Physical Dependence: The Hidden Reality of Withdrawal

Authored by

mohammad looti

June 17, 2026

Physical dependence refers to a state resulting from chronic use of a drug that has produced tolerance and where negative physical symptoms of withdrawal result from abrupt discontinuation or dosage reduction. Physical dependence can develop from low-dose therapeutic use of certain medications such as benzodiazepines, opioids, antiepileptics and antidepressants, as well as misuse of recreational drugs such as alcohol, opioids and benzodiazepines. The higher the dose used, the greater the duration of use, and the earlier age use began are predictive of worsened physical dependence and thus more severe withdrawal sydromes. Acute withdrawal syndromes can last days, weeks or months, and protracted withdrawal syndrome, also known as "post-acute withdrawal syndrome" or "PAWS" - a low-grade continuation of some of the symptoms of acute withdrawal, typically in a remitting-relapsing pattern, that often results in relapse in to active addiction and prolonged disability of a degree to preclude the possibility of lawful employment - can last for months, years, or, in relatively common to extremely rare cases, depending on individual factors, indefinitely. Protracted withdrawal syndrome is noted to be most often caused by benzodiazepines, but is also present in a majority of cases of alcohol and opioid addiction, especially that of a long-term, high-dose, adolescent-beginning, or chronic-relapsing nature (viz. a second or third addiction after withdrawal from the self-same substance of dependence). Withdrawal response will vary according to the dose used, the type of drug used, the duration of use, the age of the patient, the age of first use, and the individual person.

Symptoms

Physical dependence can manifest itself in the appearance of both physical and psychological symptoms but which are caused by physiological adaptions in the central nervous system and the brain due to chronic exposure to a substance. Symptoms which may be experienced during withdrawal or reduction in dosage include increased heart rate and/or blood pressure, sweating, and tremors. More serious withdrawal symptoms such as confusion, seizures, and visual hallucinations indicate a serious emergency and the need for immediate medical care. Sedative hypnotic drugs such as alcohol, benzodiazepines, and barbiturates are the only commonly available substances that can be fatal in withdrawal due to their propensity to induce withdrawal convulsions. Abrupt withdrawal from other drugs, such as opioids can cause an extremely physiologically and psychologically painful withdrawal that is very rarely fatal in patients of general good health and with medical treatment, but is more often fatal in patients with weakened cardiovascular systems; toxicity is generally caused by the often-extreme increases in heart rate and blood pressure (which can be treated with clonidine), or due to arrhythmia due to electrolyte imbalance caused by the inability to eat, and constant diarrhea and vomiting (which can be treated with loperamide and ondansetron respectively) associated with acute opioid withdrawal, especially in longer-acting substances where the diarrhea and emesis can continue unabated for weeks, although life-threatening complications are extremely rare, and nearly non-existent with proper medical management. Dependence itself and chronic intoxication on psychostimulants can cause

mild-to-moderate neurotoxic effects due to hyperthermia and generation of free radicals.; this is treated with discontinuation; life-threatening complications are nonexistent.

Treatment

Treatment for physical dependence depends upon the drug being withdrawn and often includes administration of another drug, especially for substances that can be dangerous when abruptly discontinued. Physical dependence is usually managed by a slow dose reduction over a period of weeks, months or sometimes longer depending on the drug, dose and the individual. A physical dependence on alcohol is often managed with a cross tolerant drug, such as long acting benzodiazepines to manage the alcohol withdrawal symptoms.

Drugs that cause physical dependence

All μ-opioids with any (even slight) agonist effect, such as (partial list) morphine, heroin, oxycodone, buprenorphine, nalbuphine, methadone, and fentanil, but not agonists specific to non-μ opioid receptors, such as salvinorin A (a k-opioid agonist), nor opioid antagonists or inverse agonists, such as naltrexone (a universal opioid inverse agonist)
All GABA agonists and positive allosteric modulators of both the GABA-A ionotropic receptor and GABA-B metabotropic receptor subunits, of which the following drugs are examples (partial list):
barbiturates such as phenobarbital, sodium thiopental and secobarbital
benzodiazepines such as diazepam (Valium), lorazepam (Ativan), and alprazolam (Xanax) (see benzodiazepine dependence and benzodiazepine withdrawal syndrome)
nonbenzodiazepines (z-drugs) such as zopiclone and zolpidem.
ethyl alcohol (alcoholic beverage) (cf. alcohol dependence, alcohol withdrawal, delirium tremens)
gamma-hydroxybutyric acid (GHB) and 1,4-butanediol
carisoprodol (Soma) and related carbamates (tybamate and meprobamate)
baclofen (Lioresal) and its non-chlorinated analogue phenibut
chloral hydrate
glutethimide
clomethiazole
methaqualone (Quaalude)
gabapentin (Neurontin) and pregabalin (Lyrica), calcium channel modifiers that affect GABA
antiepileptic drugs such as valproate, lamotrigine, tiagabine, vigabatrin, carbamazepine and oxcarbazepine, and topiramate
possibly neuroleptic drugs such as clozapine, risperidone, olanzapine, haloperidol, thioridazine, etc.
commonly prescribed antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (cf. SSRI/SNRI withdrawal syndrome)

Nicotine
blood pressure medications, including beta blockers such as propanolol and alpha-adrenergic agonists such as clonidine
androgenic-anabolic steroids
glucocorticoids

Drugs such as amphetamines (including methylamphetamine and methylenedioxymethylamphetamine (MDMA), cocaine, cathinone, hallucinogens (such as LSD, psilocin, and mescaline), cannabis (tetrahydrocannabinol) do not cause physical dependency/physical addiction, but range from extremely psychologically addictive (cocaine and methylamphetamine) to mildly psychologically addictive (MDMA).

Rebound syndrome

A wide range of drugs whilst not causing a true physical dependence can still cause withdrawal symptoms or rebound effects during dosage reduction or especially abrupt or rapid withdrawal. These can include caffeine, stimulants, steroidal drugs and antiparkinsonian drugs. It is debated if the entire antipsychotic drug class causes true physical dependency, if only a subset do, or if none do, but all, if discontinued too rapidly, cause an acute withdrawal syndrome. Drugs like cocaine, marijuana, amphetamines, and hallucinogens can be associated with minimal physical dependence but can still cause withdrawal or rebound symptoms. However, with sustained and heavy cocaine abuse signs of physiological dependence may occur. When talking about illicit drugs rebound withdrawal is, especially with stimulants, sometimes referred to as "coming down" or "crashing".

Some drugs, like anticonvulsants and antidepressants, describe the drug category and not the mechanism. The individual agents and drug classes in the anticonvulsant drug category act at many different receptors and it is not possible to generalize their potential for physical dependence or incidence or severity of rebound syndrome as a group so need to be looked at individually. Anticonvulsants as a group however are known to cause tolerance to the anti-seizure effect. SSRI drugs, which have an important use as antidepressants, are considered to cause physical dependence, although it is considered mild compared to drugs like opioids and GABA modulators, but they engender a discontinuation syndrome, which was originally called "SSRI withdrawal" until a 1997 symposium sponsored by Pfizer and Eli Lilly (the producers of several anti-depressants including Prozac and Effexor) was held, with the drug representative attendees concluding that "discontinuation syndrome" sounded less threatening than "withdrawal"; however, "SSRI discontinuation syndrome" is a withdrawal syndrome upon discontinuation of SSRI/SNRI drugs, just as "heroin discontinuation syndrome" is a synonym for "heroin withdrawal". Due to this, in Europe these drugs cannot be advertised as "non-habit forming". There have been case reports of dependence with venlafaxine (Effexor).