Wellbutrin advertisement.

[s.l.]: [s.n.], 1973

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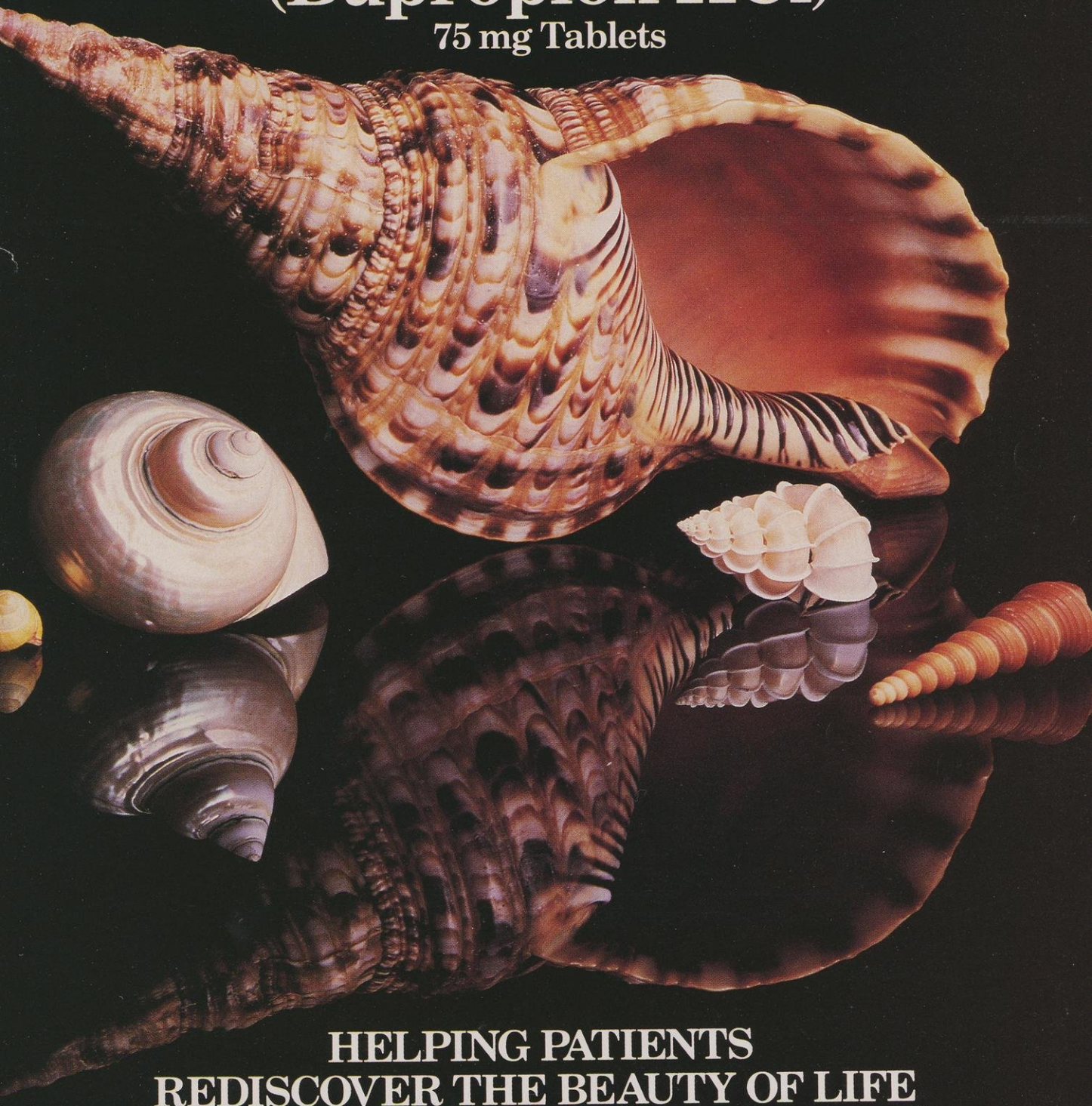
New
WELLBUTRIN®
(Bupropion HCl)
75 mg Tablets



HELPING PATIENTS REDISCOVER THE BEAUTY OF LIFE

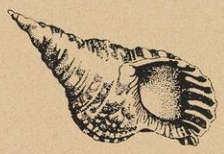
Please see final pages for summary of prescribing information.

Wellcome

New
WELLBUTRIN®
(Bupropion HCl)

75 mg Tablets

an antidepressant of the aminoketone class, chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents



FOR THE TREATMENT OF DEPRESSION

- ***In patients who fail to respond adequately to other antidepressant treatments.***

- ***In patients who cannot tolerate alternative antidepressant treatments.***

Wellbutrin may be of particular benefit in patients who have experienced orthostatic hypotension, daytime drowsiness, or excessive weight gain while on other antidepressants.

***Wellbutrin is *not* recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one-third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see WARNINGS in summary of prescribing information).**

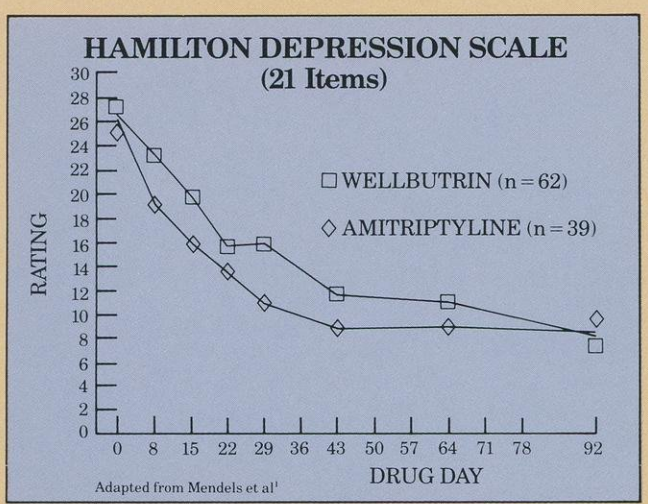
New WELLBUTRIN® (Bupropion HCl)

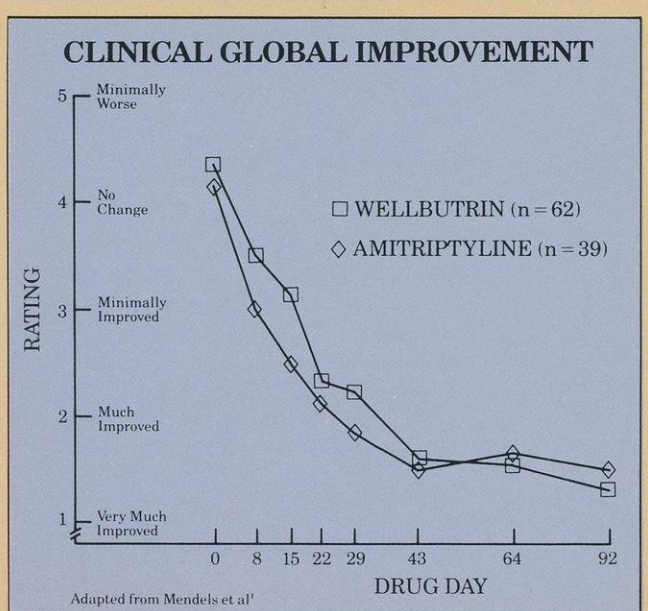
HELPING PATIENTS *who cannot tolerate the cardiovascular effects of alternative treatments*

EFFICACY COMPARABLE TO AMITRIPTYLINE

While many patients have been treated with Wellbutrin in long-term clinical trials of up to two years duration, there has been no systematic placebo-controlled evaluation of the efficacy of Wellbutrin for a period beyond three to four weeks.

A double-blind controlled trial comparing Wellbutrin to amitriptyline was conducted at six centers.[1] No significant difference was found in therapeutic response to the two drugs.

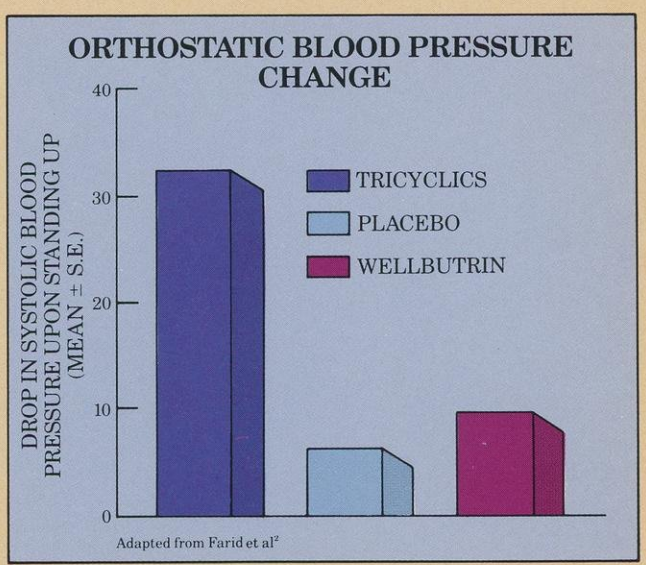




Double-blind comparison of Wellbutrin and amitriptyline. Dosages were 300-450 mg/day for Wellbutrin, 75-150 mg/day for amitriptyline.

REDUCED INCIDENCE OF ORTHOSTATIC HYPOTENSION

In a study of twelve patients who had previously exhibited significant orthostatic hypotension while on tricyclic or tetracyclic medications, not one displayed clinically significant orthostatic hypotension after being switched to Wellbutrin.[2]

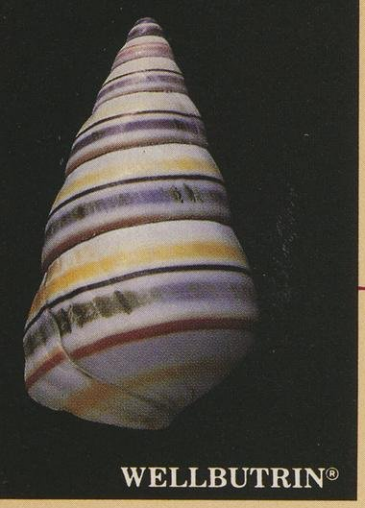


NO SIGNIFICANT EFFECT ON HEART RATE OR CARDIAC CONDUCTION

Wellbutrin has no more effect on heart rate or cardiac conduction than placebo. In a double-blind study with 23 inpatients comparing Wellbutrin (300-750 mg/day) to amitriptyline (75-225 mg/day), Wellbutrin produced no significant changes in any of the ECG parameters measured. By contrast, amitriptyline caused a significant prolongation in PR interval and QRS duration, as well as a decrease in QRS height.[3] In placebo-controlled clinical trials, the incidence of tachycardia on Wellbutrin was 10.8% vs. 8.6% on placebo.

There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Care should be exercised if Wellbutrin is used in these groups.

Please see final pages for summary of prescribing information.

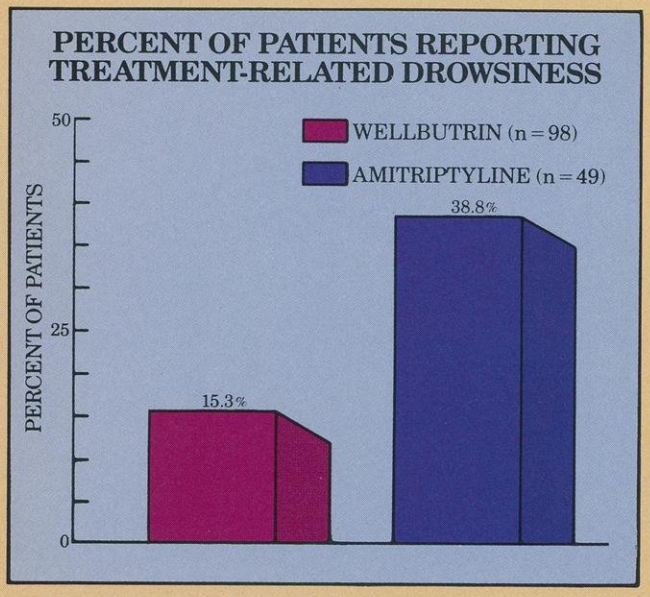


New WELLBUTRIN® (Bupropion HCl)

HELPING PATIENTS *who cannot tolerate the daytime drowsiness or weight gain associated with alternative treatments*

LOWER INCIDENCE OF DAYTIME DROWSINESS

In studies with 147 depressed patients, Wellbutrin caused substantially less drowsiness than amitriptyline.



Without daytime drowsiness, patients may be better able to function during normal daily activities. Due to its relatively low incidence of daytime drowsiness, Wellbutrin may be advantageous for patients who need to drive a car or operate machinery. In placebo-controlled clinical trials, the incidence of dizziness on Wellbutrin was 22% vs. 16% on placebo. THEREFORE, CAUTION SHOULD BE EXERCISED UNTIL REASONABLY CERTAIN THE DRUG WILL NOT AFFECT PERFORMANCE.

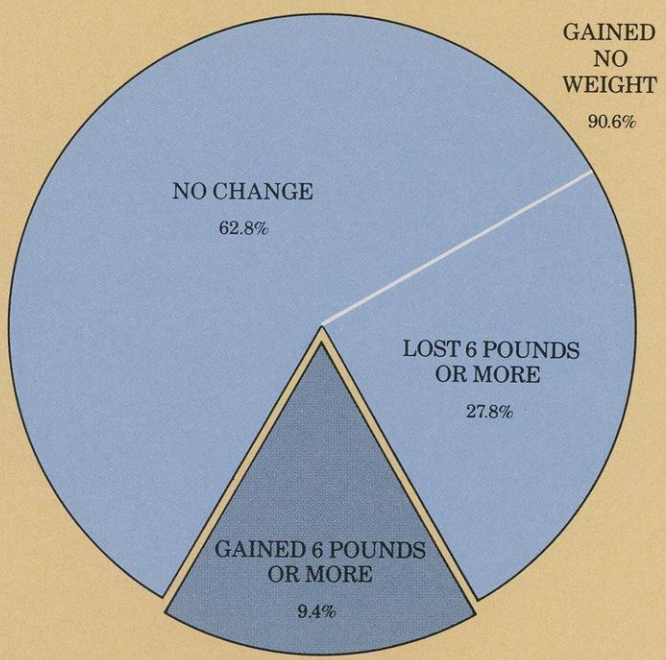
Some patients may report agitation or restlessness during the initial phase of therapy. In depressed patients with severe insomnia or pronounced agitation and restlessness, concurrent administration of a hypnotic during the first week of treatment may be helpful. For most patients, as the depression is brought under control, normal sleep patterns should return and the hypnotic may be removed.

In approximately 2% of patients in clinical trials, symptoms of restlessness, agitation, anxiety, and insomnia were sufficiently severe to require discontinuation of treatment with Wellbutrin.

LOW INCIDENCE OF WEIGHT GAIN

Long or short-term administration of Wellbutrin has not been associated with significant weight gain. The average patient should show no clinically significant weight change during treatment.

CHANGE IN BODY WEIGHT
(% of Patients)



In active and placebo-controlled trials, involving 341 Wellbutrin patients, 90.6% experienced no weight gain (±5 pounds was considered normal weight fluctuation). 27.8% of patients lost six pounds or more. This possible effect should be considered when prescribing for patients who have lost excessive weight in association with their depression. In placebo-controlled clinical trials, the incidence of nausea/vomiting on Wellbutrin was 23% vs. 19% on placebo.

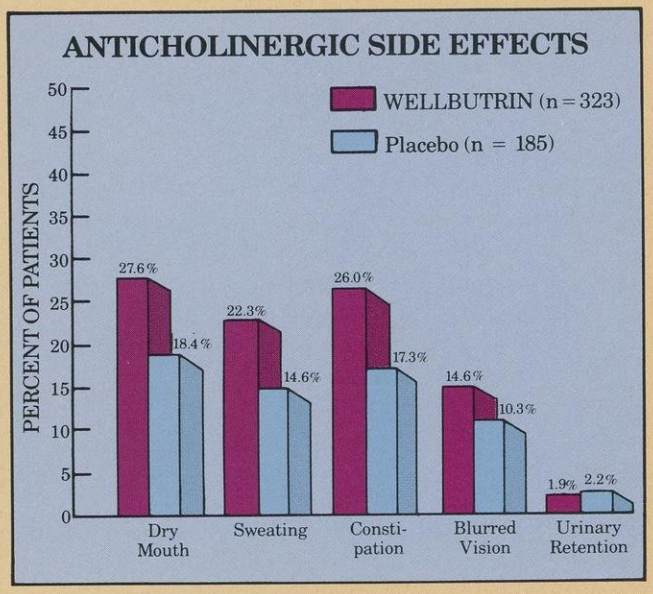
Furthermore, 34.5% of patients receiving tricyclic antidepressants in clinical trials gained weight, in contrast to only 9.4% of patients treated with Wellbutrin.

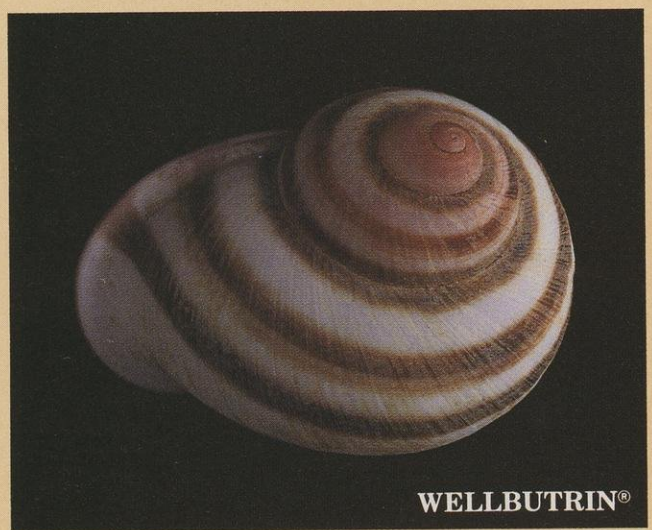
New WELLBUTRIN® (Bupropion HCl)

HELPING PATIENTS *who cannot tolerate the anticholinergic side effects of alternative treatments*

PROFILE OF SELECTED ANTICHOLINERGIC SIDE EFFECTS

Anticholinergic side effects are weak or absent in most cases. Mild and transient dry mouth, the most frequent Wellbutrin anticholinergic side effect, was reported in 27.6% of patients.





SEIZURES

At doses approximately one and one-third times greater than the usually required daily dose (450 mg), Wellbutrin is associated with a high risk of seizures. The estimated risk increases almost tenfold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, this disproportional increase in seizure incidence with dose incrementation is a cause for concern. The estimated risk of seizures at doses of 450 mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products.

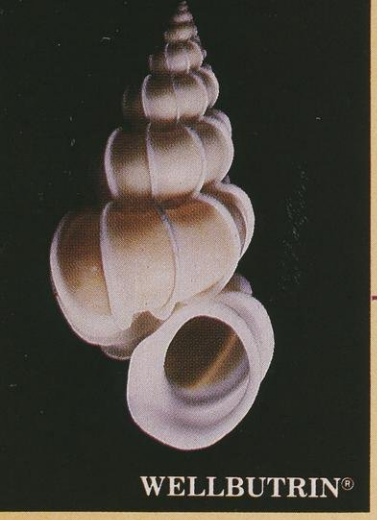
Seizures are a well-recognized consequence of tricyclic antidepressant therapy, and have been reported to occur in normal clinical use at a frequency of approximately 0.1 to 1.0%.[4,5]

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

	WELLBUTRIN Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
within the recommended dose	less than 450	0.2%	0.0%
	450	0.3%	0.2%
above the recommended dose	600	2.3%	1.3%
	600-900	2.8%	1.9%

The risk of seizures with Wellbutrin appears to be strongly associated with dose and may be increased by predisposing factors (e.g., head trauma, CNS tumor, etc.) or a history of prior seizure. Extreme caution should be used when administering Wellbutrin to these patients or when combining Wellbutrin with other agents which lower seizure threshold (see WARNINGS in summary of prescribing information).

Please see final pages for summary of prescribing information.



New WELLBUTRIN® (Bupropion HCl)

HELPING PATIENTS REDISCOVER THE BEAUTY OF LIFE

- *Cautious initial usage recommended*
- *Doses above 450 mg/day should not be used*

RECOMMENDED DOSING

Wellbutrin is available in 75 mg tablets, and should be administered three times a day (T.I.D.) to help avoid high peak concentrations. Peak plasma concentrations are usually achieved within 2 hours, followed by a biphasic decline. The average half-life of the second phase is approximately 14 hours, with a range of 8 to 24 hours.

The recommended starting dose is 225 mg/day, with a gradual ascension up to the maximum recommended dose of 450 mg/day based upon the clinical response of the patient. Dosage may be increased by 75 mg/day no sooner than every three days, and, as shown below, the maximum number of tablets for a single dose is two.

DOSING SCHEDULE

Treatment Day	75 mg Tablets Morning	Midday	Evening	Total Daily Dose
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs. Clinical trials enrolled several hundred patients 60 years of age and older. The experience with these patients and younger ones was similar.

Treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as Wellbutrin and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. These patients should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

The lowest dose which maintains remission is recommended. If patients do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, the product should be discontinued (see WARNINGS in summary of prescribing information).

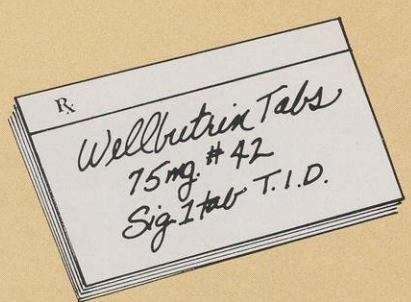
Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's premarketing clinical trials.

OVERDOSE EXPERIENCE

There has been limited clinical experience with overdosage of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae. None of these thirteen patients displayed clinically significant cardiovascular abnormalities. As with any antidepressant, care should be taken to lessen the risk of suicide by writing prescriptions for the smallest number of tablets consistent with good patient management.

References:

1. Mendels J, Amin MM, Chouinard G, et al: A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry* 1983; 44 (suppl): 118-120.
2. Farid FF, Wenger TL, Tsai SY, et al: Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry* 1983; 44 (suppl): 170-173.
3. Wenger TL, Cohn JB, Bustrack J: Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry* 1983; 44 (suppl): 174-175.
4. Lowry MR, Dunner FJ: Seizures during tricyclic therapy. *Am J Psychiatry* 1980; 137 (11): 1461-1462.
5. Jick H, Dinan BJ, Hunter JR, et al: Tricyclic antidepressants and convulsions. *J Clin Psychopharmacol* 1983; 3 (3): 182-185.



New WELLBUTRIN® (Bupropion HCl)

HELPING PATIENTS REDISCOVER THE BEAUTY OF LIFE

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets.

Brief Summary:

INDICATIONS AND USAGE:

Wellbutrin is indicated for the treatment of depression in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is *not* recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one-third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see WARNINGS).

The efficacy of Wellbutrin was demonstrated in placebo controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds to the Major Depression category of the APA Diagnostic and Statistical Manual III.

Major Depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two weeks); it should include at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Evidence to demonstrate the sustained effectiveness of Wellbutrin after three weeks of use in placebo-controlled investigations is not presently available.

CONTRAINDICATIONS:

Because of its potential to induce seizures, Wellbutrin should not be used in patients with a convulsive disorder.

The concurrent administration of Wellbutrin and a monoamine oxidase (MAO) inhibitor is contraindicated; at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

Wellbutrin is contraindicated in patients who have shown an allergic response to it.

WARNINGS:

CONVULSIONS:

Wellbutrin appears to possess a greater epileptogenic potential than other marketed antidepressants. While the estimated risk of seizure at doses of 450 mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products, the estimated risk increases almost tenfold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation is a cause for concern.

During the period of premarketing evaluation, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, seven (7) patients were receiving daily doses of Wellbutrin at or below the lowest documented effective daily dose of 450 mg. Twelve (12) patients experienced seizures at daily doses of 600 mg; six (6) additional patients had seizures at daily doses between 600 and 900 mg. The risk of seizure appears to be strongly associated with dose and may be increased by predisposing factors (e.g., head trauma, CNS tumor, etc.) or a history of prior seizure. In addition, sudden and large increments in dose may contribute to an increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks of use at fixed dose.

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

	Wellbutrin Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
Within Recommended Dose	<450	0.2%	0.0%
	450	0.3%	0.2%
Above Recommended Dose	600	2.3%	1.3%
	600-900	2.8%	1.9%

DOSAGE AND ADMINISTRATION RECOMMENDATIONS SHOULD BE STRICTLY FOLLOWED TO MINIMIZE THE RISK OF SEIZURE (see DOSAGE AND ADMINISTRATION).

Extreme caution should be used when combining Wellbutrin with other agents which lower seizure threshold or when administering Wellbutrin to patients with a history of seizure disorder or cranial trauma.

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS:

General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Physicians are advised to discuss the following issues with patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because Wellbutrin and other drugs may affect each other's metabolism.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: It is not known whether Wellbutrin is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when Wellbutrin is administered to women who are nursing.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's premarketing clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR		
CARDIAC ARRHYTHMIAS	5.3	4.3
DIZZINESS	22.3	16.2
HYPERTENSION	4.3	1.6
HYPOTENSION	2.5	2.2
PALPITATIONS	3.7	2.2
SYNCOPE	1.2	0.5
TACHYCARDIA	10.8	8.6
DERMATOLOGIC		
PRURITIS	2.2	0.0
RASH	8.0	6.5
GASTROINTESTINAL		
ANOREXIA	18.3	18.4
APPETITE INCREASE	3.7	2.2
CONSTIPATION	26.0	17.3
DIARRHEA	6.8	8.6

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
GASTROINTESTINAL		
DYSPEPSIA	3.1	2.2
NAUSEA/VOMITING	22.9	18.9
WEIGHT GAIN	13.6	22.7
WEIGHT LOSS	23.2	23.2
GENITOURINARY		
IMPOTENCE	3.4	3.1
MENSTRUAL COMPLAINTS	4.7	1.1
URINARY FREQUENCY	2.5	2.2
URINARY RETENTION	1.9	2.2
MUSCULOSKELETAL		
ARTHRITIS	3.1	2.7
NEUROLOGICAL		
AKATHISIA	1.5	1.1
AKINESIA/BRADYKINESIA	8.0	8.6
CUTANEOUS TEMP DISTURBANCE	1.9	1.6
DRY MOUTH	27.6	18.4
EXCESSIVE SWEATING	22.3	14.6
HEADACHE/MIGRAINE	25.7	22.2
IMPAIRED SLEEP QUALITY	4.0	1.6
INCREASED SALIVARY FLOW	3.4	3.8
INSOMNIA	18.6	15.7
MUSCLE SPASMS	1.9	3.2
PSEUDOPARKINSONISM	1.5	1.6
SEDATION	19.8	19.5
SENSORY DISTURBANCE	4.0	3.2
TREMOR	21.1	7.6
NEUROPSYCHIATRIC		
AGITATION	31.9	22.2
ANXIETY	3.1	1.1
CONFUSION	8.4	4.9
DECREASED LIBIDO	3.1	1.6
DELUSIONS	1.2	1.1
DISTURBED CONCENTRATION	3.1	3.8
EUPHORIA	1.2	0.5
HOSTILITY	5.6	3.8
NONSPECIFIC		
FATIGUE	5.0	8.6
FEVER/CHILLS	1.2	0.5
RESPIRATORY		
UPPER RESP COMPLAINTS	5.0	11.4
SPECIAL SENSES		
AUDITORY DISTURBANCE	5.3	3.2
BLURRED VISION	14.6	10.3
GUSTATORY DISTURBANCE	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire premarketing evaluation of Wellbutrin: During its premarketing assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

DRUG ABUSE AND DEPENDENCE:

Humans: Controlled clinical studies conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg Wellbutrin produced mild amphetamine-like activity as compared to placebo on the morphine-benzedrine subscale of the Addiction Research Center Index (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to predict the abuse potential of drugs reliably. Nonetheless, evidence from single dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses, which could not be tested because of the risk of seizure, might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of a mild stereotyped behavior and increases in rates of responding in several schedule-controlled behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to self-administer bupropion intravenously.

OVERDOSAGE:

Lethal doses in animals: In rats, the acute oral LD_{50} values were 607 mg/kg (males) and 482 mg/kg (females). Respective values for mice were 544 mg/kg and 636 mg/kg. Signs of acute toxicity included labored breathing, salivation, arched back, ptosis, ataxia, and convulsions.

Human overdose experience: There has been limited clinical experience with overdosage of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Management of overdose: Following suspected overdose, hospitalization is advised. If the patient is conscious, vomiting should be induced by syrup of ipecac. Activated charcoal also may be administered every 6 hours during the first 12 hours after ingestion. Baseline laboratory values should be obtained. Electrocardiogram and EEG monitoring also are recommended for the next 48 hours. Adequate fluid intake should be provided.

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of Wellbutrin, it is likely to be of benefit within the first 12 hours after ingestion since absorption of the drug may not yet be complete.

While diuresis, dialysis, or hemoperfusion are sometimes used to treat drug overdosage, there is no experience with their use in the management of Wellbutrin overdose. Because diffusion of Wellbutrin from tissue to plasma may be slow, dialysis may be of minimal benefit several hours after overdose.

Based on studies in animals, it is recommended that seizures be treated with an intravenous benzodiazepine preparation and other supportive measures, as appropriate.

Further information about the treatment of overdoses may be available from a poison control center.

DOSAGE AND ADMINISTRATION: At doses that are one and one-third times the usually required dose (450 mg/day) (see WARNINGS), the observed incidence of seizure increases by as much as tenfold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development suggests that the risk of seizure may be minimized if 1) the total daily dose of Wellbutrin does *not* exceed 450 mg, 2) the daily dose is administered in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

Wellbutrin should be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage: A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response, this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule, up to a total maximum daily dose of 450 mg/day. Of course, if distressing, untoward effects supervene, dose escalation should be stopped.

DOSING SCHEDULE

Treatment Day	75 mg Tablets			Total Daily Dose
	Morning	Midday	Evening	
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs. Clinical trials enrolled several hundred patients 60 years of age and older. The experience with these patients and younger ones was similar.

Maintenance: The lowest dose which maintains remission is recommended. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with Wellbutrin in long-term clinical trials of up to 2 years duration, there has been no systematic placebo-controlled evaluation of the efficacy of Wellbutrin for a period beyond three to four weeks.

HOW SUPPLIED: Wellbutrin (bupropion hydrochloride) Tablets are supplied as 75 mg (yellow-gold) round, biconvex tablets printed "WELLBUTRIN" and "75," bottles of 100 (NDC 0081-0177-55).

Store at 15°-25°C (59°-77°F).

*U.S. Patent No. 3819706
U.S. Patent No. 3885046 (Use Patent)

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