Neurobiology and Symptomatology of Post-Acute Alcohol Withdrawal: A Mixed-Studies Systematic Review

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ABSTRACT. Objective: This study aims to review the neurobiology and symptomatology of post-acute alcohol withdrawal syndrome (PAWS). **Method:** We conducted a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)-guided systematic review of articles from two databases for English-language randomized and nonrandomized studies involving PAWS published between database inception and December 2020. **Results:** Twenty-seven studies met inclusion criteria. PAWS involves predominantly negative affect, which develops in early abstinence and can persist for 4–6 months or longer. Symptoms include anxiety, dysphoria, anhedonia, sleep disturbance, cognitive impairment, cravings, and irritability. PAWS symptoms appear to be risk factors for recurrent alcohol consumption. They have been associated with reported neurobiological differences in evoked potentials; measures of orexins, cortisol, serotonin, and pancreatic polypeptides; and neuroadaptation changes in the nucleus accumbens and the prefrontal cortex. **Conclusions:** There is credible evidence to support the concept of PAWS based on this review's findings. There remains a need to develop and test specific criteria for PAWS. High-quality treatment studies involving agents addressing its neurobiological underpinnings are also recommended. (*J. Stud. Alcohol Drugs, 83,* 461–469, 2022)

ACCORDING TO THE *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; American Psychiatric Association [APA], 2013), alcohol withdrawal syndrome (AWS) involves the development of two or more of the following symptoms developing within hours to a few days of cessation of or reduction of heavy alcohol use: autonomic hyperactivity (sweating, fast pulse), increased hand tremor, insomnia, nausea and vomiting, transient hallucination or illusions, psychomotor agitation, anxiety, and grand mal seizures (APA, 2013).

Although acute AWS symptoms usually last for only a few days up to a week, some symptoms can persist, including anxiety, depression, irritability, cognitive dysfunction, cravings for alcohol, sleep disturbance, fatigue, and autonomic irregularities (Bokhan et al., 2003; De Soto et al., 1985; Stojek et al., 1990; Vik et al., 2004; Voltaire-Carlsson et al., 1996; Watanabe et al., 2001). These symptoms—termed post-acute alcohol withdrawal syndrome (PAWS)—were first described more than six decades ago (Satel et al., 1993). In 1954, Wellman described "late withdrawal symptoms" in abstinent alcoholic-dependent persons, which consisted of irritability, depression, insomnia, fatigue, restlessness, and distractibility, constituting a physical syndrome most severe during the first 6 months of abstinence (Wellman, 1954). Building on Wellman's findings, Segal and colleagues (1970) were the first to coin the term *protracted withdrawal syndrome* in 1960, describing neurovegetative and emotional instability symptoms persisting long after acute withdrawal had subsided. Following Segal et al., Kissin (1979) described several protracted alcohol abstinence syndrome cases in 1979.

However, PAWS has been a relatively neglected topic (De Soto et al., 1985). Few recent scientific studies support its existence; consequently, the notion of PAWS remains highly controversial (Satel et al., 1993). Although it has not yet gained formal recognition by the DSM (APA, 2013) or the International Classification of Disease (ICD; Hughes, 1994), PAWS has been informally recognized as a high-risk interval for return to alcohol consumption following abstinence (Melemis, 2015). There remains a need for further research regarding the post-acute withdrawal abstinent period (Williams & McBride, 1998). The lack of a shared definition may be why PAWS has not been more widely adopted. Although several studies have described PAWS symptoms, there is a need to develop a consensus definition, distinguishing PAWS from acute withdrawal or subjective patient experiences. There is no empirical basis for differentiating protracted withdrawal symptoms from PAWS from other conditions. It remains unclear if PAWS symptoms represent an underlying untreated mood, anxiety, or cognitive disorder.

Consequently, the goal of this article was to summarize the extant literature examining the neurobiology and symptomatology of PAWS, paralleling findings from a complimentary review focusing on PAWS treatment.

Method

Protocol and registration

We registered our study protocol with the PROSPERO database of systematic reviews (CRD42020208946) (National Institute for Health Research, 2019). In addition, we

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followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Liberati et al., 2009).

Definition of post-acute withdrawal

Although there are no consensus definitions of PAWS in the extant literature, the American Society of Addiction Medicine (ASAM) 2020 clinical practice guidelines describe "protracted alcohol withdrawal" as subacute symptoms of irritability, anxiety, and sleep disturbance that persist beyond 30 days from the start of acute withdrawal (ASAM, 2020). However, as this definition is relatively recent and inconsistent with the timelines of the symptoms considered by most articles that pertain to protracted withdrawal, we applied a more liberal definition, including any study that evaluated symptoms persisting beyond the acute withdrawal phase and without restriction to a particular cluster of symptoms.

Search strategy

We searched PubMed and MEDLINE for relevant articles from database inception through December 27, 2021, using relevant keyword searches and medical subject headings (MeSH), respectively, using search syntaxes related to the term *post-acute withdrawal* (Appendix 1). (A supplemental appendix appears as an online-only addendum to this article on the journal's website.)

Eligibility criteria

We restricted eligibility to human adult populations (ages ≥18), examining any descriptive component of PAWS. In addition, we restricted eligibility to English-language articles or those with an available English-language translation. We considered randomized controlled trials and nonrandomized intervention studies (e.g., pre-post studies). We excluded commentaries, reviews, editorials, and case reports; we did not restrict the study's data or location. We also excluded treatment studies, as these were the focus of a parallel review.

Study selection

We reviewed studies for eligibility using Covidence, a web-based systematic review manager, and Zotero citation manager (Roy Rosenzweig Center for History and New Media, 2018; Veritas Health Innovation, 2019). After removing duplicates, one investigator (A.B.) independently selected the studies, reviewed the main reports and supplementary materials, and extracted the relevant information from the included studies; a second author (N.E.) reviewed excluded studies for erroneous selection. Any discrepancies were resolved by consensus.

Data collection process and data items

One reviewer (A.B.) extracted the following data from included studies while the other two (D.C. and N.E.) confirmed the extracted data for accuracy. Where necessary, we contacted corresponding authors to secure data. We used a standardized tool to extract information about authors, study objectives, sample characteristics, inclusion/exclusion criteria, study design, and outcome variables in Covidence, which we transferred to a Microsoft Excel spreadsheet (Veritas Health Innovation, 2019).

Summary measures

Although there was insufficient homogeneity to enable meta-analysis, we summarized findings across studies by describing their population, intervention, comparison, outcome, and design features as per previous descriptive reviews in addiction medicine (Bahji, 2019; Bahji & Bajaj, 2018, 2019; Bahji et al., 2021).

Results

Study selection

We screened 3,024 studies, from which 2,008 were unique citations and 1,016 were duplicate citations. From these, we excluded 1,416 records during the title and abstract screening phase, leaving 592 full-text articles for review. Subsequently, 27 observational studies met the inclusion criteria (Figure 1). We did not find any additional articles by reviewing reference lists from the articles we identified.

Study findings

Our review's 27 studies encompassed PAWS symptomatology, neurobiology, and endocrinology.

Symptomatology

We stratified our results by symptom classifications, including mood and anxiety, anhedonia, cognitive impairment, cravings, trauma symptoms, and sleep (summarized in Table 1).

Mood and anxiety. In the 1980s, De Soto and colleagues furthered the concept of PAWS described earlier by Wellman (1954), Segal et al. (1970), and Kissin (1979) in noting that PAWS partially reverses with sustained alcohol abstinence (De Soto et al., 1985). They observed several characteristic mood and anxiety symptoms—such as depressed mood, interpersonal sensitivity, obsessive–compulsive symptoms,

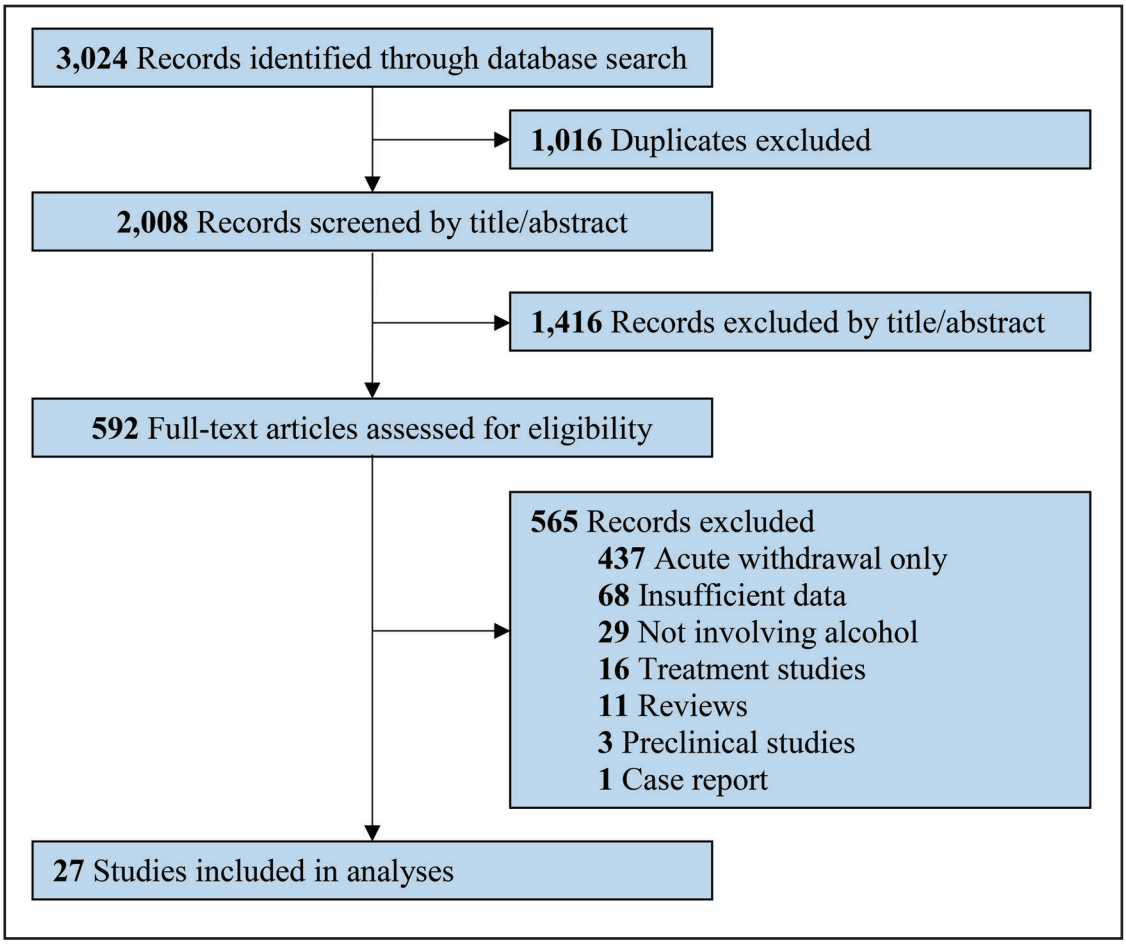

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

and guilt—during the first 3 to 4 months following acute withdrawal (De Soto et al., 1985). Fortunately, in a sample of persons who had been abstinent for nearly 10 years, most PAWS symptoms gradually diminished, with near normalization 4 months after detoxification (De Soto et al., 1985). Although recovery appears to be most rapid during the first 2 to 3 weeks of abstinence (Wetterling & Junghanns, 2000), the healing process—in terms of symptom severity and occupational functioning—continues to occur for nearly a decade, indicating the importance of both abstinence and time (De Soto et al., 1989).

Anhedonia. Anhedonia—the loss of or inability to experience pleasure—is commonly associated with depression, schizophrenia, and alcohol use disorder (AUD; Pozzi et al., 2008). During PAWS, nearly 20% report experiencing anhedonia, which appears to be caused by dopaminergic mesolimbic hypoactivity (Pozzi et al., 2008). However, anhedonia may also precede or precipitate alcohol use in individuals with PAWS. Furthermore, it remains unclear if PAWS-related anhedonia remains distinct from alcohol-induced depression stemming or an underlying depression in individuals with AUD. Still, while anhedonia seems to be linked to craving in PAWS (Janiri et al., 2005), it represents a distinct psychopathological entity independent of other factors (Pozzi et al., 2008). In one study, the severity of anhedonia and alcohol cravings diminished somewhat during the first 30 days of abstinence from alcohol (Martinotti et al., 2008). However, anhedonia and craving ratings remained higher than healthy controls even at the 1-year mark of alcohol sobriety (Martinotti et al., 2008).

Cognitive impairment. The protracted withdrawal period from alcohol appears to induce transient alterations in multiple cognitive domains, including concentration, initiative, pessimism, and even a sense of humor (Voltaire-Carlsson et al., 1996). Furthermore, persons experiencing PAWS have lower executive functioning measures, including selective attention, visual scanning ability, visual-motor scanning, and cognitive flexibility (Cordovil De Sousa Uva et al., 2010). Although these symptoms typically last a few weeks to months, some subtle residual effects often remain for up to a year of abstinence (Vik et al., 2004). Although the evidence of irreversible effects is less clear for alcohol, subtle

Table 1. Summary of protracted alcohol withdrawal syndrome (PAWS) signs and symptoms, with timelines where available

Dimension	Timeline
Mood and anxiety symptoms	First 3 to 4 months following acute withdrawal months up to 10 years
Anhedonia	Most severe during the first 30 days of abstinence from alcohol
Cognitive impairment	Few weeks to a few months, with some residual effects lasting up to a year of abstinence
Cravings for alcohol	Most severe during the first 3 weeks of abstinence from alcohol
Posttraumatic stress disorder symptoms	Decreasing severity during the first month of withdrawal, with the steepest decline during the first 2 weeks of abstinence
Sleep disturbance	Emerges during acute withdrawal, whereas prolonged insomnia can last up until approximately 6 months of abstinence

lingering cognitive impairment is often undetected and unaddressed (Vik et al., 2004). Fortunately, there appears to be a gradual normalization back to baseline levels for some cognitive symptoms, and mental symptoms are comparatively stable compared with mood and anxiety symptoms (Voltaire-Carlsson et al., 1996).

Cravings. Cravings for alcohol are prominent in early abstinence and represent a key feature of protracted withdrawal. Several studies have shown that PAWS involves the interplay between cravings, affective states, and emotional intelligence (EI; Cordovil De Sousa Uva et al., 2010; de Timary et al., 2013; Uva et al., 2010). As defined in the literature, EI is "the ability to monitor one's own and other people's emotions, to discriminate between different emotions and label them appropriately, and to use emotional information to guide thinking and behavior" (Srivastava, 2013, p. 97). In one study examining individuals during 3 weeks of protracted withdrawal (Cordovil De Sousa Uva et al., 2010), De Sousa Uva and colleagues measured participants' cravings, affective states, and EI using a battery of neuropsychological instruments. The authors observed three main findings: cravings were associated with negative—rather than positive—affective states, cravings and negative affect diminished over time, and EI was low throughout the entire study and mediated the link between negative affect and high cravings (Uva et al., 2010).

Ultimately, as EI is a trait and emotional disposition tends to be reasonably stable, "it is difficult to understand how specific interventions aimed at reinforcing emotion-related dispositions such as emotion/stress regulation (self-control factor) and trait positive affectivity (well-being factor) might reduce craving during early alcohol abstinence" (Uva et al., 2010). Another PAWS study (de Timary et al., 2013) found that alcohol cravings decreased alongside ratings of depressed mood, but only in those with higher self-consciousness, a personality trait characterized by a tendency to think and direct attention to the self. These studies indicate the potential for psychotherapeutic and metacognitive approaches to cravings addressing EI and negative affective states (de Timary et al., 2013; Uva et al., 2010).

Trauma symptoms. Symptoms from posttraumatic stress disorder (PTSD) and trauma can overlap with some of the PAWS' mood, anxiety, concentration, and sleep issues. However, they appear to improve with abstinence. For example, in a prospective study of 162 alcohol- and cocaine-dependent outpatients with a history of trauma experiencing protracted withdrawal, PTSD symptoms declined across the 28-day study period regardless of withdrawal substance. The most change occurred within 2 weeks of last substance use (Coffey et al., 2007).

Sleep. Sleep disturbance is a common finding among individuals with AUD and during PAWS. Among 27 patients with AUD investigated for impaired sleep, the authors concluded that impaired sleep emerging after the withdrawal period might be one of the hallmarks of PAWS, with 52% experiencing insomnia in the study and 33% experiencing prolonged insomnia up until the 169th day following abstinence (Watanabe et al., 2001).

Symptomatology summary. PAWS symptoms include irritability, depression, insomnia, fatigue, restlessness, alcohol cravings, and distractibility. These are most severe in the first 4 to 6 months of abstinence and diminish gradually over several years of sustained abstinence.

Neurobiological and endocrinological features

During PAWS, the brain is proposed to enter a relative state of hyperexcitability by activating central stress systems (Ahveninen et al., 1999). Several studies have attempted to describe the components of this process (summarized in Table 2).

Evoked potentials. Compared with research on social drinkers, a study involving only males with AUD demonstrates aberrations in middle-latency, auditory-evoked potentials ($p < .01$), with a significant negative correlation ($r = -.65$) with the duration of abstinence preceding PAWS

TABLE 2. Summary of the neurobiological and endocrinological features of protracted alcohol withdrawal syndrome (PAWS)

Feature	Relationship to PAWS
Evoked potentials ↓	Evoked potential profiles appear to gradually normalize over time, suggesting that PAWS is a transient, potentially reversible state.
Orexins ↓	Orexin-A levels were lowest during acute withdrawal and gradually increased during protracted withdrawal compared with abstinence.
Atrial natriuretic peptide ↓	Atrial natriuretic peptide (ANP) inhibits the effects of corticotrophin-releasing factor, corticotrophin, and cortisol. ANP levels gradually improve with sustained abstinence while remaining lower than healthy controls. Persistently low ANP may sustain the cravings, low mood, and anxiety symptoms of PAWS.
Serotonin ↑↓	Disturbance in serotonin function may mediate acute and protracted alcohol withdrawal; however, there is a lack of consensus. Although some studies show increases in serotonin breakdown during PAWS, other studies indicate no change in serotonin availability.
Pancreatic polypeptide ↑	Pancreatic polypeptide inhibits pancreatic exocrine function (e.g., enzymatic secretion). Pancreatic polypeptide levels rise with chronic alcohol consumption and remain high up to 2 weeks following abstinence but improve with time.
Neuroadaptation ↑↓	During PAWS, preliminary data suggest that the brain is more susceptible to cravings and resumption of alcohol use through glutamatergic potentiation in the nucleus accumbens.

Note: Arrows indicate change in direction (e.g., ↓ represents a relatively lower feature compared with healthy controls, whereas ↑↓ means equivocal).

(Ahveninen et al., 1999). Although these changes indicate that the brain enters a state of hyperexcitability during withdrawal, the evoked potential profiles appear to gradually normalize over 6 weeks of abstinence, suggesting that PAWS is a transient, potentially reversible state (Ahveninen et al., 1999).

Orexins. Orexins are hypothalamic neuropeptides that appear to regulate several homeostatic processes, such as the sleep–wake cycle (Nuñez et al., 2009). However, they may also play a role in moderating PAWS symptoms, particularly cravings and withdrawal (Kim et al., 2012). In one study, orexin-A levels were lowest during acute withdrawal and gradually increased during protracted withdrawal compared with abstinence (Bayerlein et al., 2011). As orexin-A expression normalized over several weeks and correlated with sleep-wake function, it may serve as a putative PAWS biomarker and mediate the associated sleep disturbance (Bayerlein et al., 2011).

Cortisol. The release of cortisol, the endogenous stress hormone, is regulated by corticotrophin-release factor (CRF), whose levels increase during alcohol withdrawal (Heilig & Koob, 2007). Accordingly, individuals experiencing acute and protracted AWS have higher reported basal serum cortisol levels (Heilig & Koob, 2007). However, CRF-like peptides also appear to maintain a negative-affective state, suggesting that they have a specific role in mediating the underlying PAWS stress response (Bruijnzeel & Gold, 2005). Animal models indicate that atrial natriuretic peptide (ANP) inhibits the effects of CRF, corticotrophin, and cortisol (Ibanez-Santos et al., 1990; Mutschler et al., 2010). However, chronic alcohol consumption and acute withdrawal suppress ANP (Kovács, 2000). Although ANP levels gradually improve over 2 weeks of sustained abstinence, they remain lower relative to healthy controls even after 12 weeks of abstinence. These persistent deficits may sustain the cravings, low mood, and anxiety characteristic of PAWS (Kiefer et al., 2002).

Serotonin. Disturbance in serotonin function may mediate acute and protracted alcohol withdrawal; however, there is a lack of consensus (Marcinkiewcz et al., 2016). One study detected a relative increase in the enzymatic degradation of tryptophan, the precursor of serotonin, by indoleamine dioxygenase, suggesting a correlation between PAWS and decreased serotonin availability (Farren & Dinan, 1996). During protracted abstinence, increased tryptophan degradation (measured by kynurenine, a tryptophan metabolite) and reduced serotonin levels appear to induce PAWS symptoms, including fatigue, irritability, and sleep disturbances (Gleissenthall et al., 2014). However, there are no differences in platelet serotonin-stimulated signal transduction in patients with PAWS over controls (Simonsson et al., 1992). To that end, impaired serotonin-stimulated signal transduction is an effect of long-term alcohol exposure; it is not a trait-dependent marker of the serotonergic system of individuals with a constitutional vulnerability to becoming an alcoholic.

Pancreatic polypeptide. Some studies have examined the relationship between protracted alcohol withdrawal and specific gastrointestinal hormones, given the established asso-

ciation between chronic alcohol use and pancreatic function. One such hormone is plasma pancreatic polypeptide (PP), which inhibits pancreatic exocrine function, such as amylase secretion and other digestive enzymes (Fink et al., 1983; Hajnal et al., 1993). PP levels were significantly higher in individuals with AUD than in controls and remained elevated even 2 weeks following acute withdrawal completion (Fink et al., 1983). Therefore, alcohol-related gastrointestinal dysfunction appears to persist into PAWS and may help explain the abnormal pancreatic function seen frequently in AUD (Fink et al., 1983).

Changes in the reward-related functions. Chronic alcohol consumption appears to induce long-lasting neuroadaptations in the nucleus accumbens and other brain reward system components, regulating intrinsic motivation and cravings for alcohol (Gass et al., 2011). During PAWS, preliminary data suggest that the brain remains in this "allostatic state," a new equilibrium defined by an ongoing functional reorganization (Le Moal, 2009), which appears to mediate susceptibility to cravings (Marty & Spigelman, 2012). In addition, some evidence indicates that protracted withdrawal lasting 3 to 4 weeks appears to induce a long-lasting potentiation of glutamatergic activity in the nucleus accumbens for up to 6 months, which plays a vital role in cue-induced alcohol-seeking behavior (Marty & Spigelman, 2012). To that end, there is a need for a better understanding of alcohol-induced, long-lasting neuroadaptive changes in the different subregions of the nucleus accumbens (Marty & Spigelman, 2012).

Neurobiology and endocrinology summary. Several neurobiological and endocrinological features appear unique to PAWS, including enhanced glutamatergic activity in the nucleus accumbens, increased hypothalamic–pituitary–adrenal axis activity, decreased serotonin, and orexin availability, and contribute to the report of subjective symptoms.

Discussion

Summary of evidence

To our knowledge, this is the first systematic review to explore PAWS, which ASAM defines as a syndrome with persistent, subacute symptoms of irritability, anxiety, and sleep disturbance (ASAM, 2020). Although PAWS symptoms were first described more than six decades ago and are impairing, the importance of PAWS is its potential association with the risk for relapse.

Although 27 studies met inclusion for our review, none formally applied the ASAM definition of PAWS. Because of a lack of sufficient homogeneity, we summarized findings descriptively. PAWS is a predominantly negative affective state that begins in early abstinence and can persist for 4–6 months or potentially longer. Typical symptoms include anxiety, dysphoria, anhedonia, sleep disturbance, cravings, cognitive impairment, and irritability. PAWS symptoms, particularly cravings, anhedonia, and anxiety, may be risk factors for drinking relapse. They have been associated with reported neurobiological differences in evoked potentials, measures of orexins, cortisol, CRF, ANP, serotonin, pancreatic polypeptides, and neuronal excitability. Neuroadaptation changes in the nucleus accumbens and the prefrontal cortex have been proposed as an underlying mechanism in PAWS symptomatology. PAWS symptoms appear to improve over time, with a near normalization over the early months of abstinence, although some may take several years of sustained abstinence.

Implications of findings

In a review of protracted withdrawal by Satel and colleagues (1993), the authors concluded that symptoms extending beyond the period of acute withdrawal from alcohol—as well as opioids, for that matter—have been relatively consistently described but not conclusively demonstrated. The authors primarily attributed their conclusions to methodological limitations in the extant PAWS studies, such as the failure of studies to do multiple time point sampling, using standardized instruments and control groups, and re-administering the substance to suppress withdrawal symptoms (Satel et al., 1993). Further, the authors mentioned that the concept of protracted withdrawal was ambiguous, confounding interpretations of the literature, and precluded derivation of a unified vision of the term, which would be necessary for adding the diagnosis to the DSM (Satel et al., 1993). Ultimately, Satel and colleagues found insufficient empirical evidence for the existence of PAWS to justify its inclusion in the DSM (Satel et al., 1993). However, they proposed that PAWS could be a "global post-use syndrome with an attenuated physiologic rebound, toxic residuals, and the expression of pre-existing symptoms unmasked by the cessation of use," indicating a need for future efforts to identify signs and symptoms of PAWS (Satel et al., 1993).

Although it has been nearly 30 years since the publication of the Satel et al. (1993) review of protracted withdrawal syndromes, the PAWS field has not advanced remarkably apart from animal studies, which was not the present review's focus. Regrettably, PAWS has not received formal recognition as a disorder in any edition of the DSM or the ICD. It remains a relatively underestimated and ambiguously defined clinical condition that follows the acute stage of AWS (Caputo et al., 2020). Protracted withdrawal syndromes, in general, have not received prominent discussion, although they are clinically relevant. Thus, research efforts into elucidating PAWS have been stalled for more than two decades, with minimal research explicitly exploring the phenomenon of protracted withdrawal, which may be a consequence of the failure to recognize PAWS as a diagnostic entity formally.

The lack of a shared, precise definition may partially explain why PAWS has not been widely adopted. The ASAM

guidelines support the existence of PAWS, which they defined as a syndrome with persistent, subacute symptoms of irritability, anxiety, and sleep disturbances (ASAM, 2020). Likely what is needed to define PAWS further is a specific timeline for symptom onset and persistence (i.e., the onset of symptoms within the first month after acute withdrawal that persists greater than 1 month), specific symptoms that define PAWS (i.e., three or more symptoms of irritability, depressed mood/anhedonia, anxiety, cravings, cognitive impairment, and sleep impairment), and its presence associated with functional impairment or predisposition to substance relapse. One of the other consequences of the relative lack of understanding of PAWS is the scarcity of published guidance on its management. For example, the ASAM 2020 clinical practice guidelines on alcohol withdrawal management identified protracted withdrawal as an area for future consideration (ASAM, 2020). Because there appears to be plausible neurobiological support for the basis of PAWS, impairment from its presence, and treatment consequences for identifying PAWS, PAWS must be more formally defined.

Another important aspect of PAWS is the variation in the symptoms occurring in the post-acute withdrawal period, degree of impairment, severity, frequency, duration, and association with the specific substance of use. To that end, it may be less clinically helpful to consider these symptoms as a single construct, particularly in the case of AUD. For instance, craving and negative affect during alcohol withdrawal may stem from underlying psychological and neurobiological changes, whereas sleep disruptions are more physiological and less likely to be relevant to relapse (Cheng et al., 2022). Furthermore, from a theoretical perspective, cravings for alcohol may be driven by the incentive value of the drug rather than be a feature necessarily related to withdrawal (Berridge & Robinson, 2016; Tiffany & Wray, 2012). Although the PAWS model has been subjected to little scientific scrutiny and there have been few studies supporting its existence outside of protracted benzodiazepine withdrawal (Ashton, 1991; Satel et al., 1993), a previous validation study involving 122 individuals with AUD found that 28 PAWS symptoms—ranging from anhedonia, depression, and memory problems to craving, anxiety, and sleep disturbance—clustered with excellent internal consistency, suggesting that PAWS symptoms were a reliable and valid predictor of alcohol relapses (Miller & Harris, 2000). Still, there is a need for a further study exploring the interrelatedness—or lack thereof—between symptoms considered to be part of PAWS.

Limitations

There are a few limitations to discuss at the study and outcome level. The primary limitation is the high heterogeneity between studies owing to the nebulous nature of PAWS, the lack of a shared consensus definition, the variable durations of symptoms presented as components of PAWS, and the small sample sizes of the component studies. In addition, much of the literature on PAWS is dated, and there is a shortage of robust, randomized, controlled trials. Furthermore, there is a lack of standardization of PAWS across studies, and the extent of post-withdrawal abstinence was highly variable. In addition, because of a lack of pertinent studies, it remains unclear whether all the symptoms described here are manifested equally in both sexes or in individuals with comorbid substance use disorders. Finally, for a systematic review, ideally, two individuals should review articles for eligibility. However, in this article, only one author (A.B.) reviewed and identified the articles for inclusion and the second reviewer only reviewed the excluded articles.

Conclusion

Following acute alcohol withdrawal, PAWS has been clinically identified to involve symptoms of irritability, depressed mood/anhedonia, anxiety, cravings, cognitive impairment, and sleep impairment. In addition, there appears to be some credible evidence to support the concept of PAWS based on neurobiological findings, including differences measured in evoked potentials, orexins, cortisol, CRF, ANP, serotonin, pancreatic polypeptides, and neuronal excitability. Nevertheless, PAWS remains an important yet controversial topic, with a lack of consensus about whether it even exists and, if it does, its causes, manifestations, and effect on relapse.

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Conflict-of-Interest Statement

The authors state that there are no conflicts of interest.

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