Chapter 7

Emotional Self-Medication and Addiction

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Abbreviations

cE Consummatory appetitive extinction
cSNC Consummatory successive negative contrast
ESM Emotional self-medication
iE Instrumental appetitive extinction
iSNC Instrumental successive negative contrast
PRCE Partial reinforcement contrast effect
PREE Partial reinforcement extinction effect
PSM Physical self-medication
PTSD Posttraumatic stress disorder
RHA Roman high-avoidance rats
RLA Roman low-avoidance rats
SNC Successive negative contrast
SUD Substance use disorder

INTRODUCTION

Humans have traditionally used psychoactive substances with a variety of purposes, including mystical ecstasy, search for pleasure, relief from physical pain, and madness treatment. Many of these practices may have been the result of the observation of self-medication behaviors in nonhuman animals. These behaviors constitute a source of knowledge regarding the therapeutic and psychoactive properties of natural substances (Huffman, 2010). Some of these drugs have been shown to have addictive effects, so it has been proposed that the scientific study of self-medication could shed light on the understanding of substance use disorders (SUDs) (Darke, 2012; Khantzian, 2013).

The *Diagnostic and Statistical Manual for Mental Disorders* (American Psychiatric Association, 2013) provides detailed criteria for the diagnosis of SUDs, including sustained excessive consumption, cravings, tolerance, and withdrawal symptoms. Unlike previous diagnostic criteria (in which abuse and dependence constructs were considered separately), addiction is therein defined as a continuum from mild to severe SUD based on the number of items met of a total of 11. SUDs are viewed as neurobehavioral disorders resulting from persistent dysregulation of neural circuits that mediate motivation, cognition, learning/memory, habits, and stress reactivity (Koob, 2013).

Several approaches have identified the motivations leading a person to consume drugs. Some views state that the positive reinforcing value of abuse drugs constitutes the critical factor that initiates consumption. This value is related to the activity of midbrain dopaminergic neurons that project to the basal forebrain—known as the reward system. Although drugs of abuse differ in their pharmacological profile, most increase dopamine levels within this circuit, particularly in the nucleus accumbens (Koob, Arenns, & LeMoal, 2014). Because the assumption underlying this approach suggests that the onset of addictive behavior relates to the "pleasure" initially induced by these substances, we will characterize this mechanism as one relying on drive induction. Thus, *drive induction* refers to the reinforcing effect of an increase in stimulation in an organism that is not necessarily in a negative internal state. For example (Figure 1), animals learn a new response, whose consequence is a simple change in stimulation (e.g., turning on a light; Levin & Forgays, 1960).

Adaptive theories postulate that environmental influence constitutes a critical determinant of addiction. Within this context, the self-medication hypothesis states that the drug chosen to be consumed depends on the drug's ability to either relieve a psychiatric disorder or reduce occasional or persistent negative emotional states induced by aversive events (Khantzian, 1985, 2013). Experimental and clinical evidence supports the self-medication hypothesis, although some contradictory results invite caution. This chapter focuses on a special case of self-medication, namely, the consumption of psychoactive drugs that modulate negative emotions induced by:

1. Acute and/or chronic stressful experiences in healthy individuals,
2. Psychiatric conditions with negative affect as a prominent symptom, and
3. Distress/dysphoria associated with drug withdrawal.

As shown below, this special case, termed emotional self-medication (ESM) hereafter, underlies some forms of drug use behaviors that contribute to the onset, progression, maintenance, and/or relapse of an SUD. This chapter is organized into four major sections. First, we look at clinical evidence testing the ESM hypothesis. Second, we review physical self-medication (PSM) and ESM behavior in nonhuman animals with two objectives: (1) identify similarities between these two forms of self-medication and (2) analyze the extent to which ESM can influence drug consumption and abuse. Third, we review studies on ESM aiming at bridging the gap between experimental and clinical research. Finally, we identify areas in which future research can have a significant impact on our understanding of the connection between ESM and addiction.

Sensory-reinforced instrumental behavior

Drug-reinforced instrumental behavior
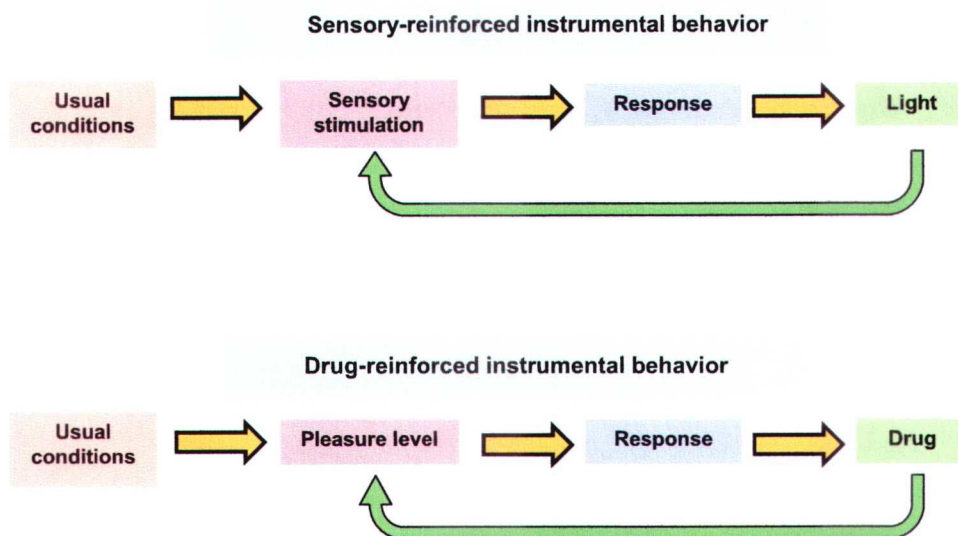
FIGURE 1 **Examples of instrumental reinforcement by drive induction.** A neutral internal state is increased in intensity by the outcome of an instrumental response (positive reinforcement). Top: in sensory reinforcement, an instrumental response is reinforced by the presentation of a light. Bottom: the initial exposure to a drug increases positive affect.
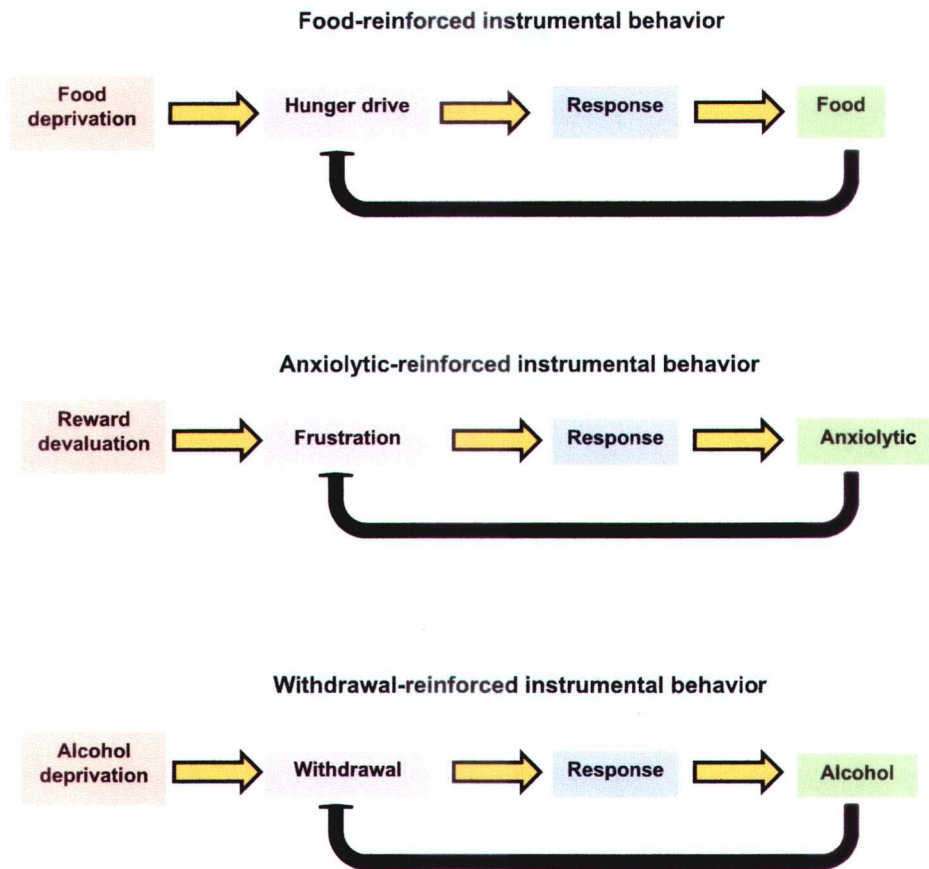
ESM AND ADDICTION IN HUMANS

Is ESM related to addictive behavior in humans? Addiction has become a public health issue with medical, social, legal, and political implications (Koob et al., 2014). Worldwide interest in this problem notwithstanding, there are few theories explaining addiction, a behavior maintained despite its self-destructive consequences. The self-medication hypothesis was initially conceived as a psychodynamic model of substance dependence in which drug consumption was viewed as a strategy to cope with disordered emotions, self-care, self-esteem, and personal relationships triggering painful and threatening emotions (Khantzian, 1985, 2013; Koob et al., 2014). The self-medication hypothesis was revised from a behavioral perspective according to which self-medication behavior is initiated and maintained by negative reinforcement (Blume, Chmaling, & Marlatt, 2000). This perspective assumes that negative reinforcement occurs when a behavior followed by the removal of an *internal* aversive state increases its future probability (Koob et al., 2014). This notion has been important in the development of psychobiological models of addiction (Koob, 2013), but it conflicts with traditional definitions of reinforcement contingencies (Ferster & Skinner, 1957). Reinforcement contingencies have been defined in terms of the response being followed by either the presentation of an *external* outcome (positive reinforcement) or the removal of an *external* outcome (negative reinforcement). Therefore, reducing an aversive internal state (e.g., hunger, negative emotion, withdrawal symptoms) by procuring an outcome is an instance of positive reinforcement, as illustrated in Figure 2. In these cases, reinforcement may be characterized in terms of drive reduction. *Drive reduction* refers to the strengthening effects of an outcome that compensates for a negative internal state, be it motivational (e.g., thirst, hunger) or emotional (e.g., frustration, drug withdrawal).

The ESM hypothesis of addiction is based on two main assumptions (Darke, 2012). First, the *psychopathology postulate*

states that substance use relates to the relief of symptoms of psychological distress. Therefore, the relief of negative affect constitutes the main motivation and provides reinforcement for substance use in distressed individuals (Li, Lu, & Miller, 2013). Consistent with this assumption, patients who suffer from anxiety disorders and cite symptom relief as the main reason for drug use are more likely to develop an SUD (Ruglass et al., 2014). From this perspective, the relationship between alcohol consumption and anxiety disorders would be explained in terms of the tension-reducing effects of alcohol (Conger, 1956). This assumption implies that it is the symptoms of negative affect accompanying a psychiatric condition, rather than the primary psychiatric condition per se, that provides the basis for ESM (Darke, 2012). Moreover, healthy individuals may use ESM as a coping strategy to deal with painful and unbearable feelings; that is, ESM need not be associated with a primary psychiatric disorder (Khantzian, 2013).

The second postulate of the ESM hypothesis, *drug specificity*, suggests that the choice reflects the drug's ability to ameliorate specific distressing symptoms. Thus, psychostimulants would be used by hypomanic patients; anxiolytics and alcohol to cope with anxiety; opiates to reduce anger, rage, or physical pain; energizers to reduce depressed mood; cognitive enhancers for attention deficits; nicotine for the negative symptoms of schizophrenia; and so on (Darke, 2012; Koob et al., 2014; Kumari & Postma, 2005). Therefore, the ESM hypothesis would be supported by showing that patients with similar psychiatric problems displayed similar patterns of substance use (Blume et al., 2000). This assumption also implies that drugs with comparable pharmacological profile would be interchangeably used for similar symptoms.

Tests of the ESM hypothesis have shown mixed results. First, several studies suggest that emotionally painful experiences are associated with the initial use, loss of control, and relapse into drug abuse (Briand & Blendy, 2009). Consistent with this, individuals exposed to either acute or chronic emotional stress are more likely to use drugs. For example, the rates of use of alcohol

Food-reinforced instrumental behavior

Food deprivation → Hunger drive → Response → Food

Anxiolytic-reinforced instrumental behavior

Reward devaluation → Frustration → Response → Anxiolytic

Withdrawal-reinforced instrumental behavior

Alcohol deprivation → Withdrawal → Response → Alcohol

FIGURE 2   Examples of instrumental reinforcement by drive reduction. An aversive internal state is reduced by the outcome of an instrumental response (positive reinforcement). Top: conventional food-reinforced instrumental behavior. Middle: emotional self-medication induced by reward loss and access to an anxiolytic. Bottom: relapse of an already established addiction induced by withdrawal symptoms resulting from drug deprivation. In all cases, behavior is reinforced by a reduction in negative emotion.

in war combatants suffering from posttraumatic stress disorder (PTSD) are higher than in veterans without PTSD (Enman, Zhang, & Unterwald, 2014; Mantsch et al., 2014). Similarly, a significant portion of individuals experiencing social phobia consume alcohol to cope with the distress derived from social situations (Carrigan & Randall, 2003). In addition, people exposed to adverse life events (e.g., physical, sexual, or domestic abuse; bullying; natural catastrophes; divorce; death of a loved one; losing a job; family conflicts; poverty; chronic pain; etc.) show higher consumption rates of alcohol, benzodiazepines, and illicit drugs (Duffing, Greiner, Mathias, & Dougherty, 2014; Hassanbeigi, Askari, Hassanbeigi, & Pourmovahed, 2013; Konopka, Pełka-Wysiecka, Grzywacz, & Samochowiec, 2013; Spanagel, Noori, & Heilig, 2014). Therefore, there is evidence of a positive correlation between emotional distress and drug consumption, some with anxiolytic effects (e.g., alcohol and benzodiazepines; Konopka et al., 2013) and some relieving from psychological pain (e.g., opioids; Hassanbeigi et al., 2013; Papini, Fuchs, & Torres, 2015).

Drug addiction is a chronically relapsing disorder characterized by a compulsion to seek and take drugs, loss of control, and the emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability, physical and emotional pain) when the drug is not available (Koob et al., 2014). Additional support for the ESM

hypothesis comes from studies showing that relapse in drug abusers is related to the reinforcing effects derived from the relief of drug-withdrawal symptoms. This drive-reduction mechanism has been proposed as critical to transform drug taking from an impulse-control disorder into compulsive behavior, the latter maintained by relief from withdrawal/negative affect (Koob, 2013). Accordingly, it has been shown that emotional distress can trigger drug abuse reinstatement (drug seeking) and relapse (drug taking). Such behaviors are dependent on neuroadaptive processes in brain circuits that counteract the reinforcing effects of drugs (Ahmed, 2012; Mantsch et al., 2014). This view involves ESM, that is, alleviation from emotional discomfort, as a motivational basis for the maintenance and relapse of drug abuse.

Another source of evidence for the ESM hypothesis comes from comorbidity studies. *Comorbidity* refers to individuals with an existing behavioral disorder who are at a higher risk of developing another disorder (Li et al., 2013). The ESM hypothesis implies that SUDs should be correlated with psychiatric conditions involving emotional distress as a core symptom. Accordingly, clinical evidence shows that a high percentage of adults and adolescents meeting diagnostic criteria for anxiety disorders, depression, or both also meet criteria for SUDs (Enman et al., 2014; Menary et al., 2011; Robinson, Sareen, Cix, & Bolton, 2011;

Tomlinson & Brown, 2012). These individuals show more severe symptomatology, health problems, and functional impairment, and relapse more frequently into drug abuse (Ruglass et al., 2014).

By contrast, other studies show that substance use is sometimes associated with the aggravation of psychiatric symptoms, rather than their amelioration (Castaneda, Galanter, & Franco, 1989). In addition, only a low percentage of individuals with anxiety disorders overtly assert to self-medicate by consuming alcohol (Menary et al., 2011), making it difficult to objectively assess the involvement of ESM in alcohol intake. In fact, most studies do not systematically explore whether drug intake actually reduces emotional distress. Finally, the direction of the causal mechanisms underlying the relationship between SUDs and psychiatric disorders is not yet clear (Robinson et al., 2011); psychiatric symptoms could be postmorbid rather than premorbid relative to substance use (Blume et al., 2000).

Clinical research provides insights into the nature of SUDs and identifies major factors in the development of addictive behavior. Animal models may contribute to isolating these factors; to identifying some of them as causally related to, rather than just correlated with, addictive behavior; and to understanding the neurobiological mechanisms underlying addiction. Animal models of self-medication are reviewed in the following section.

PSM AND ESM IN NONHUMAN ANIMALS

Animals have evolved behavioral and physiological mechanisms to treat and control disease that improve health and enhance reproductive fitness (Huffman, 2010). This field of study, referred to as PSM (or zoopharmacognosy), includes behaviors with therapeutic or symptom-relieving effects. PSM covers both prophylactic and therapeutic practices, from behaviors that prevent or reduce the risk of sickness in healthy individuals to those aimed at treating an illness in diseased individuals (Lozano, 1998; Villalba, Miller, Ungar, Landau, & Glendinning, 2014). PSM includes ingestion, absorption, topical application, and proximity to medicinal substances (Clayton & Wolfe, 1993; Huffman, 2010). PSM also includes transgenerational prophylaxis and therapeutic medication directed at offspring and social prophylaxis directed at conspecifics (De Roode, Lefèvre, & Hunter, 2013). Here we consider only ingestive behaviors with therapeutic effects.

The ability of individuals to behaviorally defend themselves against life-threatening diseases provides an adaptive advantage extensively documented across species (Huffman, 2010). Such ability includes species-typical actions patterns as well as responses emerging from individual experience, feedback mechanisms, and learning (Villalba et al., 2014). Species-typical PSM behavior is commonly observed in insects (e.g., flies, ants, butterflies, caterpillars), whereas PSM behavior based on individual and social learning is observed mainly in vertebrates (e.g., snow geese, lambs, goats, sheep, civets, chimpanzees, gorillas, bonobos; De Roode et al., 2013; Huffman, 2010).

Four conditions must be fulfilled for a behavior to be an example of PSM (Clayton & Wolfe, 1993; Huffman, 2010):

- Identify the disease or symptoms being treated.
- Distinguish the use of a therapeutic agent from that of everyday food items.

- Show a positive change in health condition following self-medication.
- Provide evidence of the pharmacological activity of the compounds extracted from therapeutic agents.

Although there is evidence that sick animals are able to select corrective dietary components that are not otherwise consumed in significant quantities, whether these examples meet the requirements listed above remains to be shown (De Roode et al., 2013).

Defensive behavior against parasites constitutes a common form of PSM (Lozano, 1998). Woolly bear caterpillars experimentally infected with parasitoid flies increase their ingestion of alkaloids (Singer, Mace, & Bernays, 2009). Monarch butterflies infected with the protozoan parasite *Ophryocystis elektroscirrha* use milkweed as medication (Lefèvre et al., 2012). Surveys and field observations, as well as controlled studies, indicate that ruminants also exhibit PSM behavior when parasitized (Villalba et al., 2014). Chimpanzees and bonobos consume plant leaves that reduce endoparasite proliferation (Fruth et al., 2014; Masi et al., 2012). The diversity of species exhibiting, at least potentially, PSM suggests the adaptive advantage of identifying, curing, and reducing the negative impact of physical diseases.

Parasitism is a main source of biotic stress faced by many species (Lozano, 1998), but would animals use substances to reduce emotional distress? ESM seems to occur in relation to negative emotional states and drugs of abuse. However, studies must meet four conditions to identify ESM behavior (Huffman, 2010; Manzo, Donaire, Sabariego, Papini, & Torres, 2015). In the following description, "emotional activation" refers to any of a number of aversive states, including anxiety, conflict, depression, and stress:

- Determine that emotional activation is present during or before substance consumption.
- Demonstrate that consumption is selectively directed at substances that reduce emotional activation.
- Show that substance consumption actually reduces emotional activation.
- Provide independent evidence that the consumed substance reduces emotional activation.

Most available evidence involves exposing animals to acute or chronic stress, having simultaneous or subsequent access to drugs such as ethanol (see Becker, Lopez, & Doremus-Fitzwater, 2011; Spanagel et al., 2014). For example, Anisman and Waller (1974) administered inescapable electric shocks to rats with simultaneous access to 10% ethanol. Stressed animals showed an increase in ethanol consumption relative to controls. Additional studies also suggested that the impact of electric shocks on ethanol intake depends on several factors, including control over shock delivery, baseline preference for ethanol versus water, and availability of a safe place with access to ethanol (Becker et al., 2011; Manzo, Gómez, Callejas-Aguilera, Fernández-Teruel, et al., 2014). Neuropathic pain induced by sciatic nerve ligation promotes cannabinoid and opioid self-administration in rats (Ewan & Martin, 2013; Gutiérrez, Crystal, Zvonok, Makriyannis, & Hohmann, 2011). These results can be interpreted in terms of ESM given the negative hedonic state that accompanies physical pain.

Chronic stress (e.g., anxiogenic social stimuli, physical restraint, isolation) may also induce self-administration of ethanol and opioids (Becker et al., 2011). Similarly, the contribution of

stress to drug reinstatement was shown using designs in which stressful stimuli reestablish a previously extinguished drug-seeking behavior (Ahmed, 2012).

Whereas the relationship between ESM and drug-taking behavior seems consistent, some results show the complexity of this relationship. The type of stressful experience (e.g., duration, intensity, quality), biological factors (e.g., strain, age, sex), and procedural variables (e.g., dose, simultaneous vs subsequent drug access, free choice vs operant self-administration, unlimited vs time-restricted access) all modulate the relationship (Becker et al., 2011; Spanagel et al., 2014).

It is safe to argue that most of the experimental evidence on ESM reviewed thus far fails to provide evidence concerning one or more of the conditions indicated above. To some extent this is understandable because most of these studies were not designed with the ESM concept in mind, but as a way of illustrating the effects of negative emotion on drug consumption. The ESM hypothesis requires not only that distress leads to drug consumption, but also that drug consumption reduces distress so as to produce a reinforcing effect (Figure 2).

There are three main problems with the available evidence. First, some tests do not provide an assessment of the animal's aversive/negative state (e.g., forced restraint) and of the extent to which this state relates to drug use. Similarly, whether drug intake causes a reduction in emotional distress is rarely assessed, making it difficult to explain the results in terms of ESM. Second, many studies do not consider individual differences in the proneness to taking drugs and in emotional reactivity (Torres & Sabariego, 2014). Such differences depend on genetic factors that contribute, separately or simultaneously, to vulnerability to stress and drug addiction (Vengeliene et al., 2003). Third, there are issues of ecological validity related to the use of certain noxious stimuli (e.g., electric shock) and routes of administration (e.g., intravenous self-administration). Although pain induced by shock and the neurochemical effects of intravenous drug infusion are ecologically valid, with some exceptions (e.g., heroin intravenous administration), these procedures do not mimic typical conditions in human addiction. To tackle some of these limitations, we now turn to studies based on procedures that more closely mimic typical conditions.

ESM INDUCED BY REWARD LOSS

When individuals rank the most stressful daily life events, most of these events are arguably related to reward loss (e.g., divorce, death of a loved one, dismissal from a job, social exclusion, natural catastrophes; Papini, Wood, Daniel, & Norris, 2006). These events trigger behavioral, affective, autonomic, hormonal, and immunological consequences that can negatively affect behavior and health (Papini et al., 2015). Interestingly, the correlation between reward loss and drug consumption is suggested by several clinical studies (Duffing et al., 2014; Egli, Koob, & Edwards, 2012; Hassanbeigi et al., 2013; Konopka et al., 2013; Spanagel et al., 2014). This link could be explained in terms of ESM, that is, the consumption of substances that reduce the negative emotional impact of reward loss.

Reward loss has been systematically studied in the animal laboratory through the devaluation or omission of an expected reward that triggers a negative emotional reaction called frustration, disappointment, anxiety, or, more recently, psychological pain

(Papini et al., 2015). These models include consummatory (cSNC) and instrumental successive negative contrast (iSNC), consummatory (cE) and instrumental appetitive extinction (iE), and partial reinforcement extinction effect (PREE) and partial reinforcement contrast effect (PRCE), among others (see Minidictionary of Terms), providing a useful tool to test the notion that reward loss induces emotional distress from a psychobiological perspective (see Papini et al., 2015; Torres & Sabariego, 2014). First, the omission of an appetitive event (or its signal) has consequences similar to those induced by an aversive event, including aggressive behavior, agitation, and a variety of anxiety-like responses (Papini & Dudley, 1997). These behaviors are selectively reduced or abolished by anxiolytics and analgesics, including alcohol, benzodiazepines, barbiturates, opioids, and cannabinoids (Flaherty, 1996; Genn, Tucci, Parikh, & File, 2004; Papini, 2009). In addition, situations involving reward devaluation or omission increase plasma levels of stress hormones (Flaherty, 1996). Lesion studies suggest that pain/fear and frustration are influenced by damage to similar brain areas (e.g., hippocampus, amygdala, prefrontal cortex; Becker, Jarvis, Wagner, & Flaherty, 1984; Flaherty, Coppotelli, Hsu, & Otto, 1998; Lin, Roman, & Reilly, 2009; Ortega, Uhelski, Fuchs, & Papini, 2011). Emotional responses triggered by exposure to aversive stimuli or removal of appetitive stimuli are also partially modulated by common genetic factors. Studies of reward loss in inbred Roman high-avoidance (RHA) and Roman low-avoidance (RLA) rats, initially selected on the basis of their good (RHA) versus poor (RLA) acquisition of a two-way active avoidance response, are especially relevant. As a result of this psychogenetic selection, Roman strains differ in anxiety-inducing situations, with RLA rats exhibiting higher anxiety levels than RHA rats (Torres & Sabariego, 2014). These strains also differ in behavioral traits associated with vulnerability to drug abuse, including novelty seeking (Manzo, Gómez, Callejas-Aguilera, Donaire, et al., 2014), impulsivity (Moreno et al., 2010), and voluntary consumption and preference for alcohol versus water (Manzo et al., 2012), with RHA exhibiting higher vulnerability than RLA rats. RLA rats are also more vulnerable than RHA rats in situations involving reward devaluation and omission: cSNC and iSNC (Gómez, Escarabajal, et al., 2009; Rosas et al., 2007; Torres et al., 2005), iE (Gómez, de la Torre, et al., 2009), PREE (Gómez et al., 2008), and PRCE (Cuenya et al., 2012). Therefore, Roman rats provide a valid animal model to assess the influence of genetic factors on individual reactivity to anxiety-provoking reward-loss events.

Although the evidence described above connects reward loss to emotional distress, the relationship between reward loss and drug consumption has been barely explored in laboratory animals. Kamenetzky, Cuenya, Pedrón, and Mustaca (2009) reported that reward devaluation (cSNC) increased approach to cues previously paired with systemic ethanol administration. The relationship between reward loss and voluntary consumption of ethanol has been more directly studied in a model involving two tasks in tandem (Figure 3). First, RHA and RLA rats were exposed to two appetitive reward omission situations: (1) cE: a downshift from 22% sucrose to water in a consummatory task and (2) iE: a downshift from 12 pellets to nonreward in the goal box of a runway. Both tests were immediately followed by a 2-h alcohol (2%) versus water preference test. Whereas RHA rats prefer ethanol over water under resting environmental conditions (Manzo et al., 2012), when exposed to cE or iE it was

Induction task
(e.g., instrumental extinction)

Preference test
(e.g., ethanol vs. water)
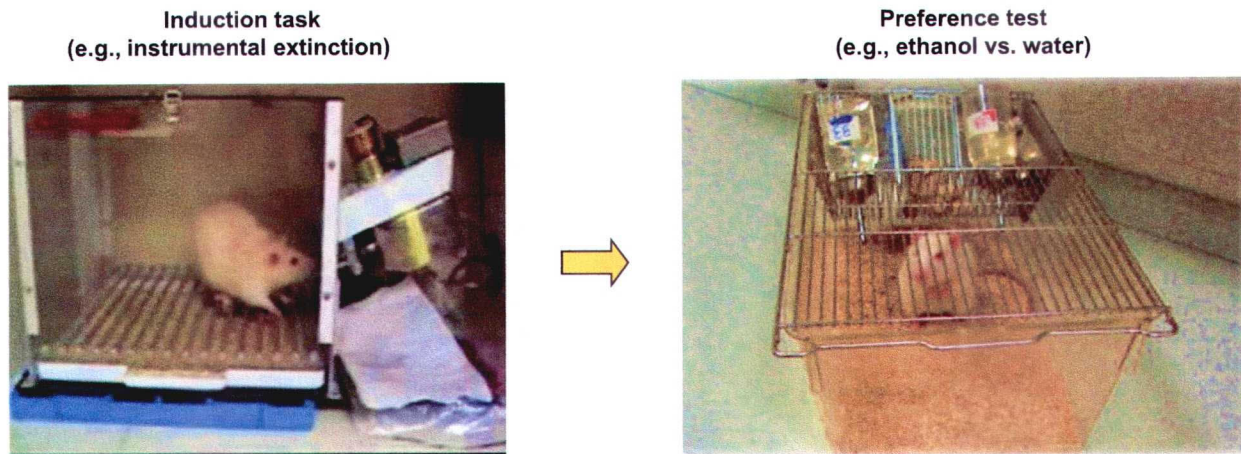
FIGURE 3   Design of emotional self-medication studies. These two tasks are presented everyday to the animals. The first task ("induction task") is designed to produce emotional distress. The second task ("preference test") is designed to measure choice of a substance that reduces negative emotion.
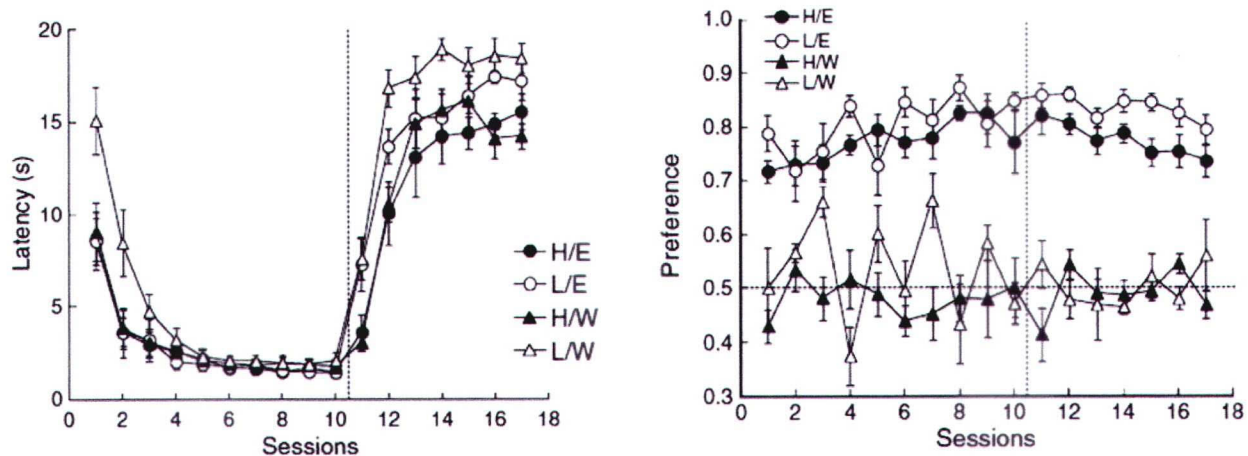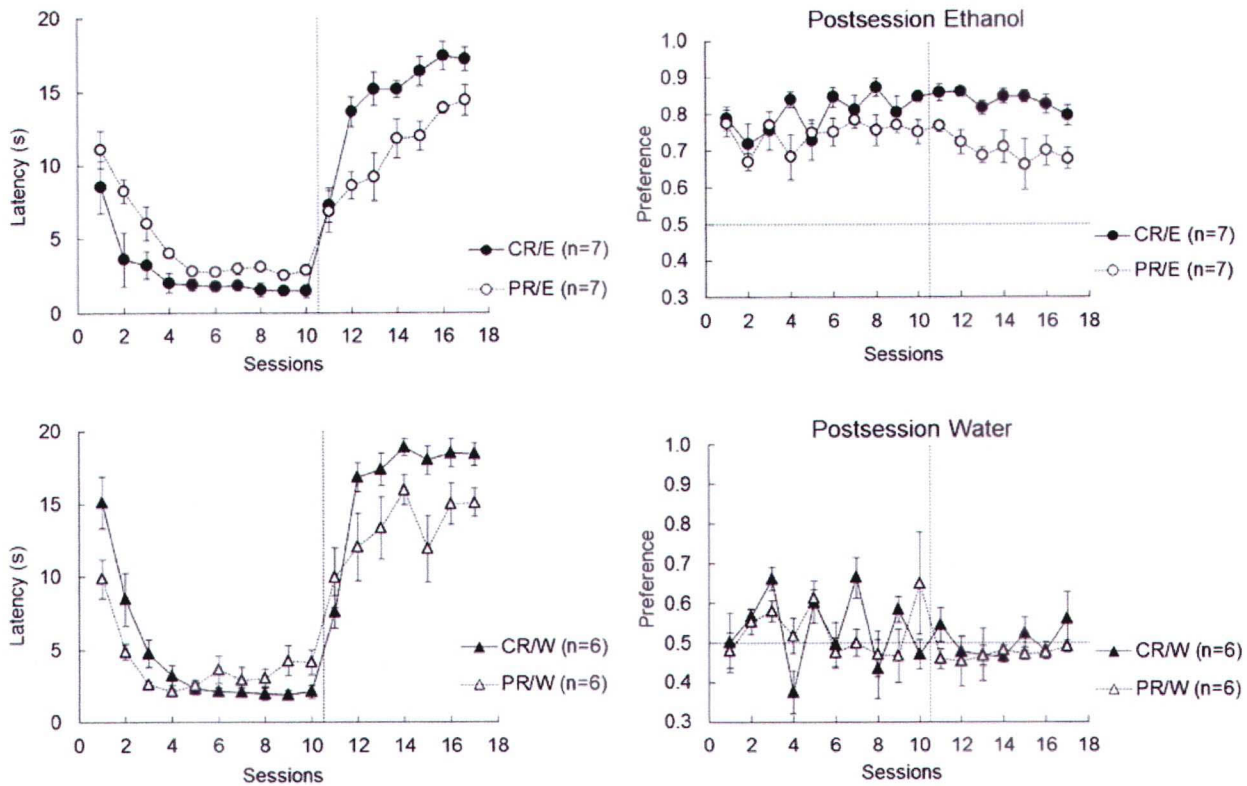

FIGURE 4   Effects of instrumental extinction on postsession ethanol consumption. Left (induction task): mean (±SEM) latency to traverse the runway in groups reinforced with food pellets on sessions 1–10 (acquisition), but not on sessions 11–17 (extinction). There were six trials per session. RLA rats (L) extinguished faster than RHA rats (H), thus showing greater vulnerability to reward loss. Right (preference test): mean (±SEM) preference for ethanol (E) or water (W) during the two-bottle test. Each day, rats received a training session in the runway (induction task) followed by access to ethanol and water in their cage (preference test). RLA rats displayed a greater preference for ethanol after extinction sessions than RHA rats. *Reproduced with permission from Manzo, Gómez, Callejas-Aguilera, Fernández-Teruel, et al. (2014), Elsevier.*

the more anxious RLA rats that showed greater preference for and consumption of ethanol (Manzo, Gómez, Callejas-Aguilera, Fernández-Teruel, et al., 2014). Figure 4 shows the results of an experiment inducing frustration via iE. Notice that all animals preferred ethanol over water; this preference was maintained after extinction sessions in RLA rats, but it was reduced in RHA rats. Moreover, preference for one of the bottles in control groups receiving iE, but only water during the preference test, showed no changes in extinction. Thus, iE did not just increase fluid consumption, but selectively increased consumption of ethanol, although only in RLA rats. These results constitute the first demonstration that reward omission increases voluntary ethanol consumption in emotionally reactive subjects. Because ethanol has anxiolytic effects in situations involving reward loss (Kamenetzky, Mustaca, & Papini, 2008), the authors interpreted the results in terms of the ESM hypothesis.

Second, the increased ethanol consumption observed in the RLA strain after iE was reduced when extinction occurred after partial reinforcement training, as opposed to continuous reinforcement (Manzo, Gómez, et al., 2015). Partial reinforcement attenuates the disrupting effects of extinction and can therefore be conceptualized as a treatment for developing resilience to loss-induced anxiety (Pellegrini, Muzio, Mustaca, & Papini, 2004). Using the same procedure described for Figure 3, although RLA rats showed the conventional PREE during runway training (see Definition of Terms), partially reinforced rats displayed lower ethanol consumption than continuously reinforced rats after extinction sessions. Controls receiving access to water during the preference tests showed no change in preference (Figure 5). These results suggest that ESM is reduced even in individuals genetically vulnerable to anxiety by extensive experience with reward uncertainty.

FIGURE 5 Effects of partial reinforcement (PR) on postsession ethanol consumption. Left (induction task): mean (±SEM) latency to traverse the runway in RLA groups reinforced with food pellets on sessions 1–10 (acquisition), but not on sessions 11–17 (extinction). There were six trials per session. Two groups received 50% PR in which a random half of the trials ended with 12 food pellets and the rest ended in nonreward. Two groups received continuous reinforcement (CR) in which each trial ended with 12 food pellets. Both pairs of groups showed the PREE (see Minidictionary of Terms). Right (preference test): mean (±SEM) preference for ethanol (E) or water (W) during the two-bottle test. Each day, rats received a training session in the runway (induction task) followed by access to ethanol and water in their cage (preference test). CR rats displayed a greater preference for ethanol after extinction sessions than PR rats. Thus, ESM can be attenuated after extended PR training, even in animals genetically vulnerable to anxiety. *Reproduced with permission from Manzo, Gómez, et al. (2015).*

Third, another study extended these results to nonselected Wistar rats and to a prescription anxiolytic, the benzodiazepine chlordiazepoxide (Manzo, Donaire, et al., 2015). This experiment followed the procedure outlined for Figure 3, except that the induction task was cSNC (see Definition of Terms). During the preference test one bottle contained water, whereas the other contained chlordiazepoxide (1 mg/kg), ethanol (2%), or water for different groups. Chlordiazepoxide is a potentially addictive benzodiazepine anxiolytic used in the treatment of anxiety (Konopka et al., 2013). Rats showed the cSNC effect, that is, a suppression of consummatory behavior after reward downshift relative to unshifted controls. This effect was accompanied by a selective increase in oral consumption of chlordiazepoxide and ethanol (Figure 6). Downshifted animals with access to water and unshifted controls with access to water, chlordiazepoxide, or ethanol exhibited no changes in preference. The results were again explained in terms of ESM, that is, the negative emotional state induced by reward devaluation (cSNC) caused an increase in the consumption of an anxiolytic substance, which, in turn, reduced the negative emotion. Both the cSNC and the ESM effects were transient, suggesting that the rewarding value of the anxiolytic ceased once the animals recovered from the

effects of reward devaluation. Such reversibility suggests that animal models of reward loss may provide insights into the connection between negative emotions and drug consumption before the animal develops full-blown addictive behavior. Such drive-reduction model (Figure 2) provides an alternative (probably complementary) to the drive-induction model of Figure 1 for an understanding of the initial stages of an SUD.

FUTURE DIRECTIONS: BRIDGING ESM AND SUDs

Over the past decades, substantial research has centered on modeling human addiction in nonhuman animals. Ahmed (2012) conceptualized such animal research as reverse psychiatry because, whereas clinicians seek to help people suffering from SUDs, preclinical research induces an addiction in a drug-naïve animal. This chapter reviewed the ESM hypothesis of addiction as a theoretical framework that integrates clinical and preclinical studies that have been often poorly connected. We first defined basic concepts, the role of ESM in addiction, the relationship between PSM and ESM in animals, and the ESM
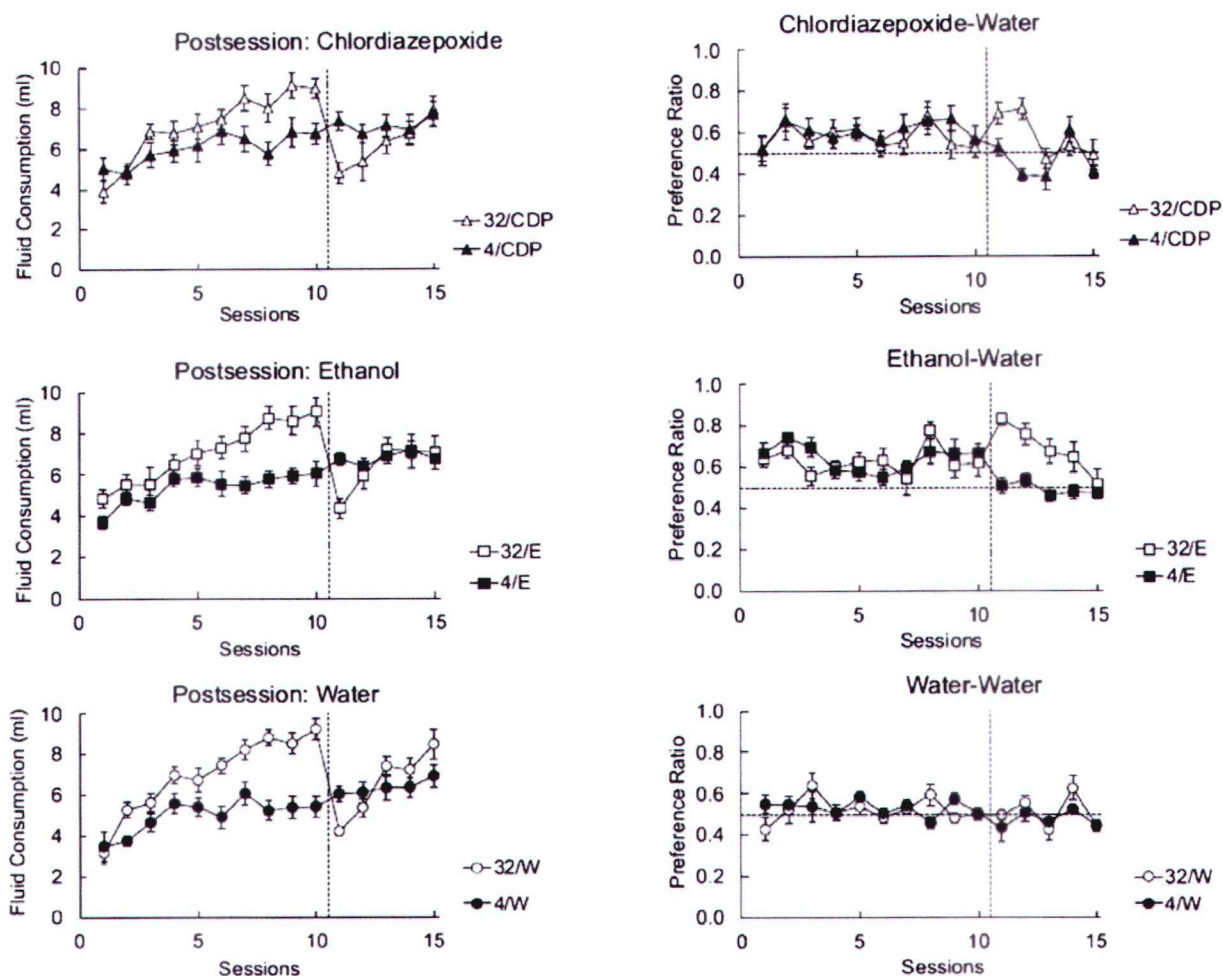
FIGURE 6   Effects of consummatory successive negative contrast on postsession consumption of chlordiazepoxide and ethanol. Left (induction task): mean (±SEM) latency to consume either 32% or 4% sucrose in Wistar rats. On sessions 11–15 all animals had access to 4% sucrose. There was a single 5-min session per day. All three pairs of groups showed the cSNC effect (see Minidictionary of Terms). Right (preference test): mean (±SEM) preference for chlordiazepoxide (CDP), ethanol (E), or water (W) during the two-bottle test. Rats displayed greater preference for chlordiazepoxide and ethanol after the initial sessions of reward devaluation. These results provide evidence of ESM tightly correlated with an event involving reward loss. 32: 32-to-4% sucrose downshift. 4: only 4% sucrose. *Reproduced with permission from Manzo, Donaire, et al. (2015), Elsevier.*

hypothesis as being developed in animal models. Although supporting evidence for the ESM hypothesis appears to be broad, several limitations make it difficult to draw firm conclusions about the implications of ESM in the initial and later stages of drug use:

1. There is insufficient *experimental* research on ESM in humans, so most evidence is correlational. For example, comorbidity studies do not determine whether the psychiatric disorder associated with addictive behavior is the cause or the consequence or whether both develop in parallel.
2. It is also unclear whether awareness of the relationship between the consumption of a drug and the reduction of emotional distress is important for the development of ESM. Given that some patients report that symptoms increase in strength, rather than decrease, after drug consumption, it is unclear whether drug use is driven by *drive reduction* or outcome-independent *habitual behavior*.

3. Experimental studies do not always objectively record the emotional state of the organism before and after drug consumption. Therefore, the *reinforcing* properties of the drug are not always empirically supported.

These limitations are even more serious given the restricted number of experimental studies based on the ESM hypothesis. In fact, as far as we know, this is the first review relating PSM and ESM in nonhuman animals to clinical studies. This chapter highlights the need for a set of basic conditions before any given behavior can be considered an example of ESM. Recent studies reviewed in the previous section can shed light on the validity of the ESM hypothesis because (1) they are based on situations involving reward loss, arguably a frequent, yet experimentally neglected, source of emotional distress in humans and also known to be associated with SUDs; (2) they allow for a clear record of behavioral indices of emotional distress; and (3) they relate ESM with individual differences in emotional reactivity and sensitivity to drugs of abuse. This

framework allows for the study of vulnerability and resilience to the effects of reward loss on drug consumption, enabling a better understanding of the relationship between ESM and addiction.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

ESM offers a general framework that can potentially be applied to an understanding of several types of addictive behaviors. Available data from animal models suggest that a variety of distressing situations can trigger corrective consummatory actions, including physical pain (e.g., sciatic nerve ligation), pain-induced fear (inescapable shock), and psychological pain (e.g., reward loss). Such research has also identified voluntary anxiolytic intake as substances preferred and consumed during periods of distress. Theoretically, there are reasons to predict that ESM will be triggered by other sources of emotional distress induced by negative changes (e.g., physical restraint, escape behavior, open spaces) and supported by the consumption of a variety of substances (e.g., opioids, over-the-counter analgesics, serotonergic anxiolytics). ESM may also be supported by nondrug substances, making the framework potentially relevant to obesity, video game addiction, and other activities that can develop properties similar to those of more traditional addictions. Furthermore, the ability to regulate emotional states suggests that the consumption of substances with anxiogenic effects may be selectively inhibited during periods of stress. Finally, the bridge between consumption limited to periods of distress and excessive consumption will require additional research. One possibility is anticipatory ESM, that is, consumption triggered in anticipation of an anxiogenic situation. If sustained, such behavior could become habitual, occurring even in the absence of a negative emotion, or acquire a new goal—reducing withdrawal symptoms generated by the very substance originally used for self-medication. Thus, a behavior that started as a way of reducing negative emotions induced by specific external events (e.g., reward loss) may become co-opted to reduce new negative emotions induced by other events, including drug deprivation.

DEFINITION OF TERMS

Comorbidity Individuals with an existing behavioral disorder are at higher risk of developing another disorder.

Consummatory extinction Following acquisition with a reward, animals are downshifted to no reward and their consummatory behavior is measured (*reward omission*). See also instrumental extinction.

Consummatory successive negative contrast Following acquisition with a large reward, animals are downshifted to a small reward and their consummatory behavior is compared to that of unshifted controls always exposed to the small reward (*reward devaluation*). See also instrumental successive negative contrast.

Drive induction An increase in motivation/emotion that can have positive reinforcing effects on contingent responses.

Drive reduction A decrease in motivation/emotion that can have positive reinforcing effects on contingent responses.

Drug specificity A postulate of ESM stating that the chosen drug reflects its ability to ameliorate distress.

Emotional self-medication Consummatory behavior motivated by hedonically aversive affective states and reinforced by a reduction in those states.

Instrumental extinction Same as consummatory extinction, except that an instrumental behavior is measured (*reward omission*).

Instrumental successive negative contrast Same as consummatory successive negative contrast, except that an instrumental behavior is measured (*reward devaluation*).

Partial reinforcement contrast effect Acquisition of a response under partial reinforcement attenuates the behavioral effects of reward downshift relative to acquisition under continuous reinforcement.

Partial reinforcement extinction effect Acquisition of a response under partial reinforcement results in slower extinction compared to acquisition under continuous reinforcement.

Physical self-medication Consummatory behavior motivated by therapeutic or symptomatic amelioration in organisms suffering from some pathology or disorder.

Psychopathology postulate A postulate of ESM stating that the onset of substance use relates to the relief of psychological distress produced by the substance consumed.

KEY FACTS ABOUT SELF-MEDICATION

- Humans consume drugs to alleviate acute or chronic distress states.
- Comorbidity studies show a positive correlation between SUDs and anxiety disorders.
- Animals self-medicate to treat physical diseases.
- PSM and ESM share behavioral components.
- ESM can underlie some forms of addictive behavior.
- ESM can be induced by reward loss.

SUMMARY POINTS

- SUDs are neurobehavioral conditions resulting from persistent dysregulation of neural circuits mediating reward, learning/memory, and stress.
- The ESM hypothesis states that the drug consumed depends on its ability to relieve a preexistent psychiatric disorder or reduce negative emotions.
- Clinical evidence suggests that stress, psychiatric condition, and drug withdrawal can sustain ESM.
- Animals can behaviorally treat and control physical disease (PSM) and emotional distress (ESM).
- Reward loss triggers a negative emotional reaction that shares commonalities with pain, fear, and anxiety.
- Reward loss supports ESM behavior.
- ESM provides a framework to understand addictions.

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