Paroxetine: current status in psychiatry

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Paroxetine is a selective serotonin reuptake inhibitor (SSRI) with antidepressant and anxiolytic properties. It is commercially available in both an immediate-release (paroxetine) and a controlled-release formulation (paroxetine CR). The latter product was developed to improve gastrointestinal tolerability. Paroxetine is the most potent inhibitor of the reuptake of serotonin among the available SSRIs. It has approved indications for the treatment of major depression, obsessive–compulsive disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder and social phobia in adults. Paroxetine CR is approved for the treatment of major depression, social anxiety disorder, panic disorder and premenstrual dysphoric disorder in adults. While the overall efficacy of paroxetine appears to be comparable with other SSRIs in the treatment of major depression, it is approved for use in a wider variety of anxiety disorders than any other antidepressant. Long-term data suggest that paroxetine is effective in preventing relapse or recurrence of depression for up to 1 year. Limited data show that paroxetine maintains a therapeutic response over 1 year in obsessive–compulsive disorder and up to 6 months in panic disorder. The side-effect profile of paroxetine is largely similar to that of the other SSRIs, although paroxetine tends to be more sedating and constipating in some patients, perhaps due to its anticholinergic activity. The potential for discontinuation syndrome and weight gain appears to be slightly higher with paroxetine than with other SSRIs. This review focuses on the immediate release and controlled-release formulations of paroxetine. It summarizes the efficacy and tolerability data for both formulations, with a particular emphasis on paroxetine CR which was introduced in 2002. It also discusses emerging evidence in other clinical areas and recent data that have led to modifications in the safety profile of paroxetine.

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Major depressive disorder (MDD) affects approximately 16% of individuals in the USA in their lifetime, with an estimated US$83.1 billion in annual costs [1,2]. Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed class of antidepressants today, primarily owing to their improved tolerability and safety if taken in overdose compared with tricyclic antidepressants (TCAs) [3]. SSRIs block the reuptake of serotonin (5-hydroxytryptamine [5-HT]) into the presynaptic nerve terminal, thereby enhancing serotonin neurotransmission, which presumably results in their antidepressant and anxiolytic effects [1].

Although this is the predominant mechanism of action shared by all drugs in this class, each SSRI has a slightly different pharmacological profile that leads to its distinct clinical activity, side effects and drug interactions [4]. Eight SSRIs are currently marketed in the USA; six of them have been approved by the US Food and Drug Administration (FDA) for the treatment of depression (citalopram, escitalopram, fluoxetine, once-weekly fluoxetine, paroxetine, controlled-release [CR] formulations of paroxetine and sertraline) and one SSRI (fluvoxamine) is approved for treatment of obsessive–compulsive disorder (OCD). Despite little data supporting the superiority of one SSRI over another, it appears that there may be interindividual differences in response and tolerability [5]. For example, results from the National Institute of Mental Health (NIMH)-supported

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Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that approximately 28% of patients who did not remit (based on ≤7 on the 17-item Hamilton Depression Rating Scale [HAM-D]) after treatment with one SSRI (citalopram), recovered after switching to another SSRI (sertraline) [6].

This review focuses on the immediate-release (IR) and CR formulations of paroxetine. It summarizes the efficacy and tolerability data for both formulations with a particular emphasis on paroxetine CR, which was introduced in 2002. It also discusses emerging evidence in other clinical areas and recent data that have led to modifications in the safety profile for paroxetine.

Clinical profile

Paroxetine

Pharmacokinetics

Paroxetine is almost completely absorbed after oral administration from the gastrointestinal tract and the absorption is not affected by food [7–9]. The peak concentration is reached in approximately 5 h after oral administration and steady-state plasma concentrations are reached in approximately 10 days [10]. Plasma protein binding of paroxetine is approximately 95% [10,11]. Paroxetine is distributed widely throughout the body, including the central nervous system (CNS), with only 1% remaining in the plasma. It is metabolized extensively into polar and conjugate products of oxidation and methylation [9]. The main metabolites have less than 1/50th of the potency of the parent compound in inhibiting 5-HT uptake and are therefore considered essentially inactive. Cytochrome P450 (CYP) 2D6 is the primary enzyme involved in the metabolism of paroxetine [9]. Inhibition of this enzyme may account for the nonlinear kinetics observed with increasing dose and duration of treatment [1,10]. Paroxetine has an elimination half-life ($t_{½}$) of approximately 21 h [9,11]. The routes of elimination are urinary and fecal excretion and the $t_{½}$ is prolonged in patients with severe renal or hepatic function impairment [9,12].

Pharmacodynamics

Most *in vitro* studies have found that paroxetine has the highest affinity for the serotonin uptake pump among all the marketed SSRIs [13]. The concentration of paroxetine needed to occupy this target is therefore lower than the concentration needed of any other SSRI. It is also a weak inhibitor of noradrenaline and dopamine reuptake [14–16]. *In vitro* studies show that paroxetine has little affinity for muscarinic cholinergic, histamine, α_1-, α_2- and β–adrenergic, and 5-HT_1/5HT_2 receptors. Although paroxetine is the most potent blocker of muscarinic acetylcholine receptors among the available SSRIs, its affinity for the muscarinic acetylcholine receptor is 210 nM, while its affinity for serotonin uptake pump is 0.29 nM. Therefore, the concentrations (and hence doses) to block muscarinic acetylcholine receptors with paroxetine are approximately 700-times greater than those needed to block the serotonin uptake pump [4,14–16].

These properties of paroxetine seem to be associated with an improved safety profile compared with TCAs [4]. The therapeutic efficacy of paroxetine appears to be related in part to the decreased responsiveness of somtodendritic (5-HT_{1A}) and terminal (5-HT_{1B}/$_{1D}$) serotonin autoreceptors after 2–3 weeks of paroxetine treatment [17,18]. Paroxetine is associated with a reduction of rapid-eye movement sleep time and prolongation of rapid-eye movement latency in a dose-dependent manner [19,20].

Clinical efficacy

The efficacy of paroxetine in the treatment of adults with MDD, panic disorder (PD), OCD, social anxiety disorder (SAD), generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) has been well established through a number of placebo-controlled, short- to medium-term (6–24 weeks) clinical trials and it has received FDA approval for the above mentioned psychiatric disorders [21]. The evidence shows that paroxetine 10–50 mg/day is significantly more effective than placebo, at least as effective as TCAs and as effective as other SSRIs for the treatment of MDD. Several long-term placebo-controlled trials also showed that paroxetine was significantly more effective than placebo in preventing the recurrence of MDD, GAD, PD, SAD and OCD [22,23]. In addition, the efficacy of paroxetine for the MDD in the elderly population has also been established in a number of short- and long-term double-blind, placebo-controlled clinical trials [24–26].

Other disorders

Open-label studies, case reports and pilot trials have shown that paroxetine may be potentially beneficial in the treatment of headache [27], borderline personality disorder [28] and chronic pain syndromes [29]. However, evidence from controlled trials is necessary to draw any definitive conclusions regarding the efficacy and safety of paroxetine in these disorders.

Dosage & administration

Paroxetine can be administered as a single daily dose with or without food. In the treatment of MDD, OCD, GAD, SAD and PTSD, paroxetine is initiated at a dosage of 20 mg/day. In elderly patients or patients with panic disorders, clinicians may start at a dosage of 10 mg/day [21]. The upper limit of the dosage range is 40–60 mg/day.

Drug interactions

Paroxetine has the potential to interact with a number of medications. *In vitro* drug interaction studies reveal that paroxetine inhibits the CYP2D6 enzyme system. Therefore, this may affect the pharmacokinetics of drugs metabolized by CYP2D6, such as cimetidine, amitryptyline, desipramine, risperidone and atomoxetine, resulting in the increased plasma level of any coadministered drugs [9,21]. In particular, coadministration of thioridazine, monoamine oxidase inhibitors (MAOIs) or pimozide is contraindicated. Concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin may increase the risk of bleeding [21].

Safety & tolerability

Since its introduction in 1992 in the USA, paroxetine has been prescribed extensively. Data from placebo-controlled clinical trials indicate that the overall incidence of adverse effects with paroxetine seem to be similar to that with other SSRIs. However, there are limited data from large, controlled, active-comparator trials to fully understand the relative safety of individual SSRIs [11,30].

In the following sections, clinical relevant safety and tolerability issues with paroxetine are reviewed. Recently emerging safety and tolerability data regarding paroxetine as well as antidepressants as a class have led to some modifications regarding risk/benefit from the use during the pregnancy and for the treatment of child and adolescent populations in the manufacturer's package insert for paroxetine and paroxetine CR regarding safety issues.

Discontinuation syndrome

Discontinuation symptoms (upon withdrawal of a drug) are recognized with TCAs, MAOIs, SSRIs and various other antidepressants, including venlafaxine and mirtazapine. Symptoms of the discontinuation syndrome typically appear within 1–3 days of cessation of SSRIs and usually resolve within 2 weeks [31]. These symptoms can usually be reversed within 24 h by reinstatement of the SSRI. The syndrome may be minimized by gradual tapering of the drug [32]. 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 [33–35]. A prospective study of 97 outpatients receiving paroxetine (n = 52; mean dose: 28.1 mg/day; 20–40 mg/day) or fluoxetine (n = 45; mean dose: 30.5 mg/day; 20–40 mg/day) found discontinuation syndrome to be reported in 26.8% of the total sample; 84.6% (n = 22) of patients had received paroxetine and 15.4% (n = 4) had received fluoxetine (mean duration of taper off: 41 days) [32]. There are no data comparing paroxetine CR with paroxetine in terms of discontinuation syndrome, although we could assume that there would be no difference between the two formulations. It is worth noting that discontinuation syndrome is not unique to SSRIs and is also well documented with venlafaxine, a serotonin and norepinephrine uptake inhibitor (SNRI) [30]. In an 8-week, double-blind, randomized study of sertraline (50–150 mg/day) versus venlafaxine XR (75–225 mg/day), followed by a 2-week taper period in depression, both drugs demonstrated comparable efficacy; however, sertraline was associated with less burden of moderate-to-severe discontinuation symptoms and a reduced risk of blood pressure increase [36].

Sudden decrease in the availability of synaptic serotonin, cholinergic rebound and disturbances in dopamine, norepinephrine or γ-aminobutyric acid (GABA) have all been hypothesized to contribute to the syndrome [37]. According to the Consensus Panel Recommendation for antidepressant discontinuation syndrome, patients should be advised to gradually taper their medication at the end of a course of treatment of 3–4 weeks or longer to minimize the occurrence of such symptoms [31]. Clinicians should taper paroxetine by 10 mg/day per week until a dose of 20 mg/day is reached. Patients should be continued on 20 mg/day for a minimum of 1 week prior to stopping paroxetine.

Sexual dysfunction

Epidemiological and clinical studies show that depression is associated with impairments of sexual function, even in untreated patients [38]. The most frequently seen problem in both men and women is the reduction in sexual desire, followed by problems with arousal (erection in men) and difficulties with orgasm or ejaculation [39]. Most antidepressant drugs, including SSRIs, have adverse effects on sexual function, but accurate identification of the incidence of treatment-emergent dysfunction has proved challenging, as disturbances of the sexual response can only be detected in a reliable fashion when systematic enquiries are made before and during the course of treatment [40]. In published studies, rates of sexual dysfunction reported with paroxetine have ranged from 22% with spontaneous reports to 65% with systemic inquiry, while the sexual dysfunction rates with other SSRIs have ranged from 16 to 20% with spontaneous reports and 54–56% with systemic inquiry [38]. The incidence of sexual dysfunction with paroxetine appears to be dose dependent and may possibly occur early in therapy [11,41]. There are few head-to-head comparisons of SSRIs for sexual dysfunction, but it appears that the rates may be slightly higher with paroxetine compared with other SSRIs. In a 24-week, double-blind, flexible-dose trial with either paroxetine (20–50 mg/day) or escitalopram (10–20 mg/day), ejaculation disorder (30.0 vs 14.8%), anorgasmia (26.2 vs 5.9%) and decreased libido (22.6 vs 4.9%) were higher in the paroxetine treatment group than in the escitalopram group, respectively [42]. In clinical trials of paroxetine, the incidence of abnormal ejaculation ranged from 13 to 28%. In females, the overall incidence of genital disorders was considerably lower (<5%) and generally included anorgasmia or difficulty reaching orgasm [9,21]. Sexual dysfunction can typically return on reintroduction. Recovery after withdrawal from fluoxetine may take up to 3 weeks. Uncontrolled studies and case reports suggest that the addition of bupropion, cyproheptadine, nefazodone or mirtazapine may decrease sexual side effects [38,40,43]. In patients with antidepressant-induced erectile dysfunction, sildenafil may be useful if the patient has no history of angina and is not taking nitrates [38,39].

Weight gain

Although weight gain was rare in short-term clinical trials with paroxetine, it is seen in clinical practice, particularly with long-term treatment. It appears that paroxetine may have a slightly higher propensity for weight gain compared with other SSRIs. Fava and colleagues reported in a randomized, double-blind

study for 26–32 weeks that the number of patients whose weight increased by more than 7% from baseline was significantly greater for paroxetine-treated (20–60 mg/day; 25%) compared with either fluoxetine-treated (20–60 mg/day; 8% vs paroxetine; p = 0.003) or sertraline-treated (50–200 mg/day 4% vs paroxetine; p = 0.016) patients [44]. In this study, paroxetine-treated patients had a 3.6% increase body weight compared with baseline, which was significantly higher than that of patients with sertraline (1.0%) or fluoxetine (0.2% decrease). A recent double-blind study for 12 weeks also found that a significantly higher proportion of paroxetine-treated patients (7%; mean daily dose: 48 mg/day) showed a 7% or less weight gain from baseline, compared with 1% of sertraline-treated patients (mean daily dose: 85 mg/day) [45]. Advice regarding modification of diet and activity may be necessary in patients with clinically significant weight gain.

Usage in pregnancy: teratogenic effects

Recently, paroxetine use in pregnancy rating was changed from Category C (animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women) to Category D (adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus; however, the benefits of therapy may outweigh the potential risk in certain patients). This was based primarily on a retrospective US cohort study based on United Health Care data [101]. In this study, there was a trend towards an increased risk for cardiovascular malformations (mainly ventricular and atrial septal defects) for paroxetine (1.5%) compared with other antidepressants (1%; odds ratio [OR]: 1.5; 95% confidence interval [CI]: 0.81–2.92). Paroxetine was also associated with a high risk for overall major congenital malformations compared with other antidepressants (OR: 8; 95% CI: 1.2–2.8). The prevalence of all congenital malformations following the first trimester exposure was 4% for paroxetine versus 2% for other antidepressants. A study based on the Swedish National Registry Database also found that infants exposed to paroxetine during early pregnancy had an increased risk of cardiovascular malformation compared with the overall registry population [46]. These recent findings for increased neonatal risk from paroxetine exposure during pregnancy are contradictory to earlier studies that failed to find an increased independent risk with paroxetine [47–49]. It is also worth noting that animal studies did not find evidence of teratogenic effect of paroxetine at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis [21].

Usage in pregnancy: nonteratogenic effects

Neonates exposed to paroxetine and other SSRIs, as well as SNRIs during late pregnancy, have developed complications requiring feeding and respiratory support and prolonged hospitalization. The symptoms (e.g., respiratory distress, jitteriness, poor feeding and irritability) are consistent with either a direct effect of the drug or a neonatal discontinuation syndrome. Sanz and colleagues 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 [50]. A total of 93 suspected cases of SSRI-induced neonatal withdrawal syndrome had been reported. Of the cases, 64 were associated with paroxetine, 14 with fluoxetine, nine with sertraline and seven with citalopram. Levinson-Casteil and colleagues found a 30% (18 out of 60) rate of neonatal abstinence syndrome in a large population-based study that included infants with a reported prolonged *in utero* exposure to SSRIs [51]. Of these neonates, 62% (37 out of 60) were exposed to paroxetine at a daily dose range of 10–40 mg.

Chambers and colleagues studied 377 infants born with persistent pulmonary hypertension (PPHN) and 836 healthy infants in a retrospective case-control evaluation and found that the risk for developing PPHN was approximately sixfold in infants who had been exposed to an SSRI after the completion of the 20th week of gestation, as compared with nonexposed infants [52]. However, there was nonsignificant reduction in the risk of PPHN when SSRI exposure was limited to the first half of gestation and, when the entire pregnancy period was examined, SSRI was not associated with an increased risk of PPHN. The number of patients in each group was too small to verify the effects of specific SSRI used. As this is the first study that investigated this potential risk, there is currently no corroborative evidence in this area.

Although the FDA recommended the revision of pregnancy labeling based on the two large epidemiological studies [101,46], it is important for clinicians to carefully weigh the risk–benefit ratio of antidepressant treatment during pregnancy. Untreated depression during pregnancy can compromise both maternal and neonatal wellbeing. Comprehensive recommendations on the management of depression during pregnancy have been published [53,54].

Suicide-related behavior

In March 2004, the FDA issued a public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with ten newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine) [102]. The FDA public health advisory recommended close observation for the emergence of suicidality in all patients treated with antidepressants, especially at the time of treatment initiation or dose increase. The FDA also mandated a black-box warning of increased risk of suicidal gestures and behavior on the label of ten antidepressants for their use in the pediatric population [103]. This was based on data from trials in children conducted from the mid-1990s that indicated a risk ratio for suicidal acts (no suicides occurred) with antidepressants compared with placebo of 2.19 (95% CI: 1.50–3.19; p = 0.00005) [55]. Apter and colleagues performed a blinded review of potential suicidal events and compared incidence rates between paroxetine- (n = 642) and placebo- (n = 549) treated pediatric patients during all five acute double-blind trials of paroxetine [102]. The results showed that

suicide-related events occurred more often in paroxetine (3.4%) than placebo groups (0.9%; OR: 3.86; 95% CI: 1.45–10.26; p = 0.003). Except one case, all suicide-related events occurred in adolescents of at least 12 years. All suicide attempts occurred in MDD; few suicide-related events occurred in patients with a primary anxiety disorder. Depression rating scale suicide item analyses did not reveal significant differences between paroxetine and placebo. GlaxoSmithKline's recent letter to doctors points to a sixfold increase in the risk of suicidal behavior in adults taking paroxetine [104]; 0.32% (11 out of 3455) treated with paroxetine attempted suicide compared with 0.05% (one out of 1978) treated with placebo (OR: 6.7; 95% CI: 1.1–149.4). This was based on a recently completed analysis of suicidal behavior and ideation in adult subjects. The analysis included that young adults (18–24 years) treated with paroxetine had a higher frequency in suicidal behavior than those treated with placebo (17 of 776 [2.19%] vs 5 out of 542 [0.92%], respectively), although this difference was not statistically significant [104,105]. In the older age groups (25–64 and ≥65 years), no such increase was observed. It is difficult to conclude a causal relationship between paroxetine and suicidality owing to the small incidence and absolute number of events, the retrospective nature of this meta-analysis and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves [105]. Clinical trials in adults submitted for regulatory approval of all new antidepressants also showed a risk ratio for suicidal acts compared with placebo of 2.17 (95%CI: 1.39–3.39; p = 0.0004) and for suicides of 4.61 (95% CI: 1.13–18.74; p = 0.0187) [56].

Currently, the FDA is undertaking pooled analysis on their own adult data related to suicidality issues, which is expected to be released late 2006–early 2007 [57,106]. We should also note that the initiation of an antidepressant treatment is a high-risk period for suicide since the early 1960s and even the same applies to psychotherapy [58].

As opposed to the signal for increased risk for suicidal ideation and behavior with SSRI treatment in clinical trials, population-level studies have failed to demonstrate this association or indicated that SSRI treatment was associated with a reduced risk of suicide. Gibbons and colleagues examined the relationship between antidepressant medication prescription and suicide rate by analyzing associations at the county level across the USA [59]. Their study incorporated National Vital Statistics from the Center for disease control and Prevention from all US states. Information for each US resident who committed suicide between 1996 and 1998 was included in the database. The primary outcome measure was the suicide rate in each county expressed as the number of suicides for a given population size. The researchers found that prescriptions for SSRIs and other new-generation non-SSRI antidepressants were associated with lower rates of suicide. However, the investigators did find a positive association between TCAs and suicide rate. The researchers concluded that the risk–benefit ratio associated with prescription of SSRIs must be favorable to explain the relationships observed in the study.

Simon and colleagues used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to initiation of antidepressant treatment [60]. Computerized health plan records were used to identify 65,103 patients with 82,285 episodes of antidepressant treatment. The results did not suggest increased risk of suicide death or serious suicide attempt during the first month of antidepressant treatment. Also in agreement with a previous study [61], the study found no evidence of greater risk for the newer drugs including SSRIs included in the FDA advisory. Notably, the highest period of risk was the month preceding treatment, confirming the link between untreated depression and the risk of suicide.

Use in pediatric & adolescent patients

Currently available randomized, placebo-controlled studies of paroxetine showed mixed results in the treatment of MDD [62,63]. Other large, randomized, placebo-controlled trials proved superior efficacy of paroxetine (10–50 mg/day) over placebo in the treatment of OCD and SAD [64,65]. However, paroxetine and paroxetine CR are not approved for use in the pediatric population and carry a black-box warning of an increased risk of suicidal thinking and behavior in children and adolescents. Both the FDA and the Medicines and Health Care Products Regulatory Agency in the UK conclude that there is insufficient evidence that paroxetine is effective in children or adolescents with MDD [107].

Paroxetine CR

Brief comparison of paroxetine CR & paroxetine

Paroxetine CR was developed to improve gastrointestinal tolerability of paroxetine, whilst maintaining the therapeutic property. The pharamcodynamic profile of paroxetine CR is not different to paroxetine, while its pharmacokinetic profile has been somewhat changed compared with paroxetine.

Paroxetine CR is an enteric film-coated tablet containing a degradable polymeric matrix. It has been developed using a technology called Geomatrix™. The enteric coat on paroxetine CR delays the drug release until the tablet has left the stomach. This effect may avoid the stimulation of gastric 5-HT receptors, which is associated with gastrointestinal side effects, in particular nausea [66]. The polymeric matrix of paroxetine CR controls the dissolution rate; approximately 80% of the dose is absorbed over 4–5 h and the remaining 20% is retained in the tablet and does not enter the systemic circulation. Therefore, the individual dose of paroxetine CR needs to be 20–25% higher than that of paroxetine in order to have dose equivalence (e.g., paroxetine 20 mg is equivalent to paroxetine CR 25 mg) [66,67]. Although pharmacodynamic properties and overall exposure (i.e., AUC) are largely similar between paroxetine and paroxetine CR, there are clear differences in terms of fluctuations in plasma levels. T_{max} was observed typically 6–10 h post dose, reflecting a reduction in absorption rate compared with paroxetine. Pharmacokinetic studies have found that fluctuations of plasma concentration were 25–30% lower with paroxetine CR 25 mg compared with paroxetine

20 mg (FIGURE 1)[68,69]. The peak and trough plasma concentrations of paroxetine CR are 30 and 20 ng/ml, respectively and 62 and 31 ng/ml for paroxetine [70]. The bioavailability is not affected by food [1,66].

In relation to indications approved by the FDA, paroxetine CR has been approved for MDD, PD, SAD and premenstrual dysphoric disorder (PMDD), while paroxetine has three more indications, such as PTSD, GAD and OCD, with the exception of PMDD [21,66]. The available tablet formulation of paroxetine CR is 12.5, 25 and 37.5 mg/day, while paroxetine has 10, 20, 30 and 40 mg/day [21,66]. The recommended initial dose of paroxetine CR is 12.5–25 mg/day and the dose range is 25–75 mg/day in the clinical trials demonstrating the efficacy of paroxetine CR for approved indications (paroxetine 10–20 and 20–60 mg/day, respectively). With regard to tolerability, paroxetine CR was associated with the lower incidence of nausea compared with paroxetine, based on currently available clinical trials data [71].

Clinical efficacy

The efficacy of paroxetine CR for the treatment of MDD [67,72,73], PD [74], SAD [75] and PMDD [76–78] has been established through several well-designed, randomized, double-blind, placebo-controlled, short-term (8–12 weeks) clinical trials. It has been approved for the treatment of the above four psychiatric disorders by the FDA (TABLE 1) [66].

MDD

In the first placebo-controlled clinical trial for the treatment of MDD [67], paroxetine CR (25–62.5 mg/day; n = 212) and paroxetine (20–50 mg/day; n = 217) were compared with placebo (n = 211). Both paroxetine CR ($p = 0.0004$) and paroxetine ($p = 0.036$) showed superior efficacy to placebo over time, based on the assessment of the reduction in HAM-D. After 6 weeks of treatment, response (≥50% reduction in HAM-D score) and remission (≤7 in HAM-D score) rates were 41.5 and 20.5% for placebo, 52.8 and 29.6% for paroxetine ($p < 0.05$) and 58.9 and 34.4% for paroxetine CR ($p < 0.05$), respectively. After 12 weeks of treatment, response and remission rates were 61.2 and 44.0% for placebo, 72.9 and 52.5% for paroxetine ($p < 0.05$) and 73.7 and 56.2% for paroxetine CR ($p < 0.05$), respectively. In addition, depressed mood ($p < 0.05$) and psychic anxiety ($p < 0.05$) symptoms improved as early as treatment week 1 in the paroxetine CR group compared with the placebo group [67]. Rapaport and colleagues [73] and Trivedi and colleagues [72] also reported similar efficacy in terms of changes in HAM-D scores from baseline to the end of treatment, as well as in responder and remission analysis in the end of treatment. A recent pooled analysis of previous studies complemented these findings regardless of symptomatology in MDD (severe or nonsevere MDD) [71]. Mean changes from baseline in HAM-D scores for whole patients (last observation carried forward [LOCF]) were significantly higher in the paroxetine CR-treated group than in the placebo-treated group by observed difference of 2.62 ($p < 0.001$; -4.37 in the severe-depression group [$p < 0.001$]; -1.89 in the nonsevere-depression group [$p < 0.001$]). The odds of Clinical Global Impression-Improvement (CGI-I) response were also significantly higher for paroxetine CR than placebo groups, regardless of baseline depressive symptomatology (2.42 in severe MDD; 95% CI: 1.50–3.91; $p < 0.001$; 1.63 in nonsevere MDD; 95% CI: 1.21–2.19; $p < 0.002$) [71].

Panic disorder

A pooled analysis that included three similar, double-blind, placebo-controlled, 10-week clinical trials evaluated the efficacy of paroxetine CR (25–75 mg/day; n = 444) for the treatment of PD with or without agoraphobia compared with placebo (n = 445) [74]. In this analysis, paroxetine CR was statistically superior to placebo in the primary outcome measure (percentage of patients who were free of panic attacks in the 2 weeks prior to end point). In the LOCF population (paroxetine CR: n = 377 vs placebo: n = 395), the rates of panic-free weeks were significantly higher in the paroxetine CR group (63%) than in the placebo group (53%; $p < 0.005$; OR: 1.63; 95% CI: 1.21–2.19). Consistent with the early response observed in MDD, a statistically significant difference in responder rate was achieved from week 3 through week 20 (all $p < 0.01$) [74]. The mean dose of paroxetine CR for completers at end point was approximately 50 mg/day in the three studies [74].

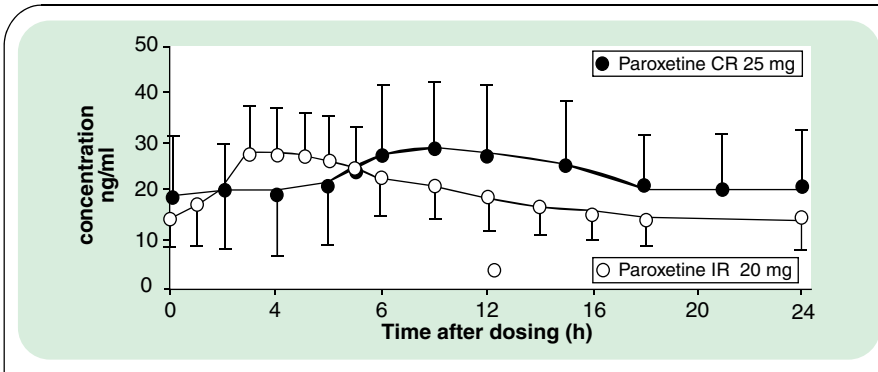

Figure 1. Mean plasma concentration–time curves at steady state for paroxetine IR 20 mg and paroxetine CR 25 mg. Results from two separate studies 419 and 564. Adapted from [69].
CR: Controlled release; IR: Immediate release.

SAD

Patients with SAD were randomly assigned to receive paroxetine CR (flexible dose of 12.5–37.5 mg/day) or placebo for 12 weeks of treatment in 35 sites in Europe and South Africa [75]. The primary efficacy measures were the change from baseline in Liebowitz Social Anxiety Scale (LSAS) score [79] and the responder rate based on CGI-I score (rated as very much improved or much improved). A total of 156 patients (83.9%) in the paroxetine CR group and 137 patients (74.5%) in the placebo group completed

Table 1. Summary of randomized, controlled clinical trials for indications of paroxetine controlled release.

Pivotal studies	Primary outcome	Results	Other comments	Ref.
MDD				
12 weeks; paroxetine CR: n = 212; placebo: n = 211	Changes on HAMD-17 score	Drug > placebo (p = 0.0004)	Responders* and remission† rates were 61.2 and 44.0% for placebo, and 73.7 and 56.2% for paroxetine CR	[68]
8 weeks; paroxetine CR 12.5 mg: n = 156; paroxetine CR 25 mg: n = 154; placebo: n = 149	Changes on HAMD-17 score	Drug (12.5 and 25 mg, respectively) > placebo (p = 0.038; p = 0.005)	Responders* and remission† rates were 63.2 and 40.6% for paroxetine CR 25 mg, and 50.7 and 26.1% for placebo; no differences between paroxetine CR 12.5 mg vs placebo	[73]
12 weeks; paroxetine CR: n = 104; placebo: n = 109	Changes on HAMD-17 score	Drug > placebo (p = 0.007)	Responders* and remission† rates were 72.0 and 43.0% for paroxetine CR, and 52.0 and 26.0% for placebo	[74]
Panic disorder				
10 weeks; paroxetine CR: n = 444; placebo: n = 445	Percentage of patients who were free of panic attacks in the 2 weeks prior to end point	Drug > placebo (p < 0.005)	Responders§ were 63.9% in paroxetine CR and 46.3% in placebo, respectively	[75]
PMDD				
10 weeks; paroxetine CR 12.5 mg: n = 131; paroxetine CR 25 mg: n = 119; placebo: n = 123	Change from baseline in the mean VAS-Mood score	Drug (12.5 and 25 mg, respectively) > placebo (p = 0.007; p < 0.001)	Responders¶ were 72% in paroxetine CR 25 mg, 66% in paroxetine CR 12.5 mg and 50% in placebo, respectively	[77]
Three menstrual cycles; paroxetine CR 12.5 mg: n = 121; paroxetine CR 25 mg: n = 125; placebo: n = 125	Change from baseline in the mean luteal VAS-Mood score	Drug (12.5 and 25 mg, respectively) > placebo (p = 0.013; p < 0.001)	Responders¶ were 76% in paroxetine CR 25 mg, 67% in paroxetine CR 12.5 mg and 50% in placebo, respectively	[78]
Three menstrual cycles; paroxetine CR 12.5 mg: n = 103; paroxetine CR 25 mg: n = 113; placebo: n = 111	Change from baseline in the mean luteal VAS-Mood score	Drug (12.5 and 25 mg, respectively) > placebo (p = 0.015; p < 0.001)	Responders¶ were 71% in paroxetine CR 25 mg, 67% in paroxetine CR 12.5 mg and 49% in placebo, respectively	[79]
SAD				
12 weeks; paroxetine CR: n = 186; placebo: n = 184	Changes from baseline in LSAS	Drug > placebo (p < 0.001)	Responders# and remission** rates were 57.0 and 24.3% for paroxetine CR and 30.4 and 8.2% for placebo	[76]

*A 50% or greater reduction from baseline on HAMD-17 score.

†≤7 on HAMD-17 score.

§CGI-I as a score of 1 (very much improved) or 2 (much improved).

¶ A 50% or greater reduction from baseline VAS-Mood scores.

#CGI-I as a score of 1 or 2.

**A ≥70% or greater reduction from baseline on LSAS score.

CGI-I: Clinical Global Impression-Improvement score; CR: Controlled release; HAM-D: Hamilton Depression Rating Scale; LSAS: Liebowitz social anxiety scale; MDD: Major depressive disorder; PMDD: Premenstrual dysphoric disorder; SAD: Social anxiety disorder; VAS: Visual Analog Scale.

the 12-week study. Statistically significant differences favoring paroxetine CR over placebo were observed in the change from baseline to week 12 LOCF dataset in LSAS total score (observed difference 13.33; 95% CI: -18.25 to -8.41; p < 0.001). In the responder analysis, 57.0% of subjects in the paroxetine CR group reached response compared with 30.4% in the placebo group (OR: 3.12; 95% CI: 2.01–4.83; p < 0.001). The mean daily dose of paroxetine CR at the study end point was 32.3 mg/day. At end point, 69% of patients in the paroxetine CR group were taking 37.5 mg/day, 20% were taking 25 mg/day and 11% remained at the starting dose of 12.5 mg/day.

PMDD

Three randomized, placebo-controlled, double-blind clinical trials were conducted for the treatment of patients with PMDD (Steiner and colleagues [76], n = 373; Pearlstein and colleagues [77], n = 371; Cohen and colleagues [78], n = 327).

The primary efficacy outcome was change from baseline to end point in mean luteal phase Visual Analog Scale (VAS)-Mood (irritability, tension, affective lability and depressed mood) score in these trials. In all three studies, paroxetine CR (12.5 and 25 mg/day) was superior to placebo on the primary outcome measure (e.g., paroxetine CR 12.5 mg/day group vs placebo; 8.7 mm difference; 95% CI: -15.7 to -1.7; p = 0.015; paroxetine CR 25 mg/day vs placebo: 12.1 mm difference; 95% CI: -18.9 to -5.3; p < 0.001) [78].

GAD

An unpublished 8-week, randomized, placebo-controlled study found some potential benefit of paroxetine CR (12.5–37.5 mg/day) over placebo for the treatment of patients with GAD [80]. In the study, secondary efficacy measures (e.g., changes from baseline to end point in Clinical Global Impressions-Severity (CGI-S) scores or proportion of responders who scored 1 or 2 in CGI-I score) showed statistically significant differences between paroxetine CR and placebo in the treatment of subjects with GAD, although primary efficacy measure (changes from baseline to end point in Hamilton Anxiety Scale [HAM-A] scores) failed to show significant differences between paroxetine CR and placebo [80].

MDD with anxiety

Paroxetine CR (12.5 and 25 mg/day) was compared with citalopram (20 and 40 mg/day) in a 6-week, randomized, placebo-controlled trial for MDD with anxiety [81]. The primary measure was a proportion of responder who had a reduction of 50% or more in Montgomery–Asberg Depression Rating Scale (MADRS) score at the end point, compared with baseline. Based on the primary efficacy measure, paroxetine CR failed to separate from placebo, while citalopram (20 and 40 mg/day) was superior to placebo in the proportion of MADRS responders at the week 6 LOCF end point [81].

Maintenance therapy

Currently, data supporting the approved indications of paroxetine CR are based on the short-term clinical trials. There are no data addressing long-term efficacy. However, since paroxetine is the active compound in both the IR and the CR version, the long-term efficacy of paroxetine CR may be comparable with that of paroxetine.

Dosing

Paroxetine CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dosage for the treatment of MDD is 25 mg/day, with a range of 25–62.5 mg/day. Dosage changes should occur at intervals of at least 1 week. In patients with PD, a starting dosage of 12.5 mg/day is recommended. Up to 75 mg/day may be used in these patients. In SAD, the starting dose should be 12.5 mg/day and can be titrated up to 37.5 mg/day. In PMDD, paroxetine CR can be administered either throughout the menstrual cycle or limited to the luteal phase depending upon physician assessment. The recommended dose is 12.5 mg/day; both 12.5 and 25 mg/day have been efficacious in clinical trials. Patients should be counseled that the tablets are to be swallowed whole and not crushed or chewed. The recommended initial dose of paroxetine CR is 12.5 mg/day for elderly patients, debilitated patients and/or patients with severe renal or hepatic impairment [66].

Other disorders

There is some evidence that paroxetine CR might be potentially useful in other conditions. Stearns and colleagues randomly assigned 165 menopausal women experiencing at least two to three daily hot flashes to either placebo, or 12.5 or 25 mg/day of paroxetine CR for 6 weeks [82]. The primary efficacy measure, mean change from baseline to week 6 in the daily hot flash composite score, was significantly decreased in both paroxetine CR 12.5 mg/day (95% CI: -8.1 to -1.3; p = 007) and the paroxetine CR 25 mg/day groups (95% CI: -6.8 to -0.4; p = 0.03) compared with placebo [82]. Patkar and colleagues examined the efficacy of paroxetine CR (12.5–62.5 mg/day) in a 12-week randomized, double-blind, placebo-controlled trial of 124 subjects with fibromyalgia [83]. Significantly more patients in the paroxetine CR group (57%) showed a 25% or more reduction in Fibromyalgia Impact Questionnaire (FIQ) scores (primary outcome) compared with placebo (33%; p = 0.016). Paroxetine CR appeared to be well tolerated and improve the overall symptomatology and global measures of change in patients with fibromyalgia syndrome without current mood or anxiety disorders. However, its effect on specific pain measures seemed to be less robust. The efficacy of paroxetine CR was also examined in patients with irritable bowel syndrome (IBS) [84]. In total, 72 patients with IBS participated in a 12-week double-blind, randomized, placebo-controlled study of paroxetine CR (12.5–50 mg/day). Efficacy was measured by Composite Pain Scores (primary outcome) on the Interactive Voice Response System (IVRS), as well as responder rate (CGI-I scores of 1 or 2). In intent-to-treat analyses, there were no significant differences between paroxetine CR and placebo on reduction in Composite Pain Scores. However, responders on CGI-I scores were significantly higher in the paroxetine CR group (69.4%) compared with placebo (16.7%; p < 0.01), highlighting the need for larger trials in this patient population. There needs to be corroborative evidence from larger controlled trials before drawing any conclusions on the efficacy of paroxetine CR in these conditions.

Safety & tolerability

Paroxetine CR was developed in an attempt to improve the tolerability of paroxetine while retaining its therapeutic benefits. In clinical trials, the overall adverse-events profile was similar to those of contemporary SSRIs with the suggestion that nausea might be less with the paroxetine CR compared with paroxetine [1]. It should be noted that information discussed above relating to discontinuation, sexual dysfunction,

weight gain, drug–drug interactions, labeling for use in pregnancy and black-box warning for the risk of suicide in the pediatric population for paroxetine are also applicable to paroxetine CR.

Improved clinical profile compared with paroxetine

Nausea

In a head-to-head comparison of paroxetine CR versus paroxetine, nausea was significantly lower in the paroxetine CR than in the paroxetine (14 vs 23%; $p \leq 0.05$) during the first week, although nausea rates began to decline in both groups by the second week [67]. This may be clinically relevant since early dropouts owing to adverse events have been frequently associated with gastrointestinal side effects such as nausea [85]. Dunner and colleagues performed a pooled analysis of four placebo-controlled, 8–12-week studies of paroxetine CR [71]. A total of 1083 patients were pooled and subgrouped (severe depression subgroup: n = 303; paroxetine CR: n = 174; placebo: n = 129). The dropout rates owing to adverse events in the paroxetine CR versus placebo groups were 9.8 versus 5.4% in the severe depression subgroup and 5.2 versus 4.5% in the nonsevere depression subgroup, respectively. Among those with severe depression, rates of nausea in the paroxetine CR group (11.5%), although numerically less, were not statistically different than those in the placebo group (15.5%). These results were also similar to a pooled analysis for eight clinical trials of MDD, SAD and panic disorders (nausea rates of 8 vs 5%, respectively) [86].

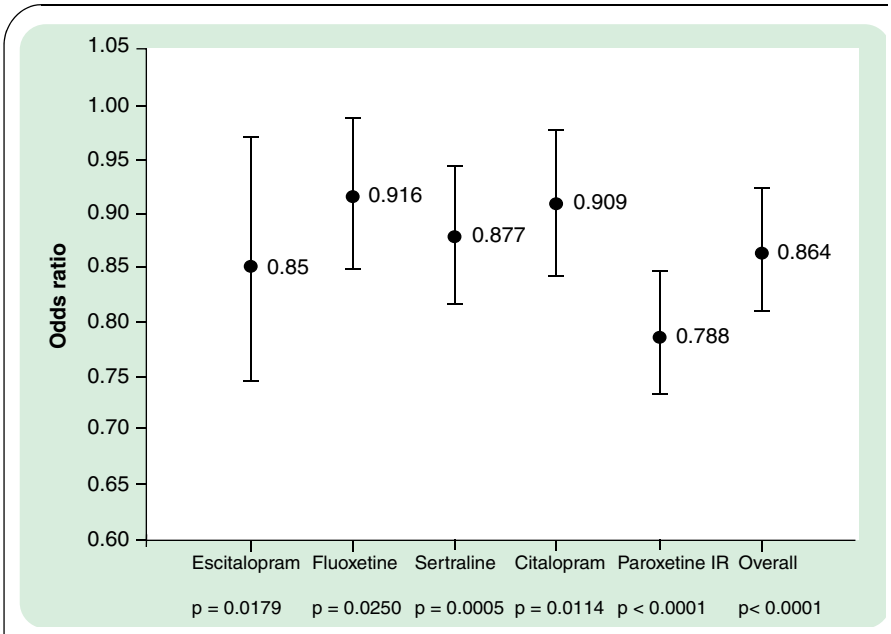

Figure 2. Likelihood of being compliant when compared with paroxetine controlled-release, controlling for age, gender, utilization of psychiatric specialty services, titration rates and the comorbidity measures.
IR: Immediate release.
Adapted from [87].

Improvement of adherence

Keene and colleagues conducted a retrospective analysis of 6-month compliance in 116,090 patients receiving SSRIs in a National Managed Care Database (between July 2001 and December 2002) [87]. A total of 96% of patients received IR-SSRIs and approximately 4% received paroxetine CR. Logistic regression analysis after controlling covariates showed that compared with paroxetine CR, paroxetine IR had the lowest adherence rate (OR: 0.79; $p < 0.0001$; 21.2% less likely) followed by escitalopram (OR: 0.85; $p = 0.0179$; 15.0% less likely), sertraline (OR: 0.87; $p = 0.0005$; 12.3% less likely), citalopram (OR: 0.91; $p = 0.0114$; 9.1% less likely) and fluoxetine (OR: 0.92 $p = 0.0250$; 8.4% less likely) (FIGURE 2). This study indicated a difference in adherence rate between paroxetine IR and CR formulations in a real-world clinical setting, as well as showing differences in the adherence rate between various other SSRIs and paroxetine CR. These findings have been replicated in head-to-head comparisons that that favored paroxetine CR over paroxetine and other SSRIs [88–90]. However, we should note that there was a time difference to the market between paroxetine CR and escitalopram, which may cause misinterpretation of the data. Another limitation was sample size in each group that may lead to overexaggeration of the between-group effect (SSRIs immediate formulation: n = 111,572 vs paroxetine CR: n = 4518).

It is also worth pointing out that the data on compliance is based on retrospective analyses and need to be confirmed in prospective head-to-head controlled trials. Also, although controlling for gender, age, specialty care, comorbidity and diagnosis, these studies were unable to control for some factors known to be associated with drug adherence, such as socioeconomic status and ethnicity [87,88].

Expert commentary

Currently, clinicians have a choice of six SSRIs (escitalopram, citalopram, fluoxetine [and its once-weekly formulation], fluvoxamine, paroxetine [and its CR formulation] and sertraline), as well as four other newer antidepressants (bupropion sustained release [SR] and extended release [XR] formulations) mirtazapine, venlafaxine (and its extended release formulation), and transdermal formulation of selegiline, as well as the older TCAs. Choice of an antidepressant depends upon available evidence regarding efficacy and safety, cost, and physician and patient preference. SSRIs have extensive evidence regarding their effectiveness and safety in clinical practice. Evidence from the recently completed STAR*D trial that was based in real-world clinical setting [6] indicate that 28% of adult patients with major depression achieve remission (based on HAM-D) with a single SSRI (citalopram). Of those

who fail to respond or are intolerant to citalopram, 18–25% responded (based on HAM-D) when switched to another SSRI, venlafaxine or bupropion (statistically indistinguishable) [91] and 30% responded (based on HAM-D) when the SSRI is augmented with bupropion or buspirone [92]. Of those who show inadequate response to the first two strategies, 20% respond when switched to nortriptyline and 12% respond when switched to mirtazapine. This indicates that approximately 45–50% of patients respond to either a first-line treatment with SSRI, or when switched to another SSRI. These results substantiate the ways many clinicians practice, although use of multiple medications is widespread in the real world.

Overall, both paroxetine and paroxetine CR are comparable in pharmacological profiles and efficacy and tolerability, although there is some evidence that paroxetine CR may have better gastrointestinal tolerability and improved adherence. Both are reasonable first-line choices for the treatment of depression or anxiety disorders and may be preferred for patients with comorbid depression and anxiety. If insomnia is prominent, paroxetine and paroxetine CR may have some benefits compared with other SSRIs since they are slightly more sedating [5]. For the same reason, it is preferable to administer paroxetine or paroxetine CR at night. It is worth remembering that up to 12 weeks of treatment may be required before remission is achieved in depression [93]. Anticholinergic side effects, such as dry mouth and constipation as well as nausea, may emerge in the initial weeks of treatment with paroxetine. Clinicians also need to assess and intervene in instances of sexual dysfunction or clinically significant weight gain; it is good clinical practice to get a baseline assessment of both measures before starting the medication. Owing to the risk of discontinuation syndrome, patients should be advised against abruptly stopping paroxetine or missing doses and the drug should be tapered before discontinuing.

The black-box warning regarding use of antidepressants in children and adolescents do not prohibit their use, but recommend a risk–benefit assessment and regular monitoring, especially early in treatment. It must be noted that other than fluoxetine and sertraline, no other SSRIs are indicated by the FDA for use in this population. Depression is an illness associated with agitation, despair and suicide. Suicide attempts may occur as depression is lifting and an individual is energized enough to act on thoughts of self harm [4]. Untreated depression, as opposed to the use of antidepressant medication, represents a greater risk for suicidal behavior. Since suicide is rare in children and adolescents, ascertaining whether there is a meaningful increased risk of suicidal ideation, suicide attempts or suicide completion associated with any medication used to treat depression will require a review of large numbers of patients. It is important to remember that paroxetine or paroxetine CR is not indicated for the treatment of psychiatric disorders in the pediatric population.

Until this issue is resolved, prudent practice in the treatment of depressive illnesses in children and adolescents must include careful attention to the decision to treat a child or adolescent with medication for MDD; clinical expertise with mental health assessment, consideration of varied treatment modes including cognitive behavioral or interpersonal psychotherapy, partnership with patients and their parents and careful attention to symptom course, particularly emotional lability and the assessment of suicidal ideation in youths who are treated with antidepressant medications [94]. Current evidence continues to support the use of SSRIs, particularly fluoxetine, in the treatment of MDD in children and adolescents. Caution is indicated at this time regarding the use of paroxetine in children and adolescents with MDD, and we cannot recommend beginning treatment with paroxetine for a patient younger than 18 years. However, each patient's treatment should be evaluated in the context of that patient's specific needs and prior response to a given therapy. Ultimately, the treatment decision is to be made by the physician, family and patient working in concert.

A similar risk–benefit assessment is required while treating depression in pregnancy. Paroxetine and paroxetine CR are category D drugs; other SSRIs and bupropion are category C. Use of paroxetine and paroxetine CR for nonapproved indications (off-label use) is a matter of clinical judgment and experience. It is important that clinicians combine medication therapy along with patient education not only about their illness, and stress the importance of compliance, as well as behavioral interventions when necessary.

Five-year view

Several antidepressants have emerged on the US market in the past 20 years. SSRIs have become the drugs of choice in the treatment of MDD and they are also effective in the treatment of various forms of anxiety disorders. In 1992, paroxetine was approved in the USA for the treatment of MDD, OCD, PD, GAD, PTSD and SAD. Although SSRIs have a superior safety profile to older antidepressants, there have been emerging tolerability concerns. Gastrointestinal side effects such as nausea continue to be a major reason for early dropout from treatment. The discontinuation syndrome was recognized to occur after abrupt discontinuation of SSRIs and SNRIs, in particular paroxetine and venlafaxine and led to recommendations for gradual tapering of medications [30]. Paroxetine was recategorized from category C to D for use in pregnancy owing to evidence that it may increase the risk for congenital malformations and neonatal complications. FDA analysis of data from short-term trials have revealed a greater risk of suicidal thinking and behavior in children and adolescents exposed to antidepressants, including paroxetine, leading to a black-box warning in 2004 for their use in the pediatric population. The FDA also issued a public health advisory reminding health care providers that they should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose is increased or decreased. The FDA has not concluded that these drugs cause worsening depression or suicidality. Heath care providers

should carefully evaluate patients in whom depression worsens, or where emergent suicidality is severe, abrupt in onset or was not part of the presenting symptoms, to determine the appropriate intervention, which may include modification or discontinuation of the current drug therapy (among other options).

Paroxetine CR was introduced in 2002 in an attempt to improve gastrointestinal tolerability. Paroxetine CR is approved for the treatment of MDD, SAD, PD and PMDD. There is some evidence of less early nausea and better adherence with paroxetine CR compared with paroxetine, but well-designed, prospective, controlled-studies comparing tolerability of the two formulations are lacking.

Currently, SSRIs including paroxetine and paroxetine CR continue to be widely used for the treatment of depression and anxiety disorders in clinical practice. However, whether they will be as widely used in the future will depend on the introduction of newer agents that offer advantages in terms of efficacy or tolerability, including nonpharmacological treatments (e.g. repetitive transcranial nerve stimulation) or novel drug-delivery systems (e.g., transdermal selegiline for depression). Public opinion regarding acceptability of medications, patient access to treatment, adoption of evidence-based guidelines by physicians, adequacy of reimbursement, formulary restrictions and federal regulatory issues are also likely to contribute toward the use of antidepressants in clinical practice.

Key issues

- Paroxetine immediate-release (IR) and paroxetine controlled-release (CR) are effective and safe for the treatment of major depressive disorder (MDD) and several anxiety disorders.
- Overall, both paroxetine IR and paroxetine CR are comparable in pharmacological profiles and efficacy and tolerability, although there is some suggestion that paroxetine CR may have better gastrointestinal tolerability and, therefore, may lead to improved adherence.
- The side-effect profile of paroxetine is largely similar to that of the other selective serotonin reuptake inhibitors (SSRIs), but the potential for discontinuation syndrome, and weight gain appears to be slightly higher with paroxetine than with other SSRIs. It is unclear whether or not rates of sexual dysfunction with paroxetine are higher relative to other SSRIs.
- The US FDA issued a public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with ten newer antidepressants, including paroxetine and paroxetine CR. The advisory recommends close observation for the emergence of suicidality in all patients treated with antidepressants, especially at the time of treatment initiation or dose increase.
- FDA analysis of data pooled from short-term trials from several antidepressants has found a greater risk of suicidal thinking and behavior in children and adolescents exposed to antidepressants compared with placebo. This finding has led to a black-box warning on the label of antidepressants for their use in the pediatric population. Paroxetine and paroxetine CR are not approved for use in pediatric and adolescent populations. Findings from MDD and non-MDD adult analyses performed by GlaxoSmithKline indicate that young adults, especially those with MDD, may be at an increased risk for suicidal behavior during treatment with paroxetine. Currently, the FDA is undertaking pooled analysis of adult data related to suicidality from all antidepressant manufacturers.
- Paroxetine and paroxetine CR were recategorized from category C to D for use in pregnancy owing to evidence that they may increase risk for congenital malformations.

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