Citalopram Therapy for Depression: A Review of 10 Years of European Experience and Data From U.S. Clinical Trials

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Background: This review summarizes and evaluates clinical experience with citalopram, the latest selective serotonin reuptake inhibitor (SSRI) to be approved for the treatment of depression in the United States.

Data Sources: Published reports of randomized, double-blind, controlled clinical studies of citalopram were retrieved using a MEDLINE literature search. Search terms included *citalopram, SSRI, TCA* (tricyclic antidepressant), *depression,* and *clinical*. For each study, data on antidepressant efficacy and adverse events were evaluated. Pharmacokinetic studies and case reports were reviewed to supplement the evaluation of citalopram's safety and tolerability. Data presented at major medical conferences and published in abstract form also were reviewed.

Study Findings: Thirty randomized, double-blind, controlled studies of the antidepressant efficacy of citalopram were located and reviewed. In 11 studies, citalopram was compared with placebo (1 of these studies also included comparison with another SSRI). In 4 additional studies, the efficacy of citalopram in preventing depression relapse or recurrence was investigated. In another 11 studies (including 1 meta-analysis of published and unpublished trials), citalopram was compared with tricyclic and tetracyclic antidepressants. Finally, results are available from 4 studies in which citalopram was compared with other SSRIs. A placebo-controlled study of citalopram for the treatment of panic disorder was reviewed for data on long-term adverse events.

Conclusion: Data published over the last decade suggest that citalopram is (1) superior to placebo in the treatment of depression, (2) has efficacy similar to that of the tricyclic and tetracyclic antidepressants and to other SSRIs, and (3) is safe and well tolerated in the therapeutic dose range of 20 to 60 mg/day. Distinct from some other agents in its class, citalopram exhibits linear pharmacokinetics and minimal drug interaction potential. These features make citalopram an attractive agent for the treatment of depression, especially among the elderly and patients with comorbid illness.

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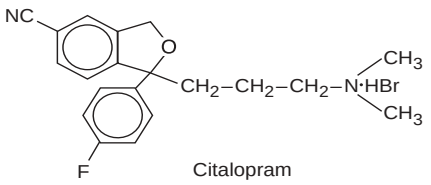
Over the past decade, selective serotonin reuptake inhibitors (SSRIs) have dramatically altered the pharmacotherapy of depression. Generally equivalent to tricyclic antidepressants (TCAs) in terms of efficacy, SSRIs also possess several characteristics that distinguish them from their predecessors. First, they have a higher therapeutic index than the TCAs; that is, relatively small increases in dose/plasma levels do not lead to toxicity. Second, SSRIs have minimal cardiac side effects and produce fewer and less pronounced anticholinergic effects. Thus, they are substantially safer (both in normal situations and in overdose) and more easily tolerated than TCAs. Better tolerability increases patient compliance, which is critical for successful therapy, since depression often relapses if treatment is discontinued prematurely.[1] These advantages over TCAs largely account for the current status of SSRIs as first-line drugs of choice for the treatment of depression.

Although related by mechanism of action, SSRIs differ from each other structurally, pharmacodynamically (in potency and selectivity) and pharmacokinetically (in half-life, metabolite activity, and cytochrome P450 enzyme inhibition). Such differences may explain the clinical observation that one SSRI may be more effective than another in a subset of patients. Likewise, one SSRI may be more suitable than another under certain circumstances, for example, if a patient is elderly or is taking multiple medications.

Figure 1. The Chemical Structure of Citalopram



Citalopram

Table 1. Potency and Selectivity of Selective Serotonin Reuptake Inhibitors for Inhibition of Serotonin (5-HT) Uptake[a]

Agent	5-HT	NE	DA	5-HT Selectivity[b]
Citalopram	1.80	6100	40,000	3400
Fluoxetine	6.80	370	5000	54
Fluvoxamine	3.80	620	42,000	160
Paroxetine	0.29	81	5100	280
Sertraline	0.19	160	48	840

[a]Data from Hyttel et al.[2] Abbreviations: DA = dopamine, NE = norepinephrine. Potency given as IC_{50} values in nM.
[b]NE/5-HT.

Citalopram, the most recent SSRI to be approved for the treatment of depression in the United States, is a bicyclic phthalane derivative with a chemical structure distinct from that of any other antidepressant agent (Figure 1). The most selective of the SSRIs approved to date, citalopram inhibits the uptake of serotonin (5-HT) 3400 times more potently than that of norepinephrine (NE) and 22,000 times more potently than that of dopamine (Table 1).[2] In addition, citalopram has little or no affinity for acetylcholine, histamine, norepinephrine, dopamine, γ-aminobutyric acid (GABA), or opiate receptors.[2] The metabolites of citalopram show selectivity similar to that of the parent drug, although they are less potent inhibitors of serotonin reuptake and are present in plasma at concentrations one third and one tenth that of the parent compound.[3] Thus, citalopram's metabolites do not appear to contribute to the overall clinical effect.[4]

Citalopram has a favorable pharmacokinetic profile, exhibiting high bioavailability, linear pharmacokinetics, and relatively low protein binding.[5] With a plasma half-life of 35 hours, citalopram can be administered once daily. Unlike fluoxetine and paroxetine, citalopram does not inhibit its own metabolism. Metabolites of citalopram also have no effect on the metabolism of the parent compound.[5] Thus, citalopram does not accumulate in the body. In addition, citalopram has minimal effects on the cytochrome P450 isoenzyme system and is generally safe to coadminister with other medications.[6–8]

Although approved in the United States relatively recently, citalopram has been prescribed to more than 20 million patients in over 70 countries since its introduction in Europe in 1989. This article reviews over a decade of experience with citalopram, focusing mainly on efficacy, safety, and tolerability data derived from randomized, well-controlled clinical trials among patients with depression.

DATA SOURCES

A MEDLINE computerized literature search (1966–2000) was conducted to identify English-language articles describing randomized, double-blind, controlled clinical studies of citalopram among depressed patients. Search terms included *citalopram*, *SSRI*, *TCA*, *depression*, and *clinical*. For each study, data on antidepressant efficacy and adverse events were evaluated. Pharmacokinetic studies and case reports were reviewed to supplement the evaluation of citalopram's safety and tolerability. Published bibliographies were cross-referenced to locate additional primary sources of information. Data presented at major medical conferences and published in abstract form also were reviewed.

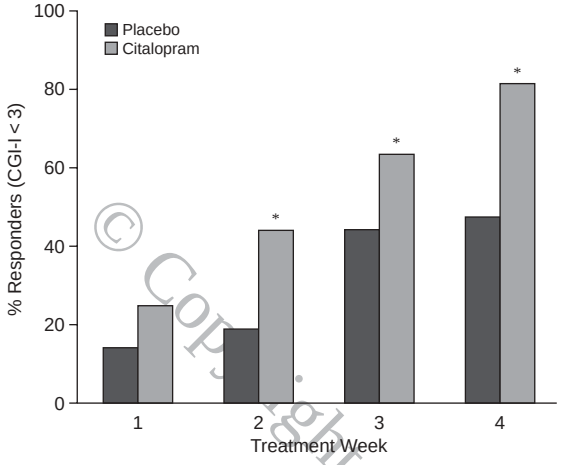
OVERVIEW OF TRIALS

Results from 30 randomized, double-blind clinical trials with citalopram in the treatment of depression have been published and/or presented at major medical conferences. Most of the trials enrolled patients with moderate-to-severe major depression, as defined by DSM-III, DSM-III-R, or DSM-IV; however, some studies also included patients with bipolar disorder or melancholia.[9] The average age of participants in the clinical trials was around 40 years. Some studies included geriatric patients, and 3 exclusively enrolled patients above the age of 60 years.[10–12] Universal exclusion criteria included psychotic disorders, drug abuse, concomitant psychotropic medication, abnormal laboratory values, or medical conditions precluding the use of any of the trial medications. In all studies, citalopram was administered as a once-daily dose either in the morning or at bedtime. All patients receiving at least 1 tablet and having at least 1 postbaseline measurement constituted the intention-to-treat (ITT) population.

The primary efficacy measures used in the trials were the Hamilton Rating Scale for Depression (HAM-D) and/or the Montgomery-Asberg Depression Rating Scale (MADRS). Most patients had a HAM-D score of ≥ 18 or a MADRS score of ≥ 22 at baseline. The rating scales most commonly employed were the HAM-D (and subscales composed of selected items from the HAM-D), the MADRS, and the Clinical Global Impressions-Improvement scale (CGI-I). In most cases, more than 1 rating instrument was used. Responders were assessed using the conventional 50% reduction from baseline rating scale score[13,14] or a CGI-I score of 1 or 2.

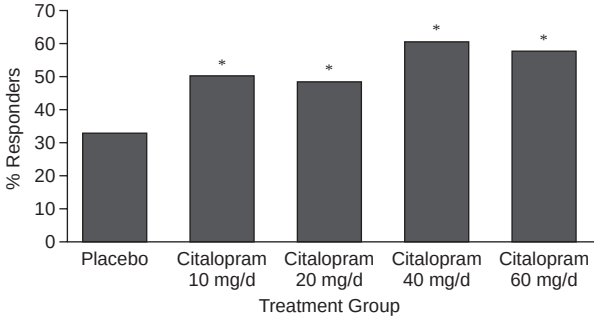
Reports of adverse events were assembled using a variety of means, including specific symptom checklists, the

Figure 2. Percentage of Responders on the Clinical Global Impressions-Improvement (CGI-I) Scale in a Flexible-Dose Study of Patients Treated With Citalopram[a]



[a]Adapted from Mendels et al.,[9] with permission. The responder criterion was a CGI-I score of 1 (very much improved) or 2 (much improved).
*Significantly improved from placebo, p < .05.

Figure 3. Percentage of MADRS Responders (≥ 50% Reduction From Baseline) in a Fixed-Dose Study of Patients Treated With Citalopram[a]



[a]Adapted from Feighner and Overø,[16] with permission. Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.
*Significantly different from placebo, p < .05.

open-question technique, and spontaneous reportage and investigator observation. All adverse events were reported according to World Health Organization adverse reaction terminology. All tolerability assessments were done in the ITT population.

ANTIDEPRESSANT EFFICACY

Antidepressant Efficacy Versus Placebo

The efficacy of citalopram has been established in 11 placebo-controlled studies. Five of these studies have been published independently.[9,10,15–17] The other studies were published as part of a meta-analysis.[18] Three large multicenter trials have been conducted in the United States.[9,15,16] One of the large U.S. studies[9] (a 4-week trial) compared a flexible daily dose of 20 to 80 mg of citalopram with placebo among 180 patients with major depression and melancholia. Patients receiving citalopram showed a significant improvement compared with those receiving placebo based on both HAM-D and CGI scores. A statistically significant ($p < .05$) improvement in the citalopram group compared with the placebo group in HAM-D score was observed by the end of week 1, which may be a result of the very rapid upward titration to a relatively high dose of citalopram per the study's protocol. Among patients who completed the trial, the response rate (CGI-I score of 1 or 2) was 81% for the citalopram group versus 47% for the placebo group at the end of 4 weeks ($p < .05$) (Figure 2).

The second large U.S. study[15] included 650 patients with moderate-to-severe major depression who were randomly assigned to a fixed dose of 10, 20, 40, or 60 mg of citalopram or placebo for 6 weeks. Across all doses studied, citalopram was significantly more efficacious than placebo ($p < .05$) on the basis of reductions in the total HAM-D score, the MADRS score, the CGI-Severity of Illness (CGI-S) rating, and the CGI-I rating. Statistically significant improvement of HAM-D depressed mood item scores was observed in all 4 dose groups of citalopram ($p < .01$), and the response rate was significantly greater for all 4 citalopram-treated groups than for placebo (Figure 3). An ITT analysis of data indicated that more citalopram-treated than placebo-treated patients were free of significant depressive symptoms at trial's end.

More recently, a third large multicenter trial with citalopram[16] has been completed in the United States. This was a placebo-controlled comparison of citalopram (20–60 mg/day) and sertraline (50–150 mg/day) in 323 patients with DSM-IV–defined major depressive disorder.[16] At endpoint, both active treatments produced significantly greater improvement than placebo on the HAM-D ($p < .05$), the MADRS ($p < .01$), the CGI-S ($p < .05$) and the CGI-I ($p < .05$). Improvement was observed at earlier timepoints with citalopram than with sertraline. Antianxiety effects were also associated only with citalopram therapy.

Meta-analyses conducted on results of published and unpublished placebo-controlled trials with citalopram have generated results consistent with those seen in the multicenter U.S. placebo-controlled trials. In an early meta-analysis[19] of 5 short-term placebo-controlled studies involving a total of 396 patients, citalopram, at doses from 20 to 80 mg/day, was significantly more effective than placebo in reducing depression according to both the completer and the efficacy (ITT) analysis (an 18% advantage and a 15% advantage for citalopram, respectively; $p < .05$ for both comparisons). A second meta-analysis[18] involving 949 patients from 9 separate trials showed that citalopram,

at doses of both 20 mg/day and 40 mg/day, produced significantly greater improvement than that seen with placebo. Finally, a more recent meta-analysis[20] involving more than 1400 patients from 5 placebo-controlled studies revealed that citalopram produced a significant reduction in depressive symptoms as measured by the HAM-D, the MADRS, and the CGI-S.

In a 6-week placebo-controlled trial[10] involving 149 depressed elderly patients with and without dementia, 60% of patients randomly assigned to citalopram, 20 to 30 mg, significantly improved (versus 24% with placebo) at trial's end as measured by the CGI-I ($p < .001$). Mean reduction in HAM-D scores from baseline also favored citalopram (9.9 vs. 5.1 for placebo, $p < .01$). Similar results were obtained in the MADRS assessment. Interestingly, several individual items on the Gottfries-Brane-Steen scale of cognitive function (a rating scale used to assess mental function in the elderly) improved significantly at endpoint ($p < .05$) among citalopram-treated patients with concomitant dementia.

Efficacy of Citalopram Versus Placebo in the Prevention of Relapse and Recurrence

Prevention of relapse. More than 50% of patients who respond to acute antidepressant therapy experience a relapse, that is, a return of symptoms from the current episode of depression, after early discontinuation of treatment.[1] Data from several placebo-controlled trials suggest that all antidepressant treatment should be maintained for a minimum of 4 to 6 months to prevent relapse and that the established effective dose should be employed for continuation therapy.[1]

Two placebo-controlled studies[21,22] demonstrated the efficacy of citalopram as a continuation therapy for prevention of depression relapse. In the first,[21] 147 patients who responded to citalopram (MADRS score ≤ 12) during an acute 6-week treatment period were randomly assigned to either placebo or citalopram (fixed daily doses of either 20 mg or 40 mg) and continued to receive therapy at the same dose level for 24 weeks. At the end of the trial, rates of relapse (defined by a threshold MADRS score of 22) were 8% and 12% with citalopram, 20 and 40 mg, respectively, and 31% with placebo ($p < .05$).[21]

In the second continuation study,[22] 216 patients who responded to citalopram (flexible daily doses of 20–60 mg) during an 8-week initial treatment phase were randomly assigned to placebo or citalopram for an additional 24-week period of therapy. Although the rate of relapse (defined as a threshold MADRS score of 25) was generally low (14% for patients treated with citalopram compared with 24% for patients treated with placebo), the difference between groups was significant ($p = .04$, Kaplan-Meier survival analysis).

Prevention of recurrence. Depression is frequently a recurring disorder. Sixty percent of recovered patients experience another depressive episode after 5 years, 75% after 10 years, and 87% after 15 years.[23] Furthermore, the risk of recurrence increases with the number of prior episodes; patients who have suffered 3 or more bouts of depression have a 95% chance of experiencing an additional episode.[23] Thus, some patients must be maintained on antidepressant treatment indefinitely.

Two placebo-controlled studies[12,24] have specifically addressed the efficacy of citalopram in preventing recurrence of depression. The first study[24] was conducted in 427 patients aged 18 to 65 years with a history of at least 2 prior depressive episodes. After 6 to 9 weeks of acute open treatment with citalopram (a flexible dose of 20–60 mg/day), responders (N = 327), defined by a total score < 12 on the MADRS, received 16 weeks of continuation treatment at their established effective dose. Patients who continued to respond (N = 269) were randomly assigned to 48 weeks or longer of double-blind treatment with either continued citalopram or placebo. Eighty percent of citalopram-treated patients remained free of recurrence (defined as a MADRS total score ≥ 22) throughout the maintenance phase of the study, compared with 50% of patients assigned to placebo ($p < .0001$). In the second study,[12] with a similar design, citalopram was shown to be effective in the prevention of depression recurrence in patients aged 65 years and older.

Comparative Efficacy of Citalopram Versus Tricyclic and Tetracyclic Antidepressants

Ten double-blind trials[11,25–27,31–36] comparing citalopram with TCAs or tetracyclic antidepressants have been published as independent studies to date (Table 2). The results of 2 additional trials—one comparing the efficacy of citalopram with nortriptyline and the other comparing citalopram with amitriptyline—were analyzed in a retrospective study by Bech and Cialdella,[19] which is reviewed at the end of this section.

Amitriptyline. In 2 randomized, double-blind, 6-week trials,[25,26] citalopram (20–60 mg/day) and amitriptyline (75–225 mg/day) were similarly efficacious among patients with major depression (N = 43 and N = 44). In a third trial,[11] citalopram (20–40 mg/day) was compared with amitriptyline (50–100 mg/day) among 365 elderly depressed patients (age > 65 years) in an 8-week, double-blind trial. Among the 265 patients (citalopram, N = 135; amitriptyline, N = 130) who completed the study, mean reduction in MADRS scores from baseline was similar in both groups. Response rate (defined as MADRS total score < 12) was almost identical in both groups (around 50%).

Clomipramine. Unlike the results obtained in the above studies, citalopram, 40 mg/day, was less effective than the tricyclic antidepressant clomipramine (150 mg/day) in a 5-week study of 102 depressed inpatients.[27] The rate of complete recovery (HAM-D score ≤ 7) was 60% in the

Table 2. Citalopram Versus Tricyclic and Tetracyclic Antidepressants in Depression[a]

Study	Patient Type and Age	Duration, wk	No. of Evaluable Patients[b]	Daily Dose, mg	Assessment Method	Concomitant Medicine	Results	Comments
Citalopram vs amitriptyline								
Gravem et al, 1987[26]	Inpatients and outpatients, age 19–74 y	6	Citalopram, 23 Amitriptyline, 20	Citalopram, 20–60 Amitriptyline, 75–225	MADRS	Benzodiazepines used for insomnia	Citalopram = Amitriptyline	Better effect on sleep disturbances in the amitriptyline group at weeks 1 and 3; more frequent side effects in the amitriptyline group
Shaw et al, 1986[25]	Inpatients and outpatients, age 18–70 y	6	Citalopram, 24 Amitriptyline, 20	Citalopram, 20–60 Amitriptyline, 75–225	HAM-D, MADRS	Diazepam and temazepam	Citalopram = Amitriptyline	Reported side effects much more common in the amitriptyline group
Kyle et al, 1998[11]	General practice, age > 65 y	8	Citalopram, 179 Amitriptyline, 186	Citalopram, 20–40 Amitriptyline, 50–100	MADRS, HAM-D, CGI	Not specified	Citalopram = Amitriptyline	Greater incidence of side effects and higher rate of discontinuations with amitriptyline than with citalopram
Citalopram vs clomipramine								
Danish University Antidepressant Group, 1986[27]	Mainly inpatients, age 18–65 y	5	Citalopram, 50 Clomipramine, 52	Citalopram, 40 Clomipramine, 150	HAM-D	Oxazepam, nitrazepam as a sedative	Clomipramine > Citalopram	Clomipramine had a better effect on sleep disturbances; citalopram was better tolerated than clomipramine
Citalopram vs imipramine								
Rosenberg et al, 1994[31]	General practice, age 18–65 y	6	Citalopram(a), 165 Citalopram(b), 163 Imipramine, 85	Citalopram(a), 10–30 Citalopram(b), 20–60 Imipramine, 50–150	HAM-D, CGI	Benzodiazepines or sedative antihistamines	Citalopram = Imipramine	Citalopram = Imipramine even in those patients who continued treatment to 22 weeks; high anticholinergic effects with imipramine
Citalopram vs maprotiline								
Bouchard et al, 1987[33]	Age 20–76 y	6	Citalopram, 46 Maprotiline, 44	Citalopram, 40–60 Maprotiline, 75–150	MADRS, CGI	Benzodiazepines	Citalopram = Maprotiline	Side effect profile similar in the 2 treatment groups
Timmerman et al, 1987[32]	Inpatients, age 30–63 y	4	Citalopram, 14 Maprotiline, 15	Citalopram, 40–60 Maprotiline, 75–150	HAM-D	Benzodiazepines	Citalopram = Maprotiline	Anticholinergic side effects more common in patients receiving maprotiline
Citalopram vs mianserin								
Ahlfors et al, 1988[35]	Inpatients, age 18–70 y	6	Citalopram, 28 Mianserin, 28	Citalopram, 40–60 Mianserin, 60–90	MADRS, CGI	Benzodiazepines	Citalopram = Mianserin in endogenous depression	In nonendogenous depression, mianserin was more effective than citalopram
de Wilde et al, 1985[34]	Inpatients, age 18–70 y	6	Citalopram, 29 Mianserin, 29	Citalopram, 40–80 Mianserin, 60–120	MADRS, CGI	Benzodiazepines	Citalopram = Mianserin	Trend toward more complete responders in citalopram group
Karlsson et al, 2000[36]	Inpatients and outpatients, age ≥ 65 y	12	Citalopram, 157 Mianserin, 163	Citalopram, 20–40 Mianserin, 30–60	MADRS	Benzodiazepines and/or other hypnotics	Citalopram = Mianserin	Fatigue and somnolence were more frequent with mianserin; insomnia was more frequent with citalopram

[a]Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]Evaluable patients = number of patients included in the efficacy analysis or intention-to-treat population (last observation carried forward to study endpoint).

clomipramine group (N = 52) and 30% in the citalopram group (N = 50) ($p < .005$). However, when compared for both complete and partial (HAM-D score ≤ 15) recovery, the response rates were similar (72% for citalopram vs. 75% for clomipramine).

The findings of this study[27] are qualitatively similar to those of a clinical comparison of paroxetine and clomipramine among psychiatric inpatients,[28] which, taken together, have contributed to the clinical impression that SSRIs are less effective than TCAs for severe depression.[29] It has been suggested that the early head-to-head SSRI-TCA trials may have been confounded by differences in side effect profiles (i.e., the pronounced sedation associated with TCAs, but not with SSRIs, may have contributed to the appearance of superior efficacy).[29,30] Although the efficacy of SSRIs versus TCAs for severe depression remains controversial, data from 2 placebo-controlled trials suggest[9,16] that citalopram is effective among patients with melancholia or severe symptoms of depression.

Imipramine. Two trials[19,31] have compared the efficacy of citalopram with that of imipramine. The first was analyzed retrospectively by Bech and Cialdella (and is discussed below).[19] The second, a multicenter study[31] conducted among more than 400 depressed patients in general practice (age range, 18–65 years), found that patients receiving citalopram, 10–30 mg/day; citalopram, 20–60 mg/day; or imipramine, 50–150 mg/day, experienced similar reductions in HAM-D scores at the end of week 6 (primary endpoint) and at week 22 (continuation phase). Response rates were similar in all treatment groups: 64%, 60%, and 58% at week 6 in the citalopram, 10–30 mg; citalopram, 20–60 mg; and imipramine groups, respectively; 82%, 87%, and 89% at week 22 for citalopram, 10–30 mg; citalopram, 20–60 mg; and imipramine, 50–150 mg, respectively.

Maprotiline. Two double-blind comparative trials[32,33] concluded that citalopram was as effective as the tetracyclic antidepressant maprotiline. In a small trial[32] (N = 29, all women, aged 30–63 years) conducted in a hospital setting, both citalopram, 40–60 mg/day, and maprotiline, 75–150 mg/day, resulted in significant improvement as measured by reduction in HAM-D total scores from baseline after 2 and 4 weeks of treatment ($p < .01$). Similarly, in a larger study[33] involving 90 depressed patients, citalopram, 40–60 mg, was as effective as maprotiline, 75–150 mg, in reducing MADRS total scores and CGI scores from baseline.

Mianserin. Varied results were reported from 2 small studies (N = 58 and N = 65)[34,35] comparing the efficacy of citalopram with that of mianserin among patients with depression. In one of these,[34] citalopram appeared to produce a more rapid onset of effect as measured by both the MADRS and the CGI score. In the other study,[35] citalopram (40–60 mg/day) and mianserin (60–90 mg/day) were equally effective in patients with endogenous depression, but mianserin was more effective among nonendogenously depressed patients.

In a recent study, Karlsson et al.[36] compared the efficacy and tolerability of citalopram, 20–40 mg/day, and mianserin, 30–60 mg/day, among 345 elderly, depressed patients with or without dementia. After 12 weeks, patients randomly assigned to either drug improved to a similar extent as measured by changes in the MADRS total score.

Tricyclics: a meta-analysis. Bech and Cialdella[19] retrospectively analyzed 5 published[25,26] and unpublished comparative trials involving a total of 294 patients. The reference TCAs compared with citalopram, 30–60 mg/day, included amitriptyline in the dose range of 75–225 mg/day (reference 25 and unpublished data), clomipramine, 150 mg/day[27]; nortriptyline, 50–125 mg/day (unpublished data); and imipramine, 100–150 mg/day (unpublished data). Based on a 50% reduction in HAM-D total scores, the efficacy of citalopram was similar to that of TCAs.

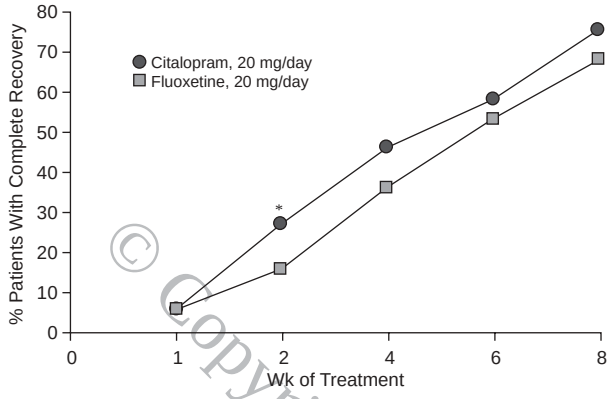
Comparative Efficacy of Citalopram Versus Other SSRIs

Four published studies[37–40] comparing the efficacy of citalopram with other SSRIs, including fluoxetine, sertraline, and fluvoxamine, are described below.

Fluoxetine. The efficacy of citalopram has been compared with that of fluoxetine in two 8-week trials among psychiatric patients[38] and among patients from general medical practice.[37] In the psychiatrist-based trial,[38] citalopram, 40 mg (N = 147), and fluoxetine, 20 mg (N = 149), were equally efficacious as measured by reductions in MADRS scores. Results from HAM-D and CGI-S assessments also indicated equivalent efficacy for both drugs. In severely depressed patients with HAM-D scores ≥ 25 (citalopram, N = 43; fluoxetine, N = 53), 16% of the citalopram-treated patients recovered (HAM-D score ≤ 7) after 2 weeks compared with none in the fluoxetine group ($p = .003$).

Similar outcomes were observed in the general medical practice setting.[37] Among the 314 patients (153 in the citalopram group, 161 in the fluoxetine group) included in the efficacy analysis, no significant differences were found between groups in the decrease in mean total MADRS scores from baseline to endpoint. However, in a subpopulation of patients not receiving benzodiazepines, the mean reduction in total MADRS scores favored citalopram at the end of weeks 2 ($p = .018$), 4 ($p < .001$), 6 ($p = .006$), and 8 ($p = .03$). While the response rate at week 8 was similar in both groups (78% in the citalopram group vs. 76% in the fluoxetine group), the response rate after 2 weeks was significantly higher in the citalopram group (35%) compared with the fluoxetine group (24%; $p = .049$). Similarly, complete recovery, defined as MADRS total score ≤ 12, was greater in the citalopram group at 2 weeks (27% vs. 16%; $p = .034$) (Figure 4).

Figure 4. Citalopram Versus Fluoxetine: Patients With Complete Recovery[a]



[a]Data from Patris et al.[37] Recovery defined as a Montgomery-Asberg Depression Rating Scale score ≤ 12.
*Significantly different from fluoxetine ($p < .05$).

Sertraline. The efficacy of citalopram (20–60 mg/day) was compared with that of sertraline (50–150 mg/day) in 308 patients with major depression in general practice in a 24-week, double-blind, multicenter trial.[39] A meaningful reduction in the total MADRS scores (the primary efficacy measure) was observed in both treatment groups as early as week 2. In the ITT population, the response rate at week 24 was 76% in the sertraline group and 81% in the citalopram group. Among patients who completed the trial, the response rates at week 24 were 90% and 93% in the sertraline and citalopram groups, respectively.

Citalopram also was compared with sertraline in a multicenter, placebo-controlled study[17] in 323 patients with DSM-IV–defined major depressive disorder. Results from this investigation are summarized in the section on antidepressant efficacy versus placebo (see above).

Fluvoxamine. A 6-week, double-blind, multicenter study[40] compared the efficacy of citalopram (20–40 mg/day) with that of fluvoxamine (100–200 mg/day) in 217 outpatients with depression. Complete plus partial response rates (based on HAM-D scores) were 42% and 39% in the citalopram and fluvoxamine groups, respectively. CGI and Zung self-rating depression scales provided similar results with regard to efficacy. The low overall response rate observed in this study was attributed to the inclusion of patients with long-standing depression that had been unsuccessfully treated with other antidepressants prior to the trial.

SAFETY AND TOLERABILITY

General Tolerability Profile

Adverse events in short-term, placebo-controlled trials. The adverse events that occur more frequently (> 5%) in patients treated with citalopram than in patients treated with placebo are somnolence, nausea, and dry mouth (Table 3). Compared with placebo, citalopram does not appear to produce clinically significant central nervous system (CNS) stimulant side effects (insomnia, tremor, anxiety, and agitation).

Table 3. Treatment-Emergent Adverse Events That Occurred With Greater Frequency in Citalopram-Treated Patients in Short-Term, Placebo-Controlled Studies (%)[a]

Adverse Event	Citalopram (N = 1063)	Placebo (N = 446)
Dry mouth	20	14
Increased sweating	11	9
Tremor	8	6
Nausea	21	14
Diarrhea	8	5
Fatigue	5	3
Abdominal pain	3	2
Somnolence	18	10
Insomnia	15	14
Anxiety	4	3
Anorexia	4	2
Decreased libido	2	< 1
Agitation	3	1
Upper respiratory tract infection	5	4
Rhinitis	5	3
Ejaculation disorder[b,c]	6	1
Impotence[b]	3	< 1

[a]Data from Mendels et al.,[9] Feighner and Overø,[15] and Montgomery et al.[17,18]
[b]Rates are based on 425 citalopram-treated male patients and 194 placebo-treated male patients.
[c]Ejaculation disorder includes ejaculatory delay and ejaculatory failure.

Long-term tolerability. Among patients enrolled in a 6-month continuation study, citalopram and placebo produced side effects of similar frequency and severity at 12 and 24 weeks.[21] In a recently published 12-month continuation study of citalopram (N = 177) versus placebo (N = 41) for the treatment of panic disorder,[41] the only adverse event that occurred more frequently among patients receiving active treatment was increased sweating ($p = .03$). In addition, some early side effects, such as anorgasmia, disappeared over time.[42] These data indicate that the frequency and severity of adverse symptoms remain relatively constant or, in some cases, decrease, during long-term treatment with citalopram.

Sexual side effects. Although it is well-known that potent serotonin reuptake inhibitors (SSRIs and venlafaxine) are associated with sexual side effects such as anorgasmia and ejaculatory delay, the treatment-emergent incidence of sexual dysfunction among patients taking antidepressants is difficult to estimate owing to inconsistencies in methods of reportage. A recent randomized, double-blind study by Waldinger et al.[43] suggested that citalopram may be associated with less pronounced sexual side effects than some other SSRIs. In that study, which measured the influence of antidepressant therapy on ejaculation latency time among 23 male subjects with a history of rapid ejaculation, citalopram produced significantly less delay in ejaculation than did paroxetine (44

seconds vs. 170 seconds; p = .0004). Other studies have shown that the ejaculatory delay produced by paroxetine is similar to that produced by fluoxetine and sertraline.[44] The applicability of these findings to patients receiving SSRI therapy for depression is unclear.

Withdrawal symptoms. It has become apparent in post-marketing observations that a syndrome of withdrawal symptoms may occur after abrupt discontinuation of SSRI treatment. Withdrawal reactions have been reported with all currently marketed SSRIs, but most frequently with paroxetine.[45,46] To date, studies directly comparing the discontinuation effects of citalopram with those of other SSRIs have not been conducted.

Potential discontinuation effects following abrupt cessation of citalopram were evaluated in 2 long-term, placebo-controlled studies described earlier[21,22] and in a recent retrospective analysis.[47] Citalopram responders during short-term treatment who were then rerandomized to placebo reported a significantly higher incidence ($p \leq .05$) of only impaired concentration (4.2% vs. 0%) and emotional indifference (5.6% vs. 0.7%) during the first 2 weeks of the continuation phase.[47] These adverse events were seen more frequently in patients randomly assigned to placebo who experienced a relapse than in patients randomly assigned to placebo who did not experience a relapse.[48] No patients who were abruptly switched from citalopram to placebo dropped out of the study owing to adverse events, which suggests that their symptoms were most likely mild and short-lived.

Adverse events in the elderly. Pooled data from 8 double-blind, placebo-controlled trials were used to evaluate the relative safety of citalopram in an elderly population as compared with a concurrently treated patient population under the age of 60 years.[49] Of the total of 1891 patients who were randomly assigned to treatment with citalopram (10–80 mg/day) or placebo, 265 were aged 60 years and over. As shown in Table 4,[49] the adverse events were similar in both groups. Only increased sweating occurred significantly more frequently ($p < .05$) in elderly patients taking citalopram compared with elderly patients taking placebo.

In a study[10] conducted among elderly individuals, 37% of the patients in the citalopram group reported adverse events, compared with 25% in the placebo group, a non-significant difference. Only asthenia/tiredness/lassitude and emotional indifference occurred more frequently among patients receiving citalopram ($p < .05$). At weeks 4 and 6 and at endpoint, no statistically significant differences were found in adverse events between the groups.

Comparison with TCAs. As with other SSRIs, citalopram is generally better tolerated than are the TCAs. In particular, citalopram appears to produce fewer and less severe CNS and anticholinergic effects than do the TCAs. In the meta-analysis by Bech and Cialdella,[19] for example, tremor and dry mouth occurred more frequently ($p < .05$) among patients receiving amitriptyline (12.5 and 27.1%, respectively) than among those receiving citalopram (0% and 3.5%, respectively). Nausea, headache, and sweating were reported with similar frequency in both groups. Pooled data from comparative clinical trials involving 682 patients randomly assigned to citalopram and 389 patients randomly assigned to various TCAs and tetracyclic antidepressants showed that citalopram is associated with an approximately 5% greater incidence of nausea and of ejaculation failure than these other drugs ($p < .05$). In contrast, dry mouth, increased sweating, tremor, somnolence, constipation, abnormalities of accommodation, dizziness, postural hypotension, palpitations, and taste perversion occurred significantly more frequently with TCAs and tetracyclics than with citalopram ($p < .05$).[50]

In a small-scale, double-blind, 5-week study[51] designed to determine whether citalopram induces orthostatic hypotension, results from 15 patients receiving citalopram were compared with data from 17 patients receiving clomipramine. Clomipramine produced a significant reduction in standing systolic blood pressure. In contrast, no significant changes in blood pressure were detected in patients given citalopram.

Comparison with other SSRIs. In the randomized, double-blind study[38] comparing citalopram with fluoxetine in psychiatric inpatients, nausea and headache were the most frequently recorded adverse events in both groups. Although the incidence of vomiting was significantly higher among citalopram-treated patients ($p = .03$), the difference was apparent only during the first week of treatment. In the trial comparing citalopram with fluoxetine among general practice patients,[37] back pain was reported more frequently among patients taking citalopram ($p = .03$), and dry mouth and weight loss tended to be reported more frequently in patients taking fluoxetine ($p = .06$ and $p = .07$, respectively).

Several differences were noted in the trial comparing citalopram with fluvoxamine,[40] which was designed mainly

Table 4. Most Frequent (>10% Incidence in any Group) Adverse Events in Citalopram- and Placebo-Treated Patients by Age Group[a]

	< 60 Years of Age		≥ 60 Years of Age	
Adverse Event	Citalopram N = 1167	Placebo N = 459	Citalopram N = 179	Placebo N = 86
Headache	29.7	29.2	12.8	16.3
Nausea	23.6*	14.6	13.4	11.6
Dry mouth	18.9*	13.1	17.3	16.3
Somnolence	16.1*	8.7	16.8	10.5
Insomnia	13.7	13.5	14.5	9.3
Increased sweating	12.9	9.6	7.3*	1.2
Dizziness	10.4	10.2	12.3	11.6
Asthenia	8.1	10.2	18.4	11.6
Constipation	7.5	7.6	10.1	10.5
Tremor	7.0	5.9	11.2	7.0

[a]Data from Hakkarainen and Tanghøj.[49]
*Significantly different from placebo, $p < .05$.

to assess side effects. For example, nausea occurred significantly more frequently (p = .017) among fluvoxamine-treated patients throughout the trial. There was also a trend toward higher incidence of vomiting in fluvoxamine-treated patients (p = .052).

In the study comparing sertraline with citalopram in major depression,[39] the most common side effects rated as probably secondary to study drugs in both treatment groups were dry mouth, increased sweating, increased dream activity, and sexual effects (change in sexual desire, erectile/ejaculatory dysfunction, or orgasmic dysfunction). There were no statistically significant differences between treatment groups for these or any other side effects reported during the trial.

Although larger, placebo-controlled trials would be required to detect definitive within-class differences, available data suggest that the tolerability profile of citalopram is similar to that of other SSRIs.

Citalopram and psychomotor function. The effects of citalopram on psychomotor function were compared with those of amitriptyline among 12 healthy individuals.[52] After 1 and 3 hours, citalopram at a single dose of 20 mg or 40 mg improved performance of several psychomotor tasks, whereas 50 mg of amitriptyline impaired performance of the same tasks (p < .05). After 9 days of once-daily dosing, citalopram (40 mg) and amitriptyline (75 mg) had no effects on psychomotor function. In another study, administration of 10, 20, and 40 mg/day of citalopram for 8 days to healthy volunteers had no detrimental effects on psychomotor performance.[53] In fact, citalopram apparently increased cognitive processing ability and improved CNS function.

Cardiovascular safety of citalopram. In preclinical studies, chronic high doses of citalopram produced fatal arrhythmias in 6 beagle dogs.[54] However, subsequent mechanistic studies demonstrated that the observed toxicity resulted from an accumulation of high plasma levels of the didemethyl metabolite of citalopram (> 1000 nM), which in humans is present only in low or negligible concentrations, suggesting a species-specific phenomenon.[54]

The effect of citalopram on cardiac conduction in human subjects has been evaluated extensively in prospective studies of healthy volunteers and patients, as well as in retrospective analyses of more than 40 clinical trials.[55] Apart from a small reduction in heart rate by 4 to 8 beats per minute (bpm)—common to all SSRIs[56]—no significant cardiac changes have been correlated to treatment with citalopram. The incidence of bradycardia (defined as a heart rate of 50 bpm or less) was less than 1% in clinical trials among general patient populations[57] and was similarly low in trials among patients 65 years of age and older.[10]

Safety in Overdose

Because suicidal thoughts and behaviors are common among depressed patients, the safety of an antidepressant in overdose situations is critically important. Because of their relatively broad therapeutic window and their minimal effects on cardiac function, SSRIs in general are much safer in overdose than TCAs, and a recent review[58] of the signs and symptoms of SSRI overdose found no apparent differences among SSRIs.

During premarketing clinical trials involving more than 4000 citalopram-treated patients, 15 cases of overdose were reported.[58] Although some patients ingested as much as 2000 mg of citalopram (33 to 100 times the recommended daily dose), no deaths resulted. Patients who ingested citalopram with other substances (e.g., benzodiazepines and alcohol) experienced more serious symptoms (such as loss of consciousness), but ultimately recovered.

In a review of 108 cases of citalopram-only overdose reported since 1993, Personne et al.[59] likewise found no deaths, although the amounts ingested ranged from 150 mg to 5200 mg (the largest overdose reported to date). Patients who ingested less than 600 mg of citalopram commonly experienced nausea, dizziness, tachycardia, tremor, drowsiness, and somnolence. Among patients who ingested larger amounts (30 to 100 times the mean recommended daily dose), convulsions and tachycardia (but not arrhythmia) were common symptoms. However, all patients recovered without sequelae.

Five reported fatal cases of citalopram overdose involved large amounts of citalopram (840–3920 mg) taken along with other sedative drugs or alcohol.[60] One apparent citalopram-alone fatality involved nearly 4000 mg of citalopram. These findings are similar to reports of overdose deaths involving other SSRIs.[61]

Although the SSRIs (including citalopram) are far safer in overdose than TCAs when taken alone, it is important for clinicians to recognize that suicide attempts involving ingestion of multiple substances are common in depressed patients and are associated with increased toxicity. Thus, patients with suicidal thoughts or tendencies should be closely monitored until remission from depression is achieved.

Drug-Drug Interactions

Because antidepressants often are coprescribed with other medications, adverse drug interactions can pose a serious threat to effective therapy, leading to premature discontinuation, hospitalization, or, in very severe cases, death. Drugs can interact with one another pharmacokinetically (i.e., by affecting absorption, distribution, metabolism, or elimination) or pharmacodynamically (i.e., through shared sites of action/biological targets). Known and potential drug interactions relevant to citalopram are reviewed below.

An important route of drug-drug interactions is via the hepatic cytochrome P450 (CYP) enzymatic system, which metabolizes most commonly prescribed medications, including analgesics, antibiotics, antihistamines,

Table 5. Inhibition of Cytochrome P450 (CYP) Isoenzymes by Selective Serotonin Reuptake Inhibitors[a]

Drug	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Fluoxetine	+	++	+ to ++	+++	+
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+
Fluvoxamine	+++	++	+++	+	++
Citalopram	+	–	–	–	–

[a]Data from Greenblatt et al.[7]
Symbols: + = mild, ++ = moderate, +++ = strong, – = none.

anticancer drugs, various heart medications, and a wide range of psychotropics. Inhibiting the metabolism of a drug elevates its plasma levels and extends its half-life. These alterations can lead to serious adverse reactions, especially for medications with narrow therapeutic indices (e.g., class IC antiarrhythmics, TCAs, anticoagulants, and anticancer drugs). Compared with fluoxetine, fluvoxamine, and paroxetine, citalopram appears to have minimal effects on the cytochrome P450 system. As shown in Table 5, in vitro data indicate that citalopram weakly inhibits CYP1A2 and has little or no effect on CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[7]

In vivo studies have largely confirmed these findings. For example, citalopram given in combination with various antipsychotics (haloperidol, chlorpromazine, zuclopenthixol, levopromazine, thioridazine, or perphenazine), all of which are substrates for CYP1A2 and/or CYP2D6, did not alter the serum concentrations of these drugs.[62] Although combined administration of citalopram (40 mg) with metoprolol, a CYP2D6 substrate, resulted in increased plasma concentrations of the β-blocker, no clinically significant effects on blood pressure or heart rate were noted.[57] In vitro studies[63] suggest that citalopram is the least potent inhibitor of metoprolol metabolism among the SSRIs. In healthy volunteers, citalopram at doses of 40 mg had no effect on the plasma concentration or half-life of imipramine, which is a substrate for all the major CYP isoenzymes except CYP3A4, but increased the area under the curve of the metabolite desipramine by 47%.[64] Coadministration of citalopram with the CYP3A4 substrate carbamazepine among healthy individuals did not affect the pharmacokinetics of carbamazepine or its epoxide metabolite, indicating that citalopram probably does not inhibit the CYP3A4 isoenzyme in vivo.[65] Similarly, the kinetics of the CYP3A4 substrate triazolam remained constant when the drug was administered to healthy volunteers who had achieved steady-state levels of citalopram.[66]

High-level (≥ 95%) plasma protein binding, which can lead to displacement of other highly protein-bound medications, is another possible mechanism by which one drug can alter the pharmacokinetics of another. Citalopram, which is approximately 80% protein bound, does not appear to carry a significant risk of such interactions. In a crossover study[67] in 12 healthy volunteers, citalopram did not affect the pharmacokinetics of warfarin, a highly protein-bound drug.

A third possible means by which one drug can alter the pharmacokinetics of another is by interfering with renal excretion. Digoxin, which is eliminated by the kidneys without undergoing significant biotransformation, may be especially susceptible to such interactions. Because digoxin has a narrow therapeutic range, interference with its elimination can lead to serious adverse effects. Concomitant administration of digoxin and citalopram resulted in no clinically significant interaction in healthy volunteers.[68]

Like other SSRIs, citalopram has the potential to interact pharmacodynamically with monoamine oxidase inhibitors (MAOIs), producing a potentially fatal reaction known as serotonin syndrome.[69] Therefore, combined administration of citalopram with MAOIs is absolutely contraindicated.

Dosing and Administration

In a meta-analysis of 9 placebo-controlled trials, Montgomery et al.[18] concluded that the minimal effective dose of citalopram in depression is 20 mg once daily. Patients suffering from severe or recurrent depression may benefit from a higher daily dose of 40 mg.[18] On the basis of this report and other clinical studies, it is recommended that antidepressant therapy with citalopram be initiated at 20 mg once daily. Depending on patient response, the starting dose can be titrated up to a maximum of 60 mg/day,[69] although most patients require no more than 40 mg/day to achieve clinical response. In fact, data from a recently completed flexible-dose, open-label study (N = 1783)[70] suggest that most patients achieve clinical response with, and can be maintained on, 20 mg/day of citalopram. Among elderly patients, the recommended starting dose also is 20 mg, whereas the recommended maximum dose is 40 mg, due to age-related physiologic and metabolic changes. In the range of 20 to 40 mg/day, citalopram displays linear pharmacokinetics among older patients; however, elimination half-life appears to be significantly (approximately 30%) longer in elderly individuals compared with younger individuals.[71]

Food does not influence the kinetics of citalopram.[5,57] Hence, citalopram can be administered with or without food, either in the morning or at bedtime.

DISCUSSION

Numerous well-controlled studies have demonstrated that citalopram effectively manages the symptoms of depression. Like other SSRIs, citalopram compares favorably with TCAs and tetracyclics, offering similar efficacy and superior safety. Fatality in overdose is very rare and is most often the result of ingestion of multiple substances.

The vast majority of overdoses with citalopram alone have been nonlethal and without serious sequelae. Because citalopram appears to produce relatively few and relatively mild side effects of any kind (nausea, somnolence, and dry mouth are the most commonly reported events), it also is generally better tolerated than older-generation agents. Several long-term studies indicate that citalopram is well suited for maintenance therapy, an important aspect of any truly effective antidepressant.

Citalopram appears to be as effective and well tolerated as other SSRIs. In head-to-head trials with fluoxetine, sertraline, and fluvoxamine, patients randomly assigned to citalopram or the comparator experienced similar reductions in depressive symptoms and reported adverse events of similar type, frequency, and severity (generally mild to moderate). In one trial[37] comparing citalopram with fluoxetine among patients in general practice, a proportion of patients treated with citalopram but not fluoxetine met response criteria at 2 weeks, suggesting that some patients may experience a reduction of depressive symptoms more rapidly with citalopram than with fluoxetine.

Although similar to other SSRIs, citalopram possesses a number of distinguishing characteristics. First, it displays linear pharmacokinetics across the entire recommended dose range; thus, up-titration tends to proceed predictably. In contrast, paroxetine and fluoxetine plasma levels increase in a nonlinear manner,[57] requiring closer monitoring during up-titration and when given in combination with potentially interacting medications. Second, citalopram appears to inhibit the cytochrome P450 enzymatic system to a lesser extent than some other SSRIs. Fluoxetine and paroxetine, for example, potently inhibit the CYP2D6 isoenzyme, which metabolizes a wide variety of drugs, including analgesics (e.g., codeine, hydrocodone, morphine), β-blockers (e.g., bisoprolol, metoprolol), antidepressants (e.g., most TCAs), antipsychotics (e.g., haloperidol, perphenazine, risperidone), and type IC antiarrhythmics (flecainide and propafenone).[72] Citalopram, on the other hand, produces little inhibition of CYP2D6 in vitro, and has been administered to people in combination with various CYP2D6 substrates with few or no clinically significant pharmacokinetic effects. Citalopram inhibition of other critical isoenzymes also appears to be minimal. Thus, citalopram is relatively unlikely to interact with other medications via the cytochrome P450 system.

The combination of robust efficacy, good tolerability, and a low potential for drug-drug interactions is advantageous in an antidepressant, since depression often accompanies chronic ailments such as heart disease, Parkinson's disease, Alzheimer's disease, and schizophrenia, all of which require long-term pharmacotherapy. Although citalopram has not been systematically studied in patients with serious chronic medical illnesses, it is probably the least likely of the SSRIs to conflict with existing drug regimens. Its clinically proven compatibility with antipsychotics is notable, since antidepressants often are combined with these agents to treat coexisting depressive and psychotic symptoms (for example, in patients with schizophrenia or Alzheimer's dementia). Likewise, the absence of drug interactions with digoxin and warfarin indicates that citalopram might be a good candidate drug for depressed patients with certain concomitant cardiovascular diseases. Of course, caution always is advised when adding a new drug to any existing regimen or when prescribing a new drug to seriously ill patients.

Citalopram also appears to be well suited among agents in its class for the treatment of geriatric depression. Chronic illness and concurrent use of multiple medications are common among older patients, and even the healthy aging body tends to process drugs less efficiently; thus, patients 65 years of age and older are especially susceptible to adverse drug reactions and interactions. A good candidate drug for the treatment of geriatric depression should have few antihistaminic, anticholinergic, and antiadrenergic side effects (especially problematic among elders), minimal cardiovascular risk, favorable pharmacokinetics in the aging body, and a low potential for drug interactions. The sum of clinical data collected to date, including several well-controlled prospective trials conducted entirely among elderly patients, suggests that citalopram fulfills these criteria. In addition, citalopram may be useful for other applications in the geriatric setting. For example, elderly patients with cognitive dysfunction appear to benefit from treatment with citalopram, as do patients with emotional and behavioral disturbances related to Alzheimer's dementia.[73–75]

While published data show citalopram to be a safe, effective, and well-tolerated antidepressant, it must be recognized that reviews of the published literature may be biased by delays in publication or the failure to publish nonsignificant or negative results.[76–79] So-called "publication bias" can be caused by the reluctance of investigators to submit failed studies for publication and is amplified by the disinclination of editors (given the limited amount of space in their journals) to publish nonsignificant findings.[76,80,81] A further concern is that manufacturers of pharmaceutical products, who sponsor the vast majority of clinical research evaluating the safety and efficacy of new compounds, have incentives not to publish negative results that may place a compound at a competitive disadvantage in the marketplace.

In the case of citalopram, results from over 90% of depressed patients participating in randomized, controlled clinical trials with the drug have been published and/or presented at major medical conferences (William E. Heydorn, Ph.D., data on file, Forest Laboratories, June 2000). A total of 41 placebo- or active-controlled trials have been completed with citalopram in depressed pa-

tients. The majority of these studies (30), involving 4800 patients, have been published or presented as either independent investigations or as part of meta-analyses. Results from 11 studies (involving approximately 500 patients, or 9% of the total population) have not been published or presented. The data derived from these unpublished studies, which were primarily small investigations conducted by affiliates of H. Lundbeck A/S (the company that originally developed citalopram), are contained in brief summaries that include limited demographic and dosing information. Because individual patient data are not available, independent verification of the results presented in the study summaries is not possible. Thus, the vast majority of data from controlled trials on the efficacy and the safety of citalopram in the treatment of depression have been made available to clinicians. This reported data set, combined with the extensive use of this SSRI by practicing physicians in the clinic over the last 12 years, suggests that citalopram is effective and safe for most patients in the treatment of depression.

Drug names: amitriptyline (Elavil and others), bisoprolol (Zebeta and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), diazepam (Valium and others), digoxin (Lanoxin and others), flecainide (Tambocor), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), hydrocodone (Duratuss and others), metoprolol (Toprol and others), morphine (Roxanol and others), nortriptyline (Pamelor and others), oxazepam (Serax and others), paroxetine (Paxil), perphenazine (Trilafon and others), propafenone (Rythmol), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril and others), thioridazine (Mellaril and others), triazolam (Halcion), venlafaxine (Effexor), warfarin (Coumadin).

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