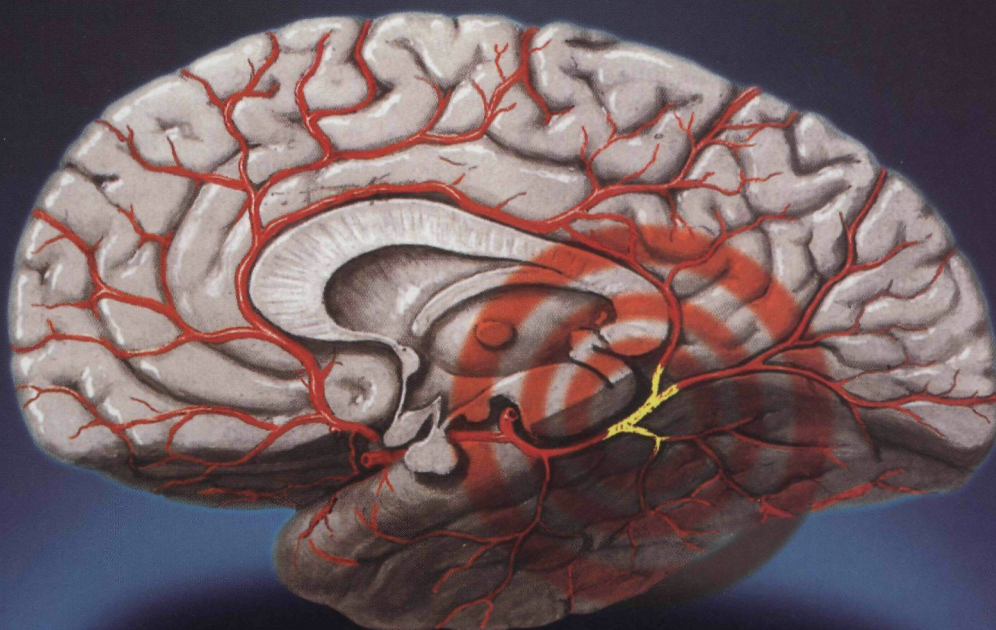


CNS SPECTRUMS™

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

Migraine

**PATHOPHYSIOLOGY & COMORBIDITY:
A WINDOW INTO PSYCHIATRY AND NEUROLOGY**



- **MIGRAINE: A BORDER BETWEEN PSYCHIATRY AND NEUROLOGY**
D. Marazziti
- **SEROTONIN FUNCTION AND GENDER EFFECTS IN MIGRAINE PRODUCTION AND OCD**
C.M. Wong, E. Hollander
- **CONSENSUS STATEMENT ON THE UNDERTREATMENT OF DEPRESSION**
R.M.A. Hirschfeld, M.B. Keller, et al.
- **CATATONIC SYNDROME IN AN ADOLESCENT MALE IMMIGRANT: A CASE REPORT**
G. P. Panikkar, D. Mayerhoff

CME Mount Sinai **3**

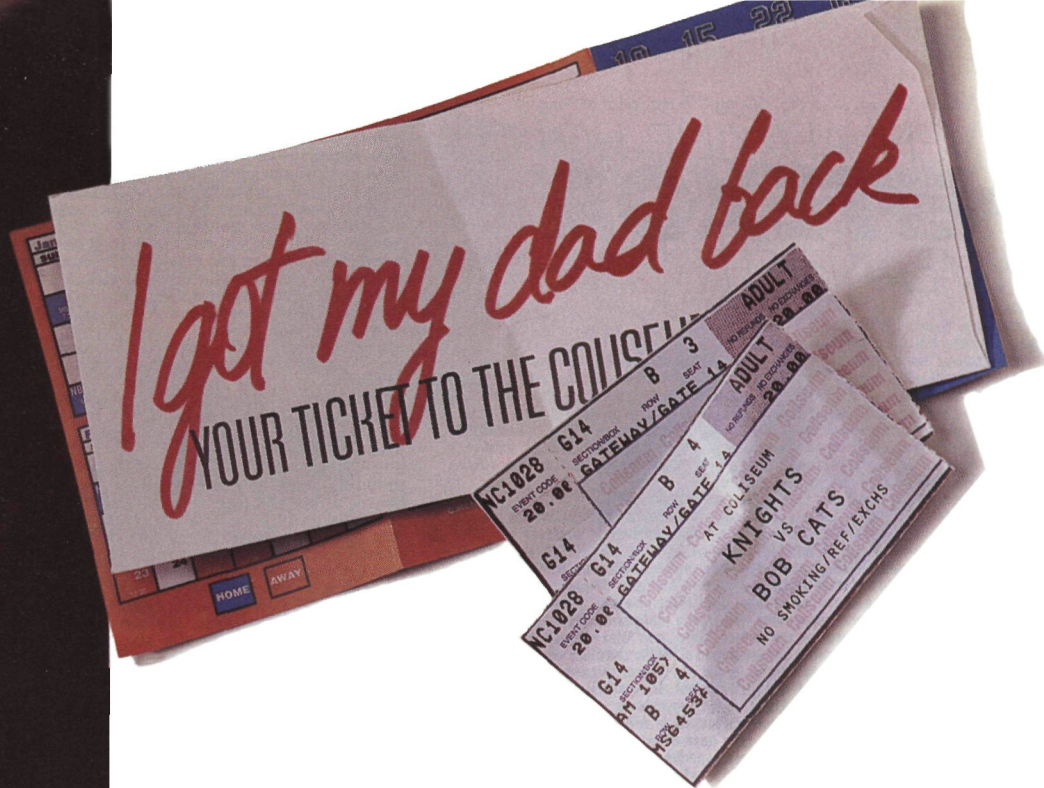
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PHOTO ESSAY

The late Frank Netter's peerless medical illustrations have informed generations of physicians on the particulars of cerebrovascular anatomy. These drawings illustrate and describe the normal arteries and veins of the brain, showing the relationship of the many arterial and venous branches to the adjacent neuroanatomy. This computer-enhanced rendition of a Netter drawing is being used to illustrate some of the biological causes of migraine headaches.

ARTICLES INSIDE.



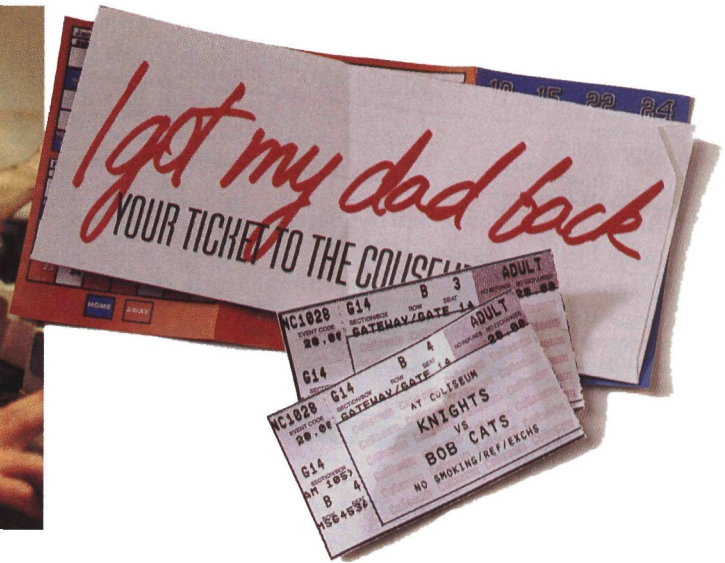


Broken hearts require special care.

When depressed patients are also suffering from cardiovascular disease, drug-drug interaction is a critical concern.^{2,3} Antidepressants that compete with cardiovascular agents utilizing the CYP2D6 and/or the CYP3A4 isoenzymes may cause potentially harmful drug interactions.^{2,3} EFFEXOR, while effectively treating depression, has a low potential to interact with other agents utilizing these CYP isoenzymes.³ By relieving depression, EFFEXOR can help bring patients and families together again.

VENLAFAXINE HCl
EFFEXOR[®]
MEANS EFFECTIVE

Please see brief summary of Prescribing Information accompanying this advertisement.



- Efficacy clearly demonstrated in depressed outpatients⁶
- Effective treatment in hospitalized depressed patients with major depressive disorder and melancholia meeting DSM-III-R™ criteria⁷

EFFEXOR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR 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, at least 7 days should be allowed after stopping EFFEXOR before starting an MAOI.

Treatment with EFFEXOR is associated with sustained increases in blood pressure (BP) in some patients. The incidence was seen at >5% at dosages above 200 mg/day and appears to be dose dependent. It is recommended that patients have regular BP monitoring. For patients experiencing a sustained increase in BP, dose reduction or treatment discontinuation should be considered.

Low potential exists for interaction in patients taking lithium, diazepam, or cimetidine.⁴

—In combination with cimetidine, EFFEXOR should be used with caution in patients with preexisting hypertension, or in elderly patients, or in patients with hepatic dysfunction, as the

interaction between the two drugs in these patients is not known and could be more pronounced.⁶

EFFEXOR at steady state increased the AUC of a single dose of haloperidol by 70%. The mechanism explaining this finding is unknown.

EFFEXOR is a relatively weak inhibitor of cytochrome P450 2D6.⁴

—Weak inhibition of cytochrome P450 2D6 is an important characteristic when considering other drugs metabolized by this enzyme.⁴

—Potential exists for a drug interaction between EFFEXOR and drugs that inhibit cytochrome P450 2D6 metabolism.⁴

The most common adverse events reported in EFFEXOR clinical trials (incidence >10% and ≥2× that of placebo) were nausea, somnolence, dry mouth, dizziness, constipation, nervousness, sweating, asthenia, abnormal ejaculation/orgasm, and anorexia.

EFFEXOR has not demonstrated any clinically significant impairment of psychomotor, cognitive, or complex behavior performance in healthy volunteers. However, as with any psychotropic drug, EFFEXOR may impair judgment, thinking, or motor skills; patients should be advised to exercise caution until they have adapted to therapy.

Please see brief summary of Prescribing Information on previous page of this advertisement.

Tablets: 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg

VENLAFAXINE HCl
EFFEXOR[®]

MEANS EFFECTIVE

SEROTONIN TRANSPORTER INHIBITOR (STI) ANTIDEPRESSANT-RELATED
INHIBITION OF CYTOCHROME P450 HEPATIC MICROSOMAL ISOENZYMES (IN VITRO)

Antidepressant Active metabolite	Isoenzyme			
	3A4	2D6	1A2	2C9
Fluoxetine	+	+++	+	++
Norfluoxetine	+/+++	+++	+	+
Sertraline	++	+	+	+
Desmethylsertraline	++	+++	+	++
Paroxetine	+	+	+++	—
Fluvoxamine	++	+	—	—
Nefazodone	+++	+	—	NA
Venlafaxine	—	NA	—	NA
O-desmethylvenlafaxine	—	NA	—	—
N-desmethylvenlafaxine	—	—	—	—

+ , mild; ++ , moderate; +++ , strong; — , no significant effect; NA, data not yet available.

From Shader et al.¹

The above data are not meant to imply clinical benefit.

The Science Makes Sense

Drug-drug interactions are a concern in the treatment of depression.

Many people who seek treatment for depression are often already receiving pharmacologic treatment for a physical or another emotional disorder. With this in mind, it is incumbent upon the physician treating the depressed patient to be cognizant of the metabolic pathways of prescribed pharmacologic treatment.

Consider the cytochrome P450 (CYP) system

The cytochrome P450 system present in the liver is involved in the oxidative metabolism of numerous drugs.² Among the more than 30 enzymes currently recognized, the following systems—CYP2D6, CYP3A4, CYP1A2, CYP2C9, and CYP2C19—have been identified as important in the metabolism of psychoactive and other commonly prescribed drugs.^{2,3} *In vitro* studies have demonstrated that venlafaxine is a relatively weak inhibitor of CYP2D6 as compared to the SSRIs and has very weak or no inhibitory potentials at CYP3A4, CYP1A2, and CYP2C9.^{2,4,5} The clinical significance of these *in vitro* data is unknown.

EFFEXOR...New data demonstrate a favorable drug interaction profile

Completed *in vivo* studies confirm the *in vitro* data stated previously. One study, using dextromethorphan as a clinical marker, indicated that there is a decrease in the relative risk of clinically significant interactions between EFFEXOR and drugs metabolized by CYP2D6.⁶ The isoenzyme CYP2D6 is involved in the metabolism of many drugs, such as codeine, propranolol, other beta-blockers, and certain antiarrhythmic agents.³ Other *in vivo* studies confirm that EFFEXOR has little or no potential to inhibit CYP3A4. EFFEXOR does not significantly inhibit the metabolism of alprazolam, diazepam, terfenadine, and carbamazepine, all substrates for CYP3A4.^{2,4}

Efficacy and safety profiles for the special needs of today's depressed patients

EFFEXOR is effective therapy for depressed outpatients. EFFEXOR is effective even in severely depressed patients.

When considering the needs of your depressed patients who are on concomitant therapies, the science makes sense in selecting EFFEXOR as proven treatment for depression.

VENLAFAXINE HCl
EFFEXOR[®]
MEANS EFFECTIVE

Please see brief summary of Prescribing Information accompanying this advertisement.

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**Now indicated for
panic disorder
and obsessive-
compulsive
disorder**

She's anxious.

She's agitated.

She can't sleep.

She's depressed.

***Paxil* effectively relieves
depression and associated
symptoms of anxiety.¹⁻⁴**

60% to 90% of depressed patients exhibit associated symptoms of anxiety such as agitation, sleep disorders, weight loss and gastrointestinal problems^{5,6}

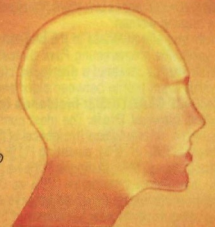
Incidence of agitation with *Paxil* is comparable to placebo (2.1% vs 1.9%); incidence of nervousness and of anxiety vs placebo is 5.2% vs 2.6% and 5.0% vs 2.9%, respectively⁷

Most common adverse events include: nausea, somnolence, asthenia, dizziness, insomnia, sweating, ejaculatory disturbance and other male genital disorders.*⁷ Concomitant use of *Paxil* in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

*Incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo.

Please see brief summary of prescribing information on adjacent page of this advertisement.

ONCE-DAILY
PAXIL[®]
PAROXETINE HCl



**LIFTS DEPRESSION.
LOWERS ASSOCIATED ANXIETY
SYMPTOMS.**

SB SmithKline Beecham
Pharmaceuticals
Philadelphia, PA 19101

JANSSEN  PHARMACEUTICA
RESEARCH FOUNDATION
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Table of Contents

FEATURE ARTICLES

- 16** Migraine: A Border Between Psychiatry and Neurology
BY DONATELLA MARAZZITI, MD
- 24** Serotonin Function and Gender Effects in Migraine Production and OCD
BY CHERYL M. WONG, MD, AND ERIC HOLLANDER, MD
- 33** Catatonic Syndrome in an Adolescent Male Immigrant: A Case Report
BY GOPAKUMAR P. PANIKKAR, MD, AND DAVID MAYERHOFF, MD
- 39** Consensus Statement: The National Depressive and Manic-Depressive Association Consensus Statement on the Undertreatment of Depression
BY ROBERT M.A. HIRSCHFELD, MD, MARTIN B. KELLER, MD, SUSAN PANICO, BERNARD S. ARONS, MD, DAVID BARLOW, PHD, FRANK DAVIDOFF, MD, JEAN ENDICOTT, PHD, JACK FROOM, MD, MICHAEL GOLDSTEIN, MD, JACK M. GORMAN, MD, DON GUTHRIE, PHD, RICHARD G. MAREK, MD, THEODOR A. MAURER, ROGER MEYER, MD, KATHARINE PHILLIPS, MD, JERILYN ROSS, MA, LCSW, THOMAS L. SCHWENCK, MD, STEVEN S. SHARFSTEIN, MD, MICHAEL E. THASE, MD, AND RICHARD J. WYATT, MD

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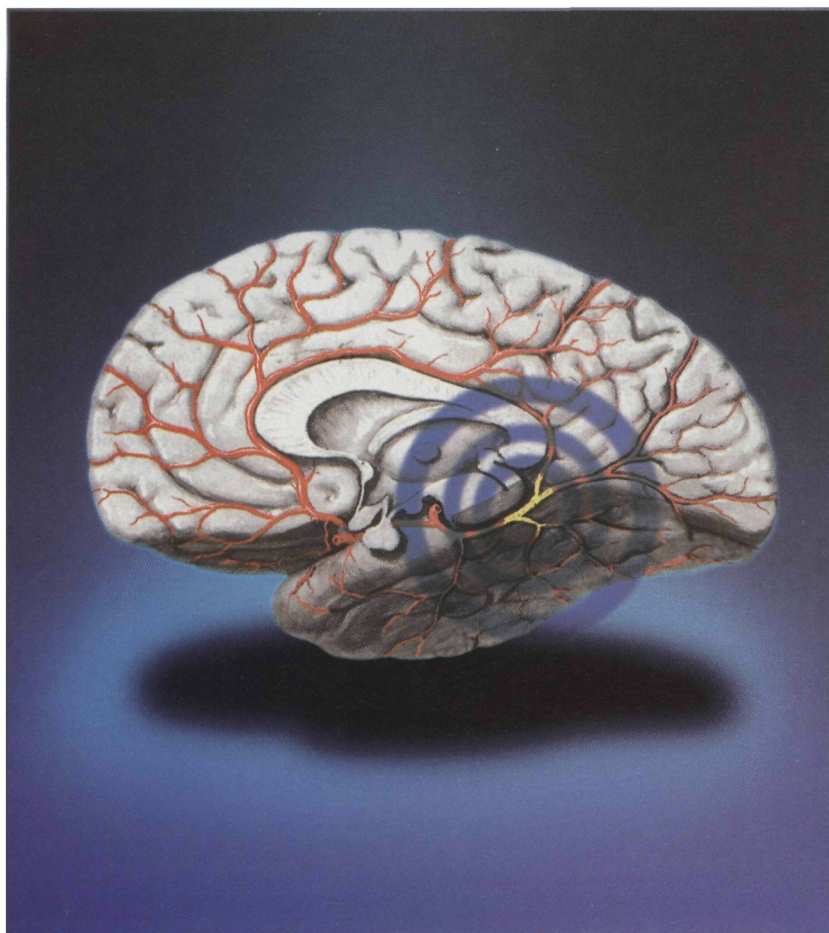


Illustration by Thomas Stevens

PHOTO ESSAY:

Dr. Frank Netter's peerless medical illustrations have informed generations of physicians on the particulars of cerebrovascular anatomy. For clinical practitioners of the neurosciences, knowledge of the cerebrovascular anatomy is especially helpful in evaluating patients with suspected cerebrovascular disease, infarct, intracerebral hemorrhage, vascular malformation, aneurysm, or tumor. In this issue, for example, Dr. Netter's drawings are being used to illustrate some of the biological and vascular causes of migraine headaches.

These drawings illustrate and describe the normal arteries and veins of the brain, showing the relationship of the many arterial and venous branches to the adjacent neuroanatomy. In addition, they identify the territories supplied and drained by these smaller vessels. In some patients, for whom computed tomography and angiography alone may not provide a definitive diagnosis, knowledge of the vascular anatomy involved enables the clinician to more effectively plan treatment.

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Table of Contents

DEPARTMENTS/MONTHLY COLUMNS

DIGEST

8 Digested excerpts in February's journal

NOTA BENE

14 Briefs from the Fields of Neurology & Psychiatry: Quality of life issues in clinical practice have major impact for epileptic patients

LETTERS

28 — Antecedents in Schizophrenics — ABO Blood Groups, Cognition and Temperature in Alzheimer's Disease and Dementia

MIDPOINT & COMMENTARY

30 Migraine: Opening the Window to Psychiatry and Neurology BY ERIC HOLLANDER, MD

AUTHORS' GUIDELINES

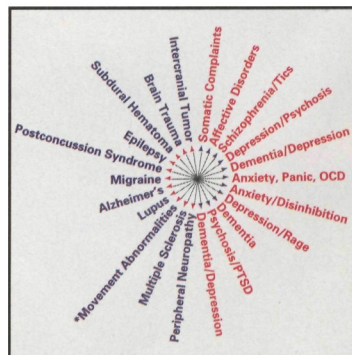
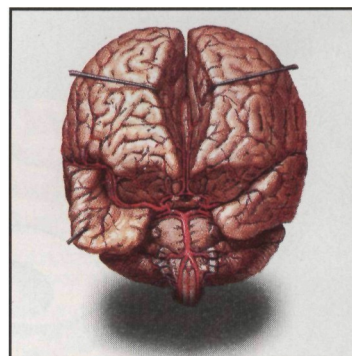
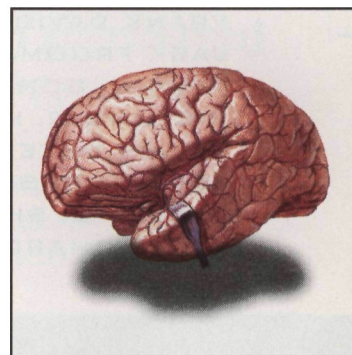
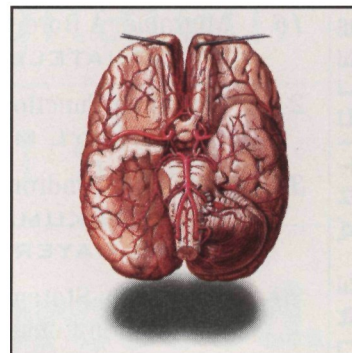
32 1997 submission for publication guidelines.

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INDICES

56 By subject and author.



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Research committed to making
memory lane last a little longer...



A collaboration dedicated to advances in Alzheimer's therapy.