Narrative Review

Experiment-Induced Nociception in Humans with Substance Use Disorders: A Review of Psychophysical Studies

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Background: Pain perception in individuals with substance use disorders (SUDs) is shaped by neuroadaptive changes in both peripheral and central nociceptive pathways. Accurate assessment of pain sensitivity in this population is essential for effective clinical management but remains challenging due to overlapping effects of drug use, tolerance, and withdrawal.

Objective: This review synthesizes findings on pain sensitivity in individuals with SUDs, focusing on experimentally induced nociception—specifically thresholds, tolerance, and perceived intensity of pain.

Study Design: A systematic narrative review.

Setting: Clinical studies that involve patients with opioid, alcohol, and stimulant use disorders and compare their pain responses to those of healthy controls.

Methods: The protocol for this review was registered on Open Science Framework (ID# XYPE6). A comprehensive PubMed search identified studies assessing nociception in SUD populations, focusing on pain threshold, tolerance, and intensity.

Results: Of 348 publications, 14 studies were included. Thermal stimuli (cold and heat) were used most frequently, followed by pressure, electrical, and chemical modalities. Findings indicate changes in pain thresholds and increased pain sensitivity in association with SUDs, with evidence of dysesthesia notably in patients with alcohol, stimulant, and tobacco use disorders, as well as in chronic pain patients receiving opioids.

Limitations: This review is limited by the scarcity of clinical psychophysical pain studies in SUD populations, since most existing research is based on animal models. Additionally, heterogeneous testing protocols across studies constrain comprehensive synthesis.

Conclusion: Changes in experimentally induced nociception among individuals with SUDs are measurable and extend beyond preclinical findings. Psychophysical assessments during specific withdrawal stages can reliably quantify nociception in this population. Further research using standardized methodologies is needed to bridge preclinical and clinical evidence and thus enhance pain management strategies for individuals with SUDs.

Key words: Pain perception, analgesics, opioid-induced hyperagesia, alcohol use disorder, stimulant use disorder, tobacco use disorder, quantitative sensory testing, hyperalgesia, dysesthesia, chronic pain

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Managing pain in patients with substance use disorders (SUDs) remains a persistent clinical challenge. These individuals report pain symptoms frequently, yet clinicians may question the authenticity or severity of their complaints due to concerns about drug-seeking behavior or psychological

comorbidities (1,2). For physicians, the dual challenge lies in ensuring adequate pain relief while managing the risk of opioid misuse and dependence (3). Pain is a complex, multifaceted process involving both sensory and emotional components (4). Reliable assessment to investigate the peripheral and central processes of pain and differentiate among true nociception, dysesthesia, and potential hyperalgesia in individuals with SUDs is urgently needed.

A body of clinical literature (5-7) suggests that opioid use can lead to nociceptive sensitization through neuroplastic changes in the peripheral and central nervous systems, a phenomenon known as opioid-induced hyperalgesia (OIH). A review by Lee (5) addressed the clinical prevalence of OIH in populations with opioid use disorder (OUD) and patients with pain-related conditions, providing valuable insights into the physiology underlying OIH. Preclinical studies also suggest that these changes extend beyond opioid exposure to include substances such as alcohol (8,9) and stimulants (10), raising critical questions about how nociception manifests across SUD patients, especially in those whose disorders are not directly related to opioid use. Despite these findings, the complex interplay between SUDs and pain sensitivity remains unclear and underexplored (11,12).

Hyperalgesia, as defined by the International Association for the Study of Pain (IASP) (13), requires increased pain in response to a normally painful (suprathreshold) stimulus. However, many human studies infer hyperalgesia from changes in pain threshold or tolerance alone, without measuring the perceived intensity of pain or comparing the intensity with that reported by healthy controls. This practice can lead to overstatements and/or misinterpretations. Furthermore, psychoactive substances with addictive potential have analgesic/anesthetic properties that can obscure underlying sensory abnormalities. Without accounting for key variables such as timing, dosage, and withdrawal status, studies may risk conflating drug-induced analgesia/anesthesia or withdrawal-related dysesthesia with true hyperalgesia—ultimately leading to misdiagnosis or misguided treatment decisions.

Psychophysical methods, which quantify pain by correlating noxious stimuli with subjective pain perception, offer reliable and reproducible measures of pain sensitivity despite challenges like response bias in this patient population (8-10). An overview of core psychophysical principles in pain research has been provided recently by McDaniel (14), emphasizing the application to the study of pain perception in clinical populations.

This review synthesizes findings from experimental pain studies of individuals with SUDs, examining nociceptive changes induced by various stimuli. By emphasizing the strengths of psychophysical methods and clarifying methodical limitations, this review aims to inform future translational research and support more accurate diagnoses of and pain management for individuals with SUDs.

Methods

Data Sources and Selection

The protocol for this review was registered in Open Science Framework (www.osf.io/xype6/overview). A systematic narrative review was conducted on PubMed for studies published between August 27, 2023, and January 1, 2025. The key search phrase was "pain perception in substance use disorders." To be included in the review, papers had to fall into at least one of the following categories: (1) peer-reviewed studies involving patients with SUDs compared with healthy matched controls, (2) studies employing noxious stimuli, and (3) studies in which patients reported the stimuli as painful. Studies were excluded if they (1) were review articles or (2) overlapped with meta-analyses by Trøstheim (7) and Higgins (6), which collectively analyzed data from over 4,000 patients. These exclusions ensured the inclusion of studies not already synthesized in recent comprehensive reviews. The study selection process is outlined in Fig. 1. ImageJ (www.imagej.net/ij/) was used to extract data from figures when numerical values were not provided.

Terminology

To ensure consistency in reporting, pain-related terms follow the IASP definitions (Table 1). Stimulus detection threshold refers to the minimal intensity needed to detect a sensation, whether painful or not. Pain is defined as a patient-reported sensation of "painful" or "hurts." Pain tolerance (or limit of endurance) refers to the duration or intensity of a noxious stimulus a patient withstands before withdrawal or signaling to stop. Pain-perceived intensity (often called pain sensitivity) measures the magnitude of pain a patient rates on a quantitative scale in response to a noxious stimulus.

Results

A total of 354 articles were identified in the initial

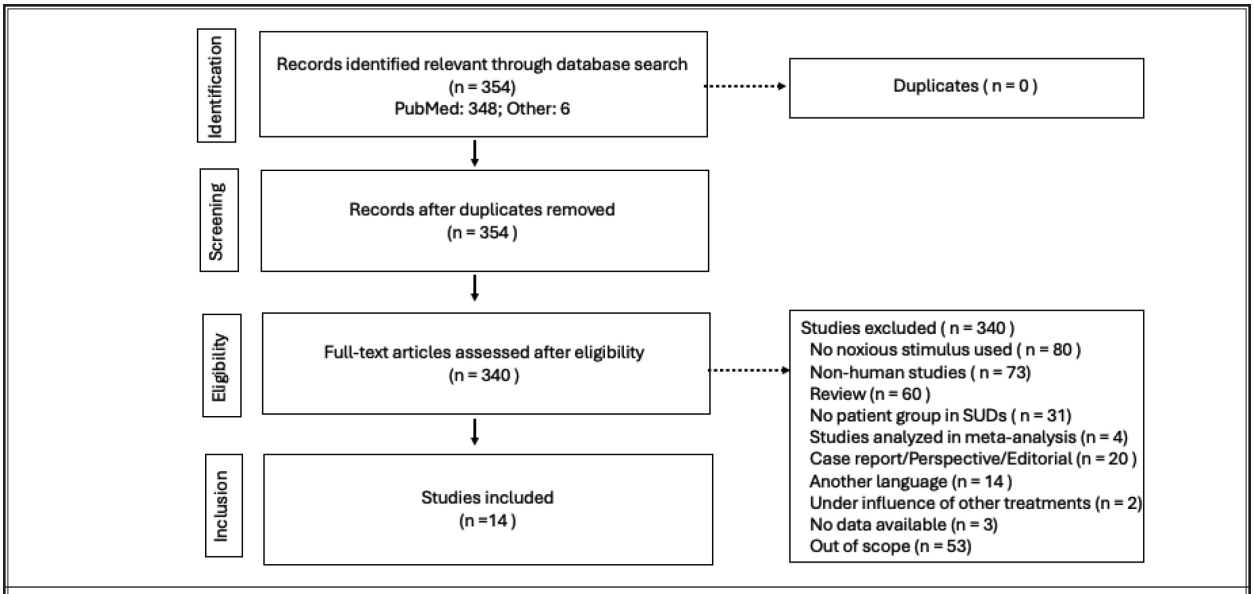


Fig. 1. *Flow chart*.

search. After titles and abstracts were screened and full texts for eligibility were assessed, 14 original studies met the inclusion criteria. Those studies were summarized by diagnosis, age, percentage of men, stimulus modality, and pain outcome measures—specifically the threshold, tolerance, and perceived intensity of pain. For the sake of presenting the findings systematically, results are organized into 2 parts. Part I details findings by stimulus modality. Cold stimuli (0–28°C), including the cold pressor test (CPT), were the most frequently used modality, appearing in 10 studies (15-24) (Table 2). Heat stimuli (45–51°C) featured in 6 studies (15,16,19,24-26) (Table 3), while pressure stimuli, including pressure algometry, were employed in 5 studies (16,19,21,24,31) (Table 4). Electrical stimuli (140–271 mA) and chemical-irritant stimuli (topical 10% capsaicin) appeared in one study each (27,28) (Table 5). Part II organizes the findings by SUD diagnosis—opioid, alcohol, stimulant, and polysubstance—to explore diagnosis-specific pain responses across these modalities.

PART I: Stimulus Modalities

Cold Stimulation

Cold stimulation using CPT (29) was the most frequently employed modality (Table 2). Typically, patients submerged their hands in an ice bath maintained at 0–4°C, activating deeper nociceptors, including those in large veins. Pain was induced during cutaneous vasoconstriction as the temperature in deeper skin layers decreased rapidly (29,30). Decreased cold pain tolerance was found in individuals actively administering opioids (17,22), methadone (17,22), or cocaine (17), as well as those who refrained from opioids for weeks (20) and in individuals with chronic pain on medication for opioid use disorder (MOUD) (23). However, 2 studies (18,22) examining opioid abstinence between 4-5 months compared with healthy patients showed opposite results in cold pain tolerance.

Heat Stimulation

Radiant heat stimulation has been the most frequently used form of natural cutaneous noxious stimulation (30). The studies included in this review (Table 3) applied an ascending temperature increment ranging between 0.5–2°C on an innocuous base temperature of 32–38°C through a thermode that contacted the skin on the patient's forearm (3.14–9 cm^2). Increased heat pain threshold and tolerance were observed in individuals with alcohol use disorder (AUD) who were abstinent for a period of 2–3 months (26), suggesting potential alcohol-induced neurotoxic hypoalgesia upon noxious heat stimulation. Conversely, decreased heat pain thresholds and tolerance were found in individuals with active AUD (26) and women who were habitual heavy active smokers (16), indicating possible hyperalgesia induced by alcohol and nicotine withdrawal. Increased heat pain thresholds were also observed in

Table 1. *Definitions of pain-related terminology.*

Term	Definition
Pain	a sensation that a patient reports to be "painful" or that the patient claims "hurts"
Nociception	the neural processes of encoding and processing noxious stimuli
Stimulus threshold	the level of a stimulus required for a patient to identify as a sensation, which may or may not be painful
Pain threshold	the level of noxious stimulus required for a patient to identify it as "painful" or "hurt[ing]"
Pain tolerance	known as tolerance threshold or limit of endurance, the amount of time or the magnitude of a noxious stimulus that a patient can withstand before escaping the pain experience
Pain sensitivity	the perceived intensity of a pain sensation that a patient rates in response to a noxious stimulus, usually on a measurable scale (e.g., 0-100, 0-10).
Central sensitization	enhanced responsiveness of nociceptive neurons in the dorsal horn of the spinal cord to their normal or subthreshold afferent input from the peripheral nervous system
Hyperalgesia	Increase in pain sensation to a stimulus that is normally painful/increased sensitivity to a painful stimulus. It results in both a decrease in pain threshold and an increase in suprathreshold response.
Hypoalgesia	Decrease in pain sensation to a stimulus that is normally painful/decreased sensitivity to a painful stimulus. It results in both an increase in pain threshold and a decrease in suprathreshold response.
Mechanical hyperalgesia	Secondary hyperalgesia to mechanical stimulation. It is usually measured with a calibrated (28) monofilament.
Analgesia	Absence of pain to a normally painful stimulus/no sensitivity to a painful stimulus
Allodynia	Pain evoked by a stimulus that does not normally provoke pain
Dysesthesia	an unpleasant abnormal sensation, whether spontaneous or evoked

individuals with OUD who were abstinent for at least 12 months without methadone maintenance therapy (MMT) (25) or who were receiving MMT for pain control (24). Decreased heat pain thresholds were noted in individuals with OUD who received MMT for reasons other than pain (24). No inconsistencies were reported among the 6 studies employing heat pain stimulation.

Mechanical Pressure Stimulation

Mechanical pressure stimulation (Table 4) was applied through 3 main methods: 1) pinching a subcutaneous bony surface or nail bed within an area of 0.5–one cm^2 using an algometer, 2) cuffing a group of muscles in a circular manner with a tourniquet to induce ischemic muscle pain, and 3) poking the skin with calibrated von Frey hairs to deliver a precise force and measure mechanical hyperalgesia. Across 5 included studies (16,19,21,24,31) involving 296 patients, pressure stimulation via algometer or tourniquet did not reveal significant differences in pressure pain threshold between groups or drug classes in the majority of patients. Only 2 studies (24,27) applied von Frey hairs to test and map secondary hyperalgesia, which measured the skin area surrounding the primary pressure stimulation site.

Electrical Stimulation

Historically, electrical stimulation (Table 5, electrical section) has been one of the most widely used methods to measure cutaneous pain thresholds, due to its ease of control (30). Among studies involving SUDs, the first to apply noxious electrical stimulation to quantify pain thresholds and tolerance was conducted by Jochum (26). This study used a pair of 1 cm diameter gold electrodes coated with electroconductive gel and taped to each patient's index finger. Pain thresholds were recorded when the patients first reported pain, and pain tolerance was noted when the stimulus became intolerable. Electrical stimulation remains one of the most popular experimental methods for inducing pain and assessing the processing of it (30,32).

Chemical Irritant Stimulation

Chemical irritant stimulation, unlike electrical pain stimulation, is selective in that a specific amount of a given chemical irritant (Table 5, chemical section) activates a particular nociceptive nerve ending. Short-term reversible dysesthesia usually develops after testing, providing valuable molecular insights into peripheral pain-encoding processes in response to chemical stimuli. One included study (27) applied capsaicin, a chemical that targets polymodal nociceptors of afferent nerves. Ditre (27) found that the nicotine-deprivation group showed 1) a higher intensity of perceived capsaicin-induced pain and enhanced mechanical hyperalgesia in the dysesthetic skin area, suggesting neuroplastic changes in polymodal nociceptors and responsiveness in the dorsal horn of the spinal cord, and 2) a larger flare area, indicating a change

Table 2. *Studies of noxious cold stimulation (n = 10).*

Study	Diagnosis		Contrast (Sample Size)		Age (Mean ± SD/SEM)		Male %		Stimulus	Pain (a)		
	Class	Criteria	Group One	Group 2	Group One	Group 2	Group One	Group 2	I Intensity	Threshold	Tolerance	Intensity
Girdler (16)	Nicotine	Unavailable (b)	Female smoker (17)	Female healthy (20)	25.6 ± 1.4	27.2 ± 1.3	0	0	4° C	ns	ns	ns
			Male smoker (20)	Male healthy (20)	25.5 ± 1.3	28 ± 1.3	100	100	4° C	ns	Increased	ns
McCann (19)	MDMA	DSM-IIIR	ABS 2wk (42)	Healthy (43)	24.5 ± 4.9	23.6 ± 3.3	67	53	4° C	NA	NA	Increased
Compton (17)	Cocaine	DSM-IIIR	Active (21)	ABS (32)	33.1 ± 5.1	31.9 ± 6	100	100	0-2° C	NA	Decreased	NA
	Cocaine/ Opioid		Opioid ABS; MMT active (26)	Cocaine ABS (32)	33.7 ± 5.7	31.9 ± 6				NA	Decreased	NA
	Opioid		MMT active; opioid active (43)	MMT active; opioid ABS (26)	35.1 ± 4.8	33.7 ± 5.7				NA	Decreased	NA
Ren (18)	Opioid	DSM-IV	ABS 4.9mo (52)	Healthy (47)	31.6 ± 0.8	30.3 ± 0.9	100	100	2± 2° C	Decreased	Decreased	ns
Pud (20)	Opioid	Unavailable (c)	ABS 4w (60)	Healthy (70)	33.1 ± 9	24.3 ± 3.9	83	54	1 ± 0.5° C	Increased	Decreased	Decreased
Treister (22)	Opioid	Unavailable	ABS ≥5mo (43)	Healthy (50)	Unavailable				1° C	ns	ns	NA
			Active (50)							Increased	Decreased	NA
Compton (15)	Opioid	DSM-IV	CP + OUD (20) (d)	CP (20) (d)	44.35 ± 10.84	49.91 ± 9.41	50	60	1 ± 0.5° C	ns	ns	Increased
McHugh (21)	Opioid	Multiple (e)	CP + opioid misuse (31) (e)	CP (20) (e)	53.39 ± 8.87	56.4 ± 7.37	55	50	4° C	NA	ns	ns
Peles (24)	Opioid	DSM-IV-TR	Opioid ABS; MMT active (31)	Healthy (17)	41 ± 8.6	39.3 ± 10	71	47	6.9 - 28° C (mid-dorsal of hand)	ns	NA	NA
			Opioid ABS; MMT active; CP (18)		42.7 ± 1.9	39.3 ± 10	67			ns	NA	NA
			Opioid ABS; MMT active; no CP (17)		38.2 ± 2.4	39.3 ± 10	77			Decreased	NA	NA
Wachholtz (23)	Opioid	DSM-IV	Methadone-active CP (30)	MOUD-naïve CP (30)	39.9 ± 1.9	39 ± 2.28	57	30	2°C	Decreased	Decreased	ns
			BUP-active CP (30)	MOUD-naïve CP (30)	42.7 ± 1.85	39 ± 2.28	37			Decreased	Decreased	ns
			MOUD-ABS CP (30)	MOUD-naïve CP (30)	46.4 ± 2.13	39 ± 2.28	33			Decreased	Decreased	ns

Abbreviations: ABS: abstinent; BUP: buprenorphine; CP: chronic pain; DSM: Diagnostic and Statistical Manual of Mental Disorders; MMT: methadone maintenance treatment; MOUD: medications for opioid use disorder; mo: month; ns: nonsignificance; NA: nonapplicable; SD: standard deviation; SEM: standard error of the mean; wk: week.
(a) Decreased/increased outcome in Group One. (b) Group 1 met the study inclusion criteria: consumed ≥ 15 cigarettes/day for at least 2 years with nicotine yields > 0.6 mg nicotine and 10 mg tar. The patients were instructed to smoke before and during the breaks of the study. (c) Group 1 was recruited from the inpatient unit for drug abuse treatment. (d) Among 40 CP patients: musculoskeletal pain (n = 16), neuropathy (n = 14), mixed (n = 10). The severity of CP was rated as moderate (VAS = 56.3/100) in the past 24 hours of participation in the study. (e) The 17-item self-report Current Opioid Misuse Measure and the 20-item Addiction Behaviors Checklist were applied. No version of the DSM was used. The severity of pain was measured by the self-reported Brief Pain Inventory (BPI), and the BPI scores showed no significant difference between the groups. Five patients in Group One (actual n = 26) and one patient in Group 2 (actual n = 19) did not complete all tests.

Table 3. *Studies of noxious heat stimulation (n = 6).*

Study	Diagnosis		Contrast (Sample Size)		Age (Mean ± SD/SEM)		Male %		Stimulus Intensity Base—Noxious	Pain (a)		
	Class	Criteria	Group One	Group 2	Group One	Group 2	Group One	Group 2	Location	Threshold	Tolerance	Intensity
Jochum (26)	Alcohol	DSM-IV	Active (30) (b)	Healthy (30)	41.5 ± 8.6	41.6 ± 8.1	100	100	32-53°C in 9 cm^2 (wrist)	Decreased	Decreased	NA
									32-53°C in 9 cm^2 (sternum)	Decreased	Decreased	NA
			ABS 2-3m (30) (c)		41.5 ± 8.6				32-53°C in 9 cm^2 (wrist)	Increased	Increased	NA
									32-53°C in 9 cm^2 (sternum)	Increased	Increased	NA
Girdler (16)	Nicotine	Unavailable (d)	Female (17)	Male (20)	25.6 ± 1.4	25.5 ± 1.3	0	100	41.5-53°C in 3.14 cm^2 (volar forearm)	Decreased	Decreased	ns
McCann (19)	MDMA	DSM-IIIR	ABS 2wk (42)	Healthy (43)	24.5 ± 4.9	23.6 ± 3.3	67	53	50°C (ventral forearm)	ns	NA	NA
Prosser (25)	Opioid	DSM-IV	MMT ABS 6mo; heroin ABS 12mo (23)	Healthy (27)	46.4 ± 6.21	39.9 ± 10.9*	61	61	32-50°C in 9 cm^2 (right dorsum of hand)	Increased	NA	ns
Compton (15)	Opioid	DSM-IV	CP + OUD (20) (e)	CP (20) (e)	44.35 ± 10.84	49.91 ± 9.41	50	60	37-47°C in 9 cm^2 (volar forearm)	NA	ns	Increased
Peles (24)	Opioid	DSM-IV-TR	Opioid ABS; MMT active (31)	Healthy (17)	41 ± 8.6	39.3 ± 10	71	47	35-51°C in 9 cm^2 (mid-dorsal of hand)	ns	NA	ns (f)
			Opioid ABS; MMT active; CP (18)		42.7 ± 1.9	39.3 ± 10	67			Increased	NA	ns
			Opioid ABS; MMT active; no CP (17)		38.2 ± 2.4	39.3 ± 10	77			Decreased	NA	Decreased

Abbreviations: ABS: abstinent; CP: chronic pain; DSM: Diagnostic and Statistical Manual of Mental Disorders; MMT: methadone maintenance treatment; mo: month; ns: nonsignificance; NA: nonapplicable; SD: Standard deviation; SEM: standard error of the mean; wk: week

(a) Decreased/increased outcome in Group One. (b) Chronic gastritis (n = 4), peptic ulcers (n = 5), and hypertension (n = 4). Exclusion criteria comprised diabetes mellitus, liver cirrhosis, and peripheral neuropathy. (c) Chronic gastritis (n = 3), peptic ulcers (n = 3), CP (n = one), and hypertension (n = 5). (d) Study inclusion criteria for smokers: consumed ≥ 15 cigarettes/day for at least 2 years with nicotine yields > 0.6 mg nicotine and 10 mg tar. The patients were instructed to smoke before and during the breaks of the study. (e) Among 40 CP patients: musculoskeletal pain (n = 16), neuropathy (n = 14), mixed (n = 10). The severity of CP was rated as moderate (VAS = 56.3/100) in the past 24 hours of participation in the study. (f) Among patients undergoing MMT, sub-group analysis showed that the perceived intensity of heat pain was lower in those who received high doses of MMT (mean ± SD: 188.1 ± 8.1 mg) than in those who were receiving low doses thereof (40.8 ± 7.8 mg).

*Age difference.

Table 4. *Studies of noxious pressure stimulation (n = 5).*

Study	Diagnosis		Contrast (Sample Size)		Age (Mean ± SD/SEM)		Male %		Stimulus Intensity Base—Noxious	Pain (a)		
	Class	Criteria	Group One	Group 2	Group One	Group 2	Group One	Group 2	Location	Threshold	Tolerance	Intensity
Pressure—Ischemic Muscle Pain												
Girdler (16)	Nicotine	Unavailable (b)	Female smoker (17)	Female healthy (20)	25.6 ± 1.4	27.2 ± 1.3	0	0	200 mmHg (arm)	NA	Increased	ns
			Male smoker (20)	Male healthy (20)	25.5 ± 1.3	28 ± 1.3	100	100		NA	ns	ns
Carcoba (31)	Opioid	DSM-IV	Opioid ABS 30.4 mo (20)	Healthy (20)	35.1 ± 7.1	29.7 ± 5.1	100	100	200 mmHg (arm)	ns	Decreased	ns
			Opioid ABS 2-72hr (60)		30.6 ± 8.3		100			Decreased	Decreased	ns
Pressure—Pinch-Like Pain												
McCann (19)	MDMA	DSM-IIIR	ABS 2wk (42)	Healthy (43)	24.5 ± 4.9	23.6 ± 3.3	67	53	3.7 -13.8 lbs, 1 cm^2 (trapezius)	Decreased	NA	NA
									(forearm)	ns	NA	NA
									(masseter)	Decreased	NA	NA
Peles (24)	Opioid	DSM-IV-TR	Opioid ABS; MMT active (31)	Healthy (17)	41 ± 8.6	39.3 ± 10	71	47	0-300kPa, in 3.14 cm^2 (dorsal of hand)	ns	NA	NA
			Opioid ABS; MMT-active CP (18)		42.7 ± 1.9		67			ns	NA	NA
			Opioid ABS; MMT active w/ no CP (17)		38.2 ± 2.4		77			ns	NA	NA
McHugh (21)	Opioid	Multiple (c)	CP + opioid misuse (31) (c)	CP (20) (c)	53.39 ± 8.87	56.4 ± 7.37	55	50	128-256 mN; 0.5 cm^2 (thumb)	ns	NA	ns
									(trapezius)	ns	NA	ns

Abbreviations: ABS: abstinent; CP: chronic pain; DSM: Diagnostic and Statistical Manual of Mental Disorders; MMT: methadone maintenance treatment; mo: month; ns: non-significance; NA: non-applicable; SD: Standard deviation; SEM: standard error of the mean; wk: week

(a) Decreased/increased outcome in Group One. (b) Group One met the study inclusion criteria: consumed ≥ 15 cigarettes/day for at least 2 years with nicotine yields > 0.6 mg nicotine and 10 mg tar. The patients were instructed to smoke before and during the breaks of the study. (c) The 17-item self-report Current Opioid Misuse Measure and the 20-item Addiction Behaviors Checklist were applied. No version of the DSM was used. The severity of pain was measured by the self-report Brief Pain Inventory (BPI), and the BPI scores showed no significant difference between the groups. Five patients in Group One (actual n = 26) and one patient in Group 2 (actual n = 19) did not complete all tests.

Table 5. *Studies of noxious electric current and chemical-irritant stimulations (n = 2).*

Study	Diagnosis		Contrast (Sample Size)		Age (Mean ± SD/SEM)		Male %		Stimulus Intensity Base—Noxious	Pain (a)		
Electrical	**Class**	**Criteria**	**Group One**	**Group 2**	**Group One**	**Group 2**	**Group One**	**Group 2**	**Location**	**Threshold**	**Tolerance**	**Intensity**
Jochum (26)	Alcohol	DSM-IV	Active (30) (b)	Healthy (30)	41.5 ± 8.6	41.6 ± 8.1	100	100	0-271 mA (finger)	ns	ns	NA
			ABS 2-3m (30) (c)	Healthy (30)	41.5 ± 8.6	41.6 ± 8.1	100	100		ns	ns	NA
			Active (30) (b)	ABS 2-3m (30) (c)	41.5 ± 8.6	41.5 ± 8.6	100	100		Decreased	Decreased	NA
Chemical												
Ditre (27)	Nicotine	Multiple (d)	ABS 12-24hr (74)	Active (63)	39.72 ± 12.19	40.86 ± 12.75	52.7	52.7	10% capsaicin, in 1.5x1.5 cm^2 (volar forearm)	NA	NA	Increased (e)
			ABS 2hr (28)	Active (63)	43.39 ± 13.18	40.86 ± 12.75	60.7	60.3		NA	NA	ns
			ABS 12-24hr (74)	ABS 2hr (28)	39.72 ± 12.19	43.39 ± 13.18	52.7	60.7		NA	NA	ns (e)

Abbreviations: ABS: abstinent; DSM: Diagnostic and Statistical Manual of Mental Disorders; hr: hour; MMT: methadone maintenance treatment; mo: month; ns: nonsignificance; NA: nonapplicable; SD: standard deviation; SEM: standard error of the mean.
(a) Decreased/increased outcome in Group One. (b) Chronic gastritis (n = 4), peptic ulcers (n = 5), and hypertension (n = 4). Exclusion criteria comprised diabetes mellitus, liver cirrhosis, and peripheral neuropathy. (c) Chronic gastritis (n = 3), peptic ulcers (n = 3), CP (n = one), and hypertension (n = 5). (d) The 6-item Fagerström Test for Nicotine Dependence (FTND 1989), the Minnesota Nicotine Withdrawal Scale (MNWS 1986), and the Brief Questionnaire of Smoking Urges (QSU-Brief 2001) were used. (e) Skin areas of mechanical hyperalgesia and flare were increased in Group One.

in neurogenic inflammation in response to acute nicotine withdrawal in patients with tobacco use disorder (TUD). Experimental pain induction by chemical irritants in humans also includes intracutaneous injections (33) or cutaneous insertion through inactive spicules (34).

PART II: SUBSTANCE USE DISORDERS

Alcohol Use Disorder (AUD)

Jochum (26) assessed thermal, vibration, and electrical detection and pain thresholds in 90 men: 30 with AUD who were in acute withdrawal, 30 who had abstained for 2–3 months, and 30 healthy controls. Compared to the controls, the patients in acute withdrawal exhibited a significantly higher warmth detection threshold (estimated mean ± SD: 35.75 ± 0.6°C vs. 34.7 ± 0.5°C), a lower heat pain threshold (42.0 ± 0.5°C vs. 46.0 ± 0.5°C), and lower heat pain tolerance (48.4 ± 0.5°C vs. 50.9 ± 0.3°C). These findings were consistent across stimulation sites, except that no difference in heat detection thresholds was observed at the sternum. The vibration detection threshold was also elevated in the withdrawal group (0.92 ± 0.20 mm/s vs. 0.50 ± 0.07 mm/s), indicating impaired sensory processing. No significant differences were noted in electrical detection thresholds, electrical pain thresholds, or electrical pain tolerance between groups. However, among patients in detoxification, those with severe withdrawal symptoms (as measured by the Alcohol Withdrawal Scale) (28) showed a lower electrical pain threshold (122 ± 15.8 mA vs. 192.7 ± 24.8 mA) and lower pain tolerance (141 ± 16.4 mA vs. 262.6 ± 30.4 mA) than did those with mild symptoms.

In patients with AUD, particularly those experiencing acute withdrawal, psychophysical testing revealed elevated warmth detection thresholds and reduced thermal pain tolerance, results consistent with thermal hypersensitivity. Additionally, patients with more severe withdrawal symptoms showed markedly lower thresholds for electrical pain, suggesting a severity-dependent change in pain processing.

Tobacco Use Disorder (TUD)

Investigators (16,27) have examined pain

elicited by chemical-irritant, cold, heat, and pressure stimulation in individuals with TUD.

Ditre (27) assessed chemical irritant–induced pain by topically applying 10% capsaicin to the forearms of 165 individuals with TUD and randomized the results into 3 groups: 1) those who abstained from smoking for 12–24 hours; 2) those who abstained from smoking for 2 hours; and 3) those who did not abstain. Patients who abstained for 12–24 hours reported higher maximal capsaicin-induced pain intensity (4.82 ± 3.52 vs. 3.47 ± 2.77 on a 0–10 scale), larger areas of mechanical hyperalgesia (71.98 ± 55.17 cm^2 vs. 45.07 ± 37.14 cm^2), and greater flare (38.52 ± 22.72 cm^2 vs. 30.24 ± 21.16 cm^2) than did the nonabstinent controls. Flare areas were also larger than in the 2-hour-abstinence group (31.95 ± 17.06 cm^2), suggesting enhanced peripheral nociceptor sensitivity and central sensitization during nicotine withdrawal.

Girdler (16) evaluated cold, heat, and ischemic pressure pain responses in 37 habitual smokers (≥ 15 cigarettes/day) and 40 nonsmokers. To control for hormonal influences, female patients were tested during the late follicular phase (days 9–12) of their menstrual cycles. Smokers smoked before and during testing to mitigate withdrawal effects. Male smokers showed greater cold pain tolerance than did nonsmokers (65.6 ± 14.8 s vs. 32.7 ± 15.7 s). Among smokers, women had lower heat pain thresholds (42.7°C vs. 43.5°C) and tolerances (47.9°C vs. 48.8°C) than did men. Female smokers also exhibited higher ischemic-pressure pain thresholds (329.9 ± 41.3 s vs. 148 ± 48.1 s) and tolerances (504.8 ± 55 s vs. 274.9 ± 51.6 s) than did female nonsmokers. Pain intensity ratings across modalities did not differ significantly across groups.

These findings suggest that nicotine withdrawal may acutely enhance both peripheral and central pain sensitivity, particularly to chemical stimuli. Additionally, chronic tobacco use appears to alter pain perception in a gender- and modality-specific manner, even in the absence of withdrawal.

Stimulant Use Disorders

Pain responses to cold, heat, and pressure stimulation have been studied in individuals with 3,4-Methylenedioxymethamphetamine (MDMA) use disorder (19) and cocaine use disorder (CUD) (17).

McCann (19) assessed pain thresholds and tolerance in 42 patients with MDMA use disorder who had used between 0.5 to 7 tablets per session for 7 to 168 months and compared the observations to those of 43 matched healthy controls. To minimize the confounding effects of polysubstance use, patients with MDMA use disorder refrained from drug use for 2 weeks prior to the study. The results indicated that patients with MDMA use disorder who refrained from drug use demonstrated higher cold pain intensity (67.0 ± 5.0 on a 0-100 pain rating scale) than did controls (55.2 ± 6.0). Additionally, the pressure pain thresholds in the trapezius (9.7 ± 0.7 lbs) and masseter (4.7 ± 0.4 lbs) muscles were lower in MDMA users than in controls (11.4 ± 0.8 lbs and 5.8 ± 0.5 lbs, respectively). There were no significant differences between the groups for the pressure-pain threshold in the forearm (9.6 ± 0.7 lbs), heat pain threshold (44 ± 1.1°C), or heat pain tolerance (48.4 ± 0.4°C).

Compton (17) employed CPT to evaluate pain tolerance in 21 active male users with CUD (years of use mean ± SD: 7.3 ± 5.9) and 32 abstinent men (weeks of abstinence: 39.3 ± 32.6; years of use: 9.5 ± 7.2). The study found that active male users had lower cold pain tolerance (estimated mean: 79.1 s) compared to abstinent male individuals (165.5 s), suggesting that continued stimulant use may affect the perceived intensity of pain in this population.

These findings suggest that both MDMA and cocaine use are linked to the persistence of heightened pain sensitivity, especially to cold and pressure stimuli, after short-term abstinence. The observed differences between active and abstinent cocaine users further suggest that stimulant-induced changes in pain perception may be partially reversible.

Opioid Use Disorder (OUD)

This review included one OUD study published recently (23) and 6 others (17,18,20,22,24,25) that were not included or discussed explicitly in Higgins (6) or Trøstheim (7). These studies investigate thresholds, tolerance, and/or perceived intensity of pain in response to cold, heat, pressure, and/or mechanical stimulation (via von Frey hair) among OUD patients.

Compton (17) further examined the effects of opioid abstinence by recruiting 69 male OUD patients who were receiving MMT, including 43 active opioid users and 26 abstinent individuals who had refrained from opioid use for a mean of 59.2 ± 102.6 weeks. The study found that active users had a lower tolerance for cold pain compared than did those who were abstinent (estimated mean: 64.6 s vs. 113.6 s, respectively).

Treister (22) studied the effects of opioid abstinence by recruiting 50 active opioid users, 43 former users who had remained abstinent for at least 5 months,

and 50 healthy patients. The results showed lower cold pain tolerance in active users (mean ± SD: 30 ± 36.2 s vs. 56.4 ± 51.4 s; CPT at 1°C) but higher pain thresholds (10.8 ± 7.7 s vs. 6.8 ± 3.5 s) than healthy patients had. However, there were no significant differences in cold pain tolerance and threshold between former opioid users and healthy patients, suggesting an amelioration of OIH during recovery.

Ren (18) observed that patients who remained abstinent from opioids for 4.9 months had a lower tolerance (mean ± SEM: 85.1 ± 14.1 s vs. healthy controls = 133.7 ± 16.7 s, CPT at 2 ± 2°C) and threshold for cold pain (37.3 ± 3.5 s vs. healthy controls = 57.4 ± 5.1 s). No significant differences were found between the groups' perceived intensity of pain.

Pud (20) also noted lower cold pain tolerance in patients who refrained from opioids for 4 weeks (mean ± SD: 29.1 ± 36.7 s vs. healthy controls = 56.4 ± 51.3 s; CPT at 1 ± 1.5°C). However, the study showed a higher pain threshold (10.6 ± 7.7 s vs. healthy controls = 6.6 ± 3.5 s) and lower intensity of perceived pain (56.8 ± 21.0 vs. 72.8 ± 15.8 on a 0-100 pain rating scale).

In summary, a lower pain tolerance in patients with OUD was observed, a result consistent with the findings of Higgins (6). However, among abstinent patients in these included studies, findings on cold pain thresholds varied. As for the perception of the intensity of heat pain, no significant differences were observed between patients who refrained from opioid use and healthy controls.

In Prosser (25), 23 patients with heroin use disorder (HUD) who had stayed abstinent for at least one year and ceased MMT for at least 4 months were compared to 27 healthy controls. The study found a higher heat detection threshold (mean [range]: 38.83°C [33.3 – 49.4] vs. controls = 35.96°C [33.2 – 43.5]) and heat pain threshold (48.73°C [39.9 – 50] vs. controls = 47.62°C [38.5 – 50]) but no significant difference in the perceived intensity of heat pain.

Peles (24) studied 31 patients with HUD who had refrained from drug use, had maintained MMT for at least 6 months, and received methadone 30 to 60 minutes before study participation. These patients were compared with 17 healthy controls. Peles (24) found no significant difference in the perceived intensity (mean: 6 on a 0-10 pain rating scale) or threshold of pain (mean ± SD: 42.36 ± 4.16°C) between the groups. Additionally, the 2 groups showed no significant difference in the threshold of algometer-induced pain or in the threshold of touch induced by mechanical stimulation that used a von Frey hair.

Together, these findings support the persistence of OIH during active use and early abstinence, particularly for cold pain. However, evidence also suggests that with prolonged abstinence, pain sensitivity may normalize, reflecting a potential gradual reversibility of OIH.

Comorbid Chronic Pain and OUD

Four studies (15,21,23,24) in this review explored nociceptive changes induced by various stimuli in individuals with chronic pain and OUD.

Compton (15) compared the perceived intensity of pain in response to heat and cold stimuli between 20 OUD patients with chronic nonmalignant pain and 20 patients with chronic pain but no OUD. The results showed that OUD patients reported a higher perceived intensity of pain in response to both heat (median [range]: 77.5 [20-100] on a 0-100 scale) and cold stimuli (50 [0-95]) than did those with chronic pain but no OUD (heat: 60 [0-90]; cold: 25 [0-75]). Furthermore, the temporal summation of the perceived intensity of heat pain was heightened significantly in the OUD group. However, their cold pain threshold (14.61 [2.6-58.6] s) and tolerance (28.07 [10-300] s) were not significantly different from those of the non-OUD group (cold pain threshold: 11.72 [0-50] s; tolerance: 21.11 [0-300] s).

Peles (24) examined the effects of chronic pain on thermal and pressure-induced pain in 18 patients with chronic pain, 13 patients without chronic pain, and 17 healthy controls, all on methadone maintenance therapy (MMT). Interestingly, patients without chronic pain exhibited the lowest heat pain threshold (40.1 ± 2.96°C) and the highest cold pain threshold (23.0 ± 5.5°C). In contrast, patients with chronic pain had a significantly increased heat pain threshold (44.5 ± 3.9°C), and no significant differences were observed for cold pain threshold (17.2 ± 10.2°C) or pressure pain thresholds across the groups.

Wachholtz (23) compared cold pain thresholds, tolerance, and intensity among 4 groups of chronic pain patients: 1) 30 on methadone, 2) 30 on buprenorphine, 3) 30 abstinent from MOUD for at least 6 months, and 4) 30 opioid-naïve controls. Patients with a history of MOUD use showed lower cold pain thresholds (methadone: 27.3 ± 2.33 s; buprenorphine: 21.1 ± 1.48 s; MOUD abstinent: 28.2 ± 5.27 s) and tolerance (methadone: 56 ± 7.63 s; buprenorphine: 52.2 ± 5.35 s; MOUD abstinent: 61.4 ± 10.5 s) than did opioid-naïve controls (pain threshold: 54.4 ± 11.39 s; tolerance: 137.1 ± 20.62 s). The perceived intensity of cold pain (63.8 ± 2.29 on a 0-100 scale) did not differ significantly across the groups.

McHugh (21) assessed the perceived intensity and tolerance of cold pain as well as pressure pain thresholds in 26 OUD patients with chronic back/neck pain who received prescribed opioids. The researcher compared those patients' results to those of 19 patients with chronic pain who were prescribed opioids but did not have OUD. The study found no significant differences in the perceived intensity of cold and pressure pain between the 2 groups.

These studies (15,21,23,24) provide evidence that opioid use, along with chronic pain, leads to altered pain processing. Specifically, OUD patients demonstrated increased pain sensitivity to certain stimuli (heat and cold) and impaired pain modulation (e.g., temporal summation), but those effects varied by the type of pain stimulus. Further research is needed to explore the underlying mechanisms of these changes and their clinical implications for managing pain in individuals with comorbid chronic pain and OUD.

Discussion

Understanding pain in individuals with SUDs requires moving beyond traditional diagnostic and treatment frameworks. Substance use—whether active, in withdrawal, or remission—affects nociceptive processing profoundly, reshaping the pain experience in ways that standard clinical models may not fully capture. Experimental pain paradigms provide critical insights into these neuroadaptive changes, offering a translational bridge from mechanistic research to improved clinical care for this vulnerable population.

Experimental Pain Modalities and Their Clinical Relevance

Cold stimulation using the CPT consistently demonstrates decreased cold pain tolerance among individuals actively using opioids, methadone, or cocaine as well as those in early abstinence (17,22,25). This pattern reflects withdrawal-associated hyperalgesia, a physiologically grounded sensitivity, rather than volitional exaggeration. Although variability across studies exists—which is partly attributable to CPT protocol differences and gender-related factors (16,23,29)—CPT remains a practical, cost-effective tool for assessing cold pain alterations. When investigators observe heightened pain sensitivity in patients during detox or medication transitions, said investigators can interpret these findings as withdrawal biomarkers, potentially reducing stigma and improving pain assessment accuracy.

Heat stimulation paradigms reveal bidirectional effects influenced by substance type and use state. For example, abstinent alcohol users often present with elevated heat pain thresholds, potentially due to alcohol-induced neurotoxicity, while active users or those in withdrawal exhibit decreased thresholds, indicative of sensitization (26). However, heat pain responses are highly sensitive to external variables such as skin temperature, vascular tone, and even electrical impedance, based on Ohm's law (30,32). This variability underscores the importance of considering environmental and physiological factors when interpreting patient reports, cautioning against premature dismissal of pain as disproportionate or psychosomatic.

Mechanical pressure thresholds are often unchanged in SUD cohorts, yet more refined techniques, such as von Frey filament testing, can uncover secondary hyperalgesia and central sensitization. These findings have significant clinical implications, since many chronic pain patients with SUDs report diffuse or spreading pain beyond identifiable peripheral injury. Quantifying secondary hyperalgesia provides objective evidence of central amplification, informing treatment strategies that incorporate NMDA antagonists or alpha-2 adrenergic agonists. Conversely, ischemic or pinch-based assessments should be avoided in patients with vascular compromise, which is common among those who use injection drugs or have stimulant-induced vasculopathy.

Electrical stimulation is widely utilized in experimental and some neurodiagnostic contexts; however, its indiscriminate activation of A-beta, A-delta, and C fibers limits its specificity for studying peripheral sensitization (35) in SUD-related pain (26). While electrical methods remain valuable for evoked potential testing or general pain induction, their clinical translation requires the careful alignment of modality with the clinical question, such as distinguishing central from peripheral mechanisms.

Chemical-irritant stimulation—including the use of topical capsaicin or intradermal agents—offers receptor-specific insights into peripheral and central sensitization. Heightened responses among nicotine-deprived individuals, characterized by increased flare and secondary hyperalgesia, exemplify withdrawal-induced neuroplasticity (27). Clinically, these phenomena correspond to patient presentations of refractory burning or aching pain during early abstinence, which often respond poorly to conventional analgesics. Recognition of such sensitization may prompt consideration of targeted nonopioid therapies (e.g., gabapentinoids, cannabinoids) or non-pharmacological desensitization protocols.

Approaching Patients with SUDs in Clinical Pain Research and Pain Management Settings

Patients with SUDs present complex challenges at the intersection of neuroplasticity, psychosocial stressors, and stigma. Pain research in this population requires methodological precision and clinical sensitivity to ensure valid findings and ethical engagement. Bridging experimental insight with clinical relevance benefits from integrated, trauma-informed, and physiologically grounded approaches, which require the physician to do the following:

1. Maintain Physiological Neutrality and Scientific Rigor. Pain reports from individuals with SUD benefit from a neutral, nonjudgmental, and physiologically grounded approach. Instead of dismissing the reporting of subjective pain as exaggerated or drug-seeking behavior, clinicians and researchers should interpret these pain reports within the context of measurable neuroadaptive changes. Psychophysical tools such as quantitative sensory testing (QST) (14,36) and standardized pain scales can assess nociceptive differences objectively while supporting both data integrity and patient trust.
2. Utilize a Structured, Multimodal Assessment Strategy. A multimodal and standardized approach improves phenotypic resolution and reduces confounding from fluctuating states such as intoxication or withdrawal. Methodologies may include thermal and mechanical QST, pressure algometry, sensory mapping (e.g., von Frey filaments) (14,25,28,36), and validated pain inventories. Selecting modalities based on specific research or clinical aims allows for better differentiation among nociceptive, neuropathic, and affective pain components, without over-relying on any single task, such as the CPT.
3. Account for Temporal Dynamics of Withdrawal and Abstinence. Pain sensitivity may fluctuate considerably during acute withdrawal and early and long-term abstinence. Human laboratory studies have demonstrated that opioid withdrawal is associated with significantly reduced pain thresholds and tolerance, often measured via cold pressor or pressure-pain tasks (17,18). To improve the interpretability of findings and guide patient care, research designs and clinical evaluations may benefit from clearly standardizing the time elapsed since the patients' last substance use and, when appropriate, from using adjunctive nonopioid medications such as α_2-agonists or gabapentinoids to reduce hyperalgesia-related noise.
4. Use Clinical Language to Reduce Stigma. Clinical language should reflect contemporary understanding of SUD-related neuroadaptation. Terms such as "pain amplification" or "neuroadaptive sensitivity" reflects underlying biology and may reduce stigma, enhance communication, and improve adherence (37,38).
5. Integrate Collaborative and Trauma-Informed Practices. When feasible, embedding behavioral health, addiction medicine, and social services into pain research or clinical protocols may enhance patient retention, reduce the risk of retraumatization, and support ethical engagement. This approach is particularly relevant for populations who have experienced stigmatization or fragmented care systems (39).
6. Ensure Equity and Ethical Fidelity. Research and care involving individuals with SUDs should address disparities actively. Equity-driven frameworks help avoid perpetuating undertreatment and ensure socially responsible dissemination (40).

Implications in SUD–Pain Research and Future Directions

This review demonstrates a clear need for more research using psychophysical methods to study pain in people with SUDs. While animal studies have provided important clues, clinical data on humans remain limited. Future studies should use standardized tools like QST (14,36) to better measure pain thresholds, tolerance, and intensity. Using scales such as the visual analog scale (VAS) or numeric rating scale (NRS) (41) and tracking pain over time will help clarify changes in nociception, including allodynia, hyperalgesia, and hypoalgesia.

Research must carefully consider factors like substance use patterns, withdrawal timing (18,19,31), and medication treatments (24,25) to improve the reliability of findings. Longitudinal studies are especially valuable to understand how pain sensitivity changes with drug use and abstinence (18,23,31).

Emerging data highlight the importance of brain reward systems in pain perception. Regions such as the ventral tegmental area and nucleus accumbens interact with pain pathways, and the disruption of these circuits may increase pain perception in people with SUDs (35, 42-46). Including assessments of emotional and motivational aspects alongside sensory testing will provide a more complete picture of pain in these patients (43).

Moving forward, collaboration across professionals in the fields of neuroscience, addiction medicine, and pain management is essential for the development of targeted, nonopioid treatments that address both the sensory and emotional components of pain. Such work will improve care for this complex patient group.

Limitations

Despite these insights, this review has several limitations that constrain the generalizability of its conclusions. Most notably, there is a paucity of human psychophysical studies in SUD populations, with much of the existing literature based on animal models. Consequently, conclusions drawn from preclinical findings may not translate fully to the complexity of human pain experiences in addiction contexts. Additionally, studies that assess only pain threshold or tolerance without evaluating perceived pain intensity may overstate the presence or severity of hyperalgesia. This narrow approach limits the ability to distinguish among sensory amplification (hyperalgesia), sensory misattribution (allodynia), and sensory dampening (hypoalgesia).

Another important limitation is the lack of demographic and clinical characterization in many studies. Variables such as age, gender, race (47), and comorbid health conditions—including diabetes, neuropathies, and liver disease—can independently influence pain perception and tolerance (31,47). Failure to control for these confounding factors may obscure true effects or introduce bias into experimental findings. Moreover, the inclusion of patients with an abnormally high or low pain tolerance can pose risks in experimental settings and may lead to injury or ethical concerns if proper safeguards are not in place.

Finally, this review did not include a formal meta-analysis, and thus the synthesis remains narrative. While qualitative interpretation provides conceptual clarity, future systematic reviews should consider aggregating psychophysical data quantitatively to better understand the magnitude of pain changes in SUD populations across different substances, pain modalities, and study designs.

Conclusion

Psychophysics offers a valuable framework to advance the understanding of changes in nociception within patients with SUDs. Evidence indicates that chronic exposure to substances such as alcohol, nicotine, cocaine, MDMA, and opioids is associated with distinct changes in pain thresholds, tolerance, and perception across various experimental modalities. The quantifiable and noninvasive assessments described above enhance mechanistic insight and support ethically grounded, personalized pain management. Future studies should emphasize methodological rigor, ecological validity, and patient-centered approaches to better translate psychophysical findings into improved clinical outcomes and compassionate care for individuals with SUDs.

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Author Contributions

HFI conceptualized, investigated, and wrote the first draft of the manuscript and then reviewed and approved the final manuscript. FG reviewed and verified the data and then wrote and approved the final manuscript.

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