

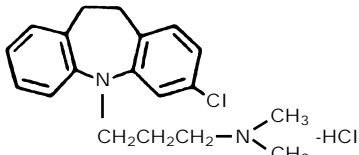
Clomipramine Hydrochloride 100 Capsules

Rx only

DESCRIPTION

Clomipramine is an antidepressant drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Each capsule for oral administration contains 25 mg, 50 mg, or 75 mg of clomipramine hydrochloride.

Clomipramine is 3-chloro-5-[3-(dimethylamino)propyl]-10, 11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3, and its molecular formula is C₁₉H₂₂ClN₂.

Each capsule contains the following inactive ingredients: Black Iron Oxide (25 mg capsules only), D&C Yellow 10 (25 mg capsules only), FD&C Blue 2 (25 mg capsules only), FD&C Red 3 (25 mg capsules only), Gelatin, Magnesium Stearate, Colloidal Silicon Dioxide, Pregelatinized Starch, Titanium Dioxide, Yellow Iron Oxide (50 mg capsules only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Pharmacokinetics

Absorption/Bioavailability: Clomipramine from clomipramine capsules is as bioavailable as clomipramine from a solution. The bioavailability of clomipramine from capsules is not significantly affected by food.

In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C₅₀) and area-under-plasma-concentration-time curves (AUC) of clomipramine and clomipramine's major active metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C₅₀ and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and clomipramine/desmethylclomipramine concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C₅₀ and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of clomipramine occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). After multiple daily doses of 150 mg of clomipramine hydrochloride, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for clomipramine and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for desmethylclomipramine. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: Clomipramine distributes into cerebrospinal fluid (CSF) and brain and into breast milk. Desmethylclomipramine also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of clomipramine is approximately 97%, principally to albumin, and is independent of clomipramine concentration. The interaction between clomipramine and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of clomipramine in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of clomipramine and desmethylclomipramine were only about 0.8-1.3% of the dose administered. Clomipramine does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C₅₀ and AUC for clomipramine and desmethylclomipramine may increase disproportionately with increasing oral dose suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of clomipramine and desmethylclomipramine are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, clomipramine and desmethylclomipramine may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for clomipramine. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for clomipramine is approximately 2.5 and for desmethylclomipramine is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of clomipramine hydrochloride have not been determined.

Interactions: Coadministration of haloperidol with clomipramine increases plasma concentrations of clomipramine. Coadministration of clomipramine with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated clomipramine better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of clomipramine were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Clomipramine hydrochloride capsules are indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable. The effectiveness of clomipramine for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26-28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OCD). Patients taking clomipramine experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. Clomipramine treated patients experienced a 3.5 unit decrement on the NIMH-OCD. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of clomipramine for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Clomipramine is contraindicated in patients with a history of hypersensitivity to clomipramine or other tricyclic antidepressants.

Clomipramine should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Clomipramine is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of clomipramine hydrochloride use.

The observed cumulative incidence of seizures among patients exposed to clomipramine hydrochloride at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7% (25 of 3519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of clomipramine greater than 250 mg is limited, given that the plasma concentration of clomipramine may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Caution should be used in administering clomipramine to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, clomipramine had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between clomipramine treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking clomipramine while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking clomipramine in clinical trials, but patients were frequently asymptomatic. Among approximately 1400 patients treated with clomipramine in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with

known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with clomipramine 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 of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with clomipramine. As with tricyclic antidepressants to which it is closely related, clomipramine may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of clomipramine in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to clomipramine.

Hepatic Changes: During premarketing testing, clomipramine was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with clomipramine, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with clomipramine use. As is the case with tricyclic antidepressants to which clomipramine is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine was used in combination with other drugs. When clomipramine and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with clomipramine in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving clomipramine, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving clomipramine had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of clomipramine with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with clomipramine hydrochloride should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, clomipramine should be used with caution in the following:

- (1) Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;
- (2) Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;
- (3) Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;
- (4) Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe clomipramine hydrochloride:

- (1) The risk of seizure (see WARNINGS);
- (2) The relatively high incidence of sexual dysfunction among males (see Sexual Dysfunction);
- (3) Since clomipramine may impair the mental and/or physical abilities required for the performance of complex tasks, and since clomipramine is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS);
- (4) Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since clomipramine may exaggerate their response to these drugs;
- (5) Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;
- (6) Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS-active drugs (see Information for Patients). Clomipramine should not be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when clomipramine is administered with anticholinergic or sympathomimetic drugs. Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin), and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Interactions).

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine, cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clomipramine by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy: Teratogenic Effects, Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine until delivery. Clomipramine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clomipramine has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in pediatric patients and adolescents (10-17 years of age), 46 outpatients received clomipramine for up to 8 weeks. In addition, 150 adolescent patients have received clomipramine in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with clomipramine may have on the growth and development of pediatric patients.

The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine in pediatric patients under the age of 10.

Use in Elderly

Clomipramine has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received clomipramine for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, includ-

ing somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received clomipramine in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received clomipramine in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving clomipramine (N=322) or placebo (N=319) or children treated with clomipramine (N=46) or placebo (N=44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Clomipramine Hydrochloride Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting Event)					Clomipramine Hydrochloride Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting Event)				
Body System/ Adverse Event*	Adults		Children and Adolescents		Body System/ Adverse Event*	Adults		Children and Adolescents	
	Clomipramine (N=322)	Placebo (N=319)	Clomipramine (N=46)	Placebo (N=44)		Clomipramine (N=322)	Placebo (N=319)	Clomipramine (N=46)	Placebo (N=44)
Nervous System					Chills	2	1	-	-
Somnolence	54	16	46	11	Weight decrease	-	-	7	-
Tremor	54	2	33	2	Otitis media	-	-	4	5
Dizziness	54	14	41	14	Asthenia	-	-	2	-
Headache	52	41	28	34	Hallucinations	-	-	2	-
Insomnia	25	15	11	7					
Libido change	21	3	-	-	Cardiovascular System				
Nervousness	18	2	4	2	Postural hypotension	6	-	4	-
Myoclonus	13	-	2	-	Palpitation	4	2	4	-
Increased appetite	11	2	-	-	Tachycardia	4	-	2	-
Paresthesia	9	3	2	2	Syncope	-	-	2	-
Memory impairment	9	1	7	2					
Anxiety	9	4	2	-	Respiratory System				
Twitching	7	1	4	5	Pharyngitis	14	9	-	5
Impaired concentration	5	2	-	-	Rhinitis	12	10	7	9
Depression	5	1	-	-	Sinusitis	6	4	2	5
Hypertonia	4	1	2	-	Coughing	6	6	4	5
Sleep disorder	4	-	9	5	Bronchospasm	2	-	7	2
Psychosomatic disorder	3	-	-	-	Epistaxis	2	-	-	2
Yawning	3	-	-	-	Dyspnea	-	-	2	-
Confusion	3	-	2	-	Laryngitis	-	1	2	-
Speech disorder	3	-	-	-					
Abnormal dreaming	3	-	-	2	Urogenital System				
Agitation	3	-	-	-	Male and Female Patients Combined				
Migraine	3	-	-	-	Micturition disorder	14	2	4	2
Depersonalization	2	-	2	-	Urinary tract infection	6	1	-	-
Irritability	2	2	2	-	Micturition frequency	5	3	-	-
Emotional lability	2	-	2	-	Urinary retention	2	-	7	-
Panic reaction	1	-	2	-	Dysuria	2	2	-	-
Aggressive reaction	-	-	2	-	Cystitis	-	-	2	-
Paresis	-	-	2	-					
					Female Patients Only (N=182)	(N=167)	(N=10)	(N=21)	
Skin and Appendages					Dysmenorrhea	12	14	10	10
Increased sweating	29	3	9	-	Lactation (nonpuerperal)	4	-	-	-
Rash	8	1	4	2	Menstrual disorder	4	2	-	-
Pruritus	6	-	2	2	Vaginitis	2	-	-	-
Dermatitis	2	-	2	-	Leukorrhea	2	-	-	-
Acne	2	2	-	5	Breast enlargement	2	-	-	-
Dry skin	2	-	-	5	Breast pain	1	-	-	-
Urticaria	1	-	-	-	Amenorrhea	1	-	-	-
Abnormal skin odor	-	-	2	-					
					Male Patients Only (N=140)	(N=152)	(N=36)	(N=23)	
Digestive System					Ejaculation failure	42	2	6	-
Dry mouth	84	17	63	16	Impotence	20	3	-	-
Constipation	47	11	22	9					
Nausea	33	14	9	11	Special Senses				
Dyspepsia	22	10	13	2	Abnormal vision	18	4	7	2
Diarrhea	13	9	7	5	Taste perversion	8	-	4	-
Anorexia	12	-	22	2	Tinnitus	6	-	4	-
Abdominal pain	11	9	13	16	Abnormal lacrimation	3	2	-	-
Vomiting	7	2	7	-	Mydriasis	2	-	-	-
Flatulence	6	3	-	2	Conjunctivitis	1	-	-	-
Tooth disorder	5	-	-	-	Anisocoria	-	-	2	-
Gastrointestinal disorder	2	-	-	2	Blepharospasm	-	-	2	-
Dysphagia	2	-	-	-	Ocular allergy	-	-	2	-
Esophagitis	1	-	-	-	Vestibular disorder	-	-	2	2
Eruaction	-	-	2	2					
Ulcerative stomatitis	-	-	2	-	Musculoskeletal				
					Myalgia	13	9	-	-
Body as a Whole					Back pain	6	6	-	-
Fatigue	39	18	35	9	Arthralgia	3	5	-	-
Weight increase	1	1	2	-	Muscle weakness	1	-	2	-
Flushing	8	-	7	-					
Hot flushes	5	-	2	-	Hemic and Lymphatic				
Chest pain	4	4	7	-	Purpura	3	-	-	-
Fever	4	-	2	7	Anemia	-	-	2	2
Allergy	3	3	7	5					
Pain	3	2	4	2	Metabolic and Nutritional				
Local edema	2	4	-	-	Thirst	2	2	-	2

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

Other Events Observed During the Premarketing Evaluation of Clomipramine

During clinical testing in the U.S., multiple doses of clomipramine were administered to approximately 3600 subjects. 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, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to clomipramine who experienced an event of the type cited at least one occasion while receiving clomipramine. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with clomipramine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/1000 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: Infrequent - general edema, increased susceptibility to infection, malaise. Rare - dependent edema, withdrawal syndrome.

Cardiovascular System: Infrequent - abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. Rare - aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: Infrequent - abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. Rare - cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: Infrequent - hypothyroidism. Rare - goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: Infrequent - lymphadenopathy. Rare - leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: Infrequent - dehydration, diabetes mellitus, drug, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. Rare - fat intolerance, glycosuria.

Musculoskeletal System: Infrequent - arthrosis. Rare - dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarthritis nodosa, torticollis.

Nervous System: Frequent - abnormal thinking, vertigo. Infrequent - abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. Rare - anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic

syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hyposthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculomotor nerve paralysis, oculomotor crisis, schizophrenic reaction, stupor, suicide.

Respiratory System: Infrequent - bronchitis, hyperventilation, increased sputum, pneumonia. Rare - cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: Infrequent - alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. Rare - chloasma, folliculitis, hypertrichosis, pilorection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: Infrequent - abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. Rare - blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: Infrequent - endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. Rare - albuminuria, anorgasmia, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Clomipramine has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with clomipramine discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential clomipramine abuse by a patient with a history of dependence on cocaine, benzodiazepines, and multiple psychoactive drugs. The patient received clomipramine hydrochloride for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for clomipramine in foreign marketing, it is not possible to predict the extent to which clomipramine might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Deaths may occur from overdose with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic overdose. Therefore, hospital monitoring is required as soon as possible.

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdose with clomipramine either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, clomipramine's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Manifestations

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic toxicity. Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity and anteheld and choreiform movements. Cardiac abnormalities may include tachycardia, signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, shock, vomiting, hyperpyrexia, mydriasis and oliguria or anuria, may also be present.

Management

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a $P_{CO_2} < 20$ mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdoses are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of clomipramine in 520 adults, and 91 children and adolescents with OCD. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both clomipramine and its active metabolite, desmethylclomipramine, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with clomipramine hydrochloride should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue clomipramine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of clomipramine after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Clomipramine Hydrochloride Capsules are supplied as follows:

25 mg - Dark blue cap/light blue body capsules, size 2, with black printing of Taro 25

Bottles of 100NDC 51672-4011-1

50 mg - Yellow opaque capsules, size 1, with black printing of Taro 50

Bottles of 100NDC 51672-4012-1

75 mg - White opaque capsules, size 1, with black printing of Taro 75

Bottles of 100NDC 51672-4013-1

Do not store above 30° C (86°F). Protect from moisture.

Dispense in light container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with clomipramine. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipids in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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