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Anhedonia as a key clinical feature in the maintenance and treatment of opioid use disorder

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Abstract

There is a critical need for research on clinical features that may influence response to treatment for opioid use disorder (OUD). Given its neurobiology and relevance to opioid use, anhedonia may be one such promising clinical feature. We identified and reviewed 11 studies that measured anhedonia in humans with OUD to characterize the current state of evidence and highlight potential implications for treatment. The majority of studies were cross-sectional, indicating higher anhedonia scores in opioid-dependent samples compared to healthy controls. Rates of participants with clinically significant anhedonia ranged from 21% to 48%. Anhedonia scores were correlated with opioid craving and use, however there are significant knowledge gaps regarding its time course and impact on treatment adherence and outcomes. Repeated assessment of anhedonia early in treatment for OUD is recommended, as it may be a unique predictor of dropout or non-response, and a potential target for behavioral and/or pharmacological intervention.

Keywords

Anhedonia; Opioid Use Disorder; Medication Assisted Treatment; Protracted Withdrawal; Treatment Response

Introduction

Anhedonia, commonly defined as a loss of the ability to experience pleasure, is considered an important symptom/characteristic across many psychiatric disorders. The word originates from the French *anhedonie*, coined by French psychologist Theodule Ribot as an opposite to analgesia (i.e., absence of pleasure contrasted to absence of pain) (Ribot, 1896). It is a hallmark symptom of schizophrenia and major depressive disorder, but is also frequently present in individuals with substance use disorders, as it is a common feature of both acute and protracted withdrawal from alcohol, cocaine, stimulant, and cannabis use (Hatzigiakoumis, Martinotti, Giannantonio, & Janiri, 2011). In addiction models, anhedonia and other reward-related disturbances are posited as a consequence of the allostatic changes associated with chronic drug use and believed to be a major contributor to risk of drug relapse (Koob & Le Moal, 2001; 2008; Koob & Volkow, 2010, 2016). This model is based on the classic opponent-process theory of motivation (Solomon & Corbit, 1974), such that

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the initial hedonic effects of a stimulus (i.e., the a-process) also trigger opposing negative hedonic effects (i.e., the b-process), which in turn, become larger over time with repeated exposure to the stimulus, ultimately masking the initial hedonic effects. A recent review of anhedonia in individuals with substance use disorders indicated that anhedonia levels are elevated across multiple drug-dependent samples, appear to diminish with prolonged abstinence, and are generally associated with increased drug cravings and risk for relapse (Garfield, Lubman, & Yucel, 2014). However, the bulk of this evidence originates from studies of nicotine dependence; the literature within opioid dependent samples is relatively limited. Given that opioids temporarily bring pleasure and relieve pain, and withdrawal from opioids is essentially characterized by reduced pleasure and increased pain (Jasinski, 1991; White, 2004), anhedonia may be an important, yet overlooked, aspect of opioid use disorder (OUD) maintenance and treatment.

In the face of the current opioid epidemic in the United States, there is a need for multiple strategies to improve treatments for opioid misuse and addiction, including research on the clinical features that influence treatment response (Collins, Koroshetz, & Volkow, 2018; Volkow, 2018). Although there are three effective FDA-approved medications (methadone, buprenorphine, and injectable naltrexone) for the treatment of OUD, referred to collectively as MAT (medication assisted treatment), with decades of research demonstrating favorable outcomes compared to placebo (Mattick, Breen, Kimber, & Davoli, 2009, 2014), not all patients respond. Rates of initiation and retention on MAT are highly variable, with reports of a majority discontinuing treatment after 30-days (Jarvis et al., 2018; Morgan, Schackman, Leff, Linas, & Walley, 2018; Timko, Schultz, Cucciare, Vittorio, & Garrison-Diehn, 2016) and 50% relapse rates at 6-months (e.g., Lee et al., 2018; Solli et al., 2018; Tkacz, Severt, Cacciola, & Ruetsch, 2012). Further, although there are international guidelines published by the World Health Organization for the selection of pharmacological treatments for OUD (World Health Organization (WHO), 2009), there is limited evidence to support treatment matching to patient characteristics and there remains uncertainty regarding the level of adjunctive psychosocial counseling needed for added benefit (Carroll & Weiss, 2017; Day & Mitcheson, 2017; Fiellin et al., 2006; McLellan, Arndt, Metzger, Woody, & O'Brien, 1993; Weiss & Rao, 2017). Important questions remain regarding patient phenotypes that predict treatment response, as well as what enduring psychological/behavioral symptoms after initiation of treatment might heighten risk of non-response to MAT or relapse during or following MAT. As anhedonia has been found to be a predictor of earlier relapse to tobacco smoking during the first month of a quit attempt (J. Cook, Spring, McChargue, & Doran, 2010), as well as a predictor of outcome from behavioral treatments for cocaine use (Crits-Christoph et al., 2018), and poor response to antidepressant medications (McMakin et al., 2012; Uher et al., 2012), it may be a promising feature to investigate in OUD treatment. The purpose of this article is to provide an updated and critical review of anhedonia in OUD, including its measurement, relevant neurobiology, treatment implications, and recommendations for future research.

Anhedonia definition and measurement

Although relevant to multiple psychiatric disorders and illnesses, defining the concept of anhedonia is rather complex. The traditional definition of anhedonia, the loss of ability

and/or decreased capacity to experience pleasure, emphasizes the consummatory aspect of reward function (i.e., the pleasure derived from experiencing a pleasurable event). However, because the definition is dependent on the concept of pleasure that is itself multi-faceted (Berrios & Olivares, 1995), anhedonia has been conceptualized more broadly to include other facets of pleasure/hedonic function, such as interest/desire (wanting a reward), anticipation (expectation of reward), motivation (initial energy expenditure to attain a reward), and decision making (learning-related) (Der-Avakian & Markou, 2012; Rizvi, Pizzagalli, Sproule, & Kennedy, 2016; Treadway & Zald, 2011). Further complicating the picture, individuals might have deficits in one area, but be relatively intact in another. For instance, anhedonia in schizophrenic populations is largely characterized by deficits in anticipatory pleasure but not consummatory pleasure, such that the extent of engagement in pleasurable activities does not necessarily reflect reduced hedonic capacity (Strauss & Cohen, 2018; Strauss & Gold, 2012). The concept of anhedonia is also distinct from negative affect or dysphoria. The consummatory aspect of anhedonia represents a lack of positive affect, which is not the equivalent of a strong negative hedonic state. Although modestly associated with emotional states such as positive and negative affect, it is clear than anhedonia is a unique construct (Cook, Lanza, Chu, Baker, & Piper, 2017; Cook, Spring, McChargue, & Hedeker, 2004; Franken, Rassin, & Muris, 2007).

Anhedonia can further be defined according to the types of activities that may produce pleasure; physical anhedonia refers to decreased ability to experience pleasure from physical activities like eating, touching, and sex, whereas social anhedonia refers to decreased pleasure from social interactions like being around others, talking and connecting. Also, anhedonia is considered to occur along a continuum of hedonic tone, rather than being present or absent, or high versus low, as some individuals with severe symptoms of anhedonia can experience pleasure from a few sources (Ho & Sommers, 2013). Anhedonia can also be characterized as a state that is acutely elevated in response to stress (Berenbaum & Connelly, 1993; Pizzagalli, Bogdan, Ratner, & Jahn, 2007) or drug withdrawal (Cook et al., 2015) for instance, or as a trait-like dimension with little fluctuation over time in some individuals (Meehl, 2001).

Although there are several laboratory-based procedures to assess the multiple components of reward-related deficits in both animals and humans (Barnes, Der-Avakian, & Markou, 2014; Der-Avakian, D'Souza, Pizzagalli, & Markou, 2013), the traditional measures of anhedonia in humans are self-report questionnaires to assess the capacity/ability to experience pleasurable events (Der-Avakian & Markou, 2012). While there is no generally agreed upon 'gold-standard' measure of anhedonia, one of the most commonly used instruments in clinical settings is the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS is a brief, 14-item self-report measure that asks respondents to indicate on a 4-point scale the degree to which they agree or disagree with a series of statements related to experiences encountered by most people (e.g., I would be able to enjoy my favorite meal). The items are relevant to a wide variety of demographic and cultural populations, with favorable psychometric properties relative to other anhedonia measures in both adult clinical and non-clinical populations (e.g., Franken et al., 2007; Nakonezny, Carmody, Morris, Kurian, & Trivedi, 2010), as well as in adolescents (Leventhal et al., 2015). Because the SHAPS does not measure anhedonia as a trait, it is expected to fluctuate somewhat over

time, particularly in clinical samples (Franken et al., 2007). However, there have been no psychometric studies evaluating the SHAPS in OUD populations.

While the SHAPS, and another self-report measure of anhedonia, the Fawcett-Clark Pleasure Scale (Fawcett, Clark, Scheftner, & Gibbons, 1983), focus exclusively on the consummatory aspect of anhedonia (i.e., liking), other validated self-report measures used in clinical research have incorporated aspects of motivation and effort, such as the such as the Chapman Physical Anhedonia Scale (CPAS) and the Chapman Social Anhedonia Scale (CSAS) (Chapman, Chapman, & Raulin, 1976). Items on the CPAS and CSAS measure anhedonia as a trait (i.e., in general) rather than a state (i.e., right now). More recently developed measures include other aspects of reward motivation that are consistent with a multicomponent view of anhedonia (Thomsen, 2015). For example, the Temporal Experience of Pleasure Scale (TEPS; Gard, Gard, Kring, & John, 2006) is an 18-item self-report questionnaire that aims to differentiate between the consummatory (feeling pleasure) and anticipatory (ability to anticipate, and/or take pleasure in anticipating, future pleasure) experiences of pleasure. This may be of particular interest in OUD, because chronic opioid use may impact the neural substrates of both consummatory and anticipatory pleasure differentially (Koob & Le Moal, Barbano & Cador, 2007; Der-Avakian & Markou, 2012; 2008). However, the only evaluation of the psychometric properties of the TEPS in an opioid dependent sample found a strong correlation between anticipatory and consummatory subscales, suggesting they may be tightly linked in this population (Garfield, Cotton, & Lubman, 2016). It should be noted that this study included a heterogeneous sample 121 of individuals with varying lengths of opioid abstinence and diverse treatment regimens (methadone, buprenorphine, no pharmacotherapy), so firm conclusions regarding consummatory and anticipatory construct validity in OUD are premature.

Other more recently developed self-report measures that take into account different facets of reward function beyond consummatory pleasure, include the Motivation and Pleasure Scale – Self Report (MAP-SR; Llerena et al., 2013), the Specific Loss of Interest Scale (SLIPS; Winer, Veilleux, & Ginger, 2014), the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding & Pflum, 2014), and the Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015). Although the psychometrics of these measures have been evaluated in clinical and non-clinical samples in some cases, they have not been examined in studies of individuals with OUD. An additional self-report scale that is often considered to measure aspects of anhedonia is the Behavioral Inhibition System and the Behavioral Activation System (BIS/BAS; Carver, 1994). Specifically, the BAS system reflects appetitive motivation, is activated by rewarding stimuli, and includes subscales measuring drive, reward response, and fun seeking. It has been examined in substance users (e.g., Franken, Muris, & Georgieva, 2006; Perry et al., 2013), but to our knowledge there are no specific reports within OUD.

While self-report instruments provide useful information regarding the conscious components of anhedonia, a number of behavioral tasks have been developed to measure the unconscious subcomponents of anhedonia and reward processes (for a comprehensive review, see Thomsen, 2015). For instance, the Effort Expenditure for Rewards Task (EEfRT; Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) is an experimental task used to

assess reward motivation and effort-based decision-making, with findings that greater self-reported anhedonia is associated with decreased motivation for rewards. Although these types of tasks have not been extensively evaluated in substance using samples, they offer promising avenues for identifying the underlying neurobiological mechanisms of anhedonia in OUD populations.

Neurobiology of anhedonia & connection with opioids

One of the merits of anhedonia as an important clinical feature (and potential phenotypic indicator) of OUD is that it has a putative neural substrate, the dopaminergic mesolimbic and mesocortical reward circuit (Nestler & Carlezon, 2006). The brain reward network mediates reward behaviors including motivation to obtain rewards and hedonic response to natural rewards and drugs of abuse including opioids. This network comprises of subcortical (nucleus accumbens, ventral pallidum and amygdala) and prefrontal cortical regions (orbitofrontal (OFC), insula and anterior cingulate cortices)(Berridge & Kringelbach, 2015). A key component to the brain reward circuitry is the mesocorticolimbic dopamine (DA) system, which includes projections from the ventral tegmental area (VTA) DA cells to the nucleus accumbens, amygdala and prefrontal cortex. While DA is closely linked to reward, its main role seems to be prediction and motivation to obtain rewards as well as anticipatory pleasure (Berridge & Kringelbach, 2008). The actual hedonic experience or consummatory pleasure is mediated mainly by the mu opioid and cannabinoid receptors, especially in nucleus accumbens and ventral pallidum. Human neuroimaging studies suggest that OFC and insula regions also encode hedonic experience (Castro & Berridge, 2014). These brain regions also contain mu opioid receptors and their activation enhances liking reactions to food in rodents (Mena, Sadeghian, & Baldo, 2011).

In contrast, naltrexone, which blocks mu and to a lesser extent delta opioid receptors, reduces consumption of pleasurable food in rodents (Taber, Zernig, & Fibiger, 1998). In humans, naltrexone treatment reduces hedonic experiences after exercise (Järvekülg & Viru, 2002), with social interactions (Inagaki, Irwin, & Eisenberger, 2015), in response to pleasant food (Yeomans & Gray, 1996), music (Mallik, Chanda, & Levitin, 2017) or sex (Murphy, Checkley, Seckl, & Lightman, 1990). These findings are consistent with the role of the endogenous opioid system in consummatory pleasure (Berridge & Kringelbach, 2008). Accordingly, blockage of the mu opioid receptors produces a state of anhedonia (i.e., naltrexone-induced anhedonia). It is important to note that the DA-mediated anticipatory pleasure and opioid-mediated are closely coupled. Blocking of opioid receptors by naltrexone reduces alcohol-induced DA release in rodents (Benjamin, Grant, & Pohorecky, 1993) and attenuates the positive subjective effects from alcohol (O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002), cocaine (Sofuoglu et al., 2003), nicotine (Wewers, Dhatt, & Tejwani, 1998) and amphetamines (Jayaram-Lindström et al., 2008).

In animal studies, withdrawal from chronic exposure to opioids is associated with reduced response to natural rewards and low sociability (i.e, a state of anhedonia) (Goeldner et al., 2011); increased preference for drug-related cues (Aston-Jones & Harris, 2004); increased response to drug rewards (Zhang et al., 2007); and increased vulnerability for relapse for several months after abstinence from opioids (Lutz & Kieffer, 2013). Further, the brain

reward threshold, assessed by intracranial self-stimulation (ICSS), is elevated after withdrawal from opioids (i.e., anhedonia) (Bruijnzeel et al., 2006; Schulteis, Markou, Gold, Stinus, & Koob, 1994), indicating diminished reward response.

Consistent with these preclinical findings, anhedonia has been proposed to be one of the main characteristics of protracted opioid withdrawal in humans (Barrot, 2015). Thus, anhedonia as an aversive and drug-reversible internal state may facilitate drug use by negative reinforcement as suggested by the 'dark side of addiction' hypothesis (Koob & Le Moal, 2008). Accordingly, in a withdrawal state, drug use does not produce its positive reinforcing effects by enhancing DA and opioid signaling from a normal hedonic level but by its negative reinforcing effect by relieving an aversive internal state (i.e., anhedonia) (Koob & Le Moal, 2008). A recent study provided insight into the molecular mechanisms underlying anhedonia that is associated with protracted opioid abstinence (Kaufling & Aston-Jones, 2015). DA neurons in the VTA receive inhibitory GABAergic interneurons and inhibition of these interneurons by opioids results in increased dopamine release in the nucleus accumbens (Kim, Ham, Hong, Moon, & Im, 2016). The GABAergic neurons that are caudal to the VTA, called tail of VTA (tVTA) have been shown to lose their ability to disinhibit VTA DA neurons following chronic opioid use (Kaufling & Aston-Jones, 2015). This neuroadaptation may result in response to aversive, but not pleasurable, responses to environmental stimuli, underlying the dysphoria and anhedonia experience by opioid users during protracted abstinence (Barrot, 2015).

Anhedonia and neural function in OUD

Functional magnetic resonance imaging (fMRI) allows for indirect assessment of neural activity in response to a stimulus or while the brain is 'at rest'. Recent meta-analytic data indicate that, among individuals with major depression and schizophrenia (both disorders characterized by high rates of anhedonia), (i) consummatory anhedonia is associated with decreased activity within primarily subcortical regions including the striatum; (ii) anticipatory anhedonia is associated with increased lateral prefrontal cortical activity as well as decreased activity within regions including the striatum, hippocampus and anterior cingulate; and (iii) emotion processing is associated with decreased activity within regions including the amygdala, putamen and anterior cingulate (B. Zhang et al., 2016). While the neural substrates of anhedonia have not been systematically assessed in OUD, existing neuroimaging data generally indicate alterations within reward and affective systems among individuals with OUD. This includes *increased* activity within regions including the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate and striatum to drug cues (Li et al., 2015; Li et al., 2012; Walter et al., 2015; Wang et al., 2014), in addition to *decreased* activity within regions including the insula and dorsolateral prefrontal cortex to non-drug reward/loss cues among individuals with OUD individuals relative to controls (Gradin, Baldacchino, Balfour, Matthews, & Steele, 2014; Yip et al., 2016). These findings are generally consistent with current theories of addictions positing increased neural reward response to drug stimuli and decreased reward responses to non-drug stimuli, yet require further research across different subgroups of individuals with OUD. For example, as both studies of non-drug reward processing were conducted in methadone-maintained individuals, very little is known about non-drug processing in unmedicated OUD. Findings

from studies of negative affect processing further indicate alterations within regions including the amygdala among individuals with OUD, relative to controls, however the direction of these alterations has not been consistent across studies (Schmidt et al., 2014; Wang et al., 2010). Thus, as with reward-related aspects of anhedonia, further work assessing affective neural circuitry among individuals with OUD in relation to anhedonia is needed.

Review of anhedonia in human studies with opioid users

A recent review of anhedonia in substance use disorders noted six studies that included opioid-dependent samples (Garfield et al., 2014). Our search of PubMed, Scopus, and PsychInfo that included the search terms "*opioid(s)*" and "*anhedonia*" produced 82 results to date (November 2018), of which we identified 5 additional studies published since the 2014 review that assessed anhedonia in humans with opioid dependence. Table 1 provides a summary of these 11 studies to date, describing the opioid dependent sample, the study design, the measures used to assess anhedonia, and main anhedonia findings. Of these 11 studies, 7 compared opioid-dependent individuals to healthy controls on self-report questionnaires of anhedonia (nearly all studies used the SHAPS). Sample sizes of opioid dependent individuals in these 7 studies ranged from 10 (Zaaijer et al., 2015) to 90 (Garfield et al., 2017) with the sample sizes of healthy controls ranging from 10 (Huhn, Meyer, et al., 2016) to 50 (Martinotti, Cloninger, & Janiri, 2008). Also, there was a wide range of abstinence duration across all studies with opioid dependent samples, with one study including participants during their first day of opioid detoxification (between 6 – 36 hours of detox; Schmidt et al., 2001) and another including individuals abstinent at least 3 months since detoxification (mean = 10 months; Martinotti et al., 2008). In general, findings indicated individuals with opioid dependence (either current or in remission) report higher levels of anhedonia compared to non-substance-using healthy controls. The two studies that reported results but did not find statistically significant differences in anhedonia scores compared to healthy controls, Zaaijer et al. (2015) and Zijlstra, Booij, van den Brink, and Franken (2008), included small samples of opioid dependent individuals (n = 10 and 12, respectively).

However, differences between opioid-dependent samples and healthy controls at a single time point do not necessarily answer the question of whether anhedonia is a precursor or a consequence of chronic opioid use, or an interaction between the two. There may be additional differences between these groups other than opioid use that might impact anhedonia scores: One recent study indicated that a significant difference in anhedonia scores remained even after controlling for other variables associated with anhedonia that are typically more common in drug-dependent individuals, such as childhood abuse, PTSD, depression and anxiety (Garfield et al., 2017). In another study, scores on a self-reported anhedonia measure (TEPS) appeared to fluctuate in accordance with the level of opioid use in a given month, with increased anhedonia scores following a month of above-average opioid use (Lubman et al., 2018). These studies provide some support for the notion that anhedonia may be in part a result of chronic substance use.

Two studies indicated drug cravings in abstinent opioid dependent individuals were correlated with anhedonia scores (Janiri et al., 2005; Martinotti et al., 2008), which suggests the experience of less pleasure from natural rewards may heighten individuals' risk for relapse. Also, although one study found the duration of abstinence from opioids was negatively correlated with anhedonia (Janiri et al., 2005), suggesting anhedonia may decline over time with continuous abstinence, another study found no relationship between duration of abstinence and anhedonia (Garfield et al., 2017). All of these studies, however, were cross-sectional in nature, so whether anhedonia changes over time during periods of sustained abstinence, as well as whether levels of anhedonia are predictive of opioid relapse and treatment response, remains unclear.

Notably, only 3 of these 11 studies of anhedonia in opioid dependent samples included a longitudinal design, obtaining repeated measures of anhedonia over the course of a clinical trial. The study by Zaaijer et al. (2015) evaluated scores on the SHAPS in 10 detoxified heroin-dependent individuals at baseline and 2-weeks after receiving an extended-release naltrexone (XR-NTX) injection. Results of a paired samples *t*-tests indicated no significant change in SHAPS scores during the 2-week period. The most recent longitudinal study was observational (Lubman et al., 2018), with a convenience sample of 121 opioid-dependent individuals consisting of those on methadone (45%), buprenorphine (29%) or no MAT (26%). In this study, anhedonia and opioid use were measured by self-report at 8 timepoints over the course of a 12-month period and random intercept linear models were used to examine the association between change in anhedonia and change in opioid use. Although results indicated a tendency for reduction in anhedonia over time, participants' anhedonia ratings increased following months of above-average opioid use, which is one of the first longitudinal demonstrations of dynamic changes in anhedonia associated with recent opioid use (Lubman et al., 2018). This finding is consistent with rodent models suggesting a proportional relationship between anhedonia and recent drug use (Ahmed, Kenny, Koob, & Markou, 2002; Markou & Koob, 1991). However, Lubman et al. (2018) did not find support that anhedonia scores predicted subsequent opioid use.

In the only longitudinal study within a randomized controlled trial, Krupitsky et al. (2016) measured anhedonia monthly using the Chapman Physical and Social Anhedonia Scale (Chapman et al., 1976), as well as an unpublished instrument (Ferguson Anhedonia Scale), in 306 opioid-dependent individuals participating in a randomized, placebo-controlled 6-month trial comparing XR-NTX with oral naltrexone and placebo. They reported that anhedonia scores were elevated at baseline but reduced to normal within the first 1–2 months among those who remained in treatment and did not relapse, with no between group differences, concluding that naltrexone treatment did not increase anhedonia. However, their approach of only analyzing those who had data at each timepoint, as well as excluding those who were known to have relapsed to opioids, resulted in an analysis sample of 81 out of 306 participants (26%). Analyses comparing the scores on the Ferguson Anhedonia Scale for those who dropped out (the last measure obtained prior to dropout) compared to those who continued treatment indicated no significant differences, which suggests anhedonia did not contribute to treatment dropout. Yet, as the majority of participants appeared to drop out after week 2 and the psychometric stability of the anhedonia measure is unknown, it is

difficult to draw firm conclusions regarding whether anhedonia may be a predictor of opioid relapse or treatment drop out.

Limitations in knowledge base regarding anhedonia and OUD

The available literature points to important gaps in our understanding of anhedonia in individuals with OUD. First, the prevalence of anhedonia in OUD populations is unclear. Although there is evidence of heightened anhedonia for those with OUD compared to healthy controls, it appears there may be significant individual differences in anhedonia within OUD patients. For instance, 3 studies examined the rates at which OUD participants met established criteria for clinically relevant anhedonia (based on SHAPS cutoff score), and the rates were as follows: 21% (Janiri et al., 2005), 39% (Huhn, Meyer, et al., 2016), and 48% (Martinotti et al., 2008). The total sample sizes of OUD participants in these 3 studies were small (n's were 24, 36, and 25, respectively), so it is difficult to draw conclusions regarding the higher rates in one study versus another, but a considerable subsample of individuals with OUD appear to experience clinically significant anhedonia. These rates are similar to that found in depression literature, which indicate that approximately one third of depressed individuals have clinically significant anhedonia, based on these cutoff scores (Pelizza & Ferrari, 2009). Larger and more diverse samples of individuals with OUD are needed to illuminate the rates of anhedonia, as well as to explore other individual differences that might correspond with anhedonia. Additionally, because the SHAPS was the most commonly used measure of anhedonia in these studies (8 out of 11), there is a need to explore other facets of anhedonia beyond consummatory pleasure in OUD.

Notably, 10 out of the 11 available studies reviewed here which assess anhedonia in individuals who are dependent on opioids, originated outside of the US. The study by Huhn, Meyer, et al. (2016) was the sole exception and included only 36 individuals with prescription opioid dependence recruited from a residential treatment facility approximately 2 weeks following medically assisted withdrawal, and who were not currently receiving any opioid agonist or antagonist pharmacotherapy. Therefore, the prevalence of anhedonia in OUD populations in the US, especially those initiating OUD treatment, is largely unknown. Moreover, only 4 of the 11 studies included individuals receiving any form of MAT for OUD (Garfield et al., 2017; Krupitsky et al., 2016; Lubman et al., 2018; Zaaijer et al., 2015), and only 2 of these included an opioid agonist medication (Garfield et al., 2017; Lubman et al., 2018). Given that MAT is considered the gold standard of treatment for OUD (Bart, 2012; Volkow, 2018), and that rates of MAT initiation, retention, and opioid relapse are so highly variable (Collins et al., 2018; Williams, Nunes, & Olfson, 2017), it is striking that so few studies have examined anhedonia in this context.

Second, it is unclear whether heightened anhedonia might be a predictor of treatment dropout or opioid relapse. As noted, anhedonia scores were significantly correlated with measures of craving in two studies, lending some support to the assumption that a loss of ability to experience pleasure from natural rewards might increase an individual's craving for opioids, thereby increasing risk for relapse. Although the study by Lubman et al (2018) did not support heightened anhedonia scores as predictive of subsequent opioid use, the relationship between anhedonia, opioid craving, and opioid relapse rates has not been

thoroughly examined in prospective studies. The only longitudinal treatment study to date indicated that anhedonia levels were not higher for those who dropped out of naltrexone treatment compared to those who completed treatment (Krupitsky et al., 2016). However, methodological limitations preclude firm conclusions regarding anhedonia in naltrexone treatment and there has been no examination within opioid agonist treatments.

Third, the time course of anhedonia in OUD is uncertain. Although some longitudinal studies in samples dependent on other types of drugs have found that anhedonia declines over time as abstinence duration increases (Garfield et al., 2014), findings from the cross-sectional studies in samples dependent on opioids reviewed here have been mixed. Again, the primary use of cross-sectional analyses to evaluate the effect of abstinence duration on anhedonia is not an ideal method for examining this question. Although Krupitsky et al. (2016) reported that anhedonia scores reduced over time for those who remained engaged in treatment and did not relapse to opioids, the analytic sample represented a small proportion of the total participants enrolled. Although depression and anhedonia are dissociable constructs (Argyropoulos & Nutt, 2013), they are interrelated, so the literature on depressive symptoms in OUD illustrates the possibility of clinically-relevant dynamic changes in anhedonia. For example, depressive symptoms are inflated upon treatment entry for those with OUD, but tend to reduce within the first few months of methadone maintenance treatment for the majority of individuals (Rounsaville, Weissman, Crits-Christoph, Wilber, & Kleber, 1982). However, a substantial minority continue to experience chronic, low-level depressive symptoms (including anhedonia) that may heighten risk for treatment drop out and drug relapse. Anhedonia may thus be an important patient phenotypic indicator associated with MAT non-response. However, the current state of the literature on anhedonia in OUD is insufficient to support or discredit this hypothesis.

Implications for assessment and treatment of OUD

If anhedonia is in fact an important clinical feature that is predictive of response to MAT, the question then becomes – can it be targeted in treatment? Unfortunately, no approved medication exists for anhedonia, and existing psychological and pharmacological treatments have shown to be relatively ineffective at treating anhedonia (Craske, Meuret, Ritz, Treanor, & Dour, 2016). Most treatments for disorders that include anhedonic features (e.g., major depressive disorder) aim to reduce negative affect and functioning, rather than specifically target deficits in positive affect. Standard medications for these disorders, such as selective serotonin reuptake inhibitors, have demonstrated little effect and may even worsen anhedonia (McCabe, Mishor, Cowen, & Harmer, 2010; McClintock et al., 2011; Nierenberg et al., 1999; Price, Cole, & Goodwin, 2009). As depressed positive affect (e.g., loss of pleasure, interest, energy and motivation) is considered mostly related to dysfunctions in dopamine and norepinephrine circuits, antidepressants that primarily act on these circuits (e.g., buprioprion, reboxetine) have been suggested to better address anhedonia (McCabe et al., 2010; Nutt et al., 2007). Other medications, such as ketamine and aripiprazole, have shown promising effects at reducing levels of anhedonia in small trials including individuals with bipolar depression (Lally et al., 2014; Mazza, Squillacioti, Pecora, Janiri, & Bria, 2009). However, any evidence supporting a medication effect specifically on anhedonia is preliminary and this has not been demonstrated specifically in OUD populations.

In terms of behavioral treatments for anhedonia, behavioral activation therapy (Lejuez, Hopko, Acierno, Daughters, & Pagoto, 2011; Martell, Dimidjian, & Herman-Dunn, 2010) is designed to increase response contingent positive reinforcement by helping patients get more active and reduce avoidance of pleasurable activities. Despite evidence of efficacy for behavioral activation at treating symptoms of depression (Trevor, Robert, & Clare, 2009), no studies have indicated significant effects on anhedonia (as defined by low positive affect). The evidence for Cognitive Behavioral Therapy (CBT), which includes behavioral activation as a primary component, has a pattern of overall efficacy for treating depression and other disorders (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012), but we found no reports for a specific effect of CBT on anhedonia. There is some evidence to suggest CBT may be effective in reducing the negative symptoms of schizophrenia (Aleman et al., 2017), yet support for an effect on anhedonia specifically is limited. It should be noted that there appear to be no CBT treatments that have directly targeted anhedonia. Other behavioral therapies, such as mindfulness and exercise have been suggested as potentially promising treatments to target anhedonia (Thomas & Garland, 2017; Toups et al., 2017), yet more studies are needed to determine whether these could be useful adjuncts to MAT for OUD.

Given CBT's focus on addressing maladaptive cognitions, in addition to behavioral activation, there would seem to be potential to target the various components of anhedonia (e.g., anticipatory, consummatory). Drawing from affective neuroscience and experimental psychopathology research, Craske et al (2016) recently developed a novel treatment for anhedonia specifically targeting components of reward processing: (1) anticipation/wanting/motivation, (2) consumption/liking, and (3) learning. This treatment, called Positive Affective Treatment, includes therapeutic techniques that directly target positive affect (many of which are components of CBT), such as pleasant events scheduling, cognitive training, and mindfulness. This treatment is currently being evaluated among anxious and unipolar depressed individuals, and if effective, has the potential to contribute to the treatment of other disorders, such as OUD (Craske et al., 2016).

Conclusions and Future Directions

In summary, anhedonia is a common component across many psychiatric disorders, including substance use, yet has received relatively little attention in the context of treatment for OUD. The available evidence suggests it is heightened in individuals who are dependent on opioids, and there may be a sizable minority of individuals in whom anhedonia does not remit through abstinence. Also, anhedonia may be a particularly important predictor of treatment dropout or nonresponse to MAT, but more research is needed to understand its prevalence, time course, and related risk factors in diverse OUD populations. Future work should emphasize the repeated assessment of anhedonia (and its components) in individuals initiating and currently maintained on MAT. In clinical settings, this might include standard self-report measures for measuring state-level anhedonia (e.g., SHAPS, TEPS) in the early months of treatment initiation, which may provide valuable information above and beyond typical measures of depressive symptoms. It has been argued that standard questionnaires for anhedonia are trait-level ratings, and more likely influenced by the individual's overall conceptualization of who they think they are, rather than their actual daily emotional experiences (Huhn, Harris, et al., 2016). Thus, researchers might also consider daily ratings

through ecological momentary assessment (EMA). EMA can permit more sensitive and detailed measurements of mood and behavior (Moskowitz & Young, 2006), and could provide greater insight into the relationship between anhedonia, craving, and opioid relapse for those currently receiving MAT. Huhn, Harris, et al. (2016) recently used EMA in a sample of individuals with prescription opioid dependence in residential treatment following medically assisted withdrawal, and found low positive affect days were associated with higher ratings of opioid craving, suggesting there may be a subset of patients who are particularly vulnerable to craving and relapse when they do not experience their environment as rewarding. This type of study provides a blueprint for future research in other samples of individuals with OUD.

Although the efforts to expand access to MAT to address the opioid epidemic in the US are vital, it is also important for the scientific community to continue to investigate the patient characteristics, such as indicators of anhedonia, that might inform treatment selection in order to improve the effectiveness of MAT for a greater proportion of individuals, as well as contribute to the development of personalized medicine for those with OUD.

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Table 1.

Summary of studies evaluating anhedonia in opioid dependent individuals

STUDY AUTHORS	OPIOID SAMPLE	DESIGN	ANHEDONIA MEASURE(S)	OTHER MEASURES	MAIN FINDINGS
Prospective Studies (ordered by most recent)					
Lubman et al., 2018	N = 121 DSM-IV criteria for current or past year opioid dependence • n=90 on methadone or buprenorphine • n=31 opioid abstinent, no medication	Observational; repeated assessment monthly for 6 months following baseline; additional 12-month follow-up	(1) TEPS • Anticipatory pleasure • Consummatory pleasure	(1) Time-line Follow-back (past month drug use)	• TEPS scores increased over time (i.e., reduced anhedonia); subscale scores not reported • TEPS decreased (i.e., increased anhedonia) in month after above-average opioid use • TEPS did not predict opioid use in subsequent month • TEPS increased (i.e., reduced anhedonia) in abstinent group compared to pharmacotherapy group • TEPS lower in those prescribed methadone (i.e., greater anhedonia)
Krupitsky et al., 2016	N = 306 DSM-IV criteria for opioid dependence; treatment seeking	Double-blind, 24-week randomized controlled trial: (1) 1000mg naltrexone implant plus oral placebo (2) placebo implant plus 50mg oral naltrexone (3) placebo implant plus oral placebo	(1) CPAS • Physical anhedonia (2) CSAS • Social anhedonia (3) Ferguson Anhedonia Scale • lack of interest • lack of pleasure		• CPAS, CSAS, and Ferguson Anhedonia Scales decreased over time (i.e., reduced anhedonia) for those who remained in treatment and did not relapse (n = 81) • No difference on anhedonia measures between those who dropped out and those who continued medication
Zaaijer et al., 2015	N = 10 DSM-IV opioid dependence; detoxified and heroin-free for 2 weeks	Brain imaging (SPECT) prior to extended-release naltrexone (XRNT) injection and two weeks later; 11 healthy controls underwent SPECT at baseline only	(1) SHAPS • Consummatory pleasure	(1) Striatal dopamine transporter (DAT) binding	• SHAPS scores did not change between baseline and after 2 weeks of XRNT • SHAPS scores did not differ at baseline between detoxified heroin dependent and healthy controls • No correlation between DAT binding and SHAPS scores at baseline or follow-up

STUDY AUTHORS	OPIOID SAMPLE	DESIGN	ANHEDONIA MEASURE(S)	OTHER MEASURES	MAIN FINDINGS
Cross-Sectional Studies (ordered by most recent)					
Garfield et al., 2017	N = 90 Opioid pharmacotherapy group • n=55 prescribed methadone • n=35 prescribed buprenorphine N = 31 Opioid abstinent group • minimum 7- days abstinent; DSM-IV opioid dependence past year	Comparison of self-report questionnaires between opioid pharmacotherapy group, opioid abstinent group, and 33 healthy controls	(1) SHAPS • Consummatory pleasure (2) TEPS • Anticipatory pleasure • Consummatory pleasure	(1) Time-line Follow-back (past month drug use)	• SHAPS scores higher (i.e., greater anhedonia) for Opioid pharm group and Opioid abstinent group compared to healthy controls • TEPS scores lower (i.e., greater anhedonia) for Opioid pharm group and Opioid abstinent group compared to healthy controls • Significant correlations indicating greater illicit opioid use associated with greater anhedonia on SHAPS and TEPS in Opioid pharm group • Duration of opioid abstinence not associated with SHAPS or TEPS in Opioid abstinent group
Huhn et al., 2016	N = 36 Prescription Opioid Dependent Patients (POPD); completed medically assisted withdrawal; in residential treatment	Laboratory session included self-report assessment, cue-reactivity task, and affect modulated startle response task; comparison with 10 healthy controls	(1) SHAPS • Consummatory pleasure	(1) AMSR • startle response (2) fNIRS • neural activity	• SHAPS scores higher (i.e., greater anhedonia) for POPD compared to healthy controls • POPD showed less startle suppression than healthy controls when viewing positive stimuli (i.e., less positive evaluation of stimuli) • POPD displayed reduced neural activation to images of positive social interactions compared to healthy controls
Zijlstra, Booij, van den Brink, & Franken, 2008[1]	N = 12 Males only; DSM-IV opioid dependence; in inpatient treatment; abstinent for minimum of 1 week (mean of 5.9 weeks)	Comparison of brain imaging (SPECT) and self-report assessments with 18 healthy controls	(1) SHAPS • Consummatory pleasure	(1) Striatal dopamine D2 receptor (D2R) availability	• SHAPS scores did not differ between abstinent opioid dependent group and healthy controls • No correlation between D2R availability and baseline SHAPS
Pozzi et al., 2008[1]	N = 24 DSM-IV opioid dependence; abstinent at time of study (at least 45 days since end of detox); recruited	Comparison of self-report and interview-based assessments with 22 alcohol dependent	(1) SHAPS • Consummatory pleasure	(1) BRMS • depressive symptoms	• SHAPS, SANS, BRMS scores did not differ between opioid dependent, alcohol dependent, or multidrug dependent groups

STUDY AUTHORS	OPIOID SAMPLE	DESIGN	ANHEDONIA MEASURE(S)	OTHER MEASURES	MAIN FINDINGS
	from self-help groups, day hospital, or therapeutic community **Same sample as Janiri et al 2005	and 24 multidrug dependent individuals	(2) SANS • anhedonia • affective flattening • avolition/apathy	(2) EuroASI • problem severity	• EuroASI composites not associated with SHAPS (i.e., anhedonia largely independent from addiction problem severity)
Martinotti, Cloninger, & Janiri, 2008 [1]	N = 25 DSM-IV opioid dependence; abstinent at time of study (minimum of 3 months after completion of detox; mean = 10.1 months); recruited from self-help groups	Evaluation of correlations across self-report measures; study included 25 alcohol dependent and 50 healthy controls	(1)SHAPS • Consummatory pleasure (2) SANS • anhedonia • affective flattening • avolition/apathy	(1) BRMS • depressive symptoms (2) VAS for craving	• SHAPS scores ≥ 3 for 12 out of 25 opioid dependent individuals (48%) (i.e., clinically relevant anhedonia) • Craving significantly positively correlated with SHAPS scores (i.e., greater anhedonia)
Stevens, Peschk, & Schwarz, 2007 [1]	N=25 Males only; Polydrug abusers; DSM-IV opioid dependence; consumed > 0.5 grams heroin intravenously on more than 3 days per week during last 2 months	Single session psychological testing study; included comparison with 26 abstinent polydrug addicts (at least 3 months abstinent), and 26 healthy controls	(1) SHAPS • Consummatory pleasure	(1) TAF • frequency and intensity of hedonic activities	• SHAPS scores differed by group - current heroin users and abstinent polydrug addicts reported greater anhedonia than healthy controls • TAF frequency and intensity scores lower for current heroin users compared to healthy controls (i.e., less hedonic activity)
Janiri et al., 2005 [1]	N = 24 DSM-IV opioid dependence; abstinent at time of study (at least 45 days since end of detox); recruited from self-help groups, day hospital, or therapeutic community ** Same sample as Pozzi et al., 2008	Psychometric evaluation and comparison of self-report assessments with 22 alcohol dependent and 24 multidrug dependent individuals	(1) SHAPS • Consummatory pleasure (2) SANS • anhedonia • affective flattening • avolition/apathy (3) VAS for pleasure • hedonic capability	(1) BRMS • depressive symptoms (2) VAS for craving (3) SOWS • withdrawal	• SHAPS, SANS, BRMS, and VAS for pleasure did not differ between opioid dependent, alcohol dependent, or multidrug dependent groups • SHAPS positively correlated w/ VAS craving and SOWS; negatively correlated with duration of abstinence • SHAPS scores ≥ 3 for 5 out of 24 opioid dependent individuals (21%) (i.e., clinically relevant anhedonia)
Schmidt et al., 2001 [1]	N = 16 ICD-10 criteria for opiate dependence; opiate abstinence of 6–36 hours (1st day of detox)	Single session assessment of psychopathology, hormonal testing, and psychomotor	(3) SANS • anhedonia • affective flattening	(1) Serum growth hormone • Dopamine receptor sensitivity	• SANS anhedonia and affective flattening scores higher in opiate dependent subjects compared to healthy controls

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STUDY AUTHORS	OPIOID SAMPLE	DESIGN	ANHEDONIA MEASURE(S)	OTHER MEASURES	MAIN FINDINGS
		performance; study included 17 individuals with alcohol dependence, 10 with major depression, 10 with schizophrenia, and 10 healthy controls	• avolition/apathy (4) Physical anhedonia assessed with "self-rating questionnaire"	(2) Psychomotor reaction time	• SANS anhedonia scores were not associated with central dopamine receptor dysfunction or psychomotor performance

1 Study included in Garfield et al 2014 Review

Notes: TEPS - Temporal Experience of Pleasure Scale; CPAS – Chapman Physical Anhedonia Scale; CSAS – Chapman Social Anhedonia Scale; SHAPS – Snaith Hamilton Pleasure Scale; AMSR - Affect-modulated acoustic startle response to emotionally positive, negative, neutral stimuli; fNIRS – functional Near Infrared Spectroscopy; SANS - Scale for Assessment of Negative Symptoms; BRMS - Bech-Rafaelsen Melancholia Scale; EuroASI - European adaptation of Addiction Severity Index; VAS – Visual Analog Scale; TAF - Tubingen Anhedonia Questionnaire; SOWS - Short Opiate Withdrawal Syndrome Scale