Dalhousie Research Day
Winning Abstracts

Each year, the Dalhousie Medical School holds a medical research competition where students present work either as a poster or an oral presentation. The following abstracts are from the presentations judged to be the best in 1997, in both the oral and poster categories.

ORAL PRESENTATIONS

First Place

Non-compensated, Informal Caregivers for Community Acquired Pneumonia

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Background: Although there is a vast amount of research on informal caregivers, the studies are overwhelmingly focused on caregivers of patients who are chronically ill. It is unclear whether the findings of this research can be transferred to caregivers of patients with acute diseases.

Objectives: (1) to describe caregivers and their importance in the management of patients diagnosed with community acquired pneumonia (CAP); (2) to identify predictors of the presence of a caregiver for patients with CAP; and (3) to determine the effects of caregiving on the daily life of the caregiver.

Setting: Four university teaching hospitals and one clinical site with an health maintenance organisation.

Subjects: 712 consecutive patients diagnosed with pneumonia and at low risk for mortality; 191 non-compensated, informal caregivers for these patients.

Design: Prospective observational study (patients) and structured prospective interviews (caregivers) at 7, 30 and 90 days post patient pneumonia diagnosis.

Measurements: Demographics (patients and caregivers), patient outcomes and assistance provided to the patient, functional disability resulting from caregiving and attitudes toward the caregiving role.

Results: 30.3% of patients received caregiver assistance during the 90 day post-diagnosis study period. Patients who were female, married, younger, treated on an inpatient basis or at a higher risk stratum (within low risk) were more likely to have a caregiver (all $p < 0.05$). The mean age of the caregivers was 44 years and caregivers were more likely to be female (61.2%), employed (55.1%) and the spouse of the patient (57.5%). Caregivers spent a mean of 9.3 hours a week on caregiving activities specific to the pneumonia illness. Inpatients received more types of assistance and more hours of assistance than did outpatients. 67.9% of employed caregivers experienced at least moderate employment interference as a result of caregiving. Caregivers admitted mild functional impairment and mild agreement with negative attitudes toward caregiving. Level of activity restriction was closely correlated with negative attitude scale (R-squared = .978).

Conclusions: A large proportion of low risk patients with CAP identify caregivers during their episode of illness. These caregivers provide considerable assistance and endure life interference as a result of caregiving activities.

Daria Manos is a third year medical student at Dalhousie University. She came to Dalhousie after finishing her BA at McGill. While there, she completed McGill's liberal arts program "Humanistic Studies" and was the first student at McGill to graduate with a minor in science for arts students. She also completed a second minor in social studies of medicine. Her research attention is currently focused on Emergency Department triage systems.

Second Place

Increased Expression of Basic Fibroblast Growth Factor (bFGF) in the Neonatal Brain Following Glutamate Induced Neurotoxicity

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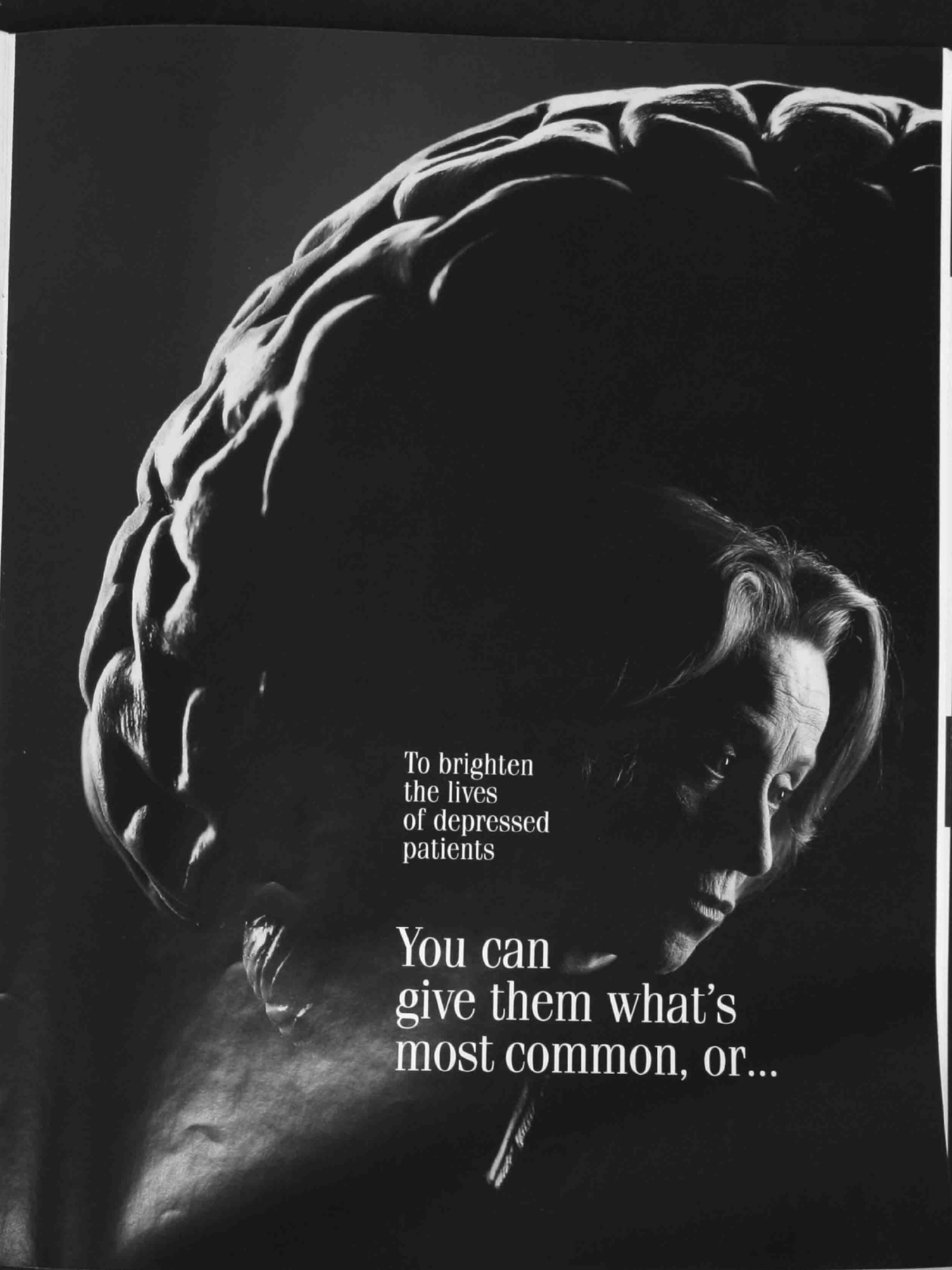
Glutamate, an excitatory neurotransmitter, is emerging as one of the key factors involved in sexual maturation. Treatment of neonatal rats with glutamate has been shown to induce precocious puberty by an unknown mechanism. Smyth and Wilkinson (1994) demonstrated that a single treatment of GLU (monosodium glutamate) shortly after birth, or treat-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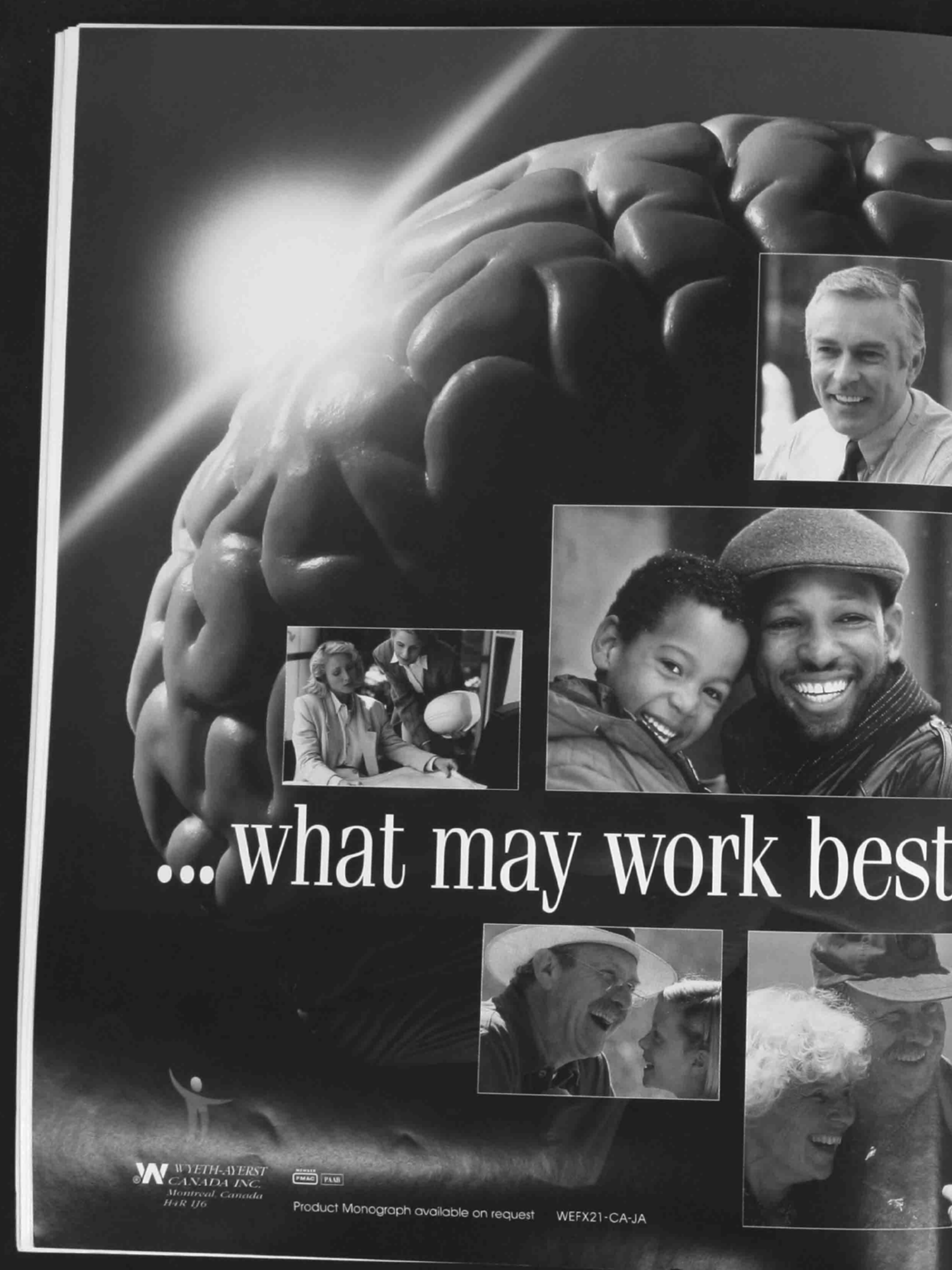
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NEW

NOW ON PROVINCIAL FORMULARIES: B.C., SASKATCHEWAN, MANITOBA, QUEBEC, NOVA SCOTIA

for them.[f]

SEROTONIN
NOREPINEPHRINE
REUPTAKE
INHIBITOR

A new day has dawned in the treatment of depression

Introducing Effexor XR

- Effective for mild, moderate and severe depression[1-5]
- Better remission rates than fluoxetine at week 8[††] and paroxetine at week 8[◇] in comparative studies[2,5]
- Effective for symptoms of associated anxiety in depressed patients[6,7]
- Generally well tolerated[1‡]
- Low potential for drug-drug interactions *in vitro* and *in vivo*[1,8-10]
- Efficacy combined with value in a once-daily formulation[†1] to help maximize compliance

Depressed patients who are currently being treated at a therapeutic dose with Effexor b.i.d. may be switched to Effexor XR once-daily at the nearest equivalent dose (mg/day).[1]

f The efficacy of Effexor XR for treating major depression has been established in adult outpatients. The effectiveness of Effexor XR in long-term use (more than 8-12 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use it for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

†† Full remission rates (HAM-D total < 7) LOCF analysis, in 8-week randomized, double-blind study of venlafaxine XR (n=95), fluoxetine (n=103) and placebo (n=97). The full remission rate at week 8 was nearly twice as high in the venlafaxine XR group as it was in the fluoxetine group, a statistically significant difference ($p \leq 0.05$) only at that time point.

◇ 8-week randomized, double-blind, placebo-controlled study of 323 patients comparing venlafaxine XR 75 mg and 150 mg and paroxetine 20 mg once-daily. Venlafaxine XR 75 mg was significantly ($p < 0.05$) more effective than paroxetine 20 mg on HAM-D scores at weeks 1, 2, 4, 6 and 8 and venlafaxine XR 150 mg was significantly ($p < 0.05$) more effective than paroxetine on the HAM-D at weeks 4, 6, and 8.

Remission rates with venlafaxine XR 75 and 150 mg were 55% compared with 46% and 44% in the placebo and paroxetine groups, respectively.

‡ In clinical trials, the most commonly observed adverse events associated with the use of Effexor XR (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients were: abnormal dreams, anorexia, dizziness, dry mouth, nausea, nervousness, somnolence, sweating, and tremor as well as abnormal ejaculation/orgasm in men. There was evidence of adaptation to some adverse events with continued therapy (e.g., dizziness and nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth). Some adverse events appeared to be dose-dependent.

† 75 mg/day is the recommended dosage for most patients. Dosage adjustment is necessary in patients with hepatic or renal impairment. Treatment with venlafaxine has also been associated with modest but sustained increases in blood pressure.[1]

New Product Monograph available on request.

NEW ONCE-DAILY

EFFEXOR® XR

Venlafaxine HCl Extended Release Capsules

MAKE IT YOUR FIRST CHOICE FOR EFFECTIVENESS

NEW ONCE-DAILY

EFFEXOR® XR

Venlafaxine HCl Extended Release Capsules

EFFEXOR® (venlafaxine hydrochloride) Tablets
EFFEXOR® XR (venlafaxine hydrochloride) Extended Release Capsules

THERAPEUTIC CLASSIFICATION
ANTIDEPRESSANT

ACTIONS AND CLINICAL PHARMACOLOGY
Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents.

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics
Venlafaxine is well absorbed, with peak plasma concentrations with EFFEXOR® Tablets occurring approximately 2 hours after dosing. Venlafaxine is extensively metabolized, with O-desmethylvenlafaxine, (ODV, the only major active metabolite) peak plasma levels occurring approximately 4 hours after dosing. Following single doses of 25 to 75 mg, mean (± SD) peak plasma concentrations of venlafaxine range from 37 ± 14 to 102 ± 41 ng/mL, respectively, and are reached in 2 ± 1 hours, and mean peak ODV plasma concentrations range from 61 ± 13 to 168 ± 37 ng/mL and are reached in 4 ± 2 hours. Approximately 87% of a single dose of venlafaxine is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%), and 92% of the radioactive dose is recovered within 72 hours. Therefore, renal elimination of venlafaxine and its metabolites is the primary route of excretion.

After administration of EFFEXOR® XR (extended release capsules), the peak plasma concentrations of venlafaxine and ODV are attained within 6.0±1.5 and 8.8±2.2 hours, respectively. The rate of absorption of venlafaxine from the EFFEXOR® XR capsule is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of EFFEXOR® XR (15±6 hours) is actually the absorption half-life instead of the true disposition half-life (5±2) hours observed following administration of an EFFEXOR® (venlafaxine hydrochloride) immediate release tablet.

Multiple-Dose Pharmacokinetic Profile (Tablets and Extended Release Capsules)
Steady-state concentrations of both venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. The clearance of venlafaxine is slightly (15%) lower following multiple doses than following a single dose.

Venlafaxine and ODV exhibited approximately linear kinetics over the dose range of 75 to 450 mg/day.

The mean±SD steady-state plasma clearances of venlafaxine and ODV are 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively.

Venlafaxine and ODV renal clearances are 49±27 and 94±56 mL/h/kg, respectively, which correspond to 5±3.0% and 25±13% of an administered venlafaxine dose recovered in urine as venlafaxine and ODV, respectively.

When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended release capsule, the exposure (AUC, area under the concentration curve) to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower following treatment with the extended release capsule. Therefore, the EFFEXOR® XR capsules provide a slower rate of absorption, but the same extent of absorption (i.e., AUC), as the venlafaxine immediate release tablet.

Venlafaxine and ODV are 27 and 30% bound to human plasma proteins, respectively. Therefore, administration of venlafaxine to a patient taking another drug that is highly protein-bound should not cause increased free concentrations of the other drug. Following intravenous administration, the steady-state volume of distribution of venlafaxine is 4.4±1.9 L/kg, indicating that venlafaxine distributes well beyond the total body water.

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is approximately 45%. The primary metabolite of venlafaxine is ODV, which is an active metabolite. Venlafaxine is also metabolized to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalysed by CYP2D6 and that the formation of N-desmethylvenlafaxine is catalysed by CYP3A3/4. The results of the *in vitro* studies have been confirmed in a clinical study with subjects who are CYP2D6 poor and extensive metabolizers. However, despite the metabolic differences between the CYP2D6 poor and extensive metabolizers, the total exposure to the sum of the two active species (venlafaxine and ODV, which have comparable activity) was similar in the two metabolizer groups.

Food has no significant effect on the absorption of venlafaxine or on the subsequent formation of ODV.

Age and Gender
Population pharmacokinetic analyses of 547 venlafaxine-treated patients from three studies involving both venlafaxine immediate release tablets and venlafaxine extended release capsules showed that age and sex do not significantly affect the pharmacokinetics of venlafaxine. A 20% reduction in clearance was noted for ODV in subjects over 60 years old; this was possibly caused by the decrease in renal function that typically occurs with aging. Dosage adjustment based upon age or gender is generally not necessary (See **Dosage and Administration**).

Extensive/Poor Metabolizers
Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, there is no need for different venlafaxine dosing regimens for these two groups.

Hepatic Disease
In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV were significantly altered. Venlafaxine elimination half-life was prolonged by about 30%, and clearance was decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects.

A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. **Dosage adjustment is necessary in patients with liver disease (See DOSAGE AND ADMINISTRATION).**

Renal Disease
In patients with moderate to severe impairment of renal function (GFR = 10-70 mL/min), venlafaxine elimination half-life was prolonged by 50%, and clearance was decreased by about 24% compared to normal subjects. ODV elimination half-life was prolonged by about 40%, but clearance was unchanged.

In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was decreased by about 57%. In dialysis patients, ODV elimination half-life was prolonged by about 142%, and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in patients with renal disease (SEE DOSAGE AND ADMINISTRATION).

Clinical Trials
The efficacy of EFFEXOR® tablets in the treatment of depression was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-II or DSM-III-R category of major depressive disorder and in a 4-week controlled trial of inpatients meeting diagnostic criteria for major depressive disorder with melancholia.

The efficacy of EFFEXOR® XR (venlafaxine hydrochloride extended release) capsules as a treatment for depression was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depression. An 8-week study utilizing EFFEXOR® XR doses in a range 75-225 mg/day (mean dose for completers was 177 mg/day) and a 12-week study utilizing EFFEXOR® XR doses in a range 75-150 mg/day (Mean dose for completers was 136 mg/day) both demonstrated superiority of EFFEXOR® XR over placebo on the HAM-D total score, the HAM-D Depressed Mood item, the MADRS total score, the CGI Severity of Illness scale, and the CGI Global Improvement scale. In both studies, EFFEXOR® XR was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

INDICATIONS AND CLINICAL USE
EFFEXOR®/EFFEXOR® XR (venlafaxine HCl) Tablets/Capsules are indicated for the symptomatic relief of depressive illness.

The effectiveness of EFFEXOR® in long-term use (i.e. for more than 4-6 weeks - immediate release tablets, or 8-12 weeks - extended release capsules) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use EFFEXOR® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS
EFFEXOR®/EFFEXOR® XR (venlafaxine HCl) Tablets/Capsules are contraindicated in patients with known hypersensitivity to venlafaxine or to any of the components of the formulations.

Monoamine Oxidase Inhibitors (MAOI's): There have been reports of serious, sometimes fatal reactions in patients receiving antidepressants with pharmacological properties similar to those of EFFEXOR®/EFFEXOR® XR in combination with a MAOI. Therefore, EFFEXOR®/EFFEXOR® XR should not be used in combination with MAOIs or within two weeks of terminating treatment with MAOIs. Treatment with MAOIs should not be started until 2 weeks after discontinuation of EFFEXOR®/EFFEXOR® XR therapy.

WARNINGS
Sustained Hypertension
Treatment with EFFEXOR® (venlafaxine HCl) Tablets was associated with modest but sustained increases in blood pressure during premarketing studies. Sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg **and** ≥ 10 mm Hg above baseline for 3 consecutive visits, showed the following incidence and dose-relationship:

	Probability of Sustained Elevation in SDBP (Pool of Premarketing Studies with EFFEXOR®/EFFEXOR® XR)	
Treatment Group	**(%) Incidence of Sustained Elevation in SDBP**	
Venlafaxine	Immediate Release	Extended Release
< 100 mg/day	2	3
101-200 mg/day	5	2
201-300 mg/day	6	4
> 300 mg/day	13	NE*
Placebo	2	NE*

*Not evaluable

An analysis of the blood pressure increases in patients with sustained hypertension and in the 19 patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) showed that most of the blood pressure increases were in the range of 10 to 15 mm Hg, SDBP.

In placebo-controlled premarketing depression studies with EFFEXOR® XR, a final on-therapy mean increase in supine diastolic pressure (SDBP) of < 1.2 mm Hg was observed for EFFEXOR® XR-treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. Less than 3% of EFFEXOR® XR patients treated with doses of 75 to 300 mg/day had sustained elevations in blood pressure (defined as treatment-emergent SDBP ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits). An insufficient number of patients received doses of EFFEXOR® XR > 300 mg/day to evaluate systematically sustained blood pressure increases. Less than 1% of EFFEXOR® XR-treated patients in double-blind, placebo-controlled premarketing depression studies discontinued treatment because of elevated blood pressure compared with 0.4% of placebo-treated patients.

Sustained increases could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have their blood pressure monitored regularly. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered after a benefit-risk assessment is made.

PRECAUTIONS
General
Suicide
The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization. In order to reduce the risk of overdose, prescriptions for EFFEXOR®/EFFEXOR® XR (venlafaxine HCl) Tablets/Capsules should be written for the smallest quantity of tablets/capsules consistent with good patient management.

Seizures
During premarketing testing, seizures were reported in 8 out of 3,082 EFFEXOR® *Tablet*-treated patients (0.26%). In 5 of the 8 cases with immediate release tablets, patients were receiving doses of 150 mg/day or less. No seizures were seen in 705 EFFEXOR® XR *Capsule*-treated patients. However, patients with a history of convulsive disorders were excluded from most of these studies. EFFEXOR®/EFFEXOR® XR should be used cautiously in patients with a history of seizures, and should be promptly discontinued in any patient who develops seizures.

Activation of Mania/Hypomania
During Phase II and III trials, mania or hypomania occurred in 0.5% of EFFEXOR® *Tablet*-treated patients and in 0.3% of EFFEXOR® *XR Capsule*-treated patients. Mania or hypomania occurred in 0.6% of all venlafaxine-treated patients. Mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, EFFEXOR®/EFFEXOR® XR should be used cautiously in patients with a history of mania.

Use in Patients with Concomitant Illness
Clinical experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine to patients with diseases or conditions that could affect hemodynamic responses or metabolism. Patients should be questioned about any prescription or "over the counter drugs" that they are taking, or planning to take, since there is a potential for interactions.

- **Cardiac Disease**
  Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's clinical trials.

  Evaluation of the electrocardiograms for 769 patients who received venlafaxine *immediate release tablets* in 4- to 6-week double-blind trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

  The electrocardiograms for 357 patients who received EFFEXOR® XR and 285 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials were analyzed. The mean change from baseline in corrected QT interval (QTc) for EFFEXOR® XR-treated patients was increased relative to that for placebo-treated patients (increase of 4.7 msec for EFFEXOR® XR and decrease of 1.9 msec for placebo). Three of 705 EFFEXOR® XR-treated patients in phase III studies experienced QTc prolongation to 500 msec during treatment. Baseline QTc was > 450 msec for all 3 patients. No case of sudden unexplained death or serious ventricular arrhythmia, which are possible clinical sequelae of QTc prolongation, was reported in EFFEXOR® XR pre-marketing studies.

  The mean heart rate was increased by about 4 beats per minute during treatment with EFFEXOR® and EFFEXOR® XR. Venlafaxine treatment has been associated with sustained hypertension **(see WARNINGS)**.

- **Hepatic and Renal Disease**
  In patients with hepatic or renal impairment (GFR=10-70 mL/min), the pharmacokinetic disposition of both venlafaxine and ODV are significantly altered. **Dosage adjustment is necessary in these patients (See DOSAGE AND ADMINISTRATION).**

Insomnia and Nervousness
Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with EFFEXOR® and EFFEXOR® XR than with placebo (see **ADVERSE REACTIONS**).

Changes in Appetite and Weight
Treatment-emergent anorexia was more commonly reported for EFFEXOR® and EFFEXOR® XR-treated than placebo-treated patients (see ADVERSE EFFECTS). Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment.

Interference with Cognitive and Motor Performance
Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgement, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Use in Pregnancy, Labour and Delivery
There are no adequate and well controlled studies with venlafaxine in pregnant women. Therefore, venlafaxine should only be used during pregnancy if clearly needed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Use in Nursing Mothers
It is not known whether venlafaxine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, lactating women should not nurse their infants while receiving venlafaxine.

Paediatric Use
Safety and efficacy in children below the age of 18 have not been established.

Use in the Elderly
Of the 2,897 patients in Phase II and III trials with EFFEXOR® Tablets, 357 (12%) were 65 years of age or older. Forty three (43%) of the patients in trials with EFFEXOR® XR Capsules, were 65 years of age or older. No overall differences in effectiveness and safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Discontinuation Symptoms
While the discontinuation effects of EFFEXOR® have not been systematically evaluated in controlled clinical trials, a retrospective survey of new events occurring during taper or following discontinuation revealed the following six events that occurred at an incidence of at least 5%, and for which the incidence for EFFEXOR® was at least twice the placebo incidence: asthenia, dizziness, headache, insomnia, nausea and nervousness.

With EFFEXOR® XR, the following six events occurred with an incidence of at least 3%, and for which the incidence of EFFEXOR® XR was at least twice the placebo incidence: dizziness, dry mouth, insomnia, nausea, nervousness and sweating.

Therefore, it is recommended that the dosage be tapered gradually and the patient monitored **(See DOSAGE AND ADMINISTRATION)**.

Drug Interactions
As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

- ***Lithium***
  The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours was not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. Venlafaxine had no effect on the pharmacokinetics of lithium.

- ***Diazepam***
  The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours was not affected when a single 10 mg oral dose of diazepam was administered to 18 healthy male subjects. Venlafaxine had no effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam. Additionally, venlafaxine administration did not affect the psychomotor and psychometric effects induced by diazepam.

- ***Cimetidine***

  Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs in 18 healthy male subjects resulted in inhibition of first-pass metabolism of venlafaxine. The oral clearance of venlafaxine was reduced by about 43%, and on the pharmacokinetics of ODV. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults.

  However, for patients with pre-existing hypertension, for elderly patients and for patients with hepatic or renal dysfunction, the interaction associated with the concomitant use of cimetidine and venlafaxine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

- ***Haloperidol***

  Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (CL/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

- ***Imipramine***

  Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, AUC, C_{max} and C_{min} of desipramine (the active metabolite of imipramine) increased by approximately 35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). The clinical significance of elevated 2-OH-desipramine levels is unknown.

  Imipramine partially inhibited the CYP2D6-mediated formation of ODV. However, the total concentration of active compounds (venlafaxine plus ODV) was not affected by coadministration with imipramine, and no dosage adjustment is required.

- ***Risperidone***

  Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

- ***Drugs Highly Bound to Plasma Proteins***

  Venlafaxine is not highly bound to plasma proteins; therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

- ***Drugs that Inhibit Cytochrome P450 Isoenzymes***

  CYP2D6-Inhibitors:

  In vitro and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6 mediated metabolism and venlafaxine. Drug interactions that reduce the metabolism of venlafaxine to ODV (see **Imipramine** above) potentially increase the plasma concentrations of venlafaxine and lower the concentrations of the active metabolite. However, the pharmacokinetic profile of venlafaxine in subjects concomitantly receiving a CYP2D6-inhibitor would not be substantially different than the pharmacokinetic profile in subjects who are CYP2D6 poor metabolizers, and no dosage adjustment is required.

  CYP3A3/4 Inhibitors:

  In vitro studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A3/4. Because CYP3A3/4 is typically a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, the potential for a clinically significant drug interaction between drugs that inhibit CYP3A3/4-mediated metabolism and venlafaxine is small. However, because the two primary metabolic pathways for venlafaxine are through CYP2D6 and, to a lesser extent, CYP3A3/4, concomitant intake of inhibitors of both of these isoenzymes is not recommended during treatment with venlafaxine. However, interactions between concomitant intake of inhibitors of both CYP2D6 and CYP3A3/4 with venlafaxine has not been studied.

- ***Drugs Metabolized by Cytochrome P450 Isoenzymes***

  CYP2D6

  In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed *in vivo* by a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

  CYP3A4

  Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

  CYP1A2

  Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

  CYP2C9

  Venlafaxine did not inhibit CYP2D9 *in vitro*. The clinical significance of this finding is unknown.

  CYP2C19

  Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see Diazepam above).

- ***Monoamine Oxidase Inhibitors:*** *See "Contraindications".*

- ***Other CNS-Active Drugs***

  The risk of using venlafaxine in combination with other CNS-active drugs (including alcohol) has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

Electroconvulsive Therapy

There are no clinical data on the use of electroconvulsive therapy combined with EFFEXOR® or EFFEXOR® XR treatment.

Drug Abuse and Dependence

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. It has no significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

While EFFEXOR®/EFFEXOR® XR have not been systematically studied in clinical trials for their potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

ADVERSE REACTIONS

Commonly Observed Adverse Reactions

The most commonly observed adverse events associated with the use of EFFEXOR® and EFFEXOR® XR (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for EFFEXOR®/EFFEXOR® XR at least twice that for placebo), derived from the 2% incidence Table 2, were:

EFFEXOR® : asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, and abnormal ejaculation/orgasm and impotence in men.

EFFEXOR® XR: abnormal dreams, anorexia, dizziness, dry mouth, nausea, nervousness, somnolence, sweating, and tremor as well as abnormal ejaculation/orgasm in men.

Adverse Reactions Associated with Discontinuation of Treatment

Nineteen percent (537/2897) of EFFEXOR® and 12% (86/705) of EFFEXOR® XR-treated patients in Phase II and III depression studies discontinued treatment due to an adverse reaction. The more common events (≥ 1%) associated with discontinuation of treatment and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) are shown in Table 1.

TABLE 1: ADVERSE REACTIONS ASSOCIATED WITH DISCONTINUATION OF TREATMENT

	EFFEXOR® (n = 2897)	Placebo (n = 609)	EFFEXOR® XR (n = 705)	Placebo (n = 285)
CNS				
Somnolence	3%	1%	2%	-
Insomnia	3%	1%	-	-
Dizziness	3%	-	#	@
Nervousness	2%	-	-	@
Dry Mouth	2%	-	-	-
Anxiety	2%	1%	-	-
Gastrointestinal				
Nausea	6%	1%	4%	-
Anorexia	1%	-	1%	-
Urogenital				
Abnormal Ejaculation*	3%	-	-	-
Other				
Headache	3%	1%	#	@
Asthenia	2%	-	-	@
Sweating	2%	-	-	-

*: percentages based on the number of males.
-: Less than 1%
#: greater than 1% but active drug rate not twice rate for placebo.
@: 1% or greater

Incidence in Controlled Trials

The table that follows (Table 2) enumerates adverse events that occurred at an incidence of 2% or more, and were more frequent than in the placebo group, among venlafaxine-treated patients.

EFFEXOR®: patients participated in 4- to 8- week placebo-controlled trials in which doses in the range of 75 to 375 mg/ day were administered.

EFFEXOR® XR: patients participated in 8- to 12-week placebo-controlled trials in which doses in the range of 75 to 225 mg/ day were administered.

Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that the cited frequencies for EFFEXOR® XR cannot be compared with figures obtained from other clinical investigations of EFFEXOR® which involved different treatments, uses and investigators. The cited figures for EFFEXOR® XR, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 2: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS (PERCENTAGE)[1]

Body System / Preferred Term	EFFEXOR® (n = 1033)	Placebo (n = 609)	EFFEXOR® XR (n = 357)	Placebo (n = 285)
Body as a whole				
Headache	25	24	#	@
Asthenia	12	6	8	7
Infection	6	5	#	@
Chills	3	-	-	-
Cardiovascular				
Vasodilation	4	3	4	2
Increased blood pressure/hypertension	2	-	4	-
Tachycardia	2	-	-	-
Dermatological				
Sweating	12	3	14	3
Rash	3	2	-	-
Gastrointestinal				
Nausea	37	11	31	12
Constipation	15	7	8	5
Anorexia	11	2	8	4
Diarrhoea	8	7	#	@
Vomiting	6	2	4	2
Dyspepsia	5	4	#	@
Flatulence	3	2	4	3
Metabolic				
Weight loss	#	-	3	-
Nervous				
Somnolence	23	9	17	8
Dry mouth	22	11	12	6
Dizziness	19	7	20	9
Insomnia	18	10	17	11
Nervousness	13	6	10	5
Anxiety	6	3	#	@
Tremor	5	-	5	2
Abnormal Dreams	4	3	7	2
Hypertonia	3	-	-	-
Paraesthesia	3	-	3	-
Libido decreased	2	-	3	-
Agitation	2	-	3	-
Depression	-	-	3	-
Respiration				
Pharyngitis	#	#	7	6
Yawn	3	-	3	-
Special Senses				
Abnormal vision	6	2	4	-
Taste perversion	2	-	-	-
Urogenital system				
Abnormal ejaculation/orgasm	12[2]	-[2]	16[2]	-[2]
Impotence	6[2]	-[2]	4[2]	-[2]
Anorgasmia	-[2]	-[2]	3[2]	-[2]
Urinary frequency	3	-	-	-
Urination impaired	2	-	-	-

1 Events reported by at least 2% of patients treated with EFFEXOR®/EFFEXOR® XR are included, and are rounded to the nearest %. Events for which the EFFEXOR®/EFFEXOR® XR incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhoea,[3] dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis and sinusitis.

\- Incidence less than 2%.

\# Incidence greater than 2%, but active drug incidence less than incidence for placebo.

@ Incidence 2% or greater

2 Incidence based on number of male patients.

3 Incidence based on number of female patients.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing EFFEXOR® Tablets 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with EFFEXOR® use, as shown in the table that follows (Table 3). The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one EFFEXOR® group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value ≤ 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 3: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN A DOSE COMPARISON TRIAL

	EFFEXOR® Tablets (mg/day)			
Body System / Preferred Term	**Placebo (n = 92)**	**75 (n = 89)**	**225 (n = 89)**	**375 (n = 88)**
Body as a Whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%
Respiratory				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special Senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/orgasm (number of men)	0.0% (n = 63)	4.5% (n = 52)	2.2% (n = 48)	12.5% (n = 56)
Impotence (number of men)	0.0% (n = 63)	5.8% (n = 52)	2.1% (n = 48)	3.6% (n = 56)

Adaptation to Certain Adverse Events

In premarketing experience with EFFEXOR® Tablets over a 6-week period, and EFFEXOR® XR capsules over a 12 week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., dizziness and nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth).

Vital Sign Changes

Treatment with EFFEXOR® Tablets (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (**see WARNINGS**).

Treatment with EFFEXOR® XR Capsules for up to 12 weeks in premarketing depression trials was associated with a mean increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 0.9 mm Hg, compared with mean decreases ranging from 0.5 to 1.4 mm Hg for placebo (**see WARNINGS**).

Laboratory Changes

Of the serum chemistry and haematology parameters monitored during clinical trials with EFFEXOR,* a statistically significant difference with placebo was seen only for serum cholesterol, i.e., patients treated with EFFEXOR® had mean increases from baseline of 3 mg/dL. In premarketing placebo-controlled depression trials for up to 12 weeks, EFFEXOR® XR was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL. The serum cholesterol changes induced by venlafaxine are of unknown clinical significance.

ECG Changes

In an analysis of EGGs obtained in 769 patients treated with EFFEXOR® Tablets and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, i.e., a mean increase from baseline of 4 beats per minute for EFFEXOR®

An analysis of EGGs obtained in 357 patients treated with EFFEXOR® XR and 285 patients treated with placebo in controlled clinical trials, revealed a mean increase in corrected QT (QTc) interval relative to placebo (see PRECAUTIONS). A mean increase in heart rate of approximately 4 beats per minute for EFFEXOR® XR compared with 1 beat per minute for placebo was observed.

Other Events Observed During the Premarketing Evaluation of Venlafaxine

During its premarketing assessment, multiple doses of EFFEXOR® XR were administered to 705 patients in phase III depression studies and EFFEXOR® Tablets were administered to 96 patients. In addition, in premarketing assessment of EFFEXOR® Tablets, multiple doses were administered to 2897 patients in phase II-III depression studies. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (EFFEXOR® Tablets only) and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 3698 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 1 and 2, and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and the frequent adverse events are provided below. Frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing).

Body as a whole – :	chest pain, chills, fever.
Cardiovascular system – :	migraine, postural hypotension, tachycardia.
Digestive system – :	eructation, increased appetite.
Hemic and lymphatic system – :	ecchymosis.
Musculoskeletal system – :	myalgia.
Nervous system – :	amnesia, emotional lability, hypesthesia, sleep disturbance, thinking abnormal, trismus.
Special senses – :	ear pain, taste perversion.
Urogenital system – :	menstrual disorder,* prostatitis,* urinary tract infection, urination impaired, vaginitis.*

*Based on the number of men and women as appropriate.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Human Experience

In postmarketing experience, venlafaxine, taken alone, has not been clearly associated with lethal overdose. However, fatal reactions have been reported in patients taking overdoses of venlafaxine in combination with alcohol and/or other drugs.

EFFEXOR® Tablets

There were 14 reports of acute overdose with EFFEXOR® (venlafaxine HCl), either alone or in combination with other drugs and/or alcohol, among the patients included in the premarketing evaluation. The majority of the reports involved ingestions in which the total dose of EFFEXOR® taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

EFFEXOR® XR Capsules

Among the patients included in the premarketing evaluation of venlafaxine extended release capsules, there were 2 reports of acute overdosage with EFFEXOR® XR, either alone or in combination with other drugs. One patient took a combination of 6 g of EFFEXOR® XR and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.5 g of EFFEXOR® XR. This patient reported paresthesia of all four limbs but recovered without sequelae.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitoring of cardiac rhythm and vital signs is recommended. General supportive and symptomatic measures are also recommended. Use of activated charcoal, induction of emesis, or gastric lavage should be considered. Due to the large volume of distribution of venlafaxine hydrochloride, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for EFFEXOR/EFFEXOR® XR are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control centre on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

ADULTS:

EFFEXOR® Tablets

The recommended treatment dose is 75 mg per day, administered in two or three divided doses, taken with food. If the expected clinical improvement does not occur after a few weeks, a gradual dose increase to 150 mg/day may be considered. If needed, the dose may be further increased up to 225 mg/day. Increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of the usefulness of doses greater than 225 mg/day for moderately depressed patients. More severely depressed inpatients have responded to higher doses, between 350 and 375 mg/day, given in three divided doses. Maximum: The maximum dose recommended is 375 mg per day (in an inpatient setting).

EFFEXOR® XR Capsules

The recommended dose for venlafaxine ER is 75 mg/day, administered once daily with food, either in the morning or in the evening. Each capsule should be swallowed whole with water. It should not be divided, crushed, chewed, or placed in water. While the relationship between dose and antidepressant response for EFFEXOR® XR has not been adequately explored patients not responding to the initial 75 mg may benefit from dose increases. Depending on tolerability and the need for further clinical effect, the dose should be increased by up to 75 mg/day up to a maximum of 225 mg/day for moderately depressed outpatients. Dose increments should be made at intervals of approximately 2 weeks or more, but not less than 4 days. There is very limited experience with EFFEXOR® XR at doses higher than 225 mg/day, or in severely depressed inpatients.

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for EFFEXOR® tablets, more severely depressed inpatients responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day).

Switching Patients from EFFEXOR® Tablets:

Depressed patients who are currently being treated at a therapeutic dose with EFFEXOR® may be switched to EFFEXOR® XR at the nearest equivalent dose (mg/day), e.g., 37.5 mg EFFEXOR® two-times-a-day to 75 mg EFFEXOR® XR once daily. However, individual dosage adjustments may be necessary.

Patients With Hepatic Impairment:

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by about 50% in patients with moderate hepatic impairment. For such patients, it may be desirable to start at 37.5 mg/day. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and increase in elimination half-life for both venlafaxine and ODV that is obse in patients with renal impairment (GFR=10-70 mL/min) compared to normal subjects (see CLINICAL PHARMACOLOGY), recommended that the total daily dose be decreased by 25%-50%. In patients undergoing hemodialysis, it is recommende the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs). For patients, it may be desirable to start at 37.5 mg/day. Since there is so much individual variability in clearance among patients renal impairment, individualization of dosing may be desirable.

Elderly Patients

No dose adjustment is recommended for elderly patients solely on the basis of their age. As with any antidepressant, how caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increa the dose.

Maintenance/Continuation/Extended Treatment

There is no body of evidence available to answer the question of how long a patient should continue to be treated with venlafax It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic thera Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthy is unknown.

Discontinuing Venlafaxine

When venlafaxine therapy that has been administered for more than 1 week is stopped, it is generally recommended that the d be tapered gradually to minimize the risk of discontinuation symptoms. Patients who have received venlafaxine for 6 weeks or m should have their dose tapered gradually over a 2-week period. Individualization of tapering may be necessary.

Switching Patients to or from a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with venlafaxine. In addition, at le 14 days should be allowed after stopping venlafaxine before starting an MAOI (see "Contraindications").

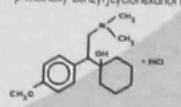
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Venlafaxine Hydrochloride

Chemical Name: (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride; or (±)-1-[α[(dimethylamino)methyl]-p-methoxy-benzyl]cyclohexanol hydrochloride.

Structural Formula:



Molecular Weight: 313.87

Physical Form: White to off-white crystalline solid

Solubility:

Water	540, 542, 501 and 21.6 mg/mL at pH 1.0, 5.38, 7.09 and 7.97
Ethanol:	91.7 mg/mL
Propylene Glycol:	200 mg/mL
Glycerin:	115 mg/mL
pKa value:	9.4

Composition:

EFFEXOR® Tablets

Medicinal Ingredients	Non-medicinal Ingredients:	
Venlafaxine Hydrochloride	Microcrystalline cellulose, NF Lactose, NF Hydrous Cosmetic Brown Iron Oxide	Ferric Oxide, NF Yellow Sodium Starch Glycolate, NF Magnesium Stearate, NF

Stability and Storage Recommendations

Store at room temperature (15-30°C), in a dry place.

EFFEXOR® XR Capsules (extended release)

Medicinal Ingredients	Non-medicinal Ingredients:	
Venlafaxine Hydrochloride	Ethylcellulose, NF Gelatin, NF Hydroxypropylmethyl Cellulose, USP Iron Oxide, NF Microcrystalline Cellulose, NF	Titanium Dioxide, USP White Tek SB-0007 and /or Opacode Red S-1-15034 ink Talc, USP

Stability and Storage Recommendations

Store at room temperature (15-30°C), in a dry place.

AVAILABILITY OF DOSAGE FORMS

"EFFEXOR® (venlafaxine HCl) Tablets are available, in bottles of 100 tablets, in the following tablet strengths *(potency is expressed in terms of venlafaxine base)*:

37.5 mg Shield-shaped, peach-coloured compressed tablet, with a score, with "**W**" on one side and "37.5" on the other side.

75 mg Shield-shaped, peach-coloured compressed tablet, with a score, with "**W**" on one side and "75" on the other.

"EFFEXOR® XR (venlafaxine HCl) Capsules are available in bottles of 100 capsules and 500 capsules, in the following dosage strengths *(potency is expressed in terms of venlafaxine base)*:

37.5 mg Hard gelatin capsule with gray cap and peach body, with "**W**" and "Effexor XR" on the cap and "37.5" on the body, in red ink.

75 mg Hard gelatin capsule with peach cap and body, with "**W**" and "Effexor XR" on the cap and "75" on the body, in red ink.

150 mg Hard gelatin capsule with dark orange cap and body, with "**W**" and "Effexor XR" on the cap and "150" on the body, in white ink.

The appearance of these capsules is a trademark of Wyeth-Ayerst Canada Inc.

REFERENCES: **1.** Effexor/Effexor XR Product Monograph, Wyeth-Ayerst Canada Inc. **2.** Rudolph R. Efficacy and tolerability of once-daily venlafaxine XR vs. fluoxetine and placebo in depressed patients. *Eur Neuropsychopharmacol*, 1997;7(Suppl 2):S168. **3.** Dunningham LA. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. *Annals Clin Psy*, 1997; 9(3):157-164. **4.** Salinas E. Once-daily venlafaxine XR versus paroxetine in outpatients with major depression. *Biol Psych*, 1997;42:244S. **5.** Poirier M-F. Venlafaxine versus paroxetine in the treatment of resistant depression. *Biol Psych*, 1997;42:243S. **6.** Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. *J Affect Disorders* 1998 (in press). **7.** Silverstone P, Iskandar H, Hamel R, Salinas E. Efficacy and tolerability of once-daily venlafaxine XR vs. fluoxetine in depressed outpatients with concomitant anxiety. *Eur Neuropsychopharmacol* 1996;16(3); Suppl 2: 37S-49S. **8.** Ereshefsky E. Drug-drug interactions involving antidepressants: focus on venlafaxine. *J Clin Psychopharmacol*, 1996;16:19S-27S. **9.** Shader *et al.* The clinician and drug interactions – an update. *J Clin Psychopharmacol*, 1996;16:19S-20S. **10.** DeVane CL. Pharmacokinetics of the newer antidepressants: clinical relevance. *Am J Med* 1997; 97(suppl 6A):6A-13S.

Product Monograph available on request.

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PMAC PAAR

ment with NMDA, a GLU agonist, after weaning, resulted in the premature induction of puberty. The mechanism by which GLU mediates this process has not been elucidated. We hypothesize that GLU may induce precocious puberty by: (1) neurotoxic removal of inhibitory cells of the GnRH system and/or (2) acceleration of normal development, perhaps via growth factors. One such factor is basic fibroblast growth factor (bFGF). The objective of this study was to examine the distribution of bFGF in the brain of the neonatal female rat following glutamate treatment.

Neonatal rats, on postnatal day 2 (P2), received a single s.c. injection of either saline solution (control) or monosodium glutamate (MSG) at a dose of 4 mg MSG/g body weight. Starting on P3, two or three animals from both experimental groups were collected and sacrificed at 2-day intervals up to the age of P9. The expression of bFGF in the neonatal brain was examined using immunocytochemical procedures. bFGF was visualized in the dorsomedial nucleus, ventromedial nucleus and arcuate nucleus of the hypothalamus, within the hippocampus and diffusely throughout the cerebral cortex of both MSG treated and control animals. Following treatment with MSG on P2, bFGF immunoreactivity in the arcuate nucleus increased between P4 and P9 compared to control animals. By P9 the difference between bFGF immunoreactivity observed in the arcuate nucleus of MSG treated and control animals had decreased. These data suggest that bFGF may be one component of the neural reorganization that leads to precocious puberty.

In conclusion, the present study determined bFGF was present in several specific regions of the neonatal brain. Treatment with MSG resulted in an increase in bFGF expression within the arcuate nucleus. These results support the possibility that the expression of bFGF following a GLU-induced lesion in the hypothalamus promotes the precocious maturation of GnRH neurons and partially stimulates the onset of precocious puberty.

Janet MacIntyre is a third year medical student at Dalhousie University. Funding for this study was supported by a Dalhousie Medical School Summer Studentship (Elizabeth Rafuse Studentship) and grants from the Medical Research Council of Canada and the IWK-Grace Foundation.

Third Place

Isolation of Two Genes from *S. cerevisiae*: Role in Phosphatidylcholine Reacylation

Janice Chisholm[1], BSc, MD '00, and Christopher McMaster[2], PhD

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The accumulation of unsaturated fatty acyl species within the backbone of phosphatidylcholine (PtdCho) is regulated by the activity and substrate specificity of lysoPtdCho acyltransferase. Neither the cDNA nor the gene for the lysoPtdCho acyltransferase have been isolated from any source. In this study, two approaches were used to attempt to isolate and characterize the gene in the eukaryotic yeast *S. cerevisiae*. The first approach was the development of a colony autoradiography assay specific for lysoPtdCho acyltransferase activity. Attempts to optimize this assay were unsuccessful, as specificity for only lysoPtdCho acyltransferase activity was not possible. The second approach used to isolate and characterize the gene was via computer algorithms to identify tentative active site motifs, in the known genome of *S. cerevisiae*, that are associated with acyltransferase reactions. The results of this, coupled with the known biochemical characteristics of lysoPtdCho acyltransferase, yielded two sequences, YBL011w and YKR067w. The genes were then amplified and transformed into wild type yeast cells under high copy (Yep).

Based on known biochemical properties of lysoPtdCho acyltransferase activity, coupled with the presence of a motif common to other glycerolipid acyltransferase enzymes, it is predicted that these two genes are good candidates for coding of glycerolipid acyltransferase activities themselves. Although this remains to be proven biochemically, this study has yielded the cloned genes that can be used as a set of molecular tools for analysis of the encoded products.

Janice Chisholm is a third year medical student at Dalhousie University. She graduated from Bishop's University in 1996 with a BSc (Hon) in biochemistry.

POSTER PRESENTATIONS

First Place

ß-Adrenergic Receptors in Fetal Rabbit Lung: Characterization and Ontogeny Studies

Philip Wornell,[1] BSc (Hon), MD '00, Kathleen Landymore,[2] MD, PhD, Margaret Oulton,[3] PhD

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The tissue punch technique using the hydrophilic radioligand [^{3}H]CGP-12177 was used to characterize ß-adrenergic receptors in fetal rabbit lung and quantify the development of this receptor population during early ontogeny. [^{3}H]CGP binding to the lung punches was saturable, rapid,

reversible, linearly related to punch number at 30°C and reached equilibrium at this temperature by 1 h. The results of the ontogeny study indicated that the number of ß-adrenergic receptors in rabbit lung increases progressively during gestation between days 24 and 30 and that this increase continues after birth during early postnatal life. The affinity of this population of receptors remains the same throughout this period. The tissue punch technique using the hydrophilic radioligand [^{3}H]CGP-12177 is suitable for the study of ß-adrenergic receptor binding in fetal lung tissue. Involving minimal tissue disruption, this technique represents a more physiologically relevant alternative to those techniques involving tissue homogenization and centrifugation.

Philip Wornell graduated from Dalhousie University in 1996 with a BSc combined Honours degree in Biochemistry and Microbiology. During the summer of 1998, he continued his research under the supervision of Drs. Landymore and Oulton, using the tissue punch technique to determine the effects of maternal hormone administration on the development of beta adrenergic receptors in the fetal rabbit lung. At this time, his career choices include internal medicine, pediatrics and family medicine. Philip hopes to be involved in research throughout his career.

Second Place

Choice of Antibiotic for the Empiric Treatment of Community-Acquired Pneumonia: Results of a Survey of Nova Scotia General Practitioners

Jacob Pendergrast[1], BSc, MD '99, Tom Marrie[2], MD, FRCPC

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[2] Department of Medicine, Division of Infectious Diseases, QEII Health Sciences Centre

Introduction: Community-acquired pneumonia (CAP) is one of the most prevalent infectious diseases in North America and is responsible for significant mortality and morbidity. Although effective treatment depends greatly on targeting antibiotic therapy towards a specific pathogen, physicians must often initiate therapy empirically, without culture and sensitivity data. As a result, there is a large variation in the types of antibiotics prescribed for CAP. By understanding the factors that predict which antibiotic a physician will choose, programs aimed at rationalizing antibiotic prescription can be made more effective.

Methods: Questionnaires were mailed during the spring of 1997 to the 841 general practitioners registered with the Medical Society of Nova Scotia. The questionnaires were based on three hypothetical cases of CAP in which a definite pathogen was not known. The first case was a 17 year-old male with an uncomplicated pneumonia and a chest x-ray showing a lobar infiltrate. The second case was a 66 year-old man with a smoking history and a Gram stain showing Gram-positive diplococci. The third case was a 45 year-old woman with a severe pneumonia requiring ICU admission whose chest x-ray revealed bilateral infiltrates. Respondents were asked to choose an antibiotic for each case and indicate the reason for their choice using a series of Likert scales. One half of the surveys included a series of knowledge-testing questions on microbiology.

Results: 188 questionnaires were returned (22.4%). For the first case, respondent choice of antibiotic correlated with respondent age, graduation year, and CCFP training. Choice also depended on the importance respondents expressed with regards to: desire to cover a specific pathogen; antimicrobial resistance; and drug side effects. For the second case, antibiotic choice depended on the importance respondents attached to: the patient's general health and smoking status; antimicrobial resistance; experience with similar cases; cost-effectiveness; and number of pathogens targeted. For the third case, the only significant predictor of antibiotic choice was respondent familiarity with the case.

Conclusion: As case complexity increased, there was greater variation in the antibiotics chosen, and decreasing consensus between general practitioners and infectious diseases specialists. The more familiar a respondent was with a particular case of pneumonia, the more explicit the decision-making strategy underlying their choice of antibiotic. Overall, general practioners prescribed appropriately for straightforward cases of CAP, and demonstrated a good understanding of the relevant microbiology.

Jacob Pendergrast is a final year medical student at Dalhousie University. He received a BA (Hon) in history and philosophy from McGill University in 1995. He is enrolled in the BSc (Med) programme. His research interests include physician practice patterns and disease epidemiology.

Third Place

Cardiac Surgery In Octogenarians: Can Elderly Patients Benefit?

Deborah Fruitman[1], BSc (Hon), MD '00, Carolyn MacDougall[2], RN and David B. Ross[2], MD, FRCSC

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[2] Department of Surgery, Division of Cardiovascular Surgery, QE II Health Sciences Centre

Purpose: Increasing numbers of the very old are developing cardiovascular disease and presenting for surgery. While risk factors and outcomes for perioperative events have been described, there is little information regarding quality of life following hospital discharge in this group.

Methods: From March 1995 to February 1997, 127 patients ≥ 80 years at operation (mean age 83±2.5 years, range 80-92) were entered into the cardiac surgery database and

analysed retrospectively. The RAND SF-36 Health Survey 1.0 and the Seattle Angina Questionnaire were used to assess quality of life by telephone interview (mean follow-up 15.7±6.9 months). No patient was lost to follow-up.

Results: Operations included isolated CABG (65.4%), CABG + Valve (15.8%), and isolated valve replacement (14.2%). Preoperatively, 63.8% were in NYHA Class IV. Thirty-day mortality was 7.9% and actuarial survival was 83% (70% CI, 79% to 87%) at one year and 80% (70% CI, 75% to 85%) at two years. Ninety-five patients (92.2%) were in NYHA Class I or II at follow-up. All but one patient improved by at least one functional class following surgery. RAND SF-36 scores were equal to or better than for the general population of age ≥ 65 years. Patients showed lower scores in physical functioning (62.9±27.1) and vitality (58.1±21.7), but had very good scores for emotional well-being (85.0±18.0), role limitations due to emotional health (89.3±27.4) and social functioning (84.9±25.1). Seattle Angina Questionnaire scores for anginal frequency (92.3±18.9), stability (94.4±18.9) and exertional capacity (86.8±25.1) indicated good relief of symptoms. Of the survivors, 83.7% were living in their own home, 74.8% rated their health as good/excellent, and 82.5% would undergo cardiac surgery again in retrospect.

Conclusion: Despite being a high risk group for cardiac surgery, octogenarians can undergo cardiac surgery at a reasonable risk and show remarkable improvement in their symptoms. Elderly patients benefit from improved functional status and quality of life following surgery.

Debbie Fruitman received her BSc (Hon) in biology and nutrition studies from the University of Guelph in 1994. Her current research interests are in pediatrics. She is presently working on a project involving complex congenital heart disease. Her career goals include pediatrics and internal medicine. Debbie wishes to combine her future clinical practice with research.

®

LANOXIN®

(digoxin) Cardiotonic glycoside

Before Prescribing Lanoxin Please Consult Full Prescribing Information.

Indications

1. Congestive heart failure.
2. Atrial fibrillation with rapid ventricular response.
3. Atrial flutter.
4. Paroxysmal atrial tachycardia.

Contraindications

1. Ventricular fibrillation.
2. A need for permanent discontinuation of other digitalis preparations usually constitutes a contra-indication to digoxin.
3. Allergy to digoxin, though rare, may occur. It may not extend to all digitalis preparations, and another may be tried.

Warnings

1. Dosage must be carefully titrated. Patients with renal insufficiency or severe carditis are especially sensitive and may require reduced dosages.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive and dosage must not only be reduced but must be individualized according to their degree of maturity. NOTE: Digitalis glycosides are an important cause of accidental poisoning in children.

2. Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of the symptoms should be attempted before further digitalis administration. If the possibility of intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.
3. Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible, especially if a therapeutic trial does not result in improvement. Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Precautions

Digitalization with a long-acting cardiac glycoside during the previous two weeks, or the presence of moderate or severe renal impairment may enhance digoxin toxicity. Patients with acute myocardial infarction, severe pulmonary disease or advanced heart failure may be unusually sensitive to digoxin-induced disturbances of rhythm.

Hypokalemia sensitizes the myocardium to digitalis, and toxicity is apt to develop even with the usual dosage.

Hypomagnesemia and hypercalcemia may also increase sensitivity to cardiac glycosides. Hypocalcemia may nullify the effects of digoxin and should be corrected before a full digitalizing dose is given.

Quinidine, verapamil and some antibiotics may cause increased serum digoxin concentrations.

Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digitalis therapy. Care must be taken to avoid digitalis toxicity if digoxin is used to help control the arrhythmia.

Special care is necessary when using cardiac glycosides during electrical cardioversion or in patients with incomplete AV block, Wolff-Parkinson-White syndrome and atrial fibrillation.

Patients with chronic constrictive pericarditis or heart failure from amyloid heart disease often respond poorly. Patients with idiopathic hypertrophic subaortic stenosis or sinus tachycardia should receive digoxin only when severe heart failure is present.

Differences in bioavailability of parenteral preparations, elixirs and tablets must be taken into account when transferring patients from one dosage form to another.

Periodic assessment of serum electrolytes and renal function is recommended.

Digoxin should be given to pregnant women only when clearly needed. Digoxin is excreted in human milk but the amount is small and should have no pharmacological effect upon the infant. Nevertheless, caution is advised in these circumstances.

Adverse Reactions

The overall incidence of adverse reactions have been reported as 5 to 20% with 15 to 20% of them being considered serious (1 to 4% of patients receiving digoxin).

Cardiac – Approximately 50% of all adverse reactions. Largely ventricular premature contractions, or ventricular tachycardia. Atrioventricular dissociation, AV block and complete heart block may occur. In children atrial tachycardias, with or without block, and junctional (nodal) tachycardia are more common.

Gastrointestinal – Anorexia, nausea, vomiting and diarrhea.

CNS – Blurred or yellow vision, headache, weakness, apathy and psychosis.

Other – Gynecomastia. Note: For severe or complete heart block due to digitalis intoxication and not primarily related to supraventricular tachycardia do not use potassium. Lidocaine, procainamide and propranolol may be useful. Temporary ventricular pacing may be beneficial.

Dosage and Administration

Digitalization should always be individualized. The following serves as a guideline only. For more information consult the Prescribing Information.

Rapid Digitalization

In previously undigitalized patients a single oral dose of 0.5 to 0.75 mg usually produces a detectable effect within 2 hours, and becomes maximal in 2 to 6 hours. Additional doses of 0.125 to 0.375 mg may be given at 6 to 8 hour intervals, until an adequate effect is noted.

The usual daily maintenance dose is 0.25 mg, based on a body weight of 70 kg and a Ccr of 60 mL/min.

For doses in infants and children consult the Prescribing Information.

Measurement of serum digoxin concentration is important in determining the state of digitalization.

Availability

LANOXIN® (Digoxin) Tablets, 0.0625 mg (62.5 µg); Bottles of 100 tablets; imprinted with LANOXIN and U3A (peach).

LANOXIN® (Digoxin) Tablets, scored 0.125 mg (125 µg); Bottles of 100 and 1000 tablets; imprinted with LANOXIN and Y3B (yellow).

LANOXIN® (Digoxin) Tablets, scored 0.25 mg (250 µg); Bottles of 100 and 1000 tablets; imprinted with LANOXIN and X3A (white).

Store at 15°-30°C in a dry place and protect from light.

Also available:

LANOXIN® (Digoxin) Elixir Pediatric, 0.05 mg (50 µg) per mL; bottles of 115 mL with calibrated dropper.

LANOXIN® (Digoxin) Injection, 0.25 mg (250 µg) per mL (0.5 mg [500 µg] in 2 mL); boxes of 10 ampoules.

LANOXIN® (Digoxin) Injection Pediatric, 0.05 mg (50 µg) per mL; boxes of 10 ampoules.

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3. Prescribing Information of PrLANOXIN®, Glaxo Wellcome Inc. 1997.

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