Immediate-Release Versus Controlled-Release Formulations: Pharmacokinetics of Newer Antidepressants in Relation to Nausea

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Newer antidepressants are generally as efficacious as but often have fewer side effects than their predecessors such as the tricyclic antidepressants and monoamine oxidase inhibitors. These newer antidepressants include the selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; venlafaxine, a serotonin-norepinephrine reuptake inhibitor; and bupropion, a selective norepinephrine and dopamine reuptake inhibitor. Most of these antidepressants have half-lives that enable them to be administered as infrequently as 1 to 3 times per day. To further improve upon the ease of use, controlled-release formulations of bupropion, fluoxetine, paroxetine, and venlafaxine have been manufactured. Potential pharmacokinetic advantages of these formulations include lower peak plasma drug concentrations and smaller fluctuations between peak and trough plasma drug concentrations, which might influence the tolerability of these medications. Tolerability advantages seen with some of these medications include diminished nausea. The 3 controlled-release agents that are designed to be taken daily—bupropion, paroxetine, and venlafaxine—are associated with lower incidences of nausea overall and nausea leading to treatment discontinuation than are their immediate-release formulations. However, the rates of nausea are similar with both formulations of fluoxetine, despite higher peak plasma drug concentrations and greater fluctuation between peak and trough plasma drug concentrations with fluoxetine weekly than with fluoxetine daily. Although the connection has not been proven, more stable pharmacokinetic profiles might be the cause for the low occurrence of nausea with some controlled-release newer antidepressants.

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In the past 20 years, several new antidepressants have been marketed in the United States: the selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; venlafaxine, a serotonin-norepinephrine reuptake inhibitor; and bupropion, a selective norepinephrine and dopamine reuptake inhibitor. Recently available controlled-release formulations of newer antidepressants include bupropion sustained release (SR), fluoxetine weekly, paroxetine controlled release (CR), and venlafaxine extended release (XR). The pharmacokinetics of the antidepressant formulation determines the recommended drug dosage regimen and contributes to the onset and duration of therapeutic and adverse effects. For most categories of drugs including antidepressants, it is intuitive that a minimal amount of drug should be maintained in the body at all times to sustain pharmacologic effects.[1] The drug's half-life serves as a major guideline of how frequently a dose should be given to avoid a complete washout of the drug before the subsequent dose is administered. The rate at which the patient's gastrointestinal tract is exposed to drug after a dose, the peak plasma drug concentration, and the fluctuations in peak and trough plasma drug concentrations during chronic administration can influence whether and how severe adverse events such as nausea occur.

Controlled-release formulations of newer antidepressants should result in uniform medication release that potentially causes fewer short-term side effects than immediate-release (IR) formulations,[2,3] which generally release a greater initial amount of medication. One short-term side effect that might be affected by the formulation of the antidepressant is nausea.[4,5] Physicians might be able

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to reduce the occurrence of this adverse event and resulting discontinuations of antidepressant therapy by prescribing an antidepressant formulation with a different pharmacokinetic profile.

PHARMACOKINETICS OF IMMEDIATE-RELEASE VERSUS CONTROLLED-RELEASE FORMULATIONS

Compared with immediate-release formulations, controlled-release formulations can decrease the frequency of administration required to maintain therapeutically effective plasma drug levels. In addition, by producing more constant blood levels, such formulations can reduce the large changes in plasma levels observed between doses.

Clearance, Half-Lives, and Steady-State Plasma Drug Concentrations

When administered regularly, the newer antidepressants generally achieve steady-state plasma drug concentrations within 7 to 10 days after treatment is begun. Two major variables control the average steady-state plasma drug concentration: the total daily dose of medication and how effectively the patient's body removes the drug, as expressed by the value for drug clearance (Table 1).

Multiple sources of variability influence drug clearance: environmental factors such as the patient's concomitant medications, diet, and smoking habits and genetic factors such as the patient's metabolic phenotype.[8] Although not directly influencing hepatic clearance, factors related to the exposure of the gastrointestinal tract to the drug such as the area exposed and the length of exposure can influence the rate and extent of drug absorption.[9,10] In turn, these attributes will influence the rate of appearance of drug in plasma and the fluctuation between doses, even though hepatic clearance is the primary determinant of drug concentration at steady-state.[11] Although the physician needs to consider each of these factors when prescribing an antidepressant, most are beyond the clinician's control. The availability of different formulations, however, helps the physician control the area and length of exposure of the gastrointestinal tract to the drug.

How often a drug must be taken to sustain a minimal steady-state plasma concentration between doses is influenced by the elimination half-life. Some of the newer antidepressants such as bupropion,[6] fluvoxamine,[7] and venlafaxine[6] have half-lives around 12 hours or less, and others such as citalopram,[7] fluoxetine,[7] paroxetine,[7] and sertraline[7] have mean half-lives of at least 18 hours (see Table 1). For drugs with half-lives of 24 hours, about 50% of the amount of the drug in a patient's body will be removed and replaced each day if administered daily. Therefore, newer antidepressants with half-lives close to 24 hours might be given as infrequently as once a day. Newer antidepressants with shorter half-lives must generally be taken at least 2 or 3 times per day to maintain plasma drug concentration in the body above a threshold for therapeutic effects. When manufactured in controlled-release formulations, antidepressants with short half-lives may be taken less frequently.

Table 1. Clearance, Half-Lives, and Average Steady-State Plasma Drug Concentrations of Newer Antidepressants[a]

Drug	Clearance (L/h)	Half-Life		Average Steady-State Plasma Concentration (ng/mL)
		Mean (h)	Range (h)	
Bupropion	116–362	10	4–23	5–50
Citalopram	23–38	33	23–38	40–300
Fluoxetine	10–36	45	24–144	90–300
Fluvoxamine	33–220	15	9–28	20–500
Paroxetine	36–176	18	7–65	10–600
Sertraline	96	26	22–36	20–200
Venlafaxine	40–129	…	2–11	50–150

[a]Data from DeVane.[6,7]
Symbol: … = not available.

Peak and Trough Plasma Drug Concentrations

The peak plasma drug concentration can affect the tolerability of antidepressants, and this concentration can be affected by the rate at which medication is released into the gastrointestinal tract and absorbed into the blood. With controlled-release formulations, the time to peak plasma concentration is extended because the amount of drug released at once is not as high as it is with immediate-release formulations. In addition, with continuous daily dosing, the trough plasma drug concentration and the difference between peak and trough plasma drug concentrations should be decreased with sustained-release versus immediate-release formulations.

A theoretical advantage of a more uniform release of drug is reducing stimulation of the 5-HT_3 receptors in the upper gastrointestinal tract.[4] The use of controlled-release formulations of antidepressants that are designed to be dosed daily might minimize serotonergic or other neurotransmitter-related adverse events because of peak plasma drug concentrations that are lower than those associated with the use of immediate-release formulations, especially during the first 1 to 2 weeks of therapy when the drug accumulates in the body to steady state (Table 2).

According to venlafaxine XR prescribing information,[13] peak plasma concentrations are generally about 150 ng/mL for venlafaxine XR and 225 ng/mL for venlafaxine IR. Fluctuation between peak and trough concentrations is reported to be lower with venlafaxine XR than IR, although trough plasma concentrations are not given.

Peak plasma concentrations of bupropion IR, 100 mg b.i.d., have been examined in adult men and women.[14] The mean peak plasma drug concentration was lower among men than women (223 ± 16 versus 279 ± 22 ng · mL^{-1}) and the time to reach mean peak plasma drug concentration was longer among men than women (1.73 ± 0.07 versus 1.62 ± 0.10 hours), although these differences were not

Table 2. Peak Plasma Drug Concentration in Healthy Subjects Receiving Newer Antidepressants

Source	Drug	Dose	C_{max}	T_{max}, h
Démolis et al[12]	Sertraline	100 mg/d	21 ng · mL^{-1}	6
Effexor XR package insert[13]	Venlafaxine XR	150 mg/d	150 ng/mL	5.5
	Venlafaxine IR	75 mg bid	225 ng/mL	2
Findlay et al[14]	Bupropion IR	200 mg/d	223–279 ng · mL^{-1}	1.6–1.7
Paxil CR package insert[15]	Paroxetine CR	25 mg/d	30 ng/mL	…
Paxil package insert[16]	Paroxetine IR	30 mg/d	62 ng/mL	5.2
Prozac package insert[17]	Fluoxetine daily	40 mg/d	15–55 ng/mL	6–8
	Fluoxetine weekly[a]	90 mg/wk	…	…

[a]Reported to be bioequivalent to immediate-release formulation.
Abbreviations: C_{max} = peak plasma concentration, CR = controlled release, IR = immediate release, T_{max} = time to peak plasma concentration, XR = extended release. Symbol: … = not available.

significant. Data for trough plasma bupropion levels and fluctuation between peak and trough levels were not given. According to the package insert for bupropion SR,[18] 100 mg t.i.d. of bupropion IR and 150 mg b.i.d. of bupropion SR are nearly bioequivalent at steady state. The main difference in their pharmacokinetics is that bupropion SR was found to achieve peak plasma concentrations of about only 85% of those reached with bupropion IR.

In their prescribing information inserts, paroxetine CR is associated with lower peak and trough plasma concentrations (30 ng/mL and 20 ng/mL)[15] than is paroxetine IR (61.7 ng/mL and 30.7 ng/mL).[16] These concentrations reflect a smaller difference between peak and trough plasma concentrations with paroxetine CR.

Fluoxetine daily and fluoxetine weekly are bioequivalent.[17] However, fluoxetine weekly is associated with higher fluctuations between peak and trough plasma drug concentrations than is fluoxetine daily.[17] When 90 mg of fluoxetine weekly was given the day after 20 mg of fluoxetine daily, the peak plasma fluoxetine concentration was about 1.7 times higher with fluoxetine weekly than it was with an established regimen of 20 mg of fluoxetine daily. However, when doses of 20 mg of fluoxetine daily and 90 mg of fluoxetine weekly were separated by a week, the peak plasma concentrations of fluoxetine were similar for the 2 doses.[17]

NAUSEA WITH IMMEDIATE-RELEASE AND CONTROLLED-RELEASE FORMULATIONS

Although newer antidepressants are efficacious in reducing the symptoms of depression,[4,5,19–24] these agents can cause short-term side effects that interfere with patients' improvement. Additionally, some patients discontinue their drug treatment because they cannot tolerate the medication side effects. However, the occurrence of nausea, one of the most troublesome side effects, is reduced with some of the controlled-release formulations.

Incidence of Nausea

Short-term, controlled studies of the newer antidepressants have evaluated the frequency of nausea as an adverse event (Table 3). Generally, high doses of medication are more likely than lower doses to cause gastrointestinal discomfort. For example, exposure to the high peak plasma drug concentration that results from a single daily dose may be associated with an intolerable amount of nausea. The rate of medication release and the part of the gastrointestinal tract in which medication is released can also affect the incidence of nausea. The enteric coating of pellets of 90-mg fluoxetine weekly dissolves only when the capsule has reached an area of the gastrointestinal tract in which the pH is greater than 5.5.[24] Because of the delayed dissolution of fluoxetine weekly pellets, rates of nausea are similar for the 90-mg once-weekly and 20-mg once-daily formulations of fluoxetine, despite the 70-mg difference in dose. Similarly, the incidence of nausea is comparable between venlafaxine IR and XR formulations.[20]

However, with some newer antidepressants, nausea might be less common with the controlled-release formulations than the immediate-release formulations. Although no controlled trials have compared rates of nausea associated with immediate-release and sustained-release formulations of bupropion, comparing the incidence of nausea in trials[5,23] of each formulation suggests that bupropion SR is associated with less nausea.

Paroxetine CR has an enteric coating to delay the release of medication.[4] Paroxetine CR tablets begin to dissolve only after they have reached the small intestine. Paroxetine CR is meant to be taken once per day, the same recommendation given for the IR formulation. However, the initial starting dose of paroxetine CR, 12.5 mg, is lower than the recommended 20-mg dose for the IR formulation. Thus, the incidence of nausea is generally lower among patients taking paroxetine CR than among those taking paroxetine IR for multiple reasons, including a lower starting dose as well as specific formulation effects.

Nausea Leading to Medication Discontinuation

Reducing the incidence of short-term side effects such as nausea is important because these adverse events can cause some patients to discontinue treatment.[25] Some patients might discontinue treatment even before the antidepressant has reached steady state plasma concentration,

Table 3. Patients With Nausea in Controlled Trials of Newer Antidepressant Formulations

Study	Total N	Length of Treatment, wk	Drug	Patients With Nausea N	Patients With Nausea %
Burke et al[19]	491	8	Citalopram 40 mg/d	…	22
			Escitalopram 10 mg/d	…	21
			Escitalopram 20 mg/d	…	14
			Placebo	…	6
Cunningham et al[20]	293	12	Venlafaxine IR 37.5–75 mg bid	43	45
			Venlafaxine XR 75–150 mg/d	44	45
			Placebo	10	10
Fabre et al[21]	369	6	Sertraline 50 mg/d	21	22.1
			Sertraline 100 mg/d	33	35.9
			Sertraline 200 mg/d	40	44.0
			Placebo	14	15.4
Golden et al[4]	640	12	Paroxetine IR 20–50 mg/d	67	30.9
			Paroxetine CR 25–62.5 mg/d	50	23.6
			Placebo	30	14.2
Itil et al[22]	69	4	Fluvoxamine 50–209 mg/d[a]	7	31.8
			Imipramine 50–210 mg/d[a]	5	20.0
			Placebo	…	…
Wellbutrin PDR entry[23]	508	…	Bupropion IR 300–600 mg/d	…	22.9
			Placebo	…	18.9
Reimherr et al[5]	353	8	Bupropion SR 150 mg/d	…	9.2
			Bupropion SR 300 mg/d	…	10.3
			Placebo	…	6.0
Schmidt et al[24]	501	25	Fluoxetine daily 20 mg	8	4.2
			Fluoxetine weekly 90 mg	12	6.3
			Placebo	9	7.4

[a]Doses above 50 mg could be given in divided dose over the day.
Abbreviations: CR = controlled release, IR = immediate release, SR = sustained release, XR = extended release. Symbol: … = not available.

and others might tolerate nausea for a while and then discontinue treatment regardless of the degree of improvement in their depressive symptoms. In a study of reasons for discontinuing or switching SSRI treatment, Bull et al.[25] found that 98 (43.4%) of the 226 patients who discontinued or switched treatment within 3 months said they ended treatment early primarily because of adverse events. Nausea was the primary reason for discontinuation given by 12 (5.3%) of the 226 patients and the secondary reason given by 29 patients (12.8%).

In a placebo-controlled trial[21] of sertraline treatment, nausea and tremor were the most common adverse events that patients said led to their discontinuation, although percentages were not given. According to the combined results[26] of several placebo-controlled trials in mood and anxiety disorders, 3% of patients treated with sertraline experienced nausea that led to treatment discontinuation. In placebo-controlled trials of citalopram lasting 6 weeks or less, 4% of patients taking citalopram and none of the patients taking placebo discontinued treatment because of nausea.[27] The rate of discontinuation because of nausea was 2% for escitalopram, the *S*-enantiomer of citalopram, in placebo-controlled trials.[28] In a 4-week, double-blind, placebo-controlled trial,[22] 3 patients (13.6%) in the fluvoxamine group and no patients in the placebo group discontinued treatment because of nausea. The number of patients in the imipramine group who discontinued was not given.

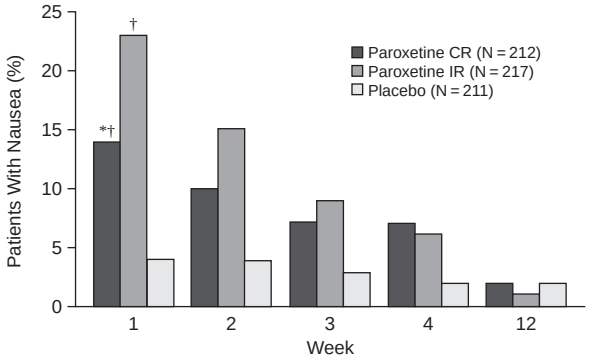
In outpatients with major depression, Cunningham and coworkers[20] reported that 13% in a venlafaxine IR group compared with 11% in a venlafaxine XR group and 2% in a placebo group discontinued treatment because of an adverse event such as asthenia, dizziness, insomnia, nausea, or nervousness. Golden et al.[4] found that the percentage of patients who discontinued treatment because of nausea was lower among patients receiving paroxetine CR (3%) and placebo (0.5%) compared with a group of patients receiving paroxetine IR (4%).

The difference in the incidence of nausea leading to discontinuation with bupropion formulations has not been compared in a single trial. According to prescribing information, the rates of discontinuation because of nausea were 0.8% to 1.8% with bupropion SR[18] and 2.1% with bupropion IR.[23]

Direct comparisons of the rates of discontinuations because of nausea with fluoxetine weekly and fluoxetine daily are also not available. In a meta-analysis of clinical trials[29] that measured multiple adverse events leading to discontinuation with fluoxetine daily, 2.5% of fluoxetine-treated patients and 0.8% of placebo-treated patients discontinued treatment because of nausea. Because rates of nausea are comparable among patients taking fluoxetine daily and those taking fluoxetine weekly,[24] the rate of discontinuation due to nausea might be similar among patients treated with either formulation.

Nausea seems to lead to more discontinuations during the beginning of any antidepressant treatment, as the incidence of nausea seems to decrease over time. Bull et al.[25] found that, compared with patients who stopped taking

Figure 1. Rates of Nausea During the First 12 Weeks of Treatment With Paroxetine CR, Paroxetine IR, and Placebo[a]



[a]Reprinted with permission from Golden et al.[4]
*p ≤ .05 vs. paroxetine IR.
†p ≤ .05 vs. placebo.
Abbreviations: CR = controlled release, IR = immediate release.

their SSRI within 3 months, fewer patients who discontinued treatment after 4 to 6 months said nausea was one of the reasons they ended treatment. Of the 62 patients who discontinued after 4 to 6 months, only 4.8% (N = 3) gave nausea as their primary reason and 9.7% (N = 6) as their secondary reason for discontinuing treatment, compared with 5.3% and 12.8%, respectively, in the group who discontinued treatment within 3 months.

Most antidepressant studies do not provide rates of nausea leading to discontinuation at different time points. However, some studies of the newer antidepressants do provide the incidence of all nausea over time. The assumption could be made that as the incidence of nausea decreased over the length of the study, rates of nausea leading to discontinuation also decreased. During the Cunningham study,[20] a total of 45% of the patients in each venlafaxine group experienced nausea at some point in the study. However, when the incidence of nausea was analyzed by week, nausea was highest during the first week, when reported by 27% of patients in the venlafaxine XR group and 37% in the venlafaxine IR group. By the second week, the percentage of patients reporting nausea in either group was only 12%. In the Golden et al. study,[4] the incidence of nausea during the first week was significantly ($p \leq .05$) lower with paroxetine CR (14%) than with paroxetine IR (23%) and greater with both formulations of paroxetine than with placebo (4%). During the second through twelfth weeks, the incidence of nausea in all groups decreased, and there were no significant differences among them (Figure 1).

CONCLUSION

The pharmacokinetics of newer antidepressants influences the tolerability of these medications. Some of these antidepressants have characteristics that make the drugs suitable for controlled-release formulations, which might have advantages over immediate-release formulations. For example, controlled-release formulations are associated with lower peak plasma drug concentrations and less fluctuation between peak and trough plasma drug concentrations. In addition to having more stable pharmacokinetic profiles, some controlled-release formulations are associated with lower incidences of nausea than are immediate-release formulations of the same medications. Therefore, some patients who experience intolerable nausea with an immediate-release formulation despite seeing improvement in their depressive symptoms might benefit from taking a controlled-release formulation of the same antidepressant or switching to another of the newer antidepressants. The serious morbidity associated with untreated or inadequately treated depression implies that major benefits may occur in the quality of life for patients who can be salvaged from discontinuing therapy with the use of the most tolerable drug formulations.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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