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risk for postpartum depressive symptoms. Psychoneuroendocrinology. 2013;38(7):1007–1013. 29.32 Tricyclics and Tetracyclics The observation in 1957 that imipramine (Tofranil) had antidepressant effects led to the development of a new class of antidepressant compounds, the tricyclics (TCAs). In turn, the finding that imipramine blocked reuptake of norepinephrine led to research into the role of catecholamines in depression. After the introduction of imipramine, several other antidepressant compounds were developed that shared a basic tricyclic structure and had relatively similar effects. Later, other heterocyclic compounds were also marketed that were somewhat similar in structure and that had relatively comparable secondary properties. At one time, amitriptyline (Elavil, Endep) and imipramine were the two most commonly prescribed antidepressants in the United States, but because of their anticholinergic and antihistaminic side effects, their use declined, and nortriptyline (Aventyl, Pamelor) and desipramine (Norpramin, Pertofrane) became more popular. Nortriptyline has the least effect on orthostatic hypotension, and desipramine is the least anticholinergic. Although introduced as antidepressants, the therapeutic indications for these agents have grown to include panic disorder, GAD, PTSD, OCD, and pain syndromes. The introduction of newer antidepressant agents with more selective actions on neurotransmitters or with unique mechanisms of action has sharply reduced the prescribing of TCAs and tetracyclics. The improved safety profiles of the newer drugs, especially when taken in overdose, also contributed to the decline in use of the older drugs. Nevertheless, the TCAs and tetracyclics remain unsurpassed in terms of their antidepressant efficacy. Table 29.32-1 lists TCA and tetracyclic drugs and their available preparations. Table 29.32-1 Tricyclic and Tetracyclic Drug Preparations PHARMACOLOGIC ACTIONS The absorption of most TCAs is complete after oral administration, and there is significant metabolism from the first-pass effect. Peak plasma concentrations occur within 2 to 8 hours, and the half-lives of the TCAs vary from 10 to 70 hours;

nortriptyline, maprotiline (Ludiomil), and particularly protriptyline (Vivactil) can have longer half-lives. The long half-lives allow all the compounds to be given once daily; 5 to 7 days is needed to reach steady-state plasma concentrations. Imipramine pamoate (Tofranil) is a depot form of the drug for intramuscular (IM) administration; indications for the use of this preparation are limited.

The TCAs undergo hepatic metabolism by the CYP450 enzyme system. Clinically relevant drug interactions may result from competition for enzyme CYP2D6 among TCAs and quinidine, cimetidine (Tagamet), fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), phenothiazines, carbamazepine (Tegretol), and the type IC antiarrhythmics propafenone (Rythmol) and flecainide (Tambocor). Concomitant administration of TCAs and these inhibitors may slow down the metabolism and raise the plasma concentrations of TCAs. Additionally, genetic variations in the activity of CYP2D6 may account for up to a 40-fold difference in plasma TCA concentrations in different persons. The dosage of the TCA may need to be adjusted to correct changes in the rate of hepatic TCA metabolism. The TCAs block the transporter site for norepinephrine and serotonin, thus increasing synaptic concentrations of these neurotransmitters. Each drug differs in its affinity for each of these transporters, with clomipramine (Anafranil) being the most serotonin selective and desipramine the most norepinephrine selective of the TCAs. Secondary effects of the TCAs include antagonism at the muscarinic acetylcholine, histamine H1, and α1- and α2-adrenergic receptors. The potency of these effects on other receptors largely determines the side effect profile of each drug. Amoxapine, nortriptyline, desipramine, and maprotiline have the least anticholinergic activity; doxepin has the most antihistaminergic activity. Although they are more likely to cause constipation, sedation, dry mouth, or lightheadedness than the SSRIs, the TCAs are less prone to cause sexual dysfunction, significant long-term weight gain, and sleep disturbances than the SSRIs. The half-lives and plasma clearance for most TCAs are very similar. THERAPEUTIC INDICATIONS Each of the following indications is also an indication for the SSRIs, which have widely replaced the TCAs in clinical practice. However, the TCAs represent a reasonable alternative for persons who cannot tolerate the adverse effects of the SSRIs. Major Depressive Disorder The treatment of a major depressive episode and the prophylactic treatment of major depressive disorder are the principal indications for using TCAs. Although the TCAs are effective in the treatment of depression in persons with bipolar I disorder, they are more likely to induce mania, hypomania, or cycling than the newer antidepressants, most notably the SSRIs and bupropion. It is thus not advised that TCAs be routinely used to treat depression associated with bipolar I or bipolar II disorder. Melancholic features, prior major depressive episodes, and a family history of

depressive disorders increase the likelihood of a therapeutic response. All of the available TCAs are equally effective in the treatment of depressive disorders. In the case of an individual person, however, one tricyclic or tetracyclic may be effective, and another one may be ineffective. The treatment of a major depressive episode with psychotic features almost always requires the coadministration of an antipsychotic drug and an antidepressant. Although it is used worldwide as an antidepressant, clomipramine is only approved in the United States for the treatment of OCD. Panic Disorder with Agoraphobia Imipramine is the TCA most studied for panic disorder with agoraphobia, but other TCAs are also effective when taken at the usual antidepressant dosages. Because of the potential initial anxiogenic effects of the TCAs, starting dosages should be small, and the dosage should be titrated upward slowly. Small doses of benzodiazepines may be used initially to deal with this side effect. Generalized Anxiety Disorder The use of doxepin for the treatment of anxiety disorders is approved by the FDA. Some research data show that imipramine may also be useful. Although rarely used anymore, a chlordiazepoxide–amitriptyline combination (Limbitrol) is available for mixed anxiety and depressive disorders. Obsessive-Compulsive Disorder Patients with OCD appear to respond specifically to clomipramine, as well as the SSRIs. Some improvement is usually seen in 2 to 4 weeks, but a further reduction in symptoms may continue for the first 4 to 5 months of treatment. None of the other TCAs appears to be nearly as effective as

clomipramine for treatment of this disorder. Clomipramine may also be a drug of choice for depressed persons with marked obsessive features. Pain The TCAs are widely used to treat chronic neuropathic pain and in prophylaxis of migraine headache. Amitriptyline is the TCA most often used in this role. During treatment of pain, doses are generally lower than those used in depression; for example, 75 mg of amitriptyline may be effective. These effects also appear more rapidly. Other Disorders Childhood enuresis is often treated with imipramine. Peptic ulcer disease can be treated with doxepin, which has marked antihistaminergic effects. Other indications for the TCAs are narcolepsy, nightmare disorder, and PTSD. The drugs are sometimes used for treatment of children and adolescents with ADHD, sleepwalking disorder, separation

anxiety disorder, and sleep terror disorder. Clomipramine has also been used to treat premature ejaculation, movement disorders, and compulsive behavior in children with autistic disorders; however, because the TCAs have caused sudden death in several children and adolescents, they should not be used in children. PRECAUTIONS AND ADVERSE REACTIONS The TCAs are associated with a wide range of problematic side effects and can be lethal when taken in overdose. Psychiatric Effects The TCAs can induce a switch to mania or hypomania in susceptible individuals. The TCAs may also exacerbate psychotic disorders in susceptible persons. At high plasma concentrations (levels above 300 ng/mL), the anticholinergic effects of the TCAs can cause confusion or delirium. Patients with dementia are particularly vulnerable to this development. Anticholinergic Effects Anticholinergic effects often limit the tolerable dosage to relatively low ranges. Some persons may develop a tolerance for the anticholinergic effects with continued treatment. Anticholinergic effects include dry mouth, constipation, blurred vision, delirium, and urinary retention. Sugarless gum, candy, or fluoride lozenges can alleviate dry mouth. Bethanechol (Urecholine), 25 to 50 mg three or four times a day, may reduce urinary hesitancy and may be helpful in erectile dysfunction when the drug is taken 30 minutes before sexual intercourse. Narrow-angle glaucoma can also be aggravated by anticholinergic drugs, and the precipitation of glaucoma requires emergency treatment with a miotic agent. The TCAs should be avoided in persons with narrow-angle glaucoma, and an SSRI should be substituted. Severe anticholinergic effects can lead to a CNS anticholinergic syndrome with confusion and delirium, especially if the TCAs are administered with dopamine receptor antagonists (DRAs) or anticholinergic drugs. IM or IV physostigmine (Antilirium, Eserine) is used to diagnose and treat anticholinergic delirium. Cardiac Effects When administered in their usual therapeutic dosages, the TCAs may cause tachycardia, flattened T waves, prolonged QT intervals, and depressed ST segments in the electrocardiographic (EKG) recording. Imipramine has a quinidine-like effect at therapeutic plasma concentrations and may reduce the number of premature ventricular contractions. Because the drugs prolong conduction time, their use in persons with preexisting conduction defects is contraindicated. In persons with a history of any type of heart disease, the TCAs should be used only after SSRIs or other newer antidepressants have been found ineffective, and if used, they should be introduced at

low dosages, with gradual increases in dosage and monitoring of cardiac functions. All of the TCAs can cause tachycardia, which may persist for months and is one of the most common reasons for drug discontinuation, especially in younger persons. At high plasma concentrations, as seen in overdoses, the drugs become arrhythmogenic. Other Autonomic Effects Orthostatic hypotension is the most common cardiovascular autonomic adverse effect and the most common reason TCAs are discontinued. It can result in falls and injuries in affected persons. Nortriptyline may be the drug least likely to cause this problem. Orthostatic hypotension is treated with avoidance of caffeine,

intake of at least 2 L of fluid per day and addition of salt to the diet unless the person is being treated for hypertension. In persons taking antihypertensive agents, reduction of the dosage may reduce the risk of orthostatic hypotension. Other possible autonomic effects are profuse sweating, palpitations, and increased blood pressure (BP). Although some persons respond to fludrocortisone (Florinef), 0.02 to 0.05 mg twice a day, substitution of an SSRI is preferable to addition of a potentially toxic mineralocorticoid such as fludrocortisone. The TCAs' use should be discontinued several days before elective surgery because of the occurrence of hypertensive episodes during surgery in persons receiving TCAs. Sedation Sedation is a common effect of the TCAs and may be welcomed if sleeplessness has been a problem. The sedative effect of the TCAs is a result of anticholinergic and antihistaminergic activities. Amitriptyline, trimipramine, and doxepin are the most sedating agents; imipramine, amoxapine, nortriptyline, and maprotiline are less sedating; and desipramine and protriptyline are the least sedating agents. Neurologic Effects A fine, rapid tremor may occur. Myoclonic twitches and tremors of the tongue and the upper extremities are common. Rare effects include speech blockage, paresthesia, peroneal palsies, and ataxia. Amoxapine is unique in causing parkinsonian symptoms, akathisia, and even dyskinesia because of the dopaminergic blocking activity of one of its metabolites. Amoxapine may also cause neuroleptic malignant syndrome in rare cases. Maprotiline may cause seizures when the dosage is increased too quickly or is kept at high levels for too long. Clomipramine and amoxapine may lower the seizure threshold more than other drugs in the class. As a class, however, the TCAs have a relatively low risk for inducing seizures except in persons who are at risk for seizures (e.g., persons with epilepsy and those with brain lesions). Although the TCAs can still be used by such persons, the initial dosages should be lower than usual, and subsequent dosage increases should be gradual.

Allergic and Hematologic Effects Exanthematous rashes are seen in 4 to 5 percent of all persons treated with maprotiline. Jaundice is rare. Agranulocytosis, leukocytosis, leukopenia, and eosinophilia are rare complications of TCA treatment. However, a person who has a sore throat or a fever during the first few months of TCA treatment should have a complete blood count (CBC) done immediately. Hepatic Effects Mild and self-limited increases in serum transaminase concentrations may occur and should be monitored. The TCAs can also produce a fulminant acute hepatitis in 0.1 to 1 percent of persons. This can be life threatening, and the antidepressant should be discontinued. Other Adverse Effects Modest weight gain is common. Amoxapine exerts a DRA effect and may cause hyperprolactinemia, impotence, galactorrhea, anorgasmia, and ejaculatory disturbances. Other TCAs have also been associated with gynecomastia and amenorrhea. The syndrome of inappropriate secretion of antidiuretic hormone has also been reported with TCAs. Other effects include nausea, vomiting, and hepatitis. Teratogenicity and Pregnancy-Related Risks. A definitive link between the tricyclic compounds and tetracyclic compounds and teratogenic effects has not been established, but isolated reports of morphogenesis have been reported. TCAs cross the placenta, and neonatal drug withdrawal can occur. This syndrome includes tachypnea, cyanosis, irritability, and poor sucking reflex. If possible, tricyclic and tetracyclic medications should be discontinued 1 week before delivery. Recently, norepinephrine and serotonin transporters have been identified in the placenta and appear to play an important role in the clearance of these amines in the fetus. The understanding of the effects of reuptake inhibitors on these transporters during pregnancy is limited, but one study compared intelligence and language development in 80 children exposed to TCAs during pregnancy with 84 children exposed to other nonteratogenic agents and found no deleterious effects of the TCAs. The TCAs are excreted in

breast milk at concentrations similar to plasma. The actual quantity delivered, however, is small, so drug levels in the infant are usually undetectable or very low. Because the risk of relapse is a serious concern in patients with recurrent depression, and these risks may be increased during pregnancy or the postpartum period, the risks and benefits of continuing or withdrawing treatment need to be discussed with the patient and weighed carefully. Precautions

The TCAs may cause a withdrawal syndrome in newborns consisting of tachypnea, cyanosis, irritability, and poor sucking reflex. The drugs do pass into breast milk but at concentrations that are usually undetectable in the infant's plasma. The drugs should be used with caution in persons with hepatic and renal diseases. The TCAs should not be administered during a course of electroconvulsive therapy, primarily because of the risk of serious adverse cardiac effects. DRUG INTERACTIONS Monoamine Oxidase Inhibitors The TCAs should not be taken within 14 days of administration of an MAOI. Antihypertensives The TCAs block the therapeutic effects of antihypertensive medication. The antihypertensive effects of the β-adrenergic receptor antagonists (e.g., propranolol [Inderal] and clonidine [Catapres]) may be blocked by the TCAs. The coadministration of a TCA and α-methyldopa (Aldomet) may cause behavioral agitation. Antiarrhythmic Drugs The antiarrhythmic properties of TCAs can be additive to those of quinidine, an effect that is further exacerbated by the inhibition of TCA metabolism by quinidine. Dopamine Receptor Antagonists Concurrent administration of TCAs and DRAs increases the plasma concentrations of both drugs. Desipramine plasma concentrations may increase twofold during concurrent administration with perphenazine (Trilafon). The DRAs also add to the anticholinergic and sedative effects of the TCAs. Concomitant use of serotonin–dopamine antagonists (SDAs) also increase those effects. Central Nervous System Depressants Opioids, alcohol, anxiolytics, hypnotics, and over-the-counter cold medications have additive effects by causing CNS depression when coadministered with TCAs. Persons should be advised to avoid driving or using dangerous equipment if sedated by TCAs. Sympathomimetics Tricyclic drug use with sympathomimetic drugs may cause serious cardiovascular effects. Oral Contraceptives Birth control pills may decrease TCA plasma concentrations through the induction of

hepatic enzymes. Other Drug Interactions Nicotine may reduce TCA concentrations. Plasma concentrations may also be lowered by ascorbic acid, ammonium chloride, barbiturates, cigarette smoking, carbamazepine, chloral hydrate, lithium (Eskalith), and primidone (Mysoline). TCA plasma concentrations may be increased by concurrent use of acetazolamide (Diamox), sodium bicarbonate, acetylsalicylic acid, cimetidine, thiazide diuretics, fluoxetine, paroxetine, and fluvoxamine (Luvox). Plasma concentrations of the TCAs may rise three- to fourfold when administered concurrently with fluoxetine, fluvoxamine, and paroxetine. LABORATORY INTERFERENCES The tricyclic compounds are present at low concentrations and are not likely to interfere with other laboratory assays. It is possible that they may interfere with the determination of conventional neuroleptic blood concentrations because of their structural similarity and the low concentrations of some neuroleptics. DOSAGE AND CLINICAL GUIDELINES Persons who intend to take TCAs should undergo routine physical and laboratory examinations, including a CBC, a white blood cell count with differential, and serum electrolytes with liver function tests. An EKG should be obtained for all persons, especially women older than 40 years of age and men older than 30 years of age. The TCAs are contraindicated in persons with a QTc greater than 450 milliseconds. The initial dose should be small and should be raised gradually. Because of the availability of highly effective alternatives to TCAs, a newer agent should be used if there is any medical condition that

may interact adversely with the TCAs. Elderly persons and children are more sensitive to TCA adverse effects than are young adults. In children, the EKG should be regularly monitored during use of a TCA. The available preparations of TCAs are presented in Table 29.32-1. The dosages and therapeutic blood levels for the TCAs vary among the drugs (Table 29.32-2). With the exception of protriptyline, all of the TCAs should be started at 25 mg a day and increased as tolerated. Divided doses at first reduce the severity of the adverse effects, although most of the dosage should be given at night to help induce sleep if a sedating drug such as amitriptyline is used. Eventually, the entire daily dose can be given at bedtime. A common clinical mistake is to stop increasing the dosage when the person is tolerating the drug but taking less than the maximum therapeutic dose and does not show clinical improvement. The clinician should routinely assess the person's pulse and orthostatic changes in BP while the dosage is being increased. Table 29.32-2 General Information for the Tricyclic and Tetracyclic Antidepressants

Nortriptyline use should be started at 25 mg a day. Most patients need only 75 mg a day to achieve a blood level of 100 mg/nL. However, the dosage may be raised to 150 mg a day if needed. Amoxapine use should be started at 150 mg a day and raised to 400 mg a day. Protriptyline use should be started at 15 mg a day and raised to 60 mg a day. Maprotiline has been associated with an increased incidence of seizures if the dosage is raised too quickly or is maintained at too high a level. Maprotiline use should be started at 25 mg a day and increased over 4 weeks to 225 mg a day. It should be kept at that level for only 6 weeks and then be reduced to 175 to 200 mg a day. Persons with chronic pain may be particularly sensitive to adverse effects when TCA use is started. Therefore, treatment should begin with low dosages that are raised in small increments. However, persons with chronic pain may experience relief on longterm low-dosage therapy, such as amitriptyline or nortriptyline at 10 to 75 mg a day. The TCAs should be avoided in children except as a last resort. Dosing guidelines in children for imipramine include initiation at 1.5 mg/kg a day. The dosage can be titrated to no more than 5 mg/kg a day. In enuresis, the dosage is usually 50 to 100 mg a day taken at bedtime. Clomipramine use can be initiated at 50 mg a day and increased to no more than 3 or 200 mg a day. When TCA treatment is discontinued, the dosage should first be decreased to threefourths the maximal dosage for a month. At that time, if no symptoms are present, drug use can be tapered by 25 mg (5 mg for protriptyline) every 4 to 7 days. Slow tapering avoids a cholinergic rebound syndrome consisting of nausea, upset stomach, sweating, headache, neck pain, and vomiting. This syndrome can be treated by reinstituting a small dosage of the drug and tapering more slowly than before. Several case reports note the appearance of rebound mania or hypomania after the abrupt discontinuation of TCA use. Plasma Concentrations and Therapeutic Drug Monitoring Clinical determinations of plasma concentrations should be conducted after 5 to 7 days on the same dosage of medication and 8 to 12 hours after the last dose. Because of variations in absorption and metabolism, there may be a 30- to 50-fold difference in the plasma concentrations in persons given the same dosage of a TCA. Nortriptyline is

unique in its association with a therapeutic window—that is, plasma concentrations below 50 ng/mL or above 150 ng/mL may reduce its efficacy. Plasma concentrations may be useful in confirming compliance, assessing reasons for drug failures, and documenting effective plasma concentrations for future treatment. Clinicians should always treat the person and not the plasma concentration. Some persons have adequate clinical responses with seemingly subtherapeutic plasma concentrations, and other persons only respond at supratherapeutic plasma concentrations without experiencing adverse effects. The latter situation, however, should alert the clinician to monitor the person's condition with, for example, serial EKG recordings. Overdose Attempts Overdose attempts

with TCAs are serious and can often be fatal. Prescriptions for these drugs should be nonrefillable and for no longer than 1 week at a time for patients at risk for suicide. Amoxapine may be more likely than the other TCAs to result in death when taken in overdose. The newer antidepressants are safer in overdose. Symptoms of overdose include agitation, delirium, convulsions, hyperactive deep tendon reflexes, bowel and bladder paralysis, dysregulation of BP and temperature, and mydriasis. The patient then progresses to coma and perhaps respiratory depression. Cardiac arrhythmias may not respond to treatment. Because of the long half-lives of TCAs, the patients are at risk of cardiac arrhythmias for 3 to 4 days after the overdose, so they should be monitored in an intensive care medical setting. REFERENCES Anderson I. Selective serotonin reuptake inhibitors versus tricyclics antidepressant: A meta-analysis of efficacy and tolerability. J Affect Disord. 2000;58:19. Anton RF, Burch EA. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. Am J Psychiatry. 1990;147:1203. Bech P, Allerup P, Larsen E, Csillag C, Licht R. Escitalopram versus nortriptyline: How to let the clinical GENDEP data tell us what they contained. Acta Psychiatr Scand. 2013;127(4):328–329. Charney DS, Delgado PL, Price LH, Heninger GR. The receptor sensitivity hypothesis of antidepressant action: A review of antidepressant effects on serotonin function. In: Brown SL, van Praag HM, eds. The Role of Serotonin in Psychiatric Disorders. New York: Brunner/Mazel; 1991:29. Choung RS, Cremonini F, Thapa P, Zinsmeister AR, Talley NJ. The effect of short-term, low-dose tricyclic and tetracyclic antidepressant treatment on satiation, postnutrient load gastrointestinal symptoms and gastric emptying: A double-blind, randomized, placebo-controlled trial. Neurogastroenterology Motility. 2008;20:220. Danish University Antidepressant Group. Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Dis. 1990;18:289. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry. 1997;54:597. Elkin I, Shea T, Watkins JT. NIMH treatment of depression collaborative research program: General effectiveness of treatments. Arch Gen Psychiatry. 1989;46:971. Frank E, Kupfer DJ, Perel JM. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen

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