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Paroxetine: A Review

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ABSTRACT

Paroxetine is a potent and selective serotonin reuptake inhibitor (SSRI) with currently approved indications for the treatment of depression, obsessive-compulsive disorder, panic disorder and social phobia. It is also used in the treatment of generalized anxiety disorder, post traumatic stress disorder, premenstrual dysphoric disorder and chronic headache.

Paroxetine, a phenylpiperidine derivative, is the most potent inhibitor of the reuptake of serotonin (5-hydroxytryptamine, 5-HT) of all the currently available antidepressants including the class of SSRIs. It is a very weak inhibitor of norepinephrine (NE) uptake but it is still more potent at this site than the other SSRIs. The selectivity of paroxetine, i.e., the ratio of inhibition of uptake of norepinephrine to serotonin (NE/5-HT) is amongst the highest of the SSRIs. Paroxetine has little affinity for catecholaminergic, dopaminergic or histaminergic systems and by comparison with tricyclic antidepressants (TCAs) has, therefore, has a reduced propensity to cause central and autonomic side effects. Paroxetine exhibits some affinity for the muscarinic cholinergic receptor but much less than the TCAs. In addition, the adaptive changes of somatodendritic (5-HT_{1A}) and terminal ($5\text{-HT}_{1B/1D}$) autoreceptors observed with paroxetine are different to those observed with TCAs; it also inhibits nitric oxide synthase. It is both a substrate and an inhibitor of cytochrome isoenzyme P450 2D6. Paroxetine is well absorbed orally and undergoes extensive first pass metabolism that is partially saturable. Its metabolites are pharmacologically inactive *in vivo*. Steady state levels are achieved after 4–14 days and an elimination half-life of 21 h is consistent with once-daily dosing. There is wide inter-individual variation in the pharmacokinetics of paroxetine in adults as well as in the young and the elderly with higher plasma concentrations and slower elimination noted in the latter. Elimi-

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nation is also reduced in severe renal and hepatic impairment. Serious adverse events are, however, extremely rare even in overdose.

In summary, paroxetine is well tolerated and effective in the treatment of both depressive and anxiety disorders across the age range.

INTRODUCTION

Depression is frequently both underdiagnosed and undertreated. Even with treatment, only about 70% of patients will demonstrate an adequate response to antidepressant drug therapy with recovery from their depression. Furthermore, a significant number of patients achieve only partial remission and will relapse over the longer term. The individual and societal costs of untreated depression are substantial (16,75).

A key factor in successful treatment is compliance. Poor adherence to what is likely to be a long-term treatment may lead to no treatment or inappropriate treatment with consequently negative impact on recovery. The presence of side effects is known to be associated with reduced compliance.

Since the late seventies, active research programs have sought to improve treatments for depression and other disorders including obsessive compulsive-disorder (OCD), panic disorder and social phobia, all of which show some response to antidepressant drugs (110). Paroxetine is an antidepressant resulting from such rational drug development. It is a potent and selective SSRI, which is approved for the treatment of depression worldwide. It demonstrates a broad spectrum of efficacy and it has also been approved for the treatment of OCD, panic disorder and social phobia in different countries. Future likely indications include the treatment of generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD). Clinical trials have recently been completed with paroxetine in the treatment of premenstrual dysphoric disorder (PMDD). It has also been used in the treatment of diabetic neuropathy, vasovagal syncope and chronic headache. Paroxetine has an elimination half-life ($t_{1/2}$ = 21 h), which allows for once-daily dosing. It is associated with a favorable side effect profile, low toxicity in overdose and is well tolerated in special populations including the elderly.

CHEMISTRY AND BIOCHEMICAL MECHANISM OF ACTION

Traditionally, the classification of antidepressant drugs has been based either upon chemical structure, e.g., the TCAs, or mechanism of action, e.g., the monoamine oxidase inhibitors (MAOIs). Paroxetine is functionally classified as a selective serotonin reuptake inhibitor (108), a class of structurally unrelated drugs which enhances serotonergic transmission by blocking the presynaptic active membrane transport mechanism for the reuptake of serotonin and consequently increases serotonergic activity at the postsynaptic receptor (53). Paroxetine's affinity for the serotonin receptor is 2 to 3 orders of magnitude greater than the K_m of serotonin and as with the other members of the class, it effectively increases the concentration of endogenous serotonin in the synaptic cleft (89).

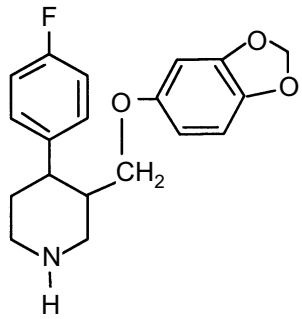

Fig. 1. Chemical structure of paroxetine.

The structure of paroxetine, a phenylpiperidine derivative, is shown in Fig. 1. It is highly lipophilic.

The specific mechanism of action of antidepressant drugs in alleviating depression has not yet been described (51). Currently available drugs show a wide range of potencies for norepinephrine (NE), serotonin (5-HT) or dopamine (DA) reuptake inhibition. Although the etiology and pathophysiology of depression remains uncertain, there is considerable evidence to suggest that 5-HT and NE systems are involved in the pathogenesis of depression and drugs acting on these two systems have been successfully used in the treatment of depressive disorders.

Paroxetine is the most potent inhibitor of 5-HT reuptake of all currently available antidepressants. It is a very weak inhibitor of norepinephrine uptake but it is still more potent at this site than the other SSRIs and this may contribute to its efficacy at higher doses. The selectivity of paroxetine, i.e., the ratio of inhibition of uptake of NE to 5-HT (NE/5-HT) is amongst the highest of the SSRIs (50). It has negligible affinity for any other receptors.

The secondary adaptive receptor changes occurring over time with paroxetine are different to those observed with TCAs. Long-term administration of paroxetine (over two to three weeks) decreases the responsiveness of somatodentritic (5-HT_{1A}) and terminal ($5\text{-HT}_{1B/1D}$) autoreceptors, leading to greater serotonin release with each action potential; in contrast to the sensitization of postsynaptic 5-HT_{1A} receptors which occurs with TCAs (11). These adaptive changes in synaptic serotonergic receptors are likely to be important with respect to the therapeutic effects of paroxetine.

PRECLINICAL PHARMACOLOGY

Actions on Neurotransmitter Reuptake

In vitro studies in rat brain synaptosomes have shown paroxetine to possess the most potent inhibition of 5-HT reuptake of the SSRIs (106), as summarized in Table 1. Since the main metabolites produced after oral administration of paroxetine have minimal activity, they do not modify the pharmacological profile of the parent compound and it is unlikely they contribute to its clinical effects (56). The blockade of serotonin reuptake by paroxetine is prolonged and maintained upon repeated administration (66). From *in vitro*

and *ex vivo* studies, the blockade of serotonin reuptake into synaptosomes is dose dependent (13). *In vivo* microdialysis experiments show that the acute administration of paroxetine at doses of 5 mg/kg increases extracellular serotonin levels (67).

The results of *in vitro* and *in vivo* studies have shown that much higher concentrations of paroxetine are required to inhibit the reuptake of NE and DA (36,45,106). Although the concentration of paroxetine necessary to inhibit NE uptake is lower than the concentrations of any other SSRIs required to achieve the same effect, as a result of its potency in 5-HT reuptake inhibition, paroxetine's selectivity (NE/5-HT) is second only to that of citalopram (36).

Interactions with Neurotransmitter Receptors

Both, *in vitro* and *in vivo* studies have demonstrated that paroxetine is devoid of any significant affinity for adrenoceptors (α_1, α_2, β), dopamine (D_2) receptors, histamine (H_1) receptors, or 5-HT receptor subtypes (5-HT_{1A}, 5-HT_2). Paroxetine has only weak affinity for muscarinic (M_3) cholinergic receptors with one-eighth of the *in vivo* anticholinergic potential of nortriptyline (13,36,93,106). Receptor radioligand binding profiles are shown in Table 2. Paroxetine has been shown to be a potent inhibitor of nitric oxide synthase *in vitro* and *in vivo*, and to possess greater potency than nortriptyline, as measured by the conversion of [^{14}C]arginine to [^{14}C]citrulline by hamster brain cytosols (35).

Effects of Repeated Administration of Paroxetine on Receptor Sensitivity

Although the inhibition of serotonin uptake occurs within hours of drug ingestion, the clinical response in psychiatric disorders such as depression represents a more delayed process, usually taking at least 2 weeks or more. This may be due to the time required for the drugs to exert their full effects through a reaction cascade following drug intake. Further adaptive changes occurring at receptor sites may be a secondary consequence of

TABLE 1. In vitro *binding profiles from rat brain tissue synaptosomes*[a]

	Mean uptake inhibition constant (K_i) (nmol/L)			
Compound	5-HT	NE	DA	NE/5-HT
Paroxetine	1.1	350	2000	320
Fluvoxamine	6.2	1100	>10,000	180
Fluoxetine	25	500	4200	20
Sertraline	7.3	1400	230	190
Citalopram	2.6	3900	NR	1500
Bupropion	15,000	2200	1500	–
Nefazodone	570	134	2380	0.23
Venlafaxine	210	39	5300	0.19
Clomipramine	7.4	96	9100	13
Imipramine	100	65	8500	0.65

[a]Adapted from ref. 45.

TABLE 2. In vitro *blockade of radioligand binding in rat brain tissue*[ab]

Receptor Ligand	α_1 prazosin	α_2 clonidine	β DHA	$DA(D_2)$ spiperone	$5\text{-}HT_1$ serotonin	$5\text{-}HT_2$ ketanserin	$5\text{-}HT_{1A}$ 8-OH-DPAT	H_1 mepyramine	Muscarinic QNB
Paroxetine	>10,000	>10,000	>5000	7700	>10,000	>1000	>1000	>1000	89
Amytriptyline	170	540	>5000	1200	1000	1000	8.3	3.3	5.1
Imipramine	440	1000	>5000	2400	8900	>1000	120	35	37
Clomipramine	150	3300	>5000	430	5200		63	47	34
Mianserin	330	94	>5000	830	590	240	2.3	3.4	270

[a]K_i values in nmol/L.
[b]Adapted from refs. 13,36,93,108.
Abbreviations: DHA, dihydroalprenolol; 8-OH-DPAT, (RS)-8-hydroxy-2-(dipropylamino)tetralin; QNB, quinuclidinyl benzilate.

repeated antidepressant drug administration and are perhaps necessary for clinical efficacy (89).

Paroxetine does not downregulate central β-adrenoceptors (45). It does induce desensitization of the terminal $5\text{-}HT_{1B/1D}$ autoreceptors and following initial administration to rats, paroxetine causes indirect activation of postsynaptic $5\text{-}HT_{1A}$ autoreceptors, leading to a reduction of serotonergic activity (93). A subsequent decrease in the responsiveness of somatodendritic $5\text{-}HT_{1A}$ autoreceptors results in serotonergic neuronal firing returning to normal. These processes may account for the delay following the initiation of treatment and the symptom response observed in clinical practice (90). Paroxetine also downregulates $5\text{-}HT_2$ receptors. The clinical significance of this adaptive change is, however, unknown.

Behavioral Tests

Multiple studies with various animal models provide evidence that paroxetine is a potent and selective inhibitor of central serotonin uptake (14). It has been shown that there is potent and prolonged potentiation of hypermobility induced by 5-hydroxytryptophan (5-HTP), potentiation of the anticonvulsant effect of 5-HTP, potent and prolonged inhibition of hypermobility induced by *p*-chloroamphetamine as well as an absence of activity against hypermobility induced by 4-dimethyl-*m*-tyramine. Paroxetine has also been shown to be active in other models including inhibition of the effects of 3-hydroxy-4-methyl-α-ethylphenylamine, the olfactory bulbectomized rat model of depression and the forced swim test in mice (53).

It has been suggested that repeated high dose administration of paroxetine may result in loss of 5-HT reuptake selectivity as well as possible effects on NE reuptake (27). Paroxetine may, therefore, induce adaptive changes similar to those observed with imipramine. Indeed, the antagonism of the hypothermic effect of apomorphine, observed with high dose paroxetine, suggests that this regimen may inhibit NE reuptake and thus restore synaptic NE levels. Furthermore, repeated treatment with paroxetine atten-

uated the clonidine induced hypothermic effect, possibly explained by a subsensitivity of α_2-adrenoceptors or a shift of these receptors to an antagonist preferring state (88).

In studies using the forced swim test in mice treated with *p*-chlorophenylalanine and paroxetine, lower doses of paroxetine (8 and 16 mg/kg) are likely to act through serotonergic mechanisms. At higher doses of paroxetine (32 mg/kg) the anti-immobility effects of the drug are not attenuated, implying that at higher doses it may display 5-HT and NE activity but not any appreciable DA activity (87).

Paroxetine displays 5-HT activity in rodent models as expected. Paroxetine does not induce any significant changes in the spontaneous locomotor activity of rodents, it does not induce stereotypies or display any appreciable DA activity (62). It does not inhibit mepyramine binding and consequently shows no sedative effects in animal tests. Paroxetine does not potentiate the ethanol-induced abolition of the erecting reflex in mice.

Effects on Electroencephalographic Measurements

Sedation is not seen on the electroencephalograph (EEG) in animals or humans with paroxetine. In rabbits paroxetine is associated with a sustained arousal pattern in spontaneous EEGs without producing central cholinergic activity or inhibition of the EEG arousal responses to external stimuli (108). The increase in arousal appears to be dose-dependent, at least, in rats and, with respect to sleep parameters, waking period is lengthened, sleep latency is delayed, slow wave sleep is decreased and rapid eye movement (REM) sleep is suppressed (61).

Cardiovascular Effects

The cardiovascular effects of paroxetine observed in studies in cats and rabbits are much weaker than those produced by tricyclics and are seen only at higher doses (108). These may be related to paroxetine's selective effect on 5-HT reuptake inhibition and weak effects on NE reuptake inhibition, muscarinic and histamine receptors, and α_1-adrenoceptors. At doses sufficient to produce 5-HT blockade paroxetine has only weak quinidine-like effects. Hypotension, tachycardia, bradycardia and slight prolongation of PQ interval have been reported in dogs (112).

Serotonin Syndrome

Studies in rats have demonstrated the development of a serotonin syndrome if a MAOI or a serotonin precursor is combined with paroxetine or any other SSRI. Clinical experience in humans indicates that paroxetine should not be prescribed with a MAOI, L-tryptophan or any drug likely to significantly increase brain serotonin levels (108).

Endocrine Effects

Increases in serum cortisol, corticotrophin-releasing hormone and adrenocorticotrophin (ACTH) have been described with SSRIs in rats. Similarly, potentiation of 5-HTP-induced increase of serum prolactin has also been reported but there is no evidence of a significant direct prolactin effect in man. Hormonal assessments of healthy male volunteers after 4 weeks of treatment with paroxetine did not demonstrate any significant changes in prolac-

tin, growth hormone, cortisol, ACTH, luteinizing hormone, testosterone or melatonin levels (94).

Clinical Pharmacology

After administration of paroxetine, 40 mg daily for 28 days to healthy volunteers, plasma samples obtained at day 7 and 28, were found to inhibit 5-HT uptake into rat cortical synaptosomal preparations but had no effect on NE uptake. Similarly no effect on 5-HT reuptake was found after a single 10 mg dose of paroxetine, or after a 14 day washout following a 28 day repeated dose administration. Repeated administration of paroxetine to volunteers, 10 to 40 mg/day for 28 days, decreased whole blood 5-HT levels (77). This has been attributed to a 5-HT reuptake inhibition effect on platelets (52). Paroxetine, single and repeated doses, did not decrease the tyramine pressor test response in healthy volunteers. This response is normally diminished by α-adrenoceptor antagonists or NE reuptake inhibitors. Desensitization of presynaptic 5-HT_{1A} receptors after 17 days of treatment with paroxetine, 20 to 30 mg/day, has been indirectly inferred from the hypothermic and endocrine responses observed in healthy volunteers. This treatment also appeared to desensitize postsynaptic 5-HT_{1A} receptors in the hypothalamus.

Single doses of paroxetine, 20 mg, do not affect parasympathetic or sympathetic activity in volunteers and after 6 weeks treatment in depressed elderly patients, the serum of paroxetine treated patients had five-fold less anticholinergic activity than the serum of nortriptyline treated patients (85).

The effects of paroxetine on sleep have been extensively investigated. Sleep disturbances such as increased rapid eye movement (REM) sleep, decreased slow wave sleep and increased number of nocturnal awakenings are frequently associated with depression. In sleep laboratory studies in healthy volunteers, paroxetine reduced total REM sleep and increased the duration of REM sleep latency in a dose-dependent fashion (45). The effects on sleep were even more marked when a 30 mg dose of paroxetine was given in the morning resulting in an earlier onset and increased duration of slow wave sleep (stages 3 and 4), an increased number of awakenings and a reduction in total sleep time. In contrast, the results from depressed patients suggested that morning doses of 30 mg of paroxetine, were associated with falling asleep more rapidly and easily, more restful sleep, lower number of nocturnal awakenings, subjectively greater alertness and less clumsiness upon wakening. Paroxetine caused significant REM suppression, and, although there was an increased number of nocturnal awakenings, there was no decrease of total sleep time (99). Subjective ratings of quality of sleep were improved in depressed patients taking paroxetine. A REM rebound phenomenon may be seen after paroxetine discontinuation.

Paroxetine, given at a dose of 20 mg/day, (the recommended therapeutic dose for depression), in single and repeated doses, did not impair psychomotor functioning, as measured by objective tests in healthy volunteers, depressed patients or elderly subjects. At a higher dosage of 40 mg/day, there was only slight impairment in certain specific tests (47). Concomitant administration of paroxetine with CNS depressants including haloperidol, amylobarbital, benzodiazepines and alcohol is not associated with any potentiation of sedative effects (108). Although paroxetine, 20 and 40 mg/day, given for 8 days to healthy volunteers did not modify driving performance, patients should be advised to exercise caution if operating machinery or driving a motor vehicle and to avoid alcohol (78).

Paroxetine, 30 to 40 mg/day, administered for 4 weeks to healthy volunteers, did not result in any significant change in heart rate, blood pressure or ECG parameters (108). As demonstrated in one study involving comparison of paroxetine with nortriptyline in 81 depressed patients with associated ischemic heart disease, paroxetine at 20–30 mg/day for 6 weeks, did not produce any significant changes in blood pressure, heart rate or ECG (92). Similarly, in panic disorder patients with decreased relative ultra low frequency power on Holter monitor recordings during sleep, paroxetine at 20–30 mg/day increased the relative ultra low frequency power during sleep (111).

As previously noted, a serotonin syndrome may occur with concomitant administration of paroxetine and drugs which markedly increase brain serotonin levels such as MAOIs or L-tryptophan. Such combinations are, therefore, contraindicated (21). Treatment with paroxetine should not be initiated until at least two weeks after the discontinuation of a MAOI and conversely, a MAOI should not be initiated until at least two weeks after paroxetine has been stopped. In patients treated with paroxetine concurrently with lithium, no changes in the plasma levels of either drug have been reported. The concomitant administration of SSRIs and lithium may, however, increase the risk of adverse neurological effects, including serotonin syndrome; it is recommended that this combination should be carefully monitored (21). Concomitant use of paroxetine and digoxin should be undertaken cautiously, given the narrow therapeutic index of the latter, although there is no evidence of significant pharmacokinetic interaction between these two drugs. The bioavailability of TCAs is increased when these drugs are co-administered with paroxetine, and again caution should be exercised with this combination (64). The same is true for procyclidine, theophylline, clozapine (22) and molindone (68). Paroxetine does not affect the pharmacokinetics of antipyrine, propranolol, sumatriptan (although adverse CNS interactions have been reported) or thiothixene and does not significantly affect plasma concentrations of phenytoin, carbamazepine, valproic acid or methadone (21). Potential interaction may theoretically occur with phenothiazines and type 1c antiarrhythmics (21). The bioavailability of paroxetine may be increased by cimetidine and decreased by phenobarbital and phenytoin (21). The pharmacokinetics of paroxetine is not modified by alcohol, aluminium hydroxide antacid, diazepam, oxazepam, propranolol or oral contraceptives (21).

In summary, the results of the clinical pharmacology studies are consistent with paroxetine's neurotransmitter receptor profile and minimal quinidine-like effects, resulting in its lack of sedation and weak cardiovascular effects.

Pharmacokinetic Properties

Paroxetine may be accurately assayed in human plasma by high-performance liquid chromatography (HPLC) (15). There is a wide inter-individual variability in the pharmacokinetics of paroxetine (56). The pharmacokinetic parameters of paroxetine, at single doses of 20 to 50 mg, are summarized in Table 3.

There is no evidence that efficacy of paroxetine correlates with its plasma concentrations, given the relatively flat dose–response curve for the antidepressant effect of paroxetine at the dose range of 20 to 40 mg/day (the dose generally used in correlation studies). The pharmacokinetics of paroxetine in depressed patients without renal or hepatic dysfunction, is similar to that in healthy volunteers.

Paroxetine is almost completely absorbed after an oral dose. Its absorption is not modified by food or concomitant antacid treatment. A first-pass effect has been described which becomes saturated leading to greater bioavailability and non-linear pharmacokinetics after repeated doses. With repeated administration the steady-state concentrations of paroxetine are achieved in 7–14 days. There is no further accumulation of the drug (29).

The distribution of paroxetine in the body is extensive and consistent with its lipophilic amine character, with only 1% of the drug remaining in the systemic circulation. The volume of distribution shows wide inter-individual variations, ranging from 3.1 to 28.0 L/kg after intravenous administration. At therapeutically relevant concentrations paroxetine is 95% plasma protein bound; it should, therefore, be prescribed cautiously with other highly protein bound drugs, e.g., warfarin (56).

Paroxetine is extensively metabolized in rat, monkey and humans by oxidation at the methylenedioxyphenyl ring to the main metabolites shown in Fig. 2.

Less than 5% of the parent compound is excreted unchanged in urine and feces. The pharmacological profile in humans is not modified by the metabolism of paroxetine and, therefore, the resulting metabolites are unlikely to contribute to its therapeutic effects. The main metabolites, sulphate- and glucuronide-conjugates of metabolite I, as well as the unconjugated metabolites, which are minimally present, have no significant inhibitory activity on either 5-HT or NE reuptake and are considered pharmacologically inactive (46).

The inactive polar metabolites are excreted in urine (65%) and feces (25%). Elimination of paroxetine metabolites is biphasic (56). In healthy subjects the mean elimination half-life of paroxetine, after repeated administration, is approximately 24 h, consistent with once-daily dosing.

Paroxetine is extensively metabolized in the liver, its metabolism involves at least two enzymes in the cytochrome P450 system that are subjects to genetic polymorphism (12). CYP2D6 is a high affinity, saturable enzyme which is the first line enzyme in extensive metabolizers (17). The other enzyme is not yet identified although it may involve CYP3A4 which has a much lower affinity and may be the first line enzyme in poor metabolizers. In most subjects, treated with paroxetine at doses of 20 to 50 mg/day, only a minimal degree of non-linearity of paroxetine pharmacokinetics is observed. Non-linear increases of plasma drug concentrations and of elimination half-life may occur with higher doses of paroxetine, secondary to the saturation of CYP2D6 (98). Given that paroxetine and metabolite II inhibit CYP2D6, there is a high potential for pharmacokinetic in-

TABLE 3. Pharmacokinetic parameters (mean values) of paroxetine in healthy volunteers after oral administration of single dose of paroxetine over the range 20–50 mg[a]

	Dose (mg)			
Parameter	20	30	40	50
C_{max} (ng/ml)	10.7	17.6	26.6	31.1
C_{min} (ng/ml)	5.1	8.5	14.2	11.7
t_{max} (h)	5.8	6.3	6.4	5.5
$t_{1/2}$ (h)	21.1	21.7	20.6	17.4
AUC (ng · h/ml)	454	797	1127	763

[a]Adapted from ref. 56.

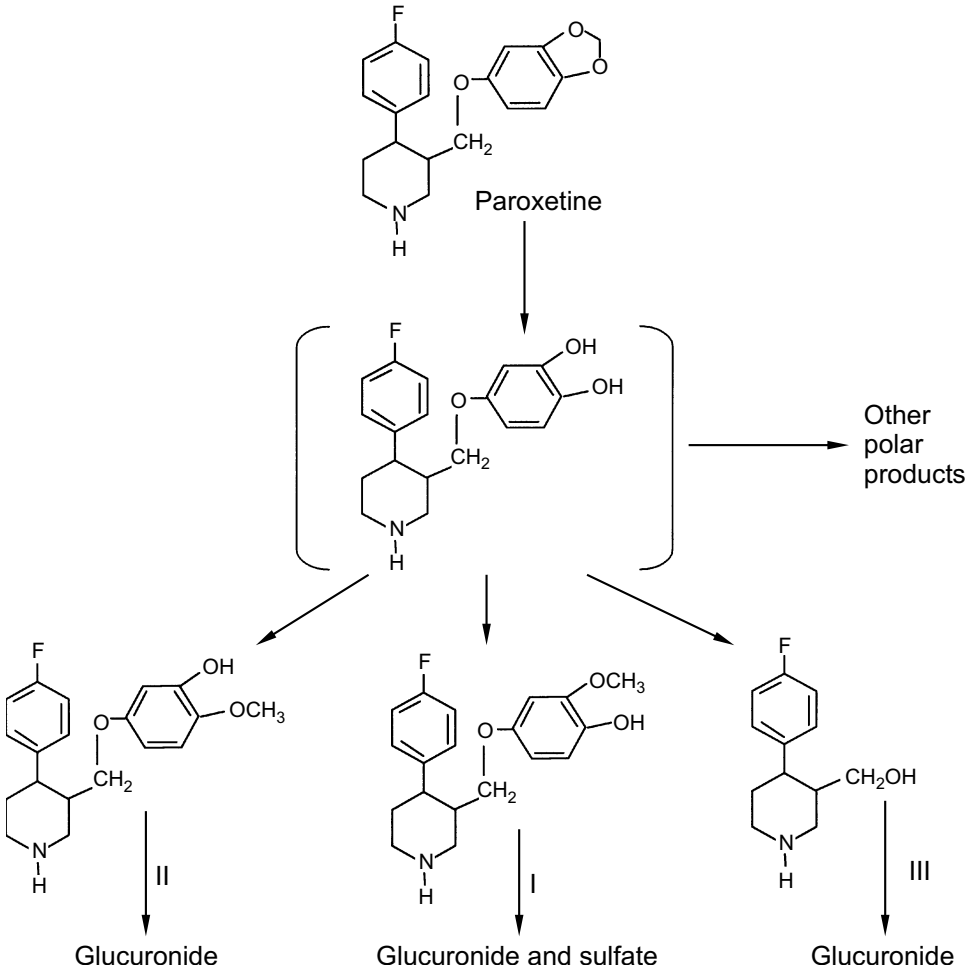

Fig. 2. Metabolic pathway of paroxetine in man. Adapted from ref. 56.

teractions with other drugs, which are also metabolized by this enzyme (17,26). Consequently, plasma levels of other drugs may be increased when co-administered with paroxetine, e.g., TCAs (1), some neuroleptics, antiarrhythmics, procyclidine, and theophylline. Paroxetine plasma levels may be increased when co-administered with an enzyme inhibitor, e.g., cimetidine, or decreased when co-administered with an enzyme inducer, e.g., phenobarbital or phenytoin. No significant pharmacokinetic interactions have been described with warfarin, digoxin or lithium. Concomitant administration of paroxetine and these drugs should, however, be monitored (114).

In elderly patients, plasma concentrations of paroxetine are higher at steady state and elimination half-life is longer than those reported in younger subjects (18). A large interindividual variability in the pharmacokinetics of paroxetine has been reported in different age groups (65). It is recommended that elderly patients should be started on lower doses

TABLE 4. Pharmacokinetic parameters (mean values) of paroxetine in the elderly after oral administration of single doses of paroxetine over the range 20–30 mg[a]

	Dose (mg)		
Parameter	15	20	30
C_{max} (ng/ml)	36.3	16.7	47.0
C_{min} (ng/ml)	15.9	6.9	10.8
t_{max} (h)	4.0	5.3	3.2
$t_{1/2}$ (h)	25.7	21.2	28.3
AUC (ng · h/ml)	1103	546	1348

[a]Data from ref. 56.

of paroxetine. Table 4 shows the pharmacokinetic parameters of paroxetine at the dose range of 15 to 30 mg (single dose) in elderly patients.

In patients with renal insufficiency, there is a trend towards higher plasma concentrations and longer elimination half-life of paroxetine. This is significant only for subjects with a creatinine clearance of less than 1.8 L/h (30 mL/min), in whom paroxetine should be initiated at the lower end of the recommended dose range and titrated cautiously. In patients with hepatic cirrhosis, as compared to healthy subjects, higher plasma concentrations and longer elimination half-life of paroxetine, have been observed. Thus again, paroxetine should be initiated at the lower end of the recommended dose range and carefully titrated. Paroxetine is excreted in breast milk as are other SSRIs, and its excretion is correlated with maternal daily dose (102). The doses of paroxetine in breast fed infants are relatively lower than reported for fluoxetine or citalopram but higher than reported for sertraline or fluvoxamine (80).

Given the potential for drug-drug interactions, it is recommended that patients discuss concomitant medications with their physician.

Overdosage and Toxicology

Neither a teratogenic effect, nor any evidence of cardiotoxicity of paroxetine have been found in animals (20). In humans, serotonin syndrome has been reported with paroxetine and a low dose trazodone. An enhanced serotonergic activity (but not serotonin syndrome) has been observed with paroxetine and moclobemide. There have been postmarketing reports of weakness, hyperreflexia and incoordination following the concomitant administration of sumatriptan and SSRIs, thus appropriate monitoring is now recommended (21). Other adverse effects that have been reported in patients receiving paroxetine concomitantly with another drug include sedation, orthostatic hypotension, dysarthria, memory disorders with trimipramine (64), extrapyramidal symptoms with molindone (68), acute dystonic reaction with haloperidol, oculogyric crisis with pimozide (48), and delirium with zolpidem and benztropine (5). Potential bleeding diathesis may be worsened with paroxetine and warfarin, although different studies give conflicting results (21).

A very low rate of extrapyramidal adverse events of approximately 1 per 10,000 prescriptions, has been reported. Manic episodes also occur with low frequency of 0.9% in unipolar depression and 2% in bipolar depression (45). Nonetheless, caution is advised in

patients with a history of manic episodes. Seizures are reported in 0.1% of patients being treated for depression, a lower rate than with tricyclics or mianserin. Caution is recommended, however, in patients with a history of seizures (45). Treatment with paroxetine is not associated with the development of DSM-IV criteria for physical or psychological dependence. However, as with all SSRIs, abrupt cessation can be associated with a discontinuation syndrome which can include dizziness, sweating, flu-like symptoms, nausea, diarrhea, insomnia, tremor, fatigue, headache, agitation, visual phenomena and confusion (21). These symptoms usually appear at 1 to 10 days following cessation of treatment and resolve spontaneously within 2 weeks. They may be avoided by tapering the dose of paroxetine over a period of several weeks.

Overdosing occurs frequently in patients with depression or similar disorders, thus the margin of safety for psychotropic drugs is most important. Paroxetine has not been reported to precipitate suicidal thoughts and may, on the contrary, reduce suicidal ideation (33). Overdoses with paroxetine have rarely been fatal; published reports show no evidence of profound toxicity, loss of consciousness or seizures after paroxetine, at doses up to 2000 mg (21).

Paroxetine is excreted in the breast milk and should, therefore, be avoided in nursing mothers, unless the benefit for the mother justifies the potential risk to the infant. Only limited data are available in humans regarding the effects of paroxetine in pregnancy.

Its use is, therefore, not recommended during pregnancy.

CLINICAL STUDIES

Depression

Depression is a disabling illness (59,81) and, given its high prevalence, it has a marked impact on occupational and social fuctioning (58). It is associated with significant morbidity and mortality (40). Untreated or suboptimally treated depressed patients have an increased risk of suicide attempts, longer periods of disability and increased rates of hospitalization (57,73). Clinical trials have compared paroxetine to placebo, imipramine, clomipramine, amitriptyline, dothiepin, doxepin (31), lofepramine, maprotiline, and mianserin (30,45,105). Paroxetine has also been campared in review articles with other SSRIs, including fluoxetine, fluvoxamine, and sertraline (41,43), nefazodone (8), as well as electroconvulsive therapy (ECT) (37).

Numerous early clinical trials demonstrated that paroxetine, at doses of 20 to 50 mg per day, was more effective than placebo in reducing symptoms of depression. A large study reported a mean reduction in Hamilton Depression Rating Scale (HDRS) score of 47.8% in patients with paroxetine as compared to 32.6% with placebo (25).

Subsequent clinical trials have compared paroxetine with tricyclic and related antidepressants, demonstrating approximate therapeutic equivalence between treatment groups (3,23,71,86,95,96,103,104). A large study, involving 717 outpatients with major depression, demonstrated reduction of baseline HDRS scores by 37.9% with paroxetine, 35.1% with imipramine, and 21.8% with placebo. In addition paroxetine had an earlier onset of antidepressant action than imipramine (34). Three studies that utilized HDRS, Montgomery Asberg Depression Rating Scale (MADRS) and Clinical Global Impression Scale (CGIS), compared paroxetine with amitriptyline. The percentage of patients

achieving ≥50% reduction from baseline in HDRS ranged from 60 to 74% with paroxetine and 70 to 87% with amitriptyline (10,71,103).

Equivalent efficacy of paroxetine, fluoxetine, fluvoxamine and sertraline has also been demonstrated in randomized, parallel, double-blind clinical trials (43,97). One study suggested that paroxetine has a more rapid onset of action and may be more effective in relieving associated anxiety than fluoxetine (28), although the differences in the onset of action and in anxiolytic activity were not confirmed in another study (107). No significant differences between paroxetine to fluvoxamine were reported in two other studies (4,60). The only study comparing paroxetine and sertraline involved hospitalized patients with delusional depression; no significant differences between the two drugs were found in patients who completed the trial (109,113). In a randomized double-blind clinical trial the efficacy of paroxetine was found to be equivalent to that of nefazodone (8).

The prevention of relapse and recurrence of depression require long-term studies, since efficacy in short-term treatment may not necessarily be translated into adequate long-term prophylaxis (41,75). Relapse studies compared paroxetine to placebo (74) and to imipramine (24). The incidence of relapse in patients on paroxetine was significantly lower than in patients on placebo (15 vs. 25%), but higher than in patients on imipramine (15 vs. 4%).

Clinically significant depression affects some 15% of the elderly population (70). Treatment of depression in the elderly is often complicated by physical co-morbidity, multiple concomitant medications and age-related alterations in drug absorption and metabolism (32). Elderly patients are, therefore, more susceptible than younger adults to adverse effects and drug–drug interactions, requiring a cautious and rational approach to the antidepressant therapy in this population (54). A meta-analysis of data in the elderly compared paroxetine to other antidepressants (31). Paroxetine has been compared to clomipramine (44) and has been shown to have equivalent efficacy to amitriptyline in elderly patients with an earlier onset in one (39) but not in another trial (49). A comparison of paroxetine to fluoxetine in 106 depressed elderly outpatients favored paroxetine and although overall response rates were quite low, either of the two drugs improved cognitive functioning. In a number of other studies, including a study in patients with depression and dementia, paroxetine was reported to have a rapid onset of action (95,55), The response to paroxetine was also accelerated in geriatric depression with the use of sleep deprivation (19).

There is relatively little data concerning paroxetine's efficacy in various subtypes of depression. In a study of bipolar depression (6), paroxetine demonstrated not only efficacy in this difficult-to-treat population but also a lower risk of manic switch. Paroxetine, at doses up to 40 mg/day (less than recommended maximum), was compared to venlafaxine, up to 300 mg/day, in defined treatment-resistant depression. The response rates were 51.9% for venlafaxine and 32.7% for paroxetine (82).

In the treatment of uncomplicated major depression, it is recommended to start paroxetine at a dose of 20 mg/day as a single morning dose (the optimum dose for most patients). Therapeutic response may be delayed until the third or fourth week of treatment. For those patients who do not respond adequately to the 20 mg/day dose, the dose may be gradually increased to a maximum daily dose of 50 mg/day.

Generalized Anxiety Disorder (GAD)

Benzodiazepines have been shown to be relatively efficacious and safe for the treatment of GAD. However, their long-term efficacy is less clear and their dependence

potential is well established. These drawbacks have led to the investigation of other agents in the treatment of this likely lifelong disorder. There is evidence that TCAs are at least as effective as benzodiazepines in the treatment of GAD. However, most of the studies of benzodiazepines and TCAs which were completed before the 1990s, used non-standardized diagnostic criteria for defining the population and, therefore, likely included a heterogeneous population of GAD with panic disorder, phobias, OCD, depression and other comorbidities. Furthermore the positive results obtained with TCAs have not been translated into clinical popularity in the treatment of GAD perhaps due to adverse side effect profiles and life threatening potential in overdose. SSRIs are not only far better tolerated at therapeutic doses but possess a significantly lower toxicity in overdose. In a pilot study of DSM-IV defined GAD (91), both paroxetine at a dose of 20 mg/day, and imipramine were more effective in reducing symptoms from week 4 than diazepam. The authors concluded that further studies were needed to confirm the efficacy of SSRIs in GAD particularly since they are safer and better tolerated agents. In another pilot study, paroxetine at a mean dose of 20 mg/day, was found to improve the scores of various items of the Temperament and Character Inventory in DSM-IV defined GAD patients, specifically harm avoidance, novelty seeking, self directedness and cooperativeness (2).

Panic Disorder

Panic disorder is an incapacitating condition with long term negative consequences. Lifetime prevalence is estimated between 1.5 and 3% and may be up to more than 15%. TCAs, MAOIs, and high potency benzodiazepines have all been used in the treatment of panic disorder. The efficacy of these drugs is established but all of them have significant drawbacks related to tolerability, dependence potential, complexity of daily regimen and toxicity in overdose.

In patients with panic disorder with or without agoraphobia, paroxetine, 10 to 60 mg/day, significantly reduced the frequency of panic attacks and led to greater improvement in generalized anxiety and phobic avoidance. The patients in this placebo-controlled study were evaluated by various scales including the Marks Sheehan Phobia, Sheehan Disability, Hamilton Anxiety Rating, CGI, Montgomery–Asberg Depression Rating, Zung Self Rating for Anxiety, and Patient Global Evaluation Scales (9). Response to paroxetine was evident after 3 to 4 weeks and its efficacy in reducing panic attack frequency was maintained for up to 48 weeks. Treated patients continued to show improvement and demonstrated a lower risk of relapse (79). Compared to clomipramine at doses of 10 to 150 mg/day, paroxetine at doses of 10 to 60 mg/day, was at least as efficacious in reducing the frequency of panic attacks and relieving associated symptoms such as anxiety, phobia, family, social life, and work problems (63). Paroxetine was significantly more effective than clomipramine with respect to the percentage of patients who had no panic attacks at all between weeks 7 and 9 of treatment (end point of study). Paroxetine had also a more rapid onset of action than clomipramine (4 to 5 weeks with paroxetine compared to 10 to 12 weeks with clomipramine) and greater efficacy than placebo.

In the treatment of panic disorder, with or without agoraphobia, it is recommended to start paroxetine at a single morning dose of 10 mg, and to increase the dose by 10 mg/day on a weekly basis to a maximum of 60 mg/day (usual effective dose is 40 mg/day).

After 6 to 12 months of treatment, an attempt to taper and to discontinue the drug is suggested. If the patient experiences relapse, the treatment should be reinitiated and con-

sideration given to indefinite maintenance therapy in situations of recurrent relapse (38). Of the currently available drugs for treating panic disorder, SSRIs appear to be more efficacious and better tolerated. Paroxetine is, therefore, a possible rational first-line choice for short term treatment of panic disorder as well as its long-term management (84). Further clinical trials comparing paroxetine to benzodiazepines, such as alprazolam, MAOIs and other SSRIs, may be helpful in the future.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a chronic and disabling condition. Its lifetime prevalence is estimated to be between 2 and 4%. The onset of OCD occurs in childhood or in adolescence in up to 80% of cases (42). There is evidence that clomipramine improves OCD independently of its antidepressant properties implying potential serotonergic involvement in the pathogenesis of OCD. In patients with OCD, paroxetine at a dose of 20 to 60 mg/day, significantly reduced the scores on the Yale-Brown Obsessive-Compulsive Scale and the National Institute of Health Obsessive-Compulsive Scale compared to placebo (115). Response to paroxetine was apparent after 2 weeks and more significant after 6 weeks. Its efficacy was maintained for up to 12 weeks. In these studies, paroxetine, 20 to 60 mg/day, appeared to be at least as efficacious as clomipramine, 50 to 250 mg/day.

In the treatment of OCD, it is recommended to start paroxetine as a single morning dose of 10 mg/day and to increase the dose at weekly intervals by 10 mg up to a maximum of 60 mg/day. The usual effective dose in adults is around 40 mg/day. Paroxetine appears to be a first-line treatment for OCD given that its efficacy is comparable to that of clomipramine but it is significantly better tolerated; the dropout rate related to adverse events in studies was significantly lower: 9% for paroxetine (not different from placebo) compared to 17% for clomipramine. Overall paroxetine treatment led to fewer premature withdrawals than with either clomipramine or placebo (115). Further clinical trials comparing paroxetine to TCAs and to other SSRIs with long term evaluation of efficacy are needed as well as studies in younger patients in the 8 to 17 years range since the prognosis for OCD is likely to be improved if early treatment is initiated (76).

Social Phobia

Social phobia, also known as social anxiety disorder, usually starts in adolescence around 15–16 years of age and follows a continuous and chronic course. It is anxiety associated with social and performance situations leading to physical symptoms including blushing, sweating, tremor and frequently avoidance behavior and negative cognitive interpretations. It seriously impairs success in multiple areas including interpersonal, academic and occupational functioning (72). Furthermore, social phobia appears to increase the risk of other psychiatric disorders such as major depression, alcohol and drug abuse, and suicide attempts. Lifetime prevalence is high ranging from 10 to 15%.

In patients with social phobia as defined by DSM-IIIR or DSM-IV, paroxetine at a dose of 20 to 60 mg/day, improved the clinical severity of symptoms, which were measured by the Clinical Global Impressions-Improvement (CGI-I), the Liebowitz Social Anxiety, the Social Avoidance and Distress, the Brief Social Phobia, the Fear of Negative Evaluation scales, as well as by the Fear Questionnaire, significantly better than placebo in a number

of studies (7,100,101). An onset of action was noted after 2 weeks and improvement with paroxetine was clearly demonstrated from weeks 3 and 4 to week 12 (end of the trial). Superiority of paroxetine was demonstrated not only on the self-rating scales but also in terms of number of patients responding. All doses of paroxetine were significantly better than placebo but there was no significant difference in the effects of 20, 40, 50 or 60 mg/day doses (69). Patient functional disability as measured by the Sheehan Disability Scale showed greater improvement with paroxetine than with placebo, although statistical significance was not reached on all subscales, likely due to the short duration of treatment. In longer-term treatment, initial data suggests the efficacy of paroxetine may be sustained for at least 24 weeks and associated with a lower risk of relapse (83).

In the treatment of social phobia, it is recommended to start paroxetine as a single morning dose of 20 mg/day. After 4 weeks the dose may be increased in 10 mg increments every 2 weeks until symptom control is achieved. The maximum recommended dose is 50 mg/day.

Adverse Effects and Tolerability

In the treatment of depression, avoiding particular side effects is an important determining factor influencing the choice of antidepressant. Some side effects may pose serious risks for the health of the patient, e.g., cardiac arrhythmia while others may interfere with daily activities, e.g., driving. Side effects impact negatively on compliance and potentially response to treatment. Table 5 summarizes some of the clinical consequences of neurotransmitter receptor blockade that can occur with antidepressant drugs.

Knowledge of drug–drug interactions may also be clinically very important and a summary of reported and potential drug interactions, that can occur with paroxetine, is provided in Table 6.

Paroxetine's side effect profile in terms of the nature and incidence of adverse events, is similar in patients treated for depression, GAD, panic disorder, OCD and social phobia, e.g., in GAD, patients receiving paroxetine at a dose of 20 mg/day, did not show any significant difference in premature study terminations due to adverse effects than patients treated with diazepam (91). Although nausea was more frequent with paroxetine and drowsiness more frequent with diazepam; in comparison with imipramine, paroxetine patients experienced fewer side effects, like constipation, drowsiness and dry mouth, all of which being more frequent with the TCA. Overall, there were no more treatment dropouts related to adverse events in paroxetine treated patients than in patients receiving placebo (around 10%) and dizziness, constipation and somnolence incidences were similar in both groups. Side effects tended to diminish after the first week of treatment and dry mouth was more frequently reported with paroxetine at doses of 40 mg/day compared to doses of 20 mg/day and placebo.

With short term administration, a trend towards dose-dependent adverse events including dry mouth, diarrhea, tremor, sweating and abnormal ejaculation has been reported. With long term administration for up to 48 weeks, paroxetine was well tolerated with premature withdrawal due to adverse events being not different than with placebo and significantly less than with a TCA comparator, such as clomipramine. Overall, paroxetine was associated with a lower incidence of anticholinergic effects (dry mouth, constipation, sweating), nausea, asthenia, dizziness, somnolence, tremor, and impotence than clomipramine, although insomnia and diarrhea were more common. No clinically significant

changes in vital signs or laboratory parameters were reported with paroxetine. An upward titration of the dose of paroxetine at the beginning of treatment appears to avoid early treatment-related jitteriness or anxiety-like symptoms, that have been described with SSRIs. During long-term treatment, weight gain with paroxetine was greater than with placebo, but significantly less than with a TCA, such as clomipramine.

Treatment with paroxetine has not been associated with the development of DSM-IV criteria for physical or psychological dependence. However, abrupt discontinuation after 12 weeks treatment in panic disorder patients receiving paroxetine, 10 to 20 mg/day, resulted in at least one symptom such as dizziness, sweating, flu-like symptoms, nausea, diarrhea, insomnia, tremor, fatigue, headache, agitation, visual phenomena, and confusion. The withdrawal symptoms have been reported in 34.5% of paroxetine treated patients versus 13% of placebo treated patients. Most of these adverse events were not clinically significant. A tapered discontinuation of paroxetine over 3 weeks is, however, recommended in panic disorder patients.

In OCD patients, studies comparing paroxetine to clomipramine showed that anticholinergic side effects were significantly less frequent with paroxetine (115). Adverse events rated by investigators as drug related, were also significantly less frequent with paroxetine. Adverse events leading to premature study termination were significantly more frequent in the clomipramine group than in the placebo or paroxetine groups with no dif-

TABLE 5. Summary of the main clinical consequences of CNS neurotransmitter receptor effects

Cholinergic muscarinic receptor antagonism	Dry mouth, constipation, urinary retention, blurred vision, cognitive impairment, worsened tardive dyskinesia, tachycardia, paralytic ileus, delirium
Histamine H_1 receptor antagonism	Sedation, cognitive slowing, hypotension, decreased gastric acid, weight gain
α_1-Adrenergic receptor antagonism	Postural hypotension, sedation, ejaculatory disturbances, reflex tachycardia, nasal congestion
α_2-Adrenergic receptor antagonism	Bradycardia, hypotension, priapism
5-HT reuptake inhibition	Antidepressant/anxiety/obsessional effects, headache, nausea, diarrhea, anorexia, akathesia, sexual dysfunction, serotonin syndrome
$5\text{-}HT_{2A/2C}$ receptor antagonism	Antipsychotic (negative symptoms?)/anxiety/aggression/parkinsonism effects, weight gain, hypotension, sedation, ejaculatory disturbances
$5\text{-}HT_{1A}$ receptor agonism	Antidepressant/anxiety/aggression effects
$5\text{-}HT_{1B/1D}$ receptor agonism	Antimigraine effects
$5\text{-}HT_3$ receptor antagonism	Antiemetic effects
Noradrenergic receptor reuptake inhibition	Antidepressant effects, tremor, hypertension, tachyarrhythmia, sweating, insommia
β_2-Adrenergic receptor antagonism	Antiaggression effects, decreased tremor, reduced akathesia, fatigue, hypotension, bradycardia
Dopamine reuptake inhibition	Antidepressant/parkinsonism effects, exacerbation of psychosis, psychomotor activation
Dopamine D_2 receptor antagonism	Antipsychotic effects, parkinsonism, prolactinemia
Complex/multiple receptor effects	Fine tremor, sweating, myoclonus, inappropriate ADH, seizures, mania, glucose dysregulation

ference between paroxetine and placebo, e.g., postural hypotension was reported in 5% of clomipramine treated patients and in 1% of placebo and paroxetine treated patients. No other changes were observed in the vital signs of the paroxetine-treated patients.

In social phobia, studies showed that paroxetine, at doses of 20 to 50 mg/day for a maximum of 12 weeks, was well tolerated and the nature and incidence of adverse events were similar to those reported in depression (7,69,100,101). Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, yawning, pharyngitis, decreased libido, female sexual disorders, abnormal ejaculation, and impotence in males, were reported with a greater incidence in patients treated with paroxetine as compared to placebo-treated patients. Similar to other studies, there was a trend for a lower incidence of adverse events to be associated with a lower dose of paroxetine, e.g., delayed ejaculation was reported in 27.5, 35, and 53.5% of patients receiving paroxetine 20, 40, and 60 mg/day, respectively. No treatment related serious adverse events have been reported with paroxetine in clinical trials for social phobia; the treatment doses were similar to those used in depression and the adverse effect profile was comparable.

In panic disorder, paroxetine's adverse effect profile was similar to that observed in depression. In studies, which compared paroxetine to clomipramine and placebo, paroxetine, at doses of 10 to 60 mg/day, was better tolerated than clomipramine. There were significantly more patients with adverse events caused by the treatment and patients withdrawing prematurely due to adverse events in the clomipramine group with no difference between paroxetine and placebo groups (9,69,79). The most frequently reported adverse event was headache, however the incidence of headache was the same in paroxetine and

TABLE 6. Reported and potential drug interactions with paroxetine

Increased adverse events
■ Antidepressants (desipramine, imipramine, nortriptyline, amitriptyline, trimipramine)
■ Antipsychotics (phenothiazines, clozapine, molindone, haloperidol, pimozide)
■ Anticonvulsants (phenytoin)
■ Type 1c antiarrhythmics (propafenone, flecainide)
■ Anticholinergics (benztropine, procyclidine)
■ Xanthines (theophylline)
■ 5-HT agonists (sumatriptan)
■ Hypnotics (zolpidem)
Potentiated serotonergic activity
■ MAOIs
■ Moclobemide
■ Trazodone, nefazodone
■ Lithium
■ Tryptophan
■ OTC cold preparations
Increased bleeding diathesis
■ Warfarin

placebo treated patients. Abnormal ejaculation (primarily delayed ejaculation) rarely led to early study termination. The adverse event leading to the greatest number of withdrawals in paroxetine-treated patients was nausea. However, it should be noted that the incidence of nausea diminished markedly with continued treatment.

In summary, paroxetine in keeping with other SSRIs, offers distinct advantages over the older antidepressants particularly the TCAs in terms of anticholinergic, sedative and cardiovascular adverse effects as well as safety in overdose. These differences are particularly important in special populations such as the elderly or the medically ill. Although the differences in tolerability and efficacy within the class of SSRIs are small; differences in pharmacokinetics as well as evidence of efficacy in different disorders, particularly given the high levels of co-morbidity, influence drug selection. Paroxetine is currently approved for the treatment of depression, OCD, panic disorder with or without agoraphobia and social phobia. In addition, paroxetine's therapeutic efficacy in a variety of psychiatric disorders, ranging from subtypes of depression to other anxiety disorders, is being explored for future indications such as GAD and PTSD.

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