FEATURES OF DRUG WITHDRAWAL SYNDROMES

It is important to recognise the physiological responses to drug withdrawal in ICU patients, and treat them when appropriate.

Alcohol Withdrawal Syndrome

Alcohol ingestion inhibits excitatory neural pathways and potentiates sedative pathways (GABA receptors). Chronic alcohol ingestion results in "up-regulation" of NMDA and down-regulation of GABA receptors. Acute alcohol withdrawal results in imbalance with excessive neural excitation. Four clinical states are described. It is difficult to predict which states will affect individual patients, and wide variation occurs.

Autonomic hyperactivity. This manifests as activation of the sympathetic nervous system: sweating, tachycardia, hypertension, agitation, tremor, nausea, fever. This typically occurs within 6-12 hours of last alcohol, and peaks at 24-48 hours.

Hallucinations. These typically occur within 8-48 hours from last alcohol and can last up to 6-7 days. They are usually tactile and visual (auditory hallucinations are unusual). Hallucinations are distinguished from Delirium Tremens by the patient having clear thinking, and generally starting earlier following withdrawal.

Neuronal excitability (Seizures). Seizures typically occur 12-48 hours from last alcohol ingestion, but can also occur when blood alcohol levels are high. Typically they are tonic-clonic and short-lived. Prolonged seizures should raise suspicion of another cause.

Delirium Tremens (DTs). DTs only affect about 10% of patients, and occur later than other symptoms (48-72 hours). The features are delirium combined with autonomic hyperactivity and alcohol hallucinosis. Increased metabolic rate, dehydration, electrolyte disturbances are common. DTs may have a genetic predisposition, and a family or personal history is a strong predictor of subsequent DTs.

Opiate Withdrawal Syndrome

Opiate withdrawal causes sympathetic nervous system activation which can result in: tremors, sweating tachycardia, hypertension, vomiting, diarrhoea, and fever. Muscle pain, cramps, and "flu-like" symptoms are common. A wide range of psychological symptoms can occur, including anxiety, agitation, and insomnia. Acute opioid withdrawal syndromes following ICU analgesic infusion are more common in younger adults and children who typically require higher doses for sedation.

Nicotine Withdrawal Syndrome

Acute nicotine withdrawal (smoking cessation) outside the ICU causes irritability, agitation, anxiety, and sometimes confusion and hallucinations. In ICU patients, nicotine withdrawal has been associated with agitation and is a risk factor for delirium.

Benzodiazepine Withdrawal Syndrome

Severe benzodiazepine withdrawal syndromes are most common in patients with long term dependence. Less severe forms may occur in ICU patients who received benzodiazepines for prolonged periods during critical illness. The features of acute benzodiazepine withdrawal are similar to alcohol, in that chronic exposure causes changes in GABA receptors in the brain.

A wide range of symptoms occur that can be grouped as:

Autonomic hyperactivity: including tachycardia, hypertension, agitation, tremor, sweating, tremor.

Central neurological features: including anxiety, agitation, delirium, sleep disturbance, seizures, psychosis.

MANAGING DRUG WITHDRAWAL SYNDROMES

Drug withdrawal syndromes need careful management to minimise harmful effects from physiological and neuropsychiatric features. There are two management approaches: *Generic approaches* to managing the autonomic consequences, principally sympathetic nervous system activation; and *Specific approaches* tailored to the drug classes involved.

Generic approaches

Most drug withdrawal syndromes are characterised by *sympathetic nervous system activation*. Common features are tachycardia, hypertension, sweating, fever, tremor, and restlessness/agitation. These are associated with increased metabolic rate, and potentially complications such as myocardial ischaemia.

Excessive sympathetic activation can be managed using:
Gradual reduction in drug dose: this approach is well-suited to opiate and benzodiazepine dependence, whether chronic or occurring during ICU stay. For patients with opiate dependence using reducing regimens of long-acting agents such as methadone may be effective.

Use of alternative sedatives which decrease sympathetic activity: the $\alpha 2$ agonists (clonidine and dexmedetomidine) have sedative and analgesic properties and specifically decrease sympathetic nervous system activity. These agents are useful adjunctive therapy during difficult drug withdrawal, typically by infusion. Clonidine can also be administered enterally.

Specific sympathetic blocking drugs: Drugs which block sympathetic activity (for example β-blockers) or with antihypertensive properties (for example vasodilators or ACE inhibitors) may be useful to treat hypertension and/or tachycardia during drug withdrawal.

Specific Approaches

Alcohol: Benzodiazepines are recommended for the management of alcohol withdrawal syndromes. Many patients will have tolerance to benzodiazepines and may require large doses. The dose should be tailored to individual requirements, by carefully monitoring patient status.

Opiate: Careful monitoring and assessment for pain is important to ensure patients receive appropriate analgesia during opiate withdrawal. Chronic opiate drug abuse is the most common scenario presenting to ICU. In this situation continuation or introduction of oral/enteral long-acting agents such as methadone, combined with short acting opiates for managing pain associated with the acute illness, is usually effective.

Nicotine: Smoking cessation is widely treated with nicotine replacement therapy using transdermal patches. At present, in critically ill patients the role of nicotine replacement is

uncertain and controversial. Smoking cessation is associated with increased agitation, but some studies suggest nicotine replacement may increase adverse outcomes.
Benzodiazepines: Patients with chronic benzodiazepine dependence will be tolerant to sedatives acting via GABA receptors, and may require high doses to achieve clinical effects. Strategies to gradually decrease benzodiazepine use, combined with alternative sedatives and management of sympathetic activation, should be effective when titrated to individual patient requirements. Chronic benzodiazepine use is a risk factor for delirium and may require specific treatment.

Key point: Recognising the key features of drug withdrawal syndromes is an important consideration when managing sedation in critically ill patients. An individualised approach should be discussed with the multidisciplinary team. Drug withdrawal should be considered as a possible cause of agitation.

SUMMARY

The main drug withdrawal syndromes observed in ICU are: Alcohol, opiate, nicotine and benzodiazepine withdrawal syndromes.

Drug withdrawal syndromes should be considered as a possible cause of agitation and should be treated using an individualized approach.

Management approaches for drug withdrawals are generic and specific.