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Drug deprescription—withdrawal risk, prevention, and treatment

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ABSTRACT

In most cases, a sudden interruption of most medications has no major consequences. There are well-recognized therapies that, when withheld, can either lead to the reappearance of the symptoms they were controlling or to signs or symptoms of withdrawal. In this article, we present a table including medications that when interrupted can produce withdrawal syndromes, the signs and symptoms of the withdrawal syndrome, the time to onset and resolution of the syndrome, information regarding alternative delivery options for the drug/s when the oral route is not possible, as well as prevention and therapy.

KEYWORDS Deprescriptions; patient safety; withdrawal

Generally there are no major consequences following sudden interruption of a medication. However, there are well-recognized therapies that, when withheld, can either lead to the reappearance of the symptoms they were controlling or to signs or symptoms of withdrawal. The interruptions may result from inappropriately reconciling the patient's medication list in every encounter, from considering certain medications redundant or unneeded in the inpatient setting without understanding the consequences of stopping them, or from the inability to use the oral route in the case of oral treatments. When there is uncertainty about deprescribing, pharmacists are integral components in the successful discontinuation of inappropriate medications, especially in elderly patients.[1] They can offer valuable information to both physicians and patients.

Symptoms of withdrawal should be distinguished from reappearance of disease symptoms that may reemerge in absence of the treatment. True withdrawal appears when the drug dose reduction is sudden rather than gradual, symptoms are more severe than what they were at baseline, or they appear in newborn infants whose mothers have been taking the drug.[2]

Table 1 summarizes medications that when interrupted can produce withdrawal syndromes. The table describes the signs and symptoms of the withdrawal syndrome, the time to onset and resolution of the syndrome, information regarding alternative delivery options when the oral route is not possible, and prevention and therapy.

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Table 1. Withdrawal syndromes associated with commonly prescribed medications

Drug	Withdrawal effects	Onset/resolution	Alternative delivery options	Prevention/intervention
Opioids[3–13]	• Anxiety, irritability, agitation • Diaphoresis, shaking, chills • Lacrimation, rhinorrhea • Anorexia, nausea, vomiting • Cramping • Mydriasis • Tachycardia, hypertension • Increased pain • Drug craving	• 6–12 hours following short-acting opioid cessation • 24–48 hours following long-acting opioid cessation • Acute withdrawal may last days to weeks • Dependent on the half-life of the drug used	Intravenous transdermal	• Long-acting opioid taper by 10% weekly or monthly • Methadone maintenance and/or detoxification taper • Buprenorphine maintenance and/or detoxification taper • Adjuvant therapies to mitigate withdrawal effects: clonidine, gabapentin, topiramate, venlafaxine, buspirone, quetiapine, benzodiazepines (controversial)
Benzodiazepines[14–17]	• Risk is higher for short-acting benzodiazepines • Somatic effects: fatigue, weakness, muscular tension, spasm, pain, sweating, shivering, tremor, tachycardia, hypertension, loss of appetite, seizures • Psychological effects: anxiety, agitation, restlessness, depression, emotional lability, difficulties concentrating, delirium, paranoia, hallucinations, derealization, insomnia • Sensory effects: hyperacusis, photophobia, dysesthesia, tinnitus, blurred vision	• 2–3 days following short-acting benzodiazepine cessation • 5–10 days following long-acting benzodiazepine cessation • Onset may vary depending on duration and dosages utilized • Withdrawal may last 10–14 days	Intravenous	• Restart benzodiazepines to stop acute withdrawal • Initiate taper: either weekly dosage reductions of 50% or reduction of daily doses by 10% to 25% every 1 to 2 weeks • Individualize the taper on patient tolerance of reduction • 4–8 weeks is generally sufficient to complete a safe discontinuation • Outpatient reduction is usually acceptable; consider inpatient discontinuation when very high doses are needed
Barbiturates[2,18,19]	• Physical/autonomic effects: weakness, sweating, nausea, vomiting, malaise, headache, dry mouth, fever • Psychological effects: insomnia, apprehension, anxiety, irritability, depression, visual hallucinations, delirium • Neurological effects: tremor, myoclonus, spasms, seizures • Severe withdrawal: repetitive grand mal seizures and delirium, death	• Within 24 hours depending on dosage and length of use • 24–115 hours generally • Neurological effects start within 24–72 hours • Hallucinations and delirium arise around 72 hours • Fever onset generally at 36–72 hours, lasting 3–4 days	Intravenous (in status epilepticus)	• Restart phenobarbital to stabilize patient followed by a gradual taper • Reductions of 30 mg/day are considered conservative • 10-day taper has also shown good success • Benzodiazepines may help mitigate symptoms • May require a minimum of 3 days inpatient for monitoring
Baclofen[20–23]	• Psychosis, visual and auditory hallucinations • Mood disturbances, agitation • Insomnia • Confusion, delirium • Tachycardia, diaphoresis • Spasms leading to rhabdomyolysis • Seizures/status epilepticus • Intrathecal baclofen withdrawal—can be fatal	• 12–24 hours after last dose • May take days to develop • Improvement shortly following reinitiation of baclofen	Nasogastric tube delivery of a liquid formulation or crushed tablets (in absence of ileus)	• Planned discontinuation: taper 5-10 mg per week as tolerated • Acute withdrawal: restart baclofen • Supportive care • Adjuvant therapies: antipyretics, benzodiazepines, anticonvulsants, dantrolene, antispasmodics, antipsychotics
Clonidine[2,24–27]	• Tachycardia • Agitation/restlessness/irritability • Insomnia	• May develop within 24 hours after discontinuation	Transdermal	• Labetalol (IV) to mitigate withdrawal effects in the short term

	• Tremors • Rebound hypertension, sometimes with hypertensive emergency—encephalopathy, retinal and intracranial hemorrhage, acute renal failure, flash pulmonary edema, myocardial infarction	• On average, 18–36 hours after last dose		• Clonidine taper: no clear guidelines, gradual (may require a protracted course) • Phentolamine + propranolol • Atenolol + prazosin • Benzodiazepines to reduce symptoms
Beta-blockers[28–34]	• Tachycardia: sinus tachycardia, supra or ventricular tachycardia • Nervousness, anxiety, agitation • Headache • Sweatiness • Tremor • Nausea • Hypertensive crisis • Severe complications: angina, myocardial infarction, sudden death	• Minor side effects may develop within 24 hours • Generally, develops within 3 days • Some are delayed to days 14–21	Intravenous (most beta-blockers have short half-lives when administered intravenously; infusions are sometimes necessary)	• In acute withdrawal, reinitiate beta-blockers • Taper regimen: reduce daily dose by 50% per week until at lowest dose • Maintain lowest dose for 1 week prior to discontinuation
Corticosteroids[2,35–38]	• Severe fatigue, malaise • Hypotension • Tachycardia • Myalgia, arthralgia • Dizziness • Mood swings, depression • Loss of appetite, nausea, vomiting • Diarrhea • Severe withdrawal: fever, shock, and death	• Shortly after prolonged steroid use (variable definition, but no less than 4–6 weeks) • Hypothalamic-pituitary-adrenal suppression may last weeks to months to a year	Intravenous (commonly used as “stress dose” in patients chronically treated with steroids requiring surgery or facing sepsis)	• Restart steroid with taper if recently inappropriately discontinued and having symptoms • Taper steroid prior to cessation to allow for adrenal function to return to normal • Doses should be reduced by an estimated 10%–20% every 1–2 weeks
Psychostimulants[2,39–41]	• Drug seeking • “Crash” • Lethargy • Irritability, aggressiveness, anxiety • Difficulties concentrating • Anhedonia, depression • Suicidal ideation • Insomnia or hypersomnia	• Start within 24 hours of the last dose • More severe shortly after discontinuation • Symptoms generally last ~2 weeks but may persist 3–4 weeks • Usually self-limited	None	• Self-limiting • Tapering not effective • Antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors), electroconvulsive therapy, dopamine agonists, and anxiolytics helpful for symptom control
Gabapentin[42–44]	• Anxiety • Restlessness • Irritability • Tachycardia • Catatonia • Seizure	• 24–72 hours after abrupt complete cessation • Resolves 24–48 hours after reinstitution of drug	None	• Reinitiate gabapentin during acute withdrawal • No clear tapering regimen • Possible regimen: taper doses by 10%-15% weekly
Pregabalin[45–47]	• Diaphoresis, tachycardia, hypertension • Diarrhea • Tremor, increased spasticity • Auditory hallucinations, self-mutilation, suicidality • Delirium, confusion	• Unusual if the drug is tapered over a week	None	• Taper the drug for at least a week
Dopamine agonists[48–50]	• Psychiatric effects: anxiety, panic attacks, depression, suicidal ideation, agitation, irritability, confusion • Autonomic/GI effects: fatigue, nausea, vomiting, orthostatic hypotension, diaphoresis, flushing • Sensory effects: diffuse pain, restless legs	• May occur immediately following first dose reduction • May last days to weeks • Only 50% fully recover	None. There is an intranasal form of levodopa, but no studies supporting beneficial use in dopamine-agonist withdrawal syndrome.	• Tapers are still generally recommended in attempt for prevention, but are not always beneficial • The only known treatment is to restart the dopamine agonist at the last known dose prior to the onset of withdrawal symptoms

(*Continued on next page*)

Table 1. Continued

Drug	Withdrawal effects	Onset/resolution	Alternative delivery options	Prevention/intervention
Antidepressants[51–55]	• Flu-like symptoms: headache, body aches, lethargy, fatigue • Sleep disturbance: insomnia, nightmares, vivid dreams • Sensory disturbance: tingling, paresthesia, burning, "electric shocks" • Psychologic disturbance: labile affect, anxiety, restlessness, mania, cognitive impairment • GI disturbance: nausea, loose stools, dry mouth • Equilibrium disturbance: ataxia, vertigo, lightheadedness, dizziness	• 2–4 days; may start as early as hours after first missed dose • May persist 1–2 weeks if not restarted on antidepressant or tapered • 4–9 months of effective therapy should be completed before elective discontinuation • Less common for fluoxetine due to its long half-life	None. In Europe, tianeptine (a tricyclic intravenous antidepressant) is available, but not tested for withdrawal	• Tapers vary based on class and specific drug • Based on expert opinion • Formulations vary between brand and generic drugs and should be taken into consideration when tapering • Fluoxetine is a known exception and generally does not require taper

GI indicates gastrointestinal.

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