Results of a large comprehensive pooled analysis of head-to-head depression studies

Significant Efficacy of EFFEXOR® XR (venlafaxine HCl) vs. SSRIs*

Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Thase ME, Entsuah AR, Rudolph RL. *British Journal of Psychiatry.* 2001;178:234-241.

*SSRIs compared were fluoxetine, paroxetine, and fluvoxamine.

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Approximately 1/3 more patients reached remission with EFFEXOR XR/EFFEXOR[1]

Results of a large pooled analysis of head-to-head studies vs. fluoxetine, paroxetine, and fluvoxamine[1]

Remission at 8 weeks*

EFFEXOR XR / EFFEXOR† (n = 851)‡

SSRIs¶ (n = 748)‡

Placebo (n = 446)‡

Pooled trial population (intent-to-treat): 2,045

Published in: *Br J Psychiatry.* 2001;178:234-241

A pooled analysis of eight randomized, double-blind studies of patients with *DSM-III-R™* major depression or *DSM-IV™* major depressive disorder. Four of the studies were active-controlled, and four were both active- and placebo-controlled. Doses ranged from 75 to 375 mg/day for EFFEXOR, 75 to 225 mg/day for EFFEXOR XR, 20 to 80 mg/day for fluoxetine, 20 to 40 mg/day for paroxetine, and 100 to 200 mg/day for fluvoxamine.

* Last-observation-carried-forward analysis.
† EFFEXOR® (venlafaxine HCl) tablets
‡ n = intent-to-treat.
§ $P<0.001$ EFFEXOR XR/EFFEXOR vs. SSRIs.¶
‖ $P<0.001$ EFFEXOR XR/EFFEXOR vs. placebo.
¶ SSRIs compared were fluoxetine, paroxetine, and fluvoxamine.
# $P<0.001$ SSRIs vs. placebo.

- In this pooled analysis, remission was defined as minimal or no symptoms (HAM-D_{17} ≤7)

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Important Treatment Considerations

EFFEXOR® XR (venlafaxine HCl) is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI because of potential for serious adverse reactions. Based on the half-life of EFFEXOR XR, at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.

Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.5% in GAD studies (doses of 37.5 to 225 mg/day) had sustained BP elevations. The incidence of sustained increases in BP at doses greater than 300 mg/day has not been fully evaluated. Less than 1% discontinued treatment because of elevated BP. Experience with immediate-release venlafaxine in depression studies showed that sustained hypertension was dose related, increasing from 3% to 7% at doses of 100 to 300 mg/day, to 13% at doses above 300 mg/day. Regular BP monitoring is recommended.

The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, delayed ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, delayed ejaculation, anorexia, constipation, nervousness, and sweating.

As with any psychotropic drug, EFFEXOR XR may impair judgment, thinking, or motor skills; patients should be advised to exercise caution until they have adapted to therapy.

Patients should not be abruptly discontinued from antidepressant medication, including EFFEXOR XR. See the Dosage and Administration section of the Prescribing Information.

Please see accompanying Prescribing Information.


EFFEXOR XR / EFFEXOR helped approximately
1/3 more patients
achieve remission* of symptoms
Results of a large pooled analysis of head-to-head studies vs. fluoxetine, paroxetine, and fluvoxamine†
Remission at 8 weeks‡
EFFEXOR XR / EFFEXOR (n =851)§
45%‖
SSRIs¶ (n = 748)§
35%#
Placebo (n = 446)§
25%
Pooled trial population (intent-to-treat): 2,045†
Published in: Br J Psychiatry. 2001;178:234-241.
† Last-observation-carried-forward analysis.
‡ n= intent-to-treat.
§ P<0.001 EFFEXOR XR/EFFEXOR vs. SSRIs.¶
‖ P<0.001 EFFEXOR XR/EFFEXOR vs. placebo.
¶ SSRIs compared were fluoxetine (n = 551), paroxetine (n = 160), and fluvoxamine (n = 34).
# P<0.001 SSRIs vs. placebo.
A pooled analysis of eight randomized, double-blind studies of patients with DSM-III-R™ major depression or DSM-IV™ major depressive disorder. Four of the studies were active-controlled, and four were both active- and placebo-controlled. Doses ranged from 75 to 375 mg/day for EFFEXOR, 75 to 225 mg/day for EFFEXOR XR, 20 to 80 mg/day for fluoxetine, 20 to 40 mg/day for paroxetine, and 100 to 200 mg/day for fluvoxamine.
* In this pooled analysis, remission was defined as HAM-D17 score ≤7.
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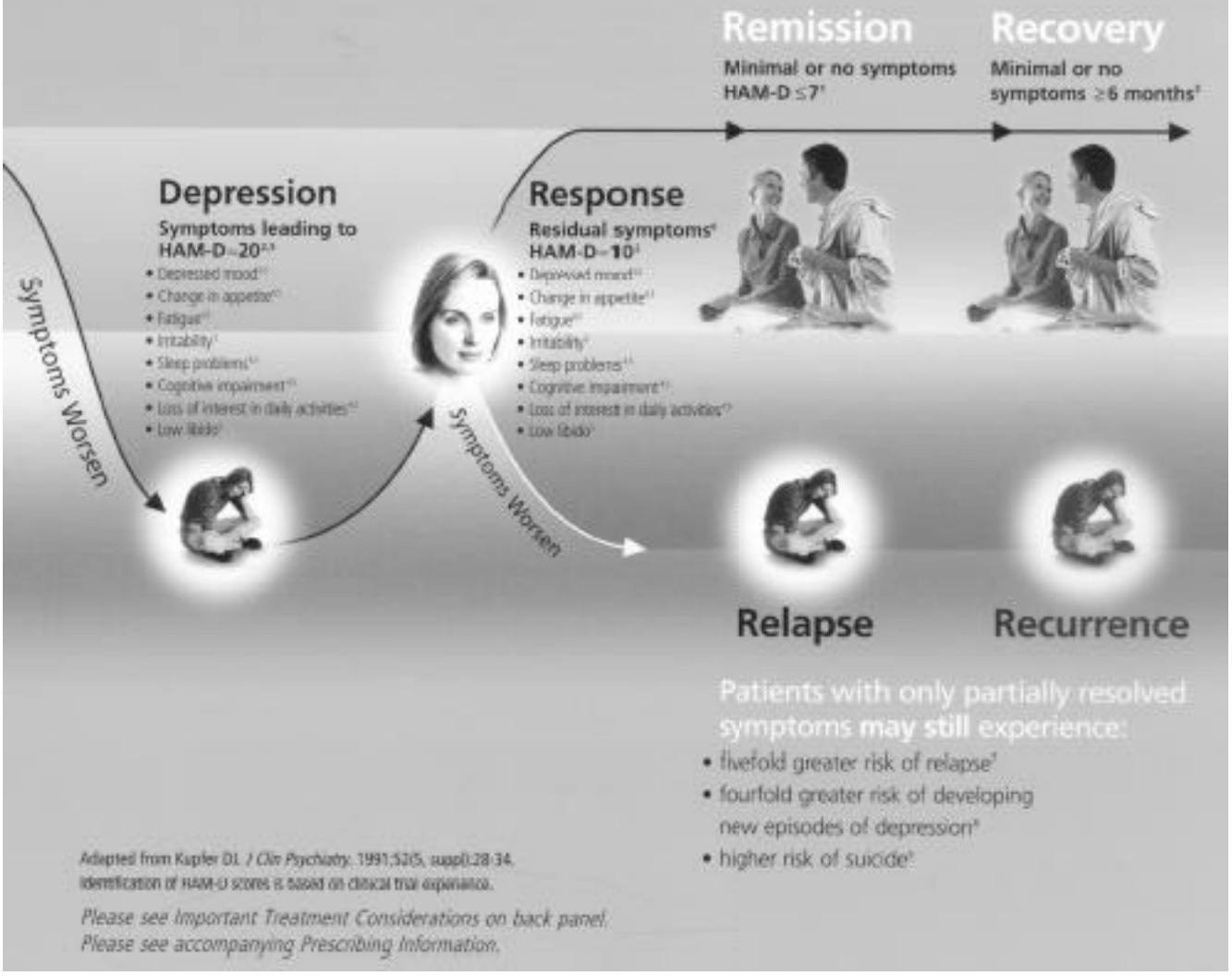
Treatment to remission helps optimize long-term results

- Patients treated to remission are less likely to relapse[1]
- EFFEXOR® XR (venlafaxine HCl) is approved for the long-term (52 weeks) prevention of relapse and recurrence of depression[2]



Patients with only partially resolved symptoms **may still** experience:

- fivefold greater risk of relapse[3]
- fourfold greater risk of developing new episodes of depression[3]
- higher risk of suicide[3]

Adapted from Kupfer DJ. *J Clin Psychiatry*. 1991;52(5, suppl):28-34.
Identification of HAM-D scores is based on clinical trial experience.

Please see Important Treatment Considerations on back panel.
Please see accompanying Prescribing Information.

In depression, when the goal is recovery…

reach for remission of symptoms

EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.

The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2x that of placebo) were nausea, dizziness, somnolence, delayed ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, delayed ejaculation, anorexia, constipation, nervousness, and sweating.

Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.5% in GAD studies (doses of 37.5 to 225 mg/day) had sustained BP elevations. Less than 1% discontinued treatment because of elevated BP. Regular BP monitoring is recommended.

Patients should not be abruptly discontinued from antidepressant medication, including EFFEXOR XR. See the Dosage and Administration section of the Prescribing Information.

References: 1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry.* 2001;178:234-241. **2.** EFFEXOR® (venlafaxine HCl) Extended Release and Immediate Release Prescribing Information. Wyeth Pharmaceuticals, Philadelphia, Pa. **3.** Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry.* 1991;52(5, suppl):28-34.

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Please see brief summary of Prescribing Information on adjacent page.

In Depression,

EFFEXOR® XR offered something extra — Remission* of symptoms in approximately **1/3 more** patients

Results of a large pooled analysis of head-to-head studies vs. fluoxetine, paroxetine, and fluvoxamine[1]

Remission at 8 weeks[1]

EFFEXOR XR / EFFEXOR (n = 851)[2]

45%[§‖]

SSRIs[¶] (n = 748)[2]

35%[#]

Placebo (n = 446)[2]

25%

Pooled trial population (intent-to-treat) = 2,045

A pooled analysis of eight randomized, double-blind studies of patients with *DSM-IV*™ major depression. Four of the studies were active-controlled, and four were both active- and placebo-controlled. Doses ranged from 75 to 375 mg/day for EFFEXOR, 75 to 225 mg/day for EFFEXOR XR, 20 to 80 mg/day for fluoxetine, 20 to 40 mg/day for paroxetine, and 100 to 200 mg/day for fluvoxamine.

[1] Last-observation-carried-forward analysis.
[2] n = intent-to-treat.
[§] P<0.001 EFFEXOR XR/EFFEXOR vs. SSRIs.[¶]
[‖] P<0.001 EFFEXOR XR/EFFEXOR vs. placebo.
[¶] SSRIs studied were fluoxetine, paroxetine, and fluvoxamine.
[#] P<0.001 SSRIs vs. placebo.

***Remission is defined as minimal or no symptoms (HAM-D_{17} ≤ 7).[1]**

EFFEXOR® (venlafaxine HCl) tablets

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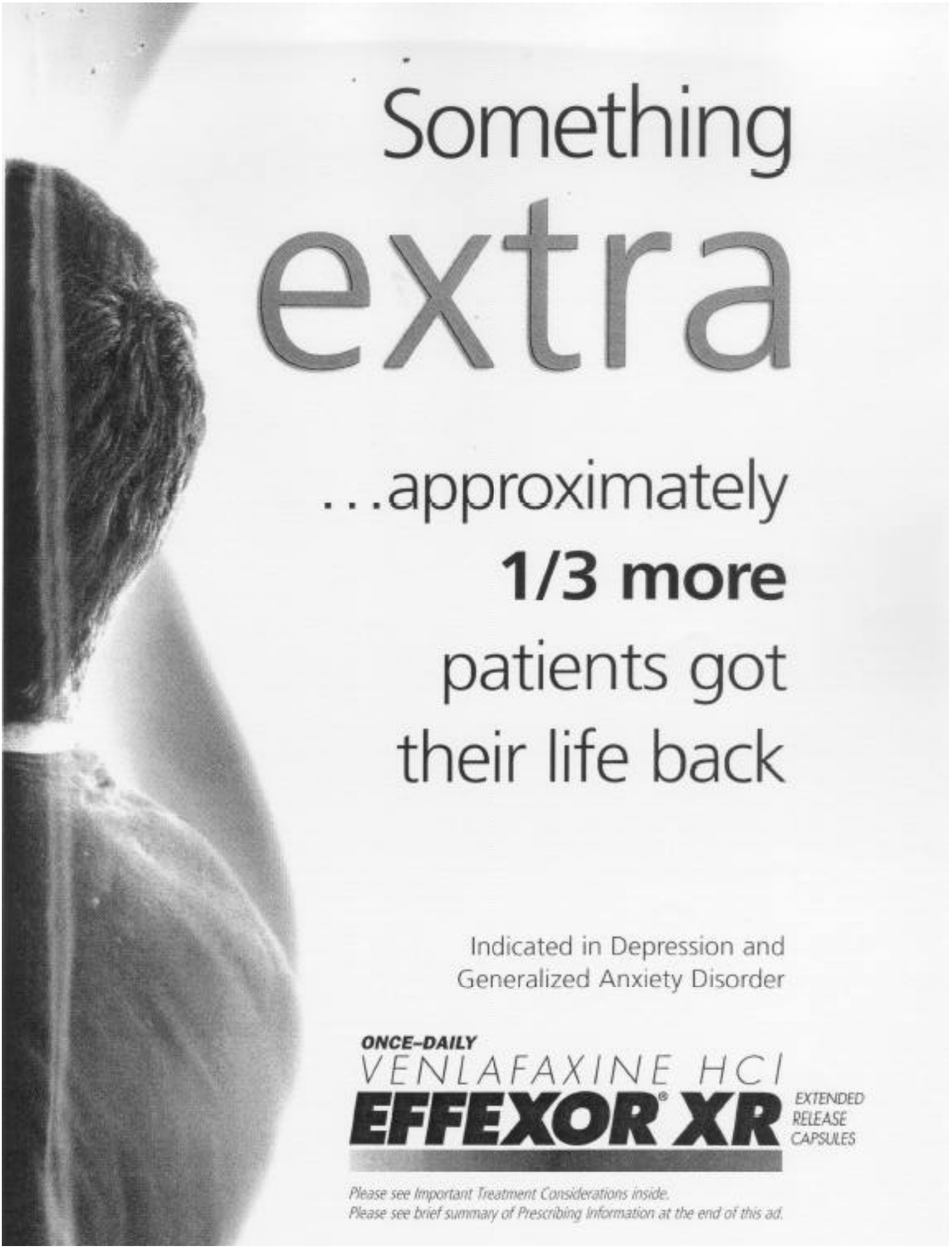
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extra
...approximately
1/3 more
patients got
their life back
Indicated in Depression and
Generalized Anxiety Disorder
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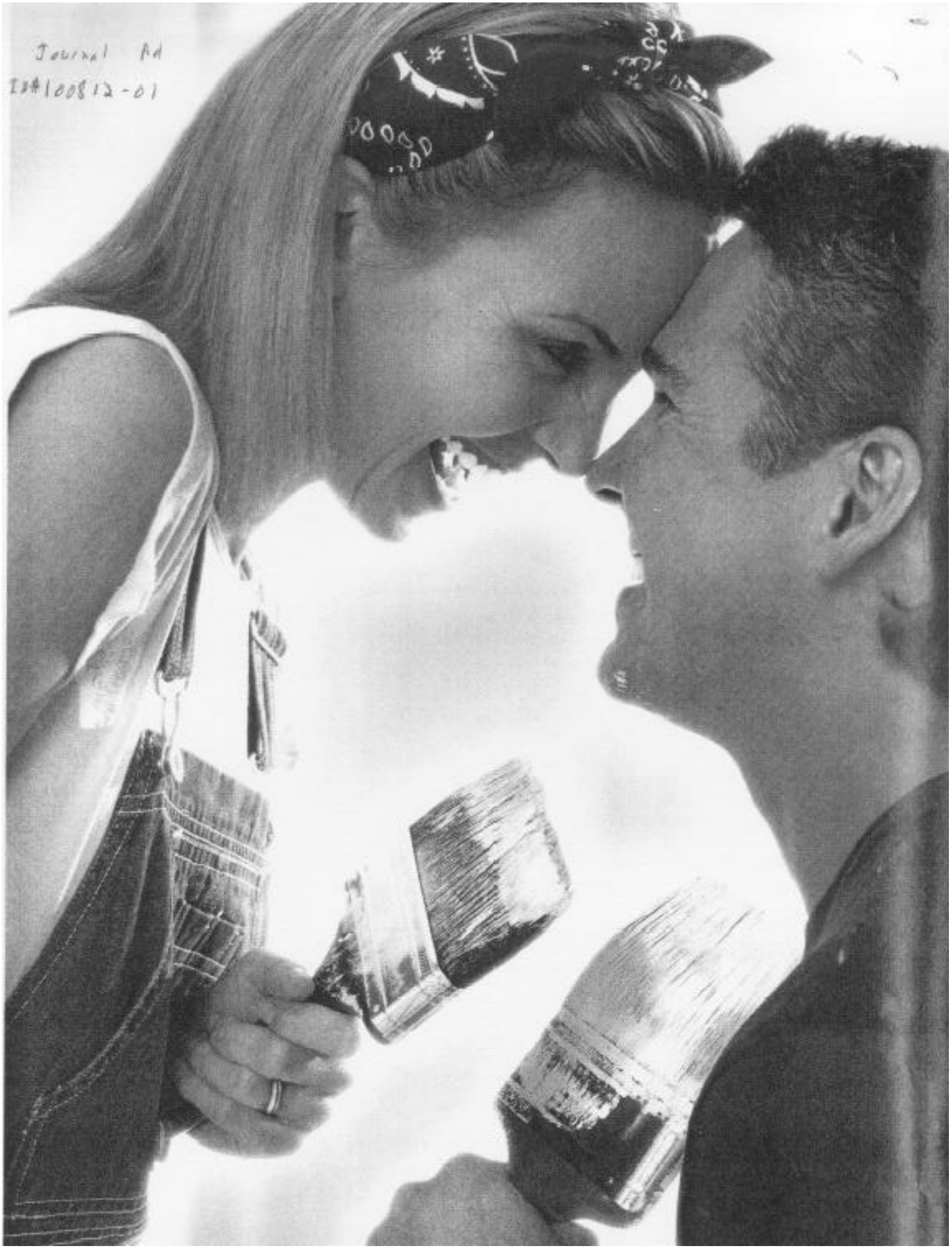
Please see brief summary of Prescribing Information at the end of this ad.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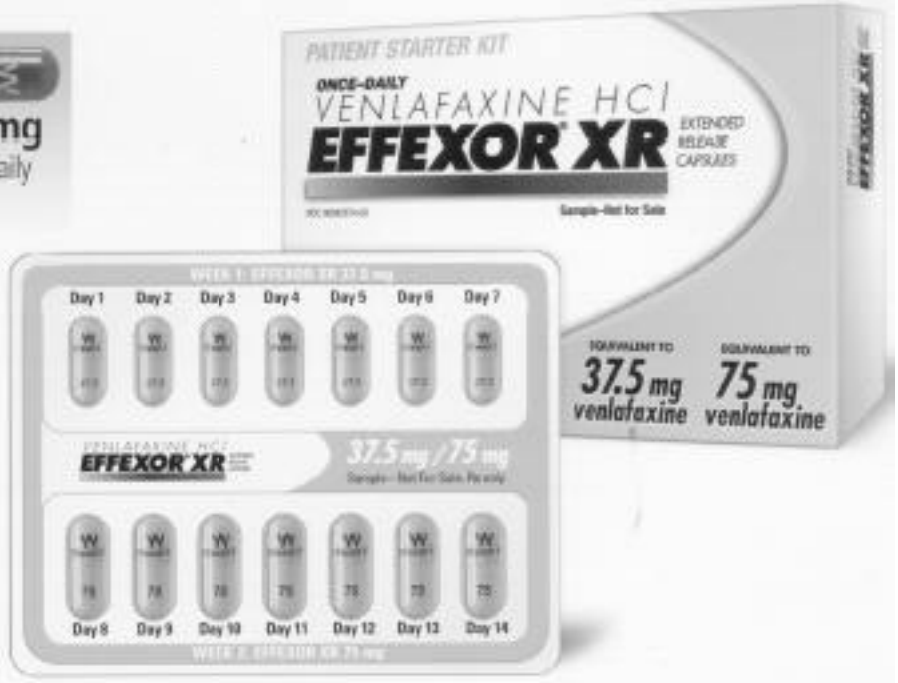
A high rate of remission

- Results of this pooled analysis have shown that approximately 1/3 more patients achieved remission with EFFEXOR XR/EFFEXOR[1]
  - — Remission rates were 45% for EFFEXOR XR/EFFEXOR, 35% for SSRIs (fluoxetine, paroxetine, and fluvoxamine), and 25% for placebo
- Inhibiting reuptake of serotonin and norepinephrine may help more patients reach remission[2]
- The efficacy of EFFEXOR XR provides strong evidence for its use as first-line therapy[1]

Simple to start

Available dosage strengths:



Initial dosing option of 37.5 mg once daily for 4 to 7 days to allow new patients to adjust to the medication before increasing to 75 mg/day.

Usual starting dose of 75 mg/day has demonstrated significant response rates in clinical trials.[3]

Increase dose by up to 75 mg/day at intervals of no less than 4 days. Upward titration to a maximum of 225 mg/day of EFFEXOR XR can be beneficial in patients who do not respond fully to 75 mg/day.[3] Experience with EFFEXOR XR at doses higher than 225 mg/day is very limited.

Note: Absorption is unaffected by food; however, dosing with meals is recommended.

The capsules pictured are actual size.

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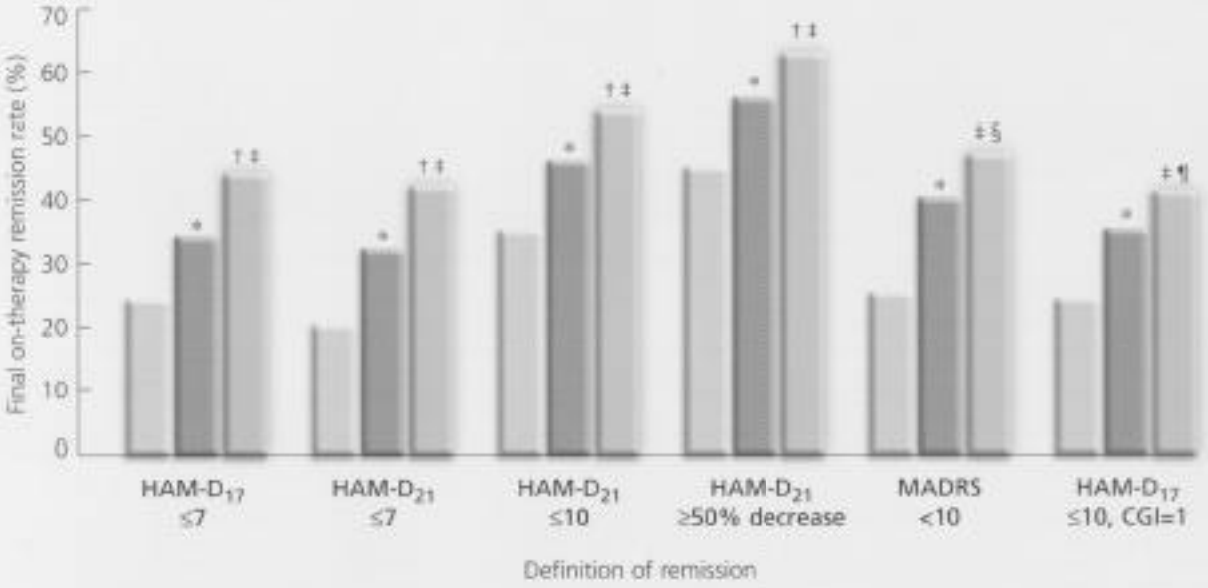
Results consistent across differing measures of remission

Regardless of the definition used, EFFEXOR XR/EFFEXOR was significantly effective in achieving remission



* $P<0.001$ SSRI vs. placebo.
† $P<0.001$ venlafaxine vs. SSRI.
‡ $P<0.001$ venlafaxine vs. placebo.
§ $P=0.023$ venlafaxine vs. SSRI.
¶ $P=0.014$ venlafaxine vs. SSRI.

- EFFEXOR XR/EFFEXOR was significantly more effective than SSRIs (fluoxetine, paroxetine, fluvoxamine) on eight alternative outcomes (remission) criteria: HAM-D_{17} ≤7, HAM-D_{21} ≤7, HAM-D_{21} ≤10, HAM-D_{21} ≥50% decrease, MADRS <10, HAM-D_{17} ≤10 [CGI=1], HAM-D_{21} ≤8, HAM-D_{17} ≤10

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Consistent, proven efficacy in head-to-head trials

Studies **included** in pooled analysis

Study	Intent-to-Treat Patient Pop.	Remission criterion	Remission rate %			Duration
			EFFEXOR XR / EFFEXOR	SSRI	Placebo	Weeks
Rudolph & Feiger, 1999	295	HAM-D_{17} ≤7	42	23 (fluoxetine)	23	8
Silverstone et al, 1999	353	HAM-D_{17} ≤7	29	28 (fluoxetine)	14	8*
Salinas et al, 1997	323	HAM-D_{17} ≤7	49	36 (paroxetine)	38	8
Rudolph et al, 1998a	439	HAM-D_{17} ≤7	44	34 (fluoxetine)	23	6
Clerc et al, 1994	67	HAM-D_{17} ≤7	55	26 (fluoxetine)	—	6
Study 347	111	HAM-D_{17} ≤7	51	35 (fluvoxamine)	—	6
Dierick et al, 1996	302	HAM-D_{17} ≤7	52	45 (fluoxetine)	—	8
Study 349	155	HAM-D_{17} ≤7	35	35 (paroxetine)	—	8

* This study lasted 12 weeks but results are presented at week 8 for consistency.

Additional studies cited in Thase et al*

Study	Intent-to-Treat Patient Pop.	Remission criterion	Remission rate %			Duration
			EFFEXOR XR / EFFEXOR	SSRI	Placebo	Weeks
Tylee et al, 1997	341	MADRS ≤6	35	34 (fluoxetine)	—	12
McPartlin et al, 1998	361	HAM-D ≤6	54	52 (paroxetine)	—	12
Diaz-Martinez et al, 1998	145	CGI=1	41	36 (fluoxetine)	—	8
Costa e Silva, 1998	382	CGI=1 HAM-D ≤7	58 60	35 60 (fluoxetine)	—	8
Poirier & Boyer, 1999	123	HAM-D <10	37	18 (paroxetine)	—	6
Alves for the Venlafaxine Study Group, 1999	87	HAM-D ≤8	30	11 (fluoxetine)	—	12
Mehtonen et al, 2000	147	HAM-D <10	53	38 (sertraline)	—	8
Ballús et al, 2000	84	HAM-D <8	59	31 (paroxetine)	—	12
Tzanakaki et al, 2000	109	CGI=1 HAM-D <7	51 41	32 36 (fluoxetine)	—	6

* Thase et al did not include these studies in the pooled analysis because they did not have access to original data sets.

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IMPORTANT TREATMENT CONSIDERATIONS

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References: 1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry.* 2001;178:234-241. **2.** EFFEXOR® (venlafaxine HCl) Extended-Release and Immediate-Release Prescribing Information, Wyeth Pharmaceuticals, Philadelphia, Pa. **3.** Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Arch Gen Psychiatry.* 1991;48:851-855. **4.** *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Text rev. Washington, DC: American Psychiatric Association; 2000:356. **5.** Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62. **6.** Stahl SM. Why settle for silver, when you can go for gold? Response vs. recovery as the goal of antidepressant therapy. *J Clin Psychiatry.* 1999;60:213-214. **7.** Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *Am J Psychiatry.* 1992;149:1046-1052. **8.** Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry.* 2000;157:1501-1504. **9.** Stahl SM. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* 2nd ed. Cambridge, UK: Cambridge University Press; 2000:152.