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The Practical Journal for Emergency Physicians

Emergency Medicine Reports

Volume 24, Number 12 June 2, 2003

Emergency medicine physicians routinely manage patients with neurologic toxicity due to drugs and chemicals. The causes of these toxicities are diverse. In the year 2001, there were more than 2 million human exposures reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System. Of these, 498,524 patients were treated in a health care facility.[1] The outcome for these patients depends on the timely identification and management of treatable causes of central nervous system (CNS) toxicity. The importance of knowing how to manage these exposures in emergency departments (EDs) cannot be overemphasized.

The manifestations of CNS toxicity have a very broad differential diagnosis, including metabolic derangements, structural lesions, psychiatric conditions, or even combinations of these. Excluding trauma and infectious etiologies is an integral part of the initial evaluation. The management of patients with evidence of CNS toxicity, thus, can be very complex and challenging. The focus of this article will be on the manifestations of drugs in the CNS, along with management recommendations.

—The Editor

Central Nervous System Manifestations of Drug Toxicity

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General Concepts

The nervous system is divided into the central and peripheral (PNS) nervous systems. The blood-brain barrier and the blood-nerve barrier have different permeability characteristics and thus are not affected equally by toxins. This accessibility variation will, in turn, determine the clinical manifestations seen in each patient.[2] Some toxins may affect the PNS and some may affect just the CNS. Botulinum toxin, for example, acts at the neuromuscular junction, resulting in paralysis. In contrast, cocaine acts directly in the CNS. Some agents, like the organophosphates, which block acetylcholinesterase at all neuronal synapses, can affect both the PNS and CNS.

The CNS capacity for repair and regeneration is very limited. If the damage produced by the toxin is structural, then there will be a limited ability to return to the original level of functioning. Also, not all areas of the CNS have the same susceptibility to the effects of toxins.[2] The brain is extremely sensitive to the effects of hypoxia and hypoglycemia due to its increased energy demands and limited ability to utilize alternative energy sources.

The CNS effects of drugs and chemicals can be divided into drugs that cause altered mental status, seizures, encephalopathy and movement disorders. Some indirect effects of drugs and toxins also will be discussed; these include cerebrovascular accidents and CNS infections.

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by Thomson American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Vice President/Group Publisher: Brenda Mooney
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GST Registration No.: R128870672

Periodicals postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to ***Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $29. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $323 each; 10 to 20 additional copies, $287 each.

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In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Drs. Rivera, Gracia, Velez (authors), Schneider, and Winograd (peer reviewers) report no relationships with companies related to the field of study covered by this CME program. Dr. Bosker (editor) is on the speaker's bureau for Pfizer, Rhone-Poulenc Rorer, and Parke-Davis. Dr. Bosker also acknowledges that he receives royalties, commissions, and other compensation relating to the sale of textbooks, reprints of articles, and other written materials to the following pharmaceutical companies: Pfizer, Genentech, Aventis, Pharmacia, and Bayer.

Manifestations of CNS Toxicity

The clinical features of all these presentations may vary among patients and depend on the degree of intoxication and any other underlying disease processes. Toxicity from multiple agents, as with co-ingestants, can influence and complicate the clinical presentation. Some toxin combinations, for example ethanol and benzodiazepines, may have additive or synergistic effects. Other combinations, such as cocaine and opiates, will have opposing effects. The final clinical manifestation may be a complicated combination of multiple factors.

Altered Mental Status. Alterations in mental status range from agitation to coma and also can include variations in thought process, such as delirium and dementia. Many drugs can produce effects on both ends of the level of consciousness spectrum. For example, patients with anticholinergic delirium or cocaine toxicity may present with agitation or sedation. Alterations of mental status result from the imbalance between excitatory and inhibitory neurotransmitters in the brain. The main inhibitory neurotransmitter of the CNS is gamma aminobutyric acid (GABA) and the main excitatory neurotransmitter is glutamate. The catecholamines and other neurotransmitters such as serotonin also frequently are involved. Toxins can affect the neurotransmitters via changes in production, release, degradation, reuptake, and receptor activity. Agitation occurs when there is excessive neuronal excitation, as with the sympathomimetics. It also can be the result of decreased neuronal inhibition, as seen with benzodiazepine withdrawal.

Agitation. Patients can present with different levels of increased mental status, ranging from nervousness to violence. These patients may develop life-threatening complications as a result of this excessive motor activity. Rhabdomyolysis resulting from breakdown of muscle tissue is a common complication of prolonged agitation and can lead to renal failure as myoglobin precipitates and occludes kidney tubules.[3-5] Agitated patients should be treated emergently, as they may pose a risk to other patients and staff.[6,7]

Delirium and dementia must be differentiated because they are associated with distinct differential diagnoses. Delirium is an acute organic brain syndrome with a fluctuating global cognitive impairment, attention abnormalities, altered level of consciousness, altered psychomotor activity, and/or a disordered sleep-wake cycle.[8] Delirium usually is reversible and treatable. In contrast, dementia is a chronic, gradual deterioration of cognitive functions that is not associated with altered level of consciousness and does not have a fluctuating course. It often is not reversible or treatable.[9]

Many toxins result in delirium, and they often are grouped based upon the specific toxidrome they cause. (*See Table 1.*) These toxidromes include the sympathomimetic (adrenergic stimulants such as cocaine and the amphetamines), and the anticholinergic (such as atropine). Tables 1 and 2 list the toxidromes and some common causative agents. Some agents, such as ethanol and benzodiazepines, that predominately cause CNS depression, also can cause agitation as part of their withdrawal syndromes. Drug interactions that result in the serotonin syn-

Table 1. Toxidrome Classifcations and Examples

CLASS	EXAMPLES
Anticholinergic (atropine)	
Antihistamines	Diphenhydramine, chlorpheniramine
Belladonna alkaloids	Hyoscamine, scopolamine
Tricyclic antidepressants	Amitriptyline
Antipsychotics	Haloperidol, thioridazine
Antiemetics	Chlorpromazine
Cholinergic	
Organoposphate and carbamate insecticides	Malathion, carbaryl
Nerve agents	Tabun, sarin, soman, VX
Sympathomimetics	
Adrenergics	Cocaine, amphetamines, phencyclidine (PCP)
Xanthines	Caffeine, theophylline
Decongestants	Phenylpropanolamine, ephedrine/pseudoephedrine
Antidepressants (neuroamine reuptake inhibition)	Trazodone, venlafaxine, selegiline
Sedative Hypnotics	
Alcohols	Ethanol, ethylene glycol, methanol, isopropanol
Barbiturates	Secobarbital, phenobarbital, pentobarbital
Benzodiazepines	Diazepam, lorazepam, alprazolam
Miscellaneous	Ethchlorvynol, meprobamate, baclofen Gamma-hydroxybutyrate (GHB), butyrolactone (GBL)
Opioids	
Opiate (natural derivatives)	Heroin, morphine, codeine
Synthetic	Meperidine, fentanyl, methadone
Opioid-like effects	Clonidine, olanzapine

drome and the neuroleptic malignant syndrome also can result in agitation.[10-12] The psychedelics and hallucinogens, with lysergic acid diethylamide (LSD) and phencyclidine (PCP) being the classic examples, affect perception, often resulting in agitation and/or delirium. The patient's perception of reality is distorted, with vivid illusions and heightened sensorium.[13,14]

Decreased Mental Status. Presenting symptoms of decreased mental status can range from drowsiness to coma. Physicians describe the levels of alertness in many different ways, sometimes leading to confusion among consultants. The following descriptions aid in the correct description of the mental status. Obtundation refers to mild to moderate reduction in alertness. Stuporous patients can be aroused only by vigorous stimulation. Comatose patients remain unarousable to any stimuli.[15]

The differential for decreased mental status is extensive and includes a multitude of drugs. These agents include sedative-hypnotics, opioids, barbiturates, anticonvulsants, and anticholinergics. Most drugs produce CNS depression by three pharmacological mechanisms: stimulation of GABA receptors; stimulation of opioid receptors; and stimulation of central muscarinic receptors. Catecholamine depletion also is a postulated mechanism for CNS depression, specifically in cocaine abusers.[16-18] This phenomenon is referred to as the "cocaine washout syndrome." It is described as CNS depression occurring after a cocaine binge. In addition, two proposed structural mechanisms mediate decreased levels of consciousness: bilateral injury to the cerebral cortex and damage to the reticular activating system within the brain stem.[15,19]

Seizures. Drugs may result in seizures as part of their direct toxicity or due to a withdrawal syndrome. A common mnemonic for the differential of toxin-induced seizures is "OTIS CAMP-BEL." (*See Table 3.*) Some of the most frequently seen causes of toxin-induced seizures include cocaine toxicity and alcohol withdrawal.[20,21] Another example of withdrawal seizures is evidenced by the multiple case reports of seizures after the use of the benzodiazepine antagonist flumazenil.[22-25]

Toxin-induced seizures are caused by imbalances between glutamate and GABA and are mostly generalized tonic-clonic in nature.[2,267] Drugs such as tricyclic antidepressants act in the sodium channel with the net effect of lowering the seizure threshold and increasing seizure potential.[26] Other drugs, like cyanide, cause seizures by affecting the oxygen utilization by the brain. This results in cellular hypoxia, membrane leakage, and neuronal firing.[27-29] There is evidence that adenosine is an important mediator in the termination of seizures. Adenosine seems to block the release of excitatory neurotransmitters. It also inhibits the excitatory neurotransmitter's action at the post-synaptic membrane. These are two negative feedback mechanisms that terminate seizures.[30,31] Any agent that blocks these adenosine receptors, like theophylline and caffeine, will precipitate intractable seizures.[32,33]

Encephalopathy. Encephalopathy is referred to as a syndrome of personality changes, decreased mental status, and diminished intellectual capacity. The direct mechanisms that produce encephalopathy are poorly understood. Drug-associated encephalopathy generally results from damage outside the CNS. For example, acetaminophen elicits liver damage, resulting in encephalopathy by the production of the toxic metabolite N-acetyl-para-quinone-imine (NAPQI) via Cytocrome P 450 (CYP2E1).[34] In a recent multicenter trial of 17 tertiary care centers, acetaminophen was found to be the most common cause of acute liver failure.[35] Carbon tetrachloride causes hepatocellular necrosis via the same CYP2E1 enzyme as acetaminophen.[36] Amatoxins from the Amanita species of hepatotoxic mushrooms inhibit protein synthesis by binding to RNA polymerase II.[37,38] The anticonvulsant valproic acid is thought to inhibit free fatty acid synthesis, resulting in microvascular steatosis, which causes accumulation of ammonia and encephalopathy.[39] Thiamine deficiency can result in Wernicke's encephalopathy due to thiamine's critical role in the pyruvate dehydrogenase complex in the Kreb's cycle.[40-43] The inhalation of heroin vapor known as "chasing the dragon" has been associated with leukoencephalopathy and elevated brain lactate levels.[44] Finally, anoxic encephalopathy can

Table 2. Toxidromes

TOXIDROME	MENTAL STATUS	PULSE	RR	BLOOD PRESSURE	PUPIL SIZE	SKIN	TEMPERATURE	SPECIFIC MANAGEMENT
Opiate	Depressed	Low	Low	Low	Pinpoint	Normal	Decreased	Naloxone
Sedative hypnotics	Depressed	Low	Low	Low	Normal	Normal	Normal	Flumazenil (controversial)
Sympathomimetics	Agitated	High	Normal	High	Increased	Diaphoretic	Increased	Benzodiazepines
Cholinergic	Agitated	High/Low	Normal	High/Low	Increased	Diaphoretic	Normal	Atropine, Pralidoxime
Anticholinergic	Agitated/ Delirium	High	High/Low	High/Low	Increased	Dry	Increased	Physostigmine Benzodiazepines
WITHDRAWAL SYNDROMES								
Sedative hypnotics	Agitated	High	High	High	Increased	Normal/Wet	Increased	Benzodiazepines
Opioids	Normal	High	Normal	High	Increased	Wet	Normal	

result indirectly from any drug toxicity that impairs oxygen delivery to the brain.

Movement Disorders. Movement disorders, such as drug-induced Parkinsonism, dystonia, akathisia, dyskinesias and the neuroleptic malignant syndrome, classically have been associated with the use of neuroleptic drugs.[45,46] Nevertheless, other drug classes also may be responsible for some of these movement disorders.[47] These drugs include tricyclic antidepressants (TCAs), monoamine oxydase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and atypical antidepressants like trazodone. Symptoms may develop within hours to weeks after initiating any of these drugs.

Drug-induced Parkinsonism is indistinguishable from idiopathic Parkinson's disease. Dystonia is a sustained muscular contraction most commonly occurring in the face, neck, or head, which is described by patients as a cramp-like sensation. Akathisia is a subjective motor restlessness that may be interpreted wrongly by physicians as anxiety, prompting an increase in the dose of the offending agent.[48] Dyskinesia is a difficulty performing voluntary movements. The pharmacologic mechanisms of these movement disorders are poorly understood, but are thought to be mediated by the effects of serotonin, acetylcholine, and dopamine in the basal ganglia.[47]

Botulinum toxin has been used successfully in the treatment of various forms of dystonia, suggesting an excess of acetylcholine as the pathological mechanism. Dopaminergic drugs, such as bromocriptine, appear to alleviate Parkinson's-like symptoms, and suggest that some movement disorders may be caused by diminished dopamine activity. In contrast, the movement disorder described as chorea is treated with agents like reserpine, which are aimed at reducing dopamine and serotonin. Regardless of the underlying pathologic mechanism, the treatment for most drug-induced movement disorders just requires the discontinuation of the causative agent.[48]

Stroke. Stroke can result as a direct effect of drugs or an indirect complication of their use. Sympathomimetics, like cocaine and the amphetamines, may cause ischemic and hemorrhagic cerebrovascular accidents.[49-54] Cocaine has been associated with several of these events, but the exact mechanism of action still is unclear. Several hypothesized mechanisms include cocaine-associated vasculitis and transient hemodynamic effects mediated by the pharmacologic action of cocaine.[55-60] Chronic ephedrine use may cause acute intracerebral hemorrhage and CNS vasculitis.[61,62] Several deaths have been reported due to cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage after the use of ephedrine and its related compounds.[62-65] One study shows that phenylpropanolamine (PPA) was an independent risk factor for hemorrhagic stroke in women.[51]

Infections. CNS infections such as meningitis and intracerebral abscesses can occur as a result of intravenous drug abuse.[66] These are not the direct effect of the drug, but are a consequence of using contaminated drugs and/or paraphernalia.

Patients usually have a history of fever, general malaise, or other systemic complaints. The clinical presentation also may involve headache, seizures, alterations in the mental status, and/or signs of focality. Symptoms of the drug toxicity initially may mask the signs and symptoms of an underlying infection, making the diagnosis of a CNS infection difficult. The incidence of neurologic complications in patients with infective endocarditis varies from 20-40%, making this a very important diagnosis in the intravenous drug abuser population.[66] Cerebral embolism is one of the most common CNS presentations in patients with infective endocarditis.[66]

History and Physical Examination

The history and physical examination are particularly important in the field of toxicology because they are used to identify toxidromes. The toxidromes often aid in narrowing the differential diagnosis and help guide management decisions. Toxidromes are general diagnostic categories based on vital signs, pupil size, bowel sounds, mental status, and skin changes. Table 2 describes the most common toxidromes along with treatment recommendations. Historical information that can influence management decisions includes a complete history of the ingestion (substance,

amount, time of ingestion, and location of event), accessible medications, and past medical and psychiatric histories.

Differential Diagnosis

The differential diagnosis of CNS toxicity is very broad, including neurologic (structural), infectious, metabolic, and psychiatric (functional) etiologies, or a combination of one or more of these groups. (*See Table 4.*) Figure 1 shows an algorithm for the diagnosis and management of alterations in mental status.

Neurologic. Any space-occupying lesion can result in alterations in mental status. Differentiation between these and toxic or metabolic alterations can be aided by assessing a few specific findings: the pupil size and response; the ocular position at rest and in response to stimulus; and the motor response to stimulus. Structural lesions will result in asymmetric or focal neurologic findings. Toxic-metabolic influences will tend to result in a dissociation of findings. In general, the pupillary reflexes seem to be relatively protected from toxic-metabolic changes, and therefore will remain intact. In cases of toxic insults to the CNS, the patients also tend to improve over time, in contrast to structural injuries.[15]

Metabolic/Electrolyte. Metabolic causes of altered mental status may occur independently of a toxicological cause, as well as being a complication of the toxic effects of the agent. For example, lithium toxicity can cause nephrogenic diabetes insipidus and worsening hypernatremia, eventually leading to compromised membrane stability and neuronal death. The hypernatremia manifests clinically as altered mental status. Life-threatening issues that require immediate attention include hypoxemia, commonly resulting from shock or respiratory failure, and hypoglycemia. Profound thiamine depletion has been the precipitating cause for Wernicke's encephalopathy.[67] Wernicke's encephalopathy is referred to as the triad of ataxia, ophthalmoplegia, and altered mental status.

Functional Psychiatric. A psychiatric (functional) etiology always is a diagnosis of exclusion. Patients with catatonia, psychosis, hallucinations, or conversion disorders can present with apparent alterations of the mental status.

General Treatments

Although the specific management is different depending on the causal agent, several general interventions are important for the treatment of these patients. Meticulous attention to airway, breathing, and circulation (ABCs) and aggressive supportive management are the only interventions needed for most cases of toxicity.[68-73]

A useful mnemonic for common treatable causes of altered mental status is the DONT, representing D-stick or Dextrose, Oxygen, Naloxone, and Thiamine. Hypoglycemia and hypoxia must be identified and corrected immediately. The administration of naloxone will reverse opioid-induced respiratory depression.[74-78] Thiamine prevents Wernicke's encephalopathy, and should be given to all malnourished patients.[67]

The electrocardiogram (ECG) is a diagnostic tool that aids in the treatment decisions for some drugs. Cyclic antidepressants, massive diphenhydramine overdoses, or some anti-convulsants may cause sodium channel blockade, which will manifest as a widening of the QRS complex on the ECG.[79-81] Several of the newer and older antipsychotics can cause a long QT, which can lead to torsades de pointes and death.[82,83]

Table 3. Drugs that Cause Seizures

The mnemonic for drugs that cause seizures is OTIS CAMPBEL
Organophosphate insecticides, opiates (tramadol, meperidine, propoxyphene)
Theophylline, TCAs
Isoniazid, insulin (hypoglycemia)
Salicylates
Cocaine, camphor, carbon monoxide, cyanide
Amphetamines, anticholinergics
Metaldehyde, monomethylhydrazine
Penicillin
Barbiturate (withdrawal), bupropion
Ethanol (withdrawal)
Lead, lithium, lindane
* Other drugs not included in this table also may cause seizures.

Specific Treatments

Agitation. Agitated patients must be restrained. Physical restraints must be followed quickly by chemical (pharmacologic) restraints. This approach prevents the patient from developing multiple complications such as hyperthermia, rhabdomyolysis, and sudden death.[3,84] Hobble or hog-tie restraints without any chemical restraints have been associated with sudden death in patients with excited delirium after cocaine use.[3] Benzodiazepines commonly are preferred first-line agents. These drugs are easy to administer and titrate, have a fast onset of action, and have relatively few side effects.[85] In extremely agitated patients, repeated doses or even the addition of other pharmacologic agents may be necessary.

Butyrophenone neuroleptics also may be used for the control of agitation. Studies comparing parenteral haloperidol vs. parenteral lorazepam[86] and droperidol vs. lorazepam[6] have demonstrated similar efficacy but a superior safety profile of the benzodiazepines.[87] These studies focus on populations with known psychotic disorders, which may bias these studies toward a positive effect of the butyrophenones. Butyrophenone neuroleptics can predispose patients to hyperthermia, as they impair the body's ability to exchange heat via dopaminergic blockade in the striatum or by directly altering central thermoregulatory centers.[88,89] Animal studies have shown increased incidence of seizures with the use of neuroleptics.[90] Cases of fatal dysrhythmias and torsades de pointes associated with droperidol have raised additional concerns.[91] For this reason, we recommend the use of benzodiazepines in the patient with an unknown cause of agitation.

Patients with agitation not controlled by high doses of benzodiazepines may need the addition of barbiturates and, ultimately, nonbenzodiazepine sedating agents like propofol. The treatment

Figure 1. Algorithm for Diagnosis and Management of Alterations in Mental Status

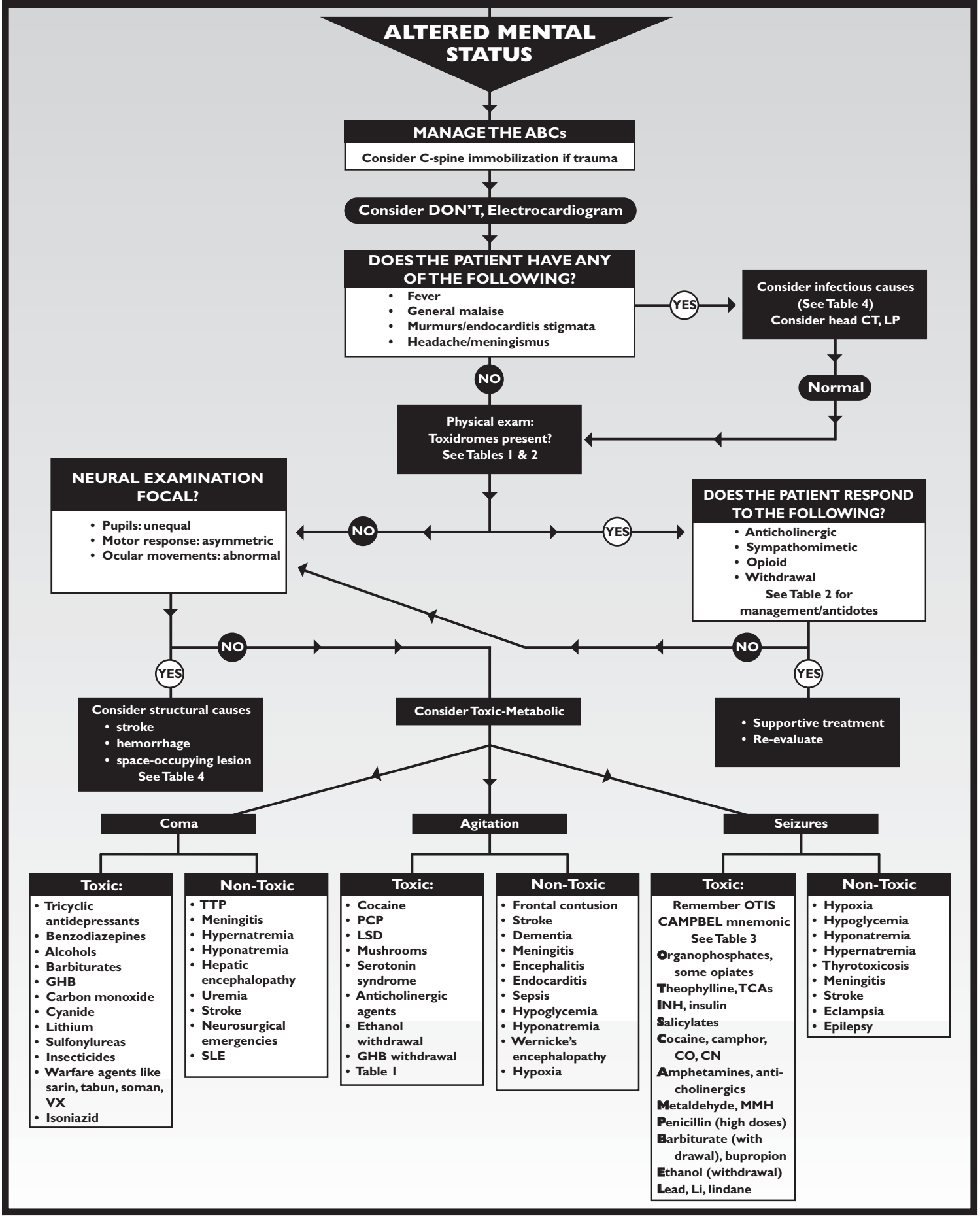

Table 4. Differential Diagnosis for CNS Manifestations of Toxicity

NEUROLOGIC/STRUCTURAL	INFECTIOUS	METABOLIC	FUNCTIONAL
Frontal contusion	Meningitis	Hypoglycemia/hyperglycemia	Schizophrenia
Hemorrhage	Encephalitis	Hyponatremia/hypernatremia	Personality disorder (antisocial, borderline)
Subdural hematomas	Brain abscess	Hypocalcemia/hypercalcemia	Psychogenic (anxiety)
Normal-pressure hydrocephalus	Sepsis	Hypothermia/hyperthermia	Bipolar disorder (mania)
Cerebrovascular accidents	Cysticercosis	Hypercarbia	
Encephalopathy: hypertensive		Hypoxemia	
Infarcts		Uremia	
Tumors		Hepatic: encephalopathy	
		Vitamin deficiency (thiamine)	
		Porphyria	
		Pheochromocytoma	
		Thyrotoxicosis, thyroid storm	
		Adrenal insufficiency, myxedema	
		Hyperosmolar states	
		Eclampsia	

of severe withdrawal syndromes, like that seen with gamma hydroxybutirate (GHB), is improved by adding barbiturates to the benzodiazepines.[92] Propofol is a sedating agent with similar action to the benzodiazepines. Its main side effect is hypotension.[93]

Newer neuroleptics have been developed with a promising safety profile for the treatment of agitation of known psychotic origin. Ziprasidone was observed to be effective in reducing the symptoms of agitation in patients with psychosis.[94,95] The study also showed that ziprasidone was well tolerated and did not result in movement disorders.[94]

Physostigmine is a specific antidote for the agitated delirium caused by anticholinergic agents. Physostigmine is a tertiary amine carbamate. This structure allows for CNS penetration. Administration of 1-2 mg of physostigmine over two minutes will reverse the CNS effects of the anticholinergics. The patient will become alert and awake and able to give a good history. This will eliminate costly tests and make the definitive diagnosis. Physostigmine has been associated with seizures and death in patients who overdosed with cyclic antidepressants.[80] For this reason, it is essential to do an ECG before administration of physostigmine. The confirmation that the QRS width is less than 100 milliseconds makes cyclic antidepressant toxicity unlikely.

Sedation or CNS Depression. Airway management is a key concept in the treatment of these patients. One element to consider before intubation is the availability of effective antidotes to reverse opiate-induced respiratory depression. The use of these antidotes often will obviate the need for intubation. Naltrexone, nalmefene, and naloxone are competitive opioid antagonists and act at the mu, kappa, and delta receptors. Naloxone is the antagonist of choice for the treatment of opioid-induced respiratory depression. Its onset of action is one minute when given intravenously and its clinical effects usually last 45-70 minutes.[96] Routes of administration for naloxone include intravenous, intramuscular, and subcutaneous. The goal of therapy with naloxone is to correct respiratory depression. The initial dose in life-threatening toxicity in adults is 2 mg intravenously. If there is no response, the dose can be repeated every three minutes, up to 10 mg. Synthetic opioids like meperidine may require doses up to 10 mg. If there is no response after 10 mg, it is highly unlikely that the manifestations are due to isolated opioid toxicity. In non-life-threatening situations, administer 0.4 mg intravenously and titrate the dose to the patient's response. The goal of treatment is reversing respiratory depression without precipitating withdrawal in opioid-dependent patients. The duration of action of most opiates is longer than that of naloxone. For this reason, a continuous infusion may be necessary in patients requiring repeated doses of naloxone. To calculate the infusion rate, identify the response dose (dose needed for reversal of respiratory depression) and infuse two-thirds of this dose every hour as a continuous infusion. Table 5 lists common antidotes and their doses. Give one-half the response dose before starting the infusion. Tramadol is a weak mu-opioid receptor agonist and has been associated with seizures. The use of naloxone in tramadol overdoses is contraindicated.[97,98]

Flumazenil is an effective benzodiazepine receptor antagonist, but generally is contraindicated in the overdose setting due to the risk of precipitating withdrawal seizures. Benzodiazepine-dependent patients have decreased seizure threshold due to down regulation of GABA receptors and decreased GABA activity. The addition of a competitive benzodiazepine antagonist may potentiate withdrawal and seizures. Flumazenil also can increase seizure risk by reversing protection of benzodiazepines in the setting of other co-ingestants that can result in seizures, like cyclic antidepressants. In the setting of conscious sedation or with a pediatric patient, with a pure benzodiazepine overdose in the benzodiazepine naïve patient, no real seizure risk exists to complicate the administration of flumazenil.

The most common dose of flumazenil is 0.1-0.3 mg IV over 30 seconds. Its onset of action is 1-2 minutes. The pediatric dose

is 10-20 mcg/kg IV or rectally. Flumazenil has a short half-life, and repeated dose up to 2-5 mg, or even a continuous infusion, may be required. If therapy fails even after repeated high doses, the depressive effects most likely stem from other sedative-hypnotic agents. Utilize small doses, such as 0.05 mg, of flumazenil for a benzodiazepine-dependant patient if the option of mechanical ventilation is not feasible. In these rare cases where intubation would be particularly difficult, slowly titrate flumazenil to avoid precipitating a life-threatening withdrawal.[99]

Seizures. Toxin-induced seizures tend to be short and self-limited. Benzodiazepines, most commonly lorazepam, are the treatment of choice. The mechanism of action of the various benzodiazepines is similar but the pharmacokinetics properties differ.[100] One comparative study showed that diazepam distributed into the brain within 10 seconds and maintained EEG seizure control for 20-30 minutes, whereas lorazepam distributed into the brain within three minutes and maintained EEG seizure control for up to three hours.[100,101] If after aggressive benzodiazepine administration the patient continues with seizures, barbiturates should be started as second-line agents. Phenytoin is not useful in toxin-induced seizures and even has been shown in animal models to be detrimental in the treatment of theophylline-induced seizures.[100]

Isoniazid toxicity ensues after depletion of pyridoxine (vitamin B_6), a substrate needed for the conversion of glutamic acid to GABA by pyridoxal 5-phosphatase. The resultant decrease in GABA leads to seizures. Status epilepticus develops rapidly. Pyridoxine, in combination with a benzodiazepine, is the mainstay of treatment. The dose of pyridoxine is 5 g intravenously empirically or 70 mg/kg in children. Give 1 g of pyridoxine for each 1 g of isoniazid ingested, if ingestion amount is known.[102] Pyridoxine also is the antidote for the hydrazines, such as monomethylhydrazine from mushrooms of the Gyromitra species.[19]

Conclusion

Many drugs and toxins affect the CNS. The main manifestations of drug toxicity in the CNS include altered mental status, encephalopathy, seizures, movement disorders, CNS infections, and stroke. Basic supportive management is the cornerstone for most of these conditions, aided by knowledge of antidotes, decontamination, and enhanced elimination techniques. Although the differential for all of these problems is extensive, a good history coupled with physical examination findings and selective use of the laboratory and radiology services will help reach the correct diagnosis.

Table 5. Empiric Dosing of Antidotes

DRUG	ADULTS	CHILDREN
NALOXONE		
	2.0 mg IV (max 10 mg) Use 0.2-0.4 mg in the dependent patient .	**0-5 y/o < 20kg:** 0.1 mg/kg IV/IM/SC/ET q 2-3 min until response **> 20 kg:** As adults
	Drip: Titrate to effect, re-bolus at effect amount and then start drip at 2/3 dose effect Q hr	
FLUMAZENIL		
	0.1-0.3 mg IV over 30 seconds (max 5 mg)	0.01 mg/kg (max 0.2 mg/dose; 0.05 mg/kg) over 3-5 min
THIAMINE		
	100 mg slow IV (over 5 min) re-dose Q6hrs	Not necessary in pediatric patients
PHYSOSTIGMINE		
	1- 2.0 mg slow IV (over 1-2 min)	0.02 mg/kg (max 0.5 mg) over 5 min

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Physician CME Questions

111. What is the first-line treatment for drug-induced seizures?
    A. Phenytoin
    B. Diazepam/lorazepam
    C. Phenobarbital
    D. Propofol

112. What is a contraindication to the use of flumazenil?
    A. Seizures or potential for seizures
    B. Decreased respirations and coma
    C. Hypotension and tachycardia
    D. Urine drug screen negative for benzodiazepines

In Future Issues: **Delirium**

113. Which of the following therapies predisposes to hyperthermia?
   A. Benzodiazepines (lorazepam, diazepam)
   B. Calming environment (darkened, quiet room)
   C. Neuroleptics (haloperidol, droperidol)
   D. Gentle physical restraints

114. What is the most appropriate treatment for a drug-induced movement disorder?
   A. Initiation of antipsychotic medication
   B. Test dose of haloperidol
   C. Increase medication dosage
   D. Remove offending agent

115. By which mechanism does acetaminophen toxicity result in hepatic encephalopathy?
   A. Production of NAPQI
   B. Inhibition of free fatty acid synthesis
   C. Unknown mechanism
   D. Thiamine deficiency

116. Which agent commonly induces seizures?
   A. Naloxone
   B. Valproic acid
   C. Morphine
   D. Amitriptyline

117. Under which circumstances should thiamine be administered?
   A. To all overdosed patients
   B. To all malnourished patients
   C. Only to pediatric patients
   D. If the thiamine levels are low

118. Which are common causes of altered mental status that can be immediately life-threatening and should be rapidly identified and remedied?
   A. Hypoglycemia and hypoxia
   B. Acetaminophen and ASA toxicity
   C. Myxedema and thyroid storm
   D. Opiate and ethanol intoxication

119. Which of the following is a contraindication to the use of physostigmine?
   A. Benzodiazepine overdose
   B. Respiratory depression
   C. Anticholinergic delirium
   D. QRS width more than 100 milliseconds

120. What is the antidote for isoniazid toxicity?
   A. Physostigmine
   B. Pyridoxine (vitamin B_6) plus benzodiazepine
   C. Sodium nitrite
   D. Haloperidol
   E. Flumazenil

Emergency Medicine Reports
CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur;
- and provide patients with any necessary discharge instructions.

CME Answers

111. B	116. D
112. A	117. B
113. C	118. A
114. D	119. D
115. A	120. B

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports
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CNS Manifestations of Drug Toxicity

Toxidrome Classifications and Examples

CLASS	EXAMPLES
Anticholinergic (atropine)	
Antihistamines	Diphenhydramine, chlorpheniramine
Belladonna alkaloids	Hyoscamine, scopolamine
Tricyclic antidepressants	Amitriptyline
Antipsychotics	Haloperidol, thioridazine
Antiemetics	Chlorpromazine
Cholinergic	
Organoposphate and carbamate insecticides	Malathion, carbaryl
Nerve agents	Tabun, sarin, soman, VX
Sympathomimetics	
Adrenergics	Cocaine, amphetamines, phencyclidine (PCP)
Xanthines	Caffeine, theophylline
Decongestants	Phenylpropanolamine, ephedrine/pseudoephedrine
Antidepressants (neuroamine reuptake inhibition)	Trazodone, venlafaxine, selegiline
Sedative Hypnotics	
Alcohols	Ethanol, ethylene glycol, methanol, isopropanol
Barbiturates	Secobarbital, phenobarbital, pentobarbital
Benzodiazepines	Diazepam, lorazepam, alprazolam
Miscellaneous	Ethchlorvynol, meprobamate, baclofen Gamma-hydroxybutyrate (GHB), butyrolactone (GBL)
Opioids	
Opiate (natural derivatives)	Heroin, morphine, codeine
Synthetic	Meperidine, fentanyl, methadone
Opioid-like effects	Clonidine, olanzapine

Drugs that Cause Seizures

The mnemonic for drugs that cause seizures is OTIS CAMPBEL
Organophosphate insecticides, opiates (tramadol, meperidine, propoxyphene)
Theophylline, TCAs
Isoniazid, insulin (hypoglycemia)
Salicylates
Cocaine, camphor, carbon monoxide, cyanide
Amphetamines, anticholinergics
Metaldehyde, monomethylhydrazine
Penicillin
Barbiturate (withdrawal), bupropion
Ethanol (withdrawal)
Lead, lithium, lindane
* Other drugs not included in this table also may cause seizures.

Empiric Dosing of Antidotes

DRUG	ADULTS	CHILDREN
NALOXONE		
	2.0 mg IV (max 10 mg) Use 0.2-0.4 mg in the dependent patient . **Drip:** Titrate to effect, re-bolus at effect amount and then start drip at 2/3 dose effect Q hr	**0-5 y/o < 20kg:** 0.1 mg/kg IV/IM/SC/ET q 2-3 min until response **> 20 kg:** As adults
FLUMAZENIL		
	0.1-0.3 mg IV over 30 seconds (max 5 mg)	0.01 mg/kg (max 0.2 mg/dose; 0.05 mg/kg) over 3-5 min
THIAMINE		
	100 mg slow IV (over 5 min) re-dose Q6hrs	Not necessary in pediatric patients
PHYSOSTIGMINE		
	1- 2.0 mg slow IV (over 1-2 min)	0.02 mg/kg (max 0.5 mg) over 5 min

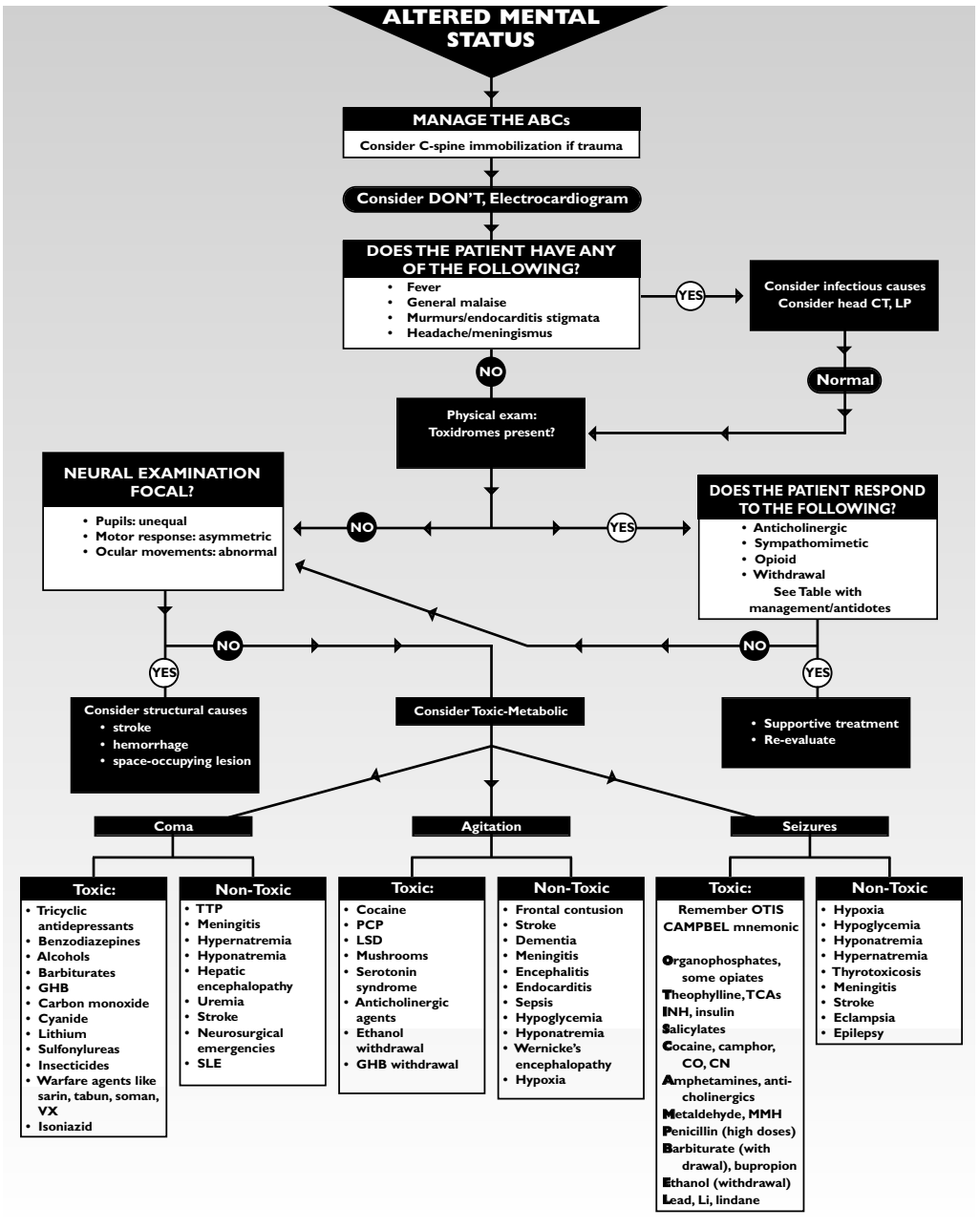
Toxidromes

TOXIDROME	MENTAL STATUS	PULSE	RR	BLOOD PRESSURE	PUPIL SIZE	SKIN	TEMPERATURE	SPECIFIC MANAGEMENT
Opiate	Depressed	Low	Low	Low	Pinpoint	Normal	Decreased	Naloxone
Sedative hypnotics	Depressed	Low	Low	Low	Normal	Normal	Normal	Flumazenil (controversial)
Sympathomimetics	Agitated	High	Normal	High	Increased	Diaphoretic	Increased	Benzodiazepines
Cholinergic	Agitated	High/Low	Normal	High/Low	Increased	Diaphoretic	Normal	Atropine, Pralidoxime
Anticholinergic	Agitated/ Delirium	High	High/Low	High/Low	Increased	Dry	Increased	Physostigmine Benzodiazepines
WITHDRAWAL SYNDROMES								
Sedative hypnotics	Agitated	High	High	High	Increased	Normal/Wet	Increased	Benzodiazepines
Opioids	Normal	High	Normal	High	Increased	Wet	Normal	

Differential Diagnosis for CNS Manifestations of Toxicity

NEUROLOGIC/STRUCTURAL	INFECTIOUS	METABOLIC	FUNCTIONAL
Frontal contusion	Meningitis	Hypoglycemia/hyperglycemia	Schizophrenia
Hemorrhage	Encephalitis	Hyponatremia/hypernatremia	Personality disorder (antisocial, borderline)
Subdural hematomas	Brain abscess	Hypocalcemia/hypercalcemia	Psychogenic (anxiety)
Normal-pressure hydrocephalus	Sepsis	Hypothermia/hyperthermia	Bipolar disorder (mania)
Cerebrovascular accidents	Cysticercosis	Hypercarbia	
Encephalopathy: hypertensive		Hypoxemia	
Infarcts		Uremia	
Tumors		Hepatic: encephalopathy	
		Vitamin deficiency (thiamine)	
		Porphyria	
		Pheochromocytoma	
		Thyrotoxicosis, thyroid storm	
		Adrenal insufficiency, myxedema	
		Hyperosmolar states	
		Eclampsia	

Algorithm for Diagnosis and Management of Alterations in Mental Status



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