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Regular Article

Paroxetine controlled-release formulation in the treatment of major depressive disorder: A randomized, double-blind, placebo-controlled study in Japan and Korea

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Aim: The main purpose of this study was to evaluate the efficacy of paroxetine controlled-release (CR) formulation compared to placebo. A secondary objective was to test the hypothesis that the CR decreases selective-serotonin-reuptake-inhibitors-induced nausea as its formulation allows more distal gastrointestinal absorption than the paroxetine immediate-release (IR) formulation.

Methods: We conducted this study in Japanese and Korean patients with major depressive disorder (MDD) in order to demonstrate the efficacy and safety of paroxetine CR compared with placebo. The primary efficacy end-point was the adjusted mean change from baseline in the 17-item Hamilton Rating Scale for Depression total score at Week 8.

Results: A total of 416 patients with MDD were randomly assigned to the CR, IR and placebo groups. The mean change from baseline in the 17-item Hamilton Rating Scale for Depression was −12.8 in the CR group, −12.5 in the IR group, and −10.4 in the placebo group, which showed a statistically significant difference compared to placebo in CR ($P < 0.001$) and IR ($P = 0.015$). The incidence of adverse events was 65% in CR, 69% in IR and 55% in placebo. The adverse events were mostly mild or moderate in severity. In the early treatment period, when initiated from 12.5 mg, the incidence of nausea in the CR group was 6%, which was comparable with that of placebo (5%).

Conclusion: Paroxetine CR is efficacious in the acute treatment of MDD and may have the potential benefit of decreasing the incidence of nausea in the early treatment period.

Key words: Japan, Korea, major depressive disorder, paroxetine, placebo.

SELECTIVE SEROTONIN REUPTAKE inhibitors (SSRI), which were developed during the 1980s–1990s, are as effective as tricyclic antidepressants (TCA) in their antidepressive effect but are associated with fewer side-effects, including anticholinergic effects and α1 adrenergic receptor antagonism. Because of a superior side-effect/safety profile, SSRI are recommended as first-line treatment for major depressive disorder (MDD).[1] While SSRI generally have a superior side-effect profile to TCA, certain side-effects persist that can lead to early discontinuation of SSRI treatment.[2]

Paroxetine hydrochloride hydrate (paroxetine) is an SSRI developed by SmithKline Beecham Pharmaceuticals (presently GlaxoSmithKline, London, UK), and has been widely used in clinical practice throughout the world.

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Paroxetine controlled-release (CR), a new formulation of paroxetine designed to decrease SSRI-induced nausea, was approved for the treatment of MDD in 1999 in the USA. Thereafter, it was approved for the treatment of panic disorder, premenstrual dysphoric disorder and social anxiety disorder, and as of 2010, it is approved for use in more than 40 countries (including South Korea). In Asian populations, two clinical studies, in Korean[3] and Chinese patients, have investigated the effectiveness and tolerability of paroxetine CR for treatment of MDD, but no placebo-controlled double-blind study had been conducted in Asian patients with MDD.

Therefore, we conducted a joint Japanese–Korean, placebo-controlled, double-blind study, primarily to assess the efficacy of paroxetine CR for the treatment of MDD.

METHODS

Study population

Patients who were aged at least 20 years with a diagnosis of non-psychotic MDD according to the DSM-IV-TR[4] were enrolled. They were also required to have a Hamilton Rating Scale for Depression (17 items, $HAMD_{17}$)[5] total score of $\geq$20, and a HAMD Item 1 ('depressed mood') score of $\geq$2 at both screening and baseline visits. The protocol of this study was prepared according to the International Conference on Harmonisation – Good Clinical Practice and reviewed and approved prior to initiation of this study by the ethics committees of the participating institutions. Written informed consent was obtained from all the patients prior to participation in this study, and this study was conducted in accordance with the Declaration of Helsinki (Edinburgh Revision 2000, Washington Addition of Remarks 2002 and Tokyo Addition of Remarks 2004).

Study design and procedure

This was a multicenter, placebo-controlled, randomized, double-blind, parallel-group comparison study of paroxetine CR administered orally to patients at dose levels of 25–50 mg/day (initial dose, 12.5 or 25 mg/day) once daily for 8 weeks. After a 1-week screening period with placebo, eligible patients were randomized in a ratio of 2:1:2 to paroxetine CR, paroxetine immediate-release (IR) and placebo. The IR group was provided to numerically compare the incidence of adverse events (AE) in the early treatment period and to determine the comparable efficacy to the CR group. Since this comparison was a secondary objective, the number of subjects in IR was set at half of those in CR, based on statistical considerations.

In addition, to evaluate AE in the early treatment period, two initial dosages were set. Patients initiated treatment at 12.5 mg for CR (CR-L), 10 mg for IR (IR-L), 25 mg for CR (CR-H), and 20 mg for IR (IR-H) at Week 0. Thereafter, patients who were in the CR-L group and IR-L group were forced to titrate to 25 mg of CR and 20 mg of IR at Week 1. After Week 2 in the treatment period, the dose range for paroxetine CR was 25–50 mg/day, and for paroxetine IR 20–40 mg/day.

Depending on the last dose level in the treatment period, the tapering period was set for 0–3 weeks. During this period, the dosage was reduced by one step (CR 12.5 mg/day, IR 10 mg/day) at weekly intervals to the lowest dose level (CR 12.5 mg/day or IR 10 mg/day). Post-study assessments were performed at 2 weeks after the last dose of the investigational product. Subjects who had completed all the study procedures (up to the post-study examinations) were defined as per protocol completers.

Efficacy measures

Efficacy was assessed using $HAMD_{17}$, Clinical Global Impression (CGI)-Improvement (CGI-I) and CGI-Severity of illness (CGI-S). The primary efficacy endpoint was the mean change from baseline in the $HAMD_{17}$ total score at Week 8 last observation carried forward (LOCF). For HAMD assessment, the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D)[6,7] was used.

Safety measures

Serious adverse events (SAE) were collected from the date the informed consent was obtained to the last follow-up contact, and other AE were collected from the start of the investigational product to the end of the follow-up period. Adverse events, including SAE, were recorded with non-leading questions.

Abrupt discontinuation during SSRI treatment or tapering the dose of SSRI after completing the SSRI treatment may be associated with characteristic AE that are sometimes referred to as 'SSRI discontinuation syndrome'.[8] In this study, for the AE noted after

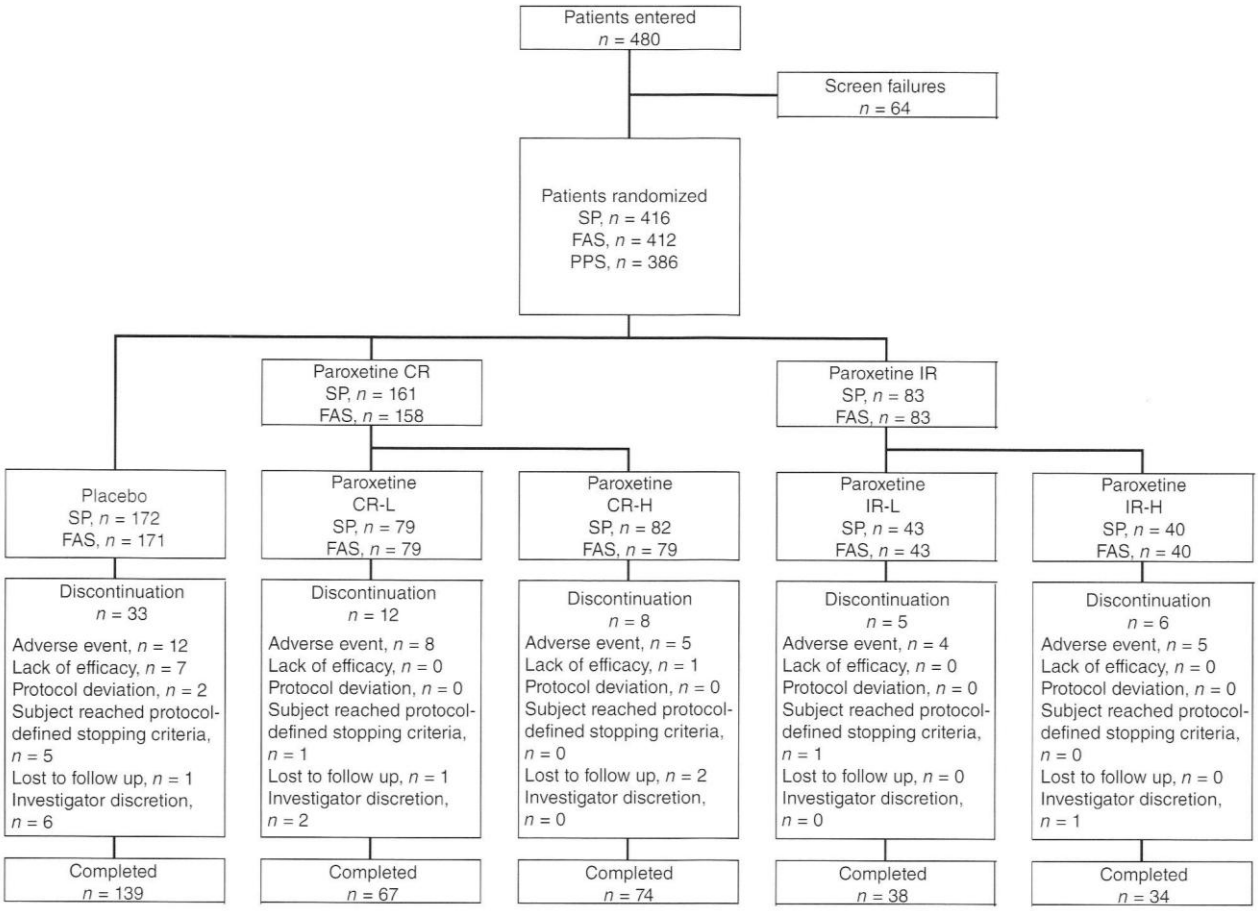

Figure 1. Flow chart of patients' disposition. CR-L: started from 12.5 mg of paroxetine CR; CR-H: started from 25 mg of paroxetine CR; IR-L: started from 10 mg of paroxetine IR; IR-H: started from 20 mg of paroxetine IR. CR, controlled-release; FAS, full analysis set; IR, immediate-release; PPS, per protocol set; SP, safety population.

completing the treatment period, the investigator evaluated whether the observed AE were applicable to discontinuation symptoms according to an evaluation worksheet developed from review of the published literature.[9,10]

The discontinuation symptoms include dizziness, sensory disturbances, sleep disturbances, anxiety, headache, agitation, nausea, tremor, confusion, sweating and diarrhea, which were comprehensively judged as discontinuation symptoms based on the type and duration of each symptom.

Statistical analysis

Considering the result of overseas studies, a mean difference of −3.0 and a standard deviation of 8.35 were assumed for the difference from baseline between paroxetine CR and placebo at Week 8 by LOCF to calculate the sample size. A total of 328 patients (164 patients for paroxetine CR and placebo, respectively) were required to detect the treatment difference with 90% power using *t*-test with a two-sided significance level of 5%. The ANCOVA for the change from baseline in $HAMD_{17}$ total score at Week 8, including baseline score and region (Japan and South Korea) as covariates, was performed to assess the superiority of paroxetine CR relative to placebo. The hypothesis test was conducted with a two-sided significance level of 5%. The point estimate of mean treatment difference adjusted for baseline score and region and its 95% confidence interval (CI) were estimated. Likewise

Table 1. Summary of background by treatment group (full analysis set)

		Placebo $n = 171$	Paroxetine CR $n = 158$	Paroxetine IR $n = 83$
Demographic characteristics				
Age (years)	Mean (SD)	36.8 (10.07)	36.4 (11.47)	35.5 (10.38)
Sex, *n* (%)	Female : male	94:77 (55:45)	84:74 (53:47)	48:35 (58:42)
Country, *n* (%)	Japan : South Korea	154:17 (90:10)	138:20 (87:13)	73:10 (88:12)
History of major depressive disorder				
Onset age (years)	Mean (SD)	33.6 (10.24)	33.9 (11.05)	33.1 (10.42)
Number of previous depressive episodes† *n* (%)	0	90 (53)	86 (54)	47 (57)
	1	51 (30)	45 (28)	22 (27)
	2	15 (9)	14 (9)	6 (7)
	3	11 (6)	4 (3)	3 (4)
	4 or more	4 (2)	9 (6)	5 (6)
DSM-IV-TR diagnosis‡ *n* (%)	296.21	8 (5)	9 (6)	5 (6)
	296.22	68 (40)	66 (42)	38 (46)
	296.23	14 (8)	11 (7)	4 (5)
	296.31	2 (1)	4 (3)	3 (4)
	296.32	68 (40)	55 (35)	31 (37)
	296.33	11 (6)	13 (8)	2 (2)
Duration of current major depressive episodes (weeks)	Mean (SD)	33.5 (23.65)	33.3 (23.06)	32.3 (21.44)
$HAMD_{17}$ total score at baseline	Mean (SD)	22.6 (2.75)	22.7 (2.62)	22.7 (2.64)

†Not including current major depressive episode.
‡DSM-IV-TR diagnosis code. 296.2: Major depressive disorder, single episode; 296.3: Major depressive disorder, recurrent. The severity was represented as .x1: mild; .x2: moderate; and .x3: severe without psychotic features.
CR, controlled-release; $HAMD_{17}$, Hamilton Rating Scale for Depression (17 items); IR, immediate-release.

the ANCOVA for the change from baseline in $HAMD_{17}$ total score at each visit was performed. The logistic regression including terms for treatment and region was performed to estimate the odds ratio of paroxetine CR relative to placebo and its 95%CI for percentage of $HAMD_{17}$ responders and CGI-I responders. The efficacy analyses were conducted for the full analysis set. The safety analyses were conducted for the safety population.

RESULTS

Demography

In this study, patients were enrolled at 57 centers in Japan and nine centers in South Korea and a total of 70 investigators participated. The study was conducted from April 2009 to February 2010.

A total of 416 patients were randomized to one of three treatment groups: 172 patients were in the placebo group, 161 patients were in the CR group and 83 patients were in the IR group (Fig. 1). The proportion of completed patients was 88% in the CR group, 87% in the IR group, and 81% in the placebo group. Patients' baseline demographics and psychiatric characteristics were similar among the treatment groups (Table 1).

Efficacy

Primary efficacy analysis

The adjusted mean change from baseline in $HAMD_{17}$ total score at Week 8 was −12.8 in the CR group, −12.5 in the IR group and −10.4 in the placebo group. These changes from baseline were similar between the IR and CR groups (Table 2). There were statistically significant differences between CR and placebo ($P < 0.001$), and between IR and placebo ($P = 0.015$).

The mean difference (two-sided 95%CI) between the CR and placebo groups was −2.4 (−3.8, −1.1). The mean difference (two-sided 95%CI) between the IR and placebo groups was −2.0 (−3.7, −0.4).

Table 2. Primary and secondary efficacy measures at Week 8 (full analysis set)

			Change by Week 8 (adjusted mean)		Treatment difference vs placebo		
Measures	Treatment	*n*	Mean	SEM	Mean	95%CI	*P*-value
Primary end-point $HAMD_{17}$ total score†	Placebo	171	−10.4	0.62	–	–	–
	Paroxetine CR	158	−12.8	0.61	−2.4	(−3.8, −1.1)	<0.001
	Paroxetine IR	83	−12.5	0.78	−2.0	(−3.7, −0.4)	0.015
					Treatment difference vs placebo		
			n	%	Odds ratio	95%CI	*P*-value
Secondary end-points $HAMD_{17}$ remitters‡	Placebo	171	40	23	–	–	–
	Paroxetine CR	158	56	35	1.79	(1.11, 2.90)	0.018
	Paroxetine IR	83	30	36	1.85	(1.04, 3.27)	0.035
CGI-I responders¶	Placebo	171	91	53	–	–	–
	Paroxetine CR	158	112	71	2.12	(1.34, 3.35)	0.001
	Paroxetine IR	83	62	75	2.58	(1.44, 4.62)	0.001
$HAMD_{17}$ responders††	Placebo	171	78	46	–	–	–
	Paroxetine CR	158	99	63	1.98	(1.27, 3.08)	0.003
	Paroxetine IR	83	47	57	1.54	(0.91, 2.62)	0.109
			Change by Week 8		Treatment difference vs placebo		
			Mean	SD	Mean	–	*P*-value
CGI-S reduction from baseline	Placebo	171	−0.9	1.02	–	NC	–
	Paroxetine CR	158	−1.2	1.02	−0.3	NC	0.009
	Paroxetine IR	83	−1.1	1.05	−0.2	NC	0.066

†The ANCOVA for the change from baseline in $HAMD_{17}$ total score at Week 8, including baseline score and country (Japan and South Korea) as covariates was performed to assess the superiority of paroxetine controlled-release relative to placebo.
‡Remitters mean patients whose $HAMD_{17}$ total score is up to 7.
¶, ††The logistic regression including terms for treatment and region was performed to estimate the odds ratio of paroxetine controlled-release relative to placebo and its 95%CI for percentage of $HAMD_{17}$ responders and CGI-I responders.
¶CGI-I responders mean patients who were assessed as 'very much improved' or 'much improved'.
††$HAMD_{17}$ responders mean patients whose $HAMD_{17}$ total score is greater than 50% reduction from Week 0.
CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity of illness; CI, confidence interval; $HAMD_{17}$, Hamilton Rating Scale for Depression (17 items); NC, not calculated.

Secondary efficacy analyses

Figure 2 shows changes in the total score in $HAMD_{17}$ over time in both paroxetine groups across visits. The decrease in the $HAMD_{17}$ total score at and after Week 4 in the CR group was significantly different from that in the placebo group ($P = 0.049$). The percentages of $HAMD_{17}$ remitters at Week 8 are summarized in Table 2. The odds ratio (two-sided 95%CI) relative to placebo was 1.79 (1.11, 2.90) for the CR group and 1.85 (1.04, 3.27) for the IR group, and the percentages of remitters were statistically significantly higher than with placebo ($P = 0.018$, CR; $P = 0.035$, IR).

Safety

The common AE (incidence ≥ 5%) of paroxetine in the treatment period are shown in Table 3. The overall incidence of AE in the treatment period was

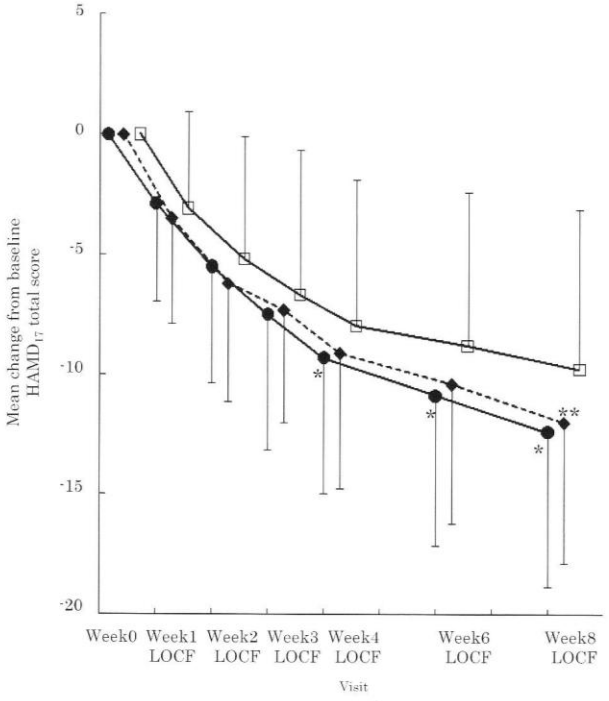

Figure 2. Mean and SD of change from baseline in the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) total score (full analysis set [FAS], last observation carried forward [LOCF]). The ANCOVA for the change from baseline in $HAMD_{17}$ total score at Week 8 including baseline score and region (Japan and South Korea) as covariates was performed to assess the superiority of paroxetine controlled-release (CR) relative to placebo. *P*-value ≤ 0.05 (*paroxetine CR vs placebo, **paroxetine immediate-release [IR] vs placebo). (—●—) Paroxetine CR; (-·-◆-·-) paroxetine IR; (—□—) placebo.

comparable between CR and IR. The incidence of AE during the taper and follow-up periods was 49% in the CR group, 48% in the IR group and 38% in the placebo group (data not shown). The incidence of discontinuation symptoms that occurred after taking the last active study medication (i.e., paroxetine treatment groups) was in the range of 23–34%.

One patient in the IR-L group died of 'completed suicide', which was considered unrelated to the investigational product and attributed to unexpected, impulsive behavior associated with improvement in MDD by the investigator. This patient had no history of self-harm and no ideation of suicide prior to the fatal event. Other SAE were reported in nine patients with 10 events: two in CR-L, four in CR-H, two in IR-L and one in placebo.

The incidence of AE leading to premature discontinuation was similar among the treatment groups: 8% in the CR group, 11% in the IR group and 7% in the placebo group ($\chi^2(2) = 1.1187$, $P = 0.572$). [Percentages for the CR group, the IR group and the placebo group amended after online publication date December 19, 2011.]

In this study, two initial dosages were used to evaluate AE in the early treatment period. The incidence of AE in the first 2 weeks of the treatment period (i.e. between Week 0 and Week 2) was 49% in the CR group, 45% in the IR group and 33% in the placebo group (Table 4). The incidence of AE between Week 0 and Week 2 was comparable between CR and IR. Regarding nausea, the incidence between Week 0 and Week 2 was 6% in the CR-L group, 18% in the CR-H group, 14% in the IR-L group, 10% in the IR-H group and 5% in the placebo group.

DISCUSSION

This study is the first ever placebo-controlled multinational trial of paroxetine CR in Asian patients with MDD. In this study, the background factors related to MDD, such as baseline $HAMD_{17}$ total score, onset of MDD and duration of current major depressive episode, were not markedly different between Japanese and Korean patients (data not shown).

Regarding the assessment of efficacy, the $HAMD_{17}$ was adopted as the scale because of its use in clinical trials of treatment for MDD, and in clinical practice worldwide. Using this scale, investigators were able to assess multiple symptoms of MDD. We found that the efficacy against MDD was comparable between CR and IR (Table 2). Furthermore, paroxetine CR showed statistically significant superiority to placebo not only in terms of a decrease in $HAMD_{17}$ total score but also in terms of the percentage of $HAMD_{17}$ remitters and the percentage of CGI-I responders (Table 2). In overseas clinical studies, paroxetine CR exhibited efficacy in MDD as assessed by a reduction in $HAMD_{17}$ compared to placebo when using 25 mg/day as an initial dose.[11]

Antidepressant drugs, including SSRI, might cause 'discontinuation symptoms' by the abrupt cessation or tapering of medication. Therefore, we tried to obtain the incidence of 'discontinuation symptoms'. In our study, the severity and duration of each symptom related to 'discontinuation symptoms' was not markedly different between CR and IR. The common symptoms reported by the patients were dizziness, sensory disturbance and sleep disturbance, and the type and incidence were not markedly

Table 3. Common adverse events (incidence ≥5%) reported in the treatment period (safety population)

		Paroxetine controlled-release			Paroxetine immediate-release		
Preferred term	Placebo $n = 172$	CR-L $n = 79$	CR-H $n = 82$	Total $n = 161$	IR-L $n = 43$	IR-H $n = 40$	Total $n = 83$
Patients with any adverse events, *n* (%)	94 (55)	51 (65)	54 (66)	105 (65)	32 (74)	25 (63)	57 (69)
Nausea	14 (8)	7 (9)	20 (24)	27 (17)	8 (19)	6 (15)	14 (17)
Constipation	5 (3)	9 (11)	8 (10)	17 (11)	4 (9)	3 (8)	7 (8)
Nasopharyngitis	27 (16)	7 (9)	10 (12)	17 (11)	4 (9)	4 (10)	8 (10)
Somnolence	3 (2)	11 (14)	5 (6)	16 (10)	4 (9)	3 (8)	7 (8)
Headache	17 (10)	5 (6)	6 (7)	11 (7)	1 (2)	1 (3)	2 (2)
Ejaculation disorder†	0 (0)	4 (11)	1 (3)	5 (7)	1 (6)	1 (6)	2 (6)
Dizziness	3 (2)	4 (5)	4 (5)	8 (5)	3 (7)	1 (3)	4 (5)
Diarrhea	8 (5)	1 (1)	6 (7)	7 (4)	3 (7)	4 (10)	7 (8)
Dry mouth	7 (4)	3 (4)	4 (5)	7 (4)	2 (5)	3 (8)	5 (6)
Hyperhidrosis	1 (<1)	4 (5)	3 (4)	7 (4)	3 (7)	0 (0)	3 (4)
Thirst	3 (2)	2 (3)	4 (5)	6 (4)	2 (5)	0 (0)	2 (2)
Abdominal pain upper	4 (2)	4 (5)	1 (1)	5 (3)	1 (2)	1 (3)	2 (2)
Dyspepsia	6 (3)	0 (0)	4 (5)	4 (2)	1 (2)	1 (3)	2 (2)
Tremor	0 (0)	3 (4)	1 (1)	4 (2)	2 (5)	3 (8)	5 (6)
Palpitations	4 (2)	2 (3)	0 (0)	2 (1)	2 (5)	1 (3)	3 (4)
Pollakiuria	3 (2)	1 (1)	1 (1)	2 (1)	2 (5)	3 (8)	5 (6)
Pyrexia	0 (0)	1 (1)	0 (0)	1 (<1)	2 (5)	0 (0)	2 (2)

†Because of a sex-specific adverse event, the % were calculated using only the number of male patients (CR-L, $n = 38$; CR-H, $n = 37$; IR-L, $n = 17$; IR-H, $n = 18$; Placebo, $n = 78$).
CR-H, patients who started from high initial dose of paroxetine controlled-release (25 mg); CR-L, patients who started from low initial dose of paroxetine controlled-release (12.5 mg); IR-H, patients who started from high initial dose of paroxetine immediate-release (20 mg); IR-L, patients who started from low initial dose of paroxetine immediate-release (10 mg).

Table 4. Common AE (incidence ≥5%) between Week 0 and Week 2 (safety population)

		Paroxetine controlled-release			Paroxetine immediate-release		
Preferred terms	Placebo $n = 172$	CR-L $n = 79$	CR-H $n = 82$	Total $n = 161$	IR-L $n = 43$	IR-H $n = 40$	Total $n = 83$
Patients with any AE within Week 2, *n* (%)	57 (33)	36 (46)	43 (52)	79 (49)	19 (44)	18 (45)	37 (45)
Nausea	8 (5)	5 (6)	15 (18)	20 (12)	6 (14)	4 (10)	10 (12)
Somnolence	3 (2)	9 (11)	5 (6)	14 (9)	3 (7)	1 (3)	4 (5)
Constipation	5 (3)	5 (6)	4 (5)	9 (6)	1 (2)	3 (8)	4 (5)
Headache	9 (5)	3 (4)	5 (6)	8 (5)	0 (0)	1 (3)	1 (1)
Nasopharyngitis	7 (4)	1 (1)	6 (7)	7 (4)	1 (2)	2 (5)	3 (4)
Diarrhea	2 (1)	0 (0)	5 (6)	5 (3)	1 (2)	4 (10)	5 (6)
Dry mouth	2 (1)	1 (1)	2 (2)	3 (2)	2 (5)	3 (8)	5 (6)
Hyperhidrosis	0 (0)	1 (1)	2 (2)	3 (2)	2 (5)	0 (0)	2 (2)

AE, adverse events; CR-H, patients who started from high initial dose of paroxetine controlled-release (25 mg); CR-L, patients who started from low initial dose of paroxetine controlled-release (12.5 mg); IR-H, patients who started from high initial dose of paroxetine immediate-release (20 mg); IR-L, patients who started from low initial dose of paroxetine immediate-release (10 mg).

different between CR and IR. In the placebo group, discontinuation symptoms were reported with an incidence of 10%, and the symptoms reported by the patients were diverse and had no distinctive features, which is different from those reported in the paroxetine groups (data not shown). As the 'discontinuation symptoms' were uniquely defined in this study, the definition is different from that described in prior studies evaluating discontinuation symptoms.[8,12–14] It is thus difficult to compare and discuss the present results with previous studies because no uniform definition has been established so far.

As mentioned above, the safety profile of paroxetine CR was shown to be comparable to that of paroxetine IR, which is widely used in clinical practice. A limitation of this study was the small sample size for sub-groups, such as the IR group and the initial dose groups. We could show the superior efficacy of paroxetine CR to placebo. Secondary objectives should be taken into consideration because the comparison of safety profile between IR and CR or between the low initial dose group and the high initial dose group was not statistically significant. The incidence of nausea, occurring in the early treatment period (Week 0 to Week 2), was 6% in the CR-L group, which was comparable with the incidence in the placebo group (5%). Table 4 also shows that the incidence of nausea in the CR-H, IR-L, and IR-H groups was numerically higher than placebo.

In past clinical studies, the efficacy and tolerability of paroxetine CR has been demonstrated with a starting dose of 25 mg.[11] The incidence of nausea within the first week of the treatment period was 14% in the CR group, 23% in the IR group and 4% in the placebo group, which was significantly lower in the CR group as compared with the IR group ($P \leq 0.05$). These results suggest that paroxetine CR may decrease the incidence of nausea in the early treatment period.

In conclusion, this study verified that paroxetine CR shows statistically significant superiority to placebo in efficacy in Asian patients with MDD to a similar extent demonstrated in overseas clinical studies.[11] It was also suggested that paroxetine CR may decrease the incidence of nausea in the early treatment period.

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