition to being metabolised by CYP2D6, paroxetine inhibits this enzyme.[43,121] This may lead to enhanced plasma concentrations of any coadministered drugs that are metabolised by this enzyme, such as certain TCAs, antipsychotics and antiarrhythmics. Studies have demonstrated that coadministration of paroxetine induced a significant elevation in the plasma concentrations of desipramine and imipramine.[122,123] Consequently, caution must be exercised when paroxetine is

coadministered with other agents that are substrates of CYP2D6, especially if the coadministered drug has a narrow therapeutic index.

In a study of 20 patients with epilepsy who were receiving long term monotherapy with phenytoin, carbamazepine or valproic acid, coadministration of oral paroxetine did not significantly affect the plasma concentrations of the anticonvulsants.[102] In a number of other drug interaction studies, paroxetine did not affect the pharmacokinetics of propranolol,[34] sumatriptan[124] or thiothixene.[125] However, a 12% reduction in the AUC of phenytoin was noted when it was coadministered with paroxetine.[34] Paroxetine may increase the bioavailability of procyclidine.[34]

Paroxetine is highly protein bound (section 2). *In vitro* studies have shown that paroxetine does not significantly alter the protein binding of warfarin, phenytoin or glibenclamide,[34] but, until *in vivo* data are available, paroxetine should be used cautiously in combination with other highly protein-bound drugs.

Concurrent therapy with lithium and paroxetine has not been associated with any pharmacodynamic or pharmacokinetic interactions.[126,127] Plasma concentrations of clozapine and its major metabolite norclozapine were increased by over 40% in a study involving coadministration of SSRIs (including paroxetine) to 80 patients.[128]

Although no significant pharmacokinetic interaction between paroxetine and warfarin has been demonstrated,[120,129] 1 study has suggested that bleeding tendency may be increased by the coadministration of the 2 drugs. Clinically significant bleeding was observed in 5 of 27 healthy volunteers who received paroxetine 30 mg/day and warfarin 5 mg/day for 14 days.[120] However, a more recent study (yet to be published) found no evidence of increased bleeding tendency in volunteers treated with paroxetine (titrated to 40 mg/day) and warfarin 2 to 7 mg/day for 28 days.[129] Since there is little clinical experience, the concomitant administration of paroxetine and warfarin should be undertaken with caution.

Paroxetine does not appear to potentiate the sedative effects or psychomotor retardation induced by haloperidol, amylobarbital, oxazepam or alcohol,[25] and no pharmacokinetic or clinical evidence of interaction was observed when paroxetine and diazepam were coadministered.[120]

Drug combinations that produce excessive serotonergic activity may lead to a potentially fatal serotonin syndrome characterised by at least 3 of the following signs and symptoms: mental status changes (confusion or hypomania), agitation, myoclonus, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination or fever. This syndrome has been reported in patients treated with fluoxetine and monoamine oxidase inhibitors (MAOIs); therefore, the use of any SSRI with MAOIs is contraindicated.[130]

Administered together in patients with depression, moclobemide and paroxetine or fluoxetine appeared to produce adverse effects indicative of potentiated serotonergic activity.[131] However, in a retrospective review of 31 patients with depressive or anxiety disorder who were concomitantly treated with SSRIs (including paroxetine) and moclobemide, there were no features of excessive serotonergic activity.[132] Development of the serotonin syndrome has been reported during the concomitant use of paroxetine and other drugs including trazodone, nefazodone and an over-the-counter cold remedy containing dextromethorphan, paracetamol (acetaminophen), doxylamine and pseudoephedrine.[133-135]

Although it has been recommended that SSRIs and sumatriptan, a 5-HT_{1D} receptor agonist, should not be coadministered,[136] recent reports suggest that these drugs can be used together without the development of significant adverse effects.[137,138]

Various case reports describe adverse events believed to be linked to the interaction between paroxetine and other drugs. These include: sedation, orthostatic hypotension, dysarthria and memory difficulties with trimipramine;[139] extrapyramidal symptoms with molindone;[140] acute dystonic reaction with haloperidol;[141] oculogyric

crisis with pimozide;[142] and delirium with benztropine.[143]

7. Dosage and Administration

The recommended starting dosage of paroxetine for adults with depression is 20mg daily.[99] This is also the minimum effective dosage to which many patients respond. Patients who do not show an adequate therapeutic response within 2 to 3 weeks of initiating therapy may benefit from increasing the dosage by 10 mg/day with at least a week between increments, to a maximum of 50 mg/day.

Paroxetine should be administered as a single oral daily dose in the morning.[38] This is based on $t_{1/2}$ of approximately 24 hours and the finding that morning, but not evening, administration is associated with significant benefits on sleep.[144] If daytime somnolence is a significant problem after morning administration, evening administration can be substituted. Paroxetine should be taken with food to minimise the possibility of gastrointestinal adverse effects.

Available data for maintenance therapy suggest that paroxetine is associated with sustained efficacy and remains well tolerated at doses averaging 30 mg/day. It is not clear whether the dose required for maintenance therapy could be less than that required to induce remission.[99]

For the treatment of patients with OCD, the recommended starting dosage of paroxetine is 20 mg/day and the optimum dosage is 40 mg/day.[99] The recommended initial dose for patients with panic disorder is 10 mg/day with an optimum dosage of 40 mg/day.[99] For both indications, the dosage can be increased in the same manner as that for depressive illness to a maximum not exceeding 60 mg/day.

For elderly or debilitated patients or those with severe renal or hepatic impairment, paroxetine therapy (in all indications) should be initiated at a dosage of 10 mg/day and should not be increased beyond 40 mg/day.[99]

Concomitant use of MAOIs and paroxetine is contraindicated, and when switching patients from an MAOI to paroxetine or vice versa, a 2-week washout period is recommended.[99]

The effects of paroxetine in pregnancy are unknown. Prescription-event monitoring identified 63 cases of potential first trimester fetal exposure to paroxetine. There were 38 successful deliveries with no congenital abnormalities, 1 stillbirth and 8 spontaneous abortions. Pregnancy was terminated in 11 patients and the outcome for 5 patients was unknown.[97] Animal data on the effect of paroxetine during pregnancy are inconclusive. Thus, paroxetine is not recommended for use during pregnancy unless the potential benefit to the mother justifies the possible risk to the fetus.[99]

Available data suggest that, unlike the TCAs, paroxetine in overdose does not cause severe reactions such as seizures, arrhythmias, coma or death. In a prescription-event monitoring study, there were no deaths or comas among 20 patients who took an overdose of paroxetine.[97] A review of the worldwide database revealed that in 15 patients who took an overdose of paroxetine alone or in combination with another drug, no seizures or loss of consciousness occurred. ECGs were normal except in 1 patient who developed sinus tachycardia. All patients recovered fully.[100]

8. Place of Paroxetine in Disease Management

8.1 Depression

Major depression is a common, debilitating psychiatric disorder, with a lifetime prevalence rate between 4.4 and 18%.[145] In addition to causing significant suffering and disability, it is associated with considerable indirect costs to society, particularly in terms of lost earnings/productivity.

The high rates of relapse and recurrence that are associated with depression have led to the current therapeutic recommendation of continuing antidepressant medication for up to 4 or 5 years following resolution of the acute episode in some patients.[146] To ensure compliance over such a period, a good tolerability profile is essential.

Traditionally, the mainstay of pharmacological treatment of depression has been the TCAs. Although their efficacy is proven, the adverse effects profile of these agents has been their main drawback. Most are associated with significant undesirable anticholinergic, CNS and cardiovascular adverse effects, which reduce compliance and limit their use in the elderly. In addition, they have a low therapeutic index (ratio of lethal to therapeutic dose), a significant consideration given the increased risk of suicide associated with depression.

The development of new antidepressant drugs has been driven by the need to reduce the frequency and severity of adverse effects observed with traditional agents. Paroxetine is a phenylpiperidine compound which belongs to the SSRI class of antidepressants. It is a potent and selective inhibitor of presynaptic serotonin reuptake. At the time of the previous review, published studies showed that paroxetine was significantly superior to placebo and of comparable efficacy to the TCAs in the short term treatment of depression. Adverse effects in patients treated with paroxetine were less serious than in those receiving TCAs and resulted in fewer withdrawals from therapy. There were no comparisons with other SSRIs, and no long term studies had been performed.

More recent data have confirmed earlier findings. In addition, there is new evidence to suggest that paroxetine may have an earlier onset of action than TCAs and that it may also be more effective in relieving associated anxiety. Paroxetine has also shown therapeutic equivalence with lofepramine, maprotiline and nefazodone, as well as the other SSRIs fluoxetine, fluvoxamine and sertraline. The drug appears to be suitable for long term maintenance therapy. The efficacy of paroxetine in elderly patients with depression was at least as good as that of several other agents including fluoxetine. Whilst previous data indicated that paroxetine may be of particular benefit in treating TCA-resistant depression, no further studies in this respect are available. Although some early studies suggested that the SSRIs, including paroxetine, may not be as effective as the TCAs in treating severe depression, recent studies with paroxetine in hospitalised patients and in outpatients with severe depression did not produce substantiating evidence.

New data confirm that the adverse events associated with paroxetine tend to be mild and transient. Although nausea occurred more commonly with paroxetine than with TCAs, it tended to subside after 2 to 3 weeks' treatment. Importantly, dry mouth and constipation, particularly problematic adverse effects with TCA treatment, occur at a much lower incidence with paroxetine. Paroxetine is well tolerated in the elderly. Furthermore, paroxetine has a wide therapeutic index, rendering it much less likely to cause death in overdose than the TCAs.

In general, there was little difference in the tolerability profile between paroxetine and other SSRIs. Although data on sexual dysfunction are inadequate to accurately determine differences among the SSRIs, male sexual dysfunction is a clinically important issue with paroxetine, particularly at the higher doses required to treat OCD and panic disorder.

Discontinuation symptoms such as dizziness, nausea, tremor and fatigue that may occur following the cessation of treatment with paroxetine and other SSRIs are generally mild to moderate, and resolve spontaneously within 2 weeks. There is some evidence to suggest that SSRIs with a shorter $t_{1/2}$, such as paroxetine, may be associated with a greater incidence of discontinuation symptoms than SSRIs with a longer $t_{1/2}$, such as fluoxetine (section 4.3). However, definitive comment on the incidence of discontinuation symptoms with paroxetine, relative to other SSRIs, must await results from well designed prospective trials.

In choosing between paroxetine and other members of the SSRI class, pharmacokinetic considerations may be important. Paroxetine has a $t_{1/2}$ of approximately 24 hours, which makes it suitable for once daily administration. Furthermore, its metabolites are largely inactive. In contrast, fluoxetine has a $t_{1/2}$ of approximately 2 days and that of its active metabolite (norfluoxetine) is 7 to 15 days. This has implications in terms of dose titration,

treatment changes, potential drug interactions, and treatment discontinuation in the event of adverse effects, which appear to favour paroxetine over fluoxetine. Conversely, however, a long $t_{1/2}$ also yields some advantages. For instance, occasional missed doses of fluoxetine are unlikely to cause a problem. In addition, because of its long $t_{1/2}$, abrupt cessation of fluoxetine, even at high dosages, is less likely to lead to the SSRI discontinuation syndrome.

The SSRIs differ considerably in their potencies for inhibiting specific hepatic cytochrome P450 (CYP) enzymes. Paroxetine and fluoxetine are the only 2 agents in this class of drugs that produce meaningful inhibition of CYP2D6 at their usually effective dose.[147] Consequently, they would be expected to share the greatest potential for interactions with drugs that are metabolised by CYP2D6 (including certain TCAs, antipsychotics and antiarrhythmics). Although paroxetine does not appear to inhibit other CYP enzyme systems, fluoxetine is thought to also substantially inhibit CYP2C9/10, moderately inhibit CYP2C19 and mildly inhibit CYP3A3/4.[147] Fluvoxamine has minimal inhibitory effects on CYP2D6. However, it is a potent inhibitor of CYP1A2 and CYP2C19 and also has moderate inhibitory effects on CYP3A3/4; potentially significant interactions may occur with substrates of these enzymes, including propranolol, carbamazepine, terfenadine, lidocaine, theophylline and warfarin.[148] Citalopram and sertraline produce only mild inhibition of CYP2D6 and little, if any, clinically meaningful effects on other CYP enzyme systems.[147] Knowledge of coadministered medications and their metabolism, therefore, could be expected to influence the choice of SSRI.

Paroxetine, fluoxetine and, to a lesser extent, fluvoxamine have nonlinear pharmacokinetics over their usual dose range.[147] Disproportionate increases in plasma concentrations may occur after dosage increases or prolonged administration of these drugs that would magnify the effects of CYP enzyme inhibition and lead to potentially more deleterious drug-drug interactions.[31] In contrast, citalopram and sertraline follow linear pharmacokinetics across their clinically relevant dosing range.[147]

8.2 Obsessive Compulsive Disorder

Recent data have shown that OCD is not as uncommon as it was once believed to be. Lifetime prevalence of OCD is now estimated to be between 2 and 3%.[149] The recurrent intrusive thoughts and unwanted repetitive actions which characterise this disorder can severely impede the ability to perform normal routine activities.

Although OCD was previously considered refractory to most forms of treatment, effective behavioural and pharmacological therapies are now available. Clomipramine has been the most widely used agent in the management of OCD, and many trials have demonstrated its therapeutic efficacy. However, because of its often troublesome adverse effects, which are typical of the TCA class, alternative agents, namely the SSRIs, are increasingly being used.

Clinical trials have shown that paroxetine is more effective than placebo in the short term treatment of OCD (section 3.2). Paroxetine had similar efficacy, but was better tolerated than clomipramine. Limited long term data suggest that paroxetine may be effective in maintaining a therapeutic response and preventing relapse over 1 year, but more studies to assess this are needed. There is also a need for further clinical trials which directly compare the efficacy of the different SSRIs in patients with OCD.

8.3 Panic Disorder

Panic disorder is a chronic debilitating illness with an estimated lifetime prevalence in the US of about 3.5%.[150] Traditionally, pharmacological treatment has centred on the use of TCAs (e.g. clomipramine and imipramine), high-potency benzodiazepines (e.g. alprazolam and clonazepam), and MAOIs (e.g. phenelzine).[151-153] However, none of these classes are entirely satisfactory. The TCAs are associated with a slow onset of action and often troublesome anticholinergic side effects, and the benzodiazepines have a well known pro-

pensity to cause physiological dependence. The usefulness of MAOIs is limited by the requirement for dietary restrictions. Increasing use is being made of the SSRIs (including paroxetine) in the treatment of this disorder.

Data from short term trials indicate that paroxetine has clear superiority to placebo and equivalent efficacy to clomipramine in the treatment of patients with panic disorder (section 3.3). Although there is some evidence suggesting an earlier onset of action for paroxetine compared with clomipramine, 3 to 4 weeks of paroxetine treatment are required to achieve a therapeutic effect. As it is well established that the beneficial effects of benzodiazepines are attained within the first week of treatment, their use as adjunctive treatment during the initial phase of paroxetine therapy is recommended.[152] Paroxetine appears to be effective in maintaining a reduction in the number of panic attacks and in preventing relapse over longer term use.

8.4 Other Disorders

Current therapy for several other disorders with a presumed serotonergic basis, including social phobia, PMDD and chronic headache, is far from satisfactory. Although clinical trials have confirmed the efficacy of irreversible MAOIs and certain benzodiazepines in the management of social phobia, concerns about toxicity with the former, and dependence with the latter agents have limited their usefulness.[154-156] Clomipramine has been shown to reduce the symptoms of PMDD; however, like all TCAs, it causes troublesome anticholinergic adverse effects.[157,158] Patients with chronic daily headache are difficult to treat. Although TCAs, such as amitriptyline, have been effective, adverse effects associated with these agents restrict their clinical use.[159]

Preliminary data suggest that paroxetine may have therapeutic potential in social phobia, PMDD and chronic headache (section 3.4). However, additional well designed studies are required before definitive recommendations concerning its use in these disorders can be made.

8.5 Conclusions

In patients with OCD or panic disorder, paroxetine appears to offer benefits which are similar to those of clomipramine without its troublesome adverse effects. Although there is insufficient evidence to draw firm conclusions, preliminary data show that paroxetine may also be useful in patients with PMDD, chronic headache and social phobia.

Data that have become available since the original review in *Drugs*[1] confirm that paroxetine is better tolerated than the TCAs and is equally effective in the treatment of depression. In addition, there appears to be little difference in antidepressant efficacy or tolerability between paroxetine and other SSRIs. However, differences in the pharmacokinetic profile between paroxetine and other members of this class may, in individual cases, influence the choice of drug. Further comparative studies with other SSRIs are necessary to more accurately determine the relative position of paroxetine in clinical practice. Nevertheless, on the basis of available data, paroxetine represents a significant advance over the TCAs and a suitable alternative to other SSRIs in the treatment of patients with depression.

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