



**DET PSYKOLOGISKE FAKULTET**

***Cue Exposure Therapy for Addiction Disorders: A Review of  
Systematic Reviews***

**HOVEDOPPGAVE**

*profesjonsstudiet i psykologi*

**Georg W. Nielsen**

Høst 2021

Veiledet av: Eilin Erevik og Ståle Pallesen

### **Acknowledgements**

I would like to thank my main supervisor, Eilin Kristine Erevik, for great supervision and encouragement. The resources and thoughtful suggestions you provided during my supervision will always be appreciated. Likewise, a warm thanks to my second supervisor, Ståle Pallesen, for providing methodological expertise and helpful corrections. Furthermore, I would like to thank Librarian, Kjersti Aksnes-Hopland, for being such a good help on short notice. Lastly, I would like to express sincere gratitude to Joakim Hellumbråten Kristensen and Sara Ebling for being research assistants for this project.

### Abstract

**Objective:** The world of Addiction research is currently undergoing a paradigm-shift with the inclusion of behavioral Addictions as part of the Addiction umbrella term. Research has documented shared neurobiology and phenomenology across various Addictions. If Addictions share similar etiologies, identifying therapeutic techniques that target these similarities should prove fruitful. One central feature common to Addictions concerns a stimulus that act as specific triggers of strong appetitive responses and elicit compulsive consumption or behavior. Cue exposure therapy (CET) is a treatment that aims to change the patient's response to such cues through exposure and subsequently response prevention. **Method:** This thesis conducts a systematic review of the previously published reviews of Cue exposure therapy to provide an account of the evidentiary basis of this intervention for different Addiction disorders. **Results:** The current review identified 13 systematic reviews or meta-analyses applying some version of CET. CET has been used in treatment of Alcohol Addiction, Opiate Addiction, Gambling Addiction, Nicotine Addiction and Binge-eating disorders and Overeating. The field is suffering methodological issues making conclusions difficult to draw. While there is some evidence for CET in the treatment of Gambling Addiction and Binge- and Overeating, there is currently little evidence that Addictions are markedly improved by CET above other known treatments. Suggestions for future research are discussed.

*Keywords:* Cue Exposure Therapy, Addiction, Psychotherapy, Review of Reviews

### Sammendrag

**Mål:** Avhengighetsforskningen går for tiden gjennom et paradigmeskifte ved inkluderingen av adferdsavhengighet under avhengighet som paraplybegrep. Forskning har dokumentert nevrobiologiske og erfaringsmessige likheter mellom ulike avhengighetslidelser. Dersom ulike avhengighetslidelser deler etiologi, burde terapeutiske teknikker som angriper disse likhetene vise seg nyttige. Et sentralt fellestrekk blant avhengighetslidelser er at bestemte stimuli aktiverer sterke appetitive reaksjoner som igangsetter tvangspreget konsum og adferd. Cue eksponeringsterapi (CET) er en behandling som prøver å endre pasientens respons til slike stimuli gjennom eksponering og medfølgende responsprevensjon. **Metode:** Denne hovedoppgaven gjennomfører en systematisk litteraturgjennomgang av tidligere litteraturgjennomganger for å undersøke evidensbasen for denne behandlingen på tvers av ulike avhengighetslidelser. **Resultater:** Litteraturgjennomgangen identifiserte 13 systematiske litteraturgjennomganger eller Meta-analyser som tok for seg ulike versjoner av CET. CET har blitt anvendt på Alkoholavhengighet, Opiatavhengighet, Nikotinavhengighet, Overspisingsslidelser og Spillavhengighet. Forskningsfeltet lider av metodologiske svakheter og konklusjoner er derfor vanskelige å trekke. Litteraturgjennomgangene finner noe støtte for bruken CET i behandlingen av Spillavhengighet og Overspising, men det er foreløpig lite støtte anvende CET for Avhengighet sammenliknet med andre intervensjoner. Forslag til videre forskning er diskutert.

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## Introduction

People are surrounded by temptations, urging them to seek out and engage in pleasurable activities. A general feature of the mammalian mind is the tendency for rewards to become less captivating the longer they are delayed, making short-term rewards a greater priority (Bickel & Marsch, 2001; Vanderveldt et al., 2016). While the benefits of becoming thin and healthy are long term, far off in the future, the benefit of the chocolate bar is immediate. Although evolved for adaptive purposes, the capacity for seeking out short term pleasure can become maladaptive (Hill, 2013).

The availability of instantly pleasurable and captivating activities is increasing with the introduction of the internet. Smartphones have made the internet an ever-present feature of daily life. In excess of 85% of adults younger than 65 year of age have smartphones in the United States (Berenguer et al., 2016). The ubiquity of the internet exacerbates the range of possible temptations. Social media sites, gambling, gaming, shopping, pornography, films, and the news are all more readily available due to the internet. This development arguably has its benefits, but it is also involving cause for concern.

One concern related to smartphone and social media use is that it may exacerbate Addiction or cause Addiction-like conditions. There are multiple reports of social media being used to distribute narcotic substances (Clark, 2021; Nichols, 2020). Furthermore, many argue that the smart-phones themselves are addictive (Scudamore, 2018, October 30). Numbers for the United Kingdom suggests 72% of 11–16-year-olds say that they could not live without their smartphone. Many online features such as social media apps are designed to exhibit a variable-ratio reinforcement schedule (Brooks, 2019). In the case of social media, this means that social stimuli, such as comments, pictures, and notifications, is displayed at random rate that depends

on how much one uses the cite. These reward patterns are similar to those used in slot machines, designed to maximize engagement.

A Norwegian magazine recently described a clinic treating children for “screen-Addiction” with the goal of being abstinent from screens (Glorvigen, 2020). Are we ushering in a new age of Addiction or is there something that can be done to inculcate individuals against the ubiquity of such temptations?

This thesis wants to investigate the efficacy of a particular treatment for Addiction. In the following, I will outline the central features of Addiction and how the treatment known as Cue-exposure therapy (CET) can address the problem of Addiction.

## **On Addiction**

### ***Defining Addiction***

The National Institute on Drug Abuse (NIDA) in the United States defines Addiction as “(...) a chronic, relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences.” (Nida, 2020). Although multiple perspectives on Addiction exist (Miller, 2013a), the mainstream view of Addiction is arguably one emphasizing the biological underpinnings of Addiction, often termed the “biomedical model of Addiction” (Heilig et al., 2021; Leshner, 1997; Lewis, 2017; Volkow et al., 2016). The compulsivity in Addiction is linked to neurobiological changes associated with increased behavioral automaticity and reduced inhibition and voluntary control (Everitt & Robbins, 2016; Goldstein & Volkow, 2011; Volkow et al., 2016).

*Addiction* is not a diagnostic term. The closest corresponding term in the diagnostic systems is *harmful substance use* and *substance dependence* in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (Saunders,

2017; World Health Organization, 1993). In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), Addiction corresponds most closely to the diagnosis of *substance use disorder* (American Psychiatric Association, 2013; Hasin et al., 2013). In the ICD-10, harmful *substance use* is meant to refer conditions in which the individual is experiencing harm due to their substance use while not necessarily having a compulsive pattern of use, while *substance dependence* more closely resembles the term Addiction. In DSM-5, substance use disorder ranges from mild (2-3 criteria), moderate (4-5 criteria), and severe (6 or more criteria) out of 11 possible criteria (Hasin et al., 2013). The criteria for substance dependence and substance disorder in ICD-10 and DSM-5, respectively, are relatively similar and includes symptoms like loss of control and withdrawal symptoms the substance use is ceased or reduced. Further, as illustrated by the inclusion of both harmful and dependent use in ICD-10 and the categorization of substance use disorder into mild, moderate, or severe in DSM-5, both manuals view these disorders as present on a spectrum of severity rather than as a clearly identifiable category.

**The Addiction Concept is Changing.** Addiction is commonly thought to involve dependence to substances such as alcohol, cannabis, opioids, cocaine or nicotine (Zhang et al., 2017, p. 24). Addiction research is, however, currently undergoing a paradigm-shift. In 2013 behavioral Addictions were included in DSM-5 in the form of gambling disorder, and Internet Gaming Disorder and Internet Addiction which were included under “Conditions for Further Study” (Hasin et al., 2013). This might signal a shift away from a narrow focus on substance-related Addiction, broadening the scope of what Addiction entails (Chamberlain et al., 2016; Kardefelt-Winther et al., 2017; Petry et al., 2018). Some further argue that also other behaviors than gambling, gaming and internet use, such as eating and having sex, shopping, exercise, and

smartphone use, can engender an addictive pattern for some individuals (Corwin & Grigson, 2009; De-Sola Gutiérrez et al., 2016; Grant et al., 2010; Pelchat, 2009; Sussman et al., 2011).

It is important to note that there is quite a lot of controversies regarding behavioral Addictions. For instance, it has been argued that the Addiction framework is unsuitable for describing excessive behaviors and that behavioral Addictions may not be a separate phenomenon but a reflection of underlying conditions (e.g., depression)(Colder & Kardefelt-Winther, 2018; Van Rooij et al., 2018). The concept of Addiction applied to eating disorders has also been vehemently debated(Corwin & Grigson, 2009; Gordon et al., 2018; Hauck et al., 2020; Pelchat, 2009; Schulte et al., 2016; Ziauddeen et al., 2012). For simplicity, the term *Addiction* will be used throughout the thesis, although I recognize the need for more research and theorizing before concluding on the most precise term to describe excessive behaviors.

**Working Definition.** Throughout this thesis, I will use the term *Addiction* to refer to all the different conditions described above. Terms used throughout the literature such as *dependence, Addiction, disorder* have different connotations. However, as the terms used are dependent on research fields, diagnostic manuals, and date of publications, a single phrase is used to ensure consistency. Particular conditions, such as alcohol use disorder, will be simply labeled *Alcohol Addiction*. By extension, *addictive behavior* will be used to refer to both addictive substance use and the behaviors associated with behavioral Addictions. As the operational definition of Addiction is still subject to discussion (Kardefelt-Winther et al., 2017), As a working definition, I will use it the one provided by Marlatt et al. (1988):

A repetitive habit pattern that increases the risk of disease and/or associated personal and social problems. Addictive behaviors are often experienced subjectively as “loss of control” – the behavior contrives to occur despite volitional attempts to abstain or

moderate use. These habit patterns are typically characterized by immediate gratification (short term reward), often coupled with delayed deleterious effects (long term costs).

Attempts to change an addictive behavior (via treatment or self-initiation) are typically marked with high relapse rates. (p. 224)

### ***Prevalence of Addiction Disorders***

The estimation of prevalence of Addiction varies based on the assumptions researchers make about what constitutes Addiction both in terms of severity and in terms of which substances and behaviors that are regarded as addictive. Using a very encompassing definition, a systematic review including 11 substance and behavioral Addiction disorders (AD) estimated that 47% of the U.S. adult population shows maladaptive signs of an addictive disorder over a 12-month period (Sussman et al., 2011). They also found that these disorders are highly comorbid with each condition having a 10% to 50% overlap with other condition, especially amongst Substance Addiction. Substance Addiction estimates varied, in which illicit drugs, alcohol and Nicotine Addiction were estimated to be present in 5%, 10% and 15% of the population, respectively.

Other research suggest Addiction to illicit drugs have lower prevalence than the one given above (2%) (Grant et al., 2006), while the number for Alcohol Addiction seem to be around 7.5-14.3% Northern Europe and the US (Gowing et al., 2015; Hasin et al., 2013; World Health, 2018). Research shows that men are overrepresented in Substance Addiction samples (e.g., Gowing et al., 2015; World Health, 2018).

In Sussman et al. (2011)'s review prevalence of specific behavioral Addictions were each estimated to be 3% or less for eating, gambling, internet, sex, love, and exercise Addictions, respectively. More recent research estimates a seven percent prevalence rate for internet Addiction, and studies suggest that this prevalence rate increasing (Pan et al., 2020).

As illustrated, Addiction is something that affects a lot of people although the precise prevalence rates are difficult to determine. The rather high prevalence rates combined with the negative effects Addictions can involve for the affected individual, those close to the individual (Lander et al., 2013), and society (Sacks et al., 2015) underscores the importance of identifying measures to counteract it (Kemp, 2019; Lander et al., 2013; Sacks et al., 2015). To counteract and treat Addictions we need both an understanding of how Addiction operates and what causes it.

### ***Common Features of Addiction***

Addiction is generally thought to involve several areas of dysfunction and is thought to develop gradually in a self-perpetuating fashion (Lewis, 2017). Griffiths (2005) proposes a biopsychosocial model that describe a set of central features involved in Addiction. In the following, these features will be outlined to give an account of Addiction as a phenomenon. Although there are salient differences between different conditions in terms of risks and social acceptability (Sussman et al., 2011), the features below are to thought to be common features across different Addictions. The features are *Tolerance*, *Withdrawal*, *Mood Regulation*, *Conflict*, *Relapse*, and *Salience*. The feature of *Salience* is of particular interest to the intervention of interest to the current thesis and will therefore be more elaborated upon in more depth.

**Tolerance and Withdrawal.** Two central features commonly associated with Addiction is *tolerance* and *withdrawal*. Tolerance is the observed tendency of the hedonic impact of the substances or behavior of abuse to decrease over time (Koob, 2013). This is associated with the tendency of addicts to require larger and larger doses to receive the same high, leading to escalation of the disorder (Robinson et al., 2016, p. 114; Zernig et al., 2007).

Withdrawal involves negative physical and emotional states when not consuming the substance or engaging in the addictive behavior. This includes states such as emotional pain, malaise, dysphoria, alexithymia, stress and lack of motivation for other rewards (Koob & Volkow, 2016). The features of tolerance and withdrawal have long been considered a mark of physical dependence to particular substances (Edwards & Gross, 1976; O'Brien, 2011), and some argue that withdrawal and tolerance are not useful for understanding the behavioral Addictions (Starcevic, 2016). For instance, some argue that escalation of gambling bets, which is the DSM-5 criterion for tolerance in gambling disorder, is an attempt to win back previous losses rather than due to tolerance (Blaszczynski et al., 2008). However, many argue that behavioral Addictions also exhibit these features (Griffiths, 2005; Hasin et al., 2013; Lee et al., 2020), although research of these features on behavioral Addictions is still in its nascent stage (Kaptis et al., 2016).

**Mood Regulation.** Addictive behaviors are often initiated as a response to negative feeling and distress (Khantzian, 1997). In this sense, people engage in addictive patterns as a way of regulating negative feelings. For example, people who smoke might have a morning cigarette to get in the right mood to start the day. Engaging in addictive behavior to alleviate distress signals a shift away from positive to negative reinforcement, whereby the addict consumes drugs

to alleviate distress rather than gaining pleasure (Koob, 2013; Koob & Le Moal, 1997; Koob & Volkow, 2016).

**Conflict.** As the Addiction takes hold, the addictive behavior becomes an increasing priority in life. This involves a narrowing of interests and activities and result in conflict between the addictive behavior and the individuals' goals, relationship and/or obligations. People may lack engagement in daily activities, fail to fulfil their responsibilities, and neglect to care for themselves and others. The addictive behavior/substance use persists despite the occurrence of social, occupational, financial and health problems. These symptoms of loss of function are regarded as the clearest marker of severity of Addictions (Colder & Kardefelt-Winther, 2018; Hasin et al., 2013, p. 25).

**Relapse.** An addictive condition is characterized by difficulty maintaining an appropriate level of consumption or engagement with a particular substance or activity. Therefore, people attempt to cut down or abstain from the addictive behavior. A feature of Addiction is the tendency to revert to the addictive behavior after attempted abstinence or control, also known as a relapse (Griffiths, 2005; Kirshenbaum et al., 2009). Relapse is common. For example, amongst individuals who remised from with Alcohol Addiction without professional help, 60,5% relapsed over a 16 year period (Moos & Moos, 2006). This number was 43,5% for those seeking professional help over the same timeframe.

**Salience.** Central for the purposes of this thesis, Addiction involves changes in salience towards the addictive behavior. According to Griffiths (2005) salience is reflected in both behavior, cognition, and affect. As the Addiction takes hold, the time spend engaging with the addictive behavior increases to the detriment of other life priorities. Secondly, the thoughts of the person become increasingly preoccupied with the activity and fixated on anticipating and planning



for future engagement with these activities/substances. Thirdly, increases in salience is marked by affective states related to the desire to engage with the activities/substances. This affective component has can be understood as *craving* for the particular substance or activity.

Craving has recently been included as a symptom criterion for substance use disorder in the DSM-5 (Hasin et al., 2013) and is defined as a “subjective experience of wanting to use a drug” (Tiffany & Wray, 2012, p. 24). In other words, craving involves an appetitive response that motivate behavior, although people may vary in their conscious awareness of this process (Sayette, 2016; Tiffany & Wray, 2012). Craving is readily induced by cues that signal reward but has also been shown to increase in the presence of negative emotional states and interoceptive cues such as certain bodily states, and mental imagery.

These changes in the subjective experience of salience in the form of cravings have been found to correlate with neurobiological changes. Robinson and Berridge (1993) have proposed the incentive salience sensitization theory of Addiction. This theory proposes that Addiction is characterized by a sensitization of the brain’s mesolimbic dopaminergic system. The dopaminergic system is responsible for producing approach behavior and responds to signs of reward in the environment (Alcaro et al., 2021; Schultz, 2002). Incentive salience sensitization theory predicts that Addiction is characterized by the dual processes of reduced pleasure in the addictive behavior, (which correspond to tolerance), and increased reactivity to features of the environment that signal reward (Berridge & Robinson, 2016; Robinson et al., 2016; Robinson & Berridge, 1993).

This means that addicted individuals have stronger cognitive and emotional reactions (including cravings) to cues associated with addictive behavior compared to non-addicted individuals(Drummond, 2000). Cue-reactivity (i.e., rather strong physical, cognitive and/or emotional reactions to cues related to the addictive behavior) has been shown towards food in

people who overeat (Pelchat et al., 2005; Schulte et al., 2019; Tang et al., 2012), substances among individuals with various substance use disorders (Carter & Tiffany, 1999; Courtney et al., 2016; Drummond, 2000), and stimuli associated with the specific behavior among individuals with behavioral Addictions (Starcke et al., 2018). Studies have also found such reactivity patterns to predict later consumption or relapse under abstinence (Courtney et al., 2016; Heinz et al., 2017). If Addictions share a similar etiology in respect to cue-reactivity in general, and perhaps in particular cravings, finding therapeutic techniques that target this similarity should prove fruitful. Therefore, cravings are considered an important treatment target (Drummond, 2000).

### ***Causes of Addiction***

Research has uncovered genetic contributions for substance use disorders, accounting for around 50% of the variance (Agrawal & Lynskey, 2008; Kendler et al., 2012). Although such estimates have not been established for behavioral Addictions research suggest that a common genetic contribution may be present for a variety of addition disorders as well (Leeman & Potenza, 2013; Zhang et al., 2017, p. 60). Some research suggests that it is through personality traits that genetics contributions to the development and maintenance of Addictions manifest (Belcher et al., 2014). Current research suggests that several personality traits such as impulsivity, sensation-seeking, social anxiety, pessimism, depression, extraversion, aggressiveness, and unconventionality are risk factors for Addiction (Goodman, 2008). Environmental factors are also evidently contributing to Addiction. Substance exposure and availability during adolescence in addition to other factors such as social isolation, adversity and socioeconomic status and seems to be important factors for the onset of addiction (Nida, 2020).

**Learning Theory.** Addiction can be seen as learned behavioral patterns that is strengthened and develops gradually over the course of early adulthood (Lewis, 2017). In this

view, Addiction can be seen as learned behavioral patterns (Everitt & Robbins, 2016; Hall et al., 2015; Heinz et al., 2019). Therefore, behaviorist learning theory has been used for understanding Addiction.

Both classical and operant learning is thought to be involved in Addiction (Heinz et al., 2019). In classical conditioning, an organism learns that a conditional stimulus (CS) is predictive of an unconditional stimulus (US), which causes the CS to elicit a conditioned response (CR) response (Rescorla, 1988). If the predicted stimuli is rewarding, the CS will elicit an appetitive motivational response (CR) (Robinson & Berridge, 1993). Applied in alcoholism for instance, stimuli such as the sight and smell of alcohol, become conditional stimuli that predict the effects of alcohol such that these stimuli elicit an appetitive craving response. It is important to note that this form of learning is context dependent (Bouton & Moody, 2004), and can occur both as a response to proximal cues (sight and smell of alcohol), and distal cues (bar, home, social situation).

Instrumental conditioning involves the learning of contingencies that result from behavior. In the case of addictive behaviors, the consequences are pleasure (at least initially), and this increases the rate of seeking them out. Current learning theory distinguishes between two operant processes (Everitt & Robbins, 2016). First, an action-outcome (A-O) model, where a certain behavior (A) is increased or diminished based on whether it produced the desired outcomes (O). Second, a Stimuli-response (SR) model in which behavior is initiated based on contextual cues in which behavior is not reduced based on outcome. This latter process develops over time and corresponds to the formation of habit. This latter operant process is initiated by cues established through classical conditioning and has recently been termed the Pavlovian-to-instrumental transfer (PIT) (Cartoni et al., 2016; Heinz et al., 2019). PIT is the process by which

a classically conditioned response activates instrumentally learned behavior such as drug seeking (Cartoni et al., 2016). This explains how Addiction cues motivate Addiction behavior, and why reduced hedonic related to engaging in the behavior/consuming the substance (tolerance) does not decrease the rate of responding (i.e. because responding does not decrease based on outcome in the SR-model).

**Social cognitive theory.** Social-cognitive theory (SCT) builds on and expands on classical learning theory (Bandura, 1986). It proposes that the individual and its environment is reciprocally determined in which individuals both are conditioned by and select their environments. This theory proposes that the two cognitive processes of outcome expectancies and self-efficacy is important for understanding Addiction and relapse (Bandura, 1977; Larimer et al., 1999; Marlatt, 1990; Niaura, 2000). SCT predicts that the tendency to engage with an addictive behavior or relapse is the result of the outcome the individual expects in a given situation. For instance, smoking is initiated because the person believes it to deliver pleasure, relaxation, or something else positive. Alternatively, it also explains why someone is unlikely to quit addictive behavior “my friends will not hang with me if I do not drink”. Self-efficacy beliefs are a type of outcome expectancy, that relates to the individual belief in his or her ability to deal effectively with a situation. For instance, individuals with Alcohol Addiction often come to believe that if they see a bottle of alcohol, they will be incapable of controlling themselves. Outcome expectancies are proposed to develop through personal experience, but it also adds the importance of social influence, self-reflection, and arousal.

### **Treatment of Addiction**

Treating Addictions is a challenging task. A meta-analysis using a conservative estimate (including counting every loss to follow-up as relapse), shows that the remission rates for

Substance Addiction is approximately 35% (Fleury et al., 2016). However, the authors also found that these estimates varied from 15.5% and 95.7% between studies. The latter observation might suggest that there are conditions under which Addiction can successfully treated.

Psychotherapy attempts to solve the problem of Addiction by understanding its biopsychosocial mechanisms and finding ways to modify or counteract them. Pharmacotherapy aims to target the hypothesized biological drivers of the disorder (Leshner, 1997). Research suggests that pharmacotherapy can be effective for Substance Addiction, but the effect sizes are small (Hall et al., 2015, p. 654).

There are several proposed therapeutic interventions for Addiction (Miller, 2013b). Brief interventions and motivational enhancement approaches seeks to increase the individual's awareness of own consumption and motivation for change, respectively (Martino, 2013). These approaches are often used in conjunction with each other.

Alcoholics Anonymous and Narcotics Anonymous and other 12 step-approaches provide group therapy and support with the goal of achieving total abstinence from drugs and alcohol (Kingree, 2013). A great emphasis is placed on the disease model of Addiction, framing Addiction as something out of the individual's control. Hence 12 step approaches encourage the detachment of social relationships and environments that facilitate the addictive behavior (e.g., drinking).

Addiction results not only from an increased sensitivity to the reinforcing effects of drugs, but also as a response to lack of positive reinforcers in the individual's life. Several therapies target and seek to increase the availability of reinforcers. Contingency management seeks to find tangible incentives and rewards that patient can reward themselves with when they stay abstinent (Alessi, 2013). For instance, paying money upfront that the client will receive back

if they show a positive urine test. Increasing reinforcement more broadly, Environmental Enrichment seeks to counteract Addiction by increasing vocational and social engagement in everyday life. Similarly, behavioral couples therapy tries to increase marital satisfaction and social support between partners to facilitate recovery from Addiction (Miller, 2013b).

Cognitive behavioral therapy (CBT) is informed by both classical and social learning theory (Carroll, 2013). It attempts to identify and target behavioral and psychological contingencies (e.g., “when I am at home alone, I’ll have a drink” or “when I feel unmotivated before work, I need cocaine”). CBT then attempts to help the individual develop skills that will help them break or alter these contingencies. Such techniques can include urge-specific coping skills (techniques to avoid succumbing to craving) or social skills training (learning how to say no a drink).

Research shows that these abovementioned interventions do have some merit, but also that they do not show consistent and universal improvements for people with ADs (Cutler & Fishbain, 2005; Fleury et al., 2016). One way to respond to this problem is to further attempt to specify and refine our understanding of the mechanisms involved in Addiction and target these mechanisms. To this aim, CET is expounded upon in the following, and is the treatment investigated in this thesis.

### **Cue Exposure Therapy**

CET has long been considered a candidate for treatment of ADs (Blakey & Baker, 1980; Bradley & Moorey, 1988; Drummond et al., 1990). In its most basic form, the treatment consists of exposing the patient to stimuli associated with addictive behavior while the patient is refrained from further consumption. One early study by Rankin and Hodgson (1977) reported the case a 43-year-old man who had been drinking his entire adult life and sought treatment. The treatment

consisted of giving the man one or several shots of vodka, and then asking him to wait in a until his desire for further drinking had subsided. His desire reportedly did subside, and both him and his wife reported him being sober during Christmas for the first time in years. Before the turn of the century, CET had garnered both theoretical and empirical interest (Drummond & Glautier, 1994; Drummond et al., 1990; Hammersley, 1992; Marlatt, 1990; Monti et al., 1993; Sitharthan et al., 1997).

### ***Treatment Rationale***

Cases such as the one reported above seem almost too good to be true but comes out of the behaviorist tradition and has a clear treatment rationale (Blakey & Baker, 1980; Drummond et al., 1990; Hammersley, 1992; Marlatt, 1990).

Within a behavioral perspective, CET is proposed to work by the process of extinction (Drummond et al., 1990). It is thought that if the CS (e.g., the sight and smell of a drink) is exposed to the patient repeatedly without the US (e.g., drinking), the CS will eventually not be experienced as predictive of the US and thus the appetitive craving response to such cues will subside (Conklin & Tiffany, 2002; Lovibond et al., 2015). It is then thought that Addiction-related stimuli will have less power to evoke appetitive craving responses, thus reducing the frequency by which drinking is initiated.

Ludwig et al. (1974) (reported in Drummond et al. (1990)) noted that individuals who have received treatments that focus on instilling insight and understanding within the context of therapy, will still be subject to the strong reactions that Addictions can involve when outside therapy. Thus, unless the therapy addresses these responses, treatment is destined for failure. CET has therefore been proposed as an important ad-on to other treatments to facilitate relapse prevention (Marlatt, 1990)

CET is also predicted to work from a SCT perspective (Marlatt, 1990). Firstly, CET is posited to work through changing outcome expectancies by violating them through exposure paired with response change (Byrne et al., 2019; Schyns et al., 2016). Changes in outcome expectancies means that the individual with Addiction has a change in the cognitive prediction of what is the likely outcome in a particular context, and he will act accordingly. For instance, “if I see a beer, I will drink it”. Secondly, from the perspective of SCT, CET may work through changing self-efficacy beliefs (which is a specific class of outcome expectancies) (Marlatt, 1990). After many failed attempts to moderate their addictive behavior individuals with Addiction’s belief in their ability to moderate Addiction-related behavior (e.g., their drinking) is likely to be low. Self- efficacy is thought to be learned through different sources, one of which is experience of managing difficult task-relevant situations (Bandura, 1977; Larimer et al., 1999). In other words, CET is thought to increase self-efficacy by giving the patient the opportunity to effectively manage situations with high risk of relapse (Marlatt, 1990). More to it, as research shows that learning is highly context specific, there is an hypothesis that CET might increase the context-specificity of the learning of coping skills training taught in CBT (Loeber et al., 2006; Marlatt, 1990).

Another mechanism through which CET may work is distress tolerance. In reviewing the concept of craving Tiffany and Wray (2012) note that some may experience Addiction craving as distressing. Some propose that CET should increase the capacity to tolerate the distress associated with appetitive cues which could be a mechanism though which CET works (Norberg et al., 2018).

### ***The Current State of CET***



Cue exposure therapy is usually delivered in five to 20 sessions delivered on a daily, weekly, or monthly basis. Exposures typically last around 10-to-90-minutes per session and involves one or more cues relevant to the individual patient's Addiction. The exposures are guided by a therapist (Conklin & Tiffany, 2002).

CET has been applied to wide variety of ADs with similar treatment rationales. There are studies including exposure to alcohol (Mellentin et al., 2019), nicotine (Unrod et al., 2014) cocaine (Prisciandaro et al., 2013) and opiates (Marissen et al., 2007). CET has also been applied to gambling disorder (Riley et al., 2018), Internet gaming disorder (Zhang et al., 2017) and binge- and overeating disorders (Jansen et al., 1992; Schyns et al., 2016).

CET has received renewed interest in relation to the developments within virtual reality (VR) technology, VR is one mode of CET delivery (Hone-Blanchet et al., 2014). Virtual reality technology attempts to simulate real- world scenarios using a head mounted device or other immersive technology (Hone-Blanchet et al., 2014). Using VR, clinicians and researchers hope to gain higher generalizability of treatment by making exposure more congruent with real-life, high-risk situations.

Initial studies into the efficacy of CET showed promising results (Drummond & Glautier, 1994; Monti et al., 1993; Rohsenow et al., 2001; Sitharthan et al., 1997), but CET has received inconsistent support in the review literature (Conklin & Tiffany, 2002; Martin et al., 2010; Mellentin et al., 2017). The reviews published are limited to specific ADs, treatment modalities, and/or time-frame. Given these variations in scope, a synthesis across different reviews disorders is warranted.

## **Methodological Background**

In recent decades, systematic reviews (SR) and/or meta-analyses (MA) have become extremely popular methods for systematizing and synthesizing research on a given topic (Tebala, 2015). As the number of published empirical studies grows each year, so does the need for synthesizing evidence. Individual studies frequently find inconsistent results (Linden & Hönekopp, 2021), and conducting SRs and/or MAs is one way of trying to avoid selectively emphasizing a section of the body of evidence on a given topic (Littell, 2008). In addition, as information abounds, it is important that researchers gain a concise picture of the evidence that can serve as the basis for decision making and guiding future research (Donnelly, 2018).

The two methods, SR and MA, can be conducted together or separately (Borenstein et al., 2009). They both serve different but complementary functions. The purpose of the systematic review is to consider *all* relevant studies such that the evidentiary status on a given topic can be judged based on the entire body of evidence. An MA is conducted in order to give a statistical synthesis, by pooling different study results into a common effect size (Borenstein et al., 2009).

In recent years, the number of SRs has grown exponentially (Hoffmann et al., 2021; Tebala, 2015). Consequently, the factors that warrant for synthesis of primary studies, arguably pertains to SRs as well. To address this, the method of reviewing systematic reviews has recently emerged (Aromataris et al., 2015; Faulkner et al., 2021; Smith et al., 2011)

Different names have been used for this method such as “review of reviews”, and “umbrella review”, “review of systematic reviews”, and these names are being used interchangeably (Faulkner et al., 2021). Hereafter, this thesis will use the term “review of reviews” for this method. In principle, a review of reviews is systematic review that analyses systematic reviews instead of primary studies.

### **Purpose of the Study**

This thesis seeks to conduct review of reviews of the efficacy of CET for treating ADs. Specifically, this thesis wants to investigate CET's efficacy in changing Addiction behaviors, craving, clinical symptoms, and self-efficacy for different ADs.

### **Research Question**

This study seeks to answer the following question: What is the efficacy of Cue Exposure Therapy for treating behavioral- and substance additions?

### **Significance of the Study**

Several factors underscore the need for the current study. Firstly, as Addiction might be a growing problem due to increased internet access, finding ways to mitigate it is an increasing need. Despite progress in the development of treatment for drug use disorder there is still room for improvement (Ray et al., 2019). Therapy research often seeks to identify the processes within therapy that are efficacious (Wampold & Imel, 2015). As many therapies include an amalgamation of different techniques, knowing what specific techniques that works (or does not work) can contribute to more "process-pure" psychotherapies. CET is an example of a specific technique and hopefully investigating the efficacy of CET can be of benefit to the people struggling with Addiction.

Secondly, this review of reviews should provide a comprehensive overview of the field of cue exposure therapy, helping decision making for other researchers and mental-health clinicians.

Thirdly, it offers the possibility to compare the efficacy of CET for different conditions. In doing so, a broad definition for Addiction will be used, involving both well-established ADs and newly proposed ones. This is not done to foreclose theoretical disputes around the delimiting features of Addiction, nor to ignore salient differences between different conditions. While

notable differences between ADs exists, CET is applied to them with a similar treatment rationale. Because the rationale of this treatment is similar across ADs, CET should theoretically work in the same way across conditions. If this proves not to be the case, theoretical refinements of either the condition and/or the treatment are warranted. Gaining an understanding of how CET works across these disorders is therefore of both theoretical and clinical importance.

Fourthly, this study also seeks to evaluate the quality of published SRs and MAs. Like primary studies, these methods are subject to biases. As SRs are often treated as the gold standard for evidence-based treatments, evaluating the quality of SRs is an important and often ignored control. By comparing the results and conclusions of overlapping SRs on CET for Addiction, the current study will contribute with a critical evaluation of the CET literature.

## **Methodology**

### **Registration**

The study was pre-registered in PROSPERO October 4, 2021, in accordance with PRISMA guidelines (Registration number CRD42021276065) (Moher et al., 2009). A protocol specifying the relevant inclusions and exclusion criteria was developed in parallel with the registration.

The purpose of a preregistration is to prespecify and make transparent what studies and data will be sought and how the researchers intends to analyzed the data (Nosek et al., 2018). This procedure ensures that resources are not allocated/used on the exact same questions, hence ensuring that resources are used more efficiently as well as avoiding publication bias (Stewart et al., 2012). Registration also counteracts the unseemly tendency of “data fishing” in which the data and studies are selected based on their results and not their research question and methodology (Lakens, 2019).

**Eligibility Criteria**

In the following, I will not describe all eligibility criteria, but comment on some of the decisions that was made. The full set of eligibility criteria for this review of reviews are available in Table 1. Using a broad definition of Addiction, this review will include conditions such as overeating/binge eating disorders, internet use disorder, gambling disorder, gaming disorder, hypersexuality/sex Addiction, and shopping Addiction. An inclusion criterion is that the study under review seeks to investigate treatment for pathological consumption and not normal behavior. There is a lack of consensus regarding the distinction between what is deemed pathological and normal for some of these symptoms/disorders. In the current study, abnormal or pathological use/behavior was defined as conditions in which the study itself considered the condition under treatment abnormal or pathological.

Studies that systematically review evidence for CET for ADs including behavioral or substance use Addictions will be reviewed. CET is hereby defined as studies that for therapeutic purposes exposes patients to cues associated with addictive behavior while the patients are being limited in their capacity to engage with the addictive stimuli. There exist several treatments that expose patients to cues associated addictive behavior, but that also involves technique during exposure such as coping skills training and mindfulness. Furthermore, several studies include CET as an ad-on to other therapies such as cognitive behavioral therapy. Reviews that include studies with these amendments will be included in this review. The reason for this is firstly that much of the CET literature involves combination treatments, and that there is a theoretical justification for assuming that CET is effective in combination with the aforementioned therapeutic components/techniques (Loeber et al., 2006). Excluding studies on combined treatments would limit the review of the full potential of CET effectiveness.

A series of interventions noted in Table 1 (i.e., Cognitive Bias Modification, Attentional Bias Modification, Inhibitory training, Eye Movement Desensitization and Reprocessing, Aversion therapy), exposures patients to stimuli associated Addiction behavior but is not included in the present review. These interventions have specific research paradigms and treatment rationales and is not defined as a form of CET in this review.

The present review will include systematic reviews and/or meta-analysis of CET interventions. They may include any study designs that allow for some estimation of efficacy including randomized controlled trials (RCT), controlled trials (CT), pre-post designs and case series and case studies. The justification for this is that previous reviews have shown a dearth of RCTs in the CET literature (Mellentin et al., 2017). To provide a comprehensive overview of the current empirical status of CET, less stringent designs will thus need to be included.

### **Search Strategy**

A complex search strategy including three main concepts/facets was developed. The facets were: Cue exposure Therapy, Addiction Disorders and Systematic Review. A full overview of search terms can be found in Appendix A. A cursory search of the literature on CET, exposure therapy for anxiety, and Addiction was used to identify key concepts to be included for each facet.

In developing the search strategy, care was made to strike a balance between sensitivity and specificity. This means identifying the research of interest (sensitivity) while excluding research not of interest (specificity). The initial list of search terms was modified based on supervisor feedback, further reading and consultation with a librarian. Several test-searches were made to assess whether the words used were relevant. A total of six databases were selected.

Because the search was limited to reviews, it has much stronger specificity compared reviews of primary studies. Therefore, six databases seemed manageable.

Truncations/wildcards, “\*”, were used for most terms to increase sensitivity. In some cases, it was not used for specific terms that seemed to give too general results. For instance, “inhibitory learning” is relevant to the search because the term is used in the theorizing around exposure therapy (Craske et al., 2014) and has been applied to the treatment of CET of overeating (Van Den Akker et al., 2016). However, the truncated “inhibit\*” seemed to target a high proportion of unwanted results from molecular biology and neuropsychology. The truncation was therefore removed to increase specificity.

The number of substances and substance synonyms was not exhaustive because many drug terms did not impact search results. For instance, the word “weed” did not increase hits in test searches. The word was therefore considered superfluous. Testing whether including search terms for several specific substances would increase the sensitivity, a more comprehensive list of substances of abuse from (Zhang et al., 2017, p. 24) was included as search terms in a search in Web of Science (WoC). This increased the search hits with two entries, none of which were relevant to the research question, hence these search terms were not included in the final searches.

The search was adapted to the different databases. This included adapting the mesh terms and subject headings that vary between databases. These modifications were done by exploring the different trees in each database and considering whether they could be relevant to the two first facets. No mesh terms were used for facet 3 as they would have severely reduced the specificity. The third facet was only used in four out of six databases because the Cochrane

database and The Database of Abstracts of Reviews of Effects (DARE) only index reviews. The third facet was therefore not relevant for searching in these databases.

### *Conducting the Search*

The search was conducted October 4, 2021, in PsycInfo, Medline, WoC, The Cochrane Library, and DARE. An overview of the search results can be found in Figure 1.

The records were downloaded in RIS file type from all databases except DARE. Records from the DARE database could not be exported directly, and each entry was therefore manually downloaded. The search records were then put in a folder for each database.

A total of 2,598 records were then uploaded into Endnote x9, a reference manager software (Hupe, 2019). This was done to make use of the program's "find duplicates" function. A total of 561 records were deleted due to being identified as duplicates, leaving 2,037 records as the full search result.

The whole Endnote library was then exported and imported into Rayyan, a web-browser software developed for collaboration on the study selection process for systematic reviews (Ouzzani et al., 2016; Rayyan Systems Inc., n.d.). Additional duplicates were found using the "detect duplicates" tool in Rayyan that were not identified by EndNote. Rayyan detects duplicates by giving a percentage of overlap of text match. Because it does not require an exact match, it can detect more duplicates than by using Endnote. Records detected as duplicates in Rayyan were screened manually based on similarity of authorship, title, and year of publication and abstract. A total of 175 entries were deleted as duplicates amounting to a final 1862 articles eligible for the screening process.

### **Screening Process**



Two reviewers screened title and abstract of each entry of the search result. Interrater reliability was calculated for the screening process and is shown in Table 2. Initially, two reviewers investigated the level of agreement on 100 abstracts. After the first 100 entries were screened, differences between screening decisions were discussed to ensure that the two reviewers had the same perception of which type of studies that constituted the review's target studies. Every entry was screened by at least two reviewers and each entry was given at least one justification for exclusion.

After title and abstract screening, 140 entries were included by at least one reviewer of which 48 of these were shared by both reviewers which corresponded to a moderate level of interrater agreement (Cohen's kappa = 0.486). The principal reason for the somewhat low reliability was uncertainty about how to judge abstracts that did not explicitly identify themselves as systematic reviews. Another reason was the judgment about the delimiting features of "food-Addiction" where one review included everything related to eating disorder and exposure, whereas another had a more conservative threshold. During discussion we decided to air on the side of caution and include entries if there was uncertainty. After discussion, the reviewers reached agreement on 86 entries being eligible for full text review. The two reviewers reached substantial agreement after full-text review (Cohen's kappa = 0.79).

In checking with the protocol and discussing the issue with the supervisor, 6 studies were excluded because they did not present an independent section on CET neither in tabular nor text-format and did not explicitly identify itself as a SR or MA (Cassin et al., 2020; Durl et al., 2018; İnce et al., 2021; Orchowski & Johnson, 2012; Pallesen et al., 2005; Roggi et al., 2015).

### **Data Extraction Process**

An extraction template was developed based on recommendations from Aromataris et al. (2015). The author of this thesis conducted the data extraction. Most data were extracted from the reviews' 'summary of studies' tables and supplemented by in-text descriptions of the major findings of each review. When available, quantitative outcome-data were extracted in detail. When such data was absent, text summary made by the review authors was used instead and paraphrased. Primary studies were not sought for data extraction, except for clarification when findings in the review seemed unclear.

### **Quality Rating of Reviews**

Each review included in this thesis was rated for quality using the AMSTAR tool (Shea et al., 2017). AMSTAR is a validated and reliable tool rating the quality of systematic reviews and meta-analyses along 16 criteria and provides an overall rating of studies into either High, Moderate, Low or Critically Low-quality.

A dynamic excel sheet was developed by using the exact criteria of the AMSTAR tool to allow for easier interrater comparison and resolution of disagreements. Two raters independently rated each article on each of the 16 criteria. Training was done by assessing one of the articles independently and later discussing potential disagreements. Thereafter, the rest of the articles were rated independently. Disagreements were solved through discussion.

### **Data Synthesis**

A method based on Smith et al. (2011) was used for evaluate the level of scientific evidence. Here, synthesis was made by analyzing number of studies showing favorable outcomes, non-significant and unfavorable outcomes respectively. Where statistical information was reported, an effect-size range was compiled. Risk of bias as described in each systematic review was also noted and summarized. If such tools were not used, limitations as discussed in

the articles were compiled. The examples of how to present findings in tables presented in Smith et al. (2011) was modified in order to better fit the scope and questions of the present review.

## **Results**

### **Search Results**

Results of the review identification process can be found in Figure 1. Out of a total of 1862 unique entries, the study selection process yielded 13 entries eligible for this review.

### **Review Characteristics**

The 13 review papers were all published between 2002-2021. A total of 70% were published during the last 4 years, supporting the timeliness of this review. In the following I will present the aims and findings of the included reviews.

The 13 reviews included 90 references to CET primary studies, of which 52 were unique. This amounts to of 42.2% overlap in primary studies between reviews. This overlap was much higher in studies with similar scope. An overview of the aims, search strategies, overlap, and limitations of each review and their included studies can be found in Table 3.

Across the 13 reviews, 1,235 participants of a total of 2,295, received some form of CET. Median sample size in the reviews was 41 participants, indicating that the reviews included studies with mostly small samples.

### ***Aims***

The systematic reviews and meta-analyses varied widely in terms of scope. All reviews had aims that addressed some form of CET intervention. All but one review had other aims in addition to reviewing CET literature (Mellentin et al., 2017).

In terms of their main aims relevant to CET, two out of 13 reviews aimed to give meta-analytic estimates of the effectiveness of CET for one or more ADs (Conklin & Tiffany, 2002;

Mellentin et al., 2017). Five out of 13 reviews stated as one of their aims was to review the effectiveness of VR-CET for one or more ADs (Ghiță & Gutiérrez-Maldonado, 2018; Keijsers et al., 2021; Langener et al., 2021; Segawa et al., 2019; Trahan et al., 2019). Two out of 13 reviews wanted to investigate exposure therapy for eating disorders generally (Butler & Heimberg, 2020; Koskina et al., 2013), while one wanted to investigate specifically CET for Binge Eating Disorders (Magson et al., 2021). Two reviews wanted to investigate the efficacy of psychotherapeutic interventions for a specific ADs (Mayet et al., 2005; Ribeiro et al., 2021). Lastly, one review wanted to assess whether different types of CBT, including one treatment approach which also included a form of CET, would be differentially efficacious for Gambling Addiction (Gooding & Tarrier, 2009).

### *Search Strategies*

The comprehensiveness of search strategies also varied widely. The number of databases searched varied from 1 to 19. Further, search hits varied from 107 to 10,045. Four reviews reported less than 500 search hits for their review (Ghiță & Gutiérrez-Maldonado, 2018; Keijsers et al., 2021; Ribeiro et al., 2021; Segawa et al., 2019), while five reviews had search results of more than 700 hits (Butler & Heimberg, 2020; Koskina et al., 2013; Langener et al., 2021; Magson et al., 2021; Mellentin et al., 2017; Trahan et al., 2019). Three reviews provide no information about their search results (Conklin & Tiffany, 2002; Gooding & Tarrier, 2009; Mayet et al., 2005)

**Language Restrictions.** One study had no language restrictions (Mayet et al., 2005). Three were restricted to the English and one additional language; Spanish, Portuguese, and French respectively (Ghiță & Gutiérrez-Maldonado, 2018; Ribeiro et al., 2021; Segawa et al., 2019). The rest were restricted to studies in English (Butler & Heimberg, 2020; Gooding & Tarrier,

2009; Keijsers et al., 2021; Langener et al., 2021; Magson et al., 2021; Mellentin et al., 2017; Trahan et al., 2019) or did not provide such information (Conklin & Tiffany, 2002; Koskina et al., 2013).

**Study Design Criteria.** Five reviews included all study designs that allowed for some assessment of efficacy of CET on one or more Addictions (Butler & Heimberg, 2020; Ghiță & Gutiérrez-Maldonado, 2018; Koskina et al., 2013; Magson et al., 2021; Segawa et al., 2019). Furthermore, three reviews were limited to studies including pre-post or controlled designs (Gooding & Tarrier, 2009; Keijsers et al., 2021; Langener et al., 2021; Trahan et al., 2019). Lastly, four reviews were limited to controlled trials or RCTs (Conklin & Tiffany, 2002; Mayet et al., 2005; Mellentin et al., 2017; Ribeiro et al., 2021).

#### ***Addiction Disorders Investigated***

**Disorders Sought.** Two reviews sought the full range of ADs (Langener et al., 2021; Segawa et al., 2019). One review investigated Substance Addictions (Conklin & Tiffany, 2002). Six reviews were restricted a specific AD. These included gambling- (Gooding & Tarrier, 2009; Ribeiro et al., 2021), Smoking- (Keijsers et al., 2021), Alcohol- (Ghiță & Gutiérrez-Maldonado, 2018; Mellentin et al., 2017), and Opiate Addictions (Mayet et al., 2005). One review sought both smoking and Alcohol Addiction (Trahan et al., 2019). Two reviews sought samples with eating disorders (Butler & Heimberg, 2020; Koskina et al., 2013), while one sought specifically binge- and overeating samples (Magson et al., 2021).

**Disorders Identified.** The Substance Addictions found across reviews were Addiction related to alcohol, nicotine, and/or opiates (Conklin & Tiffany, 2002; Ghiță & Gutiérrez-Maldonado, 2018; Keijsers et al., 2021; Langener et al., 2021; Mayet et al., 2005; Mellentin et al., 2017; Segawa et al., 2019; Trahan et al., 2019). Samples with Behavioral Addiction was

limited to Gambling Disorder (Gooding & Tarrier, 2009; Langener et al., 2021; Ribeiro et al., 2021; Segawa et al., 2019). Samples that related to eating Addiction included samples with Binge-eating disorder (BED), Bulimia nervosa (BN), Binge-eating subtype of Anorexia Nervosa, overweight and obese overeaters (Butler & Heimberg, 2020; Koskina et al., 2013; Magson et al., 2021). The appropriateness of including these latter conditions as a reflection of an Addiction-like conditions in the present review is discussed later. However, for the sake of simplicity in the following *Food Addiction* will be used as an umbrella term.

***Assessment of Pathology.*** The reviews included studies who used different instruments to assess pathology. Diagnostic criteria following the DSMs different versions was the most common method and the main methods employed across studies in all reviews.

Often used in conjunction with diagnostic assessment, psychometrically validated instruments for assessing the severity of each specific disorder were common. Common measures used were: Alcohol; Severity of alcohol dependence questionnaire (SADQ), alcohol dependence scale (ADS), Severity of alcohol dependence questionnaire SADQ, Severity of alcohol dependence -form C (SADQ-C), Alcohol Use Disorder Identification Test (AUDIT). Gambling; Canadian Problem Gambling Index (CPGI), South oaks pathological gambling screen (SOGS). Nicotine; cigarettes per day Fagerström Test for Nicotine Dependence (FTND), Cigarette dependence scale (CDS). No such measures were reported for Food Addiction.

### ***Method of Synthesis***

Three reviews provide meta-analytic results of their reviews (Conklin & Tiffany, 2002; Gooding & Tarrier, 2009; Mellentin et al., 2017) The rest of the reviews relied on narrative synthesis of study results (Butler & Heimberg, 2020; Ghiță & Gutiérrez-Maldonado, 2018; Keijsers et al., 2021; Koskina et al., 2013; Langener et al., 2021; Ribeiro et al., 2021; Segawa et al., 2019)

Three reviews planned meta-analysis but reported that their findings were not fitted for meta-analysis (Magson et al., 2021; Mayet et al., 2005; Trahan et al., 2019)

### *Assessment of Risk of Bias*

There was a predominant lack of sufficient quality appraisal of the reviewed primary studies. Only seven reviews included a systematic risk of bias, or quality assessment (Gooding & TARRIER, 2009; Magson et al., 2021; Mayet et al., 2005; Mellentin et al., 2017; Ribeiro et al., 2021; Trahan et al., 2019).

**Risk of bias identified.** A list of limitations identified with the included studies as noted by the review authors can be found in Table 3. Mellentin et al. (2017) rated all their studies on CET for alcoholism at high risk of bias using the Cochrane risk bias tool. Using the same tool Mayet et al. (2005) rated their single included study on opiates as ‘uncertain’ risk for bias. Also using the Cochrane Risk For Bias tool, Trahan et al. (2019) rated their studies of VR-CET on Alcohol Addiction as having a high to moderate level of bias.

For studies of CET for eating disorders, Magson et al. (2021) employed the Checklist for assessing the Quality of Quantitative Studies, in which 10 out of 18 studies were considered of adequate quality.

For reviews investigating CET for Gambling, Gooding and TARRIER (2009) judged their studies to be of very low study quality, while the four studies in (Ribeiro et al., 2021) were reported as being moderate to high in study quality. They each used The Clinical Trials Assessment Measure and Critical Appraisal Skills Program Checklist respectively.

One review found the VR-CET-research field too premature to rate using structured risk of bias tools (Langener et al., 2021). Instead, they used the Recommendations for Methodology of Virtual Reality Clinical Trials in Healthcare, to assess the level of development for each

study. They found that all but one study was designed primarily to assess feasibility rather than efficacy. The rest of the reviews provide only general discussions of risk of bias.

Concerns regarding primary studies reported in the reviews include lack of a control-groups, small sample sizes, lack of statistical power, high attrition rates, baseline differences between treatment groups, lack of blinding and lack of preregistration. Within the limited number of primary studies that has been evaluated using structured tools in the included reviews, there seems to be a pattern of high risk of bias for substance use disorder CET studies, and mixed study quality for eating disorders and gambling disorder.

### **Primary Studies Characteristics**

In the following, characteristics of the samples and designs of the studies included in each review will be described. This is done to provide some understanding of the primary studies which the conclusion of the included reviews is based upon. Primary study data was not sought in the present review, and the following information is therefore limited to that presented in the included reviews.

#### ***Sample Characteristics***

Reporting on sample characteristics was not consistent across reviews. This makes it difficult to give an accurate description of the samples included. Within the Substance Addiction and Gambling Addiction samples, there were generally an overweight of men in the samples (Gooding & Tarrier, 2009; Langener et al., 2021; Ribeiro et al., 2021; Segawa et al., 2019; Trahan et al., 2019). Reviews of Food Addiction included almost exclusively women in the samples (Butler & Heimberg, 2020; Koskina et al., 2013; Magson et al., 2021).

Participant were generally middle-aged adults for Substance Addiction and gambling samples, although adolescent samples were reported for Nicotine Addiction (Ghiță & Gutiérrez-



Maldonado, 2018; Langener et al., 2021). Food Addiction samples comprised of adults and adolescents (Butler & Heimberg, 2020; Koskina et al., 2013; Magson et al., 2021).

**Severity of Disorders** Across reviews there was variation in participant condition severity although participants in the majority of reviews met DSM diagnostic criteria. Mellentin et al. (2017) included both clinical and “sub-clinical” Alcohol Addiction samples, although it was not clear what their cut-off was. Reviews of Nicotine Addiction included samples with low to high severity of nicotine dependence with a mix of treatment seeking and non-treatment seeking samples (Keijsers et al., 2021; Langener et al., 2021). Reviews investigating Food Addiction included resistant, often samples with severe eating disorders (Butler & Heimberg, 2020; Koskina et al., 2013; Magson et al., 2021). Ghiță and Gutiérrez-Maldonado (2018) reported including samples with clinical diagnosis, recruited from Alcoholics Anonymous.

### *Study designs*

Out of the 52 studies being included across reviews, 33 included a control group. To give context to results of the identified reviews, I will here outline central features of studies included. This will include study design, interventions features, and controls.

Conklin and Tiffany (2002) reports results from nine CTs of CET for Opiate Addiction, Nicotine Addiction, Alcohol Addiction. Conklin does not describe which control conditions or randomization procedures the studies they included used. It is reported that CET is in 8 out of 9 studies given with adjunct treatments (not described). They also report a range of 5-10 exposure sessions lasting between 40 to 90 minutes per session. These were delivered on a daily more than daily interval. Both in vivo, photographs, audio and imagery were used during exposure.

Ghiță and Gutiérrez-Maldonado (2018) identified two VR-CET studies utilizing a pre-post design for Alcohol Addiction. Interventions were comprised of eight biweekly cue exposure

sessions using VR-technology. The VR-technology involved a beam projector and surround-sound speakers. The review also included two other controlled trials labeled as VR-CET but included aversive conditions and was therefore not considered a CET intervention by the present review.

Gooding and Tarrrier (2009) described two trials using pre-post designs for Gambling Addiction. The interventions included 14-15 sessions of 15-20 minutes of Imaginal Desensitization (ID) in which participants were asked to imagine a gambling situation. This was administered by listening to a self-administered audio cassette or being guided by a therapist.

Keijsers et al. (2021) report on 9 studies. Unfortunately, their supplementary materials are not matched with their in-text references and their study design descriptions are therefore unintelligible. However, almost all the studies reported in Keijsers et al. (2021) are reported in other reviews (Langener et al., 2021; Segawa et al., 2019; Trahan et al., 2019). The one study not reported in any other review was a small RCT comparing CBT + VR-CET with CBT + VR placebo.

Langener et al. (2021) identified 10 VR-CET studies on Nicotine, Alcohol and Gambling Addiction. Additionally, three studies used exposure as an adjunct to CBT coping skills training and were therefore considered a CET intervention by this review. These are included in the review's "Other Virtual Reality (VR) treatment studies" table. Six studies used pre-post design and seven studies used a randomized controlled design. Five of the studies had adjunct treatment in Addiction to VR-CET. These include CBT, Mindfulness, brief advice, and Treatment as usual. VR-CET interventions consisted of 1-15 VR-CET sessions lasting 20-60 minutes each session. VR-CET was delivered using head-mounted VR devices. Complex stimuli including simulated social situations, bar, environments and smoking, alcohol, and gambling activities. Control

conditions included access to smoking cessation manual, cognitive behavioral therapy, and imaginal exposure.

Butler and Heimberg (2020) and Koskina et al. (2013) identified 8 and 7 studies respectively. They had completely overlapping studies with Magson et al. (2021) and the interventions in the studies they included will be described below.

Magson et al. (2021) identified 18 studies for Food Addiction. The review does not describe the designs of their studies in detail but distinguishes between within- and between study designs. They report three case studies (within group design), four pre-post studies (within group design) and 11 studies with a control group (between studies design). Interventions are labeled cue exposure and response prevention (CERP) and according to the authors uses the same treatment rationale as CET. Interventions consisted of 2-36 sessions of 45–90-minute exposure sessions. Controls included non-active controls, life-style advice, self-control treatment, CBT, Relaxation treatment and CET-CET plus medication. Three studies had CBT as an adjunct treatment. Active control conditions were given in equal time and frequency to intervention groups. A total of 16 studies used in-vivo exposures while two studies used VR-CET as exposure medium.

Mayet et al. (2005) describes one RCT for Opiate Addiction in which patients received six CET session over two-three weeks. Controls received treatment as usual at a drug dependency unit or behavior/general ward. The CET group received the same treatment as control with the addition of CET.

Mellentini et al. (2017) identified two CTs and five RCTs. The interventions in the included studies ranged from 6-10 exposure sessions given with or without coping skills training.

The included studies utilized both active and/or non-active control conditions. These included CBT, Relaxation training and assessment with daily contact.

Ribeiro et al. (2021) identified four RCTs. The two studies with *in-vivo* CET interventions consisted of 6-12 sessions of 20-60 minutes exposure. One RCT included 5 session of 20 minutes of ID and another 4 sessions of VR-CBT with graded exposures. Controls included waitlist, imaginal relaxation, cognitive therapy, and ID.

Segawa et al. (2019) identifies 9 studies. Study designs included four pre-post trials, three CTs, and two RCTs. Interventions in the included studies consisted of 1-5 session of 20–30-minute exposures. Some VR-CET interventions were given with adjunct CBT coping skills training. Controls included CBT, nicotine replacement therapy and ID.

Trahan et al. (2019) identified four VR-CET trials. Study designs included two pre post designs, one CT, and one RCT. Exposures consisted of 4-10 session of 20-30 minutes exposures. Controlled trials were compared to nicotine replacement therapy or CBT. Adjunct treatments included nicotine replacement therapy, counselling, and coping skills training.

### ***Outcome measures***

**Consumption/Behavior.** The reviews report different measures used by the included studies related to outcomes of consumption or behavior. The majority of reviews (10) included studies measuring consumption in different ways, including frequency, abstinence rates, and relapse measures (Butler & Heimberg, 2020; Conklin & Tiffany, 2002; Gooding & Tarrier, 2009; Keijsers et al., 2021; Koskina et al., 2013; Langener et al., 2021; Magson et al., 2021; Mayet et al., 2005; Segawa et al., 2019; Trahan et al., 2019). Mellentin et al. (2017) only included studies which measured consumption in terms of frequency of drinking. One review

reported on outcomes in terms of rates of controlled gambling behavior (Ribeiro et al., 2021), while Ghiță and Gutiérrez-Maldonado (2018) does not report consumption measures.

**Craving.** All reviews reporting studies with craving measuring craving use self-report measures. In most cases validated psychometric measures are used for craving measurements (Ghiță & Gutiérrez-Maldonado, 2018; Langener et al., 2021; Magson et al., 2021; Trahan et al., 2019). Magson et al. (2021) reports on studies with levels of salivation in addition to self-report measures.

**Other Measures.** Self-efficacy and diagnostic severity measures are likewise given measures using self-reports with psychometrically validated instruments (Langener et al., 2021; Ribeiro et al., 2021; Segawa et al., 2019; Trahan et al., 2019)

### **Review Findings**

The reviews identified, give no definitive conclusions about the efficacy of CET. Given the variation in conditions studied, specific interventions and controls used, quality of studies, samples used, different follow-up measures and different effect size measures, make it difficult to succinctly summarize the findings. This is further compounded by the large overlap between reviews.

With these caveats in mind, an overview of the major conclusions drawn by each review can be found in Table 4. Three reviews show that CET failed to demonstrate its utility (Conklin & Tiffany, 2002; Mayet et al., 2005; Mellentin et al., 2017). Six reviews provide a more mixed results but still maintain that the efficacy of CET remains to be demonstrated (Butler & Heimberg, 2020; Ghiță & Gutiérrez-Maldonado, 2018; Keijsers et al., 2021; Koskina et al., 2013; Langener et al., 2021; Segawa et al., 2019). Finally, four reviews seem to conclude that CET provides some benefits, but their conclusions are still very tentative given the limitations of

their included studies (Gooding & Tarrier, 2009; Magson et al., 2021; Ribeiro et al., 2021; Trahan et al., 2019).

### **Addiction-Specific Outcomes**

The present review identified a high degree of overlap in included studies between the included reviews. In order to give some account of the efficacy of CET without double counting the results, overlap between studies will be omitted in the following.

The results presented below will be based the reviews that identified the largest number of unique studies, supplemented by additional unique studies found in other reviews. This means that if a review has reviews overlapping studies with other, they are not presented. However, the overlap between meta-analyses and other reviews has not been omitted.

Results will follow the format of results resented in the summary of findings in Table 5. Effect sized are not given in text but a range of effect sizes (those that were available) can also be found in table 5. The results will be stratified by Addiction Disorder and with overall evidence and outcome-specific results presented for each disorder.

### ***Mixed Addiction Disorders***

The meta-analysis by Conklin and Tiffany (2002), identified nine controlled studies including individuals with alcohol-, opiate- and Nicotine Addiction. CET did not seem to provide benefits compared to controls in terms of abstinence and consumption rates. There was, however, significant heterogeneity between the studies, making the appropriateness of this meta-analysis questionable.

### ***Opiate Addiction***

CET for Opiate Addiction seems to be understudied compared to other ADs. One RCT was identified across two reviews (Conklin & Tiffany, 2002; Mayet et al., 2005) The study found

insignificant result for CET on relapse rates at both 6-weeks and 6-months follow-up, compared to treatment as usual. The study did not calculate between group differences for craving.

### ***Alcohol Addiction***

Across reviews 10 studies were identified (Conklin & Tiffany, 2002; Ghiță & Gutiérrez-Maldonado, 2018; Langener et al., 2021; Mellentin et al., 2017; Trahan et al., 2019). Overall, the evidence for CET for alcohol Addiction seem to be limited. There is little reason to suppose that alcohol consumption is reduced by CET relative to controls. There is slight preliminary evidence that VR-CET reduces craving, but there are no follow-up measures or control comparisons.

**Consumption Measures.** Mellentin et al. (2017) identified seven CTs investigating the efficacy of CET on consumption compared to both active and non-active control conditions. They synthesized their findings using meta-analysis of six of these seven studies. The meta-analysis showed no effects on drinking outcomes at 3 months follow-up, and an insignificant small effect at 6-months follow-up compared to both active and non-active controls.

**Craving.** Ghiță and Gutiérrez-Maldonado (2018) reported on two small pre-post studies that investigated the efficacy of VR-CET on alcohol cravings. Both studies reportedly showed reductions, but there were no tests for significance or effect size reported. It should be noted that this review also included three studies labeled as VR-CET but that included aversive conditions as part of the treatment protocol. Thus, is not considered a CET treatment by the current review. Similarity, Langener et al. (2021) reported on a RCT using VR-CET that found that craving did reduce from pre- to post-treatment for the VR-CET groups but not in the treatment as usual controls.

### ***Nicotine Addiction***

Across five reviews, 16 studies were reported CET for Nicotine Addiction (Conklin & Tiffany, 2002; Keijsers et al., 2021; Langener et al., 2021; Segawa et al., 2019; Trahan et al., 2019). Overall, results are very inconsistent on consumption and relapse measures, craving, diagnostic measures, and self-efficacy. There seems to be some indication of improvements on craving measures post treatment, although follow-up measures are lacking.

**Consumption Measures.** Conklin and Tiffany (2002) references four *in-vivo* studies on Nicotine Addiction, that were also included in their meta-analysis, which show results mostly favoring controls on abstinence and relapse measures at 6-month follow-up ( $d = -0.0251$  to  $d = -0.518$ ).

Langener et al. (2021) reports that one out of three pre-post studies show significant improvements. Two out of three RCTs show improvements. One of these trials show that improvements are stable at 1 to 6 months. No other follow-up measures are reported. One RCT was insignificant and reported increases in relapse rates in the VR-CET group at 12-month follow-up.

Trahan et al. (2019) reports two trials with significant pre-post decreases in consumption. One of these trials was a CT, and failed to show between group effects. Keijsers et al. (2021) report on one small RCT that shows significant reductions in consumption measures.

**Craving.** Langener et al. (2021) reports that two out of five pre-post studies showed significant improvements. One trial reported reductions with no significance test and the rest were insignificant. Three out of four RCTs identified in Langener et al. (2021) showed improvements post-treatment. Trahan et al. (2019) report two trials that show significant pre-post reductions in craving, but no significant between group-effects.



**Diagnostic Measures.** Langener et al. (2021) shows no improvements in Nicotine Addiction severity measures in one pre-post trial and two RCTs. Trahan et al. (2019) does report two within group changes, but no reductions between group changes.

**Self-Efficacy.** One RCT shows improvement in self efficacy compared to controls post-treatment and at 6-months follow-up (Langener et al., 2021).

### ***Food Addiction***

Across three reviews, 18 studies were identified (Butler & Heimberg, 2020; Koskina et al., 2013; Magson et al., 2021). In general, exposing binge eaters to foods and stimuli associated with bingeing seems to reduce binge-eating frequency post treatment. All results are reported with reference to Magson et al. (2021) because this is the most comprehensive review.

**Consumption Measures.** Three out of three case studies show improvements in binge frequency post treatment and at 2-9 months follow-up.

Six out of seven studies investigating pre-post effects showed statistically significant reductions in binge eating behavior post-treatment with small to very large post treatment-effects. Five of these studies indicate that treatment gains were maintained (and in some instances increased) over time, with follow-ups ranging from 3 to 60 months. Two trials show that most patients reduced binge frequency post treatment with one reporting treatment gains at and at 1-6 months follow-up, but no significance test was reported.

Three out of six between-group effect estimates were significant, with one showing improvements maintained at 3 months follow-up. Of the three trials showing insignificant between group effects post treatment, two show that the CET groups were superior at 1- and 5 years follow-up respectively. Conversely, one study reported controls being superior to CET at 12 months follow-up.

**Craving.** One case study shows improvements at post treatment. Five out of 11 studies reporting within subject effects report significant improvements post-treatment. Three studies show trends towards improvements, but no significance is reported. Two out of three CTs show improvements in craving.

### ***Gambling Disorder***

The studies seem to provide some evidence for that CET reduces gambling behavior in the long-term behavior either delivered in-vivo or through ID. It is less clear if interventions are superior to other active treatments.

**Gambling Frequency and Relapse Rates.** Ribeiro et al. (2021) shows both trials reporting gambling frequency/relapse rates significantly improved compared to controls. These effects are also reported to be stable at 6–12 months and 2–9 years follow-up, respectively, for the two studies. Gooding and Tarrier (2009) reports a significant within group improvements in gambling frequency in their meta-analysis combining the effects of two studies.

**Craving.** One out of two pre-post effect measures were significant (Langener et al., 2021). One study showed insignificant effects between groups.

**Diagnostic Measures.** Ribeiro et al. (2021) reports on one study showing significant pre-post improvements after CET, but no significant differences compared to active controls.

Langener et al. (2021) reports one RCT with insignificant effects.

**Self-Efficacy:** One RCT showed non-significant effects on self-efficacy.

### **Review Quality Rating**

Quality was independently assessed by two reviewers and later compared and discussed. There was substantial interrater agreement on the summary judgment across the reviews (Cohens Kappa = 0.76) (Mchugh, 2012). However, the interrater reliability for specific criteria were less

impressive. For instance, the interrater reliability of item number 14, assessing the adequacy of the discussion of heterogeneity, was below chance (Cohens Kappa= -0.08). It is clear from this that more training should have been conducted prior to assessing the reviews. Through discussion, it became evident that the raters had very different conceptions as to what should be considered adequate. One rater considered it necessary for the articles to provide statistical investigation into heterogeneity and discuss this. The other thought it sufficient to provide a general discussion for what could be contributing to inconsistent findings. In the end, the latter view was applied, and agreement was reached.

The criteria specific, and summary quality judgements of the included studies can be found in Table 6. In the main, the studies selected for this review show a consistent pattern of critically low quality. One exception to this is the review by Trahan et al. (2019), who received a moderate quality rating.

The major limitations of the articles were a consistent lack of justifying their study inclusion criteria (10 out of 13), uncomprehensive search strategies (10 out of 13), study selection and data extraction not performed in duplicate (7 out of 13 and 11 out of 13, respectively), failure to report funding for their included studies (13 out of 13), and lack of risk of bias assessments (7 out of 13). It should also be noted that the included reviews varied widely in what details they reported on. Criterion 8 in AMSTAR that has to do with quality of reporting, was not rated as adequate (12 out of 13). This has likely been judged too leniently by both raters. This deficiency became very evident during the extraction process.

Due to the consistent low quality of the included reviews, caution should be employed when judging the results presented above. Limitations include a risk that the evidence synthesis represent only a selection of the relevant primary studies and/or that these are not adequately

appraised in terms of risk of biases. However, due to the lack of variation in review quality, it is not possible to stratify the following results by highlighting evidence from high quality reviews.

### **Discussion**

To the best of my knowledge, this is the first review of reviews of Cue Exposure Therapy to date. The main aim of the present review was to investigate the efficacy of CET therapy across different ADs. The present review of reviews identified 13 systematic reviews and/or meta-analyses spanning Addiction related to alcohol, opiate, nicotine, gambling, and binge- and overeating. For the treatment of Substance Addiction, there is little evidence CET provides benefit above those of existing therapies. There seems to be some evidence for CET in the treatment of Gambling Addiction and Food Addiction. There are indications that CET is effective for reducing craving in Nicotine Addiction, Alcohol Addiction, and Food Addiction, although follow-up measures are lacking.

### **Interpreting The Results**

The present review identified 52 studies across the 13 reviews. A concise conclusion about their findings is difficult to reach given the different study designs and complex outcome patterns. The condition being most frequently studied is Nicotine Addiction. For Nicotine Addiction, reductions in craving are paradoxically fairly consistent in between-group studies, while pre-post designs tend not to show statistically significant improvements. Given that pre-post generally overestimates study effects (Pallisen et al., 2005), this differential effect is peculiar. The pre-post studies were, however, much smaller in sample size. It is therefore conceivable that abovementioned pattern is due to a lack of statistical power. The same studies also show non-significant measures for Nicotine Addiction diagnostic measures and so lack of power could also explain this finding. Long term follow-ups including craving measures and

general investigations of self-efficacy are lacking and suggest a gap in the reviewed literature concerning the effectiveness of CET for Nicotine Addiction. In terms of consumption measures, both Conklin and Tiffany (2002) and Langener et al. (2021) reported studies where outcomes favored control at follow-up. To date, there thus does not seem to be good reasons to recommend CET over established treatments such as CBT for people seeking treatment for tobacco use disorder.

CET for Alcohol Addiction seemed promising in some early studies (Conklin & Tiffany, 2002), but seems to provide insignificant benefits compared to controls on consumption measures (Mellentin et al., 2017). These findings are in line with a recent trial not identified in this review (Mellentin et al., 2019). It seems that VR-CET has been more rarely applied to Alcohol Addiction compared to Nicotine Addiction (Langener et al., 2021). However, it should be noted that several reviews have included intervention studies labeled virtual reality exposure therapy (VRET) applied to Alcohol Addiction that were not included in the present review (Ghiță & Gutiérrez-Maldonado, 2018; Segawa et al., 2019; Trahan et al., 2019). The reason for exclusion of such studies was that these interventions included aversive conditions, such as exposures to pictures of vomit. Disambiguating the CET terminology is recommended for future research.

The reviews included in the present review found one single study for Opiate Addiction. This is clearly insufficient to provide an account of the efficacy of CET for Opiate Addiction. However, the insignificant findings are in line with other known research on CET for Opiate addiction not identified in the present review (Marissen et al., 2007; Martin et al., 2010).

The limited number of studies on Gambling disorder shows favorable results before and after treatment as well as at follow-up, although treatment compared to active controls are not

consistent (Gooding & Tarrrier, 2009; Ribeiro et al., 2021). Although more research is needed, the results are thus promising.

Binge- and overeating patients might benefit from cue exposure with response prevention (Magson et al., 2021). Despite limitations (small samples, attrition, lack of controls), the outcomes seem to give some support for this patient group. As such, this is in line with findings from newly published research (Norberg et al., 2021).

One central theoretical limitation is, however, that food- and weight related anxiety is a potential confounder. Patients with Eating Disorders such often exhibit strong anxiety in response to food (Koskina et al., 2013). It might therefore be the case that exposure to food for people with Binge Eating symptoms works by reducing food-related anxiety and not by reducing craving. Although an attenuation of appetitive responses was found with most studies investigating craving in Magson et al. (2021), reduction in food and weight-related anxiety is an important alternative explanation to reductions in binge-eating frequency (Butler & Heimberg, 2020). Crucially, if treatment gains are mediated by reduction in anxiety, it would be mistaken to label this treatment a form of CET. It would be better labeled a form of Exposure Therapy, akin to that given to people with Obsessive-Compulsive Disorder (Lindsay et al., 1997). This point could further be used as an argument against the labeling binge- and overeating disorders a form of Addiction (Corwin & Grigson, 2009; Gordon et al., 2018; Leslie et al., 2018). For this reason, the present review's inclusion of Binge Eating disorders as part of the Addiction umbrella term might reasonably be subject to critique.

Overall, there seems to be inconsistent support for CET as an intervention of Addiction Disorders. The mixed findings should give pause to consider the reasons for this being the case. It should firstly be noted that many reviews do find that CET is comparable to other treatments

shown to be effective such as CBT (Magill et al., 2019). One key reason might therefore be the impact of control conditions (Mellentin et al., 2017). However, some argued that CET could be a way of optimizing the processes that occur withing CBT (Loeber et al., 2006), and this does not yet, seem to be the case. Given that there are a few studies being reported that seems to show increased relapse rates in CET condition (Langener et al., 2021; Magson et al., 2021), there seems to be few good reasons for preferring CET as a treatment.

Several theoretical questions could also be raised about why CET has not proven to be efficacious. On this topic (Conklin & Tiffany, 2002)'s review of animal research shows multiple reasons why reductions in cravings due to exposure are likely to be unstable (i.e., the renewal effect, spontaneous recovery, and reinstatement). However, given the low study quality of the included reviews it is difficult to determine to what extent the findings have theoretical import.

### **Limitations**

The result of the present review is subject to limitations across three levels. Firstly, evidence is dependent on the quality of primary studies. Secondly, conclusions drawn from across these studies are limited by the quality of the reviews appraising them. Thirdly, limitations of the present review likely impact the overall conclusion of the efficacy of CET.

#### ***Limitations of Primary Studies***

The present review has identified several limitations of the individual studies that should be mentioned in order to appropriately appraise the research findings. The median sample size was very small ( $n = 41$ ). This is concerning for several reasons. Firstly, it makes the research more likely to be subject to sampling biases. This means that whatever the outcomes of the study, it is uncertain if the findings will be generalizable. As  $n$  decreases, individual variation, rather than the study conditions, may account for the outcome variance (Netz et al., 2019).

Secondly, with low  $n$ , studies lack sufficient statistical power to detect small to moderate effect sizes (Cohen, 1992). Taken together, this has the joint deficiency of being at risk for not being able to detect effects, hence increasing the risk of type 2 error), while sometimes showing inflated effect sizes.

Another limitation is the high attrition rates being reported in several reviews (Gooding & Tarrier, 2009; Keijsers et al., 2021; Langener et al., 2021; Magson et al., 2021; Mayet et al., 2005; Segawa et al., 2019). This can bias the results since there can be systematic differences between those who drop out and those who do not. This is of special concern in CTs where there are differences in attrition between groups which was reported by three reviews (Keijsers et al., 2021; Langener et al., 2021; Segawa et al., 2019). This represents a major limitation when studies fail to analyze results based on the intent-to-treat (ITT) principle (Langener et al., 2021; Segawa et al., 2019). The ITT principle involves including all participants that are allocated to each condition in the final analysis and is the appropriate method to minimize risk of bias (Mccoy, 2017). With a treatment like CET, this is of particular importance as there has been several studies reporting high drop-out rates in the CET condition (Marissen et al., 2007).

Another methodological concern of the present literature is the risk of random significant results due to selective outcome reporting. Many studies have several outcome measures for one outcome and tests for both between- and within-group effects. For example, studies like Schyns et al. (2016) (reported in (Magson et al., 2021)), reported four different significance tests for evaluating craving. Similarly, Hernández-Serrano et al. (2020) (reported in (Langener et al., 2021)) did not report testing of between-group differences even though they planned for it. This makes the study at risk for selective outcome reporting. As the number of tests increase, so does the likelihood of finding a random significant effect. As the alpha-level in most psychological



research is  $p \leq .05$  this means that at minimum five per 100 significant tests are type 1 errors, and some argue that the majority of significant research is type 1 errors (Ioannidis, 2005). The lack of pre-registered protocols in many of the primary studies further adds to the risk selective outcome reporting.

Additionally, many studies lack control groups and/or randomization. For pre-post studies, the lack of a control group makes it very difficult to rule out the impact of confounding variables, placebo effects and spontaneous recovery. Hence, based on such study designs it is difficult to assess if any observed differences from pre to post treatment are in fact due to the CET intervention (Wampold & Imel, 2015). This is especially true for pre-post designs with a combination of treatment features.

Lastly, most studies did not investigate publication bias directly and the one study that did, found evidence for a risk of publication bias (Mellentin et al., 2017). Publication bias results from an the increased likelihood for significant and interesting research findings to be published over insignificant research findings (Easterbrook et al., 1991). This means that evidence syntheses show a biased sample of the relevant research.

The abovementioned criticisms should be tempered by the fact the studies on VR-CET included many feasibility studies, which are designed to provide a starting point for more rigorous large-scale studies in the future. It might thus be too premature to give a final judgment of VR-CET interventions before more large-scale studies have been conducted (Langener et al., 2021).

### ***Review Limitations***

The result of the present review is limited both by the quality of the primary studies and the quality of the included reviews. The AMSTAR rating revealed several methodological

weaknesses that may make the results of each review at risk for bias. A lack of comprehensive search strategies, lack of preregistrations, lack of justification for included study designs, sub-standard study selection and extraction procedures, and lack of risk of bias assessments were the limitations that characterizes the included reviews. This increases the risk that all relevant primary studies were not identified, and that the field is inappropriately appraised.

Other limitations also deserve mention. One important weakness across the reviews is that different terms are used for the same phenomenon while also the same terms are used for different phenomena. This is also known as the jingle-jangle fallacy (Reschly & Christenson, 2012). The terms cue exposure (CE), cue exposure therapy (CET), Virtual reality-cue exposure therapy (VR-CET), Virtual reality exposure therapy (VRET), cue exposure and response prevention (CERP) are all terms that have been used for describing treatments proposed to target the same process – the attenuation of appetitive responses by exposure to relevant stimuli cues. However, several trials labeled “VERT” include aversive conditions (Ghiță & Gutiérrez-Maldonado, 2018; Trahan et al., 2019). Aversion therapy has a long history in behavioral treatment but has a different treatment rationale than CET (Hallam & Rachman, 1976).

There is also inconsistent reporting of outcomes across reviews, making a synthesis and accurate appraisal of research findings difficult. For instance, some provide effect sizes but not significance tests (Magson et al., 2021), some provide significance test and some simply indicate direction of the effects (Segawa et al., 2019). Descriptions of treatment, controls, and participants also very variable. This limits the interpretations possible to the present review.

### ***Strengths and Limitations of the Present Review***

**Strengths.** The present review has several strengths and provides some contributions to the CET-field. Firstly, this was a pre-registered review, with a comprehensive search strategy

used across 6 databases. Study-selection procedures and quality rating was conducted in duplicate. Using a wide definition of Addiction, the present review was able to give some account of the current evidence for the efficacy of CET for different disorders, although the picture is not clear. The number of reviews identified, and the fact that many of them were published rather recently, indicates that the present review is timely.

Furthermore, this review addresses the large overlap between reviews of similar scope and the findings presented in this review therefore avoids double counting the evidence.

Also, Using the AMSTAR tool, the present view revealed that the included reviews is of overall poor quality. As the label “systematic review” often is considered a stamp indicating quality of evidence, this review puts the findings of each review into a more critical perspective.

In addition, the present review was also able to identify trends and gaps in the literature with implications for future research. A swell of interest in VR-technology applications for ADs is evident from the present review, with a majority of the most recent reviews being limited to this mode of delivery. Conversely, it is seems that the interest in in-vivo CET is waning, with the latest review of RCTs for substance use disorder using that approach identified in this review being published in 2006 (Loeber et al., 2006). It seems likely that the inconclusive results found early reviews on Substance Addiction (e.g., Conklin & Tiffany, 2002), might deter researchers from further investigating in-vivo-CET for substance use disorders.

**Limitations.** The present study has several limitations. Firstly, although the present study was pre-registered, in hindsight, the exact study procedures, inclusion criteria and information that was sought could have been more precisely described. Specifically, exactly what constitutes a systematic review and what type of eating disorders should be considered indicative of “Food

Addiction” were issues that had to be discussed throughout the review process. While these things were address by the protocol, they could have been more specific.

Secondly, although study selection and quality assessment were performed in duplicate, only one central limitation of the present review is that extraction and synthesizing the results conducted by one person.

Thirdly, this review can be criticized for lacking a more concise method of synthesis. Authors describing the umbrella review method suggest using GRADE or providing a degree of confidence regarding the level of evidence (Aromataris et al., 2015; Fusar-Poli & Radua, 2018). This was not done due to variation in reporting and time constraints. Ioannidis (2005) criticized reviews for overemphasizing the importance of statistical significance tests instead of that which is “clinically significant”. Such critique is also relevant for the present review. In retrospect, where data were inadequately reported on, information from primary studies could be sought, including sample sizes, risk of bias assessments, outcomes, treatment features and non-significant outcomes. This would allow for a more streamlined and concise method of synthesis. However, as this is a review of reviews, the main focus has been the synthesized findings, not on the findings from the single studies.

Another limitation of the current review concerns the risk that some relevant reviews were not identified. This review applied the criterion that the review had to identify itself as a systematic review or meta-analysis to be included. Several possibly relevant reviews were excluded for not meeting this criterion (Byrne et al., 2019; Hone-Blanchet et al., 2014; Lebiecka et al., 2021; Martin et al., 2010). Also, six reviews were excluded after study selection due to lacking a systematic methodology or because they failed to include an independent section on CET (Cassin et al., 2020; Durl et al., 2018; İnce et al., 2021; Orchowski & Johnson, 2012;

Pallesen et al., 2005; Roggi et al., 2015). This can be considered a breach protocol and is therefore worthy of critique. Lastly, Gay literature and reference lists were not searched as part of the search strategy which confers some risk that some relevant reviews may not have been detected.

### **Future Directions**

There is a growing concerns that there is too many published systematic reviews relative to published primary studies (Tebala, 2015). The current review can attest to this tendency. Most of the reviews included are of low quality, published in the last four years on very similar topics with overlapping studies. Future reviews should pre-register and use assessment tools like PRISMA and AMSTAR to guide their reporting.

As often suggested, adequately powered, quality RCTs are needed to establish the efficacy of CET for various Addiction Disorders. However, it is also important that research is focused on the joint task of finding what works and why it works in a systematic and economical fashion. With this in mind Magson et al. (2021) provides an excellent overview of all the different techniques used in terms of exposure techniques in different trials for binge- and overeating. They show that most studies do not employ the techniques that are theoretically predicted to maximize exposure efficacy. Future CET research should exhaust the full arsenal of theoretically derived exposure principles (Byrne et al., 2019; Conklin & Tiffany, 2002; Craske et al., 2014). VR technology may provide a context in which the target stimuli might easily be controlled and manipulated (Lebiecka et al., 2021).

Clearer hypotheses for hypothesized mediator variables should also be systematically investigated in future research. For instance, the relationship between reductions in craving within exposure sessions and between exposure sessions and their relationship to consumption

outcomes should be clarified. For instance, whether it is necessary for craving to go down within each exposure session to observe a reductions in craving after treatment is ended. Langener et al. (2021, p. 21) note that many study protocols pre-specify the amount of time patients undergo exposure. However, in exposures for anxiety it is common that exposures are tailored to individual levels of anxiety in order to allow for proper habituation (Benito & Walther, 2015).

Several modifications to CET are currently being explored. These include CET targeting or including memory reconsolidation (Liu et al., 2020; Rafei et al., 2021; Taylor et al., 2009), outcome-expectancies (Norberg et al., 2021; Schyns et al., 2016), mindfulness (Chen et al., 2018; Vinci et al., 2021), enhancement of exposure effects through pharmacology (Papini et al., 2020), aversive conditioning (Wang et al., 2019), and training avoidance responses in response to cues (Mellentin et al., 2020). Qualitative research is virtually absent in the CET literature and should be conducted in conjunction with quantitative studies. How exposure and craving are experienced by patients undergoing CET might reveal important insights.

CET has as of yet not been applied to the full a range of addictive disorders. The effect of CET has not been investigated for Internet Addiction, Gaming Addiction, Sex and Pornography Addiction, Shopping Addiction and others, hence large gaps exist in the literature. Some interest in CET for Internet Addiction is emerging, but treatment studies are still lacking (Zhang et al., 2016). This is worth considering given the hypothesis that CET would be most effective in treating addictive disorders which are triggered by cues frequently present in everyday life-experiences (Mellentin et al., 2017). Much of work, education and entertainment involves computers or smart phones with readily access to the internet. As such, these cues are difficult to avoid.

High quality future research exploring the above research topics could potentially provide more effective treatment for a number of undertreated patient groups. In addition, such studies could provide important theoretical insights that can guide future theory and research.

### **Conclusion**

Systematic reviews on Cue Exposure Therapy (CET) does not seem to find a clear benefit to this treatment for Addiction Disorders. Although there is some promise in the application for Gambling Addiction and Food Addiction, the field is suffering from methodological issues making definitive conclusions difficult to draw. There seems to be a growing interest into the application of this treatment using Virtual Reality Technology. However, applications of this treatment for Behavioral Addictions are still limited. Future research should be systematic in investigating the conditions under which exposure is helpful to people with Addiction Disorders.

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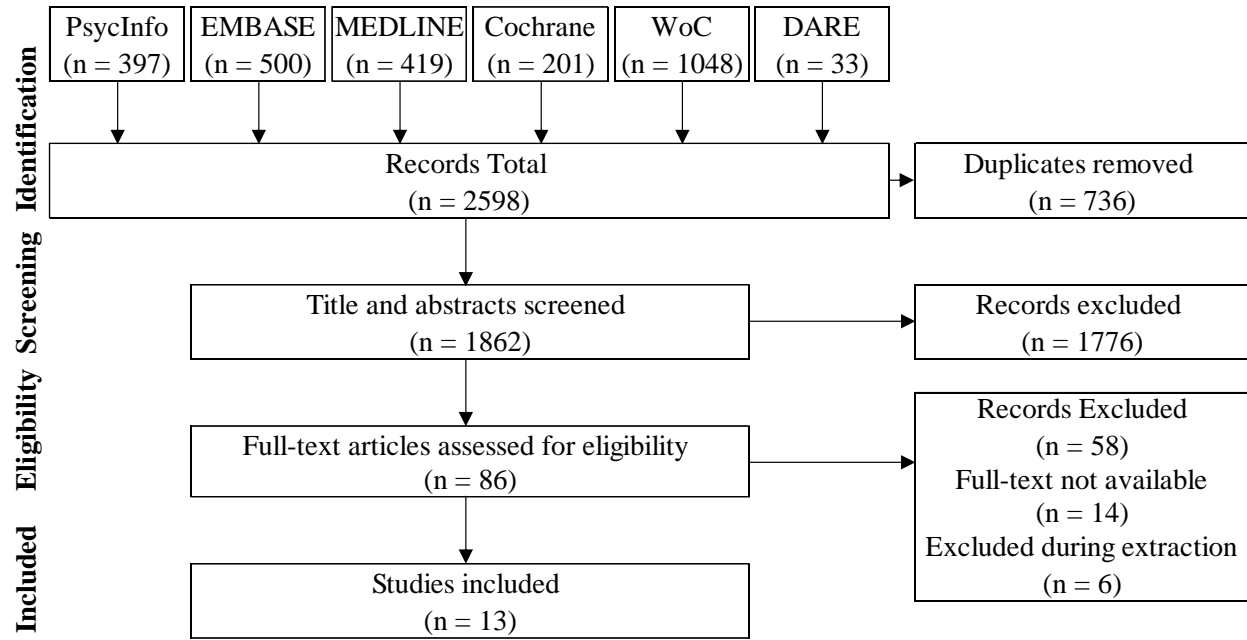
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Tables and Figures

Figure 1

PRISMA Flow Diagram



**Table 1.***Inclusion and Exclusion Criteria*

	Inclusion	Exclusion criteria
Population	Behavioral Addictions, substance use disorder, other Addiction-adjacent disorders (binge/over-eating, sex Addiction, internet use disorder).	Non-pathological consumption of addictive substances/behavior.
Intervention	Interventions that for therapeutic purposes exposes patients to cues associated with addictive behavior while they are limited in their capacity to engage with the addictive stimuli. May include amendments such as coping skills training, mindfulness.	Cognitive bias modification (CBM), Attentional bias modification (ATM), Inhibitory training (IT), Eye movement desensitization and reprocessing (EDMR), Aversion therapy (AT), Cue exposure for measurement of cue reactivity.
Comparators	Wait-list, attention placebo or other assumed non-effective interventions, treatment as usual, other known effective psychotherapy or medication treatment used to treat the ADs. Pre-post designs are also included.	

Outcomes	One of the following: Symptoms of the specific condition, Substance consumption, Addiction behaviors, Craving/Cue reactivity, Self-efficacy in relation to the addictive behavior/substance use.	
Review designs	Systematic reviews or Meta-analyses. Reviews that have a broad scope that encompass cue-exposure therapy may be included if the evidence for CET is reviewed independently from other interventions in text of tabular form.	Studies that do not identify themselves as either a systematic review or meta-analysis. Reviews that do not assess the efficacy of CET in an independent section.
Study designs	Any design that assesses the efficacy of CET	
Timing	Reviews of studies that include at least post-treatment data	
Language	No restrictions	

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*Note.* Abbreviations: CET: Cue Exposure Therapy, AD: Addiction Disorder,

**Table 2***Study Selection Process With Interrater Reliability*

		Rater 1 Total	Rater 2 Total	R1 NOT R2	R2 NOT R1	R1 AND R2	Base rate	Cohen's kappa
Abstract screening	Included	90	98	42	50	48	1862	0.486
	Excluded					1814		
Discussion I	Included					86	140	1
	Excluded					44		
Full-text screening	Included	20	25	1	6	19	86	0.79
	Excluded			6	1	60		
Discussion II	Included					19	26	
	Excluded					7		
Extraction	Included					13		
	Excluded					6 <sup>a</sup>		

*Note.* Numbers indicate *n* of entries. Abbreviations: R1: Rater 1, R2: Rater 2.

<sup>a</sup> Six studies were excluded through discussion with supervisor. These studies were excluded due to the fact that the articles did not treat CET in an independent section and/or lacked a systematic review methodology.

**Table 3***Review Characteristics.*

Author (year)	Aims	Conditions	Search strategy	N/n <sup>1</sup>	Overlap <sup>2</sup> %	Major limitations of included studies
Butler and Heimberg (2020)	1) Establish the type of stimuli used in exposure therapy for eating disorders (ED) Examine whether these methods have been effective in treatment 3) Examining whether core fears in eating disorders have been confronted through appropriate application of exposure therapy	DSM-5 eating disorders including AN-binge, BN, and BED	PsycINFO, PubMed, and Google Scholar (Feb 2020)  Reference lists searched  1,009 hits	N = 8  n = 239	100%	No ROB assessment.  Noted limitations: Baseline differences, high attrition rates, underpowered studies
Conklin and Tiffany (2002)	(1) Review the methods utilized in CET Addiction treatment studies (2) Meta-analyze cue-exposure's effectiveness as a treatment for Addiction (3) Review specific threats to extinction as derived from animal extinction research (4) Translating findings from animal research for improving cue-exposure treatment	Opiate dependence, Nicotine dependence, Alcohol dependence.	Not reported	N = 9  n = No info	55%	NO ROB assessment
Ghiță and Gutiérrez-	1) Review VR studies for assessment for alcohol misuse 2) Review VR studies for	Alcohol dependence	Web of Science, Scopus, Embase,	N = 2  n = 16		NO ROB assessment

Maldonado (2018)	treatment alcohol misuse. Emphasis on Craving		Google Scholar, and PsycInfo.  (Timeframe not reported)  107 hits			No control group, underpowered
Gooding and Tarrier (2009)	1) Review effectiveness of CBT for reducing Gambling behavior 2) Assess whether effect sizes are stronger for proximal outcome measures 3) Assess whether treatment mode would impact effect sizes 4) Assess whether different types of CBT would be differentially efficacious 5) Assess whether CBT would be effective across a number of different types of gambling behaviors 6) Assess whether session number, treatment hours, attrition rate and the quality of the studies would be associated with effect sizes	Pathological gambling (DSM IV)	Web of Science (1980-2008)	N = 2  n = 67	0%	The Clinical Trials Assessment Measure indicate low trial quality
Keijsers et al. (2021)	1) Review research findings on virtual reality technology (VRT) for smoking cessation therapy 2) Does VRT elicit craving? 3) What VRT interventions exist and how do they compare	Nicotine dependence (DSM)	MEDLINE, Embase, Scopus, Cochrane, and EbscoHost (July 2020)	N = 9  n = 442	89%	No ROB assessment  Noted limitations: Small samples, lack of control for smoking history, included

	with regular interventions in terms of smoking cessation outcomes? 4) What are the potential future directions for VRT in smoking cessation therapy?		Reference lists searched  299 hits			non-treatment seeking samples, single item-self-report measures, lack of blinding, lack of controlgroups.
Koskina et al. (2013)	1) Review the evidence for exposure techniques for eating disorders (ED) 2) Identify deficits in knowledge 3) Suggest improvements for exposure for ED	Eating disorders including AN-binge, BN, and BED (DSM)	PubMed and Web of Science (2012)  708 hits	N = 7  n = 182	100%	No ROB assessment  Small samples sizes, heterogenous sample characteristics, treatment resistant patients, high attrition rates
Langener et al. (2021)	1) Evaluate the diagnostic/prognostic value of VR-induced cue-reactivity for the clinical assessment of ADs 2) Evaluate the effectiveness of VR in the treatment of patients with ADs	Alcohol dependence, Nicotine dependence, Gambling disorder, Non-treatment seeking gamblers	PubMed and PsycINFO (November 2020)  References lists rearched  4519 hits	N = 13 <sup>3</sup>  n = 584		No ROB assessment, was not possible due to limited trial information  Noted limitations: Mostly feasibility studies, small sample sizes, heterogeneous samples and study designs, poorly validated outcome measures, lack of follow-up, lack of control groups



Magson et al. (2021)	<p>1) The use of research based recommendations in previous CERP treatment studies for binge eating</p> <p>2) Investigate whether CERP effectively reduces binge eating</p> <p>3) Evaluate the effect of CERP on change processes (i.e., cue reactivity and CS-US expectancies)</p>	Eating disorders including AN-binge, BN, and BED, Treatment seeking overeaters	<p>Cochrane Library, Google Scholar, PsychExtra, PsychInfo, and Pubmed (1980-2019).</p> <p>Grey literature and reference lists searched</p> <p>10 045 hits</p>	N = 18 n = 521	44%	<p>Checklist for Assessing the Quality of Quantitative Studies (scale 0-1): Studies ranged from poor (.28) to adequate (.88) quality. Mean quality rating was adequate (.70).</p> <p>Limitations noted: Mostly underpowered studies, differences in sample type, sample size, study design and treatment components</p>
Mayet et al. (2005)	To assess the efficacy and acceptability of psychosocial interventions for treating opioid dependence compared to non-psychosocial interventions (pharmacological, placebo or no intervention)	Opioid dependence (DSM)	<p>Cochrane drugs and Alcohol Group Register of Trials, CENTRAL, Medline, LILACS, EMBASE (2004)</p> <p>Grey literature and reference lists searched</p>	N = 1 n = 69	100%	<p>Rated at unclear ROB</p> <p>Limitations noted: Failed to follow intent-to treat principle, high attrition rates, participants were treated before CET.</p>
Mellentin et al. (2017)	1) Examine the efficacy of CET on alcohol use disorder compared to active controls	Alcohol use disorder (DSM),	MEDLINE, PsycINFO, EMBASE,	N = 7 n = 447	57%	ROB rated as High for all studies included.

	using systematic review and meta-analytic methods	Sub-clinical Alcohol use disorder	CENTRAL (January 2017)			Quality of evidence rated as low.
	2) Assess whether overall effects were influenced by the study design characteristics		5254 hits			Limitations noted: Risk of publication bias.
Ribeiro et al. (2021)	1. Evaluate the efficacy and durability of treatment effects for Gambling disorder compared to controls 2. Assess if there is a difference between short- and long-term treatments 3. Make a direct comparison between different therapies and assess the benefits of combining them 4. Evaluate the characteristics of some included studies that may have influenced part of the results and conclusions	Gambling disorder, Pathological gambling (DSM)	Pubmed and Cochrane Library (Feb 2020) 227 Hits	N = 4 n = 308	25%	CASP: Studies in the review were generally rated as moderate to high quality (ratings for specific studies not provided)  Limitations noted: Small samples, study personnel were not blinded to treatment, high drop-out rates
Segawa et al. (2019)	1) Evaluate the usefulness and efficacy of VR in cue-reactivity assessment for ADs 2) Evaluate whether VR be used as an effective tool for craving reduction compared to standard therapy in patients with ADs	Nicotine dependence (FTND)	PubMed and Embase 471 hits	N = 9 <sup>3</sup> n = 351	100%	ROB not assessed  Limitations noted: some non-treatment seeking samples, lack of statistical power, absence of control groups, lack of randomization, high attrition, lack of intent-to treat analysis.

Trahan et al. (2019)	<p>1) What is the state of evidence regarding the use of VRET for the treatment of alcohol or nicotine dependence and</p> <p>2) What are the effects of VRET on alcohol or nicotine craving, dependence, and usage with adults identified as nicotine or alcohol dependent</p>	Nicotine dependence (DSM, FTND)	<p>Academic Search Complete, Academic Search Ultimate, Applied Science &amp; Technology Source Ultimate, Business Source Ultimate, CINAHL, Complementary Index, Directory of Open Access Journals, Education Source, Food Science Source, MEDLINE, PsycARTICLES, PsychINFO, Science Citation Index, ScienceDirect, Scopus, Social Sciences Citation Index, Sociology Source Ultimate, and SPorTDiscuss, Google Scholar. (2000-2017)</p>	N = 4 n = 174	100%	<p>Cochrane ROB tool. Moderate to High risk of bias.</p> <p>Limitations noted: feasibility studies, convenience samples, small samples, lack of controls, lack of pre-registration, high attrition rates.</p>
			Reference lists and gray litteraure searched			
			Hits 1267			

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*Note.* This table presents information that is relevant to the current review. Study N, sample n, limitations and % overlap are only presented for CET interventions included in each review. Abbreviations: ROB: Risk of bias, ED: Eating disorders, AN-binge; Anorexia Nervosa-binge eating subtype, BN: Bulimia Nervosa, BED: Binge Eating Disorder, CBT: Cognitive Behavioral Therapy, VRT: Virtual reality Technology, VR: Virtual reality, CERP: Cue Exposure and Response Prevention, CS-US: Conditional Stimuli-Unconditional stimuli, CASP: Critical Appraisal Skills Programme, FTND: Fagerström Test for Nicotine Dependence

<sup>1</sup> n of samples includes control groups of trials.

<sup>2</sup> % Overlap are given as percentage of CET studies that are reported in at least one other review.

<sup>3</sup> One of the included papers includes two trials (counted)

**Table 4***Major Findings of Each Review*

Author (year)	Narrative findings
Butler and Heimberg (2020)	Evidence for CET for BN is mixed; the few RCTs show only marginal benefits over that of other treatments such as CBT. Exposure and response prevention for BN may be useful for those who are non-responders to treatments such as CBT.
Conklin and Tiffany (2002)	Meta-analysis showed that CET thus far has failed to prove efficacious in treating Substance Addiction compared to controls. Review shows that the treatment methods used have not addressed important threats to extinction such as spontaneous recovery, reinstatement, and renewal effects.
Ghiță and Gutiérrez-Maldonado (2018)	Studies were not designed to primarily investigate the efficacy of CET. Regardless, there is preliminary support for VR reduced alcohol craving with generally consistent results. Review suggests that VR provides benefits for assessment and treatment of alcohol craving and VR technology provides high ecological validity.

- Gooding and Tarrier (2009) Meta-analytic results of studies on ID show improvements on gambling behavior at short term (0–3 months) follow-up. Small studies of low study quality, with no controls provide preliminary evidence for ID for gambling behavior.
- Keijsers et al. (2021) VR-CET interventions have been shown to reduce craving in response to smoking-related cues. However, results in terms of smoking cessation are underwhelming. The efficacy of VR-CET above and beyond alternative interventions such as CBT is inconclusive.
- Koskina et al. (2013) Case studies and other non-RCT data show positive results in terms of symptom reduction of BN, and the treatment was acceptable to patients. Exposure and response prevention for BN may be useful for those who are non-responders to treatments such as CBT. RCTs studies show inconsistent results post-treatment and at follow-up. One study provides some evidence of a “conditioned inoculation” in those who received exposure treatment after 5-year follow-up, but findings are mixed. In terms of exposure to food cues, patients often experience complex mixed emotions including both dread and desire, the nature of which often changes rapidly.
- Langener et al. (2021) The clinical value for using VR-CET in treating ADs remains unclear. We only identified a single clinical effect study showing negative long-term effects. Treatment studies comprised mostly of

pilot studies showing limited effectiveness on relapse rates, dependence severity and consumption measures. This review showed short-term reductions in cue-reactivity, but long-term follow-ups are missing.

- Magson et al. (2021) There seems to be evidence for CET being effective for reducing binge eating pre- to post-treatment, but that it may not be better than other treatments in the short-term. Although post-treatment between-group effects showed no advantage to CET, follow-up data also suggest that advantages emerge over time. Virtual reality studies indicated that VR-CET was moderately more effective than CBT in reducing frequency of binge eating. The largest effects seem to be evidence for samples with the most severe binge-eating samples that are resistant to alternative treatments. Results indicate that CET is effective in reducing subjective cue reactivity from pre-to post-treatment and between sessions, but it has little effect on physiological reactivity. Limited follow-up data suggests that within-subject and between-group effects for reductions in subjective cue reactivity are maintained over time.

- Mayet et al. (2005) The efficacy of CET for Opiate Addiction has not been demonstrated and research is lacking.

- Mellentin et al. (2017) CET for treating Alcohol Addiction had not been demonstrated to be effective compared to controls. Meta-analyses show no to small additional effects on the primary outcome of alcohol consumption.
- Ribeiro et al. (2021) There is some evidence that CET and ID reduces gambling behavior, and it has been demonstrated over the long term. Comparative efficacy with other behavioral therapies is less clear. Imaginal desensitization seems to be effective, although more research is needed.
- Segawa et al. (2019) Virtual Exposure Therapy has been shown to be effective on craving reductions in nicotine and gambling disorders. Pre-post trials show some evidence for reductions in consumption. However, controlled trials found mixed results with one trial finding increases in 1-year relapse rate for the VR-CET condition. The inclusion of negative affective in VR-CET could lead to a restructuring of the conditioned stimulus response relation in Addiction and should eventually result in avoidance of the administered drug.
- Trahan et al. (2019) Despite quality of evidence being low, the included studies points to potential promise of VR-CET interventions for alcohol and Nicotine Addiction, particularly when combined with CBT. Included studies show positive results, with some studies reporting effect sizes indicating moderate to large
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effects for reducing craving, dependence, and cigarettes smoked. Comparison to other evidence-based interventions such as CBT show that further evidence is necessary to show VR has an additive effect.

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*Note.* Abbreviations: CET: Cue Exposure Therapy, BN: Bulimia Nervosa, VR: Virtual Reality, ID: Imaginal Desensitization, VR-CET Virtual Reality Cue Exposure Therapy, CBT: Cognitive behavioral therapy, RCT: Randomized controlled Trial, AD: Addiction Disorder.

**Table 5***Summary of Findings*

Condition	Review	Consumption, behavior, and relapse rates	Craving	Other outcomes
Mixed: Alcohol, Nicotine and Opium Addiction	Conklin and Tiffany (2002)	9 trials ( <i>n</i> not reported)  BG <sup>a, b</sup> : Meta-analyses for 6-month follow-up n.s. ( <i>d</i> = 0.0868, 95% <i>CI</i> : – 0.11 ± 0.28)  Test for heterogeneity was significant ( <i>Q</i> (9) = 16.078; <i>p</i> = 0.0413)		
Opium Addiction	Mayet et al. (2005)	1 Trial <sup>c</sup> ( <i>n</i> = 69)  BG <sup>a</sup> : n.s. at 1.5- and 6-months follow-up.		
Alcohol Addiction	Mellentin et al. (2017)	6 trials <sup>d</sup> ( <i>n</i> = 413)  BG <sup>a, b</sup> : Meta analysis n.s. at 3-month follow-up. Meta-analysis n.s. at 6-months follow-up ( <i>g</i> = 0.16, 95% <i>CI</i> : 0.52 to -0.19) <sup>f</sup>		
	Ghiță and Gutiérrez-Maldonado (2018)		2 trials ( <i>n</i> = 16)	

			WG: Trend towards improvement (no significance Tested)	
	Langener et al. (2021)	1 trial ( $n = 42$ )	WG: Significant	BG: Not tested, controls did not show WG decreases.
Nicotine Addiction	Conklin and Tiffany (2002)	4 trials <sup>d</sup> ( $n$ not reported) BG <sup>a, b</sup> : Results favoring controls at 6 months follow-up, significance not reported ( $d = -.251$ to $d = -.518$ , <i>CI: not reported</i> )		
	Langener et al. (2021)	6 trials ( $n = 339$ ) WG: 1 Trial significant ( $\eta p^2 = .49-.82$ ) 2 trials n.s. BG <sup>a, b</sup> : 2 trials significant post treatment. 1 trial significant at follow-up (1-6 months) 1 trial n.s. 1 trial show significant increase in relapse in CET group at 12-month follow-up (Experimental 62% vs. control: 37%)	9 trials ( $n = 473$ ) WG: 2 trials show significant pre-post improvements ( $d = .44$ , $\eta p^2 = 0.66-72$ ). 1 trial trend towards improvement. (Sign. not tested) 2 trials n.s. BG <sup>a, b</sup> : 3 trial significant ( $\eta p^2 = 0.37-0.76$ ) 1 trial n.s.	Severity of nicotine dependence: 3 trials ( $n = 196$ ) WG: 1 trial n.s. for changes in severity BG <sup>a, b</sup> : 2 trials n.s. for changes in nicotine dependence Self-efficacy: 1 trial ( $n = 46$ ) BG: Significant improvements post

			treatment ( $\eta p^2 = 0.13$ ), Significant and at follow-up (1-6 months)
	Trahan et al. (2019)	2 trials ( $n = 40$ ) WG: 2 trials significant BG <sup>a</sup> : 1 trial n.s.	2 trials ( $n = 40$ ) WG: 2 trials significant BG <sup>a</sup> : 1 trial n.s. Severity of Nicotine dependence: 2 trials ( $n = 40$ ) WG: 2 trial significant BG <sup>a</sup> : 1 trial n.s.
	Keijsers et al. (2021)	1 trial ( $n = 15$ ) BG <sup>a</sup> : Significant post-treatment	1 trial ( $n = 15$ ) BG <sup>a</sup> : Significant post-treatment
Food Addiction	Magson et al. (2021)	16 trials ( $n = 497$ ) 3 case series/studies. Pre-post and follow-up (2–9 months) Improvements reported (no sign. test) WG: 6 trials significant ( $d = 0.3-3.26$ ) 5 trials significant at follow-up (3-60 months) 2 trials show trends towards improvement post. (no sign. tested) 1 report improvements maintained at 1–6-month follow-up (no sign. tested) 1 trial n.s.	12 trials ( $n = 442$ ) 1 case series. Pre-post improvements (no sign. Test) WG: 5 trials show significant improvements ( $d = 0.37-1.99$ ) 1 trial significant at follow-up (6 Months) ( $d = .37 - 1.02$ ) 3 trials show trends towards improvement (No sign. Test) 3 trial n.s. BG <sup>a, b</sup> : 2 trials significant ( $d=.37-.41$ )

		<p>BG<sup>a, b</sup>: 3 trials significant at post-treatment (<math>d = .35-59</math>), 1 of which reported significant at 3 months follow-up</p> <p>3 trials n.s. Complex follow-up pattern. 2 trials show improvements after 12 and 60 months respectively not evident at post. 1 trial show control are better at 12 months.</p>	<p>1 trial n.s. post treatment and at 6-month follow-up</p>	
Gambling Addiction	Langener et al. (2021)		<p>2 trials (<math>n = 44</math>)</p> <p>WG: 1 trial significant. 1 trial n.s. BG<sup>a</sup>: 1 trial n.s.</p>	<p>Severity of problem gambling and diagnostic criteria: 1 Trial (<math>n = 25</math>)</p> <p>BG<sup>a</sup>: n.s.</p> <p>Self-efficacy: 1 trial (<math>n = 10</math>)</p> <p>WG: n.s</p>
	Ribeiro et al. (2021)	<p>2 trials (<math>n = 184</math>)</p> <p>BG<sup>a</sup>: 2 trials significant post treatment. 2 trials significant at 6–9 years follow-up.</p>		<p>Severity of gambling disorder symptoms: 1 trial (<math>n = 99</math>)</p> <p>WG: significant decrease</p> <p>BG<sup>a</sup>: n.s.</p>

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Gooding and TARRIER (2009)	2 trials ( $n = 67$ ) WG: Meta-analysis for 2 trials significant at 0–3-month follow-up ( $g$ $= .92$ , $CI$ : 1.65 to 0.18)
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*Note.* Table shows the result of the most detailed and comprehensive reviews. Duplicate studies are removed, and reviews are not presented in the table if they do not provide additional studies to the ones identified by other reviews. Effect sizes are ranges of available estimates, but do not apply to all studies referenced.  $n$  includes dropouts and control groups. All numbers with a positive sign indicate CET efficacy. Abbreviations. n.s.: Nonsignificant at  $p \geq .05$ , BG: Between group comparison, WG: Within-group (pre-post) comparison, CI: Confidence interval,  $d$ : Cohen's  $d$ ,  $g$ : Hedge's  $g$ .

<sup>a</sup> Active (assumed effective) control group

<sup>b</sup> Non-active control group such as waitlist, brief information, placebo conditions

<sup>c</sup> Includes one of the same studies as in Conklin and Tiffany (2002)

<sup>d</sup> Includes four of the same studies as the meta-analysis by Conklin and Tiffany (2002)

<sup>f</sup> Mellentin et al. (2017) gives several meta-analytic estimates for different drinking outcome measures, all insignificant. The numbers presented above is the one with largest number of participants included.

**Table 6.***AMSTAR Quality Rating for Each Included Review*

Author (year)	1	2	3	4	5	6	7	8	9a	9b	10	11a	11b	12	13	14	15	16	Rating
Butler and Heimberg (2020)	N	N	N	N	N	N	N	Y	N	N	N	-	-	-	N	Y	-	Y	C
Conklin and Tiffany (2002)	Y	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N	Y	C
Ghiță and Gutiérrez-Maldonado (2018)	Y	N	N	N	N	N	N	Y	N	N	N	-	-	-	N	Y	-	Y	C
Gooding and Tarrier (2009)	Y	N	Y	N	N	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	C
Keijsers et al. (2021)	Y	N	Y	N	N	N	N	Y	N	N	N	-	-	-	Y	Y	-	Y	C
Koskina et al. (2013)	Y	N	N	Y	N	N	N	Y	N	N	N	-	-	-	N	Y	-	Y	C
Langener et al. (2021)	Y	N	Y	N	Y	Y	N	Y	N	N	N	-	-	-	Y	Y	-	Y	C
Magson et al. (2021)	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	-	-	-	Y	Y	-	Y	C

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Mayet et al. (2005)	Y	N	Y	Y	Y	Y	Y	Y	Y	-	N	-	-	-	Y	Y	-	Y	L
Mellentin et al. (2017)	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	-	N	Y	Y	Y	Y	C
Ribeiro et al. (2021)	Y	N	N	N	N	N	N	Y	Y	-	N	-	-	-	N	Y	Y	Y	C
Segawa et al. (2019)	Y	N	N	N	N	N	N	Y	N	N	N	-	-	-	N	Y	-	Y	C
Trahan et al. (2019)	Y	Y	Y	Y	N	Y	Y	Y	-	Y	N	-	-	-	Y	Y	-	Y	M

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*Note.* Y=Yes, N =No, - =not applicable, H= High Quality, L = Low quality, Moderate quality, C = Critically low quality.

1. Research question includes components of population, interventions, controls and outcomes. .
2. Review methods were established prior to the conduct of the review.
3. Explanation for the designs is included in the review.
4. Use of a comprehensive literature search strategy.
5. Duplicate study selection.
6. Duplicate data extraction.
7. A list of excluded studies with justification is provided.
8. Included studies are described in adequate detail.



- 9a. Adequate risk of bias assessment of randomized controlled trials
- 9b. Adequate risk of bias assessment of non-randomized studies of therapeutic interventions.
- 10. Sources of funding for the studies reported.
- 11a. Use of appropriate methods for statistical combination of results of randomized controlled trials.
- 11b. Use of appropriate methods for statistical combination of results of non-randomized studies of therapeutic interventions.
- 12. Assessed the potential impact of risk of bias in evidence synthesis.
- 13. Accounted for risk of bias in individual studies when interpreting/discussing the results.
- 14. Satisfactory explanation for, and discussion of, any heterogeneity.
- 15. Adequate investigation of publication bias and discusses its likely impact.
- 16. Reports any potential sources of conflict of interest

**Appendix A**

*Full Search Strategy for Each Database*

	PsychInfo	EMBASE	Medline	Cochrane	WoC	DARE
	Facet 1: Cue exposure therapy					
Mesh Terms /subject headings	Exposure therapy Implosive Therapy Exp Extinction (learning)	Exp exposure therapy	Extinction, Psychological Desensitization, Psychologic	Implosive Therapy, Desensitization, Psychologic Extinction, Psychological	NA	Desensitization, Psychologic, Extinction, Psychological Implosive Therapy
	((((Desensitiz* or Expos* or inhibitory or Conditioning or extinction or extinguish) adj4 (therap* or intervention* or Treat* or training or learn* or virtual or cue)) or ("response prevention" or CERP or CET or VRET)).mp.	((((Desensitiz* or Expos* or inhibitory or Conditioning or extinction or extinguish) adj4 (therap* or intervention* or Treat* or training or learn* or virtual or cue)) or ("response prevention" or CERP or CET or VRET)).mp.	((((Desensitiz* or Expos* or inhibitory or Conditioning or extinction or extinguish) adj4 (therap* or intervention* or Treat* or training or learn* or virtual or cue)) or ("response prevention" or CERP or CET or VRET)).mp.	((((Desensitiz* or Expos* or inhibitory or Conditioning or extinction or extinguish) NEAR/3 (therap* or intervention* or Treat* or training or learn* or virtual or cue)) or ("response prevention" or CERP or CET or VRET))	TS=((((Desensitiz* or Expos* or inhibitory or Conditioning or extinction or extinguish) NEAR/3 (therap* or intervention* or Treat* or training or learn* or virtual or cue)) or ("response prevention" or CERP or CET or VRET))	((Desensitiz* or Expos* or inhibitory or Conditioning or extinction or extinguish) adj4 (therap* or intervention* or Treat* or training or learn* or virtual or cue)) or ("response prevention" or CERP or CET or VRET))

Facet 2: Addiction disorders

Mesh Terms /subject headings	"substance use disorder"	Addiction	Substance-Related Disorders	Substance-Related Disorders	Substance-Related Disorders
	nonsubstance related Addictions		Impulsive Behavior Gambling	Behavior, Addictive	Impulsive Behavior
	drug Addiction			Disruptive, Impulse Control, and Conduct Disorders	Gambling
	Addiction treatment				
	((Abus* or Depend* or Compulsi* or Bing* or Excess* or Problem* or misuse** or Hazard* or Patholog*) adj3 (Substance* or Drug* or narcotic* or Drink* or Stimulant* or Smok* or Nicotine or Tobacco or opiate* or Cocaine or Amphetamine* or	((Abus* or Depend* or Compulsi* or Bing* or Excess* or Problem* or misuse* or Hazard* or Patholog*) adj3 (Substance* or Drug* or narcotic* or Drink* or Stimulant* or Nicotine or Tobacco or opiate* or Cocaine or Amphetamine* or	((Abus* or Depend* or Compulsi* or Bing* or Excess* or Problem* or misuse* or Hazard* or Patholog*) adj3 (Substance* or Drug* or narcotic* or Drink* or Stimulant* or Nicotine or Tobacco or opiate* or Cocaine or Amphetamine* or	((Abus* or Depend* or Compulsi* or Bing* or Excess* or Problem* or misuse* or Hazard* or Patholog*) adj3 NEAR/3 (Substance* or Drug* or narcotic* or Drink* or Stimulant* or Nicotine or Tobacco or opiate* or Cocaine or	TS=((Abus* or Depend* or Compulsi* or Bing* or Excess* or Problem* or misuse* or Hazard* or Patholog*) adj4 (Substance* or Drug* or narcotic* or Drink* or Stimulant* or Nicotine or Tobacco or opiate* or Cocaine or Amphetamine* or

alcohol* or Marijuana or Cannabis or Food or Eat* or Internet or Sex or Porn or Game* or Gambling or Buying or Shopping)) or (addict* or "use disorder*" or SUD or Hypersex*)).mp.	alcohol* or Marijuana or Cannabis or Food or Eat* or Internet or Sex or Porn or Game* or Gambling or Buying or Shopping)) or (addict* or "use disorder*" or SUD or Hypersex*)).mp.	alcohol* or Marijuana or Cannabis or Food or Eat* or Internet or Sex or Porn or Game* or Gambling or Buying or Shopping)) or (addict* or "use disorder*" or SUD or Hypersex*)).mp.	Amphetamine* or alcohol* or Marijuana or Cannabis or Food or Eat* or Internet or Sex or Porn or Game* or Gambling or Buying or Shopping)) or (addict* or SUD or Hypersex*) or (use NEXT disorder*)	Amphetamine* or alcohol* or Marijuana or Cannabis or Food or Eat* or Internet or Sex or Porn or Game* or Gambling or Buying or Shopping)) or (addict* or "use disorder*" or SUD or Hypersex*))	alcohol* or Marijuana or Cannabis or Food or Eat* or Internet or Sex or Porn or Game* or Gambling or Buying or Shopping)) or (addict* or "SUD" or Hypersex*))
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Facet 3: Systematic reviews and meta-analyses

(meta-anal* or systematic or overview or review).ti,ab.	(meta-anal* or systematic or overview or review).ti,ab.	(meta-anal* or systematic or overview or review).ti,ab.	NA	TS=(meta-anal* or systematic* or overview or review)	NA
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*Note.* Facets are combined using the AND operator. Search terms are given in exact form as searched in the database. MeSH terms and subject headings are formatted and would have to be searched in each database manually to reproduce the search. Abbreviations.

WOC: Web of science, DARE: Database for abstract review of effects, NA: not applicable,