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Efficacy and Tolerability of Controlled-Release Paroxetine

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Efficacy and Tolerability of Controlled-Release Paroxetine

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ABSTRACT *~ Paroxetine controlled-release (CR) was developed with the objective of minimizing the occurrence and severity of selective serotonin reuptake inhibitor (SSRI)-associated adverse events, thereby improving clinical outcomes. Paroxetine CR delays the onset and controls the rate of absorption of medication. Multicenter controlled clinical trials have found lower rates of early-onset, treatment-associated nausea and lower dropout rates from adverse events in depressed patients treated with paroxetine CR compared with those treated with the conventional, immediate-release formulation. At the same time, clinical response and remission rates are favorable. Other studies have demonstrated the efficacy and tolerability of paroxetine CR in geriatric depression, panic disorder, and social anxiety disorder. The CR formulation of paroxetine appears to represent an effective pharmacokinetic approach to minimizing SSRI adverse events and thereby enhancing clinical outcomes.* Psychopharmacology Bulletin. *2003;37(Suppl 1):176-186.*

INTRODUCTION

Paroxetine has become a mainstay in the pharmacotherapy of mood and anxiety disorders since its introduction in the United States a decade ago. The safety and efficacy of paroxetine are now well established. As with all of the selective serotonin reuptake inhibitors (SSRIs), certain adverse events are associated with the use of paroxetine, which reflect the psychobiological effects of enhanced serotonergic neurotransmission. Although most of the adverse events associated with the SSRIs are relatively mild when compared with those associated with the earlier generation of tricyclic antidepressants and monoamine oxidase inhibitors, they nonetheless may contribute to diminished medication adherence and clinical response. Paroxetine controlled-release (CR) was developed with the goal of minimizing SSRI adverse events by controlling the site and rate of medication absorption, thereby improving clinical outcomes. Paroxetine CR became available for use in the

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US in the spring of 2002. Below, we will briefly review the rationale behind the development of a controlled-release formulation of paroxetine and then review the evidence to date regarding its efficacy and tolerability in the treatment of mood and anxiety disorders.

RATIONALE FOR DEVELOPMENT OF PAROXETINE CR

SSRI Adverse Events: A Threat to Medication Adherence and Clinical Outcome

The SSRIs have emerged as the most widely prescribed class of antidepressant medications in the US and throughout the world. They offer efficacy in a broad range of mood and anxiety disorders, coupled with a side-effect profile that is considerably safer than those of the older tricyclic and monoamine oxidase inhibitor antidepressants. However, the SSRIs do possess adverse events that may interfere with medication adherence, thus adversely impacting clinical outcomes. The findings of prospectively designed studies have demonstrated that more than 25% of patients discontinue antidepressant pharmacotherapy during the first month of treatment.[1] The strongest predictor of nonadherence to antidepressant therapy in primary care patients is the emergence of drug-related adverse events,[2] which are also a more important causal factor in the early discontinuation of antidepressant therapy than in discontinuation later in the course of treatment.[3] Poor adherence is the leading cause of both relapse and less than optimal clinical outcomes.[4] Thus, seemingly "minor" SSRI adverse events have the potential to exert major deleterious effects on clinical course by sabotaging patient adherence to antidepressant treatment.

Nausea is one of the most frequently reported adverse events associated with SSRI treatment. The findings of numerous studies of various SSRIs, including fluoxetine, sertraline, paroxetine, and citalopram, have consistently reported nausea as one of the most common complaints in patients receiving these treatments.[5-10] Nausea is also a leading cause of premature treatment discontinuation for patients receiving SSRIs[11-14] or serotonin-norepinephrine reuptake inhibitors (SNRIs).[15] The nausea that is typically associated with SSRI treatment usually occurs early in the course of therapy and generally subsides with continued administration of the drug.

Other mild, and often transient, side effects have been linked to early treatment discontinuation. In a study examining the reasons for nonadherence, somnolence, anxiety, and headache were reported along with nausea as the leading causes of treatment discontinuation.[3] Most often, these side effects appear within the first weeks of therapy and subside with continued treatment.

Nonetheless, the presence of nausea and other side effects in the first few weeks of SSRI therapy may reduce medication adherence, delay or prevent patients from reaching full therapeutic doses, lead to premature treatment discontinuation, and, thus, compromise clinical outcomes.

Paroxetine CR: A Pharmacokinetic Approach to Address Centrally Mediated and Locally Mediated Side Effects

The mechanism underlying SSRI-associated side effects is mediated through a central effect in the central nervous system, or via a direct effect in the gastrointestinal tract. Paroxetine, like all SSRIs, exerts its therapeutic effects by increasing serotonin (5-hydroxytryptamine, or 5-HT) transmission within the central nervous system. This mechanism, however, may induce adverse events which are also mediated by 5-HT, such as somnolence, anxiety, and sexual dysfunction. The presence of these side effects may be associated with serum concentrations of the medication. Minimizing the dose of the SSRI is a strategy often employed to reduce the side-effect potential; however, this approach may also minimize the therapeutic gain with lower serum concentrations. Thus, controlling blood levels of SSRIs in a manner that maximizes therapeutic effects while minimizing side-effect potential may lead to better clinical outcomes.

Nausea involves, at least in part, local stimulation of 5-HT receptors in the proximal small intestine. This section of the bowel is richly innervated with 5-HT receptors within the submucosal and myenteric plexi. When stimulated, these 5-HT receptors evoke contractions in the smooth muscle tissues of the small intestine. During the process of absorption of conventional, immediate-release SSRI formulations in the upper gastrointestinal tract, local 5-HT concentrations become elevated, leading to increased stimulation of the 5-HT receptors, increased smooth muscle contractions, and the experience of nausea.

The development of the paroxetine CR formulation represents a pharmacokinetic strategy for minimizing this pathway to SSRI-associated side effects. The enteric coating delays the start of tablet disintegration until the tablet has left the stomach. Then the polymeric matrix (Geomatrix™) core containing the paroxetine erodes slowly, resulting in a more gradual, sustained release of the medication. Together, these features delay and target the site of absorption for more distal sites in the gastrointestinal tract, away from the dense serotonergic innervation of the proximal small intestine. Thus, in theory, there should be less stimulation of upper gastrointestinal tract 5-HT receptors and, consequently, less nausea. In addition, other adverse events may be ameliorated because the circadian (ie, peak-to-trough) plasma concentration range is reduced compared with that observed with conventional, immediate-release SSRI formulations.

Pharmacokinetic studies in healthy volunteers lend support to this approach. As expected, the T_{max} (time to maximum serum concentration) for paroxetine CR is delayed by approximately 4 to 5 hours compared with the immediate-release (IR) formulation of paroxetine. Also, the circadian fluctuation between peak and trough plasma concentrations is approximately 20% to 30% lower with paroxetine CR compared with paroxetine IR.[16] Thus, the CR formulation delays the absorption of the SSRI, and at the same time "smoothes out" the difference between peak and trough plasma concentrations.

Approximately 20% of the active medication imbedded within the polymeric core of paroxetine CR tablet is not absorbed and is eliminated unchanged. Thus, a given dose of paroxetine CR has 80% bioavailability, compared with conventional paroxetine IR. A dose of 25 mg of paroxetine CR is similar to a dose of 20 mg of paroxetine IR.

EFFICACY OF PAROXETINE CR

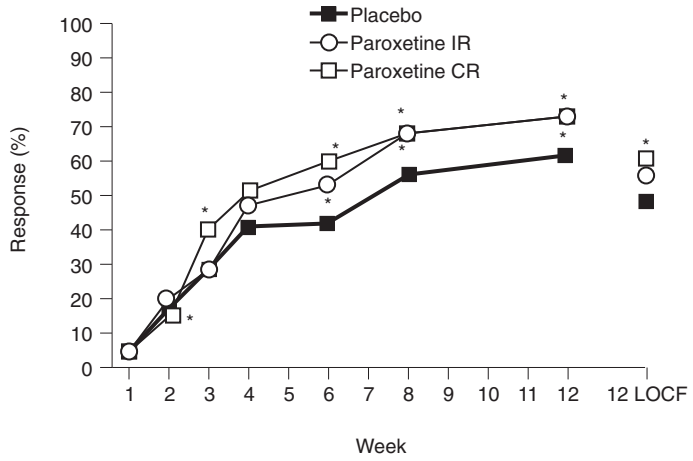
Major Depressive Disorder

General Adult Population. The first published report of the clinical efficacy and tolerability of paroxetine CR examined data from 2 randomized, double-blind, placebo-controlled, multicenter clinical trials of identical design of adults with major depressive disorder.[17] Patients between the ages of 18 and 65 years were assigned to treatment with paroxetine CR (25-62.5 mg/d; N=206), paroxetine IR (20–50 mg/d; N=211), or placebo (N=205) for a 12-week trial. Both paroxetine CR and paroxetine IR had significantly greater efficacy than placebo, as assessed by improvement in Hamilton Depression Rating Scale (HAM-D) scores. Following 12 weeks of treatment, response and remission rates were 74% and 56% for paroxetine CR, 73% and 53% for paroxetine IR, and 61% and 44% for placebo (Figures 1 and 2). As predicted by the theoretical considerations described above, there was a significantly lower rate of nausea in the paroxetine CR group (14%) compared with the paroxetine IR group (23%) in the critical first week of treatment. Dropout rates from adverse events were not significantly different in the paroxetine CR group compared with the placebo group, whereas the paroxetine IR group experienced significantly higher dropout rates secondary to adverse events compared with the placebo group (*P*=.0008; Figure 3).

The antidepressant efficacy and tolerability of paroxetine CR have also been examined in a randomized, double-blind, placebo-controlled multicenter study with a fixed-dose design. Patients were assigned to an 8-week treatment trial with paroxetine CR 12.5 mg/day (N=153), 25 mg/day (N=148), or placebo (N=146). Patients in both active treatment groups

FIGURE 1

WEEKLY RESPONSE RATES AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH PAROXETINE CR, PAROXETINE IR, AND PLACEBO



Weekly Hamilton Depression Rating Scale (HAM-D) response rates among patients with major depressive disorder who were treated with paroxetine controlled-release (CR), paroxetine immediate-release (IR), or placebo (observed cases [OC] population) and last observation carried forward (LOCF) end point dataset. Response: ≥50% reduction in baseline HAM-D total score.
*$P \leq .05$. Reproduced with permission.[17]

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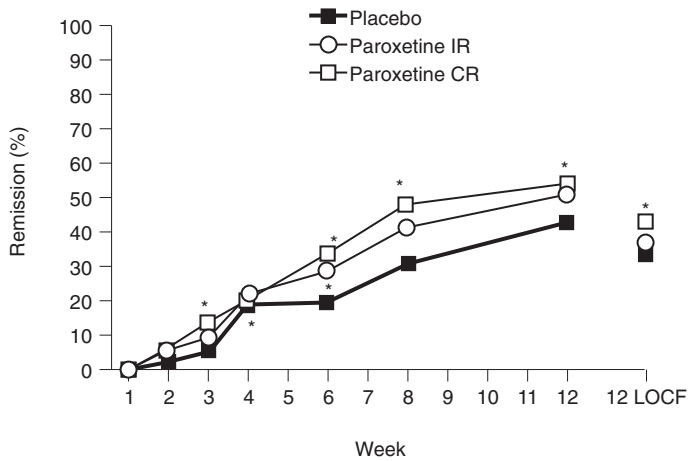
FIGURE 2

WEEKLY REMISSION RATES AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH PAROXETINE CR, PAROXETINE IR, AND PLACEBO



Weekly Hamilton Depression Rating Scale (HAM-D) remission rates (HAM-D total score ≤7) among patients with major depressive disorder who were treated with paroxetine controlled-release (CR), paroxetine immediate-release (IR), or placebo (observed cases [OC] dataset and last observation carried forward [LOCF] end point dataset).
*$P \leq .05$. Reproduced with permission.[17]

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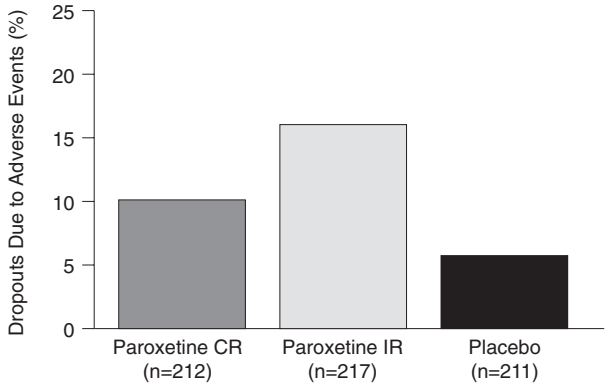
FIGURE 3

OVERALL DROPOUT RATES FROM ADVERSE EVENTS AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH PAROXETINE CR, PAROXETIINE IR, AND PLACEBO



Overall dropout rates from adverse events for paroxetine controlled-release (CR), paroxetine immediate-release (IR), and placebo during a 12-week study in patients with major depressive disorder (paroxetine IR vs placebo, *P*=.0008).
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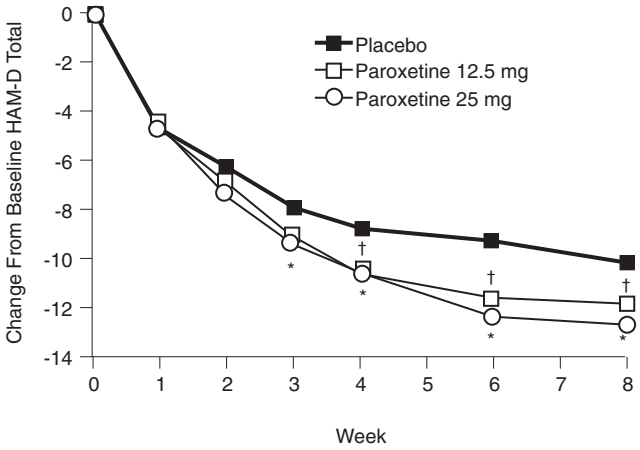
FIGURE 4

WEEKLY TOTAL SCORES AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH PAROXETINE CR OR PLACEBO



Weekly Hamilton Rating Scale for Depression (HAM-D) total scores among patients with major depressive disorder who were treated with paroxetine controlled-release (CR) (12.5 mg), paroxetine CR (25 mg), or placebo (observed cases [OC] dataset).
**P*<.05 paroxetine CR 12.5 mg vs placebo; †*P*<.05 paroxetine CR 25 mg vs placebo.
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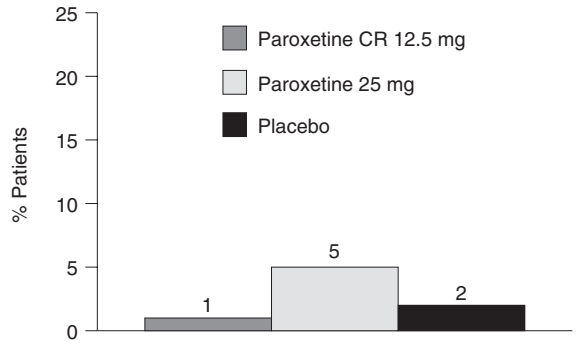
demonstrated significantly greater improvement in HAM-D scores compared with patients in the placebo group (Figure 4).[18] Moreover, the dropout rate from adverse events was significantly lower in the 12.5-mg/day paroxetine CR group than in the placebo group (Figure 5). These findings suggest that a relatively low dose of paroxetine CR may be quite useful in treating those patients with major depression who are especially sensitive to medication adverse events.

Elderly Patients. The clinical efficacy of paroxetine CR has also been studied in geriatric patients with depression in a multicenter, placebo-controlled, double-blind trial, which included a flexible-dose design.[19] The study included 319 elderly patients with major depressive disorder (mean age 70 years). More than 90% of the patients had concurrent medical diagnoses, reflecting the typical presentation of medical comorbidity that is seen in this clinical population. Patients were randomly assigned to a course of 12 weeks of treatment with either paroxetine CR (with an upper dose limit of 50 mg/d), paroxetine IR (up to 40 mg/d), or placebo. Both paroxetine CR and paroxetine IR were significantly more effective than placebo based on end-point HAM-D ratings. In this population of geriatric patients with depression, the response rates were 72% and 65% for paroxetine CR and paroxetine IR, respectively, compared with a response rate of 52% for placebo. Rates of remission, which were rigorously defined as an end-point HAM-D total score of ≤7, were 43% and 44% for paroxetine CR and paroxetine IR, respectively, compared with 26% for placebo.

FIGURE 5

OVERALL DROPOUT RATES FROM ADVERSE EVENTS AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH PAROXETINE CR



Overall dropout rates from adverse events for paroxetine controlled-release (CR) (12.5 mg), paroxetine CR (25 mg), and placebo among patients with major depressive disorder.
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A post hoc analysis revealed that each formulation of paroxetine was significantly more effective than placebo in both chronically depressed patients (ie, those with a duration of illness >2 years) and "short-term" depressed patients (duration of illness ≤2 years).

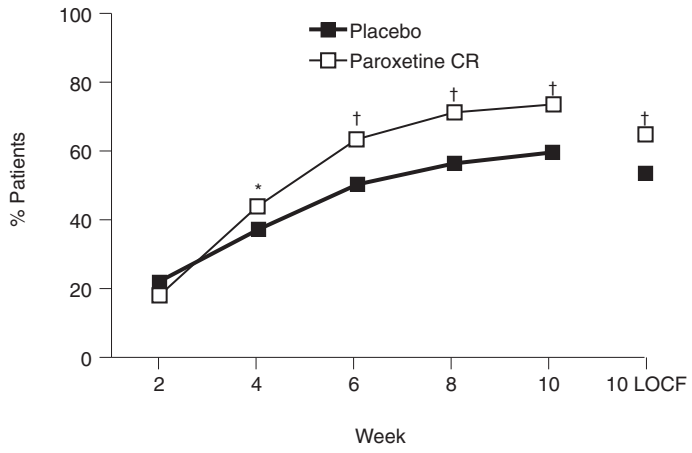
Paroxetine CR was very well tolerated in this medically ill, elderly group of patients with depression.[19] The weekly rate of premature treatment withdrawal from adverse events was consistently lower for the paroxetine CR group compared with the paroxetine IR group. In the geriatric patient population, hypotension is of particular concern, because it may lead to falls, hip fractures, and related serious sequelae. The emergence of hypotension was not significantly different in the paroxetine CR treatment group (4.8%) compared with the placebo group (3.7%). Reports of insomnia, a common complaint in the elderly, were similar in the paroxetine CR group and in the placebo group (9.6% and 8.3%, respectively).

Anxiety Disorders

Panic Disorder. Based on the established record of paroxetine IR in the treatment of anxiety disorders, one would anticipate that paroxetine CR would also be effective in these patient populations. Paroxetine CR (25-75 mg/d; N=444) was compared with placebo (N=445)

FIGURE 6

PERCENTAGE OF PATIENTS WITH PANIC DISORDER WHO BECAME PANIC-FREE AFTER A 10-WEEK COURSE OF PAROXETINE CR VS PLACEBO



Percentage of patients with panic disorder who became panic-free (observed cases [OC] and end point last observation carried forward [LOCF] dataset) during a 10-week course of paroxetine controlled-release (CR) or placebo. Comparisons of change in score versus placebo: **P*<.05; †*P*<.005. LOCF from week 1 dataset (paroxetine CR, N=377; placebo, N=395). OC dataset (paroxetine CR, N=263; placebo, N=296). D.V. Sheehan et al, unpublished data.

in 3 identical, double-blind, placebo-controlled, 10-week clinical trials of patients with panic disorder (Sheehan DV and colleagues, unpublished data). Patients in the paroxetine CR group were significantly more likely to become panic-free compared with patients in the placebo group (Figure 6). During the final 2 weeks of the study, 73% and 60% of paroxetine CR- and placebo-treated patients, respectively, became panic-free ($P<.005$). The paroxetine CR group experienced significantly greater global improvement than the placebo group and significantly greater improvement in anxiety symptoms as measured by Hamilton Anxiety Rating Scale (HAM-A) total score, and agoraphobic fear and avoidance on the Marks-Sheehan Phobia Scale (MSPS). Adverse events leading to study withdrawal were minimal and occurred in 11% of the paroxetine CR group and 6% of the placebo group.

Social Anxiety Disorder. A recent report[20] describes the efficacy of paroxetine CR in the treatment of patients with social anxiety disorder. This 12-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated paroxetine CR (12.5 - 37.5 mg/d) in 375 outpatients meeting *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*)[21] criteria for social anxiety disorder. At the study end point, paroxetine CR was superior to placebo on the primary measures (change from baseline in the Liebowitz Social Anxiety Scale and the proportion of responders defined by a Clinical Global Impression-Improvement scale score of 1, "very much improved", or 2, "much improved"), as well as in the numerous secondary outcome measures. Treatment dropout rates from adverse events were similar in the paroxetine CR and placebo groups (2.7% versus 1.6%, respectively), and fewer patients dropped out secondary to lack of efficacy in the paroxetine CR group compared with the placebo group.[20]

TOLERABILITY OF PAROXETINE CR

A recent pooled analysis was completed in an effort to further assess the relationship between tolerability and adherence in SSRI treatment. Data from all available placebo-controlled clinical trials in major depression using paroxetine IR and paroxetine CR formulations were analyzed. Each formulation was compared with placebo in terms of premature treatment discontinuation because of adverse events (Figure 7). The overall rate of discontinuation with paroxetine IR was 20%, compared with a rate of 9% with placebo.[12] In treatment trials that included both the IR and the CR formulations, the rate of discontinuation for paroxetine IR was significantly higher than that of placebo ($P<.001$). According to the data from 4 trials in major depression, the rate of discontinuation with paroxetine CR (7%) was not significantly different from the rate of discontinuation with placebo (6%). Thus, the CR formulation of paroxetine appears to

offer improved tolerability and, potentially, improved adherence compared with the immediate-release formulation.[16]

CONCLUSION

Controlling the site and rate of absorption of an SSRI medication should, in theory, decrease the risk of nausea by minimizing the stimulation of 5-HT receptors and associated smooth muscle contraction in the upper gastrointestinal tract, and may also potentially lower the rate and severity of other adverse events by depressing the peak of plasma drug concentrations. Paroxetine CR formulation appears to represent a positive "proof of concept" test of this approach. The CR formulation is associated with lower rates of nausea and lower rates of premature treatment dropout as a result of adverse events compared with the conventional immediate-release formulation. At the same time, clinical response and clinical remission rates are quite favorable in studies to date, which have included patients with major depression and social anxiety disorder, as well as geriatric patients with depression and considerable comorbid medical illnesses. Thus, paroxetine CR may represent a successful pharmacokinetic approach to decreasing SSRI adverse events, thereby enhancing tolerability, adherence, and clinical outcomes. ✤

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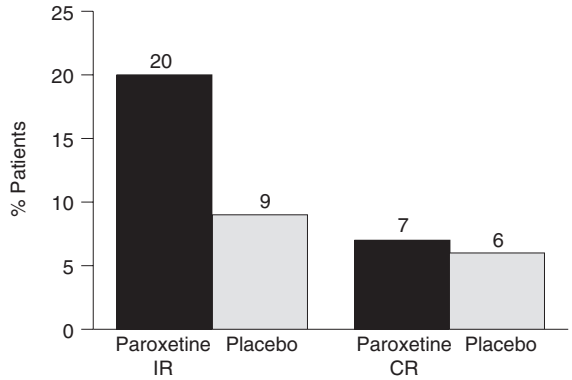
FIGURE 7

OVERALL DROPOUT RATES FROM ADVERSE EVENTS AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH PAROXETINE IR OR PAROXETINE CR VS PLACEBO [12,16]



Overall dropout rates from adverse events for paroxetine immediate-release (IR) (20 mg) vs placebo and paroxetine controlled-release (CR) (25 mg) vs placebo among patients with major depressive disorder.

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DISCLOSURE

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