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Lisdexamfetamine and Binge-Eating Disorder: A systematic review and meta-analysis of the preclinical and clinical data with a focus on mechanism of drug action in treating the disorder.

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Abstract

Binge-Eating Disorder (BED) is the most common eating disorder in the United States. Lisdexamfetamine (LDX) was approved in 2015 by the FDA for treatment of BED and is the only drug approved for treating the disorder. There has been no systematic evaluation of the published clinical and preclinical evidence for efficacy of LDX in treating BED and the mechanisms responsible for the therapeutic action of the drug. To address this gap, we conducted a systematic review and meta-analysis using PRISMA guidelines. Fourteen clinical and seven preclinical articles were included. There is consistent evidence from clinical studies that LDX is an effective treatment for BED and that the drug reduces the BED symptoms and body weight of patients with the disorder. There is also consistent evidence from preclinical studies that LDX reduces food intake but no consistent evidence for a preferential reduction of palatable food consumption by the drug in rodents. The evidence on mechanism of action is more limited and suggests LDX may reduce binge eating by a combination of effects on appetite/satiety, reward, and cognitive processes that are mediated by catecholamine and serotonin mechanisms in the brain. There is an urgent need for adequately powered, placebo-controlled, behavioural and neuroimaging studies with LDX (recruiting patients and/or individuals with subclinical BED symptoms) to further investigate the mechanism of action of the drug in treating BED. An improved understanding of the behavioural and neurochemical mechanisms of action of LDX could lead to the development of improved drug therapies to treat BED.

1. Introduction

Binge-eating disorder (BED) is defined by recurrent episodes of binge eating in the absence of compensatory behaviours (e.g. vomiting, laxative use, excessive dieting) (American Psychiatric Association, 2013). An episode of binge eating is characterised by eating in a discrete period of time an amount that is definitely larger than that which most people would eat in a similar period of time under similar circumstances (American Psychiatric Association, 2013). Binge-eating episodes are also usually accompanied by a sense of lack of control during the episode and an individual may experience rapid eating, uncomfortable fullness, eating in the absence of hunger, embarrassment, disgust, depression, and guilt (American Psychiatric Association, 2013). BED is the most common eating disorder and the estimated lifetime global prevalence is between 0.9-2.2.% (Erskine & Whiteford, 2018; Qian et al., 2013). BED is often co-morbid with obesity and obesity-related physical symptoms (Citrome, 2019; Kessler et al., 2013; Papelbaum et al., 2019). In addition to impairing physical health, BED is associated with mood and anxiety disorders, bipolar disorder, self-harm, and addiction disorders (Grilo et al., 2013; Peters et al., 2019; Schulz & Laessle, 2010; Swanson et al., 2011).

Current treatments for BED include cognitive behavioural therapy (CBT) and behavioural weight loss therapy (BWLT) (Wilson et al., 2010). CBT is effective in reducing binge-eating frequency but not in reducing weight, while BWLT is effective in reducing weight but not in decreasing binge-eating frequency (McElroy et al., 2015a; Palavras et al., 2017; Peat et al., 2017). Pharmacotherapy options for BED include antidepressants (e.g., sertraline and bupropion) and the anticonvulsant topiramate. These treatments show modest short term efficacy in reducing binge eating, but antidepressants do not cause weight loss and topiramate use is limited by adverse effects and thus discontinuation rates are high (McElroy et al., 2015a).

In 2015, the United States Food and Drug Administration (FDA) approved lisdexamfetamine dimesylate (LDX) (Vyvanse®, Takeda) as the first and, to date, only drug for the treatment of BED (FDA, 2015). LDX is a pro-drug of *d*-amphetamine that was first approved by the FDA in 2007 for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). Taken orally, LDX is hydrolysed to the active metabolite, *d*-amphetamine (Adler et al., 2017), which crosses the blood-brain barrier to increase central noradrenergic, dopaminergic, and serotonergic neurotransmission (Ermer et al., 2016; Hutson et al., 2014). Approval for the use of LDX in the treatment of BED was based on a clinical development program that included an 11-week phase II randomised controlled clinical trial assessing doses of 30, 50, and 70mg/day LDX (McElroy et al., 2015b) and two 12-week phase III randomised controlled clinical trials investigating 50 and 70mg/day doses (McElroy et al., 2016a) for the treatment of BED. Both these studies demonstrated a reduction in binge-eating episodes and BED-related symptoms after 50 and 70mg LDX. Subsequent studies have confirmed the efficacy of LDX in the treatment of BED (Citrome, 2015; Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017). Although LDX is approved to treat BED, little is known about the specific neural, pharmacological, and behavioural processes that are responsible for its efficacy in treating BED symptoms. An improved understanding of the pharmacological and neuropsychological processes that mediate the therapeutic effects of LDX could aid in the development of novel medications to treat BED which have improved efficacy and fewer side effects.

For example, LDX reduces self-reported binge-eating symptoms in individuals with BED (Hudson et al., 2017; McElroy et al., 2016b), which could be due to effects of the drug on appetite, as self-reported appetite is decreased following LDX administration (McElroy et al., 2016a; McElroy et al., 2015c). Thus, LDX increases monoamine neurotransmission, and there is extensive evidence for a role of dopamine, noradrenaline, and serotonin in the control

of appetite (Dourish et al., 2008). Further, LDX reduces palatable food intake in preclinical models of binge eating, suggesting a possible effect of LDX on food reward (Vickers et al., 2015). In clinical studies, LDX reduced self-reported impulsivity symptoms (McElroy et al., 2015b), which may be significant as emerging evidence suggests higher order cognitive processes such as attention, memory, and cognitive inhibition, modulate food intake (Higgs & Spetter, 2018). Increased impulsivity is also associated with BED and is considered a contributing factor to binge-eating episodes (Fischer et al., 2008; Giel et al., 2017). To investigate the mechanism of action of LDX in the treatment of BED, effects of the drug on appetite, reward, and cognition will be examined.

To date, there have been several narrative reviews of the efficacy of pharmacological treatment of BED (Goracci et al., 2015; Heo & Duggan, 2017; McElroy et al., 2015d; Ward & Citrome, 2018), but only two systematic reviews of the efficacy of LDX. The first systematic review to assess the safety and efficacy of LDX in the treatment of BED concluded that the drug had robust effects on binge-eating symptoms and low discontinuation rates (Citrome, 2015). A subsequent systematic review and meta-analysis reported that LDX was more effective than placebo in reducing binge-eating days per week, BED-related obsessive-compulsive symptoms, weight, and remission rates, but also that discontinuation rates were higher for LDX than for placebo (Fornaro et al., 2016). These reviews focused on the safety and efficacy of LDX rather than mechanism of action and neither included results from preclinical studies. To investigate pharmacological and behavioural mechanisms of therapeutic drug action, it is recommended that both preclinical studies and clinical studies are included (Sena et al., 2014). The current systematic review and meta-analysis extends the scope of previous reviews by 1) including more recently published clinical studies 2) assessing both the efficacy of LDX in binge eating and the neural mechanisms that may underlie its therapeutic effects and 3) including both preclinical and clinical studies.

2. Experimental Procedures

The protocol for this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as a preclinical (CRD42020198117) and clinical (CRD42020198102) review.

2.1. Literature Search

A search for original research articles in English was performed in June 2020 by a single researcher (ES). The databases used to perform the search were Web of Science, PubMed Central, PsycInfo, and Ovid SP. The following search terms were used: lisdexamfetamine, lisdexamfetamine dimesylate, lisdexamphetamine dimesylate, lisdexamphetamine, SPD489, Vyvanse, Elvanse, or LDX and binge, binge-eating disorder, binge eating disorder, binging, bingeing, binge eating, binge-eating, or binge disorder (see supplementary materials for full search terms). The search included human participants of all ages and non-human animal subjects. The Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to guide the search of articles (Liberati et al., 2009) (see Figure 1). Supplemental article searches were performed by searching reference lists of related articles and reviews.

2.2. Study Selection

All original, peer-reviewed research articles (i.e. no conference abstracts, press releases, reviews or meta-analyses) assessing LDX and binge eating or food intake in humans and non-human animals were included. Studies that were conducted on a different clinical sample (i.e. not BED) were included if a measure of binge eating/food intake was reported. Mechanistic studies, including pharmacokinetic studies that did not recruit participants with BED symptoms or include a binge-eating/food intake measure, were not included. Studies

examining the active metabolite of LDX, d-amphetamine, only were not included. There were no restrictions on age, gender, or BED status (i.e. sub-clinical or clinical).

2.3. Data Extraction

Data extraction was performed using standardised templates created for the review. Each article was extracted by one investigator (ES) and reviewed by another investigator (SH) for accuracy and completeness. The information extracted from each clinical study included: study design, clinical phase, intervention, duration, eligibility, comparator, sample size, participant characteristics, adverse effects, primary outcome measures, and secondary outcome measures, declaration of interests. Information extracted from preclinical studies included: behavioural model, sex, species and strain, drug regimen (acute versus chronic), dose of drug, route of administration, comparator, sample size, and outcome measures. The quality assessment of each study was completed by two reviewers (ES and SH) using an adapted tool for assessment of clinical studies (Kmet et al., 2004) and an adapted tool for assessment of preclinical studies (Zeng et al., 2015). The quality criteria for clinical studies included: validity of research design, reporting of participant characteristics, randomisation, double-blinding, appropriate reporting of outcomes, and reporting of conflicts of interests. The quality criteria for preclinical studies included: sample size, randomisation, blinding, exclusion reporting, and reporting of conflicts of interest. Each criterion was rated as 1) met; 2) partially met; or 3) not met to determine an overall quality rating (scored as low, moderate, or high). Scoring was completed by two reviewers (ES and SH) independently. Moderate and large differences in quality ratings were discussed by the two reviewers until a consensus was reached. A third reviewer (CD) was available to arbitrate disagreements, but this was not required.

2.4. Data Synthesis

An inverse variance meta-analysis was used to analyse results from both the clinical and preclinical studies. For the clinical studies, randomised controlled trials that compared the efficacy of placebo and LDX were included in the meta-analysis. One measure of LDX efficacy at treatment endpoint was extracted. Efficacy was operationalised as self-reported changes on validated binge-eating symptoms questionnaires (i.e. Binge Eating Scale (BES), Clinical Global Improvement (CGI), and Yale-Brown Obsessive Compulsive Scale – Binge Eating (YBOCS-BE)). Preclinical studies were compared by placebo and LDX effects on chow intake and palatable food intake. Given the variety of study design and assessment measures, a random effects analysis model was used. Revman (Cochrane, 2020) version 5.4 was used to calculate the weight and standardised mean difference (SMD) between the placebo and LDX conditions for both subject types. I^2 values and confidence intervals (95%) were provided to assess statistical heterogeneity. Means that were presented graphically were extracted using WebPlotDigitizer Version 4.3 (Rohatgi, 2020). When standard error was used to represent variance, the Cochrane method for obtaining standard deviation from standard error was used to determine the standard deviation: $SD = SE * \sqrt{N}$ (Higgins et al., 2019). Where relevant data were missing, study authors were contacted to obtain this information. When data for multiple LDX doses were available, the dose with the highest effect size was selected as the LDX comparison for data analysis. When chronic doses of LDX were reported (Ekstrand et al., 2019; Sachdeo et al., 2019), a single average across all data points was calculated for pooled analysis. All studies reported efficacy measures as endpoint data only; one study (Guerdjikova et al., 2016) reported efficacy endpoint as change from baseline. In this instance, the change from baseline score was included with the other endpoint data, as combining endpoint and change from baseline score has been shown to be an acceptable method for pooling data (Higgins et al., 2019). With the exception of one study (Hudson et al., 2017), all RCTs were placebo-controlled trials investigating the acute treatment efficacy

of LDX for the treatment of BED. However, Hudson et al. (2017) randomly assigned responders from an open-label phase of the study to receive either placebo or LDX to measure BED relapse and is thus a relapse-prevention trial as opposed to a treatment efficacy trial. As such, the Hudson et al. (2017) study was excluded from the meta-analysis. The preclinical articles included multiple experiments with food intake measures comparing vehicle to LDX, hereafter referred to as comparisons. In these instances, eligible data included any vehicle-LDX comparison regardless of sample type (i.e., transgenic mice, non-bingeing controls).

3. Results

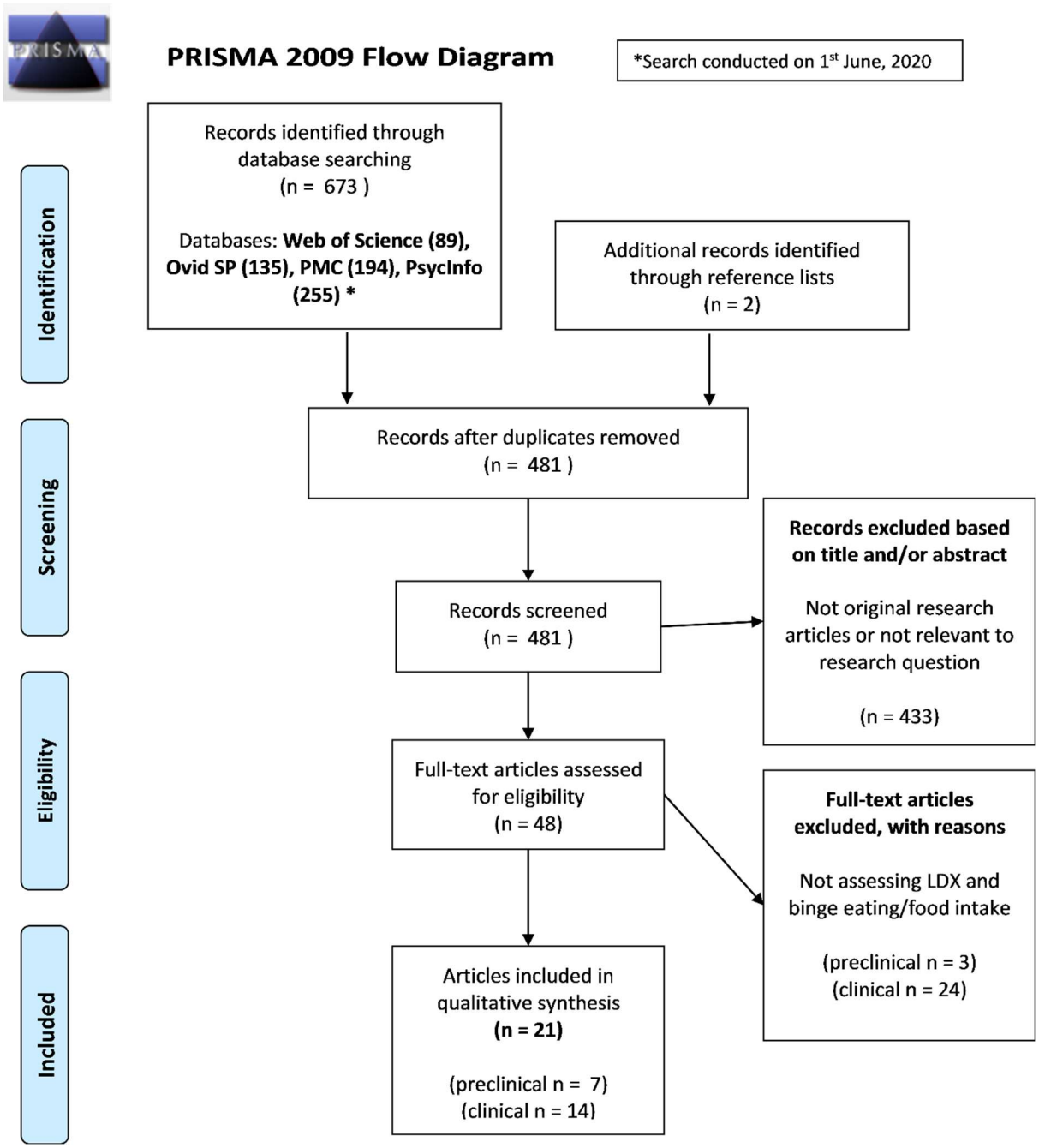
3.1. Study Selection

A total of 21 articles were included in this review (see Figure 1). A search of Web of Science, PubMed Central, Ovid SP, and PsycInfo yielded 673 results. After removal of duplicates, 481 records remained. Of these records, 433 were removed after determining the abstracts did not meet the criteria resulting in 48 articles eligible for full-text screening. Twenty-four clinical articles and 3 preclinical articles were removed during full-text screening for lacking a measure of LDX on binge eating/food intake, resulting in 13 clinical and 6 preclinical articles. An additional clinical and an additional preclinical article were included through a manual search of references of relevant papers and for studies that have cited these papers. This resulted in a final total of 14 clinical and 7 preclinical articles that met inclusion criteria for this review.

A total of 47 comparisons were extracted from the 7 preclinical articles, as some articles included multiple relevant comparisons. Three clinical articles (Kornstein et al., 2019; McElroy et al., 2017; McElroy et al., 2016b) reported secondary analyses from previously published studies. The results of these three studies were excluded from the meta-analysis but

are included in Table 1 and are discussed in the narrative synthesis section. One study (Keshen & Helson, 2017) administered extended release amphetamine/dextroamphetamine instead of LDX in one of the six case reports and so this case report is not included in the results.

Figure 1: PRISMA Flow Diagram for Study Selection



3.2. Study Characteristics

3.2.1. Clinical studies

Of the 14 clinical articles, four (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015a; McElroy et al., 2015c) reported the results of a randomised controlled trial (RCT), and one reported the results of two RCTs (McElroy et al., 2016a). Three articles reported the results of open-label studies (Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017), two were case reports (Brucar et al., 2018; Srivastava et al., 2019), two were retrospective medical record reviews (Guerdjikova et al., 2019; Keshen & Helson, 2017) and three were secondary data analyses (Kornstein et al., 2019; McElroy et al., 2017; McElroy et al., 2016b). Note that Hudson et al. (2017) is included in both the RCT and open label design as results of both designs are reported in the article. As such, the results of Hudson et al. (2017) are included in both sections with accompanying relevant data. BED was a primary diagnosis in all but two studies (McElroy et al., 2015c; Keshan et al., 2017). Primary diagnoses for these two studies were Bipolar Disorder and Bulimia Nervosa.

3.2.1.1. Randomised Controlled Clinical Trials

Across the five RCTs, data were collected from a total of 1349 participants who had a clinical diagnosis of BED across 175 sites (North America and Europe). Only adults were eligible to take part and the mean age range was 37.7-43.0 years. All studies recruited men and women, but women represented the majority of participants in all studies. The mean body mass index (BMI) ranged from 33.45-34.90 kg/m^2. Only one study (McElroy et al., 2016a) reported co-morbidities and of these Major Depressive Disorder was the most prevalent. Treatment duration ranged from 8 weeks-26 weeks. Chronic LDX doses ranging from 20mg-70mg were compared against a placebo. Outcome measures for symptom improvement included binge eating days/week (n=4) or binge eating episodes per week (n=2) and changes on the Clinical

Global Improvement CGI (n=4), YBOCS-BE (n=4), and BES (n=2). All RCTs were sponsored by the manufacturer of the drug, Shire (now Takeda).

3.2.1.2. Non-Randomised Controlled Clinical Trials

Across all non-RCT articles (n=7), data were collected from a total of 1081 participants across 141 sites. Eligibility for participation included a diagnosis of BED (n=4), a score of 21 on the BES (n=1), 45-year history of BED (n=1), and a diagnosis of Bulimia Nervosa (n=1). Ages ranged from 12-56 years. Three studies (Gasior et al., 2017; Guerdjikova et al., 2019; Hudson et al., 2017) recruited men and women (although the majority of participants were women), three studies (Brucar et al., 2018; Fleck et al., 2019; Srivastava et al., 2019) included only women, and one study did not report sex/gender (Keshan et al., 2017). Adult BMI ranged from 33.75-48.89 kg/m^2 and mean paediatric BMI percentile was 97.5 (Guerdjikova et al., 2019). Two studies did not report BMI (Brucar et al., 2018; Keshan et al., 2017). Of the studies that reported co-morbidities (n=2), the disorders reported included: depressive disorders, generalised anxiety disorder, ADHD, developmental delay/autism, milieu instability, marijuana use disorder, dependent traits, avoidant personality traits, dependent personality traits, obsessive-compulsive personality traits, and social anxiety disorder. Treatment duration ranged from 1-19.1 months. Chronic dosing of LDX ranged from 30-70mg LDX and were compared against a control group (n=1) or had no comparator (n=6). Outcome measures of symptom improvement included: binge eating frequency (n=4), CGI (n=2), YBCOS-BE (n=2), BES (n=2), neural activity in relevant brain areas (n=2), self-report BED symptoms (n=1), and binge/purge days per month (n=1). Of the studies that reported a funding source (n=4), three were funded by Shire (now Takeda) the manufacturer of the drug, and five of the seven non-RCTs reported a conflict of interest due to various links with Shire (now Takeda).

3.2.2. Preclinical Studies

Of the 7 articles included in this review, 6 reported measures of food intake after administration of LDX (either free feeding intake or intake of food obtained via lever pressing). One article reported the results of a study that assessed the ability of rats to delay responding on a lever to obtain a larger reward (3 pellets after a delay versus 1 pellet delivered immediately) (Vickers et al., 2017). The number of pellets consumed by the rats was assessed in this study, but given that higher intake in this paradigm reflects a greater ability to delay gratification, any effect of LDX on pellets consumed reflects an effect of the drug on impulsivity rather than on intake *per se.* Therefore, this study was excluded from the narrative synthesis of the efficacy of LDX for treating BED and the meta-analysis and is discussed only in the section on mechanisms. Most articles reported assessment of the effects of acute dosing of LDX on intake of both palatable food (usually chocolate) and standard laboratory rodent chow when offered as a choice in a rat model of binge eating (Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2015; Yohn et al., 2016). Of these studies, two used an effort-based choice paradigm that involved rats choosing between lever pressing for palatable food pellets versus free access to chow (Presby et al., 2020; Yohn et al., 2016). One study assessed intake of both palatable food and chow but offered sequentially in a test session (palatable food) and later in the home cage (chow) (Heal et al., 2016). Another study assessed daily home cage chow intake during chronic dosing with LDX (Ekstrand et al., 2019). Comparisons of interest were between LDX treated animals and vehicle treated animals. One article included an assessment of the effects of co-administration of catecholamine receptor antagonists to assess underlying pharmacological mechanisms (Vickers et al., 2015). The results of the comparisons between LDX and vehicle treated rats from these assessments are reported in the section on food intake and the comparisons with the antagonist drugs are reported in the section on mechanisms. Five articles reported testing

female rodents (Heal et al., 2016; Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2017, 2015) and 2 male rodents (Ekstrand et al., 2019; Yohn et al., 2016). All studies tested rats except for one that used female transgenic mice with genetically altered μ-opioid receptor signalling (Sachdeo et al., 2019). The doses examined ranged from 0.09mg/kg to 1.5mg/kg LDX which were administered either orally or intraperitoneally (IP). Most animals were not deprived of food but in two reports the animals had food restriction (Sachdeo et al., 2019; Yohn et al., 2016). All but one article (Ekstrand et al. 2019) reported funding from Shire (now Takeda).

3.3. Risk of Bias within Studies

For the clinical studies, high quality ratings were given to RCT studies only. Study designs such as open-label, case report, and medical record review are inherently less robust than RCTs due to small sample size, lack of comparator, and lack of randomisation. Thus, study design was a common limitation resulting in a poorer quality score for the non-RCT studies. The overall preclinical study quality was determined to be moderate. This was due to unblinded outcomes and variability among studies in reporting of sample size calculations, randomisation, and lack of reporting of animals excluded from the analysis.

3.4. Study Findings

To answer the questions posed by this review, in the following sections we present data on the evidence of the efficacy of LDX for the treatment of BED from clinical studies in humans and any potential moderators of this effect that have been identified. These results are organised according to outcome measure (binge eating frequency, global binge eating symptoms, and body weight and food-intake related outcomes). We then present the data from preclinical studies that have examined the effects of LDX on measures of food intake in rodents. Here, we distinguish between effects on palatable food intake and effects on standard

laboratory chow intake to assess any selective effects of drug administration on different food types. A summary of the studies included in this narrative review are included in Table 1 and Table 2. We then present the results of two meta-analyses: one of the outcomes of the RCTs using change in binge-eating symptoms on validated questionnaires (i.e. BES, CGI, and YBOCS-BE) as the outcome and one of the results of the preclinical studies of the effects of LDX on food intake measures including a subgroup analysis of the effect of LDX on the intake of chow versus palatable food. Finally, we present the results of a narrative synthesis of data that are relevant to understanding the mechanisms of action that might underlie the effectiveness of LDX in treating BED.

3.4.1. Narrative Synthesis of the Efficacy of LDX for the Treatment of Binge-Eating Disorder

3.4.1.1. Clinical Studies

3.4.1.1.1. Binge Eating Frequency

In the five RCTs, binge eating frequency was measured in all but one study (McElroy et al., 2015c). McElroy et al. (2015b) reported a reduction in weekly binge-eating days per week and binge-eating episodes for 50 and 70mg LDX at treatment endpoint. Endpoint one and four-week binge-eating cessation was also reported following 50 and 70mg LDX. Similar results were observed by McElroy et al. (2016a), in which LDX reduced baseline binge-eating days per week and increased 4-week binge-eating cessation rates at treatment endpoint. Secondary analyses of these data reported by McElroy et al. (2016b) concluded that these changes in binge-eating episodes and days and cessation rates were also evident during treatment, in addition to at endpoint (McElroy et al., 2017). In the RCT phase, Hudson et al. (2017) reported a reduction in binge-eating days per week and a greater time to binge-eating relapse at treatment endpoint following LDX dosing. At treatment endpoint, Guerdjikova et al. (2016) found LDX reduced binge-eating days and episodes per week compared to baseline

but found no differences in 4-week cessation rates for LDX and placebo. During treatment, there was a trend for a reduction of binge-eating days/week, but this was not statistically significant (Guerdjikova et al., 2016). Notably, the Guerdjikova et al. (2016) study had a smaller sample size (N=50). The results of the RCTs indicate LDX is more effective than placebo in reducing binge-eating episodes and binge eating days and in increasing cessation rates from baseline to endpoint. Interestingly, the results of Guerdjikova et al. (2016) suggest that LDX may be more effective with longer use. Across the seven non-RCT studies (including the open-label phase of Hudson et al., 2017), LDX was shown to significantly reduce binge-eating days and episodes in two studies (Fleck et al., 2019; Hudson et al., 2017). The remaining studies reported only frequency data. In two case studies, Srivistava et al. (2019) did not measure binge eating frequency, while Brucar et al. (2018) reported that LDX reduced binge-eating episodes and induced cessation of binge eating. An analysis of 25 records showed LDX reduced binge eating frequency in 6 cases (Guerdjikova et al., 2019). One study investigating the effects of LDX in participants with Bulimia Nervosa found that the drug reduced combined binge/purge days per month from one month of treatment onward (Keshen et al., 2017). In an Open-Label, 12-Month Extension Safety and Tolerability study, Gasior et al. (2017) reported a reduction in binge-eating days for the previous 28 days at the end of 52 weeks of LDX treatment in participants with BED.

3.4.1.1.2. Global Binge-Eating Symptoms

A range of global BED symptom measures were used across all RCTs. In studies that administered a version of the CGI (n=4), LDX improved BED symptoms at endpoint in three studies compared to placebo (Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a). Similarly, in studies that measured obsessive-compulsive BED symptoms via the YBOCS-BE (n=4), LDX reduced YBOCS-BE scores at treatment endpoint in three studies compared to placebo (McElroy et al., 2015b; McElroy et al., 2016a; Hudson et al., 2017).

Notably, an extension study investigating symptom changes over the course of treatment also confirmed improvements in symptoms following LDX administration using the CGI and YBOCS-BE during treatment (McElroy et al., 2017). However, Guerdjikova et al. (2016) reported LDX improved symptoms on the CGI, but not on the YBOCS-BE during treatment. Only two studies (McElroy et al., 2015b; McElroy et al., 2015c) reported BES data and both studies reported improvements in ratings following LDX treatment. Two non-RCT studies did not use validated BED symptom measures (Keshan et al., 2017; Guerdjikova et al., 2019). These studies reported percentage improvements in self-reported symptoms in most of the participants, but a worsening of symptoms after LDX treatment in 2 of 25 cases (Guerdjikova et al., 2019). The results of Brucar et al. (2018) did not include a symptom improvement outcome. Fleck et al. (2019) reported that LDX improved BED symptoms using the CGI, YBOCS-BE, and BES. Gasior et al. (2017) reported a percentage improvement in symptoms on the CGI following LDX treatment. In the open-label phase, Hudson et al. (2017) reported an improvement in CGI scores following LDX treatment. Finally, LDX numerically improved BES scores in a paediatric case study (Srivastava et al., 2019).

3.4.1.1.3. Body weight and food-intake related outcomes

Across the five RCTs, LDX reduced weight/BMI compared to placebo (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a; McElroy et al., 2015c). Weight was also reduced in a majority of the non-RCT studies (Gasior et al., 2017; Srivastava et al., 2019; Hudson et al., 2017; Fleck et al., 2019). However, one study found no reduction in BMI following LDX treatment (Guerdjikova et al., 2019). In five participants with Bulimia Nervosa, weight gain was reported in one case following LDX treatment (Keshen et al., 2017). LDX also reduced triglyceride levels (McElroy et al., 2016a; McElroy et al., 2015c) and cholesterol levels (McElroy et al., 2015c) at study endpoints. During treatment, Guerdjikova et al. (2016) reported a reduction in weight and triglyceride levels

following LDX treatment but no differences on measures of cholesterol, glucose, insulin, and HbA1c. In measurements of general eating pathology, LDX reduced food cravings (Srivastava et al., 2019), food sneaking (Guerdjikova et al., 2019), disordered eating (Gasior et al., 2017), stress-triggered binge eating (Guerdjikova et al., 2019), and reaction time on an emotional eating cognitive task (Fleck et al., 2019). However, two studies found LDX did not change self-reported food cravings (Guerdjikova et al., 2016; McElroy et al., 2015c). Conflicting results were found on measures of eating disinhibition and eating restraint with one study reporting improvement following LDX (McElroy et al., 2015b) and the other reporting no change (Guerdjikova et al., 2016).

3.4.1.1.4. Moderators of LDX Effects

No studies formally analysed potential moderators of the relationship between LDX and BED improvement. Only one study (Kornstein et al., 2019) directly assessed sex/gender and age differences in the effects of LDX using previously published RCT data (McElroy et al., 2016b). These authors found that neither sex/gender nor age (18-40 years versus ≥ 40 years) moderated the effects of LDX on binge eating frequency or BED symptoms (CGI and YBOCS-BE). Paediatric participants were generally responsive to treatment with LDX as indicated by improved symptoms and greater weight loss (Srivastava et al., 2019; Guerdjikova et al., 2019). However, as noted previously, two participants had a worsening of symptoms and in four cases there were no changes in BED symptoms with LDX treatment (Guerdjikova et al., 2019).

3.4.1.2. Preclinical Studies

3.4.1.2.1. Food Intake

The first study to assess the effects of LDX in a rat model of binge eating reported 7 assessments where LDX was compared with a vehicle control condition (Vickers et al.,

2015). In one cohort of rats, the effects of a range of LDX doses on food intake in a 2-hour binge session and over 24 hours was assessed. In the binge session, LDX reduced chocolate but not chow intake and reduced total food intake over 24 hours (chow intake plus chocolate consumption in the binge-eating session). In another cohort of rats, the pharmacological characteristics of the actions of LDX on binge-eating behaviour were investigated using selective dopamine receptor and adrenoceptor antagonists. The antagonist effects are discussed below in the section on pharmacological mechanisms (Vickers et al., 2015). Four comparisons in this cohort between LDX and vehicle only showed that LDX reduced chocolate intake in 2/2 comparisons and reduced chow intake in 1/2 comparisons. Another article from the same group using a food reward/punished responding conflict model of binge eating reported that LDX reduced intake of chocolate in the conflict test and reduced intake of chow in the home cage in both binge eating and non-binge eating female rats (Heal et al., 2016). Two studies examined the effect of LDX on effortful responding for palatable pellets (progressive ratio lever responding) versus freely accessible chow in either a binge-like eating model (Presby et al., 2020) or in food restricted rats (Yohn et al., 2016). Free intake of chocolate and chow (when presented as a choice) was also examined. In the binge-eating model, rats were either pre-exposed to chocolate (binge-like model), pre-exposed to lab chow, or had no pre-exposure (control groups). Free intake of chow and chocolate decreased after LDX administration in the chocolate exposed group, and chow was decreased in the group that only had access to chow (chow pre-exposed group). Lever pressing for chocolate was reduced in both the LDX and combined control groups (chow pre-exposed group and no-exposure group), and chow intake was also reduced in the chocolate exposure group. There was no reduction of chow intake in the control group, but levels of chow intake were low and so floor effects may have been evident. In contrast, using a similar paradigm, Yohn et al. (2016) found that LDX had no effect on intake of pellets or of chow for one reported set of

comparisons and increased responding for pellets while decreasing chow intake for another comparison. No effects of LDX (either acute or chronic dosing) were observed in groups of transgenic mice that were subjected to different feeding regimes (bingeing or restricting and their combination) (Sachdeo et al. 2019). Finally, a study by Ekstrand and colleagues (2019) assessed the effect of chronic dosing with LDX on performance in a spatial working memory task and also measured home cage intake of chow. These authors reported that body weight, but not chow intake, was reduced significantly by LDX during the drug treatment period (20 days).

3.4.1.2.2. Body weight

Heal et al. (2016) and Vickers et al. (2015) reported no changes in weight with LDX treatment, while Ekstrand et al. (2019) reported that LDX-treated rats weighed less than vehicle-treated rats at endpoint. Further, LDX-treated rats also had lower renal and mesenteric adiposity scores, as well as less epididymal fat mass (Ekstrand et al., 2019). Notably, the studies that reported no effect of LDX on body weight were acute designs where weight loss would not be expected in such a short duration of drug treatment (Heal et al., 2016; Vickers et al., 2015), whereas Ekstrand et al. (2019) used a chronic dosing design.

3.5. Meta-Analysis Results

3.5.1 Clinical studies

There were five RCTs, but one study did not report the means and standard deviations for binge-eating symptom outcome (McElroy et al., 2015c). All RCTs utilised a placebo-controlled design to assess acute treatment efficacy, but Hudson et al. (2017) randomly assigned participants to placebo or LDX after responding to an open-label phase of treatment to measure relapse-prevention efficacy as opposed to acute treatment efficacy. Given that McElroy et al. (2016a) reported the results of two RCTs separately, these two data sets were

also treated separately in the current meta-analysis. Thus, three articles and four data sets were eligible for inclusion in the meta-analysis (Guerdjikova et al., 2016; McElroy et al., 2015b; McElroy et al., 2016a). All the RCTs were affiliated with the drug manufacturer, Shire (now Takeda). The meta-analysis revealed an overall significant effect of LDX on binge-eating symptom change (Z = 9.51; $P < 0.001$; SMD = 0.93, 95% CI: 0.74, 1.12; Figure 2). The forest plot suggests that LDX improved binge-eating symptoms compared to placebo. A low level of heterogeneity was detected ($I^2 = 38\%$). This heterogeneity is likely explained by the variability in doses (ranging from 30-70mg LDX) and the scales used for binge-eating symptom measurements, which were the Clinical Global Improvement (Guerdjikova et al., 2016), Binge Eating Scale (McElroy et al., 2015b), or the Yale-Brown Obsessive Compulsive Scale – Binge Eating (Hudson et al., 2017; McElroy et al., 2016a). A visual inspection of the funnel plot (Figure 3) shows overall symmetry suggesting there was no publication bias.

Figure 2: Forest Plot of Binge-Eating Symptoms in Clinical Studies

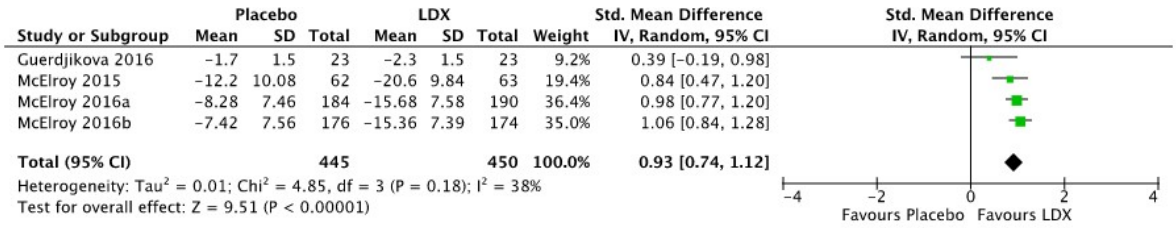
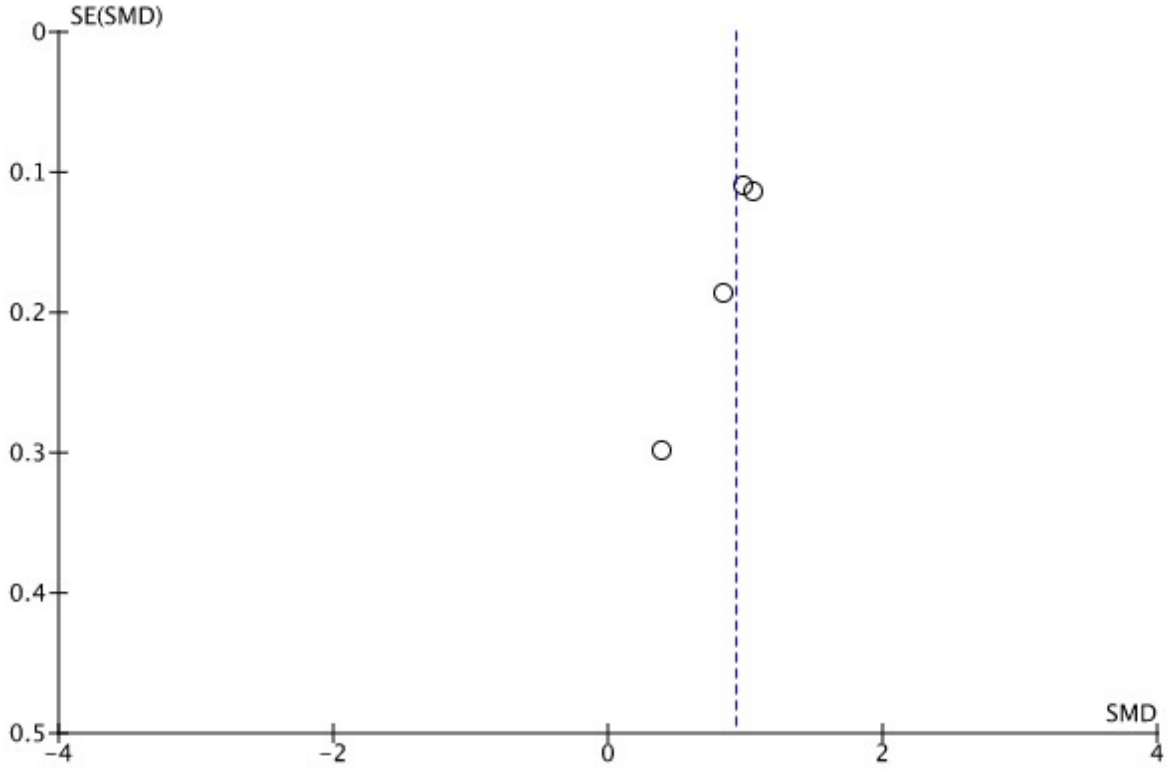


Figure 3: Funnel Plot of Binge-Eating Symptoms in Clinical Studies



3.5.2. Preclinical studies

Six preclinical articles (Ekstrand et al., 2019; Heal et al., 2016; Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2015; Yohn et al., 2016) reporting 46 LDX-vehicle comparisons were pooled for analysis of the effects of LDX on food intake (the Vickers et al., 2017 delay discounting article was excluded, see above). Subgroup analyses of chow and palatable food intake (i.e., chocolate, shortening, high-carbohydrate pellets) were performed to identify potential differential effects of LDX on food types. Given that the majority of eligible comparisons (24/46) are extracted from the Sachdeo et al. (2019) article, which is the only study that tested mice, two separate preclinical meta-analyses (with and without the Sachdeo et al. 2019 data sets) were performed to control for homogeneity within published data.

The results from the first preclinical meta-analysis (excluding the Sachdeo et al., 2019 data sets) revealed an overall significant effect of LDX on food intake ($Z = 6.10$; $P < 0.01$; SMD = 0.87, 95% CI: 0.59, 1.15; Figure 4), indicating LDX reduces food intake compared to vehicle.

A high level of heterogeneity was detected across comparisons (I^2 = 64%). Pooled analysis of chow intake revealed a significant effect of LDX (Z = 7.07; *P* < 0.01; SMD = 0.76, 95% CI: 0.55, 0.98; Figure 4), suggesting LDX reduces chow intake. Heterogeneity was low across comparisons (I^2 = 0%). The reduction of palatable food intake by LDX was also significant (Z = 3.25; *P* = 0.001; SMD = 1.04, 95% CI: 0.41, 1.66; Figure 4). A high level of heterogeneity was detected across comparisons (I^2 = 82%). The test for subgroup differences revealed no significant difference between the effects of LDX on chow intake and palatable food intake (χ_2 = 0.65, P = 0.42) with a low level of heterogeneity across subgroups (I^2 = 0%). The high heterogeneity detected within the palatable food intake data sets likely reflects differences in preclinical models (binge-eating and non-binge-eating models), LDX doses, palatable food types (chocolate, shortening, and high-carbohydrate pellets), and quantitative measures of chocolate intake (grams, kilojoules, and lever presses). Determining the source of the heterogeneity through subgroup analyses was not feasible due to the small sample size. Inspection of the funnel plot (Figure 5) revealed approximate symmetry suggesting low risk of publication bias.

Figure 4: Forest Plot of Preclinical Food Intake Data

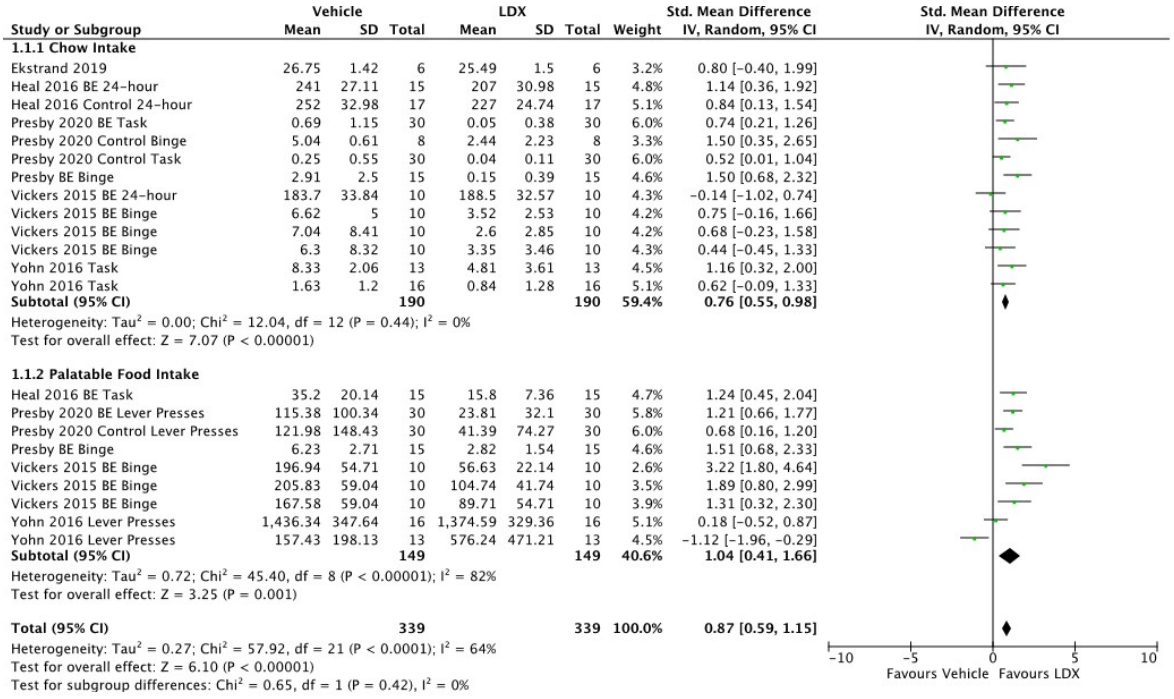
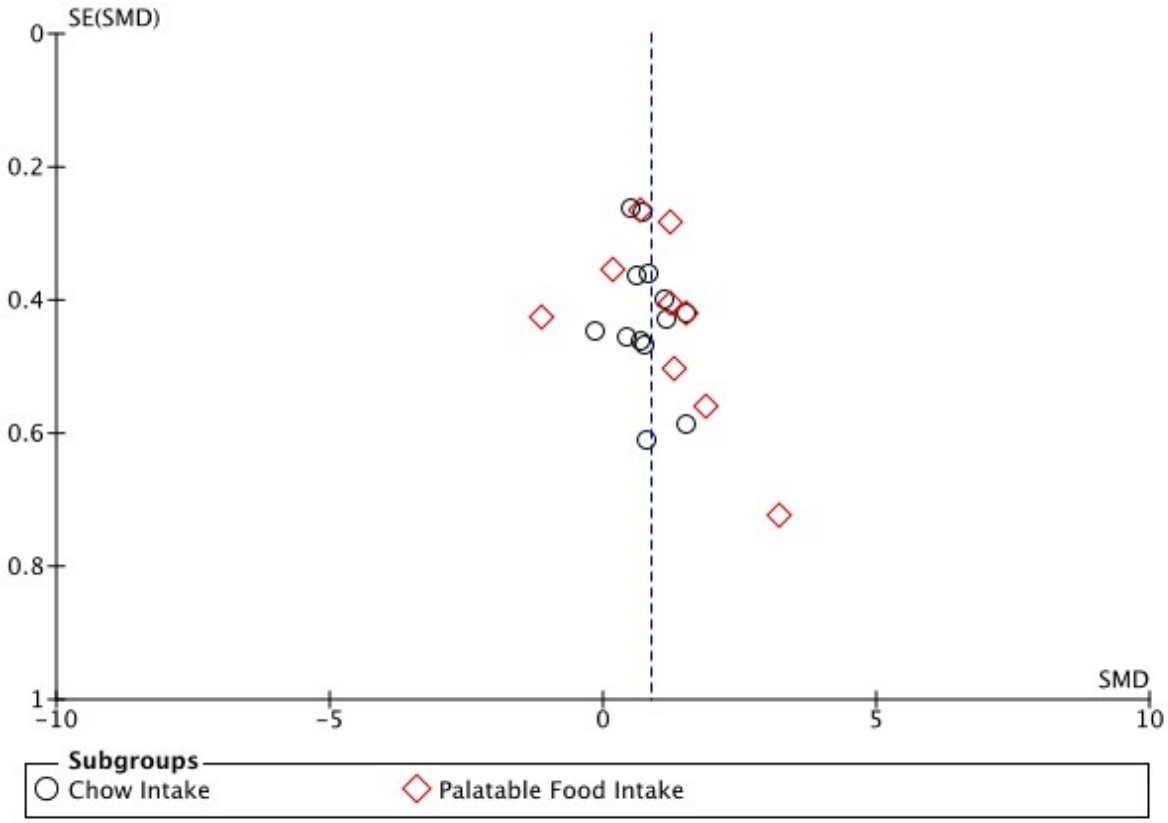


Figure 4. Data label presented as: author, year, rodent model (i.e., control or binge eating (BE)), intake session (i.e., binge or 24-hours) or task.

Figure 5: Funnel Plot of Preclinical Food Intake Data



Analysis of all eligible preclinical comparisons (with Sachdeo et al., 2019 data sets included) revealed a similar pattern, whereby LDX reduced food intake compared to vehicle (Z = 4.55; $P < 0.01$; SMD = 0.47, 95% CI: 0.27, 0.67; Figure 6). A moderate-high level of heterogeneity was detected across comparisons ($I^2 = 58\%$). Pooled analysis of chow intake revealed a significant effect of LDX (Z = 4.45; $P < 0.01$; SMD = 0.45, 95% CI: 0.25, 0.65; Figure 6), suggesting LDX reduces chow intake. Heterogeneity was low across comparisons ($I^2 = 31\%$). The reduction of palatable food intake by LDX was also significant (Z = 2.43; $P = 0.02$; SMD = 0.54, 95% CI: 0.10, 0.97; Figure 6). A high level of heterogeneity was detected across comparisons ($I^2 = 76\%$). The test for subgroup differences revealed no significant difference between the effects of LDX on chow intake and palatable food intake ($\chi_2 = 0.12$, P = 0.73) with a low level of heterogeneity across subgroups ($I^2 = 0\%$). Inspection of the funnel plot (Figure 7) revealed approximate symmetry suggesting low risk of publication bias.

Figure 6: Forest Plot of All Eligible Preclinical Comparisons

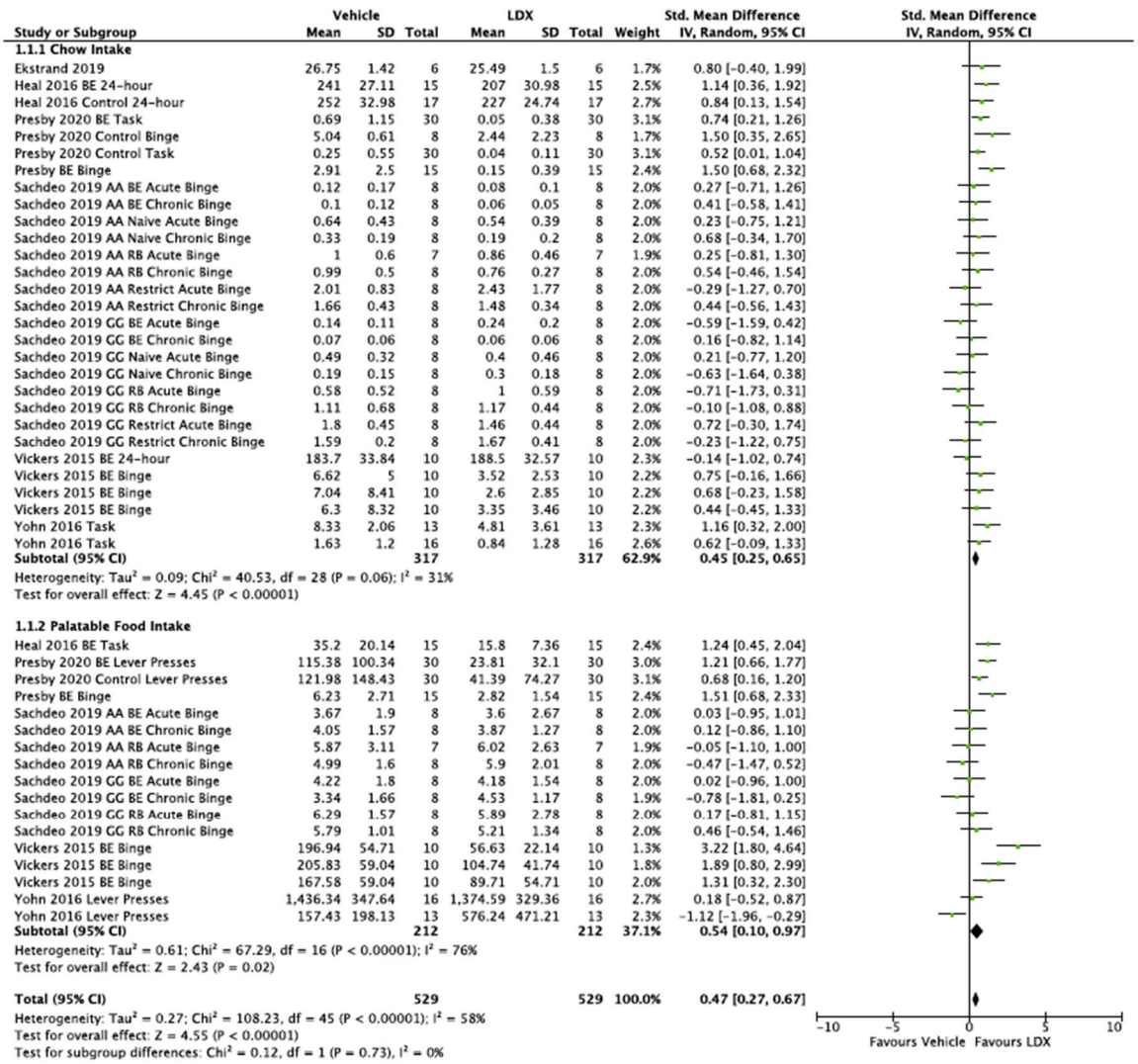
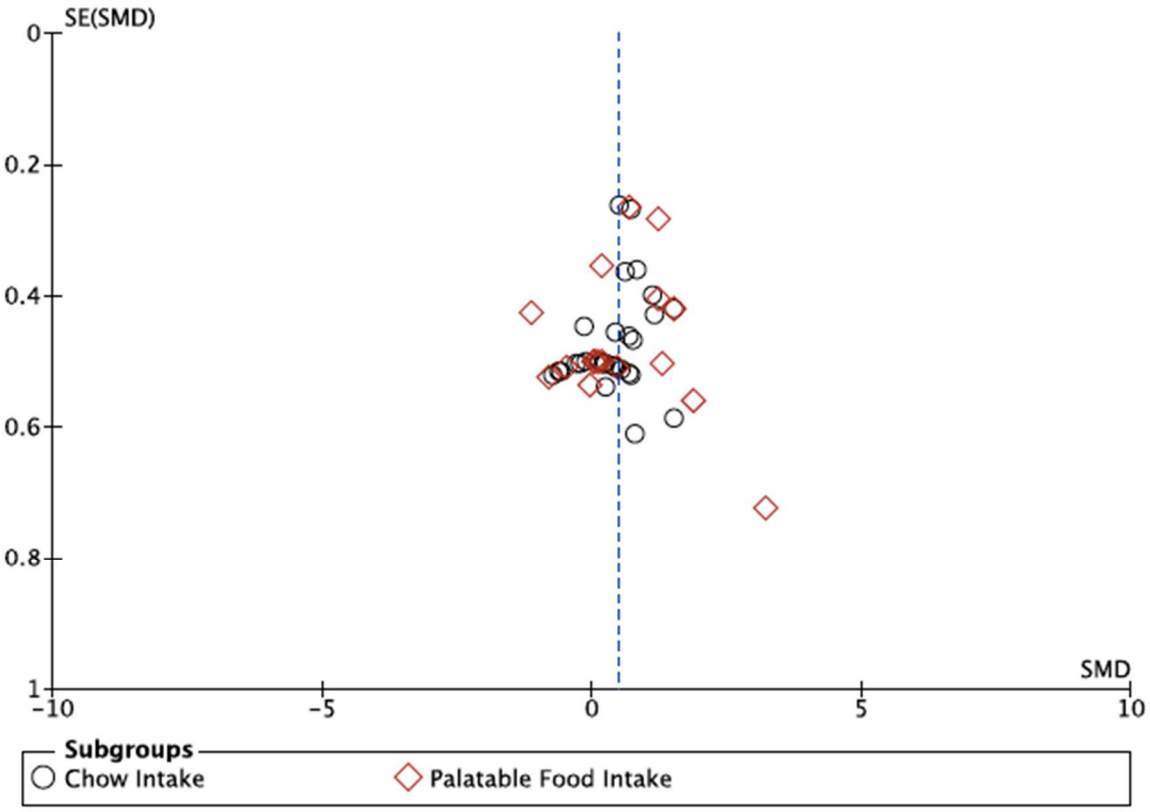


Figure 6. Data label presented as: author, year, genotype (i.e., AA or GG) where relevant, rodent model (i.e., control/naïve, binge eating (BE), restrict binge (RB), restrict), dosing regimen (i.e., acute or chronic) where relevant, intake session (i.e., binge or 24-hours) or task.

Figure 7: Funnel Plot of All Eligible Preclinical Comparisons



3.6. Mechanisms of Action of LDX in the Treatment of Binge-Eating Disorder

3.6.1. Pharmacological mechanisms

One preclinical study has reported data relevant to understanding the pharmacological mechanisms underlying the effects of LDX on binge eating (Vickers et al., 2015). In this study, the dopamine D_1 receptor antagonist SCH-23390, the dopamine D_2 receptor antagonist raclopride, the α_1 adrenoceptor antagonist prazosin, and the α_2 adrenoceptor antagonist RX821002 were co-administered with LDX (except for SCH-23390 which was given 45 minutes after LDX due to its short half-life in rats). LDX decreased chocolate intake across 4 phases of the antagonist assessment. Prazosin partially reversed the effects of LDX on chocolate intake. There was also evidence to suggest that SCH-23390 may partially attenuate the effects of LDX on chocolate intake at the lowest dose administered. Thus, chocolate

intake in the LDX/ SCH-23390 condition was not significantly less than that of the control group but was also not significantly greater than the LDX/vehicle group. Raclopride, and RX821002 had no effect on the ability of LDX to decrease chocolate intake. Neither prazosin nor SCH-23390 reversed the reduction in chow intake after LDX administration. These results suggest that LDX may reduce chocolate binge eating via enhanced transmission at α_1 adrenoceptors and possibly dopamine D_1 receptors.

3.6.2. Behavioural mechanisms

3.6.2.1. Drug-induced adverse effects

Common side effects of treatment with LDX such as nausea, constipation, and diarrhoea have been reported to reduce food intake and so could explain at least in part its effect on binge eating (Crozier et al., 2017; Islam et al., 2008). In the three RCTs that reported an overall percentage of treatment-emergent adverse events (TEAE), percentages of participants experiencing any TEAE ranged from 23.5% (Hudson et al., 2017) to 67.75% (McElroy et al., 2016a) and 84.7% (McElroy et al., 2015b). A list of all TEAEs reported in the RCTs can be found in Table 1. Symptoms such as dry mouth (range 5.1-38%), nausea (range 4.4-18%), diarrhoea (range 1.5-16%), and constipation (range 0-7.1%) were reported by participants across all RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a; McElroy et al., 2015c). Reductions in food intake can also be brought about by changes in mood or stress (Kazes et al., 1993; Oliver & Wardle, 1999). Two studies reported no effect of LDX on self-reported depression and anxiety (Fleck et al., 2019; McElroy et al., 2015c) whereas in other studies, LDX was reported to reduce self-reported depression (McElroy et al., 2015c), anxiety (Srivastava et al., 2019), stress-triggered binge eating (Guerdjikova et al., 2019), and stress (Srivastava et al., 2019) which suggests there are no consistent effects of the drug on mood and/or stress.

3.6.2.2. Appetite

A general reduction in hunger or enhanced satiety could contribute to the ability of LDX to attenuate binge eating. Across the five RCTs, LDX was found to decrease self-reported appetite in 0-21.4% of participants (reported as an adverse event), suggesting that up to a quarter of participants on LDX experienced a general reduction in appetite. In preclinical studies, LDX was also found to reduce standard chow intake in both bingeing and non-bingeing rats which suggests that the drug may have a general appetite suppressant effect (see Figure 4) (Heal et al., 2016; Presby et al., 2020).

3.6.2.3. Reward

Binge eating has been linked to increased reward sensitivity in BED (Schienle et al., 2009) and so LDX could attenuate binge eating via an effect on food reward responses. Two clinical studies reported brain neuroimaging data relevant to understanding mechanisms, and both reported some evidence that LDX reduces activity in brain areas associated with reward. However, both studies have limitations and therefore caution must be applied in interpreting the results. In a pilot Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) study, LDX significantly reduced activity in globus pallidus in response to viewing of a palatable food in the context of an attentional task. The authors also reported that changes in ventromedial prefrontal cortex (VMPFC) and thalamus activation were positively correlated with changes in binge scores (Fleck et al., 2019). However, this study had a small sample size, did not include a placebo group, and the obese control group had only a baseline scan and were not scanned at the study endpoint. In an EEG study, LDX treatment normalised neuronal activity in brain reward areas including the insular cortex, VMPFC, and orbitofrontal cortex (OFC) (Brucar et al., 2018). However, these results are derived from a single case study in which the subject was also prescribed sertraline, thus

limiting the conclusions that can be drawn. Two preclinical studies used an effort-based operant choice paradigm to assess whether LDX selectively reduces the willingness to work for a palatable food reward, which would be indicative of reduced reward value of the palatable food pellets (Presby et al., 2020; Yohn et al., 2016). In one study, LDX had a general effect to reduce food intake and food-reinforced operant behaviour (Presby et al., 2020), and in the second study LDX actually increased effort expended to lever press for palatable food and decreased concurrent intake of standard chow (Yohn et al., 2016).

3.6.2.4. Cognitive Functioning

It is possible that LDX decreases binge eating via a reduction in impulsive responding. BED has been associated with higher scores on measures of the tendency to act without thinking (motor impulsivity) and the tendency to act without regard for future consequences (non-planning impulsivity), and these impulsive traits may contribute to the onset or maintenance of binge eating (Nasser et al., 2004). Only one clinical study included a measure of impulsivity (McElroy et al., 2015b). In this RCT, LDX was reported to reduce total impulsivity on the Barratt Impulsiveness Scale (Version 11 (BIS-11; Patton et al., 1995)). Secondary analysis of the McElroy et al. (2015b) impulsivity results revealed that LDX dose dependently improved total impulsivity symptoms, motor impulsivity, and non-planning impulsivity on the BIS-11 (McElroy et al., 2016b).

The tendency to act without regard for future consequences can be modelled preclinically using the delay discounting task which involves a making a choice between a small immediate reward versus a larger delayed reward (Odum, 2011). The impulsive choice is to take the immediate reward and not the delayed reward. The effects of LDX on delay discounting in rats was assessed by Vickers et al. (2017). Binge-eating rats had greater intolerance of delayed rewards (were more impulsive) and LDX dose-dependently reversed

the reduced preference of binge-eating rats for larger delayed rewards but this shift to choice of a larger delayed reward did not translate into an increase in intake (Vickers et al., 2017). BED is also associated with compulsive responding, which is the tendency toward repetitive, habitual actions that are repeated despite adverse consequences (Robbins et al., 2012). In a study by Heal and colleagues (2016), rats were administered a shock after a conditioned stimulus (tone and light) to mimic binge eating despite negative consequences. LDX reduced compulsive and perseverative responding in this model (Heal et al., 2016). In line with this finding, LDX significantly reduced the obsessional and compulsive subscales score of the Yale–Brown obsessive compulsive scale modified for binge eating (Y-BOCS-BE) (McElroy et al., 2016a, 2016b). A reduction in impulsive responding may also have contributed to the ability of LDX to improve scores of eating restraint reported in one clinical study (McElroy et al., 2015b).

The ability to act in a self-controlled rather than impulsive or compulsive manner relies on cognitive processes such as working memory and attention which are associated with binge-like eating (Gisbert Cury et al., 2020; Kaisari et al., 2017; Kaisari et al., 2018). Accordingly, an action of LDX to improve these cognitive functions might also contribute to the efficacy of the drug in reducing binge-eating episodes. In clinical studies, LDX improved reaction time on an attention-demanding target detection task ("visual oddball" paradigm), potentially reflecting improvements in attention (Fleck et al., 2019) and self-reported focus (Srivastava et al., 2019). Finally, a preclinical study assessed the effect of the drug on spatial working memory and found that LDX-treated rats showed better performance than vehicle treated rats in the Morris Water Maze (Ekstrand et al., 2019).

4. Discussion

To the best of our knowledge, this is the first review and meta-analysis to systematically assess both the preclinical and clinical literature on the effects of LDX on BED and to investigate the potential therapeutic mechanism of action of the drug in treating the disorder. This review set out to address three questions: First, what are the strengths and limitations of the preclinical and clinical data on the use of LDX to treat BED; Second, what do the preclinical and clinical data reveal in terms of specificity of the effects of LDX in BED; Third, what is the current level of understanding of the behavioural and neuropharmacological mechanisms of action of LDX in treating BED.

With regard to the third question, it is relevant that LDX was initially approved by the regulatory authorities for the treatment of ADHD in children in 2007 and in adults in 2008. Subsequently, in 2015, the United States FDA approved a supplemental New Drug Application (NDA) to expand the approved uses of the drug to include treatment of BED in adults and, at present, LDX is the only approved drug in the United States for the treatment of BED. As the drug was approved for use in BED on the basis of a supplemental NDA, it had an accelerated development path to approval and thus there are limited data on the mechanism of action of LDX in treating the disorder.

Fourteen clinical articles were identified and included in this review, and the overall evidence suggests that LDX is an effective treatment for BED which is consistent with the previous findings of a systematic review (Citrome, 2015) and an exploratory meta-analysis of three RCTs (Fornaro et al. 2016). Five of the clinical studies in this review were RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b, 2015c; McElroy et al., 2016a) which included 1349 participants who had a clinical diagnosis of BED across 175 sites in North America and Europe. In non-RCTs, data were collected from a total of 1081 participants across 141 sites. Study quality for the RCTs was high and for the non-RCTs was moderate or poor due to limitations of small sample size, lack of comparator, and lack of

randomisation. In all but one of the RCTs, binge-eating frequency was the key outcome measure reported (weekly binge-eating days per week and binge-eating episodes), and LDX was consistently effective in improving binge-eating symptoms. In two of the non-RCTs, LDX was also reported to significantly reduce binge-eating days and binge-eating episodes (Fleck et al., 2019; Hudson et al., 2017). The RCTs used a range of BED symptom measures, and improvements in CGI and obsessive-compulsive symptoms after LDX were reported in three of four studies (Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a).

Our meta-analysis of the four RCT data sets (Guerdjikova et al., 2016; McElroy et al., 2015b; McElroy et al., 2016a) showed an overall significant effect of LDX on binge-eating symptom change. Though, the results of Hudson et al. (2017) was excluded from the meta-analysis due to design differences (acute efficacy vs. relapse-prevention), the results from this study was commensurate with the other included RCTs in that LDX reduced BED symptomology. There was a low level of heterogeneity, due to variation in LDX dose and in the scales used for binge-eating symptom measurements, but no evidence of publication bias as indicated by symmetry of the funnel plot.

Body weight was reduced by LDX in all five RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a) and in the majority of non-RCTs (Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017; Srivastava et al., 2019). There were also reports of LDX-induced reductions in triglyceride and cholesterol levels although these changes were less consistent across studies (McElroy et al., 2016a; McElroy et al., 2015c; Guerdjikova et al., 2016). Similarly, there are reports in some studies of beneficial effects of LDX on food cravings (Srivastava et al., 2019), eating disinhibition, and eating restraint (McElroy et al., 2015b), but these reports are inconsistent and not replicated in other studies (Guerdjikova et al., 2016; McElroy et al., 2015c).

There is limited evidence on the role of potential moderators of the relationship between LDX and BED symptoms. The only study to assess the role of sex/gender and age reported that neither influenced the effects of LDX on BED symptoms (Kornstein et al., 2019).

Seven preclinical articles were identified and included in this review, and the overall evidence suggests that LDX decreases food intake in rodents. The preclinical study quality was moderate due to limitations of unblinded outcomes, reporting of sample size calculations, randomisation, and lack of reporting of animals excluded from analysis. Our meta-analysis of 46 comparisons of LDX and vehicle treatment from six articles showed a significant effect of LDX on food intake (Ekstrand et al., 2019; Heal et al., 2016; Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2015; Yohn et al., 2016). The seventh article (Vickers et al., 2017) was excluded from the meta-analysis as it reported on a delay discounting model in which a drug effect on consumption of chocolate reflects an action on impulsivity rather than on food intake. Five of the articles reported data from studies in rats and one article (Sachdeo et al. 2019) reported studies in transgenic mice with a mutation of the μ opioid receptor gene. As 52% of the eligible comparisons were from the Sachdeo et al. (2019) article, we were concerned that this could introduce bias in the results. Therefore, the meta-analysis was conducted on two separate occasions with and without the data from this article. LDX significantly reduced consumption of chow and palatable food in both meta-analyses with and without the comparisons from the Sachdeo et al. (2019) article. There was a low level of heterogeneity across chow intake comparisons but a high level of heterogeneity across palatable food intake comparisons and this pattern was evident in both meta-analyses. The high level of heterogeneity across palatable food intake comparisons is likely due to differences in preclinical models, food types, intake measures, and LDX dose used. Despite a previous report to the contrary (Vickers et al., 2015), there was no consistent evidence for a differential effect of LDX on the intake of chow and palatable food in either analysis which

has potential implications for understanding the mechanism of action of the drug in treating BED (see below). There was also no evidence of publication bias as indicated by symmetry of the funnel plot.

The preclinical data included in this review relied upon animal models of BED. In a review, Corwin et al. (2004) specify that valid preclinical models resembling binge-like eating in humans should include 1) repeated occurrences of behaviour over an extended period of time and 2) increased consumption of food in brief, discrete periods of time compared to controls. All of the binge-eating models included in this review demonstrated reliable increases in food intake over time and thus meet the criteria put forth by Corwin et al. (2004). The majority (Sachdeo et al., 2019; Vickers et al., 2015; Vickers et al., 2017) of the animal models induced binge eating by intermittent, irregular, and/or limited access to palatable foods to model the behavioural symptom of binge eating in humans. However, BED in humans is a complex disorder that includes behavioural symptoms such as binge eating in addition to psychoemotional symptoms such as embarrassment, guilt, and depression (American Psychiatric Association, 2013). To model binge eating despite adverse consequences observed in BED, Heal et al. (2016) utilised a reward/punishment conflict model in which rodents received a shock for accessing palatable food. Nonetheless, none of the models included in this review capture the full range of symptoms (e.g., negative affect) present in BED. As such, this review included preclinical data to elucidate mechanisms not otherwise gained in the available human studies in additional to clinical data to determine efficacy.

4.1. Mechanism of Action

4.1.1. Pharmacological mechanisms

LDX is a prodrug (a therapeutically inactive molecule) in which d-amphetamine is covalently bonded to L-lysine. After administration of LDX in humans and animals, the mechanism of drug delivery is cleavage of L-lysine by enzymatic hydrolysis in red blood cells to convert the prodrug to the active drug, d-amphetamine (Goodman, 2010). It is well established that d-amphetamine increases the in vivo release of catecholamines and serotonin in rodent brain (Kuroki et al., 1996; Philips et al., 1982). Similarly, in more recent microdialysis studies, LDX has been shown to increase the in vivo release of dopamine, noradrenaline, and serotonin in the prefrontal cortex (PFC) and striatum of rats (Rowley et al., 2012, 2014). The therapeutic effect of LDX and other stimulants in both BED and ADHD has been proposed to involve catecholamine neurotransmission in the PFC (Berridge et al., 2006; Fleck et al., 2019; Rowley et al., 2012, 2014), and BED has been associated with PFC dysfunction (Fleck et al., 2019; Karhunen et al., 2000; Schienle et al., 2009, see section below on reward). This hypothesis is supported by the results of catecholamine receptor antagonist studies in rats where the ability of LDX to decrease the consumption of chocolate was attenuated by the α_1 adrenoceptor antagonist prazosin and the dopamine D_1 receptor antagonist SCH-23390 (Vickers et al., 2015). The dopamine D_2 receptor antagonist raclopride and the α_2 adrenoceptor antagonist RX821002 had no effect suggesting that α_1 adrenoceptors and dopamine D_1 receptors may play an important role in mediating the effects of LDX on chocolate bingeing. As d-amphetamine and LDX also increase the in vivo release of serotonin in rat brain (Kuroki et al., 1996; Rowley et al., 2012, 2014), and given the well-established role of multiple 5-HT receptors in the control of appetite and obesity (Dourish, 1995; Dourish et al., 2008), it is possible that 5-HT receptor mechanisms may play a role in mediating the effects of LDX on binge eating. For example, 5-HT_{2C} receptors were identified over 25 years ago as a target for appetite suppressant drugs (Dourish, 1995), and in 2012 the selective 5-HT_{2C} receptor agonist lorcaserin was approved by the FDA to treat obesity.

Subsequently, the FDA requested that the drug be withdrawn from the market due to an increased occurrence of cancer in post-marketing safety trials (FDA, 2020). However, recent studies with another 5-HT_{2C} receptor agonist meta-chlorophenylpiperazine (mCPP) have provided evidence that 5-HT_{2C} receptor activation in humans reduces appetite in both hungry and satiated states and inhibits food reward-related responding (Thomas et al., 2014, 2018). Thus, mCPP decreased the consumption of palatable chocolate chip cookies eaten in the absence of hunger but had no significant effect on the consumption of a pasta lunch, although pasta eating rate was reduced (Thomas et al., 2018). In this study mCPP also decreased BOLD fMRI responses to the sight of food pictures in areas of reward-associated circuitry which is consistent with preclinical evidence for a role of 5-HT_{2C} receptors in drug reward (Fletcher et al., 2010; Higgins & Fletcher, 2003, 2015). Interestingly, lorcaserin was reported to decrease binge eating of high-fat food in rats and mice, an action which has been proposed to be mediated by a serotonin and dopamine neural reward circuit in the midbrain (Price et al., 2018; Xu et al., 2017). It has been proposed that patients with BED may consume excessive food at least in part due to disrupted satiety signals (Sysko et al., 2007), suggesting that a 5-HT_{2C} receptor agonist could decrease food intake during a binge-eating episode by enhancing satiety. In addition, in BED palatable foods may be more rewarding, and patients can exhibit greater motivation to consume these foods compared to healthy individuals (Dalton et al., 2013; Finlayson et al., 2011; Schebendach et al., 2013). 5-HT_{2C} receptor activation attenuates reward-related behaviours such as drug-seeking and drug-taking (Fletcher et al., 2010; Higgins & Fletcher, 2003, 2015) and may therefore decrease palatable food intake by restoring normal reward-related behaviour (Thomas et al., 2018). Thus, it has been suggested (Price et al., 2018) that selective 5-HT_{2C} receptor agonists could be effective in treating BED but to date no clinical trials have been reported. Similarly, to the best of our knowledge, there have been no 5-HT receptor antagonist studies conducted to investigate the

potential contribution of LDX-induced serotonin release to the therapeutic actions of the drug in BED.

4.1.2. Behavioural mechanisms

LDX is a psychostimulant in animals and humans but its stimulant effects are less pronounced than those of d-amphetamine which is thought to be due to the pharmacokinetic profile of the drug (Ermer et al., 2016; Hutson et al., 2014; Jasinski & Krishnan, 2009a, 2009b). In RCTs, LDX was reported to cause nausea, diarrhoea, and constipation (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a). As adverse gastrointestinal effects and stimulant effects have been reported to reduce food intake (Crozier et al., 2017; Islam et al., 2008; Rasmussen, 2015), it is conceivable that the therapeutic effects of LDX in treating BED are secondary to these actions of the drug. This appears unlikely given the low incidence of gastrointestinal side-effects in RCTs with LDX and its weak stimulant properties in humans (Guerdjikova et al., 2016; Hudson et al., 2017b; Jasinski and Krishnan, 2009a, 2009b; McElroy et al., 2015b; McElroy et al., 2016a).

LDX has effects on appetite/satiety, reward and cognitive processes and it is possible that the therapeutic action of the drug in treating BED may involve one of more of these actions.

4.1.3. Appetite and Satiety

LDX reduced body weight in all five RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a) and in a majority of the non-RCT studies (Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017; Srivastava et al., 2019), indicating a pronounced suppressant effect of the drug on food consumption although this was not measured directly in any of the studies. Furthermore, in the five RCTs up to a quarter of patients reported reduced appetite although this could not be included in the meta-analysis as it was not quantified and reported only as an adverse event. Interestingly, a low daily dose

of 30 mg LDX did not significantly reduce binge-eating frequency but produced a significant decrease in body weight compared to placebo (McElroy et al., 2016a) suggesting that an appetite suppressant effect of the drug may be apparent at a dose that is subthreshold for treating BED. In a recent study, an acute dose of 50 mg LDX reduced the consumption of both a pasta lunch (eaten when hungry) and a cookie snack (eaten after lunch when satiated) in women with binge eating symptoms (Schneider et al., 2021). LDX also reduced appetite, had a greater effect on cookie intake than pasta intake, and decreased the eating rate for pasta but not for cookies (Schneider et al., 2021). It is conceivable that in BED patients a low 30 mg dose of LDX could reduce food intake by suppressing appetite or enhancing satiety and higher (50 and 70 mg) doses of the drug may have a dual suppressant effect on food intake and binge-eating frequency.

In preclinical studies, there is one report (Vickers et al., 2015) using a rat binge-eating model that LDX dose-dependently and preferentially reduced the consumption of chocolate compared to standard chow. However, our meta-analyses of 46 comparisons of LDX and vehicle treatment from six articles showed that LDX significantly reduced consumption of both chow and palatable food and overall, there was there was no evidence for a preferential effect of the drug on the intake of palatable food. This is consistent with a previous suggestion (Presby et al., 2020) that LDX has a general appetite suppressant effect in rats.

4.1.4. Reward

An extensive body of evidence indicates that brain dopamine, noradrenaline, and serotonin neuronal pathways play an important role in the mediation of food reward processes (Fallon et al., 2007; Fletcher et al., 2010; Higgins et al., 2003; Volkow et al., 2011). Further, the results of neuroimaging studies using Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), and BOLD fMRI have identified that sensitivity

to both monetary and food reward may be altered in BED (Balodis et al., 2013a; Bodell et al., 2018; Fleck et al., 2019; Geliebter et al., 2016; Karhunen et al., 2000; Lee et al., 2017; Schienle et al., 2009; Wang et al., 2011). Thus, BED patients had decreased BOLD fMRI responses in ventral striatum during anticipatory reward/loss processing in a monetary reward/loss task compared to obese controls (Balodis et al., 2013a). Similarly, in adolescent girls, VMPFC and caudate BOLD fMRI responses to winning money were correlated with greater severity of binge eating (Bodell et al., 2018). PET scans using the dopamine receptor antagonist radioligand [^{11}C]raclopride showed that food stimuli combined with methylphenidate, a structurally related stimulant which like LDX is also used to treat ADHD (Faraone, 2018), increased dopamine release in the caudate of participants with BED compared to controls, and the dopamine release correlated with binge eating symptoms (Wang et al., 2011). Similarly, food pictures elicited a greater increase in cerebral blood flow (measured by 99mTc ethyl cysteinate dimer SPECT) in the left frontal and prefrontal cortex of patients with BED compared to controls (Karhunen et al., 2000). Further, BED patients had stronger BOLD fMRI responses in ventral striatum, medial OFC, and ventral prefrontal cortex (VPFC) to viewing food pictures than controls or patients with bulimia nervosa (Lee et al., 2017; Schienle et al., 2009). Geliebter and colleagues (2016) reported increased anterior cingulate cortex (ACC) activation and connectivity in response to visual and auditory high-calorie food cues in BED patients compared to controls. In addition, patients with BED displayed a tendency towards generalised BOLD fMRI over-activation throughout the brain compared to controls when viewing pictures of palatable food which reached statistical significance in VLPFC, striatum, and globus pallidus (Fleck et al., 2019). Taken together, these data suggest that patients with BED may be supersensitive to food stimuli as indicated by their neuroimaging responses to food cues in regions of the brain that mediate reward processing.

As LDX increases the in vivo release of dopamine, noradrenaline, and serotonin in the cortex and striatum of rodent brain (Rowley et al., 2012, 2014), it is plausible that the therapeutic efficacy of the drug in treating BED could be mediated at least in part by an action on brain reward mechanisms to attenuate hypersensitivity to food stimuli. There is some limited evidence to support this hypothesis from recent fMRI and EEG studies with LDX. In an fMRI study, where BED patients displayed stronger BOLD activations than controls in VLPFC, striatum, and globus pallidus to viewing pictures of palatable food, 12 weeks of treatment with LDX significantly reduced the hyperactivation in globus pallidus but not in VLPFC and striatum (Fleck et al., 2019). Thus, it has been proposed that the globus pallidus could play a crucial role in the functional neuropathogenesis of BED (Fleck et al., 2019) and by implication the efficacy of LDX in treating the disorder. Exploratory analysis of change scores after LDX indicated that changes in VMPFC activation positively correlated with changes on the binge eating scale and changes in thalamus activation were positively correlated with changes on the YBOCS-BE (Fleck et al., 2019). Fleck and colleagues (2019) interpret these correlational results as support for the hypothesis that the ventromedial reward circuit including VMPFC, subgenual ACC, and thalamus is of primary importance in BED and its treatment with LDX. A potential role of the ventromedial reward circuit in mediating the therapeutic action of LDX in BED is also supported by preliminary results of an EEG study. Thus, in a patient with a long history of BED, treatment with LDX prevented binge eating and this action was associated with normalised neuronal activity in brain reward areas including the insular cortex, VMPFC, and OFC (Brucar et al., 2018).

However, both of these studies have limitations that restrict the extent of the conclusions that can be drawn from the results. Fleck et al. (2019) is a pilot study which did not include a placebo treated group or a scan of the control group with obesity at the study endpoint, and

Brucar et al. (2018) is a case report in which the patient was also prescribed the antidepressant drug sertraline in addition to LDX.

There is little preclinical evidence for the efficacy of LDX in treating BED being mediated by an action on brain reward mechanisms. As discussed above in relation to appetite, there is one report that LDX preferentially reduced the consumption of chocolate compared to standard chow in rats (Vickers et al., 2015). In contrast, in an effort-based operant choice paradigm to assess the willingness of rats to work for a palatable food reward, LDX either had a general effect to reduce food intake (Presby et al., 2020) or increased effort to lever press for palatable food and decreased intake of standard chow (Yohn et al., 2016). Similarly, our meta-analyses of preclinical data provided no evidence for a preferential reduction of palatable food consumption by LDX.

4.1.5. Cognitive Processes

BED has been described as an impulse control disorder since one of the key symptoms of the disorder is a lack of control over eating (American Psychiatric Association, 2013) and it is possible that LDX may be effective in treating BED at least in part by reducing impulsivity, compulsivity, and the repetitive nature of binge eating. There is extensive evidence that loss of impulse control in BED is a causal factor in provoking bingeing symptoms (Colles et al., 2008; Galanti et al., 2007; Giel et al., 2017; McElroy et al., 2016a; Nasser et al., 2004; Schag et al., 2013). More specifically, BED is associated with motor impulsivity and non-planning impulsivity which could initiate and maintain binge eating (Nasser et al., 2004). Neuroimaging studies using the Stroop task to measure impulse control have shown that BED patients have decreased BOLD fMRI activity in brain areas involved in self-regulation and impulse control including VMPFC, inferior frontal gyrus (IFG), and insula during performance of the task compared to lean and obese controls (Balodis et al., 2013b). Further,

dietary restraint scores were reported to be negatively correlated with IFG and VMPFC activation in BED patients (Balodis et al., 2013b).

Clinical reports on the effects of LDX on impulsivity in BED patients are limited to a single clinical trial in which a reduction was reported in total impulsivity (McElroy et al., 2015b). Secondary analysis of these data indicated that LDX improved total impulsivity, motor impulsivity, and non-planning impulsivity compared with placebo (McElroy et al., 2016b). Similarly, LDX significantly reduced the obsessional and compulsive subscales score of the Y-BOCS-BE (McElroy et al., 2016b).

The role of impulse control in BED has been investigated in both clinical and preclinical studies using the delay discounting task which measures the discounting of the value of a reward based on how quickly a reward loses its value over time. An inability to delay gratification will result in preference for a small immediate reward relative to a larger delayed reward (MacKillop et al., 2011). BED patients display enhanced delay discounting compared to controls (Davis et al., 2010; Mole et al., 2015). Similarly, binge-eating rats exhibit greater intolerance of delayed rewards and delay discounting in rats has been used as a preclinical model of BED (Vickers et al., 2017). LDX reversed the reduced preference of binge-eating rats for larger rewards at increasingly longer delays (Vickers et al., 2017), a finding that is consistent with the ability of the drug to decrease impulsiveness in patients with BED (McElroy et al., 2015b, 2016a). The finding that LDX treated binge-eating rats did not differ significantly from either the vehicle-treated, non-binge-eating controls, or vehicle-treated, binge-eating rats in intake of chocolate pellets suggests that there may have been some additional effects of LDX on appetite to reduce overall responding for pellets. Alternatively, the doses at which LDX reduce impulsive responding may be lower than those that have significant effects on appetite and further work is required to test this possibility.

A modified rat shuttle box conditioned avoidance model has been used to explore the effects of LDX on the compulsive and preservative nature of binge eating (Heal et al., 2016). In this model, rats are trained to avoid one compartment of a shuttle box by the administration of foot shock preceded by a conditioned stimulus. When the rats are trained to avoid the shock associated compartment, a conflict is introduced by placing chocolate in this compartment. Binge-eating rats spend a greater proportion of their time in the compartment associated with the negative stimuli, eating more chocolate and receiving more foot shocks than controls as a result. LDX significantly decreased the consumption of chocolate and the compulsive and repetitive responding in the model (Heal et al., 2016).

The role of cognitive processes in mediating BED has largely focussed on the importance of impulsivity and compulsivity in the disorder. However, recent evidence suggests that attentional processes, more specifically inattention, may play an important role in binge eating associated with ADHD (Kaisari et al., 2017, 2018). LDX is approved to treat both ADHD and BED, and it is concievable that an action on attentional processes could contibute to the efficacy of the drug in treating BED and binge eating associated with ADHD. There is limited evidence to date from clinical studies on the effects of LDX on attention in BED. In a visual oddball task that engages the attentional sytem, LDX improved performance of patients with BED (Fleck et al., 2019). Further, a case report of an adolescent patient with BED described improved focus on school-work and other tasks (Srivastava et al., 2019). Finally, in a recent laboratory study using a measure of sustained attention, LDX reduced commission errors in women with binge-eating symptoms (Schneider et al., 2021). These results suggest that the efficacy of LDX in treating BED could be related in part to actions of the drug to increase cognitive control but further studies are needed to test this hypothesis.

4.2. Strengths and limitations of this systematic review and meta-analysis

This systematic review and meta-analysis has a number of strengths and some limitations. This is the first systematic review of LXD and BED to include both clinical and preclinical studies, and the first review to consider the mechanism of action of LDX in treating the disorder. This is also the first meta-analysis of the results of studies on LDX and BED, and the results of both clinical and preclinical studies are included in the meta-analyses. There are limitations which require the results of this review and meta-analysis to be interpreted with some caution. The number of articles included in the review is relatively small, 14 clinical studies and 7 preclinical articles. Similarly, the number of data sets used in the clinical meta-analysis was small comprising 4 data sets from RCTs reported in 3 articles and the data were collected by a relatively small number of research groups. The preclinical meta-analysis comprised 46 comparisons of LDX and vehicle treatment but these were obtained from a relatively small number of articles and 24 of these comparisons were from a single article. There was also a relatively small number of studies on the mechanism of action of LDX in treating BED that could be included in the review. There may be a language and a publication bias as the search was limited to studies written and published in the English language.

4.3. Clinical Implications

The results of this review and meta-analysis confirm that LDX is an effective treatment for BED and that the drug reduces both the BED symptoms and the body weight of patients with the disorder. Patients with BED can present as underweight, healthy weight, overweight, or obese (Fairburn et al., 2000; Hudson et al., 2007). A WHO World Mental Health Survey on the prevalence of BED reported that 1.3% of patients were underweight, 31.7% were healthy weight, 30.7% were overweight, and 36.2% were obese (Kessler et al., 2013). Further, it has been proposed that underweight and healthy weight individuals may be a distinct subset of BED patients who exhibit greater usage of healthy and unhealthy weight control behaviours compared to overweight and obese BED patients (Goldschmidt et al., 2011). Therefore, given

the propensity of LDX to reduce body weight, the BMI of the patient on presentation is an important consideration when prescribing LDX to treat BED. None of the BED diagnostic criteria (American Psychiatric Association, 2013) reference body weight and the effectiveness of BED treatments is judged on enabling the patient to regain self-control and decrease the frequency and severity of binge eating symptoms. Therefore, it would be valuable for physicians to have a broad spectrum of drug therapy options available (including for example drugs that can treat BED symptoms without decreasing body weight) to treat patients with BED across a range of BMI categories. LDX is the only approved drug treatment for BED and is approved in only a limited number of countries. Thus, drug treatment options in some countries (such as the United States and Canada) are limited to one marketed drug and in many countries (including most countries in Europe) there is no approved drug therapy for the disorder. Further LDX, like the majority of other commonly prescribed drug treatments for BED, is a stimulant and a Schedule 2 controlled drug in the United States and the United Kingdom. Clearly, there is an urgent need to identify new drug treatment options for BED. An improved understanding of the pathogenesis of BED, and the mechanism of action of LDX in treating the disorder, which as discussed above is limited, could lead to the discovery of a broader range of improved drug therapies with a lower risk of side-effects and abuse potential.

4.4. Future Research

Only one analysis (using data from a previously published RCT by McElroy et al., 2016a) has been published on the role of potential moderators of the relationship between LDX and BED symptoms. This study found that neither sex/gender nor age moderated the effects of LDX on BED symptoms (Kornstein et al., 2019). Thus, there is a clear need for future studies to formally assess potential moderators of the efficacy of LDX in treating BED.

There have been few preclinical or clinical studies on the mechanism of action of LDX in treating BED. For example, preclinical studies have examined the effects of catecholamine receptor antagonists on the ability of LDX to decrease chocolate bingeing in rats (Vickers et al., 2015). However, although LDX is known to increase serotonin release in vivo the effects of 5-HT receptor antagonists on the action LDX in a bingeing model in rodents remain to be explored. Additionally, the effects of 5-HT receptor antagonists on the action of LDX in delay discounting measures of inhibition has yet to be investigated. Similarly, although it has been suggested on the basis of results from preclinical studies (Price et al., 2018) that selective 5-HT_{2C} receptor agonists could be effective in treating BED no experimental medicine studies or clinical trials have been conducted.

There is considerable potential to use the power of experimental medicine to explore the mechanism of action of LDX in treating BED. However, only a single pilot fMRI study with LDX has been conducted to date (Fleck et al., 2019) and although the results are interesting, its conclusions are limited by a small sample size and the absence of a placebo control group. Therefore, there is an urgent need for adequately powered, placebo-controlled, behavioural and neuroimaging studies with LDX to further investigate the mechanism of action of the drug in treating BED. These studies could recruit patients with BED (as in the study by Fleck et al., 2019) or use an intermediate phenotype approach such as that used successfully to study binge eating associated with ADHD (Kaisari et al., 2018).

4.5. Conclusions

There is consistent evidence from this review and meta-analyses that LDX is an effective treatment for BED and that the drug reduces both the BED symptoms and the body weight of patients with the disorder. There is also consistent evidence that LDX reduces food intake in preclinical studies but no consistent evidence for a preferential reduction of palatable food

consumption by the drug in rodents. The evidence from mechanism of action studies suggests that LDX may reduce binge eating through a combination of effects on appetite/satiety, reward, and cognitive processes with a predominant effect on impulsivity/inhibition that are mediated by catecholamine and serotonin neuronal pathways in the brain. The mechanism of action evidence is limited and an improved understanding of the behavioural and neurochemical mechanisms of action of LDX could lead to the development of improved drug therapies to treat BED.

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Table 1 Characteristics of Clinical studies

Source	**Study Design/ clinical phase**	**Intervention**	**Study Duration**	**Eligibility**	**Comparator**	**Sample Size**	**Participant characteristics**	**Primary Outcome Measures**	**Secondary Outcome Measures**	**Adverse Effects (RCTs only)**	**Declaration of interests**
Author, year	**RCT** **Open label** **Case report** **Medical record review**	**Acute** **Chronic** **Dosing**	**Days, weeks, months**	**Inclusion criteria**	**Placebo** **SSRIs** **TCAs** **Bupropion** **Topiramate** **Dasotraline**		**Age, sex, BMI, co-morbidity**	**Binge eating**	**Physical health outcomes, mood improvement, cognitive changes**	**LDX dosages only**	**Funding source** **Author-industry ties**
Brucar et al.(2018)	Literature review and case report	Chronic Flexible dosing 30mg LDX (6 months) with potential	6 months	45-year history of BED	None reported	N = 1	Age = 56 Sex = F BMI not reported	Cessation of BE episode and behaviours immediately after beginning LDX and continued treatment response at time of article	NA	NA	Funding source not reported Authors declare no conflicts of interest

		to titrate to 50 or 70mg LDX Adjunctive 25mg Zoloft prescribed					No psychological co-morbidities reported	publication Normalisation of EEG activity in insular cortex and prefrontal cortex pathways from pre-post treatment LDX reduced theta band power in right inferior frontal gyrus overlap with orbitofrontal cortex			
Fleck et al.(2019)	Open-label Phase Post-approval	Chronic Flexible dose 30mg (first week only)-70mg LDX LDX titrations	12 weeks treatment, 1 week follow-up	BED diagnosis	Control group: women with obesity and without BED	N = 40:	BED group M_{Age} = 38.6 Women only BED group M_{BMI} = 36.85	Remission of BE episode and improvement in global BED symptoms (CGI-I) at endpoint for BED group Reduction in BE days/week, BE episodes/week, and self-reported	Reduction in BED-related obsessive-compulsive symptoms (YBOCS-BE), BMI, and reaction time on an emotional eating continuous performance	NA	Study partially funded by Shire Authors consult, co-investigate, hold membership on

		weeks 1-3, LDX maintenance weeks 4-12 Endpoint doses: 50mg (n= 4) 70mg (n=11)					Co-morbidities: Major depressive disorder (n=2) and generalised anxiety disorder (n=1)	BE scores (BES) for BED group BED group treated with LDX had reduced activation in globus pallidus at endpoint Reductions by LDX in vmPFC and thalamus activation correlated with BE and obsessive-compulsive symptom reduction	task for BED group BED group did not differ in depression scores after treatment		scientific advisory board, receive employment, and receive grant support from Shire
Gasior et al.(2017)	Open-label Phase III	Chronic Dose optimisation 30mg (first week only) Week 2 50mg LDX	12 months treatment, 1 week follow-up	Completion of McElroy, et al., 2016 or McElroy, et al., 2015 with no significant	None reported	Safety analysis set N = 599, full analysis	M_{Age} = 39.0 Sex F: 521 (87%) M_{BMI} = 33.75	Improvement in global BED symptoms (CGI-I) during the study and Reduction of BE days in the past 28 days (descriptive only)	A non-significant reduction in weight (greatest reduction at week 44) that stabilises toward end of treatment	NA	Study funded by Shire Authors are employees, consultants, stock

		70mg LDX titrated if tolerated 4 weeks dose optimisation and 48 weeks dose maintenance. At end of dose optimisation period, 179 (29.9%) participants had 50mg and 389 participants (64.9%) had 70mg		adverse effects		set N = 597	No co-morbidities reported		Reduction in self-reported eating psychopathology (EDE-Q)		holders, grant recipient, and scientific advisory board members of Shire
Guerdjikova et	RCT	Chronic	12 weeks	BED Diagnosi	Placebo	Total N =	M_{Age} total = 37.7	Over the study period, no	No improvement	Dry mouth: 48%	Study funded by

al.(2016)	Phase I	Flexible dose 20mg-70mg dose at endpoint = 59.6mg	treatment, 1 week follow-up	s		50	Sex total F: 46 (92%) M_{BMI} Total = 39.8 No co-morbidities reported	reduction in BE episodes/week or BE symptoms (CGI-I) From baseline-endpoint, reduced BE days/week and BE episode/week From baseline-endpoint, improvements of reported BED symptoms (CGI-I) LDX did not differ from placebo in 4-week BE cessation rates	in: food cravings (FCI); BED-related obsessive-compulsive features (Y-BOCS-BE); or cognitive control of eating, disinhibition, or eating restraint (EI) Greater loss of weight/BMI and triglyceride levels No change in self-reported ADHD symptoms (CAARS), cholesterol, glucose, insulin, or HbA1c	Insomnia: 44% Jitteriness: 28% Headache: 20% Respiratory disorder: 20% Diarrhea: 16% Disturbance in attention: 12% Dizziness: 12% Increased talkativeness: 12% Anxiety: 8% Fatigue: 8% GI disturbance: 8% Hand	Shire Authors co-investigate, hold membership position on scientific advisory board, and consult for Shire Medication provided by Shire

									From baseline-endpoint, reduced weight/BMI From baseline to endpoint, no change in YBOCS-BE scores	tremor: 8% Influenza-like illness: 8% Nausea: 8% Sinus problems: 8% Back pain: 4% Increased dreaming: 4% Irritability: 4% Palpitations: 4% Paresthesias: 4% Constipation: 0%	
Guerdjikova et al.(2019)	Retrospective medical record	Chronic *M* dose =	*M* duration = 19.1	BED Diagnosis	None reported	25 records	M_{Age} = 16.5	Reduced BED symptoms in a subset of the	LDX did not reduce BMI	NA	Funding source not reported

	review Phase Post-approval	58.0mg	months				Sex F: 18 (72%) M_{BMI} = 38.7 Most common co-morbidity: depressive disorders and ADHD	sample (15 cases) Complete remission of BED symptoms achieved (4 cases) Improved BE symptoms or reduced BE frequency in a subset of the sample (6 cases) A small number of participants reported likelihood to binge eat if LDX skipped (2 cases) Subset reported no improvement in BED symptoms (4 cases) and some reported	A small number of participants reported less sneaking of food (1 case) and stress-triggered BE (2 cases)		Conflicts of interest not reported

								worsening of BED (2 cases), while some reported no response (4 cases)			
Hudson et al. (2017)	Open-label and RCT Phase III	Chronic Open-label phase: Dose optimisation 30mg (week 1 only), 50mg, or 70mg LDX 4 weeks dose optimisation (50 or 70mg), 8 weeks dose maintenan	Open-label phase: 12 weeks RCT phase: 26 weeks 1 week follow-up	BED diagnosis	Open-label phase: none reported RCT phase: Placebo	Open-label phase: N = 411 RCT phase: N = 270	Open-label phase and RCT phase: M_{Age} = 38.7 Sex = F: 234 (87.64%) M_{BMI} = 33.91 No co-morbidities reported	Open-label phase: Reduction of BE days/week Improvement in self-reported global BED scores (CGI-S) RCT phase: Increase in BED-related obsessive-compulsive features (Y-BOCS-BE) for placebo compared to LDX Increased time to BE relapse greater in LDX	Open-label phase: Reduction in weight. RCT phase: Reduction in weight at week 38 in LDX condition	Any adverse event related to study drug: 23.5% Dry mouth: 5.1% Headache: 8.8% Insomnia: 0.7% Decreased appetite: 0% Nausea: 4.4% Anxiety: 1.5% Constipation: 2.9% Hyperhidros	Funding and conflicts of interest not reported

		ce RCT phase: Dose optimisation of 50mg or 70mg LDX Open-label *M* LDX dose = 57.13mg RCT *M* LDX dose = 64.05mg						condition Reduction in BE days/week at weeks 37-38 greater for LDX		is: 2.2% Feeling jittery: 0% Diarrhea: 1.5% Nasopharyngitis: 9.6% Fatigue: 2.9% Upper respiratory tract infection: 8.1%	
Keshen et al.(2017)	Retrospective medical record review	Chronic Dose optimisation 30mg-	Variable durations:	Bulimia Nervosa diagnosis	None reported	N = 6	M_{Age} = 26 Sex not reported	Binge/purge days/month decreased at month 1 and remained consistent at	Improvement of symptoms in most cases Weight gain (2	NA	Funding source not reported Author on

	Phase Post-approval	70mg daily total Doses given in the morning and afternoon for most cases 5 cases received LDX and 1 case received extended-release amphetamine/dextroamphetamine (titrated to 40mg/day) 3 weeks titration and then maintenan	Case 1 = 4 months Case 2 = 13 months Case 3 = 5 months Case 4 = 1 month Case 5 = 14 months Case 6 = 11				Baseline BMI not numerically reported Co-morbidities: marijuana use disorder; dependent traits; avoidant, dependent, obsessive-compulsive personality traits; social anxiety disorder; persistent depressive disorder	follow-up in most cases Complete remission of symptoms (1 case)	patients) following initiation of medicine and minimal weight loss (4 cases)		advisory board for Shire

		ce	months								
McElroy et al.(2015)	RCT Phase II	Chronic 30, 50, 70mg/d titration 3 weeks forced dose titration, 8 weeks dose maintenance	14 weeks total: 11 weeks treatment	BED diagnosis	Placebo	N=259	M_{Age} = 38.7 Sex = M: 48 (18.5%) F: 211 (81.5%) M_{BMI} = 34.9 Co-morbidities: not reported	Reduction in weekly BE days/week at week 11 for 50 and 70mg/d, but not 30mg/d Clinician-rated BED obsessive-compulsive features (Y-BOCS-BE) improved all doses Reduction in BE episode at 11 weeks of treatment for 50 and 70mg/d Improvement of self-reported global BE symptoms (CGI-	No significant changes in self-reported mood ratings (MADRS & HAM-A) Improvement of self-reported impulsivity symptoms (BIS-11) at 30 and 70mg/d Improvement of self-reported physical health symptoms at 70mg/d only Improvement of self-reported disinhibition of	84.7% experienced some adverse event Dry mouth: 36.2% Decreased appetite: 21.4% Insomnia: 13.3% Headache: 11.7% Nausea: 7.7% Constipation: 7.1% Nasopharyngitis: 6.1% Weight decrease: 6.1%	Partially funded by Shire Authors consult and co-investigate for Shire, receive research support from Shire, and hold stock in Shire

McElroy et al.								I) all doses At week 11, one-week cessation of BE observed in 50 and 70mg/d doses At week 11, 4-week cessation of BE observed in 50 and 70mg/d Improvement of self-reported BE symptoms (BES) at week 11 all doses ***Greater improvement of self-reported BE symptoms (BES) during treatment***	eating and perceived hunger symptoms (TFEQ) with all doses Improvement in cognitive restraint of eating (TFEQ) at 30 and 70mg only Reduction in mean weight all doses ***Reduction in BED obsessive-compulsive features (Y-BOCS-BE)***	Irritability: 5.6% Diarrhoea: 5.1% Anxiety: 4.6% Jittery: 4.6% Palpitations: 4.6% Respiratory tract infection: 4.6% Sleep disorder: 4.1%	

(2016) ***(extension study of McElroy et al. 2015)***								***for all doses***	***throughout treatment for all doses*** ***During treatment, self-reported impulsivity symptoms (BIS-11) decreased all doses.*** ***Reductions from baseline to week 11 for impulsivity (BIS-11) with 70mg/d, but not with 30 or 50mg/d***		
McElroy et al.(2016)	RCT Phase III	Chronic 30mg/d (first week only), 50	12 weeks treatment	BED diagnosis	Placebo	Study 1: N = 379	Study 1 M_{Age} = 38.05 Study 2 M_{Age} =	Reduction of BE days/week at weeks 11-12 4-week cessation	Reduction in body weight at week 12 Reduction in	Combined adverse event related to study drug: 67.75%	Funded by Shire. Authors consult,

		or 70mg/d titration 4 weeks dose optimisation; 8 weeks dose maintenance	1-week follow-up			Study 2: N = 366	37.90 Study 1 Sex = F: 328 (86.54%) Study 2 Sex = F: 312 (85.25%) Study 1 M_{BMI} = 33.45 Study 2 M_{BMI} = 33.53 Low proportion of co-morbidities, Major Depressive Disorder most prevalent	of BE week 12 Reduction in self-reported BED-related obsessive-compulsive symptoms week 12 (YBOCS-BE) Improved self-reported global BED symptoms week 12 (CGI-I)	triglyceride levels at week 12	Dry mouth: 36.35% Insomnia: 14.1% Headache: 15.6% Decreased appetite: 7.5% Fatigue: 6.5% Nausea: 8.55% Irritability: 6.65% Diarrhoea: 6.1% Heart rate increased: 7.3% Anxiety: 6.8% Constipation: 5.6% Hyperhidros	receive grant funding, employment, and hold stock shares in Shire

										is: 5.2% Jittery: 5.6% Blood pressure increased: 5.0% Respiratory tract infection: 4.2%	
Kornstein et al. (2019) ***(extension study of McElroy et al. 2016)***						***Age < 40:*** ***N = 398*** ***Age ≥***	***Demographics for age < 40y*** ***M_{Age} =***	***Greater reduction of BE days/week 12 weeks, no difference between genders*** ***Greater improvement of global BED symptoms at 12 weeks no difference between genders*** ***Greater reduction of BE days/week***	***Greater improvement in BED-related obsessive-compulsive symptoms at weeks 11/12 no difference between genders***		***Funding by Shire*** ***Authors consult and hold stock in Shire Authors receive research support, and employme***

						40: ***N = 347***	***29.82*** ***Sex =*** ***F: 347 (87.2%)*** ***M_{BMI} = 33.45*** ***Demographics for age ≥*** ***40y, Study 2*** ***M_{Age} = 47.35*** ***Sex =*** ***F: 293 (84.4%)*** ***LDX M_{BMI}***	***at 12 weeks no difference between age subgroups*** ***Greater improvement of global BED symptoms at 12 weeks no difference between age subgroups*** ***Greater change in BE days/week,***	***Greater improvement in BED-related obsessive-compulsive symptoms at weeks 11/12 no difference between age subgroups***		***nt from Shire***

McElroy et al. (2017) ***(extension study of McElroy et al. 2016)***							***= 33.52***	***and BE episodes/week decreased from week 1 through weeks 11/12*** ***Greater improvement of self-reported global BE symptoms (CGI-I)*** ***Greater partial to full cessation of BE episode from week 1-week 12***	***Greater change in body weight from baseline to weeks 10 and 12*** ***Improvement in BED-related obsessive-compulsive symptoms at weeks 4, 8, and 12 (YBOCS- BE)***		***Funding by Shire*** ***Authors consult, receive grant support, and hold scientific advisory board membership from Shire***
McElroy, Martens	RCT	Chronic	8-week	Clinical Bipolar I	Placebo	N =	M_{Age} = 43.0	Improved self-reported BE	Reduced self-reported	Headache:	Funded by

et al.(2015)	Phase I	Flexible-dose ranging from 20-70mg/d average daily dose LDX = 38.8mg final daily dose LDX = 52.7mg	treatment, 4-week follow-up	and II Disorder and syndromal depression		25	Sex = F: 17 (68%) Total M_{BMI} = 34.5	symptoms (BES) during treatment and at endpoint (8-weeks)	depression during treatment and at endpoint (IDS-SR) Reduced cholesterol during treatment and at endpoint and reduced triglycerides at endpoint Improved self-reported fatigue ratings at endpoint (FSS)	45% Insomnia: 36% Decreased appetite: 18% Dry mouth: 36% Feeling jittery: 36% Fatigue: 9% Nausea: 18% Pyrexia: 18% Tremor: 27% Anxiety: 18% Diarrhea: 9% Irritability: 18% Palpitations: 9%	Shire Authors are consultants, co-investigators, and members of Shire advisory boards

										Gastroenteritis: 0% Sinus congestion: 18% Strep throat: 9% Upper respiratory infection symptoms: 9%	
Srivastava et al.(2019)	Case report Phase Post-approval	Chronic Intensive lifestyle modification therapy and LDX 20-70mg titration: 20mg LDX from weeks 0-4 30mg	18 months	A score of 21 on the BES	None reported	N = 1	Age = 16 at treatment onset, 17 at treatment end Sex = F BMI at treatment onset = 48.89, 40.91 at treatment	Reduction of self-reported BED symptoms (BES) at 6 months of treatment	Reduction in BMI at 2 weeks and sustained until end of treatment Reduction of self-reported food cravings at 6 months and reduction reported again at 13 months	NA	Received no external funding No conflicts of interest reported

		from months 1-11 40mg from months 11-17 50mg from months 17-18					end Co-morbid ADHD symptoms Diagnosis of developmental delay/autism and milieu instability		Self-reported reduction in hunger at 13 months Improvement in focus reported at 2 weeks and sustained until end of treatment with exception of LDX non-compliance periods Self-reported reduction in stress and anxiety at 16 months of treatment		

Table 1 Extension studies utilising the same data set are listed in bold and italics under the original study. Results of these studies that provide new findings beyond the original publication are listed in bold and italics under the results of the original study. Abbreviations: ADHD: Attention-Deficit Hyperactivity Disorder; BE: binge eating; BED: Binge Eating Disorder; BES: Binge Eating Scale; BIS-11: Barratt Impulsiveness Scale – Version 11; BMI: body mass index (kg/m^2); CAARS: Conners' Adult ADHD Rating Scales; CGI-I/S: Clinical Global Impressions – Improvement/Severity; EDE-Q: Eating Disorder Examination Questionnaire; EEG: electroencephalography; EI: Eating Inventory;

F: female; FCI: Food Craving Inventory; FSS: Fatigue Severity Scale; HAM-A: Hamilton Rating Scale for Anxiety; HbA1c: Haemoglobin A1C; IDS-SR: Inventory of Depressive Symptomatology – Self Report; LDX: lisdexamfetamine dimesylate; M: male; *M*: mean; MADRS: Montgomery-Asberg Depression Rating Scale; RCT: randomised controlled trial; TFEQ: Three Factor Eating Questionnaire; YBOCS-BE: Yale-Brown Obsessive Compulsive Scale for Binge Eating.

Table 2. Characteristics of Preclinical studies

Source	Model	Species /Strain/ restriction	Dose/ route of Administration	Comparator	Sample Size	Behavioural Outcome measures	Declaration of interests
Ekstrand et al. (2019)	Ad-libitum water and food	Long-Evans male rats Non-food restricted	Chronic Oral 1.5mg/kg 20-day experimental period	Vehicle	N = 12	LDX-treated rats weighed less at the end of treatment than vehicle-treated rats LDX-treated rats had lower renal and mesenteric adiposity, as well as less epididymal fat mass than vehicle-treated rats No difference in running wheel activity, water intake, or food intake between vehicle and LDX-treated rats. No difference in anxiety between vehicle and LDX-treated rats LDX-treated rats were faster at performing a spatial working memory task (Water Maze)	Funding source and conflicts of interest not reported
Heal et al. (2016)	Food reward/punished responding conflict	Female Wistar rats	Acute Oral	Non-binge-eating rats	N = 34	LDX reduced chocolate consumption in BE rats in 2-hour test session:	Funding provided by Shire

	model for chocolate 24-hour home cage chow intake	Non-food restricted	0.8mg/kg	and vehicle		LDX reduced 24-hour home cage chow intake in BE rats. LDX reduced 24-hour home cage chow intake in non-BE rats. LDX did not affect water intake or body weight over 24 hours in BE rats or non-BE rats Conflict task In BE rats LDX reduced: the number of escapes, time receiving foot shocks; the % of trials foot-shocks were received; time taken to respond to the warning tone/light and avoid a shock. LDX increased avoidances in BE rats	Authors are employees and shareholders of Shire
Presby et al. (2020)	Chocolate exposure training (CE) group versus chow exposure (LChE) / versus empty dish Intake of chocolate and chow presented	Female Wistar rats Non-food restricted	Acute IP 0.1875, 0.375, 0.75, or 1.5 mg/kg	Vehicle and control chow-only exposure group (LChE)	N=30	LDX decreased free intake of chow and chocolate in CE group and tended to decrease chow intake in LChE group For operant sessions: LDX reduced lever pressing for chocolate pellets in CE group and control group (LChE group and the empty food dish group combined) and chow intake reduced	Funding provided by Shire Conflicts of interest not reported

	as choice (CE group) or chow intake only (LChE) Effort-related motivational choice model: Lever pressing for chocolate pellets versus concurrent chow access					in CE group. In control group no reduction in chow in intake	
Sachdeo et al. (2019)	Repeated limited access to palatable foods (sweetened hydrogenated vegetable shortening	*OPRM1 A112G* female mice – either AA or GG homozygous	Once/week acute oral dosing: 0.15, 0.5, and 1.5 mg/kg 14 days chronic oral administration 1.5 mg/kg	4 groups (restrict, restrict binge, binge, naïve) vehicle	N=254	No significant effects of either acute or chronic administration of LDX on intake or weight in any groups for either AA or GG mice	Funding provided by Shire Reported no conflicts of interest
Vickers et al. (2015)	Time-limited, intermittent, irregular access to a palatable food (ground milk chocolate) in	Female Wistar rats Non-food	Acute oral 0.1, 0.3, 0.6, 0.8, 1.0 and 1.5 mg/kg	Vehicle	Cohort 4 sample size N=75	LDX (doses ≥ 0.3 mg/kg) reduced chocolate but not chow intake during 2-hour binge session. LDX (doses ≥ 0.3 mg/kg) reduced total food intake (chocolate and chow) but had no effect on water intake or body weight over 24 hours	Funding provided by Shire Authors are

	addition to freely available standard powdered diet	restricted	Alone and in combination with *SCH-23390, raclopride, prazosin and RX821002*			*LDX and SCH-23390 / raclopride* SCH-23390 (0.1 mg/kg) attenuated LDX (0.1 mg/kg) reduction in chocolate intake in 2-hour binge session. SCH-23390 (0.1 mg/kg)/LDX (1.0 mg/kg) combination did not consume less chocolate than vehicle, but ate non-significantly more than LDX alone group. The LDX (1.0 mg/kg) reduction in chow intake in the 2-hour binge test was not modified by SCH-23390 (0.1 or 0.3 mg/kg). Raclopride (0.1 or 0.5 mg/kg) did not attenuate LDX (1.0 mg/kg) reduction of chocolate and chow intake in 2-hour binge test *LDX & prazosin / RX821002* Prazosin (0.3 and 1.0 mg/kg) attenuated the reduction in chocolate consumption induced by LDX. LDX (1.0 mg/kg) did not alter chow intake in 2-hour binge session, but prazosin (0.3 mg/kg)/LDX (1.0 mg/kg) reduced chow intake in 2-hour binge session compared to vehicle. RX821002 (0.1 or 0.3 mg/kg) did not attenuate LDX (1.0 mg/kg) reduction of chocolate in 2-hour binge session	employees of Shire and hold stock in Shire
Vickers et al.	Two-lever, delay-discounting task:	Female Wistar rats	Acute oral	Non-binge-	N = 28		Funding provided by

(2017)	one lever delivered a single chocolate-flavoured pellet immediately and the other a three-pellet reward after increasing delay	Non-food restricted	0.3 and 0.8mg/kg	eating control group and vehicle	19 BE rats and 9 controls	0.8mg/kg LDX reversed BE rats' reduced preference for a larger and more delayed reward.	Shire. Authors are employees and shareholders of Shire
Yohn et al. (2016)	Effort-related motivational choice model: Lever pressing for chocolate pellets versus concurrent chow access	Male Sprague Dawley rats Food restricted	Acute IP 0.09, 0.1875, 0.375, 0.75, and 1.5 mg/kg	Vehicle	Study 3: N = 16 Study 4: N= 12	Study 3: LDX (0.75 mg/kg) had no effect on chow intake nor lever pressing for pellets Study 4: LDX (0.75 and 1.5 mg/kg) increased lever pressing for pellets and reduced intake of concurrently available chow	Funding multi-grant supported (no funding from Shire). Author has received grants, employment, consultation work, and stock in Shire

Table 2. Abbreviations: BE: binge eating; IP: intraperitoneal injection; LDX: lisdexamfetamine dimesylate.