

Post-Acute Withdrawal Syndrome: The Major Cause of Relapse among Psychoactive Substances Addicted Users

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Abstract

The aim was to summarize post-acute withdrawal syndrome (PAWS) for the most common psychoactive substances, including alcohol, benzodiazepines, opioids, stimulants, and cannabis. A narrative review of relevant literature was identified through existing meta-analyses, systematic reviews, Google Scholar searches, and authoritative grey literature. PAWS associated with alcohol, benzodiazepines, opioids, stimulants, cannabis, and management and maintaining abstinence are discussed. PAWS is a relatively less known phenomenon of dependence and withdrawal; however, its severity and duration impact patients' capacity to stop using abused/addictive substances. PAWS may cause very slowly reversible or permanent physicochemical neuronal damage in the central nervous system (CNS). Managing PAWS symptoms are significant for preventing relapse during the first 12 months after cessation of abused/addictive substances, where the risk of relapse is highest. The longer abstinence is maintained, the lower the risk of relapse becomes. This review covers a knowledge gap in information that is generally not easily available and is almost non-existent in the literature.

Keywords: Withdrawal, PAWS, Psychoactive substance, Relapse

INTRODUCTION

Patients addicted to psychoactive substances experience what are called withdrawal effects after the abrupt discontinuation or rapid reduction of the abused/addictive substances. Withdrawal effects involve a variety of physical, mental, and emotional signs and symptoms, some of which are serious, potentially life-threatening, or fatal if not addressed properly [1-3]. Healthcare professionals usually work with addicts to mitigate these withdrawal symptoms. Healthcare professionals must detect and deal with withdrawal symptoms early and effectively since they might lead to serious safety risks, such as relapse or death. Withdrawal symptoms occur within the central nervous system (CNS) after cessation or decreased use of active substances including, alcohol, opiates, antipsychotics, antidepressants, benzodiazepines, Z-Drugs (Zolpidem, Zaleplon, and Eszopiclone), barbiturates, ketamine, cannabis, anabolic steroids, stimulants (amphetamine, cocaine, and methamphetamine), caffeine, and tobacco [2, 4-9].

The definition of withdrawal, as reported by the American Society of Addiction Medicine (ASAM), is '*The onset of a predictable constellation of signs and symptoms following the abrupt discontinuation of, or rapid reduction in, the dose of a psychoactive substance*' [10]. Not every addicted patient will experience all possible withdrawal symptoms. The severity and persistence of withdrawal symptoms are dependent on the nature of the abused/addictive substances, physical health of the addicted person, gender, age, and duration of addiction [7, 8, 11-20]. There are different

withdrawal-related phenomena, as described in Chouinard and Chouinard, 2015, including new withdrawal symptoms, rebound, protracted withdrawal syndrome, relapse, and recurrence [7].

The first withdrawal-related phenomenon is new withdrawal symptoms, also called acute withdrawal symptoms. These new symptoms are extreme physical withdrawal symptoms that appear immediately after the cessation of abused/addictive substances or, in some cases, even after a dosage reduction. They are reversible with complete recovery, transient, and typically last 1–8 weeks depending on abused/addictive substance elimination half-life [2, 21-23].

The second withdrawal-related phenomenon is a rebound, in which patients experience recurrence of signs and symptoms

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of the treated disorder that are more severe than before therapy. Rebound symptoms are also transient, short-lasting, and reversible with complete recovery [21-24]. However, relapse phenomenon is when patients experience returns of signs and symptoms of the original disorder after a remission due to natural causes or cessation of therapy, while recurrence phenomenon is when patients experience a new episode of the original disorder [7, 8, 23, 25].

Another withdrawal phenomenon is called post-acute withdrawal syndrome (PAWS), which has also been termed as protracted withdrawal syndrome, protracted abstinence syndrome, persistent/chronic withdrawal, persistent post-withdrawal disorder, prolonged withdrawal syndrome, extended withdrawal, late withdrawal, long-term withdrawal, post-use syndrome, sobriety-based symptoms, and subacute withdrawal syndrome [8, 23, 26]. Published evidence on PAWS is sparse. In this article, we present a brief condensed review of PAWS for the most common substances of abuse and addiction; this fills a gap in knowledge of information usually not readily available and is hardly existent in the literature. This review is not pre-registered on a publicly available platform and thus the results should be considered exploratory.

PAWS is a relatively less known withdrawal phenomenon. It was described by Gorski and Miller, 1986 as a biopsychosocial syndrome that is caused by CNS damage due to substance dependence and the psychosocial stress of coping with life without the use of abused/addictive substances [27]. PAWS makes staying sober and clean a seriously challenging part of the recovery process. The symptoms of PAWS might become a major risk factor for relapse because of their negative repercussions on physical, spiritual, emotional, and mental well-being [7, 8, 25-29]. Around 90% of recovering opioid addicts experience some level of PAWS, which also affects around 75% of recovering alcoholics and psychotropic abusers [30].

The peak onset of PAWS symptoms is within 4–6 weeks or later after cessation of a substance depending on the abused/addictive substances and the duration of abuse. The most distinguishing characteristic of PAWS is its duration. The PAWS symptoms refer to a set of impairments that can last much longer than during the acute withdrawal phase, from 6 months up to 2 years, and sometimes irreversible as a newly emerging disorder depending on abused/addictive substances elimination half-life. Unfortunately, there is no well-defined timeframe for the duration of PAWS. Typically, the process of brain recalibration after neuroadaptations in neurotransmitter systems and brain regions might take anywhere from 6 months to 2 years before the brain generates endorphins and dopamine normally again [8, 23, 26, 29-32].

PAWS is a multifaceted syndrome without a specific cause. The exact factors that cause PAWS symptoms are still being studied; however, these symptoms are frequently triggered by stress or events involving people, places, or things that

remind the addict of using the abused/addictive substances [29, 30]. Moreover, there are some theories about the possible causes of PAWS, including the neuroadaptations in neurotransmitter systems and brain regions resulting in physicochemical neuronal damage, nutritional deficiencies, stress, habit, and undiagnosed mental disorders that all occurred during addiction, that may negatively affect the body's ability to function properly and normally [20, 25, 31, 33-35].

Fewer physical symptoms but more extensive psychological and emotional withdrawal symptoms occur during the beginning phase of PAWS than in the acute withdrawal phase [8, 23, 26]. The PAWS symptoms can feel like waves or have "up and down" rollercoaster effects, which appear and disappear unexpectedly. These PAWS waves may strike at any time and without previous warning. With time, the waves become less frequent with much longer positive intervals in between as addicts progress toward long-term recovery [20, 29].

Not every patient in recovery experiences PAWS; some patients experience no symptoms after the acute withdrawal phase, whereas others have persistent symptoms [26]. The time of onset, severity, and persistence of the withdrawal symptoms involved in PAWS vary, fluctuate and are dependent on the type of abused/addictive substances, pharmacokinetic variables, dose and route of administration, physical size and health of the addicted person, gender, age, duration of active addiction, and the use of concomitant treatments [7, 8, 11-20, 36, 37].

PAWS symptoms are divided into six different symptom clusters: absentmindedness, difficulty thinking, restless sleep, difficulty regulating emotions, decreased physical coordination, and stress sensitivity [27]. The most common PAWS symptoms include cognitive impairment, sexual impairment, gastrointestinal disturbances, headache, anxiety, panic, mood swings, depression, psychosis, stress sensitivity, irritability, chronic pain, fatigue, urges/cravings, sleep disturbances/insomnia, issues with fine sensory and motor coordination, and lack of initiative [23, 29].

Although many of the symptoms of PAWS are similar to those of depression, PAWS symptoms are predicted to improve over time [27]. Unlike the acute withdrawal phase, which has specific symptoms for each addiction, PAWS symptoms tend to be comparable across different abused substances but not identical. Each class of psychoactive substance has distinct effects on the brain [26, 27]. There are some classes of substances that are more commonly associated with PAWS symptoms than others. Though many are described below, the following list of substances is not exhaustive. There also may be other substances that are associated with PAWS symptoms but have not yet been recognized [26, 38].

Alcohol PAWS

Alcohol is a CNS depressant. It acts by enhancing the effect of γ -aminobutyric acid (GABA) on γ -aminobutyric acid A (GABAA) neuroreceptors, resulting in neurochemical imbalance by decreasing overall brain excitatory neurotransmitters, glutamate. Glutamate acts through the N-methyl-D-aspartate (NMDA) neuroreceptor, which is inhibited by alcohol consumption. Chronic alcohol consumption causes a compensatory reduction of GABAA neuroreceptor sensitivity to GABA and up-regulation of NMDA neuroreceptors [6, 39].

Alcohol is lipid-soluble and highly concentrated in the brain, so sudden cessation of long alcohol consumption causes brain hyperexcitability because neuroreceptors, which are previously inhibited by alcohol, are no longer inhibited. Brain hyperexcitability clinically manifests as anxiety, agitation, irritability, and tremors. Severe brain hyperexcitability can induce delirium tremens (seizures and psychosis), increase the risk of PAWS, and can be potentially fatal [6, 20, 40].

PAWS symptoms associated with alcohol use disorder were first defined in the 1990s, even though people have been struggling with alcohol addiction for much longer [20]. PAWS symptoms peak around 4–8 weeks from cessation and last from a few weeks up to 2 years depending on the intensity of the alcohol consumption [26, 41]. PAWS symptoms occur in cyclical waves. Recovering alcoholics may feel good one day and the next they are tormented by poor energy and severe alcohol cravings. These unpredictable withdrawal cyclical waves may make it difficult to resist relapse. Typically, each PAWS cyclical wave lasts only a few days at a time. If a recovering alcoholic can maintain his/her abstinence and sobriety throughout that time, the symptoms will typically disappear quickly [41].

Common PAWS symptoms associated with alcohol use disorder include anxiety, protracted insomnia, sleep disturbances, cognitive impairment, severe cravings, chronic nausea, dizziness, irritability and emotional outbursts, low energy, increased accident proneness, and delayed reflexes [26, 39, 41, 42]. Tapering alcohol consumption can be helpful for long-term users in reducing the intensity of acute withdrawal, but not the probability of PAWS, and in regulating the body's reactions during recovery [38].

Benzodiazepines PAWS

According to the U.S. Drug Enforcement Administration (DEA), benzodiazepines (BZDs) are classified as Schedule IV controlled substances, including alprazolam, clonazepam, temazepam, lorazepam, and diazepam [37]. BZDs are approved by the U.S. Food and Drug Administration (FDA) to treat insomnia, generalized anxiety disorder, seizure disorders, muscle tensions, social phobia, and panic disorder. Like alcohol, BZDs act by enhancing the function of the GABAA receptor, the main inhibitory neurotransmitter in the CNS [43-45]. The long-term use of BZDs could result in physicochemical neuronal changes, such as cortical atrophy,

which may be permanent or only very slowly reversible. This is because BZDs, like alcohol, are lipid-soluble, highly concentrated in the brain, and disrupt the function of the cerebral cortical, cerebellar, and limbic systems [44].

People recovering from abusing BZDs appear to experience PAWS more often and for longer periods than other people recovering from abusing other substances [46]. About 40% of people who have been using BZDs for more than six months may experience moderate to severe withdrawal syndrome, whereas the remaining 60% will experience a very mild withdrawal syndrome [45]. The exact mechanism of BZDs withdrawal symptoms is still mostly unknown; however, there is some evidence indicating down-regulation of BZDs binding sites in the GABAA complex, sudden reduction of dopamine, and increased calcium flow and serotonin activity during withdrawal [43, 45].

According to the DEA classification, BZDs have a low potential for abuse and a low risk of dependence and withdrawal. However, there is evidence to refute this classification [45]. Physical dependence and withdrawal symptoms are very prevalent with BZDs and may begin in just a few weeks, even while strictly adhering to therapeutic doses and directions. BZDs users tend to be the most at-risk of PAWS among other substances users [30, 45]. It has been estimated that 10–25% of chronic BZDs users experience symptoms of PAWS for years after cessation [36, 45]. Because of the similarities to alcohol in the body's reactions to BZDs, tapering BZDs consumption is not an effective strategy for preventing PAWS [38].

PAWS symptoms associated with BZD withdrawal are many and variable, including anxiety, depression, protracted insomnia, fatigue, panic and psychotic reactions, cognitive impairment, formication, hyperventilation, cravings, motor phenomena (i.e., weakness, jerks, spasms, muscle pain, tremor, shaking attacks, painful cramps), sensory phenomena (i.e., tinnitus, paresthesia, tingling, deep or burning pain in limbs, numbness, strange skin sensations, feeling of inner trembling or vibration), and gastrointestinal symptoms (food intolerance and flatulence) [26, 36, 42, 46, 47].

Some of the symptoms of PAWS associated with BZDs mimic anxiety and panic disorders, making it difficult for patients who have taken BZDs for anxiety and panic disorders to quit taking them [26, 45, 48]. Typically, the symptoms of PAWS begin 4–6 weeks after medication cessation and last 6–12 months; however, some symptoms, such as anxiety, insomnia, fatigue, and cravings, may continue up to two years [36].

Opioids PAWS

Opioids refer to a broad class of drugs including heroin, hydrocodone, oxycodone, oxymorphone, morphine, fentanyl, and codeine that interact with opioid receptors on nerve cells in the brain and nervous system to produce pain relief, euphoria, and reduction of emotional distress [37, 49].

According to the U.S. DEA, opioids are classified into five distinct schedules depending on the potential for abuse or dependency, of which Schedule I represents the highest potential for abuse and is not legal, and Schedule V represents the least potential for abuse [37].

Opioids are the most harmful substance worldwide, with an estimated death rate increasing by 71 percent [50]. Chronic opioid consumption causes neuroadaptations in neurotransmitter systems (dopamine and glutamate) and brain areas (the ventral tegmental area and the prefrontal cortex), all of which are implicated in the manifestation of the opioid withdrawal syndrome's unpleasant consequences [51, 52].

PAWS symptoms associated with opioid withdrawal are more likely to occur in people who experience the full intensity of acute withdrawal symptoms [20]. PAWS symptoms for opioid abuse include anxiety, fatigue, insomnia, sleep disturbances, opioid cravings, memory problems, depression, inability to think, dysphoria, irritability, palpitations, nausea, stomach cramps, periodic diarrhea, and hypomania [8, 26, 52]. In some cases, symptoms such as fatigue, insomnia, and anxiety can last from weeks up to 6–9 months following withdrawal from opioids [8]. It has been reported that PAWS symptoms for morphine users generally began between 6–9 weeks following the acute withdrawal phase and persist until 26–30 weeks. PAWS symptoms associate with morphine use include hypotension, bradycardia, hypothermia, miosis, and hyposensitivity of the respiratory center to carbon dioxide [53]. People in recovery from heroin addiction have impairments in executive control functions that can last for months after the acute withdrawal episode has passed [52].

Stimulants PAWS

Psychostimulants, including cocaine, amphetamines, and methamphetamines, are a class of substances that exert their action through excitation of the CNS to enhance mental alertness, concentration, and energy with positive mood properties, euphoria, and arousal attitude as well as reduction of drowsiness and fatigue [37, 54]. Among the illicit psychostimulants, cocaine and amphetamines are the most commonly abused substances [37]. It has been reported that the percentage of people who abuse or are addicted to psychostimulants is greater than those who are abused or are addicted to opioids in the USA [55]. The hallmark of cocaine addiction and the critical concern in its treatment is the high rate of relapse after recovery [56].

In general, the mechanism of action of psychostimulants is to increase the activity of the neurotransmitters, such as dopamine, adrenaline, noradrenaline, and serotonin. Although amphetamines and methamphetamines act to increase the release of monoamines, cocaine inhibits monoamine reuptake and blocks sodium channel activity. [54, 57]. Chronic psychostimulant consumption causes

neuroadaptations in neurons that release the excitatory neurotransmitter glutamate [56, 58].

Psychostimulant substances provide some of the most compelling evidence that PAWS is a real medical disorder that may last for weeks to months, and not just an extension of acute withdrawal. Animal and human research has proven that the amphetamine and methamphetamine withdrawal syndrome may be persistent and tend to be more severe than cocaine withdrawal [31, 59, 60].

It has been reported that emotion regulation difficulties and impulse control disorders are the most common symptoms of PAWS associated with cocaine withdrawal and may last up to 4 weeks after sobriety [61]. On the other hand, long-term issues with executive control function were reported as symptoms of PAWS associated with methamphetamines withdrawal [31, 62].

Other psychological symptoms of PAWS associated with psychostimulants withdrawal include fluctuations in mood and energy levels, paranoia, extreme fatigue, agitation, anxiety, irritability, restlessness, major depression/dysphoria, lacking energy and anhedonia, cravings, and disturbed sleep [20, 26, 31, 42, 54]. These PAWS symptoms, like those induced by other addictive substances, are caused by neuroadaptations in neurotransmitter systems to long-term psychostimulants use, and they can take months or even years to overcome [54].

Cannabis PAWS

Cannabis (marijuana) is the most widely used illegal psychoactive substance worldwide [9, 50, 63]. According to the DEA classification, cannabis is classified as a Schedule I drug, which has the highest potential for abuse and is not legal to use except for medical purposes in some states [37]. Cannabis is a psychoactive substance, and its primary psychoactive component is δ -9-tetrahydrocannabinol (THC). THC acts on the endocannabinoid system in the brain and other body tissues by binding to two distinct kinds of cannabinoid (CB) receptors on cell membranes (cannabinoid 1 (CB1) receptor and cannabinoid 2 (CB2) receptor) and inhibiting neurotransmission in acetylcholine, GABA, and glutamatergic pathways [63-65]. Chronic cannabis consumption is linked to CB1 receptor function desensitization and down-regulation in the brain [64, 66].

Although cannabis is infrequently psychologically addictive, chronic cannabis consumption may cause withdrawal symptoms after cessation [67-71]. The withdrawal was experienced by those using cannabis less than daily. There is reliable scientific evidence that cannabis withdrawal symptoms happen in ~90% of the people diagnosed with cannabis dependence [68, 69] and those who used cannabis less than daily [72]. Cannabis withdrawal does not usually cause major medical or psychological disorders, as it does in some alcohol, opiate, or benzodiazepine withdrawals [69]. It

is not life-threatening but may lead to relapse in someone who truly wants or needs to quit, and this is a legitimate focus of management efforts. Cannabis-recovered users have relapse rates that are comparable to other substances of addiction [63, 73-76].

It has been reported that the severity of withdrawal is positively correlated to the intensity of cannabis consumption before the abrupt cessation [67, 68, 72]. Cannabis withdrawal symptoms might last anywhere from 1.5 weeks to over a year [72]. Sleep disturbance with vivid nightmares may last up to 45 days or more as well as other common symptoms of PAWS associated with cannabis withdrawal such as aggression, weight loss, irritability, nervousness, anxiety, depression, and restlessness [16, 26, 66-68, 70, 71].

PAWS Management and Maintaining Abstinence

Although it is clinically challenging to avoid PAWS because of its unpredictable and fluctuating symptoms, these symptoms can be efficiently managed with professional oversight and medical interventions [29]. Initial and rapid reduction of PAWS symptoms helps recovered patients resist an early relapse [77]. According to American Addiction Centers, managing PAWS symptoms is crucial for preventing relapse where the risk of relapse is highest in the first 12 months after cessation. The longer abstinence is maintained, the lower the risk of relapse becomes [3].

The duration of PAWS symptoms management may vary from months to years [36, 78]. Outpatient management is suitable for patients with mild to moderate PAWS who have no significant concomitant psychiatric and medical disorders and have a support person willing to monitor their progress carefully. On the other hand, inpatient management is a demand for patients with severe complications [42, 79].

An evidence-based post-withdrawal plan with access to resources such as psychological supports and/or pharmacotherapies would be effectively helpful in managing the symptoms of PAWS and maintaining abstinence [26, 30]. Psychological supports, such as support groups, motivational enhancement, counseling, cognitive-behavioral therapy (CBT), and mutual aid may be needed to minimize withdrawal distress, which mitigates the likelihood of patient abstinence and treatment compliance [36, 42, 51, 73, 74, 78-80].

Patients can often achieve abstinence without the need for pharmacotherapies; however, the threshold for the pharmacotherapies varies among abused/addictive substances. Pharmacotherapies often involve substituting a long-acting medication for the abused/addictive substance, then progressively tapering its dosage. Appropriate substitute outpatient medications must be administered orally, have a low potential for abuse and overdose, and have a low incidence of side effects [42].

It has been reported that citalopram significantly reduces the severity of PAWS symptoms in patients with heroin addiction. It shows a reduction of heroin craving symptoms and anxiety during the first and second week of the treatment [77]. In addition, naltrexone helps to reduce cravings in patients with opioid addiction [20]. Acamprosate and naltrexone have also been found to be effective in managing some PAWS symptoms in recovered alcoholics [20, 30, 40, 81]. Previous studies showed flumazenil might be useful in decreasing feelings of hostility and aggression in patients with PAWS symptoms associated with BZD withdrawal [45, 82]. In 2001, Lader found that treatment with flumazenil was more effective than tapering or placebo [47]. Moreover, it is suggested that antidepressants and non-addictive SSRIs may help stabilize mood for patients with psychostimulants or other psychoactive substances addiction [20]. Generally, buspirone is recommended to help people with severe anxiety symptoms, and it is the only medication that has been demonstrated to be effective in a controlled clinical trial for controlling cannabis withdrawal symptoms [63].

Furthermore, there are some effective coping strategies for PAWS and maintaining abstinence, such as practicing trigger preventions, developing a supportive social circle away from drug users, and maintaining a balanced diet to overcome nutritional deficiencies, as well as daily physical activity, meditation, and sufficient sleep to improve body and mental well-being, self-care to handle the PAWS waves when they arise, positive stress and craving management, and remember that the symptoms of PAWS are temporary and better days are ahead [26, 38].

CONCLUSION

The evidence concerning PAWS of psychoactive substances is sparse in comparison to that available for acute withdrawal symptoms. This review covers a knowledge gap in information that is generally not easily available and is almost non-existent in the literature. PAWS has similar symptoms for each addiction, but not identical; however, its severity and duration impact patients' capacity to stop using abused/addictive substances. Managing PAWS symptoms are substantial for avoiding relapse during the first year after cessation of abused/addictive substances, where the risk of relapse is highest. The longer abstinence is maintained, the lower the risk of relapse becomes.

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