Escitalopram in the Treatment of Panic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

Stephen M. Stahl, M.D.; Ivan Gergel, M.D.; and Dayong Li, Ph.D.

Background: Escitalopram, the therapeutically active isomer of the racemic selective serotonin reuptake inhibitor antidepressant citalopram, has shown significant anxiolytic effects in placebo-controlled clinical trials of social anxiety disorder, generalized anxiety disorder, and anxiety symptoms associated with major depression. This study evaluated the safety and efficacy of escitalopram in outpatients diagnosed with panic disorder.

Method: Male and female outpatients between 18 and 80 years of age meeting DSM-IV criteria for panic disorder, with or without agoraphobia, were randomly assigned to 10 weeks of double-blind treatment with escitalopram, citalopram, or placebo in a study conducted from September 1999 to July 2001. The primary measure of efficacy was panic attack frequency at week 10 relative to baseline, as assessed by the Modified Sheehan Panic and Anticipatory Anxiety Scale.

Results: A total of 366 subjects (128 escitalopram patients, 119 citalopram patients, and 119 placebo patients) received at least 1 dose of double-blind treatment. The frequency of panic attacks was statistically significantly improved ($p = .04$), and the increase in percentage of patients with zero panic attacks reached borderline significance ($p = .051$), in the escitalopram-treated group relative to the placebo-treated group. Both escitalopram and citalopram statistically significantly reduced panic disorder symptoms and severity versus placebo at endpoint ($p \leq .05$), as measured by the Panic and Agoraphobia Scale total score, the Clinical Global Impressions scale, the Patient Global Evaluation, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Treatment with escitalopram was safe and well tolerated, with a similar incidence of the most common adverse events for the escitalopram and placebo groups. The rate of discontinuation for adverse events was 6.3% for escitalopram, 8.4% for citalopram, and 7.6% for placebo.

***Conclusion*:** Escitalopram is efficacious, safe, and well tolerated in the treatment of panic disorder.

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Corresponding author and reprints: Stephen M. Stahl, M.D., 5857 Owens Avenue, Suite 102, Carlsbad, CA 92009 (e-mail: smstahl@neiglobal.com).

Panic disorder is a chronic and recurrent psychiatric illness with a lifetime prevalence of 1.6% to 2.2% worldwide.[1] Pharmacologic approaches to the treatment of panic disorder have included benzodiazepines and antidepressants.[2] As a class, the benzodiazepines are limited by a high incidence of patient dependence and withdrawal symptoms after long-term treatment.[3] Furthermore, the benzodiazepines do not offer robust efficacy in the treatment of comorbid depression, which has been estimated to occur in up to 60% of panic disorder patients.[4]

Among the antidepressants, monoamine oxidase inhibitors such as phenelzine[5,6] and tricyclic antidepressants such as clomipramine[7] have demonstrated efficacy in the treatment of panic disorder.[8] However, both of these drug classes are associated with unfavorable side effect profiles, which can lead patients to discontinue treatment.[9] Most recently, the selective serotonin reuptake inhibitors (SSRIs) have become the first-line choice for anxiolytic therapy.[10] The SSRIs have well-established antidepressant activity and also have demonstrated efficacy in a number of anxiety disorders, including panic disorder, suggesting a serotonergic component for this disease state.[2,9,11–22] Utility of SSRIs in the treatment of panic disorder, however, can be limited by activating side effects, particularly early in treatment,[23] which may necessitate concomitant treatment with benzodiazepines.[2,24] An SSRI with a low incidence of side effects, especially early in treatment, could lead to therapeutic advantages in the treatment of panic disorder.

The SSRI citalopram exists as a racemic mixture of *R*- and *S*-isomers.[25] The ability of citalopram to inhibit serotonin reuptake at therapeutic doses resides exclusively in the *S*-isomer, escitalopram.[26–28] Escitalopram has been shown to have a benign side effect profile in the treatment of depression, and has also demonstrated both efficacy and tolerability advantages over citalopram in

treating depression.[29,30] Escitalopram has a broad spectrum of anxiolytic activity as well, as demonstrated in clinical trials of anxiety symptoms associated with major depression, social anxiety disorder, and generalized anxiety disorder.[31–33] Thus, this study examined the safety and efficacy of escitalopram in the treatment of panic disorder.

METHOD

Patients

The study group consisted of male and female outpatients (18 to 80 years of age) meeting DSM-IV[34] criteria for panic disorder (with or without agoraphobia). Patients were required to have a minimum of 4 DSM-IV–defined panic attacks, at least 1 of which was unanticipated, during the 4 weeks prior to the screening visit and at least 3 panic attacks during the 2-week placebo lead-in period.

Patients with a score greater than 17 on the Hamilton Rating Scale for Depression[35] at the screening visit were excluded. Patients with bipolar disorder, schizophrenia, obsessive-compulsive disorder, or other psychotic disorders, as well as those with a psychoactive substance use disorder within the past 6 months, were not eligible for the study. Pregnant women and patients with clinically significant abnormalities in laboratory evaluations or electrocardiographic readings were also excluded.

Eligible subjects were not allowed to take any psychotropic medication, with the exception of zolpidem as needed for sleep. Patients who had received treatment with any neuroleptic, antidepressant, or anxiolytic medication within 2 weeks prior to study entry were excluded from the trial. Patients also were excluded if they were receiving regular daily therapy with any benzodiazepine within 1 month prior to the first administration of study medication. All participants provided informed written consent prior to study entry. The study protocol was approved by the institutional review boards for the participating study centers.

Design

This was a randomized, double-blind, parallel-group, flexible-dose, placebo-controlled, multicenter study of patients with panic disorder, with or without agoraphobia, conducted from September 1999 to July 2001. A single-blind, 2-week placebo lead-in preceded the 10-week double-blind treatment phase. Patients who met all eligibility criteria at the end of the lead-in period were randomly assigned to 1 of 3 treatment groups: placebo, escitalopram, or citalopram. Patients were seen at study entry (screening at days 1 and 8 of the lead-in period), day of randomization (baseline), and at the end of weeks 1, 2, 4, 6, 8, and 10 of double-blind treatment.

Dosing began for all groups at 1 tablet/day (placebo, escitalopram 5 mg/day, or citalopram 10 mg/day) and was increased to 2 tablets/day (placebo, escitalopram 10 mg/day, or citalopram 20 mg/day) at the end of week 1. At the end of week 4, dosage could be increased to 20 mg/day for escitalopram, 40 mg/day for citalopram, or matching placebo, in the absence of both dose-limiting adverse events and a satisfactory therapeutic response. Following up-titration, dosing could be reduced at any time because of adverse events. All study medication was administered as a single daily dose.

Clinical Assessment and Data Analyses

All efficacy analyses were based on the intent-to-treat (ITT) population, i.e., all patients who received at least 1 dose of double-blind study medication and had at least 1 post-baseline assessment of panic attack frequency based on the Modified Sheehan Panic and Anticipatory Anxiety Scale (PAAS)[36] using the last-observation-carried-forward (LOCF) approach. All statistical tests were 2-sided with a 5% significance level.

The primary measure of efficacy was panic attack frequency at week 10 relative to baseline. Data were normalized by logarithmic transformation prior to analysis. Pairwise comparisons between treatment groups (escitalopram vs. placebo and citalopram vs. placebo) were carried out using a 2-way analysis of covariance (ANCOVA) model with treatment and center as factors and baseline score as a covariate. Panic attack frequency was derived from the PAAS and was based on the 2-week interval preceding assessment.

Secondary assessments included the Panic and Agoraphobia (P&A) Scale,[37] the Clinical Global Impressions-Improvement (CGI-I) and -Severity of Illness (CGI-S) scales,[38] the Hamilton Rating Scale for Anxiety (HAM-A),[39] the Patient Global Evaluation (PGE), anticipatory anxiety duration (derived from the PAAS score), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[40] For the CGI-I, patients were rated by the investigator in terms of overall improvement to produce the CGI-I total score and, separately, in terms of the degree of phobic avoidance (CGI-Phobic Avoidance).

CGI-I total score and CGI-Phobic Avoidance score were analyzed with a 2-way analysis of variance model with treatment and center as factors. The percentage of responders on the P&A Scale (0 panic attacks in the previous week) was analyzed using the Cochran-Mantel-Haenszel test, stratified by center. Additional by-visit analyses for changes from baseline in efficacy parameters were analyzed using an ANCOVA model.

Safety assessments included vital signs, electrocardiogram parameters, laboratory measurements, physical examination, and a record of adverse events. All safety analyses were based on the population of patients who took at least 1 dose of double-blind study medication.

Table 1. Mean Demographic and Baseline Clinical Characteristics for the Intent-to-Treat Population[a]

Variable	Placebo (N = 114)	Escitalopram (N = 125)	Citalopram (N = 112)
Age, mean, y	38.6	37.5	37.1
Sex, % female	55.3	57.6	61.6
Race, % white	71.1	70.4	75.9
Panic attacks/week	5.1 ± 5.5	5.0 ± 4.5	4.9 ± 4.3
P&A Scale score	25.0 ± 8.4	25.0 ± 8.9	24.6 ± 8.5
HAM-A score	17.6 ± 6.9	15.6 ± 6.7	15.6 ± 6.9
CGI-S score	4.4 ± 0.6	4.3 ± 0.6	4.3 ± 0.6
Q-LES-Q score	52.7 ± 10.1	52.7 ± 10.9	53.1 ± 9.2
Anticipatory anxiety duration, % of time ± SD	42.4 ± 30.5	45.7 ± 31.5	44.7 ± 28.3

[a]Values shown as mean ± SD unless otherwise noted.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, P&A = Panic and Agoraphobia, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Table 2. Efficacy Results at Endpoint[a]

Variable	Placebo (N = 114)	Escitalopram (N = 125)	Citalopram (N = 112)
Panic attack frequency,[b] log (endpoint/baseline)	–1.32 ± 0.1	–1.61 ± 0.1*	–1.43 ± 0.1
Zero panic attacks, %	38	50†	39
P&A Scale total score	–3.9 ± 0.9	–8.9 ± 0.9**	–7.4 ± 0.8**
Anticipatory anxiety duration, % of time	–11.7	–24.3*	–22.1
HAM-A score	–4.6 ± 0.8	–6.1 ± 0.7**	–4.9 ± 0.7
CGI-I score	2.8 ± 0.1	2.2 ± 0.1**	2.2 ± 0.1**
CGI-Phobic Avoidance score	3.1 ± 0.1	2.5 ± 0.1**	2.6 ± 0.1**
CGI-S score	–1.2 ± 0.1	–1.6 ± 0.1**	–1.5 ± 0.1*
PGE score	2.8 ± 0.1	2.3 ± 0.1**	2.2 ± 0.1**
Q-LES-Q score	2.8 ± 1.1	7.2 ± 1.1**	5.8 ± 1.0*

[a]Values represent changes from baseline except for zero panic attacks and CGI-I, CGI-Phobic Avoidance, and PGE scores, for which values are those at endpoint. Values shown as mean ± SEM.
[b]Primary efficacy measure.
*$p \leq .05$ vs. placebo.
**$p < .01$ vs. placebo.
†$p = .051$, escitalopram vs. placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, P&A = Panic and Agoraphobia, PGE = Patient Global Evaluation, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

RESULTS

Patient Characteristics

A total of 366 patients (128 in the escitalopram treatment group, 119 in the citalopram treatment group, and 119 in the placebo treatment group) received at least 1 dose of double-blind study medication and are included in the safety analyses. Efficacy analyses were performed on the ITT subset of this sample (i.e., patients with at least 1 postbaseline assessment on the PAAS) that included 125 escitalopram-treated patients, 112 citalopram-treated patients, and 114 placebo-treated patients.

The baseline characteristics of the 351 patients in the ITT population are summarized in Table 1. Following randomization, there were no statistically significant differences between the 3 treatment groups with respect to age, gender, and clinical features of panic disorder. Sixty-nine percent of all patients had comorbid agoraphobia, and the incidence of comorbid agoraphobia was similar across treatment groups. On average, patients reported 5 panic attacks per week and estimated that they spent 44% of their waking day worrying about having another panic attack.

Sixty-eight percent of all randomized patients (75.8% of escitalopram patients, 68.1% of citalopram patients, and 60.5% of placebo patients) completed the study. Reasons for discontinuation included patient lost to follow-up (10.7%), adverse events (7.4%), insufficient therapeutic response (5.7%), withdrawal of consent (4.4%), protocol violation (3.0%), and other (0.5%). The overall mean daily dose was 10.8 mg for escitalopram and 21.3 mg for citalopram.

Efficacy

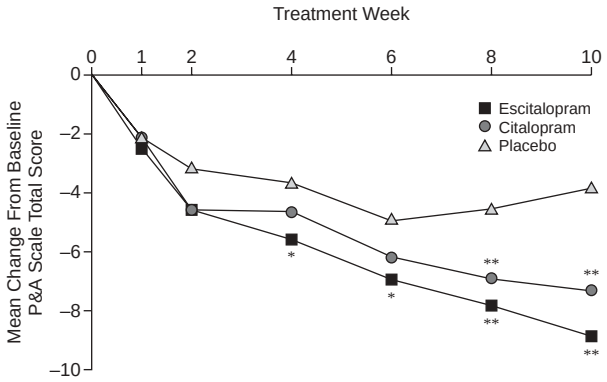
Efficacy results are presented in Table 2. The primary efficacy measure was change in panic attack frequency relative to baseline; the data were normalized using logarithmic transformation with a constant added to accommodate patients with zero panic attacks at endpoint. The log-transformed, relative panic attack frequency was –0.32 for the placebo group and –1.61 for the escitalopram group ($p = .04$). The proportion of patients with zero panic attacks at study endpoint (derived from the P&A Scale) was 50% and 38% for the escitalopram and placebo groups, respectively ($p = .051$). The citalopram treatment group was not statistically different from the placebo treatment group on either measure (Table 2).

Mean changes in P&A Scale total score by visit are presented in Figure 1. Escitalopram treatment produced statistically significant improvement relative to placebo treatment at every visit starting at week 4. For citalopram treatment, statistically significant improvement compared with placebo treatment was observed at weeks 8 and 10.

Other efficacy measures were also statistically significantly improved at endpoint by escitalopram treatment relative to placebo treatment, including CGI-I, CGI-S, CGI-Phobic Avoidance, HAM-A, PGE, and anticipatory anxiety duration scores (Table 2). Furthermore, escitalopram treatment produced statistically significantly greater mean changes than placebo treatment from baseline to endpoint on the Q-LES-Q (7.2 vs. 2.8; $p < .01$; Table 2).

Citalopram treatment led to statistically significant improvement relative to placebo treatment in panic disorder symptomatology, as assessed by P&A Scale, CGI-I, CGI-S, CGI-Phobic Avoidance, PGE, and Q-LES-Q scores (Table 2).

Figure 1. Mean Changes From Baseline in Panic and Agoraphobia (P&A) Scale Total Score for Patients Treated With Escitalopram, Citalopram, or Placebo



*p ≤ .05, escitalopram vs. placebo.
**p < .01, escitalopram or citalopram vs. placebo.

Table 3. Most Frequent Adverse Events (% of subjects)[a]

Adverse Event	Placebo (N = 119)	Escitalopram (N = 128)	Citalopram (N = 119)
Headache	15	16	24
Nausea	13	13	18
Insomnia	14	14	17
Dry mouth	4	8	14
Somnolence	6	8	13
Fatigue	9	13	8
Dizziness	10	6	5

[a]Incidence at least 10% in any treatment group.

Safety

Treatment with escitalopram was safe and well tolerated, with a rate of discontinuation due to adverse events of 6.3%, compared with 7.6% for placebo. The incidence of the most common adverse events (frequency of 10% or more) was similar for escitalopram- and placebo-treated patients (Table 3). Citalopram treatment was also well tolerated, with a discontinuation rate due to adverse events of 8.4%. No clinically meaningful changes from baseline in vital signs, electrocardiogram values, or laboratory measurements were observed in any treatment group.

DISCUSSION

This study demonstrates that escitalopram is a safe, well tolerated, and effective treatment for panic disorder and supports previous studies demonstrating the efficacy of citalopram in treating this illness.[18–20] These data also add to our understanding of the broad potential for escitalopram in the treatment of anxiety disorders. Previously reported clinical trial data support the use of escitalopram in the treatment of social anxiety disorder and generalized anxiety disorder.[31,32] Furthermore, in studies evaluating antidepressant efficacy, treatment with escitalopram resulted in statistically significant improvement in depression-associated anxiety symptoms,[33] consistent with the demonstrated anxiolytic activity of escitalopram in several validated animal models of anxiety.[41,42]

Most panic disorder patients experience symptoms other than the panic attacks, including phobic avoidance and anticipatory anxiety. Such symptoms often greatly impact the patient's social functioning and quality of life, and resolution of general anxiety symptoms and global improvements in patients' conditions can be better predictors of eventual outcome than symptoms specific to panic disorder (such as panic attack frequency).[43] The effects of escitalopram observed on a wide variety of symptoms may therefore be considered clinically significant.

Citalopram treatment clearly led to global improvements in patients' conditions, as assessed by several rating scales. It has been reported in a placebo-controlled trial of the SSRI sertraline in panic disorder patients that drug responders can be differentiated from placebo responders on the basis of significantly greater improvement in quality of life measures. The interpretation was that placebo "responders" do not receive the same benefits as SSRI-treated patients.[44] It is interesting that in the present study, statistically significantly greater mean improvements in quality of life were reported for both drug treatment groups relative to placebo, despite similar proportions of responders being observed in the citalopram- and placebo-treated groups.

In a prior multicenter, double-blind, placebo-controlled investigation of citalopram in the treatment of panic disorder, citalopram statistically significantly reduced the number of panic attacks, and increased the proportion of patients with no panic attacks, relative to placebo; the minimum effective dose range was 20 to 30 mg/day (with an aggressive titration schedule).[18] However, in the present study there was no statistical separation of citalopram treatment from placebo treatment in terms of relative panic attack frequency (the primary efficacy variable) or in the proportion of patients with zero panic attacks at endpoint. The findings from these 2 trials are not necessarily in contradiction, both because different scales were employed and because citalopram did produce statistically significant improvement in panic disorder symptoms in the present trial. Nevertheless, there are differences between the prior trial and the present trial that could account for the apparent disparity in outcome. For example, the placebo effect was much larger in the present trial. It is possible that differences in the dosing regimen had an impact on the placebo effect, since patients in the present trial could be up-titrated at several timepoints. Mean baseline HAM-A scores were 23 in the prior trial and 16 in the present one; differences

in baseline disease severity could possibly account for the likelihood of response in placebo-treated patients.

The efficacy advantage in reduction of panic attack frequency for the escitalopram-treated group relative to the citalopram-treated group in this study was observed even though approximately the same amount of escitalopram was administered daily to both groups. Similar results were obtained in depression trials. Escitalopram has been shown to have statistically significant efficacy advantages over citalopram in the treatment of major depressive disorder when administered at comparable doses[29]; one fixed-dose trial showed that escitalopram, 10 mg/day, is at least as effective as citalopram, 40 mg/day, in depressed patients.[26] A superior therapeutic profile is predicted for single-isomer compounds relative to racemates when the single isomer exerts essentially all the therapeutic activity of the racemate.[45] The finding that co-administration of *R*-citalopram to rat cerebral neurons reduces the amount of serotonin reuptake inhibition produced by escitalopram[46] provides a potential mechanistic basis for the superior clinical efficacy of escitalopram relative to citalopram.[25]

Escitalopram treatment had a rate of discontinuation due to adverse events lower than that for placebo treatment. The incidence of the most common adverse events was similar for escitalopram and placebo, although somewhat higher for citalopram. Notably, the higher rate of somnolence observed in the citalopram group relative to escitalopram or placebo (13% versus 8% and 6%, respectively) is consistent with the finding that the weak affinity of citalopram for the histamine H_1 receptor is attributable only to the *R*-isomer.[27] These results suggest that escitalopram is very well tolerated in panic disorder patients, including at initiation of treatment, a much desired feature for treatment of panic disorder.

In conclusion, escitalopram treatment resulted in significant improvements in panic disorder symptomatology, including panic attack frequency, agoraphobia, anticipatory anxiety, and quality of life. The favorable tolerability profile exhibited by escitalopram is of particular importance to the panic disorder patient population due to the chronic and persistent nature of the disease and the recommended 12-month minimum duration of treatment.[47] Further research is needed to examine the safety and efficacy of escitalopram in the long-term treatment of panic disorder.

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), escitalopram (Lexapro), phenelzine (Nardil), sertraline (Zoloft), zolpidem (Ambien).

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REFERENCES

1. Pollack MH, Marzol PC. Panic: course, complications and treatment of panic disorder. J Psychopharmacol (Oxf) 2000;14:S25–S30
2. Stahl SM. Independent actions on fear circuits may lead to therapeutic synergy for anxiety when combining serotonergic and GABAergic agents [BRAINSTORMS]. J Clin Psychiatry 2002;63:854–855
3. Kasper S, Resinger E. Panic disorder: the place of benzodiazepines and selective serotonin reuptake inhibitors. Eur Neuropsychopharmacol 2001;11:307–321
4. Lesser IM, Rubin RT, Pecknold JC, et al. Secondary depression in panic disorder and agoraphobia, pt 1: frequency, severity, and response to treatment. Arch Gen Psychiatry 1988;45:437–443
5. Tyrer P, Candy J, Kelly D. Phenelzine in phobic anxiety: a controlled trial. Psychol Med 1973;3:120–124
6. Mountjoy CQ, Roth M, Garside RF, et al. A clinical trial of phenelzine in anxiety depressive and phobic neuroses. Br J Psychiatry 1977;131: 486–492
7. Modigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. J Clin Psychopharmacol 1992;12:251–261
8. Roy-Byrne P, Wingerson D, Cowley D, et al. Psychopharmacologic treatment of panic, generalized anxiety disorder, and social phobia. Psychiatr Clin North Am 1993;16:719–735
9. Zohar J, Westenberg HG. Anxiety disorders: a review of tricyclic antidepressants and selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 2000;403:39–49
10. American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Panic Disorder. Am J Psychiatry 1998;155:1–34
11. Ballenger JC, Wheadon DE, Steiner M, et al. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 1998;155:36–42
12. Lecrubier Y, Bakker A, Dunbar G, et al. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand 1997;95:145–152
13. Lecrubier Y, Judge R. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand 1997;95:153–160
14. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder: a double-blind multicenter trial. Am J Psychiatry 1998;155: 1189–1195
15. Pollack MH, Otto MW, Worthington JJ, et al. Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. Arch Gen Psychiatry 1998;55:1010–1016
16. Londborg PD, Wolkow R, Smith WT, et al. Sertraline in the treatment of panic disorder: a multi-site, double-blind, placebo-controlled, fixed-dose investigation. Br J Psychiatry 1998;173:54–60
17. Goddard AW, Charney DS. SSRIs in the treatment of panic disorder. Depress Anxiety 1998;8(suppl 1):114–120
18. Wade AG, Lepola U, Koponen HJ, et al. The effect of citalopram in panic disorder. Br J Psychiatry 1997;170:549–553
19. Lepola UM, Wade AG, Leinonen EV, et al. A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. J Clin Psychiatry 1998;59:528–534
20. Leinonen E, Lepola U, Koponen H, et al. Citalopram controls phobic symptoms in patients with panic disorder: randomized controlled trial. J Psychiatry Neurosci 2000;25:25–32
21. Michelson D, Allgulander C, Dantendorfer K, et al. Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder:

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randomised, placebo-controlled trial. Br J Psychiatry 2001;179:514–518
22. Asnis GM, Hameedi FA, Goddard AW, et al. Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. Psychiatry Res 2001;103:1–14
23. Nesse RM, Zamorski MA. Anxiety disorders in primary care. In: Knespar DJ, Riba MB, Schwenk TL, eds. Primary Care Psychiatry. Philadelphia, Pa: Saunders; 1997:132–162
24. Zamorski MA, Albucher RC. What to do when SSRIs fail: eight strategies for optimizing treatment of panic disorder. Am Fam Physician 2002; 66:1477–1484
25. Stahl SM. Mirror, mirror on the wall, which enantiomer is fairest of them all? [BRAINSTORMS] J Clin Psychiatry 2002;63:656–657
26. Burke WJ, Gergel I, Bose A. Fixed dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002;63: 331–336
27. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345–350
28. Hyttel J, Bogeso KP, Perregaard J, et al. The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J Neural Transm Gen Sect 1992;88:157–160
29. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. CNS Spectrums 2002;7:40–44
30. Owens M, Rosenbaum J. Escitalopram: a second-generation SSRI. CNS Spectrums 2002;7:34–39
31. Davidson J, Bose A, Su G. Escitalopram in the treatment of generalized anxiety disorder [abstract]. Int J Neuropsychopharmacol 2002;5:S214
32. Kasper S, Loft H, Smith JR. Escitalopram is efficacious and well tolerated in the treatment of social anxiety disorder [abstract]. Int J Neuropsychopharmacol 2002;5:S131
33. Lydiard RB. Effects of escitalopram on anxiety symptoms in depression. World J Biol Psychiatry 2001;2:S1
34. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
35. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
36. Sheehan D. The Anxiety Disease. New York, NY: Bantam Books; 1986:113–117
37. Bandelow B, Broocks A, Pekrun G, et al. The use of the Panic and Agoraphobia Scale (P&A) in a controlled clinical trial. Pharmacopsychiatry 2000;33:174–81
38. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
39. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
40. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29:321–326
41. Hogg S, Jessa M. Effects of escitalopram in the dorsal peri-acquaductal grey stimulation model of panic anxiety [abstract]. Biol Psychiatry 2002;51:S124
42. Sanchez C. Escitalopram: potent anxiolytic effects in rodent models [abstract]. World J Biol Psychiatry 2002;S328
43. Pollack MH, Rapaport MH, Fayyad R, et al. Early improvement predicts endpoint remission status in sertraline and placebo treatments of panic disorder. J Psychiatr Res 2002;36:229–236
44. Rapaport MH, Pollack M, Wolkow R, et al. Is placebo response the same as drug response in panic disorder? Am J Psychiatry 2000;157: 1014–1016
45. Hutt AJ, Tan SC. Drug chirality and its clinical significance. Drugs 1996;52 (suppl 5):1–12
46. Mork A, Kreilgaard M, Sanchez C. Escitalopram: a comparative study of in vitro and in vivo 5-HT uptake inhibitory activity [abstract]. Int J Neuropsychopharmacol 2002;5:S66
47. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 1998;59(suppl 8):47–54

