Dawson AH. Cyclic antidepressant drugs. Detailed monograph in HyperTox

CHAPTER 134

Cyclic Antidepressant Drugs

Andrew H. Dawson

See Figure 1.	
Compounds included:	**See Table 1.**
Molecular formula and weight:	**See Table 1.**
SI conversion:	**[AUQ: Dr. Rivard 7/29.]**
CAS Registry No.:	**See Table 1.**
Therapeutic levels:	**See Table 8.**
Special concerns:	**Abrupt deterioration with seizures or ventricular dysrhythmias**
Antidotes:	**Sodium bicarbonate, hypertonic sodium chloride**

OVERVIEW

Cyclic antidepressants are pharmacologically *dirty* drugs: although their primary therapeutic effect is to block presynaptic catecholamine and serotonin reuptake, most of their adverse effects and toxicity is mediated by their effects of blocking of cellular ion channels as well as α-adrenergic, histaminergic, and muscarinic receptors. Common adverse effects are sedation and anticholinergic symptoms. The group is dominated by tricyclic antidepressants (TCA) in number, clinical experience, and extent of toxicity.

Despite changes in antidepressant prescribing patterns, TCA remain a common cause for admission (1) and death from poisoning (2–4). Up to 90% of TCA suicide deaths occur outside of hospital (5,6). One-half of the in-hospital fatalities have trivial toxicity on arrival to hospital but develop major toxicity within 1 hour (5). This reflects the rapid absorption of TCA and onset of cardiac and central nervous system toxicity. Whereas a number of electrocardiogram (ECG) abnormalities are predictive of serious toxicity, a normal ECG does not exclude serious toxicity. Decontamination, management of airway, and adjustment of pH to a mild systemic alkalosis with sodium bicarbonate are the mainstays of successful management.

The primary indication for all of these drugs is depression. TCAs have also been used for panic disorder (imipramine),

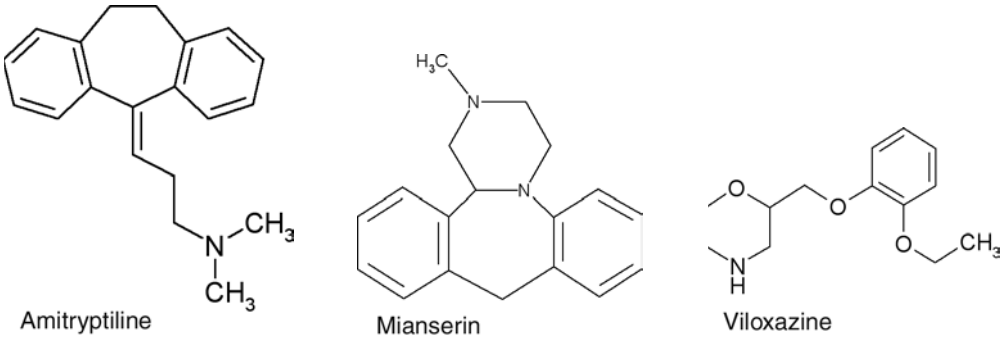

Figure 1. Structures of the cyclic antidepressant drugs.

obsessive-compulsive disorders (clomipramine), cataplexy associated with narcolepsy (clomipramine), and attention deficit hyperactivity disorder (imipramine, nortriptyline). Medical uses include adjunctive treatment in pain management (amitriptyline, doxepin) and treatment of nocturnal enuresis or urge incontinence (amitriptyline, imipramine, nortriptyline) (7). Viloxazine is a bicyclic antidepressant with predominant serotonin reuptake inhibition; no deaths are reported. Mianserin and maprotiline are both tetracyclic compounds with similar indications and mechanism of action to TCAs.

TOXIC DOSE

The *adult and pediatric therapeutic dose* is provided in Table 1. The normal therapeutic dose of most TCAs in both adults and children is 1 to 3 mg/kg given once a day. The doses for the bicyclic and tetracyclics vary (Table 1). Many TCAs have active metabolites that contribute to their therapeutic effect (Table 2).

The ingestion of 15 to 20 mg/kg or more of a TCA is potentially fatal, although there are significant differences in toxicity within the drug class (8–10). Tetracyclics and bicyclics appear to be less toxic in overdose than TCA. Small children can potentially develop life-threatening toxicity with ingestion of 1 to 2 tablets.

In a pediatric series of TCA poisonings, all single ingestions of less than 5 mg remained asymptomatic. Minor toxicity can result from ingestion of more than 5 mg/kg (11). Deaths have been reported rarely with chronic therapeutic doses (desipramine, 3.3 mg/kg per day; imipramine, 6 mg/kg per day) (12). In these cases, other factors such as impaired metabolism due to either genetic variation, drug-induced enzyme inhibition, or preexisting cardiac conduction defects have been implicated.

Risk for major toxicity varies within the class. Initially, a number of mortality studies examined the relative risk of death

TABLE 1. Physical characteristics and dosage and elimination half-life of the cyclic antidepressants

Compounds included	Molecular formula, molecular weight (g/mol), CAS Registry No.	Formulation	Oral dose range (mg/d)	Elimination half-lives of drug and active metabolites[a,b] (h)
Amineptine hydrochloride (Survector)	$C_{22}H_{27}NO_2$,HCl; 373.9; 30272-08-3	NR	100–200	1, 2.5
Amitriptyline hydrochloride (Elavil, Laroxyl)	$C_{20}H_{23}N$,HCl; 313.9; 549-18-8	10 mg/ml solution; 10, 25, 50, 75, 100, 150 mg tablets	75–150	19, 28
Amoxapine (Asendin)	$C_{17}H_{16}ClN_3O$; 313.8; 14028-44-5	25, 50, 100, 150 mg tablets	100–300	8, (30 and 76.5)
Carpipramine hydrochloride (Prazinil)	$C_{28}H_{38}N_4O$,2HCl,H_2O; 537.6; 7075-03-8	NR	50–400	NR
Clomipramine hydrochloride (Anafranil)	$C_{19}H_{23}ClN_2$,HCl; 351.3; 17321-77-6	25, 50, 75 mg capsules; 10, 25, 50 mg tablets	75–150	20, 40
Dothiepin (Thaden)	$C_{19}H_{21}NS$,HCl; 331.9; 897-15-4	25 mg capsule; 75 mg tablet	75–150	25, 34
Doxepin (Sinequan, Quitaxon)	$C_{19}H_{21}NO$,HCl; 315.8; 4698-39-9	10, 25, 50, 75, 100, 150 capsules; 50 mg/g cream	75–150	17, 37
Imipramine hydrochloride (Tofranil)	$C_{19}H_{24}N_2$,HCl; 316.9; 113-52-0	12.5 mg/ml solution; 10, 25, 50, 75 mg tablets	75–150	18, 22
Lofepramine hydrochloride (Tymelyt)	$C_{26}H_{27}ClN_2O$,HCl; 455.4; 26786-32-3	70 mg tablet; 70 mg/5 ml suspension	140–210	2
Loxapine succinate (Loxitane)	$C_{18}H_{18}ClN_3O$,$C_4H_6O_4$; 445.9; 27833-64-3	5, 10, 25, 50 mg capsules	20–100	NR
Maprotiline hydrochloride (Ludiomil)	$C_{20}H_{23}N$,HCl; 313.9; 10347-81-6	10, 25, 50, 75 mg tablets	75–225	51, 70
Metapramine fumarate (Timaxil)	$C_{16}H_{18}N_2$,$C_4H_4O_4$; 354.4; 93841-84-0	NR	150–300	4.4
Mianserin (Norval)	$C_{18}H_{20}N_2$,HCl; 300.8; 21535-47-7	10, 20, 30 mg tablets	30–90	33
Minaprine hydrochloride (Cantor)	$C_{17}H_{22}N_4O$,2HCl; 371.3; 25953-17-7	100 mg tablet	100–300	—
Nortriptyline hydrochloride (Aventyl, Pamelor)	$C_{19}H_{21}N$,HCl; 299.8; 894-71-3	10, 25, 50, 75 capsule; 10 mg/5 ml solution	75–150	28
Trimipramine maleate (Surmontil)	$C_{20}H_{26}N_2$,$C_4H_4O_4$; 410.5; 521-78-8	25, 50, 100 capsules; 12.5, 25, 50, 100 mg tablets	75–150	23
Viloxazine (Vivalan)	$C_{13}H_{19}NO_3$,HCl; 273.8; 35604-67-2	NR	100	2–5

[a]The stated half-lives are generally in the middle of the range of reported values; there is considerable individual variation.
[b]Where clinically significant (40).

TABLE 2. Metabolism of antidepressants to active moieties

Parent	Metabolite
Demethylation to active metabolites	
Imipramine	Desipramine
Amitriptyline	Nortriptyline
Maprotiline	Desmethylmaprotiline
Doxepin	Desmethyldoxepin
Metapramine	*N*-desmethylmetapramine
Demethylated:parent-drug ratio 0.1–3.0	
Hydroxylation to active metabolites	
Imipramine	2-Hydroxyimipramine
Lofepramine	Desipramine
Desipramine	2-Hydroxydesipramine
Amitriptyline	10-Hydroxyamitriptyline
Nortriptyline	10-Hydroxynortriptyline
Amoxapine	8-Hydroxyamoxapine
	7-Hydroxyamoxapine
Loxapine	7-Hydroxyloxapine
	8-Hydroxyloxapine

From Ereshefsky L, Tran-Johnson T, Davis DM, et al. Pharmacokinetic factors affecting antidepressant drug clearance and clinical effect: evaluation of doxepin and imipramine: new data and review. *Clin Chem* 1988;34:863–880, with permission.

compared to prescription rates and suggested an increased fatal toxicity index (deaths per million prescriptions) for amitriptyline, dothiepin, doxepin, trimipramine, and maprotiline compared with mianserin and carpipramine (Tables 3 and 4) (13). Subsequent work demonstrated an increased risk of seizures for dothiepin compared with other TCA (9,10).

TOXICOKINETICS AND TOXICODYNAMICS

Absorption and Distribution

Antidepressants are highly lipid soluble and rapidly absorbed with peak levels occurring within 2 hours and extensive distribution into tissues (14). However, the anticholinergic side effects associated with symptomatic TCA poisoning may delay absorption and cause delayed peak concentrations. Delayed release formulations of amitriptyline can produce peak concentrations and delayed effects up to 42 hours after ingestion (15).

Less than 10% of a TCA circulates as free drug; the rest is bound to circulating proteins (albumin and α_1-acid glycoprotein) or dissolved in circulating free fatty acids. α_1-Acid glycoprotein has high and low affinity binding sites for TCA (16). It is more important for TCA binding than albumin; additional α_1-acid glycoprotein can reverse TCA toxicity whereas albumin has no effect (17). The *bound* fraction is sensitive to changes in pH with acidosis causing an increase in free fraction. Doses of 1000 mg per day of acetylsalicylic acid significantly increased the free fraction of imipramine (18). Alkalinization causes a significant decrease in percentage of free amitriptyline; 20% over a pH range of 7.0 to 7.4 and 42% over a pH range of 7.4 to 7.8 (19).

All the cyclic antidepressants have large volumes of distribution ranging from 5 to 20 L/kg or more. Clinical toxicity usually develops when the drugs are still in the distribution phase. As they are all weak bases (pK_a around 8.5), acidosis causes the fraction of ionized drug to increase. An increase in the ionized fraction could theoretically slow diffusion across membranes and prolong redistribution time.

TABLE 3. Relative risk of death and antidepressant overdose

Category	Medications
Relatively safe	Lofepramine, mianserin, fluvoxamine, fluoxetine, viloxazine
FTI <10	
Potentially dangerous	Clomipramine, protriptyline, trazodone
FTI >10	
Clearly dangerous	Phenelzine, imipramine
FTI >20	
Very dangerous	Maprotiline
FTI >30	
Unacceptable risk	Dothiepin, amitriptyline, tranylcypromine
FTI >40	

FTI, number of reported deaths per 1 million prescriptions for the drug.
Modified from Montgomery SA, Baldwin D, Green M. Why do amitriptyline and dothiepin appear to be so dangerous in overdose? *Acta Psychiatr Scand Suppl* 1989;354:47–53.

TABLE 4. Fatal toxicity indices (1982–1986) for antidepressant drugs in England, Scotland, and Wales

Drug	Year	Fatal toxicity index (number of deaths per million prescriptions)	
Early tricyclic drugs introduced up to and including 1970			
Desipramine	1963	148.9	p <.001
Dothiepin	1969	59.6	p <.001
Amitriptyline	1961	56.1	p <.001
Nortriptyline	1963	42.3	NS
Doxepin	1969	40.6	NS
Imipramine	1959	30.0	p <.05
Trimipramine	1966	30.0	NS
Clomipramine	1970	9.9	p <.001
Protriptyline	1966	6.5	p <.05
Iprindole	1967	0.0	NS
Monoamine oxidase inhibitors			
Tranylcypromine	1960	43.8	NS
Phenelzine	1959	20.0	p <.05
Isocarboxazid	1960	11.0	NS
Iproniazid	1958	0.0	NS
Antidepressants introduced after 1973			
Maprotiline	1974	19.8	p <.05
Trazodone	1980	12.3	p <.01
Viloxazine	1974	0.0	NS
Butriptyline	1975	0.0	NS
Mianserin	1976	7.8	p <.001
Nomifensine	1977	2.4	p <.001
Lofepramine	1983	0.0	p <.001
All antidepressants		37.6	

NS, Not significantly different (p >.05).
From Reid F, Henry JA. Lofepramine overdosage. *Pharmacopsychiatry* 1990;23[Suppl. 1]:23–27, with permission.

Elimination

Clearance of cyclic antidepressants is dependent primarily on hepatic cytochrome P-450 (CYP) oxidative enzymes. Although the activities of some P-450 isoenzymes are largely under genetic control, they may be influenced by external factors, such as the concomitant use of other medications, hepatic disease, and intercurrent illness. Patient variables such as ethnicity and age also affect TCA metabolism. Metabolism of TCA, especially their hydroxylation, results in the formation of active metabolites, which contribute to both the therapeutic and the adverse effects of these compounds (Table 2). Both the

TABLE 5. *In vitro* short-term biochemical activity of selected older and newer antidepressant drugs

	Reuptake inhibition			Receptor affinity				
Drug	NA	5-HT	D	α_1	α_2	H_1	MUSC	D_2
Older drugs[a] **[AU: Q2]**								
Amitriptyline	±	++	0	+++	±	++++	++++	0
Clomipramine	±	+++	0	++	0	+	++	++
Desipramine	+++	0	0	+	0	±	+	0
Dothiepin	±	+	0	±	0	+++	+++	0
Doxepin	++	+	0	+++	0	++++	++	0
Imipramine	+	+	0	++	0	+	++	0
Nortriptyline	++	±	0	++	0	+	++	0
Trimipramine	+	0	0	+++	±	++++	++	++
Newer drugs								
Amoxapine	++	0	0	++	0	+	0	++
Lofepramine	+++	0	0	+	0	—	+	++
Maprotiline	++	0	0	++	0	+++	+	+
Mianserin	0	0	0	+++	++	++++	0	0
Trazodone	0	+	0	+++	±	±	0	0

α_1, α_1-adrenergic receptor; α_2, α_2-adrenergic receptor; D, dopamine; D_2, D_2 dopamine receptor; H_1, H_1 histamine receptor; 5-HT, 5-hydroxytryptamine (serotonin); MUSC, muscarinic (cholinergic) receptor; NA, noradrenaline (norepinephrine); 0, no effect; ±, equivocal effect; +, small effect; ++, moderate effect; +++, large effect; ++++, maximal effect.
Modified from Rudorfer MW, Manji HE, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. *Drug Saf* 1994;10:18–42.

parent drug and the active metabolites may undergo enterohepatic circulation. Renal excretion is low (3% to 10%). The elimination half-life averages approximately 1 day (up to 3 days for protriptyline) (14).

Zero order kinetics can be reached at the top end of the therapeutic range in some patients (20). After overdose the P-450 enzymes responsible for TCA benzyl-hydroxylation become saturated and thus reduce TCA elimination to zero-order kinetics (21). The elimination half-life becomes significantly longer (21). Amitriptyline elimination half-life in overdose ranges from 25 to 81 hours (22).

PATHOPHYSIOLOGY

Cyclic antidepressants variably inhibit reuptake of norepinephrine and serotonin into presynaptic terminals (Table 5). Although unrelated to their therapeutic effects, TCA also block cholinergic, histaminergic, α_1-adrenergic, $GABA_A$ and serotonergic receptors. Mianserin has a tetracyclic structure and antagonizes α_2-adrenoceptors, but has little anticholinergic effect. It also blocks postsynaptic serotonergic receptors. Clomipramine has a greater effect on serotonin transport than other TCA (7).

The exact mechanism of action in depression has not been clearly established but involves blocking reuptake of norepinephrine and serotonin and possibly the resetting of serotonin receptors. These effects are probably unimportant in overdose except in combined overdose with selective serotonin reuptake inhibitors.

Blockade of histamine receptors leads to sedation, α-receptor blockade leads to vasodilation, $GABA_A$ blockade may contribute to seizures, and anticholinergic effects result from muscarinic receptor blockade. Cardiac toxicity is predominantly due to rate-dependent blockade of sodium ion channels (23). The influx of sodium is the major event responsible for the zero phase of depolarization in cardiac muscle and Purkinje fibers. This initiates cardiac muscle contraction (systole). The duration of phase 0 in the heart as a whole is measured indirectly by the duration of the QRS complex on the ECG. Prolongation of the QRS is a correlate of TCA concentration (24) and is predictive of both seizures and cardiac dysrhythmias. Clinically, a widening QRS should be interpreted as increasing concentration of drug within the ion channel. In common with local anesthetic agents, the sodium channel preferentially binds ionized TCA (25); these effects can be reversed by alkalinization (26). As TCAs are weak bases, the ionized fraction increases with acidosis and the degree of block increases. As the sodium channel block is rate dependent, the QRS width increases with increasing heart rates (27). Eventually, the heart rate slows with increasing sodium channel blockade.

Other cardiac channel effects include reversible inhibition of the outward potassium channels responsible for repolarization giving a mechanism for QT prolongation and dysrhythmia generation (28). TCA demonstrate a dose-dependent direct depressant effect on myocardial contractility that is independent of impaired conduction (29). Although the mechanism is not well defined, it is known that TCA alter mitochondrial function and uncouple oxidative phosphorylation (30).

Animal models have shown direct vasoconstrictive effects on pulmonary vasculature with rupture of capillaries and alveolar epithelium causing pulmonary edema (31). These changes are linearly related to concentration over the range of 0.01 to 1.0 mM and have been demonstrated with wide range of cyclic antidepressants (32).

PREGNANCY AND LACTATION

The U.S. Food and Drug Administration and Australian pregnancy categories for all these agents are C (Appendix I), with the exception of imipramine and nortriptyline (U.S. Food and Drug Administration category D). No adverse events were found, and amitriptyline and nortriptyline blood levels were undetectable in nursing mothers treated with amitriptyline, nortriptyline, desipramine, and imipramine (33). A metaanalysis of maternal exposure (34) found no greater risk of major malformations after antidepressant exposure. A case control study found no association between TCA exposure and either congenital malformations or developmental delay (35).

CLINICAL PRESENTATION

Acute Overdosage

After overdose there are three major components to the clinical presentation. These are anticholinergic symptoms, cardiovascular toxicity, and central nervous system toxicity. Symptoms and signs at presentation depend on the dose and the time since ingestion. The rapid absorption of TCA can cause a patient with initially trivial symptoms to deteriorate and develop life-threatening toxicity within an hour (5). Patients who are asymptomatic at 3 hours post-ingestion of normal release medication do not normally develop major toxicity (36). With good supportive care the mortality of patients presenting to hospital is less than 0.5%.

Serious complications of TCA ingestion—ventricular dysrhythmias, seizures, and severe hypotension—usually develop within 6 hours. Patients at high risk are identified by a history of high-ingested dose, early onset of deteriorating level of consciousness, and the presence of ECG conduction abnormalities. The QRS duration correlates with the unbound amitriptyline and nortriptyline concentrations in the distribution (α) phase. The level of consciousness correlated with plasma and unbound amitriptyline concentrations in both α and β (elimination) phases and with red blood cell amitriptyline concentration in the alpha phase. Generally, patients wake up within 24 hours, even after a severe TCA overdose (24). As TCA concentrations are still high, this suggests some tolerance to the sedative effects.

Two separate series of consecutive admissions to one unit included 157 dothiepin and 417 other TCA ingestions. Seizures occurred in 11.5% of the dothiepin group and 2.8% of the other TCA group (9,10). Although QRS prolongation more than 100 msec occurred in 47% of the groups, only 2.3% had life-threatening dysrhythmias (10). In the same unit, 80% of patients who presented with seizures and QRS prolongation had ingested a TCA (37).

Anticholinergic Effects

Anticholinergic effects can occur early or late in the course of TCA toxicity. Patients who present early or who have not developed unconsciousness may experience a central cholinergic syndrome and other anticholinergic effects. The pupils may be dilated but are often found to be mid range and poorly reactive to light. Paralysis of accommodation may lead to blurred vision. The other anticholinergic effects lead to a dry mouth, dry skin, tachycardia, and occasionally urinary retention. Bowel sounds may be absent. These early anticholinergic symptoms or signs are a sensitive indicator for ingestion of TCAs but are a poor predictor for life-threatening toxicity.

Severely poisoned patients commonly have an anticholinergic delirium at the time of extubation, which may persist for some days. This can occur in the relative absence of peripheral anticholinergic symptoms.

Cardiovascular Effects

Hypotension is usually due to α-receptor blockade–mediated peripheral vasodilatation and relative volume depletion. Most patients respond to volume expansion with intravenous fluids. TCAs can also cause direct myocardial depression, which is generally associated with conduction defects. Broad complex bradycardia associated with hypotension is a marker of severe toxicity. Untreated, it is likely that the patient will die in the next 10 minutes.

Sinus tachycardia is present in most patients with clinically significant TCA poisoning. Persistent tachycardia after regaining consciousness is most frequently due to persisting anticholinergic effect or volume depletion. Other possible etiologies that should be considered include anxiety, delirium, and drug withdrawal.

Broad complex tachycardia may develop in serious cases. It may be difficult to distinguish between a supraventricular tachycardia with QRS widening and a ventricular tachycardia. Both are poor prognostic signs as the extent of the QRS duration correlates with TCA blood levels (38). Acutely poisoned patients with QRS widening are normally unconscious. If the patient is conscious and has QRS widening at presentation, consider chronic toxicity or other cardiac disease.

Central Nervous System Effects

In most patients, a significantly impaired level of consciousness precedes cardiac complications or seizures. Patients often have a rapid onset of decreasing level of consciousness and coma because of rapid absorption. Patients should be assessed on admission to see if their deep tendon reflexes are overly reactive of if they have myoclonic jerks, which may predict subsequent seizures. A number of TCA (dothiepin, desipramine, and amoxapine) cause seizures after a smaller ingestion, with fewer ECG abnormalities and occasionally in conscious patients (9). Although seizures are often self-limited, they are associated with an increased mortality. Acidosis associated with seizure increases the risk of cardiotoxicity.

Other Clinical Effects

Pulmonary complications include aspiration, as well as cardiac and noncardiogenic pulmonary edema. Rhabdomyolysis may occur after seizures or pressure necrosis. Hyperthermia occurs rarely; the etiology is multifactorial; and includes central temperature dysregulation, seizures, sepsis, and reduced heat loss (23).

Chronic Overdosage

Patients with chronic toxicity may develop the tolerance to the sedative effects and not be sedated. They can present with seizure or dysrhythmia and may have ECG changes consistent with TCA. Unlike acute poisonings, chronic poisonings show high concentrations of active metabolite (39). Chronic poisoning can occur with the continued ingestion of a high dose or the ingestion of an otherwise normal therapeutic dose in a cytochrome CYP2D6 *slow metabolizer* or in the presence of drugs that compete for the relevant cytochrome.

Adverse Events

Common adverse effects during therapeutic use include sedation, dry mouth, blurred vision, constipation, weight gain, orthostatic hypotension, urinary hesitancy or retention, reduced gastrointestinal motility, anticholinergic delirium (particularly in the elderly and in Parkinson's disease), impotence, loss of libido, other sexual adverse effects, tremor, dizziness, sweating, agitation, and insomnia (7) (Table 6).

Infrequent adverse effects include slowed cardiac conduction, T-wave inversion or flattening (particularly at high doses), dysrhythmias, sinus tachycardia, nausea, hyperglycemia, gynecomastia in men, breast enlargement and galactorrhea in women, allergic skin reactions, and manic episodes (7).

Rare adverse effects include blood dyscrasias, hepatitis, paralytic ileus, syndrome of inappropriate secretion of antidiuretic hormone with hyponatremia, seizures, and neuroleptic malignant syndrome (7). The most significant, although rare, adverse effect of tetracyclics is the development of neutropenia, which is usually reversible. Mianserin is a sedating antidepressant and may also produce a polyarthritis (40).

TABLE 6. Comparative adverse effects of the antidepressants

Comparative adverse effects of tricyclic antidepressants and mianserin drug	Sedation	Anticholinergic effect	Orthostatic hypotension
Amitriptyline	+++	+++	+++
Clomipramine	++	++	++
Dothiepin	++	++	++
Doxepin	+++	+++	+++
Imipramine	++	++	++
Nortriptyline	++	+	+
Trimipramine	+++	+++	+++
Mianserin	+++	+	++

[AU: Q3]
Modified from Rossi S. Tricyclic antidepressants and mianserin. In: Rossi S, ed. *Australian medicines handbook*. Adelaide: Australian Medicines Handbook Pty Ltd, 2002.

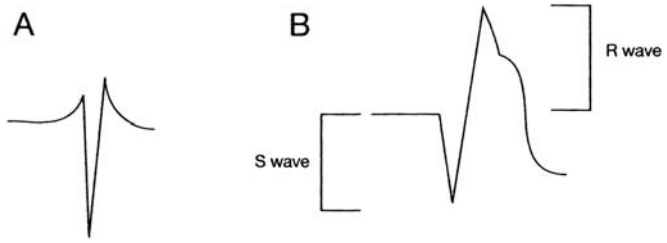

Figure 2. Electrocardiogram lead aVR in patients with tricyclic antidepressant toxicity. **A:** Normal QRS interval in lead aVR. **B:** An abnormal QRS interval as it appears in a patient with severe tricyclic antidepressant poisoning. R_{aVR} was measured as the maximal height in millimeters of the terminal upward deflection in the QRS complex, with the PQ segment used as the baseline. The S wave was measured in millimeters as the depth of the initial downward deflection. (From Liebelt EL, Francis PD, Woolf AD. ECG lead aVR versus QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med* 1995;26:195–201, with permission.)

DIAGNOSTIC TESTS

Acute Overdosage

In conjunction with a physical examination that includes careful assessment of the level of coma, the most useful investigations are the ECG, arterial blood gas, and serum electrolytes.

Electrocardiogram

An ECG should be performed on admission and at 6 hours after the self-poisoning in asymptomatic patients. The ECG is the most accurate predictor of toxicity for the majority of TCA poisonings. Minor ECG changes are common and include an increase in the PR interval, dimpling of the T-wave, and narrow complex sinus tachycardia. The more serious changes reflect altered conduction through Purkinje fibers due predominately to sodium channel blockade (Table 7).

The majority of the studies on predicting outcome from ECG abnormalities have been too small to allow a confident estimate of sensitivity and specificity and have been weakened by the use of arbitrary cut points defined during post hoc analysis. Invariably, the prediction has not been as definitive when others have tried to replicate the findings. In addition, the observer variation (inter-rater agreement) has not been defined, particularly as it applies to these arbitrary cut points (41).

Clinical experience indicates that the majority of patients at significant risk for developing cardiac or neurologic toxicity have a QRS complex more than 0.10 seconds or a rightward shift of the terminal 40 ms of the frontal plane QRS complex vector (42). Boehnert and Lovejoy (43) described the association of a QRS duration of 100 ms or more with the development of seizures and dysrhythmias. Although subsequent experience has confirmed this as a sensitive marker, it is also clear that a QRS less than 100 ms cannot be used to definitely exclude major complications (44). A normal ECG does not exclude major complications (9). All patients with an abnormal ECG or altered level of consciousness require ECG monitoring.

A right axis deviation or a pattern of right bundle branch block producing a terminal 40 ms frontal plane axis more than 120 degrees is often observed in TCA poisoning. The association is not absolute but appears stronger than that observed with QRS width (44). The height of the R wave and the R/S ratio in ECG lead aVR also have predictive value. The sensitivity of a R_{aVR} of 3 mm or more was 81% and that of a R/S_{aVR} of 0.7 or more was 75% for predicting seizures or dysrhythmias (Fig. 2) (36). A group of patients who would satisfy these criteria but have additional ST segment abnormalities have been described as a TCA-induced Brugada syndrome (45). The Brugada syndrome is a genetically determined sodium-channel dysfunction. The ECG characteristically shows a right bundle-branch block and unusual ST-segment elevation in the right precordial leads. It was reported in 12 of 95 patients presenting with overdose of TCAs. The ECG changes resolved when plasma TCA concentrations dropped below 1000 ng/ml. It is not clear whether the presence the Brugada pattern has additional prognostic importance (45).

TABLE 7. Electrocardiographic changes predictive of complications in tricyclic antidepressant poisoning

Predictive measurements that have been suggested include the following:
- QRS of 100 ms or more
- Terminal 40 ms frontal plane axis greater than 120 degrees
- Height of R wave and R/S ratio greater than 0.7 in aVR

Brugada syndrome

Other Tests

Arterial blood gases assist in monitoring treatment with systemic alkalinization. In severe poisonings, a mixed respiratory and metabolic acidosis is common. Respiratory acidosis is an absolute indication for ventilation. Hypoxia may be due to a number of the pulmonary complications seen in TCA poisoning including aspiration, cardiac, and noncardiac pulmonary edema.

Urine screens confirm exposure but do not add any prognostic information to the clinical examination and ECG. Blood TCA concentrations do not contribute to the acute management of most TCA poisoning. They are useful in helping to define the relative contribution of drug toxicity to neurologic dysfunction in patients who have sustained hypoxic brain injury. Therapeutic blood concentration ranges for antidepressant drugs available in the United States are listed in Table 8 (46). Patients with plasma TCA levels greater than 450 ng/ml tend to develop cognitive or behavioral toxicity (agitation, disorientation, confusion, memory impairments, fragmented speech, pacing, decreased concentration). Major toxicity and death is associated with levels above 1000 ng/ml. The ratio of parent drug to metabolite is greater than 2 in acute poisonings (47).

TABLE 8. Suggested or expected therapeutic ranges for the antidepressant drugs available in the United States

Drug	Therapeutic range (μg/L)
Tricyclic drugs	
Imipramine desipramine	150–250
Nortriptyline	50–150
Amitriptyline nortriptyline	80–250
Desipramine	125–300
Protriptyline	70–260
Doxepin desmethyldoxepin	150–250
Trimipramine	Similar to other tricyclic drugs
Other antidepressant drugs	
Maprotiline	200–600
Amoxapine 8-hydroxyamoxapine	200–600
Trazodone	800–1600
Alprazolam	20–55
Fluoxetine	Not available

Modified from Orsulak PJ. Therapeutic monitoring of antidepressant drugs: guidelines updated. *Ther Drug Monit* 1989;11:497–507.

Postmortem Considerations

In overdose cases in which the total blood TCA concentration (parent drug and major active metabolite) exceeds 1000 ng/ml, toxicity and resulting fatality are probable (48). Postmortem blood concentrations can be substantially higher than concentrations at the time of death (49). The ratio of parent drug to major metabolite may aid in the decision process for cases in which the manner of death was ambiguous. Death soon after acute poisoning has a high parent to metabolite ratio. Postmortem blood concentrations may not reflect the drug concentration at the time of death (50). In chronic toxicity, tissue concentrations may be a better guide than plasma concentrations (51,52).

TREATMENT

Acute Overdosage

The key acute issues are airway management and correction of acidosis. A significant ingestion in a suicidal patient is generally associated with a decreasing level of consciousness that necessitates intubation to facilitate decontamination and subsequent management. Patients who are conscious at 3 hours after ingestion are unlikely to develop major toxicity. Mortality is low when patients receive good supportive care and alkalinization. An overview of management is presented in Table 9.

Decontamination

If the patient is alert, cooperative, and has potentially ingested more than 5 mg/kg, activated charcoal may be administered orally. In practice, this is only relevant for patients who present within 1 to 2 hours of ingestion. Most patients with an ingestion more than 10 mg/kg are either unconscious or have a deteriorating level of consciousness with 2 hours and should be intubated. These patients should have either a nasogastric or orogastric tube to administer charcoal. The published evidence is insufficient to support or refute orogastric lavage in this group. A trend favoring benefit of administering activated charcoal, then gastric lavage, then repeated charcoal has been reported in an underpowered study (53). If a gastric tube is inserted, it is reasonable to aspirate stomach contents before giving charcoal. There is no evidence supporting the use of cathartics or whole bowel irrigation.

TABLE 9. Management of tricyclic antidepressant overdose

- Check vital signs, level of coma, 12-lead ECG, arterial blood gases
- Administer oxygen, establish IV access, and start fluids
- Intubate and ventilate
  - Ingestion of >10 mg/g with impaired consciousness if <2 h since ingestion
  - Any respiratory acidosis or failure
  - Inability to protect airway
- Decontaminate: activated charcoal in water 1 g/kg
  - All patients less than 2 hours from ingestion
  - All patients who have intubation indicated in 3
- Treat complications
  - Acidosis
    - Uncomplicated
      - Sodium bicarbonate 1 mEq/kg bolus (or in adult 50 mEq bolus) and review
    - Complicated by hypotension or QRS >120 msec
      - Sodium bicarbonate 2 mEq/kg bolus
  - Seizures
    - Diazepam 0.1 mg/kg IV as needed; Phenobarbital infusion (15 mg/kg IV) over 30 minutes if refractory
    - Check the ECG and acid-base status
  - Hypotension
    - If QRS <100 msec
      - 20 ml/kg normal saline stat
      - Trendelenburg position
    - If QRS >120 msec
      - Sodium bicarbonate 2 mEq/kg bolus repeated until QRS narrows or arterial pH reaches 7.55
      - Give fluid bolus if not already done
    - Volume loading may require 3 to 5 liters in an adult, which is best done with central venous pressure monitoring
    - Consider vasopressors
  - Broad complex tachydysrhythmias
    - With detectable output
      - Sodium bicarbonate 2 mEq/kg bolus repeated until QRS narrows or pH reaches 7.55
    - With no output
      - Sodium bicarbonate 3–6 mEq/kg bolus repeat until improvement or pH reaches 7.55
      - Standard, but prolonged ACLS resuscitation; do not stop until you have a toxicology consultation
    - Other measures
      - Consider magnesium
      - Overdrive pacing
      - Consider hypertonic saline[a]
  - Broad complex bradydysrhythmia
    - With detectable output
      - Sodium bicarbonate 2 mEq/kg bolus repeated until QRS narrows or pH reaches 7.55
    - With no output
      - Sodium bicarbonate 3–6 mEq/kg bolus repeat until improved or pH reached 7.55
      - Standard, but prolonged ACLS resuscitation; do not stop until you have a toxicology consultation
    - Other measures
      - Consider pacing or isoproterenol
      - Consider hypertonic saline[a]

IV, intravenous.
[a]Hypertonic saline: ensure you have achieved a pH of at least 7.55, and give 3 mEq of hypertonic saline as a bolus injection. The role of this treatment is not well defined. Note the clinical effects and report your findings
From Buckley NA, Dawson AH, Whyte IM. Tricyclic antidepressants. In: *HyperTox: assessment and treatment of poisoning*, v1229 ed. Newcastle, Australia: MediTox Pty Ltd, 2002, with permission.

Enhancement of Elimination

Repeated doses of activated charcoal increase the clearance of several TCA, but there is no evidence of improved outcome. It should not be used routinely, but may be reasonable for modified-release preparations. In practice, most patients with TCA

poisoning who are ventilated have an ileus, which precludes the use of multiple dose activated charcoal.

Hemoperfusion or hemodialysis has been proposed as a treatment option for severe TCA poisoning (54). At steady state, the protein binding and volume of distribution is so high that dialysis would not be considered effective (55). Protagonists of the technique argue for benefit in the early distribution phase; however, there is no supporting clinical or animal work for this view. Calculations of the amount of TCA actually removed the amount to less than 3% of the ingested dose (56,57).

Antidotes

Magnesium sulfate may terminate persistent ventricular tachycardia; in one case a bolus followed by 7 days of continuous infusion was required (58). The use of other antidysrhythmic agents is less clear; Class 1A and Class 1C drugs and procainamide are contraindicated (59). Although lidocaine has been used with varying success, there is no proven efficacy for class 3 or 4 agents. Overdrive pacing should be considered for refractory ventricular tachycardia (60).

Sodium bicarbonate is the drug of choice for the treatment of all TCA-associated conduction defects, ventricular dysrhythmias, and hypotension due to TCA poisoning (59). Details regarding the use of hypertonic sodium bicarbonate are provided in Chapter 75. Sodium bicarbonate provides hypertonicity, sodium loading, and alkalinization. Sodium loading and alkalinization have been effective in reversing TCA-induced conduction defects and hypotension (61); both are supplied by hypertonic sodium bicarbonate. It should be administered by intermittent bolus injections of 1 to 3 mEq/kg body weight, not by continuous infusion. The initial treatment in critically ill patients is often titrated against clinical response with bolus injections repeated at 3 to 5 minute intervals. When the clinical situation allows it, arterial blood pH should be checked. The goal of sodium bicarbonate therapy is to narrow the QRS complex without exceeding an arterial pH of 7.50 to 7.55. Sustained elevations of pH greater than this are associated with impaired oxygen dissociation from hemoglobin. As the patient is normally ventilated, the pH can be maintained with mild hyperventilation ($PaCO_2$ of 30 mm Hg).

The mechanism of the therapeutic effect is multifactorial (62). Alkalosis decreases the free drug concentration by increasing protein binding. However pH change is effective in the absence of protein (63,64) and probably directly affects the binding affinity of TCA in the sodium channel.

Although it is common practice for patients with conduction defects to receive sodium bicarbonate in the absence of dysrhythmias or hypotension, there is little evidence to support or refute this practice (62). The pH in these patients should be carefully monitored. It is rational to give bicarbonate to any patient with a wide QRS who has had a seizure or needs to be intubated as both these situations may increase acidosis. Once patients have received sodium bicarbonate their maintenance fluid should be reassessed to avoid sodium overload.

Hypertonic saline had greater efficacy than alkalinization in improving cardiac conduction and hypotension in a swine model (61). The dose used in this study was 10 ml/kg of hypertonic saline solution in the form of a 7.5% sodium chloride solution (15 mEq/kg NaCl). The mean peak serum sodium after treatment was 157 mEq/L. This dose was selected, as it had been the maximal dose used previously in the treatment of trauma in humans.

As standard supportive care and sodium bicarbonate have been so effective, the clinical use of hypertonic saline is rarely reported. A 34-year-old man with dothiepin-induced ventricular tachycardia and hypotension responded to 170 mmol of hypertonic saline given over 5 minutes; subsequent episodes responded to bolus doses of 100 mmol (65). The administration of 200 ml of 7.5% saline over 3 minutes improved refractory hypotension and conduction defects in a 29-year-old woman (66). A 6-year-old with imipramine poisoning had no response to a slow infusion of 60 mEq of hypertonic saline (67). The role of hypertonic saline remains undefined, but it could be considered in situations of refractory hypotension and dysrhythmia. It appears that it should be administered as a bolus injection rather than an infusion. The potential risks of this treatment include fluid and sodium overload and complications of hypernatremia such as central pontine myelinolysis.

Supportive Care

Intravenous access should be established in all patients; the initial fluid should be normal saline. All patients should have assessment of the adequacy of their airway protection and ventilation. Mechanical ventilation should be provided to any patient who cannot protect his or her airway, has a respiratory acidosis, or presents within 2 hours with altered level of consciousness and ingestion of greater than 10 mg/kg. Ventilation should not be the primary method of achieving systemic alkalinization (Chapter 75). **[AU: Q1]** Mild hyperventilation can maintain a patient in alkalosis but the $PaCO_2$ should not fall below 25 mm Hg. Patients should have continuous ECG monitoring for at least 6 hours after ingestion.

Delirium can often be managed with reassurance but occasionally requires benzodiazepines to control agitation. Neuroleptics should be avoided as most of them have either anticholinergic activity or ion channel blocking effects. Although physostigmine is effective, the short half-life of this drug and its occasional life-threatening adverse effects (particularly in TCA overdose) make it contraindicated.

Seizures are often self-limited. If prolonged or repeated, seizures are treated with diazepam 5 to 20 mg IV. If benzodiazepines do not control the seizures, patients may require phenobarbital 15 to 18 mg/kg IV and elective intubation and ventilation. If neuromuscular blockade is required for management, electroencephalogram monitoring is mandatory. The major complication of seizures is increased acidosis precipitating major cardiovascular toxicity. All patients who have seized should be assessed for the presence of indications to receive sodium bicarbonate.

Hypotension in the conscious patient is usually due to peripheral vasodilation (68) and responds to volume expansion. The initial fluid challenge should be 10 to 20 ml/kg of normal saline. As TCA concentrations increase, other factors may contribute to hypotension. This includes further volume loss into third spaces such as intestinal ileus and direct myocardial depression. Myocardial depression is commonly associated with conduction defects and should be initially treated with sodium bicarbonate (59). Most hypotension responds to these measures. Temporary pacing should also be considered for ventricular bradydysrhythmias and bifascicular block.

Refractory hypotension requires central venous pressure monitoring and correction of volume and acid-base status. If hypotension persists, drugs with α agonist properties (e.g., epinephrine and norepinephrine) should be used cautiously (59) as they may precipitate ventricular tachycardia. Epinephrine was superior to norepinephrine when used both with and without sodium bicarbonate in an animal model (69). Glucagon was reported to be effective in one case report (70); however, it appeared that adequate correction of acidosis had not been achieved (71).

Monitoring

Monitoring consists primarily of serial evaluation of the 12 lead ECG. Patients are medically fit for discharge if they have no symptoms or signs of toxicity (including no anticholinergic features such as tachycardia) and a normal ECG performed 6 hours after the overdose (especially if they have passed a charcoal stool). A patient with persistent isolated tachycardia should generally be kept in hospital and observed. As the usual cause is volume depletion, IV fluid to ensure adequate volume replacement should be given.

A patient with a QRS complex equal to or greater than 100 ms should be monitored until this has returned to normal. Typically QRS duration returns to normal within 1 day but may persist for longer periods in severe poisoning (72). Reports of occasional late cardiac arrest have occurred in patients with persistently abnormal ECG. Continued drug absorption or exposure may be the cause for late deterioration in this group, and markedly delayed toxicity (greater than 24 hours) has only been reported in patients who did not receive gastrointestinal decontamination or, more recently, in modified release amitriptyline overdose.

Management Pitfalls

Flumazenil should not be administered in any patient suspected of taking a TCA even if benzodiazepines are coingested. Its use may precipitate seizures and death (73,74).

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