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Psychiatric Disorders: Drug Withdrawal Syndromes

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Treatment of drug withdrawal syndromes requires attention to both the biological (medical) model and the behavioural (psychosocial) model. Alcohol and benzodiazepine withdrawal can result in medically important sequelae such as seizures and autonomic instability. Opioid withdrawal results in markedly unpleasant symptoms without important medical sequelae. Stimulant withdrawal is almost exclusively behavioural with the most important risks being suicidality and, less commonly, hallucinosis with amphetamines.

Withdrawal syndrome diagnosis requires:[1]

- The development of a substance-specific syndrome due to cessation or reduction of prolonged substance use
- Clinically significant distress or impairment of functioning
- The absence of a medical or other psychiatric disorder that can cause the syndrome

Table 1: Diagnostic Criteria for Substance-specific Withdrawal Syndromes[1]

Alcohol		**Stimulants (Cocaine and Amphetamines)**	
	Autonomic hyperactivity (e.g., sweating, pulse >100 bpm) Increased hand tremor Insomnia Nausea/vomiting Transient visual, tactile or auditory hallucinations Psychomotor agitation Anxiety Grand mal seizures Depression		Fatigue Vivid, unpleasant dreams Insomnia or hypersomnia Increased appetite Psychomotor retardation or agitation Anxiety Depression Craving for stimulant Psychotic symptoms (amphetamines)
Opioids		**Benzodiazepines**	
	Dysphoric mood Nausea/vomiting Muscle aches Lacrimation, rhinorrhea Pupillary dilation, piloerection, sweating Diarrhea Yawning Fever Insomnia		Autonomic hyperactivity (e.g., sweating, pulse >100 bpm) Increased hand tremor Insomnia Nausea/vomiting Transient visual, tactile or auditory hallucinations Psychomotor agitation Anxiety Grand mal seizures (only after abrupt cessation of high doses)

Goals of Therapy

- Anticipate, prevent and treat complications
- Relieve symptoms
- Assess for and treat comorbidities (medical and psychiatric)
- Facilitate definitive psychosocial/behavioural treatment
- Prevent relapse

Investigations

- Detailed history and physical examination to evaluate severity of abuse of the substance (amount, frequency, duration) and comorbid medical and psychiatric (Axis II, depression or psychosis) conditions
- Specific assessment tools such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)[2] or CIWA-Benzo[3]

- Laboratory tests and/or imaging to assess comorbidities/complications revealed in history and physical (complete blood count, renal/liver function, electrolytes, magnesium, phosphorus, chest x-ray, CT of head)
- Drug screening: blood alcohol or urine screen for benzodiazepines may be helpful in the trauma or emergency patient where history is inadequate

Therapeutic Choices (Figure 1 - Management of Drug Withdrawal Syndromes)

Nonpharmacologic Choices

- Nonjudgmental approach to explain process, reassure and support.
- Psychosocial treatment program (cognitive behavioural therapy, motivational enhancement therapy, interpersonal therapy, 12-step, group and family therapies).[4]

Pharmacologic Choices

General principles:

- Monitor signs and symptoms.
- Treat specific symptoms of withdrawal and associated complications and comorbidities (medical and psychiatric).
- Substitute abused drug with one of same or similar class (a cross-tolerant agonist that is less likely to be abused, usually with longer half-life).
- Substitute abused drug with one that blocks its reinforcing effects (antagonist).

Alcohol Withdrawal Syndrome

Assessment (Table 1)

The severity of the alcohol withdrawal syndrome and its complications correlate directly but inconsistently with the intensity and duration of alcohol use. These complications can include undernutrition (thiamine deficiency), low potassium, magnesium and phosphorus, liver disease and bleeding diathesis (increased INR, impaired platelet function/thrombocytopenia), CNS disorders (seizures, Wernicke encephalopathy, trauma) autonomic dysfunction (hypertension, dehydration, pyrexia), infections (pneumonia, aspiration, cellulitis) and psychosis (hallucinations, delusions). Mild withdrawal symptoms include tremor, irritability and insomnia, usually lasting 48–72 hours. A minority of patients experience more severe symptoms with onset around 48 hours and lasting up to about 5 days, which may include autonomic instability, seizures, hallucinations, delusions and hyperthermia. In the small proportion of fatalities following acute alcohol withdrawal (approximately 0.25%), cardiac complications such as arrhythmias are the most common cause. The CIWA-Ar is an effective assessment tool.[2]

Management (Table 3)

Approximately two-thirds of patients with mild to moderate withdrawal symptoms can be managed with supportive treatment and monitoring, although comparison with pharmacotherapy is not described in the literature.[5] Blunting symptoms with low-dose, short-duration **benzodiazepine** therapy may be helpful and is of low risk.

Severe alcohol withdrawal syndrome always requires pharmacologic treatment, and guidelines usually recommend it for moderate cases as well. Larger than usually recommended doses of **benzodiazepines** (>50 mg diazepam iv in the first hour or >200 mg in 3 hours) and/or addition of a different GABA-active drug like **phenobarbital** (130–1430 mg, mean dose 390 mg) may be required for resistant alcohol withdrawal (<5% of cases), and these patients require monitoring in a critical care area (emergency room, intensive care unit or intermediate care unit).[6] , [7]

Although many emergency room physicians add an antipsychotic (usually **haloperidol** 5–10 mg) in resistant alcohol withdrawal, there is no good evidence to support its use, and there is a risk of dystonia, akathisia, hypotension and lowered seizure threshold.

There is insufficient evidence to support the use of **antiepileptic drugs** in alcohol withdrawal.[8] Many other agents such as **beta-blockers**, **clonidine** and **phenothiazines** have been evaluated and show lower efficacy and more adverse effects than benzodiazepines and phenobarbital. These agents should never be used alone, but phenothiazines may be used adjunctively if delirium persists in spite of high doses of benzodiazepine and phenobarbital. There is also no evidence or rationale to support the use of **baclofen** in alcohol withdrawal.[9]

Patients admitted to hospital for surgical illness may have occult alcohol dependence, and appropriate prophylaxis

and management of alcohol withdrawal syndromes with benzodiazepines can prevent complications.[10]

Rehabilitation

Cognitive behavioural therapy, group therapy and self-help groups such as Alcoholics Anonymous form the mainstay of long-term rehabilitation and maintenance of abstinence; there is conflicting evidence to support the use of pharmacotherapy (**acamprosate**, **naltrexone**) in this setting.[11] A Cochrane review reported a modest effect of naltrexone on reducing the quantity of alcohol intake.[12] There is a risk of precipitating withdrawal in opioid-dependent patients. Results from clinical trials of acamprosate have been mixed.[13] , [14] , [15]

Stimulant (Cocaine and Amphetamine) Withdrawal Syndrome

Assessment (Table 1)

Symptoms of cocaine withdrawal include mostly psychosocial, subtle and medically unimportant symptoms and signs, except for the risk of acute severe depression and suicidality in a small percentage of patients. The toxic state is manifested by agitation, tachycardia and anorexia, and conversely the withdrawal state is characterized by somnolence and increased appetite. Depression, anxiety, anhedonia and sleep disturbance may also occur, resolving over several weeks. Suicidality is uncommon and requires direct assessment.

Amphetamine withdrawal shares most of the characteristics of cocaine withdrawal, but may include psychotic features or a more severe depressed mood and may last longer. Drug craving replaces the withdrawal syndrome and may last several months. **After withdrawal from methamphetamine ("crystal meth"), a persistent psychosis may occur and become permanent (uncommon) or last several weeks, usually responding well to low-dose antipsychotics (for dosing information see Psychiatric Disorders: Psychoses).**[16] Useful Info?
Look for medical complications of stimulant use such as cardiomyopathy, local or systemic abscess, endocarditis, HIV and hepatitis B and C.

Management

Evaluation of a variety of pharmacotherapy approaches both for treatment of stimulant withdrawal syndrome and for relapse prevention has yielded inconsistent results, reflecting lack of efficacy. Dopamine agonists, such as **amantadine** [17] or **bromocriptine** [18] have demonstrated no significant benefit. **Desipramine** and other antidepressants have little or no effectiveness for withdrawal or relapse prevention, but may have a role in comorbid depression or anxiety. Agonist replacement therapy with sustained-release **amphetamine** or **methylphenidate** has shown benefit in relapse prevention, but regulatory concerns may limit their use, unless underlying attention deficit disorder co-exists.[19] Making this diagnosis requires psychiatric expertise.

Rehabilitation

Although **buprenorphine** and **methadone** may offer benefit to patients with mixed opioid and stimulant dependence, no drug therapy is consistently effective for treating pure stimulant dependence. Intensive outpatient, abstinence-oriented psychosocial treatment, especially *cognitive behavioural therapy*, is the most effective treatment, in addition to addressing the psychiatric comorbidities.

Opioid Withdrawal Syndrome

Assessment (Table 1)

Symptoms of opioid withdrawal are not medically serious, with muscle aches, restlessness and insomnia predominating. The acute withdrawal syndrome usually lasts about 1 week, except for withdrawal from methadone, with drug craving often persisting for several months.

Management (Table 4)

Abstinence-based treatment may be desirable, but the most effective treatment by far continues to be replacement therapy with a long-acting agonist like methadone or the partial agonist buprenorphine, available as a sublingual combination product with naloxone, an opioid antagonist that is not sufficiently absorbed orally/sublingually to cause opioid withdrawal, but is included to discourage injection use.

Methadone and buprenorphine can be initiated with the first withdrawal symptoms. Higher *maintenance* doses (methadone 60–100 mg or buprenorphine 8–24 mg/day) are more effective than lower doses. Because of methadone's long half-life of about 30 hours, the risk of narcosis (opioid-induced stupor or unconsciousness) in patients with an unknown degree of opioid tolerance is high in the first few days, and requires expertise and vigilance. Buprenorphine is a partial opiate agonist with a long half-life (36 hours) and generally does not cause narcosis in overdose.[20] Useful Info?

Clonidine, an alpha-2 agonist that decreases the neuronal output of norepinephrine, can be used to blunt the neuradrenergic signs/symptoms of withdrawal such as chills and flushing, but muscle aches and cravings usually persist. **Naltrexone**, a long-acting opioid antagonist, is ineffective in decreasing long-term opioid use, even with psychosocial support.[21] In addition, naltrexone-based withdrawal, alone or with anesthesia, results in no benefit compared to other detoxification treatments, and anesthesia or heavy sedation carries unacceptable risks.[22] When there is a need to withdraw prescribed opioid therapy, a gradual reduction of the drug by approximately 10% weekly is safe, avoids withdrawal symptoms and is best done as an outpatient.

Rehabilitation

The best long-term results are obtained with replacement therapy (methadone or buprenorphine) combined with cognitive behavioural or group therapy, counselling and 12-step support. If methadone or buprenorphine discontinuation is considered, the best outcomes occur with slow tapering over many weeks.[4]

Benzodiazepine Withdrawal Syndrome

Assessment (Table 1)

Assessing benzodiazepine withdrawal syndrome is associated with 3 challenges:

- distinguishing recurrence of anxiety, panic or insomnia from the onset of withdrawal symptoms
- assessing risk of seizures and autonomic hyperactivity
- selecting the best treatment for any underlying psychiatric condition.

The withdrawal syndrome begins within 1–2 days of abrupt discontinuation (up to 5–10 days for benzodiazepines with longer half-lives) and can be severe, with hypertension, tachycardia and hyperreflexia progressing to seizures if there was long-term, high-dose use. In chronic anxiety and panic disorders, chronic dosing may be very high (even >100 mg diazepam per day) and may be associated with alcohol overuse, i.e., sedative self-treatment. A number of factors correlate with severity of the benzodiazepine withdrawal syndrome: high daily dose, use of agents with short half-life, long duration of use, diagnosis of panic disorder, presence of severe Axis II disorders (personality disorders) and concomitant alcohol or substance abuse.

Management

Switching to a benzodiazepine with a long half-life (if not already taking one) and prolonged tapering of daily dose, combined with supportive and eventually cognitive therapy for the underlying condition, form the only effective treatment for prolonged high-dose benzodiazepine dependence. Most Canadian experts use **diazepam** or **clonazepam** for replacement therapy (Table 2). Initial tapering of the daily dose of diazepam or clonazepam to 50% of the starting dose can usually occur over a 2–4 week period; the last 50% frequently takes many weeks, sometimes with periods of weeks with no dosage change.[23]

Because patients with personality disorders tolerate distress poorly, they often drop out early, and an intensive supportive and cognitive behavioural program should coincide with benzodiazepine tapering and may include periods of maintenance. Patients can be managed in an intensive outpatient program. Few patients (those with associated cardiovascular disease, severe alcoholism or previous seizures) require a short hospitalization.

Table 2: Dose Equivalents of Benzodiazepines

Benzodiazepine	Elimination Half-life[a]	Approximate Equivalent Oral Dosage[24] (mg)
Clorazepate	Long	10
Chlordiazepoxide	Long	25
Diazepam	Long	5

Flurazepam	Long	15
Alprazolam	Intermediate	0.5
Bromazepam	Intermediate	3
Clonazepam	Intermediate	0.25
Lorazepam	Intermediate	1
Nitrazepam	Intermediate	2.5
Oxazepam	Intermediate	15
Temazepam	Intermediate	10
Triazolam	Short	0.25

a. Short = ≤5 h; Intermediate = 5–60 h; Long = ≥100 h.

Rehabilitation

For patients being treated for benzodiazepine dependence, the best strategy for managing an underlying psychiatric condition such as insomnia, generalized anxiety, panic disorder or mood disorder is *cognitive behavioural therapy*.[4, 25] Pharmacotherapy should be directed to the specific underlying condition and should have a low risk for dependence; options include low-dose, low-potency antipsychotics. Insomnia can be treated with these agents or with **trazodone** (25–100 mg at bedtime). **Buspirone** can be used for generalized anxiety, and has low abuse potential and reasonable but not dramatic efficacy. See also Psychiatric Disorders: Insomnia, Psychiatric Disorders: Anxiety Disorders and Psychiatric Disorders: Depression.

Neonatal Withdrawal Syndrome

Neonates may suffer withdrawal symptoms due to in utero exposure to drugs such as alcohol, benzodiazepines, opioids, barbiturates, nicotine, cannabinoids, cocaine, amphetamines and SSRI antidepressants. Neonatal abstinence syndrome usually refers specifically to neonatal opioid withdrawal.

For management of irritability, tachycardia, insomnia and for prevention of seizures associated with neonatal alcohol or benzodiazepine withdrawal, benzodiazepines and phenobarbital are effective and safe. Phenobarbital withdrawal usually does not require pharmacotherapy due to its long half-life. Neonatal withdrawal from cannabinoids, nicotine, SSRI antidepressants, cocaine or amphetamines is treated with supportive care only. Nicotine-associated small-for-dates babies and fetal alcohol spectrum disorder are potential long-term sequelae associated with use of those substances during pregnancy.

Neonatal Abstinence Syndrome

Assessment

Neonatal abstinence syndrome (NAS) refers specifically to neonatal withdrawal from maternal opioid use, usually methadone or heroin. The onset of symptoms is usually 48–72 hours after birth for most opioids, but about 4–14 days for methadone. Expression of NAS is widely variable and is unrelated to the maternal daily dose of methadone.[26] Clinical manifestations relate to the central/autonomic nervous systems and the gastrointestinal tract. Affected infants display a characteristic high-pitched cry, as well as irritability, insomnia, hypertonia, hyperreflexia, tremor and convulsions. They often experience vomiting, diarrhea, feeding problems, sweating, yawning, tachypnea, congestion/sneezing and fever. It is important to evaluate for potential differential diagnoses including neonatal sepsis, meningitis, hypoglycemia, hypocalcemia, hypomagnesemia or colic.

There are several scoring systems for assessment and guiding treatment of NAS; the modified Finnegan Neonatal Abstinence Scoring System (31 items) is the most widely used for both research and treatment.[26] The Finnegan score is assessed every 2–4 hours.

Management

Nonpharmacologic treatment is the standard of care for babies with NAS, and includes swaddling, holding, gentle rocking, pacifier use, frequent small feeds with hypercaloric formula, frequent diaper changes with barrier ointment, and most importantly an environment that is quiet, has low light and white noise. Use of **methadone** in a

breastfeeding mother may ameliorate withdrawal symptoms in the infant through transfer of approximately 2.8% of the maternal dose to breast milk. The American Academy of Pediatrics considers any maternal dose of methadone to be compatible with breastfeeding.[27] For infants with moderate to severe withdrawal, pharmacotherapy may provide additional benefits. A Cochrane review compared opioid treatment to supportive care alone, phenobarbital or diazepam.[28] Compared to supportive care alone, opioid treatment resulted in reduction in time to regain birth weight and shorter duration of supportive care, but longer hospital stay (possibly due to a policy-based requirement for hospitalization to receive opioids). Opioid therapy reduced seizure incidence and special care nursery admissions compared to phenobarbital, and reduced treatment failure (inadequate control of symptoms, requirement for additional pharmacotherapy, seizures, mortality) compared to diazepam.

The best studied opioid treatment regimen uses *diluted* **tincture of opium** (equivalent to morphine 0.4 mg/mL), with or without **phenobarbital** (added when there was polydrug withdrawal or maximum doses of opioid had been achieved).[29] This treatment regimen was safe and effective, with many of the infants sent home on phenobarbital which was weaned by the pediatrician. There was a 48% decrease in the length of hospitalization, less time with severe withdrawal scores and markedly decreased cost. It is important to be aware of the neonatal half-life of phenobarbital of 200–400 hours (around 100 hours in adults).

Clonidine should not be used alone, but when used adjunctively with opioids can reduce length of hospital stay, decrease seizures and decrease treatment failures, in doses of 1 µg/kg every 4 hours.[30]

Figure 1 - Management of Drug Withdrawal Syndromes

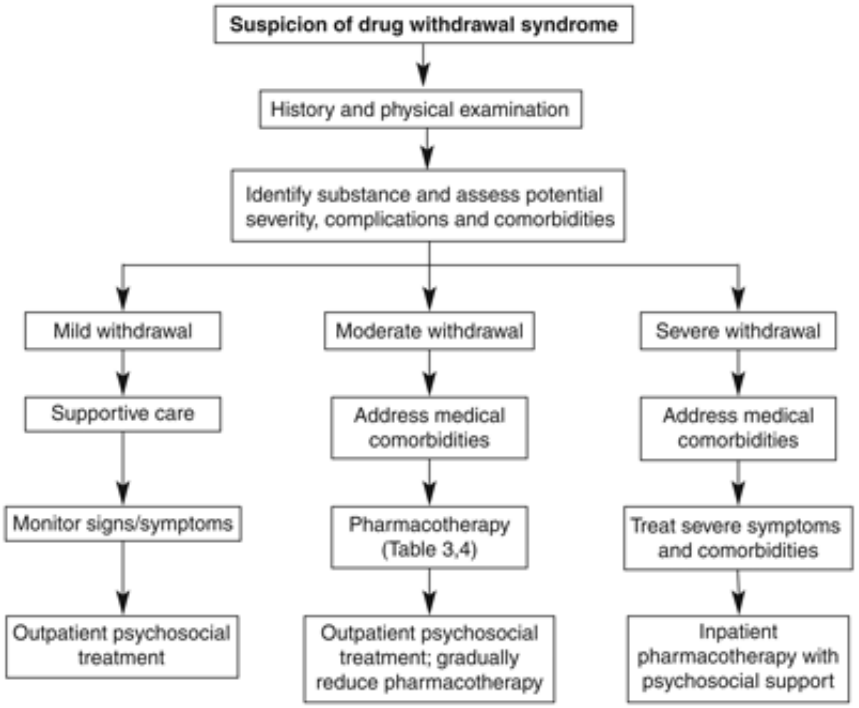

Table 3: Pharmacologic Management of Alcohol Withdrawal

Class	Drug	Indication/Symptom	Dose	Comments	Cost[a]
Vitamins	*thiamine* (vitamin B_1) Thiamiject, generics	Treatment/ prevention of Wernicke's encephalopathy.	50 mg daily iv or po × 3 days	Best practice is to administer thiamine to all patients with alcohol withdrawal. Should be administered prior to iv dextrose, to avoid precipitation of Wernicke's encephalopathy.	$$
Benzodiazepines	*diazepam* Diazemuls, Valium, generics	Autonomic hyperactivity, agitation/tremor, hallucinations, seizures.	5–10 mg po or iv Q10–20 min; see Comments.	Goal is suppression of symptoms with no more than mild sedation. Mild withdrawal: give Q1H. Moderate withdrawal: give	po:$ iv:$$

				Q20–60 min. Severe withdrawal: give Q10–20 min. Onset of action 1 min for diazepam iv.	
Benzodiazepines	*lorazepam* Ativan, generics	Autonomic hyperactivity, agitation/tremor, hallucinations, seizures.	1–2 mg po or iv Q20–60 min	Goal is suppression of symptoms with no more than mild sedation. Onset of action 5–15 min for lorazepam iv.	po:$ iv:$$
Benzodiazepines	*chlordiazepoxide* generics	Autonomic hyperactivity, agitation/tremor, hallucinations, seizures.	10–50 mg po Q10–20 min	Goal is suppression of symptoms with no more than mild sedation. Onset of action 1–2 h for chlordiazepoxide po.	$
Barbiturates	*phenobarbital* [6], [7] generics	Severe withdrawal refractory to benzodiazepine therapy (>50 mg diazepam given in 1 h or >200 mg in 3 h).	60 mg po or iv Q20–30 min	High dose may be required (up to total of 1000 mg). Should be used in a critical care area.	po:$ iv:$$$

a. Cost of a single administration; includes drug cost only.

Legend: $ < $1 $$ $1–5 $$$ $5–10

Table 4: Pharmacologic Management of Opioid Withdrawal in Adults

Class	Treatment Drug	Dose	Comments	Cost[a]
Opioid Agonists	*methadone* Metadol, generics	Acute withdrawal symptoms in new patients: 10–20 mg po Q2–4H until stable (usually 20–60 mg). If not to be continued as maintenance, taper by 5 mg/day over 1–2 wk Maintenance: 40–100 mg/day po	High relapse rate without maintenance therapy. Long half-life (24–36 h). Higher maintenance doses (60–100 mg) associated with better outcomes.	$$
Partial Opioid Agonists	*buprenorphine / naloxone* Suboxone	Long-term maintenance : 8–24 mg (buprenorphine) sl daily. Dose is usually initiated at 4 mg (1 or 2 doses the first day) and titrated to the lowest effective maintenance dose	Start with first signs of withdrawal (if switching from methadone, start at least 24 h after last dose). Prescribed and dispensed in accordance with Suboxone Education Program (www.suboxonecme.ca)	$$$
Alpha$_2$-adrenergic Agonists	*clonidine* Catapres, Dixarit, generics	0.1–0.5 mg/day Q8H po for 7 days, then taper over 3–5 days	Blunts some withdrawal symptoms. Use only for acute detoxification and when patient prefers over methadone. Maintain fluid intake and monitor for hypotensive effects; hold next dose if blood pressure <85/55.	$

a. Cost of 7-day supply of mean dose; includes drug cost only.

Legend: $ < $25 $$ $25–50 $$$ $50–75

Suggested Readings

Practice guideline for the treatment of patients with substance use disorders. 2nd ed. American Psychiatric Association. *Am J Psychiatry* 2007;164(4 Suppl):1-124.

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