CNS Drugs 2004; 18 (6): 355-364
1172-7047/04/0006-0355/$31.00/0

Paroxetine Controlled Release

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Contents

Abstract

▲ A controlled-release (CR) formulation of the SSRI paroxetine has been developed. This CR formulation delays the release of paroxetine until the tablet has passed through the stomach; the drug is then released over 4–5 hours.

▲ In well designed placebo-controlled trials in patients with major depressive disorder (including a study in the elderly), social anxiety disorder or premenstrual dysphoric disorder (PMDD), paroxetine CR was consistently superior to placebo with regards to primary endpoints (i.e. mean Hamilton Rating Scale for Depression total score [major depressive disorder], Liebowitz social anxiety scale total score and Clinical Global Impressions-Global Improvement score [social anxiety disorder] and Visual Analogue Scale-Mood score [PMDD]). The duration of treatment was 12 weeks or, in PMDD, over three menstrual cycles (intermittent or continuous administration).

▲ Paroxetine CR also demonstrated efficacy in three well designed studies in patients with panic disorder with or without agoraphobia.

▲ Paroxetine CR was generally well tolerated in clinical trials, with an adverse-event profile typical of SSRIs, although recipients of paroxetine CR experienced significantly less nausea than recipients of immediate-release paroxetine in the first week of treatment.

Features and properties of paroxetine controlled release (CR) [Paxil CR™]	
Indications	
Major depressive disorder, social anxiety disorder, panic disorder and premenstrual dysphoric disorder	
Mechanism of action	
Selective inhibition of serotonin reuptake	
Dosage and Administration	
Recommended dosage	12.5 or 25 mg/day titrated to a maximum of 25–75 mg/day (depending on the disorder)
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (25 mg/day at steady state)	
Mean peak plasma concentration	30.6 ng/mL
Mean time to peak plasma concentration	10 hours
Mean area under the plasma concentration-time curve	550 ng • h/mL
Adverse events	
Most frequent	Abnormal ejaculation, nausea, somnolence, dizziness, diarrhoea, female genital disorders, constipation, infection, tremor and sweating

Conditions such as major depressive disorder, social anxiety disorder, panic disorder and premenstrual dysphoric disorder (PMDD) can be associated with significant morbidity and pharmacotherapy (including the use of SSRIs) is the most suitable treatment option for many patients.[1-4] However, patient adherence to drug treatment is often poor. For example, almost 25% of patients receiving antidepressants discontinue treatment in the first month.[5]

A common reason for nonadherence to treatment is the occurrence of adverse events. Certain adverse events associated with SSRIs are thought to be linked to increased serotonin in the CNS (e.g. sexual dysfunction, somnolence) and periphery (e.g. diarrhoea, nausea).[5]

Immediate-release (IR) paroxetine is an SSRI with established efficacy in patients with various psychiatric disorders.[6] A new controlled-release (CR) formulation of paroxetine (Paxil CR™)[1] has been developed with a view to improving the tolerability profile of the drug whilst maintaining its therapeutic benefits.[7] Paroxetine CR tablets comprise an enteric coat and a degradable polymeric matrix (Geomatrix™) core. This profile reviews the pharmacological properties of paroxetine CR, as well as its clinical efficacy and tolerability in major depressive disorder, social anxiety disorder, panic disorder and PMDD.

1. Pharmacodynamic Profile

The pharmacodynamic profile of paroxetine has been reviewed previously.[6,8-11] This section provides a brief overview of the pharmacodynamic properties of the drug; data from human studies were obtained using paroxetine IR.

- Paroxetine selectively and potently inhibits presynaptic serotonin reuptake and enhances serotonergic neurotransmission by prolonging the activity of serotonin at its postsynaptic receptors.[6] *In vitro*, the binding affinity (K_i) of paroxetine for human serotonin transporters was 0.10 nmol/L.[12] Paroxetine inhibited serotonin reuptake more potently than citalopram, fluoxetine or fluvoxamine (16-, 11- and 23-fold differences, respectively).[12]
- Neuroadaptive changes in the synaptic serotonergic receptors (e.g. desensitisation of somatodendritic 5-HT_{1A} autoreceptors) occurred with repeat paroxetine administration, consistent with the delayed onset of action of the drug.[13,14]
- Paroxetine also moderately inhibited human noradrenaline (norepinephrine) transporters (K_i = 45 nmol/L) and weakly inhibited human dopamine transporters (K_i = 268 nmol/L) *in vitro*.[12] Moreover, an *ex vivo* assay demonstrated inhibition of noradrenaline uptake in patients with major depressive disorder receiving paroxetine (titrated to 60 mg/day).[15]
- In rat brain studies, paroxetine demonstrated little affinity for α- and β-adrenoceptors, histamine H_1, dopamine D_2 and serotonin 5-HT_1 and 5-HT_2 receptors at concentrations <1000 nmol/L and weak affinity for muscarinic receptors (K_i = 89 nmol/L).[16]
- Paroxetine, like other SSRIs, has a suppressant effect on rapid eye movement sleep.[17-21] The clinical significance of this is uncertain; mixed results were seen regarding the effects of paroxetine on sleep parameters such as sleep efficiency.[17,19-21]
- Paroxetine 20 mg/day did not affect psychomotor function in studies in healthy volunteers (reviewed by Hawley et al.[22]). Paroxetine 40 mg/day was associated with slight psychomotor impairment, although the impairment was significantly less than that associated with amitriptyline (p value not reported).[22] Other comparators such as lorazepam and doxepin were also associated with impaired psychomotor function.[22]
- Paroxetine had no clinically significant haemodynamic or electrophysiological cardiovascular effects in healthy volunteers,[23] and it decreased platelet activation in patients with major depression who did[24] or did not[25] have ischaemic heart disease.

2. Pharmacokinetic Profile

Most of the data in this section concerning the pharmacokinetics of paroxetine CR were obtained from the manufacturer's prescribing information[26] and from a pharmacokinetic study.[5] Data obtained

1 The use of trade names is for product identification purposes only and does not imply endorsement.

with the IR formulation of paroxetine are included where appropriate.

Absorption and Distribution

- The enteric coat on paroxetine CR tablets means that drug release is delayed until the tablet has passed through the stomach.[26] It is thought that by avoiding the stomach, the stimulation of serotonin receptors in the upper gastrointestinal tract may be reduced, which may in turn minimise the occurrence of nausea.[5]
- The polymeric matrix of paroxetine CR controls the dissolution rate;[26] 80% of the dose is released over ≈4–5 hours and the remaining 20% remains in the tablet and is not available for systemic absorption.[7] The bioavailability of paroxetine CR 25mg is not affected by food.[26]
- In 23 healthy volunteers receiving a single dose of paroxetine CR 12.5, 25, 37.5 or 50mg, the mean peak plasma concentration (C_{max}) was 2.0, 5.5, 9.0 and 12.5 ng/mL, respectively, and the mean area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) was 121, 261, 338 and 540 ng • h/mL, respectively.[26] The time to C_{max} (t_{max}) was 6–10 hours.
- Steady state was reached within 2 weeks with repeat administration of paroxetine CR 25mg once daily.[26] At steady state, this dosage of paroxetine CR was associated with a mean C_{max} of 30.6 ng/mL, a mean t_{max} of 10.0 hours, a mean minimum plasma concentration (C_{min}) of 16.7 ng/mL and a mean AUC_{24h} of 550 ng • h/mL (22 individuals included in the study).[5]
- In contrast, mean steady-state C_{max}, t_{max}, C_{min} and AUC_{24h} values of 30.0 ng/mL, 4.4 hours, 14.3 ng/mL and 456 ng • h/mL occurred with paroxetine IR 20 mg/day (28 individuals included in the study).[5] The degree of fluctuation in plasma drug concentrations was reduced by 25–30% with paroxetine CR compared with paroxetine IR.[5]
- Paroxetine is distributed throughout the body, including the CNS.[26] Only 1% of the administered dose remains in the plasma.[26] Plasma protein binding of paroxetine is ≈95% and 93% at concentrations of 100 and 400 ng/mL (paroxetine concentrations are expected to be <400 ng/mL under clinical conditions).[26]

Metabolism and Elimination

- Paroxetine undergoes extensive hepatic metabolism following oral administration.[26] The metabolites are essentially inactive, having potencies at least 50-fold lower than that of the parent compound in terms of inhibiting serotonin uptake.[26] Paroxetine is metabolised at least in part by the cytochrome P450 (CYP) isoenzyme CYP2D6. The nonlinearity of pharmacokinetic parameters seen with increasing doses of paroxetine suggests saturation of CYP2D6 at clinically relevant doses.[26]
- After administration of a single dose of paroxetine CR 12.5–50mg to 23 healthy volunteers, the mean elimination half-life ($t_{1/2}$) was 15–20 hours.[26]
- Over the 10 days following administration of a single dose of paroxetine 30mg as oral solution, ≈64% was excreted in the urine (2% as parent compound and 62% as metabolites) and ≈34% was excreted in the faeces (<1% as parent compound).[26]

Special Patient Populations

- Mean plasma paroxetine concentrations were ≈4-fold higher in patients with creatinine clearance (CL_{CR}) of <1.8 L/h (<30 mL/min) than in healthy volunteers.[26] C_{max} and AUC values were ≈2-fold higher in patients with CL_{CR} of 1.8–3.6 L/h (30–60 mL/min) or hepatic impairment than in healthy volunteers (section 5).[26]
- Repeat administration of paroxetine IR 20–40 mg/day to elderly patients was associated with C_{min} concentrations that were ≈70–80% higher than those in younger patients (section 5).[26]

Potential Drug Interactions

- Paroxetine has the potential to interact with a number of other drugs (reviewed by Prakash and Foster[11]). Briefly, paroxetine may interact with serotonergic agents such as tryptophan and monoamine oxidase inhibitors (section 5).[11] Paroxetine may also interact with drugs that induce (e.g. phenytoin) or inhibit (e.g. cimetidine) hepatic CYP isoenzymes.[11] Moreover, interaction may occur between paroxetine and other drugs that are also metabolised by CYP2D6 (e.g. nortriptyline, amitriptyline, imipramine, desipramine, fluoxetine, phenothiazines and type 1C antiarrhythmics).[11,26]

3. Therapeutic Efficacy

The efficacy of paroxetine CR has been examined in adults with major depressive disorder,[7,27,28] social anxiety disorder,[29] panic disorder[26] and PMDD.[30-32] Patients had to fulfil DSM-IV[33] criteria for their particular condition to be eligible for study inclusion.[7,27-29,31,32] With the exception of two fully published trials in major depressive disorder,[7,27] study data are only available as abstracts and/or posters.[28-32,34] Data from the three studies in panic disorder were obtained from the manufacturer's prescribing information.[26]

Major Depressive Disorder

Three reports compared the efficacy of paroxetine CR and paroxetine IR with placebo in patients with major depressive disorder; patients had 17-item Hamilton Rating Scale for Depression (HAM-D) total scores of ≥18[7] or ≥20.[27,28] Trivedi et al. was a randomised, double-blind, multicentre, fixed-dose, 8-week trial in which patients (mean age ≈39 years; n = 447) received paroxetine CR 12.5 or 25 mg/day or placebo.[28] Rapaport et al.[7] was a randomised, double-blind, multicentre, flexible-dose, 12-week trial conducted in elderly patients (mean age ≈70 years; n = 319) and Golden et al.[27] was a pooled analysis of two randomised, double-blind, multicentre, flexible-dose, 12-week trials of identical design (mean patient age ≈40 years; n = 640). In Rapaport et al.,[7] starting dosages of paroxetine CR and IR were 12.5 and 10 mg/day, titrated to a maximum of 50 and 40 mg/day. In the pooled analysis,[27] starting dosages of paroxetine CR and IR were 25 and 20 mg/day, titrated to a maximum of 62.5 and 50 mg/day. Dosages of paroxetine CR were 25% higher than those of the IR formulation because of the 20% dose retention that occurs with the CR tablet (section 2). These studies were designed to compare active treatment with placebo, rather than comparing active treatments with each other.[7,27]

The primary endpoint was the change from baseline in the HAM-D total score.[7,27,28] Secondary endpoints included the Clinical Global Impressions-Global Improvement (CGI-I) score[7,28] and changes from baseline in the CGI-Severity of Illness (CGI-S) score,[7] HAM-D depressed mood and psychic anxiety item scores[7,27] and the Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q) total score.[28] Endpoints were assessed in the intent-to-treat (ITT) population using last observation carried forward (LOCF) analysis and in the observed cases (OC) population.[7,27,28]

Flexible-Dose Studies

- Paroxetine CR was effective in patients (including the elderly) with major depressive disorder in flexible-dose studies.[7,27] The pooled analysis revealed that mean HAM-D total scores were significantly lower with paroxetine CR than with placebo after 12 weeks' therapy in both the ITT (10.6 vs 13.0; $p = 0.002$) and OC populations (8.5 vs 11.0; $p < 0.005$).[27] The mean HAM-D total score was significantly lower with paroxetine IR than with placebo in only the OC population (9.2 vs 11.0; $p < 0.05$).[27]
- A random-effects mixed model analysis showed statistically significant differences between paroxetine CR and placebo from weeks 2–3 onwards and between paroxetine IR and placebo from weeks 4–6 onwards.[27]
- In elderly patients with major depressive disorder, significantly greater reductions from baseline in HAM-D total scores occurred with paroxetine CR or IR than with placebo after 12 weeks' treatment in both the ITT (all $p < 0.01$) and OC (all $p < 0.001$) populations.[7] In the ITT population, reductions in HAM-D total scores were −12.1 and −12.3 versus −9.5 points with paroxetine CR, paroxetine IR and placebo, respectively.[7] At endpoint, HAM-D total scores were 10.0, 10.0 and 12.6 (ITT population) and 7.7, 8.4 and 11.6 (OC population) in paroxetine CR, paroxetine IR and placebo recipients, respectively.[7]
- Significantly greater improvements from baseline in HAM-D depressed mood item scores occurred with paroxetine CR or IR than with placebo (all $p \leq 0.05$) in both the ITT and OC populations in both studies[7,27] (see figure 1 for the results of Rapaport et al.[7]).
- In Golden et al.,[27] improvements from baseline in HAM-D psychic anxiety item scores were also significantly greater with paroxetine CR or IR than with placebo in both the ITT and OC populations (all $p \leq 0.05$). However, in Rapaport et al.,[7] the only significant between-group difference for the im-

provement in HAM-D psychic anxiety item scores was for paroxetine CR versus placebo in the OC population (figure 1).

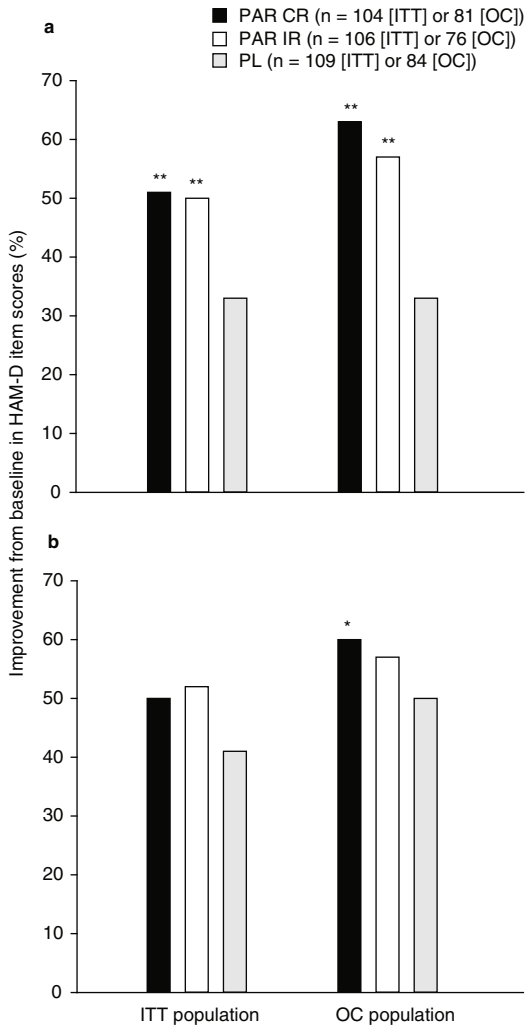

Fig. 1. Efficacy of paroxetine controlled release (PAR CR) in elderly patients with major depressive disorder. Percentage improvement from baseline in Hamilton Rating Scale for Depression (HAM-D) scores for (**a**) depressed mood and (**b**) psychic anxiety items. Results of a randomised, double-blind, multicentre, flexible-dose study conducted in elderly patients (mean age ≈70 years) receiving PAR CR 12.5–50 mg/day, PAR immediate release (IR) 10–40 mg/day or placebo (PL) for 12 weeks.[7] Endpoints were assessed in the intent-to-treat (ITT) population using last observation carried forward analysis or in the observed cases (OC) population. * $p < 0.05$; ** $p < 0.001$ vs PL.

- In elderly patients, median CGI-S scores were reduced from baseline (baseline score of 4 points) to a significantly greater extent in paroxetine CR and IR recipients than in placebo recipients (median reductions of −2 and −2 vs −1 points; $p < 0.05$) at week 12.[7]
- Significantly more elderly patients receiving paroxetine CR compared with placebo experienced clinically relevant improvement in symptoms (i.e. a CGI-I score of 1 or 2) in both the ITT (72% vs 52%; $p < 0.002$) and OC (86% vs 55%; $p < 0.001$) populations.[7] A significant difference between paroxetine IR and placebo occurred only in the OC population (73% vs 55%; $p = 0.04$).
- Furthermore, significantly more paroxetine CR than placebo recipients experienced disease remission at week 12 (defined as a HAM-D total score of ≤7) in both the ITT and OC populations in both studies (figure 2).[7,27] Remission rates were significantly higher with paroxetine IR than with placebo in the ITT and OC populations in Rapaport et al.,[7] but not in Golden et al.[27] (figure 2).

Fixed-Dose Study

- In the fixed-dose study, reductions from baseline in the HAM-D total score were significantly greater with paroxetine CR 12.5 or 25 mg/day than with placebo (−11.7 and −12.4 vs −10.0; $p \leq 0.038$).[28]
- In addition, significantly more paroxetine CR 25 mg/day recipients than placebo recipients achieved a therapeutic response (i.e. a CGI-I score of 1 or 2) [63.2% vs 50.7%; $p = 0.035$] or remission (i.e. a HAM-D total score of ≤7) [40.6% vs 26.1%; p 0.013].[28] Response and remission rates in paroxetine IR recipients were 54.3% and 33.8%.
- The increase from baseline in the Q-LES-Q total score was significantly greater with paroxetine 25 mg/day than with placebo (+12.3 vs +8.2; $p = 0.041$). A change from baseline of +11.9 occurred with paroxetine IR 12.5 mg/day.[28]

Social Anxiety Disorder

The efficacy of paroxetine CR in patients with social anxiety disorder was assessed in a randomised, double-blind, multicentre, flexible-dose, 12-week study.[29] Patients initially received paroxetine CR 12.5 mg/day (n = 186) or placebo (n = 184). After 2 weeks' treatment, the paroxetine dosage

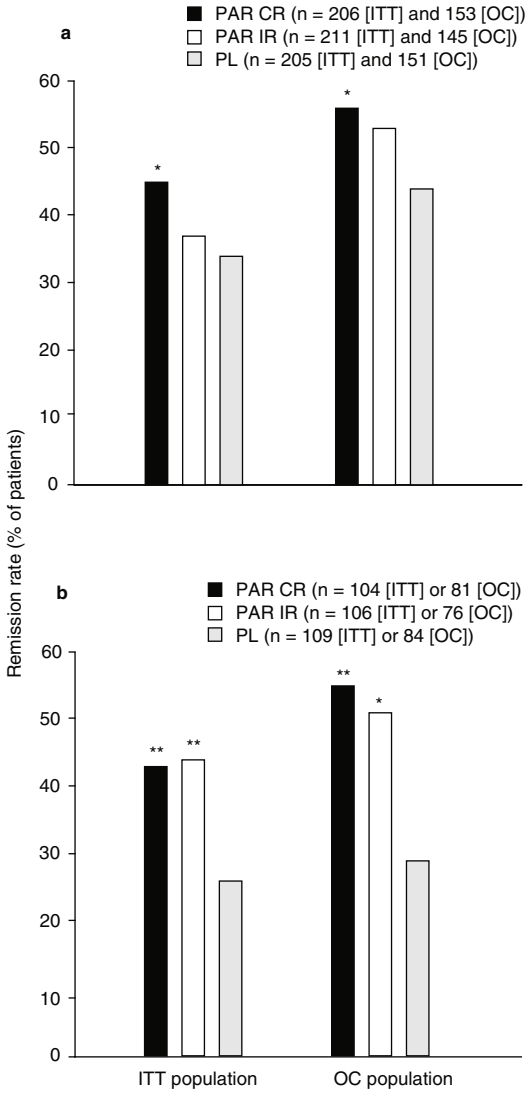

Fig. 2. Remission rates associated with paroxetine controlled release (PAR CR) in patients with major depressive disorder. Remission was defined as a 17-item Hamilton Rating Scale for Depression total score of ≤7. Results of (**a**) a pooled analysis of two randomised, double-blind, flexible-dose studies of identical design (mean patient age ≈40 years)[27] and (**b**) a randomised, double-blind, multicentre, flexible-dose study conducted in elderly patients (mean age ≈70 years).[7] Patients received PAR CR 12.5–50[7] or 25–62.5[27] mg/day, PAR immediate release (IR) 10–40[7] or 20–50[27] mg/day or placebo (PL) for 12 weeks. Endpoint was assessed in the intent-to-treat (ITT) population using last observation carried forward analysis or in the observed cases (OC) population. * $p < 0.05$; ** $p \leq 0.01$ vs PL.

could be increased by increments of 12.5mg at intervals of ≥7 days to a maximum dosage of 37.5 mg/day.[29]

Primary endpoints were the change from baseline in Liebowitz Social Anxiety Scale (LSAS) total scores and the proportion of responders (response was defined as a CGI-I score of 1 [very much improved] or 2 [much improved]).[29] Secondary endpoints included the CGI-S score,[29] LSAS fear and avoidance subscale scores,[29] Social Avoidance and Distress Scale (SADS) scores and Sheehan Disability Scale (SDS) scores.[29] Endpoints were assessed in the ITT population using LOCF analysis.

- Paroxetine CR was significantly more effective than placebo in patients with social anxiety disorder. After 12 weeks' therapy, the reduction from baseline in the LSAS total score significantly favoured paroxetine CR versus placebo recipients (adjusted mean between-group difference of −13.33 points; $p < 0.001$).[29] In addition, significantly more paroxetine CR than placebo recipients achieved a CGI-I score of 1 or 2 at week 12 (57% vs 30%; $p = 0.001$).[29]
- At week 12, significantly more paroxetine CR than placebo recipients achieved remission, regardless of whether remission was defined as a ≥70% reduction from baseline in LSAS total score (24% vs 8%; $p < 0.001$) or a CGI-I score of 1 (28% vs 12%; $p < 0.001$).[29]
- Furthermore, significantly greater mean reductions from baseline in the CGI-S score (−1.4 vs −0.7; $p < 0.001$), SADS total score (−6.6 vs −4.1; $p < 0.001$) and LSAS fear (−15.7 vs −8.9; $p < 0.001$) and avoidance (−15.2 vs −8.7; $p < 0.001$) subscale scores occurred with paroxetine CR than with placebo after 12 weeks' therapy.[29]
- In addition, adjusted mean between-group differences for the reductions from baseline in SDS total (−2.78), family life (−0.64), work (−1.10) and social life (−1.10) scores significantly favoured paroxetine CR recipients (all $p < 0.001$ vs placebo).[29]

Panic Disorder

Three 10-week, placebo-controlled, flexible-dose, multicentre studies examined the efficacy of paroxetine CR 12.5–75 mg/day in patients with panic disorder with or without agoraphobia.[26] Among

patients who completed the studies, the mean paroxetine CR dosage at endpoint was ≈50 mg/day. Outcomes in these trials included the proportion of patients who were free of full panic attacks, the change from baseline in the median number of full panic attacks and the change from baseline in the CGI-S score at the end of the study.[26]

- In two studies, paroxetine recipients had consistently superior outcomes to placebo recipients for two of the three endpoints (quantitative data not reported).[26] In the third study, significant differences between paroxetine CR and placebo recipients were not consistently shown for any of the three endpoints.[26]

Premenstrual Dysphoric Disorder

Three reports examined the efficacy of paroxetine CR in patients with PMDD.[30-32] Gee et al.[31] and Cohen et al.[30] were randomised, double-blind, multicentre, placebo-controlled, fixed-dose trials (n = 366[31] and 313[30]) and Yonkers et al.[32] was a pooled analysis of three randomised, double-blind, multicentre, placebo-controlled, fixed-dose trials (n = 1030). Patients received paroxetine CR 12.5 or 25 mg/day or placebo for up to three menstrual cycles. Study medication was administered continuously in Cohen et al.[30] and only during the luteal phase in Gee et al.[31] In an extension[34] of the pooled analysis,[32] patients with a CGI-I score of 1, 2 or 3 (very much, much or minimally improved) continued to receive their assigned study drug for a further three cycles.

The primary endpoint was the change from baseline in the mean luteal phase Visual Analogue Scale (VAS)-Mood score after three treatment cycles (the VAS-Mood score assesses the core symptoms of irritability, tension, affective lability and depressed mood).[30-32] Secondary endpoints included VAS-Total scores,[31] CGI-S scores,[31] observer-rated Premenstrual Tension Scale (PMTS) total scores[31] and SDS total scores.[31,32] Endpoints were assessed in the ITT population (LOCF analysis).

- Paroxetine CR improved core symptoms of PMDD to a significantly greater extent than placebo.[30-32] The between-group differences in the improvement from baseline in the mean luteal phase VAS-Mood score were −7.66,[31] −8.7[30] and −7.44mm[32] with paroxetine CR 12.5 mg/day versus placebo (all $p < 0.05$) and −10.79,[31] −12.1[30] and −11.03mm[32] with paroxetine CR 25 mg/day versus placebo (all $p < 0.001$).
- Similarly, the between-group differences in the improvement from baseline in SDS total scores significantly favoured paroxetine CR recipients. Between-group differences were −2.33[31] and −2.5[32] points with paroxetine CR 12.5 mg/day versus placebo ($p = 0.028$[31] and $p < 0.001$[32]) and −2.74[31] and −3.3[32] points with paroxetine CR 25 mg/day versus placebo ($p = 0.016$[31] and $p < 0.001$[32]).
- Moreover, in Gee et al.,[31] the between-group differences significantly favoured paroxetine CR 25 mg/day versus placebo for the improvements from baseline in the VAS-Total score (−77.82mm; $p = 0.006$), PMTS total score (−3.21; $p = 0.005$) and CGI-S score (−0.61; $p = 0.004$). The difference between paroxetine CR 12.5 mg/day and placebo recipients for the VAS-Total score was −73.13mm ($p = 0.009$), for the PMTS total score was −1.78 ($p = 0.093$) and for the CGI-S score was −0.27 ($p = 0.177$).
- At the end of the extension study, a significant difference was observed in favour of paroxetine CR 12.5 or 25 mg/day versus placebo for the mean improvement from baseline in luteal phase VAS-Mood scores (between-group difference −6.81 and −10.52mm; both $p < 0.001$).[34] Furthermore, the proportion of patients achieving a ≥50% reduction in VAS-Mood scores (66% and 72% vs 52%) or a CGI-I score of 1 or 2 (59% and 69% vs 42%) was significantly higher with paroxetine CR 12.5 or 25 mg/day than with placebo (all $p < 0.001$).[34]

4. Tolerability

Tolerability data were obtained from the well designed trials in patients with major depressive disorder,[7,27] social anxiety disorder[29] and premenstrual dysphoric disorder[31,32] discussed in section 3, supplemented by data from the prescribing information.[26] The duration of treatment was 12 weeks[7,27,29] or over three menstrual cycles.[31,32] Two publications reported pooled analyses of trial data.[27,32] A third pooled analysis examined withdrawal rates due to adverse events using data from eight trials in patients with major depressive disor-

der (4 trials), panic disorder (3 trials) or social anxiety disorder (1 trial).[5] Statistical analyses were reported for two studies;[5,27] most studies reported only descriptive analyses.

- Paroxetine CR was generally well tolerated in clinical trials; most adverse events were of mild to moderate severity.[7,27,31] The adverse-event profile was typical of that expected with SSRIs.
- In patients with major depressive disorder receiving paroxetine CR 25–62.5 mg/day, the most commonly occurring adverse events (i.e. those with an incidence of ≥5% and twice the rate of placebo) included abnormal ejaculation, nausea, somnolence, dizziness, diarrhoea, female genital disorders, constipation, infection, tremor and sweating.[27] The incidence of these adverse events was significantly higher in paroxetine CR or IR recipients than in placebo recipients, with the exception of infection (no significant difference between paroxetine CR and placebo recipients) [figure 3].
- The incidence of nausea was lower with paroxetine CR than paroxetine IR during the first week of treatment (14% vs 23%; $p \leq 0.05$).[27] However, no significant difference between these treatment groups was observed for the incidence of nausea throughout the remainder of the trial.[27]
- A similar adverse-event profile was seen in placebo-controlled trials in patients with social anxiety disorder[29] or PMDD,[31,32] with some additional adverse events (asthenia, impotence, insomnia, headache, respiratory disorder, sinusitis and decreased libido) also reported. Clinically significant changes in bodyweight,[7,27] laboratory values[27,31] or vital signs[27,31] were generally not observed in patients with major depressive disorder[7,27] or PMDD.[31]
- During the discontinuation or tapering of treatment, adverse events reported with paroxetine CR or placebo included dizziness (11.9% vs 1.3%), nausea (5.4% vs 2.7%), nervousness (2.4% vs 1.1%) and other symptoms such as emotional lability, headache or agitation (2.4% vs 0.3%).[26] In these studies, patients receiving a maximum dosage of paroxetine CR 37.5 mg/day were tapered down to 25 mg/day for 1 week before stopping treatment. Patients re-

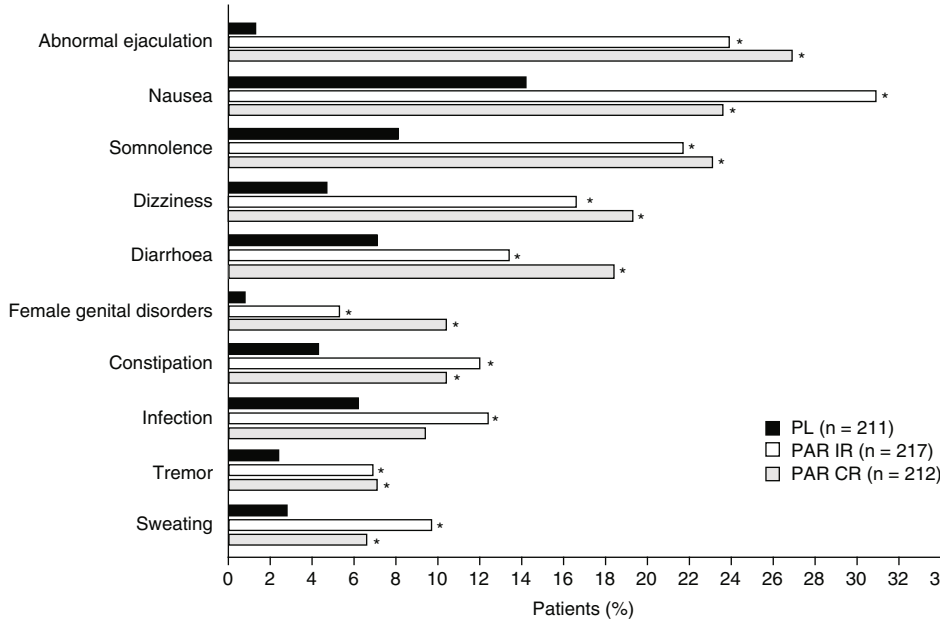

Fig. 3. Incidence of adverse events in patients with major depressive disorder receiving paroxetine controlled release (PAR CR). Pooled analysis of two randomised, double-blind, multicentre, flexible-dose trials.[27] Patients received PAR CR 25–62.5 mg/day, PAR immediate release (IR) 20–50 mg/day or placebo (PL) for 12 weeks. The rates of abnormal ejaculation and female genital disorders were corrected for gender. * $p < 0.05$ vs PL.

ceiving paroxetine CR 12.5 or 25 mg/day discontinued treatment without tapering.

Withdrawal Rates

- Paroxetine CR recipients were no more likely than placebo recipients to withdraw from treatment because of adverse events when trials in patients with major depressive disorder (drop-out rate 7% vs 6%) or social anxiety disorder (3% vs 2%) were considered (figure 4).[5] However, recipients of paroxetine CR were significantly more likely than placebo recipients to withdraw from treatment because of adverse events when all eight trials were considered together (drop-out rate 8% vs 5%; p = 0.005) and when only trials in patients with panic disorder were considered (11% vs 6%; p = 0.005) [figure 4].[5]
- In three trials in patients with major depressive disorder, paroxetine IR recipients were significantly more likely than placebo recipients to withdraw from treatment because of adverse events (drop-out rate 16% vs 7%; p < 0.001) [figure 4].[5]

5. Dosage and Administration

US prescribing information states that paroxetine CR should be administered once daily, preferably in the morning, with or without food.[26] In PMDD, paroxetine CR may be administered daily throughout the menstrual cycle or just during the luteal phase. The recommended starting dosage is 12.5 mg/day in patients with social anxiety disorder, panic disorder or PMDD, and 25 mg/day in patients with major depressive disorder. In patients who do not respond adequately, the dosage can be increased in 12.5 mg/day increments (at intervals of ≥1 week) to a maximum of 25, 37.5, 62.5 and 75 mg/day in patients with PMDD, social anxiety disorder, major depressive disorder and panic disorder, respectively.

Elderly and debilitated patients, as well as those with severe renal or hepatic impairment, should be given a starting dosage of paroxetine CR 12.5 mg/day, titrated to a maximum of 50 mg/day as required (section 2).[26] The efficacy and tolerability of paroxetine CR in paediatric patients has not been established.[26] Concomitant use of paroxetine CR with monoamine oxidase inhibitors or thioridazine is contraindicated (section 2).[26] In addition, concomitant use of paroxetine CR and tryptophan is not recommended.

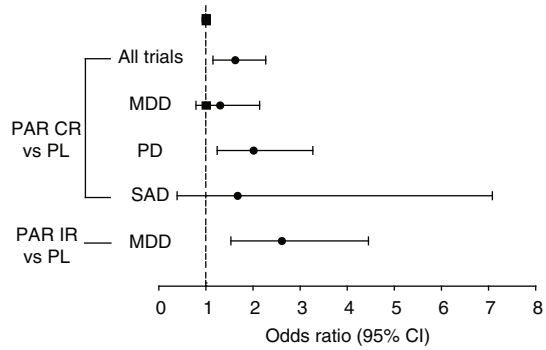

Fig. 4. Odds of patients receiving paroxetine (PAR) controlled release (CR) or immediate release (IR) vs placebo (PL) withdrawing from trials because of adverse events. Results presented for a pooled analysis of eight trials and for trials in each disorder.[5] For PAR CR, four trials in major depressive disorder (MDD), three trials in panic disorder (PD) and one trial in social anxiety disorder (SAD) were considered. For PAR IR, three trials in MDD were considered.

On discontinuation of paroxetine CR, a gradual reduction in dosage is recommended, rather than abrupt cessation.[26]

6. Paroxetine Controlled Release: Current Status

In the US, paroxetine CR is approved for use in major depressive disorder, social anxiety disorder, panic disorder and PMDD. Paroxetine CR demonstrated efficacy in patients with these disorders, including elderly patients with major depressive disorder, in well designed clinical trials. The drug was generally well tolerated. Trials in patients with major depressive disorder or social anxiety disorder found that paroxetine CR recipients were no more likely than placebo recipients to withdraw from treatment because of adverse events.

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