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Expert Opinion

Paroxetine: safety and tolerability issues

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Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) available in immediate release and controlled release (CR) formulations. Paroxetine is the most potent inhibitor of serotonin re-uptake among the now available SSRIs. Paroxetine has been approved for the treatment of major depressive disorder (MDD), obsessive–compulsive disorder, panic disorder (PD), generalised anxiety disorder, post traumatic stress disorder (PTSD), and social anxiety disorder (SAD) in adults, whereas paroxetine CR is approved for the treatment of MDD, SAD, PD and premenstrual dysphoric disorder in adults. The overall efficacy of paroxetine seems to be comparable to other SSRIs in the treatment of approved indications, although paroxetine treatment induces more sedation, constipation, sexual dysfunction, discontinuation syndrome and weight gain than other SSRIs. Recent data suggest that paroxetine treatment leads to increased rates of congenital malformations, although this evidence is not conclusive. Paroxetine and paroxetine CR are not indicated for use in the paediatric population and are categorised as Pregnancy Class D. In conclusion, whether the tolerability profile of paroxetine differs substantially from other new antidepressants (including other SSRIs) needs to be determined in adequately powered well-designed randomised controlled comparative clinical trials.

Keywords: newer antidepressants, paroxetine, paroxetine safety, selective serotonin re-uptake inhibitor, tolerability

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1. Introduction

Paroxetine is a widely prescribed selective serotonin re-uptake inhibitor (SSRI) that has demonstrated efficacy in a variety of psychiatric disorders [1]. Since 1992, the immediate release formulation (IR) has been approved by the FDA for major depressive disorder (MDD), obsessive–compulsive disorder (OCD), panic disorder (PD), generalised anxiety disorder (GAD), post traumatic stress disorder (PTSD) and social anxiety disorder (SAD) in adults [2]. Paroxetine is also commercially available as a controlled-release formulation (CR) as an enteric coated degradable polymeric matrix [3]; paroxetine CR was FDA-approved for the treatment of MDD on February 1999 and then indication of the drug has been extended for SAD, PD, and premenstrual dysphoric disorder (PMDD) in adults [2]. This review summarises and focuses on the now available data regarding safety and tolerability issues in the use of paroxetine.

2. Pharmacology

2.1 Pharmacokinetics

Paroxetine is almost completely absorbed after oral administration from the gastrointestinal tract, and the absorption is not affected by food [4-6]. Peak

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concentration is reached in about 5 h after oral administration, with steady-state plasma concentration being reached in about 10 days. Paroxetine is ~ 95% protein bound [7,8] and is widely distributed throughout the body, including the CNS. It is extensively oxidated and methylated (half-life of 21 h) by CYP450 2D6 into inactive metabolites [6]. Nonlinear kinetics probably reflects saturation of CYP450 2D6 at increased paroxetine doses [9]. Severe renal or hepatic function impairment increases plasma paroxetine concentrations two to fourfold [6,8].

2.2 Pharmacodynamics

Paroxetine seems to have the highest affinity for human serotonin transporters compared to other marketed SSRIs, with a binding affinity (K_i) of 0.10 nmol/l [10,11]. It also is a modest inhibitor of human noradrenaline transporter (K_i = 45 nmol/l) and a weak inhibitor of human dopamine transporter (K_i = 268 nmol/l) [3]. Animal studies demonstrates that paroxetine has modest affinity (K_i = 89 nmol/l) for muscarinic cholinergic receptors (functional antagonist) and virtually no affinity for histaminic, α- or β-adrenoceptor, dopaminergic or serotonergic (5HT1, 5HT2) receptors [12]. Paroxetine has been shown to lack haemodynamic or electrophysiological cardiovascular effects [13]. Sleep architecture effects of paroxetine include a reduction in rapid eye movement sleep and prolonged rapid eye movement latency in a dose-dependent manner [14,15].

3. Overall safety and tolerability in clinical trials

The side effect profiles of paroxetine IR and paroxetine CR are similar to those observed with other SSRIs. Data from GlaxoSmithKline worldwide clinical trials show that discontinuation rates of paroxetine treatment owing to adverse events among the various indications vary from 9.4 to 20% (MDD 20%, n = 1199/6145; SAD 16.1%, n = 84/522; OCD 11.8%, n = 64/542; PD 9.4%, n = 44/469; GAD 10.7%, n = 79/735; PTSD 11.7%, n = 79/676) [9]. Similar discontinuation rates owing to adverse events have been also observed in the studies of paroxetine CR (MDD 10%, n = 21/212; PMDD 13%, n = 88/681) [9].

The most commonly observed adverse events in clinical trials with paroxetine IR (afterward described as paroxetine) are listed in **Table 1**. Data were collected from clinical trials for MDD, OCD, PD, SAD, GAD and PTSD. Adverse events occurring at rates ≥ 5% in paroxetine-treated subjects and at twice the incidence of placebo-treated subjects across approved indications include asthenia, sweating, nausea, decreased appetite, constipation, dry mouth, somnolence, dizziness, tremor and sexual side effects [9]. Data from one placebo-controlled dose-comparison study of paroxetine IR (10 – 40 mg/d) in patients with MDD indicate that most adverse events are dose-related, with the exception of nervousness [9].

Similar adverse event data in clinical trials with paroxetine CR appear in **Table 2**. Adverse events occurring at rates ≥ 5% in paroxetine-treated subjects and at twice the incidence of placebo-treated subjects across several indications include asthenia, sweating, nausea, constipation, diarrhoea, insomnia, tremor and sexual side effects. Not included in **Table 2** are data from one placebo-controlled study of paroxetine CR in elderly patients with MDD and one placebo-controlled study of luteal phase dosing of paroxetine CR in patients with PMDD. Adverse event data in the elderly MDD study mimics data from the adult studies. The luteal phase dosing in PMDD study reveals lower rates of female genital disorders (2% for paroxetine CR, 0% for placebo) compared to continuous dosing [16]. Pooled data from three fixed-dose continuous dosing PMDD studies with paroxetine CR indicate that adverse events tend to be dose-related [17].

In a comparative study of paroxetine CR versus paroxetine IR, nausea was significantly lower with paroxetine CR compared to paroxetine IR (14 versus 23%, $p \leq 0.05$) during the first week, although the rate of nausea declined in both groups by the second week [18]. Similarly, a pooled analysis of data from clinical trials of paroxetine IR and paroxetine CR in patients with MDD (n = 1083) showed lower rate of early discontinuation owing to adverse events in the paroxetine CR group compared to the paroxetine IR group, particularly in a subgroup of severely depressed patients [19].

4. Drug interactions

In vitro studies reveal that paroxetine inhibits CYP450 2D6 enzyme system, and thus it may increase plasma levels of other drugs metabolised by CYP450 2D6 including cimetidine, amitryptyline, desipramine, risperidone and atomoxetine [20]. In particular, co-administration of thioridazine or pimozide is contraindicated owing to these effects, and concomitant treatment with monoamine oxidase inhibitors is contraindicated due to the risk of serotonin syndrome. Concurrent use of an NSAID or aspirin may increase the risk of bleeding [9].

5. Discontinuation syndrome

The most common symptoms associated with discontinuation of SSRIs include dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. Retrospective studies have found that discontinuation syndrome was reported more frequently with paroxetine than other SSRIs [21-23]. A prospective study of 97 out-patients receiving paroxetine (n = 52) (mean dose = 28.1 mg/d, range = 20 – 40 mg/d) or fluoxetine (n = 45) (mean dose = 30.5 mg/d, range = 20 – 40 mg/d) found discontinuation syndrome rates of 26.8% in the total sample; 84.6% (n = 22) of patients had received paroxetine

Table 1. Treatment-emergent adverse event incidence in placebo-controlled clinical trials of paroxetine for MDD, OCD, panic D/O, SAD, GAD and PTSD.*

	MDD		OCD		Panic D/O		SAD		GAD		PTSD	
	Paroxetine (n = 421)	Placebo (n = 421)	Paroxetine (n = 542)	Placebo (n = 265)	Paroxetine (n = 469)	Placebo (n = 324)	Paroxetine (n = 425)	Placebo (n = 339)	Paroxetine (n = 735)	Placebo (n = 529)	Paroxetine (n = 676)	Placebo (n = 504)
Asthenia	15%	6%			14%	5%			14%	6%	12%	4%
Sweating	11%	2%	9%	3%	14%	6%	9%	2%	6%	2%	5%	1%
Nausea	26%	9%	23%	10%			25%	7%	20%	5%	19%	8%
Decreased appetite	6%	2%	9%	3%	7%	3%	8%	2%	5%	1%	6%	3%
Constipation			16%	6%			5%	2%	10%	2%		
Diarrhoea											11%	5%
Dry mouth			18%	9%			9%	3%	11%	5%	10%	5%
Somnolence	23%	9%	24%	7%			22%	5%	15%	5%	16%	5%
Dizziness	13%	6%	12%	6%								
Insomnia	13%	6%										
Tremor	8%	2%	11%	1%	9%	1%	9%	1%	5%	1%	4%	1%
Nervousness												
Ejaculatory disturbance	13%	0%	23%	1%	21%	1%	28%	1%	25%	2%	13%	2%
Other male genital disorders‡§	10%	0%	8%	1%	5%	0%	5%	1%			9%	1%
Decreased libido					9%	1%	12%	1%	9%	2%	5%	2%
Other female genital disorders§					9%	1%	9%	1%			5%	1%
Yawn							5%	1%				
Infection									6%	3%		

*Includes all adverse events occurring at incidence of 5% or greater and incidence for paroxetine at least twice that for placebo.

‡Includes anorgasmia, delayed ejaculation/orgasm, erectile difficulties, impotence and sexual dysfunction.

§Percentage corrected for gender; where numbers are not provided, the incidence of adverse event in paroxetine-treated subjects was < 5% and/or was not greater than or equal to twice the incidence in placebo-treated subjects.

D/O: Disorder; GAD: Generalised anxiety disorder; MDD: Major depressive disorder; OCD: Obsessive compulsive disorder; PTSD: Post traumatic stress disorder; SAD: Social anxiety disorder.

Table 2. Treatment-emergent adverse event incidence in placebo-controlled clinical trials of paroxetine CR for MDD, panic disorder, SAD and PMDD.*

	MDD‡		Panic disorder		SAD		PMDD§	
	Paroxetine (n = 212)	Placebo (n = 211)	Paroxetine (n = 444)	Placebo (n = 445)	Paroxetine (n = 186)	Placebo (n = 184)	Paroxetine (n = 681)	Placebo (n = 349)
Asthenia					18%	7%	17%	6%
Sweating	6%	2%	7%	2%	14%	3%	7%	1%
Nausea	22%	10%			22%	6%	17%	7%
Constipation	10%	4%			5%	2%	5%	1%
Diarrhoea	18%	7%					6%	2%
Somnolence	22%	8%	20%	9%	9%	4%	9%	2%
Dizziness	14%	4%					7%	3%
Insomnia					9%	4%	8%	2%
Tremor	7%	1%	8%	2%				
Ejaculatory disturbance¶#	26%	1%	27%	3%	15%	1%		
Impotence¶			10%	1%	9%	0%		
Decreased libido	7%	3%	9%	4%	8%	1%	12%	5%
Other female genital disorders¶**	10%	1%	7%	1%			8%	1%
Yawn	5%	0%						
Vision disturbance‡‡	5%	1%						
Trauma	5%	1%						

*Includes all adverse events occurring at incidence of 5% or greater and incidence for paroxetine CR at least twice that for placebo.
‡Includes two studies of MDD in non-elderly adults.
§Includes three studies of continuous dosing in PMDD; does not include data in luteal phase only dosing.
¶Percentage corrected for gender.
#Mostly anorgasmia or delayed ejaculation.
**Mostly anorgasmia or delayed/difficulty reaching orgasm.
‡‡Mostly blurred vision; where numbers are not provided, the incidence of adverse event in paroxetine-treated subjects was < 5% and/or was not greater than or equal to twice the incidence in placebo-treated subjects.
CR: Controlled Release; MDD: Major depressive disorder; PMDD: Premenstrual dysphoric disorder; SAD: Social anxiety disorder.

and 15.4% (n = 4) had received fluoxetine (mean duration of taper = 41 days) [23]. These findings were replicated in a recent retrospective study [24], in which 10.6% of patients (n = 41/385) discontinued paroxetine for any reason during the study period. Although clinical factors associated with paroxetine discontinuation syndrome have not been extensively studied, young age and adverse events early in treatment have been linked to discontinuation syndrome [24]. Thus, increased vigilance is warranted in young patients who have presented with adverse reactions in the early phase of paroxetine therapy [24].

According to the Consensus Panel recommendation for antidepressant discontinuation syndrome, patients should be advised to gradually taper antidepressant medication at the end of a course of treatment of 3 – 4 weeks or longer to minimise the occurrence of such symptoms [25]. Hence, patients should be monitored for these symptoms when discontinuing treatment with paroxetine. If intolerable symptoms occur following a dose decrease or on discontinuation of treatment, the previously prescribed dose should be resumed followed by a more gradual taper [9]. In our clinical experience, discontinuation symptoms deleteriously affect patients' attitudes towards pharmacological treatment of depression and anxiety, ultimately resulting in decreased compliance.

6. Weight gain

Although weight gain was rare in short-term clinical trials with paroxetine, it is more commonly seen in clinical practice with long-term treatment. It seems that paroxetine may have a higher propensity for weight gain compared to other SSRIs. Fava *et al.* [26] reported in a randomised, double-blind study for 26 – 32 weeks that the number of patients whose weight increased > 7.0% from baseline was

significantly greater with paroxetine (20 – 60 mg/d) (25%) compared with either fluoxetine (20 – 60 mg/d) (8%) (versus paroxetine, p = 0.003) or sertraline (50 – 200 mg/d) (4%) (versus paroxetine, p = 0.016). In this study, paroxetine-treated patients had a 3.6% increase in body weight compared to baseline, which was significantly higher than that of patients treated with sertraline (1% increase) or fluoxetine (0.2% decrease). A recent 12-week study also found that a significantly higher proportion of paroxetine-treated patients (7%) gained substantial weight (defined as ≥ 7% weight gain from baseline) compared with sertraline-treated patients (1%) [27].

7. Sexual dysfunction

Rates of sexual dysfunction with paroxetine have been reported to range from 22 to 65%, whereas other SSRIs have shown rates between 16 and 56% [28]. The incidence of sexual dysfunction with paroxetine seems to be dose-dependent and tends to occur early in therapy [8,29]. Limited comparative study data suggest higher rates of sexual dysfunction with paroxetine. For example, in one study paroxetine (20 – 50 mg/d) led to higher incidence of ejaculation disorder (30 versus 14.8%), anorgasmia (26.2 versus 5.9%) and decreased libido (22.6 versus 4.9%) compared to escitalopram (10 – 20 mg/d) [30]. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, as patients and physicians may be reluctant to discuss such adverse events. Accordingly, data on the occurrence of sexual side effects cited in product labelling are likely to underestimate their actual incidence. Also, sexual side effects may induce poor medication compliance. For these reasons clinicians should weigh the risks of sexual dysfunction before choosing to prescribe paroxetine. However, adequately powered and well-controlled studies examining comparative rates of sexual dysfunction with paroxetine treatment are lacking.

8. Pregnancy-related safety

The FDA has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations. The manufacturer has changed paroxetine's pregnancy category from C to D and added new data and recommendations to the Warnings section of paroxetine's prescribing information [31,32].

A retrospective US cohort study based on United Healthcare data [33] showed that paroxetine had a trend towards an increased risk for cardiovascular malformations (mainly ventricular and atrial septal defects) (1.5%) compared to other antidepressants (1%) (odds ratio, OR = 1.5, 95% CI = 0.81 – 2.92). Paroxetine was also associated with a high risk for overall major congenital malformations compared to other antidepressants (OR = 1.8, 95% CI = 1.2 – 2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine versus 2% for other antidepressants. The Swedish Medical Birth Registry has also supported an increased risk of paroxetine use in the first trimester of pregnancy, when paroxetine was found to increase the risk of congenital cardiac malformations by approximately twofold compared with registry population [34]. This study reported that the other SSRIs examined (citalopram, fluoxetine and sertraline) are not associated with an increased risk of congenital malformations. In line with such data, a recent meta-analysis has also shown that first-trimester paroxetine exposure was associated with a significant increase in the risk for cardiac malformation (OR = 1.72, 95% CI = 1.22 – 2.42) [35].

However, these recent findings of increased neonatal risk from paroxetine exposure during pregnancy are contradictory to earlier studies that failed to find an increased independent risk with paroxetine [36-38]. In line with these negative studies, the most recent study has also found that the rates of cardiac defects in the paroxetine group and in the unexposed group were not significantly different (both 0.7%) [39].

Interestingly, according to a recent Canadian Medication and Pregnancy registry data [40] (01/01/1997 – 06/30/2003) that included 1403 women and 101 infants with major congenital malformations, the use of paroxetine and the use of other SSRIs during the first trimester of pregnancy did not increase the risk of congenital cardiac malformations compared with the use of non-SSRI antidepressants. However, > 25 mg/d of paroxetine use during the first trimester of pregnancy increased risk of major congenital malformations (OR = 2.23, 95% CI = 1.19 – 4.17), and major cardiac malformations (OR = 3.07, 95% CI = 1.00 – 9.42), possibly indicating a dose–response relationship between first trimester use of paroxetine and increased risk of congenital malformation.

It was found that neonates exposed to paroxetine and other SSRIs as well as serotonin and noradrenaline re-uptake inhibitors (SNRIs) during late pregnancy developed complications requiring feeding and respiratory support and prolonged hospitalisation. The symptoms (e.g., respiratory distress, jitteriness, poor feeding and irritability) are consistent with either a direct effect of the medication or a neonatal discontinuation syndrome. Sanz *et al.* [41] conducted a review of spontaneously reported cases of suspected SSRI-induced neonatal withdrawal syndrome to the WHO Collaborating Centre for International Drug Monitoring before the second quarter of 2003. A total of 93 suspected cases of SSRI-induced neonatal withdrawal syndrome had been reported. Sixty-four of the cases were associated with paroxetine, fourteen with fluoxetine, nine with sertraline and seven with citalopram. Another study [42] also reported a 30% (18/60) rate of neonatal abstinence syndrome in a large population-based study that included infants with a reported prolonged in-utero exposure to SSRIs. Of these neonates 62% (37/60) were exposed to paroxetine at a daily dose range of 10 – 40 mg/d.

It is difficult to draw definitive conclusions about the safety of paroxetine in pregnancy, in part owing to methodological problems in relevant studies [32,33]. Data available now indicate that paroxetine should not be used during pregnancy, particularly given the availability of other antidepressant options. It is conceivable that if a patient has demonstrated superior response to paroxetine compared to other agents, paroxetine use is justified due to the fact that untreated MDD during pregnancy can severely compromise both maternal and neonatal well-being. It is important for clinicians to carefully consider the risk–benefit ratio of SSRI treatment during pregnancy and be familiar with published comprehensive recommendations regarding the management of MDD during pregnancy [43,44].

9. Children and adolescent population

9.1 Overall safety and tolerability

There has been increased attention lately on the need for pharmacological therapies of depression and anxiety disorders in children and adolescents. In the paediatric population, paroxetine should be initiated at a dose of 10 mg/d and increased as needed by 10 mg/d up to a maximum daily dose of 60 mg/d. It should be considered that the starting dosage for very young children may be as low as 5 mg/d [45].

The safety of paroxetine in children and adolescents has been demonstrated in a number of studies, including an 8-week, double-blind, placebo-controlled clinical trial of paroxetine in 275 adolescent out-patients (from 12 to 18 years old) with MDD. In this study, patients were randomly allocated to paroxetine (mean dose: 28 mg/d, range = 20 – 40 mg/d), imipramine (mean dose: 205 mg/d, range = 200 – 300 mg/d) or placebo. Paroxetine was generally well tolerated and most adverse effects were not considered serious. The discontinuation rate owing to adverse events in the paroxetine group was 9.7% compared to 31.5% in the imipramine group (6.9% in placebo group). The most commonly reported adverse events for paroxetine therapy were headache (34.4%), nausea (23.7%), dizziness (23.7%), dry mouth (20.4%) and somnolence (17%). Except for somnolence (3% in placebo group), other side effects occurred at similar rates in the placebo group. Serious adverse effects occurred in 11 patients in the paroxetine group, 5 in the imipramine group and 2 in the placebo group. However, the numbers of serious side effects that were attributable to the treatment were only one to paroxetine treatment, two to imipramine treatment and one to placebo treatment. Among those who discontinued treatment owing to adverse events in the imipramine group, nearly one-third (13.7%) discontinued owing to cardiovascular effects (tachycardia, postural hypotension, prolonged QT interval). Mean standing heart rate increased by 17 bpm over baseline among subjects treated with imipramine. Neither paroxetine nor placebo was associated with cardiovascular adverse effects [46], indicating a favourable cardiovascular profile with paroxetine compared to imipramine.

Another double-blind, placebo-controlled trial of paroxetine (dose range = 10 – 50 mg/d, mean dose = 23 mg/d) was conducted with 203 child and adolescent out-patients (from 7 to 17 years old). The most common (> 10%) adverse events in the paroxetine-treated patients were headache, abdominal pain, respiratory disorder, infection, nausea and rhinitis. Other adverse events to paroxetine included hyperkinesia, trauma, decreased appetite, hostility, diarrhoea, asthenia, vomiting, agitation and neurosis, which occurred at an incidence ≥ 5% and at least twice as frequently as with placebo [47].

A placebo-controlled study in children and adolescent patients with SAD (n = 319) supports the safety and tolerability of paroxetine. In this trial, only insomnia, decreased appetite and vomiting occurred with paroxetine at an incidence ≥ 5% and at least twice as frequently as with placebo [48].

9.2 Suicidality in children and adolescents

In September 2004, the FDA recommended a 'black-box' warning for all antidepressant drugs related to an increased risk for suicidality in paediatric patients [49]. The black-box warning was based on the conclusion of their meta-analysis of 23 placebo-controlled trials with paediatric patients. The study concluded that antidepressants increase suicidality by twofold in paediatric patients who were not actively suicidal. Yet, there are important caveats to this conclusion. Chief among them is the lack of statistical significance of many of the subanalyses and posthoc analyses. Additionally, the report contains only short-term data (4 – 16 weeks), which limits the ability to extrapolate to information about long-term consequences [50,51]. Furthermore, according to a recent study in both the US and the Netherlands, SSRI prescriptions for children and adolescents decreased after US and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in paediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents [52]. Finally, a recent reanalysis indicates that antidepressants are efficacious in the treatment of childhood depression and that the overall benefit to risk ratio is clearly positive [53]. These studies lead us to a preliminary conclusion that the evidence from the FDA report does not support a causal relationship that SSRIs increase suicide rates in paediatric patients.

10. Elderly population

Depression and anxiety disorders are common in the elderly population, and the prevalence of depression in this population reaches ~ 15% [54]. In the treatment of elderly patients, clinicians have to pay more careful attention to comorbid medical illnesses and potential drug–drug interactions from frequent use of several medications.

Table 3. Double blind, randomised trials in the elderly patients with paroxetine and other drugs.

Comparative drugs	Number of subjects	Dosage for paroxetine (mg/d)	Dosage for comparative drugs (mg/d)	Efficacy*	Tolerabilty‡	Ref.
Doxepine	271	10 – 40	75 – 200	Paroxetine = doxepine	Paroxetine > doxepine	[61]
Clomipramine	79	30	75	Paroxetine = clomipramine	Paroxetine > clomipramine	[62]
Amitriptyline	91	20 – 30	100 – 150	Paroxetine = amitriptyline	Paroxetine > amitriptyline	[63]
Imipramine	198	20 – 40	50 – 100	Paroxetine = imipramine	Paroxetine > imipramine	[58]
Nortriptyline	80	20	50	Paroxetine = nortriptyline	Paroxetine = nortriptyline	[64]
Fluoxetine	242	20 – 40	20 – 60	Paroxetine = fluoxetine	Paroxetine = fluoxetine	[66]
Fluoxetine	106	20 – 40	20	Paroxetine > fluoxetine	Paroxetine = fluoxetine	[67]

*'=' represents equivalence between paroxetine and comparative antidepressant.
‡'>' means superiority of paroxetine to comparative antidepressant.

Table 4. Pharmacokinetic parameters of paroxetine in the elderly patients (single oral dose).

Dose (mg)	20	30
C_{max} (ng/ml)	10.25	15.3 (3.59 – 35.3)
T_{max} (h)	1 – 10	2.33 – 12.83
$t_{1/2}$ (h)	22.5 (4.1 – 79.5)	27.3 (11.1 – 21.1)
AUC (ng h/ml)	582 (30.5 – 4240)	391 (74 – 920)

Data represent values of mean (range).

Medical illnesses (and their treatments) have the potential to induce depression, and depression itself has been linked to increased mortality and morbidity from concomitant medical conditions. Additionally, the ageing process itself can cause alterations in drug metabolism, absorption and distribution by virtue of decreased renal clearance, decreased hepatic metabolism, reduced cardiac output, decreased gastric acid secretion, decreased lean body mass and increased body fat [55,56].

Susceptibility of elderly patients to adverse events from pharmacotherapies lead to more safety and tolerability issues than younger patients, and paradoxically this point leads to the exclusion of elderly patients from many clinical trials [57-59].

In particular, paroxetine has been commonly prescribed as anxiolytic agent in the elderly. Hence clinician should be familiar with potential harmful effects in the elderly population. In a recent large safety evaluation study of paroxetine in elderly patients (n = 1364), adverse events were reported in 253 (19%) subjects, with the most frequent events being nausea, somnolence, tremor and dry mouth [60].

Several randomised, double-blind studies showed no differences in efficacy between paroxetine and tricyclic antidepressants (TCAs) (such as doxepine, clomipramine, imipramine, amitriptyline and nortriptylene) in elderly depression, whereas paroxetine may have better tolerability over TCAs [58,61-64]. The summary of such studies are presented in **Table 3**. Although there is a lack of dose finding studies in the elderly, it seems that the lower dose of paroxetine CR (12.5 – 25 mg/d) is associated with a relatively reduced rate of adverse events and overall improved tolerability compared to the customary dose range of paroxetine CR (25 – 62.5 mg/d) [65]. In several direct comparison studies between paroxetine and fluoxetine in elderly patients, no difference in safety or tolerability was detected, and efficacy data were modestly in favour of paroxetine [66,67]. In elderly patients, plasma concentrations of paroxetine at steady-state are higher and the terminal elimination half-life is longer compared to younger patients [68]; thus, it is advised that paroxetine should be given at lower doses in elderly patients. **Table 4** shows the pharmacokinetic parameters in elderly patients across the dose range of 20 – 30 mg/d (single dose) [1].

In a recent retrospective cohort study, risks of completed suicide and poisoning were compared during the periods of SSRI treatment versus periods without any antidepressant treatment among elderly patients. Paroxetine was not found to increase the risks of completed suicide or poisoning in the elderly population compared to other SSRIs [69].

It seems clear that paroxetine would be a safe alternative first-line therapy over older antidepressants (e.g., TCAs) and should be given priority when treating elderly patients. However, whether paroxetine is safer than other SSRIs and newer antidepressants in the elderly is undetermined and should be further explored in large, randomised, well-designed, controlled clinical trials.

11. Postmarket surveillance

In a number of open-label trials and randomised controlled clinical trials, paroxetine has been shown to be generally well tolerated. Commonly reported adverse events with paroxetine

treatment have been mild-to-moderate in severity, including headache, nausea, somnolence, dry mouth and dizziness. However, a true understanding of efficacy and safety data can only be obtained through postmarket surveillance (PMS) and spontaneous adverse event reporting systems [70]. Worldwide, a number of PMS studies have confirmed the safety and tolerability of paroxetine, showing variable reported incidences of any adverse event: 16.3% (n = 1243, Korea, Study No.: 29060/516) [71], 70% (n = 170, Japan, Study No.: BRL29060A/104228) [72], 44.9% (n = 263, the Netherlands, Study No.: 29060/650) [73]; this data are similar to the incidence and profile of adverse events seen in registry clinical trials.

In such PMS studies, serious adverse events were reported in patients treated with paroxetine at a rate of < 0.5%. Because efficacy is roughly similar across antidepressants, prescription pattern studies have shown that clinicians may choose antidepressants based on their side effects profiles. In this context, postmarketing data reveals relatively high incidence of nausea and vomiting with venlafaxine treatment, higher rates of diarrhoea with sertraline, treatment-emergent weight gain with mirtazepine, somnolence as a result of trazodone and decreased incidence of sexual dysfunction with bupropion [74,75]. In short, PMS data reflects real clinical practice settings, and accordingly one generalisation about the overall benefit/risk ratio of paroxetine can be determined by how widely practicing clinicians prescribe it in light of the common lore that antidepressant agents are roughly similar in efficacy.

12. Direct comparison studies

Several studies have demonstrated the superior safety profile of paroxetine compared to TCAs [8]. Such studies reveal a lower incidence of adverse events and lower discontinuation rates with paroxetine compared to TCAs [76].

Montgomery *et al.* meta-analysed tolerability data from 39 randomised, double-blind trials comparing paroxetine (n = 1924) with clomipramine (n = 141) or other TCAs (n = 1693), and results point to tolerability benefit with paroxetine [77]. The proportion of patients who experienced adverse events with > 1% incidence was significantly lower with paroxetine (64%) than with clomipramine (77%) or other TCAs (71%). The incidence of early drop-out owing to adverse events was also significantly lower with paroxetine (17%) than with clomipramine (27%) and other TCAs (20%) [77]. Another randomised, double-blind, placebo-controlled, comparison study with paroxetine (n = 39), imipramine (n = 35) and placebo (n = 43) in patients with bipolar depression showed similar results in that the paroxetine group showed a lower incidence of adverse events including treatment-emergent manic symptoms (paroxetine [mean dose = 32.6 mg/d, range = 20 – 50 mg/d] versus imipramine [mean dose = 166.7 mg/d, range = 50 – 300 mg/d)] versus placebo; 0, 7.7 and 2.3%, respectively) [78]. The differences in incidence of adverse events between paroxetine and TCAs may be owing to relatively different affinities for cholinergic, adrenergic, dopaminergic and histaminergic receptors [79].

However, there has been a paucity of adequately-powered and well-designed controlled comparison studies between paroxetine and antidepressants other than TCAs. Limited research until now has suggested no significant differences in the rates of adverse events between paroxetine and other agents such as SSRIs [80], SNRIs [81,82] and NaSSAs (noradrenergic and specific serotonergic antidepressants) [83,84], although modest differences in side effects profiles have been elicited. For example, in a study by Benkert *et al.* [84] comparing paroxetine with mirtazepine, both treatments were well tolerated, although paroxetine led to more nausea, vomiting, tremor and sweating whereas mirtazepine led to more weight gain and influenza-like symptoms.

13. Conclusion

The overall safety and tolerability profile of paroxetine appear to be comparable to other SSRIs and newer antidepressants based on currently available evidences, although slight differences in sedation, discontinuation syndrome, weight gain and pregnancy-related issues may exist. However, whether the safety and tolerability profile of paroxetine differs substantially from other new antidepressants (including other SSRIs), needs to be determined in adequately powered, well-designed randomized, controlled comparative clinical trials.

14. Expert opinion

Antidepressant choices are made by clinicians on the basis of cost, patient preference, available data and clinical consensus regarding efficacy and safety. At present available antidepressants include six SSRIs (escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four other newer antidepressants; some antidepressants such as paroxetine are available in different formulations, which may vary in cost and side effect profile. Older antidepressants such as TCAs and monoamine oxidase inhibitors are also available, and despite their less benign safety and tolerability profile, they confer certain advantages such as low cost. Approximately one-third of depressed patients show only partial or no response to treatment with antidepressants, with intolerance being a frequent cause of treatment failure or discontinuation resulting in unfavourable clinical outcomes [26].

It is generally accepted that the overall efficacy of paroxetine seems to be comparable to other SSRIs and newer antidepressants in the treatment of mood and anxiety disorders. Paroxetine does seem to have slightly greater risks of sedation, constipation, discontinuation syndrome and weight gain compared to other SSRIs. Also, data suggests that rates of sexual dysfunction are higher with paroxetine relative to

other SSRIs. Emerging data have also shown a possibility of increased risk of congenital malformation with the use of paroxetine, although this issue remains controversial. In any case, paroxetine has been categorised as a Class D drug for its use in pregnancy. Paroxetine and paroxetine CR are not indicated for use in the paediatric population. According to a recent study [85], > 50% of patients on SSRIs were noncompliant over a 6-month period, with the lowest level of compliance observed in patients receiving IR formulations of SSRIs. Hence, we expect that paroxetine CR formulation may improve the risk of poor compliance in comparison with paroxetine IR. In fact, actual improvement in adverse events with the advent of paroxetine CR has been reported in several randomised, controlled, direct comparison studies [18,85] between paroxetine and paroxetine CR. As a result, paroxetine CR may effectively replace the older IR formulation because the impact of adverse events and tolerability of medication on physicians' treatment decisions and patients' acceptance of antidepressant treatment is clear.

Declaration of interest

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DM Marks is on speaker bureau of Eli Lilly Co. and Bristol-Myers Squibb.

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AA Patkar is a consultant for Bristol-Myers Squibb, GlaxoSmithKline and Reckitt Benckiser; is on the speakers' bureaus of Bristol-Myers Squibb, GlaxoSmithKline and Reckitt Benckiser; and has received research support from National Institutes of Health, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, McNeil Consumer and Specialty Inc., Organon, Jazz Pharmaceuticals and Pfizer.

PS Masand is a consultant for Bristol-Myers Squibb Co., Cephalon, Inc., Eli Lilly and Co., Forest laboratories, Inc., GlaxoSmithKline, i3CME, Janssen Pharmaceutica, Jazz Pharmaceuticals, Organon, Pfizer, Inc., Targacept, Inc. and Wyeth Pharmaceuticals; is on the speakers' bureaus of AstraZeneca, Bristol-Myers Squibb Co., Forest laboratories, Inc., GlaxoSmithKline, Janssen Pharmaceutica, Pfizer, Inc., and Wyeth Pharmaceuticals; and has received research support from AstraZeneca, Bristol-Myers Squibb Co., Cephalon, Inc., Eli Lilly and Co., Forest laboratories, Inc., GlaxoSmithKline, Ortho McNeil Pharmaceutical, Inc., Janssen Pharmaceutica and Wyeth Pharmaceuticals.

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