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Review

Does Dexamphetamine Cause Addiction? A Narrative Review

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Abstract: Dexamphetamine (DEX) is widely used in treatments, but concerns persist about its potential for addiction. This review aimed to assess the risks of DEX addiction by examining the existing literature. Originally planned as a systematic review, it was adjusted to a narrative review due to a lack of qualifying studies. A search of the literature on addiction to DEX was conducted on three databases including PubMed, Scopus, and Embase. Seven articles consisting of three reviews and four papers with original data were identified and reviewed. In total, four poorly documented cases of possible DEX addiction were found. The commonly cited papers on prescription DEX addiction did not hold up to scrutiny. Overall, the evidence that DEX is addictive is limited and inconclusive, highlighting the need for more rigorous research to clarify its true addiction risk.

Keywords: dexamphetamine; addiction; dependence; substance use disorder; stimulants; psychostimulants

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1. Introduction

Dexamphetamine (DEX) is an isomer of the amphetamine molecule that exhibits a more significant impact on dopaminergic neurons [1]. Classified within the β-phenylethylamines category, amphetamines encompass various types such as DEX, lisdexamfetamine (LDEX), methamphetamine, cocaine, methylphenidate, and phentermine. Structurally resembling monoamine neurotransmitters like noradrenaline, dopamine, and serotonin, amphetamines enhance the effects of these endogenous molecules through multiple mechanisms. They heighten neurotransmission by directly binding to neurotransmitter receptors, elevate synaptic neurotransmitter concentrations by displacing endogenous molecules from the cytosolic pool, and facilitate monoamine transportation out of neurons into the synapse through reverse transport [2,3]. Additionally, they decrease the re-uptake of monoamines into neurons by binding with monoamine transporters and inhibiting monoamine oxidase, an enzyme which breaks down the monoamine neurotransmitters [4,5]. Amphetamines have a number of effects on behavior and physiology via their enhancement of monoamine neurotransmission. They have effects in various areas of the brain, including the nucleus accumbens, which plays a critical role in mediating goal-directed behaviors [6].

Amphetamines have cognitive enhancing effects at lower doses, including increased arousal and improved performance on some cognitive tasks, while at higher doses they

may be associated with aggression, with feelings of power and euphoria, and can lead to psychosis [2,7–10]. Amphetamines also act to stimulate reward mechanisms and are associated with appetite suppression [11–13], along with a dose-related improvement in executive function [14]. These properties of stimulants including DEX are advantageous for treating obesity as research suggests an association between issues such as poor impulse control and the development of obesity [15]. There are, therefore, a wide range of amphetamine effects, which can have beneficial or adverse consequences, depending on amphetamine dose, type, and the circumstances of use.

Dopamine dysregulation is believed to be the physiological driver of addiction, and stimulants such as DEX have been shown to act on dopamine and dopamine transporters [16–18]. While the inherent nature of DEX contributes to its addiction potential, this has not deterred its clinical use, both historically and currently. In the early to mid-1900s, DEX was widely used to treat conditions such as asthma, depression, and various psychiatric disorders [19]. DEX was also found to be a useful drug for weight management [20]. Its use extended into military settings to reduce fatigue and enhance the confidence and mood of soldiers in training and combat [21].

However, despite widespread use, addiction to DEX was not seen as a problem. In 1955, an editorial in the British Medical Journal mentioned that an "amphetamine habit" could develop in "unstable" individuals using DEX for the purpose of restoring their confidence, but stated that "there is no evidence that true drug addiction develops to it, as tolerance, craving, and the withdrawal syndrome are not associated with its use. There is no risk of cumulative ill effects from even the prolonged administration of DEX in therapeutic doses" [22].

In 1962, a pivotal article was published in the British Medical Journal with new evidence from case reports of amphetamine addiction, with psychosis and psychiatric disturbance in patients who had been hospitalized following the consumption of massive doses of amphetamines [23]. Subsequently, in 1970, the US Food and Drug Administration declared that the use of amphetamines for obesity and depression was unproven, and that they could be used only for the treatment of narcolepsy and Attention Deficit Hyperactivity Disorder (ADHD), unless the manufacturers of amphetamines could provide evidence of their efficacy and safety [24,25].

DEX is commonly used as therapy for ADHD on account of its effects of increasing alertness and concentration, as well as improving impulse control [26]. Due to their use in ADHD treatments, DEX and its prodrug LDEX are among the most frequently prescribed stimulants worldwide [27–29]. The efficacy of stimulants, including amphetamines, DEX, and LDEX, is well established for both short- and long-term ADHD treatment [30–32]. In combination with behavioral intervention, stimulants are generally accepted as a safe and effective treatment for ADHD in both children and adults [30,32–35]. Commonly reported side effects include a loss of appetite, insomnia, mood disturbances, nausea, and headaches [36].

In 2001, a pilot randomized controlled trial (RCT) using DEX for treating methamphetamine dependence and addiction found it reduced street amphetamine use and increased compliance with the treatment protocol [37]. Two randomized placebo-controlled trials ten years later also found that treating methamphetamine dependence with DEX led to a reduction in the symptoms of methamphetamine withdrawal and cravings [38,39]. In this high-risk population, there were no reports of addiction to DEX as a complication of treatment.

Although stimulants such as phentermine are still used and approved for weight management in many countries, the cheaper alternative DEX is not recommended for obesity management due to its perceived addiction potential [40]. However, there may be

potential for DEX to be reconsidered for treating obesity. The value of DEX for obesity was documented in an observational cohort study published in 1947, where 110 patients lost an average of 13.3% of their total body weight [20]. More recently, an observational pre- and post-intervention study published in 2015 [41] administered DEX in doses of up to 30 mg twice daily for six months and was associated with a mean weight loss of 10.6 kg ($p < 0.0001$). The study reported no problems with abuse or withdrawal syndrome.

It is clear the main constraint to the wider use of DEX, including for the treatment of obesity, remains the concern about its addictive potential [24]. At the same time, it is still in common use for the treatment of children with ADHD [42,43]. We set out to investigate this apparent contradiction in logic by reviewing the literature for evidence of DEX addiction.

2. Evolving Definitions of Drug Addiction

As a background to interpreting the literature for evidence of DEX addiction, it is essential to first define addiction. The definition of drug addiction has evolved from simple descriptions, such as habitual use [44], to physiological and/or psychological addiction [45], to abuse and dependence [46–49], and finally to the term substance use disorder (SUD) [48]. These changes can be tracked through previous versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and The International Classification of Diseases (ICD). The term "drug addiction" was phased out in the updates to the DSM in favor of "drug dependence" [49], which is a component of substance use disorder (SUD).

The DSM-5 defines Substance Use Disorder (SUD) as requiring at least 2 out of the 11 criteria to be met within the past 12 months. SUD is categorized by severity [48]:

- Mild: when 2–3 criteria are met;
- Moderate: when 4–5 criteria are met;
- Severe: when 6 or more criteria are met.

In contrast, the ICD-11 offers a more streamlined approach and describes dependence using three key criteria [50]:

- Impaired control over substance use;
- Increasing precedence of substance use over other aspects of life, including the maintenance of health, and daily activities and responsibilities, such that the substance use continues or escalates despite the occurrence of harm or negative consequences;
- Physiological features indicative of neuroadaptation to the substance, including: (1) tolerance to the effects of a substance or a need to use increasing amounts of a substance to achieve the same effect; (2) withdrawal symptoms following a cessation or reduction in use of a substance; or (3) repeated use of a substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms.

Both, however, do not discuss addiction. It cannot be inferred that severe SUD, as defined by the DSM 5, is equivalent to addiction as a person may meet the requisite six criteria without having drug cravings or a withdrawal syndrome. A literature review of the definition of addiction published by Sussman and Sussman in 2011 sought to resolve the variability in the definitions of addiction, suggesting that five elements would appear to encapsulate addiction [51]. Given the complexities and the changing definitions, for the purposes of this review we have chosen to use Sussman's five elements of addiction (Table 1). These elements all help to define addiction, with the limitation that it is unclear whether all the criteria are required to be met in order to confirm true addiction. The elements of Sussman and Sussman allows us to subsume both the ICD-11 and DSM 5 definitions of dependence. An important limitation of the framework proposed by Sussman and Sussman is that it is unclear whether all the criteria are required to be met to confirm a diagnosis of addiction.

Table 1. Sussman and Sussman's five elements of addiction [51].

1	Engagement in behavior that can become addictive (for example: abuse of an illicit substance)
2	Preoccupation with the behavior including planning, engaging, and recovering from its desired effects
3	Temporary satiation
4	Loss of control
5	Suffering negative consequences

3. Method

A search of the literature was conducted on PubMed, Scopus, and Embase in September 2022 and updated for records up to January 2024 using the keywords "dexamphetamine", "addiction", and "dependence". The inclusion criteria were human studies and articles published in English. The types of studies included were case reports, database audits, cohort studies, and randomized controlled trials and reviews. The initial screening involved excluding abstracts that did not mention "amphetamine". Only the abstracts containing the phrases (amphetamine OR stimulant) and (addiction OR dependence) were kept. The papers published after DSM 5 acceptance (2013 onwards) required the additional search terms "amphetamine use disorder" or "stimulant use disorder". This was to detect the studies using SUD as per the DSM 5. Only the papers discussing and investigating addiction, dependence, or stimulant use disorder were included. Studies that investigated stimulant use disorder to a level equivalent to that of DSM IV substance abuse, or to a level that was considered less than moderate to severe SUD were also excluded. One paper that reported addiction to a drug combination of DEX plus a barbiturate was excluded [52]. The reference lists of the relevant papers were examined for additional papers not found during the original search.

Due to the small number of relevant studies and their methodological diversity, their findings could not be used for a meta-analysis. Instead, a detailed description of each is given, including a statement as to whether the findings meet any of Sussman and Sussman's five elements of addiction. The level of the evidence of the study type, based on the National Health and Medical Research Council (NHMRC) [53], is also included. This tool is adapted from the grading of recommendations, assessment, development, and evaluation framework, which is the most widely adopted tool for making recommendations and grading the quality of evidence [54–57]. Because the most common use of DEX and lisDEX is for the treatment of ADHD, we also conducted a search of randomized controlled trials with the keywords "ADHD" and "Dexamphetamine" on PubMed, Scopus, and Embase. Of 250 trials, three studies inferred that DEX may have an inherent potential to cause addiction, but none provided direct evidence [58–60]. The remaining studies did not mention addiction or dependence. Additionally, from this search only four RCTs directly investigated the use of DEX in ADHD therapy.

4. Results

The search produced 1740 articles (Figure 1). Three papers with original data met the search criteria initially, and a fourth was sourced from a review of the reference lists of the relevant papers. Three reviews have also been included as they specifically discussed DEX in relation to addiction and have been highly cited as evidence of DEX addiction. Therefore, it was important to examine their underlying evidence.

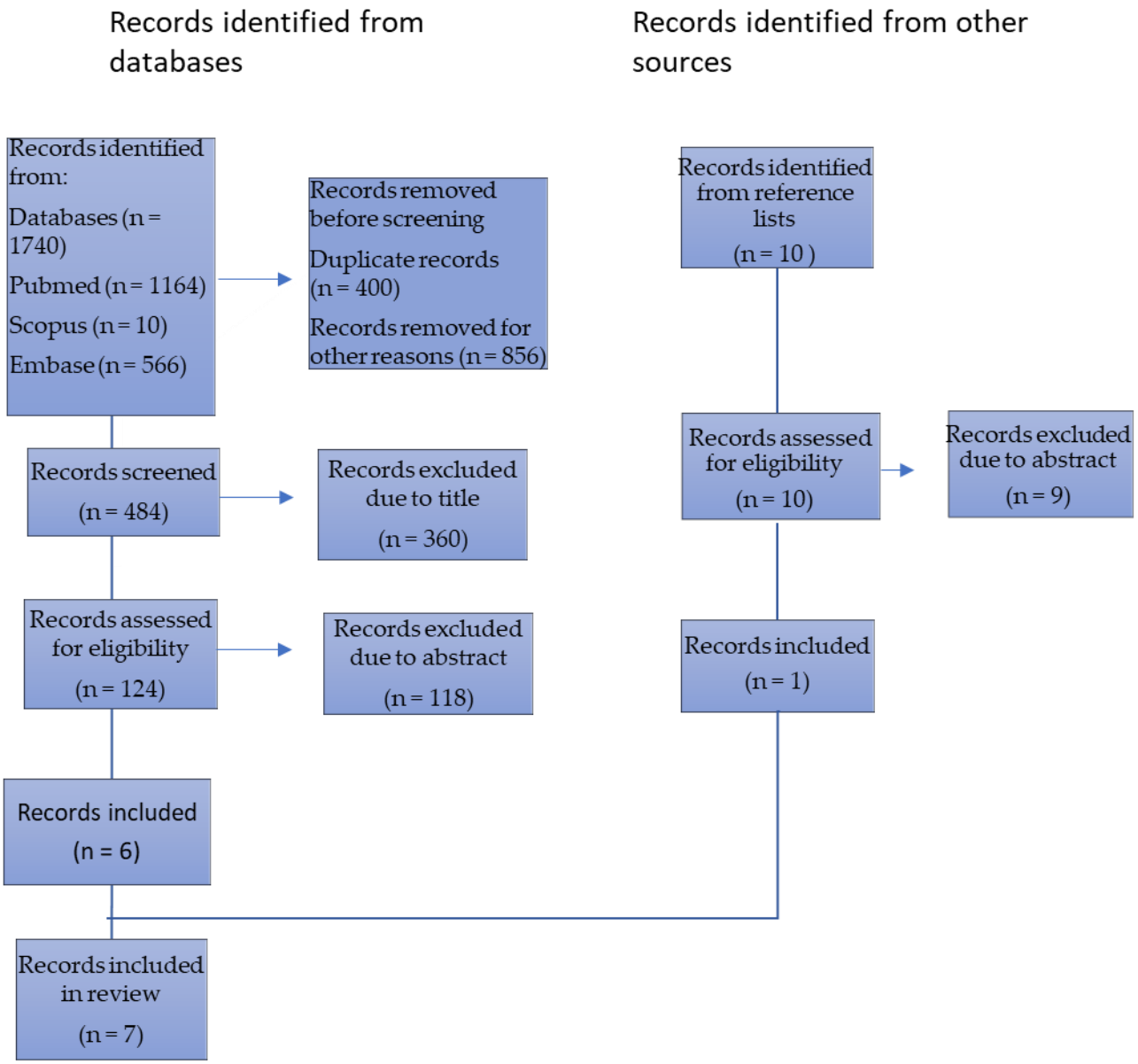

Figure 1. Flow chart of the literature review.

Paper 1: Amphetamine addiction and habituation Grahn, 1958 [61].

This case series from a single physician described 32 patients using different types of amphetamines, including Benzedrine (amphetamine) and Dexedrine (DEX), at dosages ranging from 10 mg to 30 mg daily. Addiction was based on the World Health Organization (WHO) definition, which, at the time of the study, included elements of the DSM 5 criteria of SUD and DSM IV dependence. The study identified only one patient who met the WHO definition of addiction as determined by the author as the "continuous use of a drug in such a way or quantity that the user, society, or both are harmed" (Sussman's element 5). This individual had anxiety, chronic anemia, and early Parkinsonism. It was reported that after release from a mental hospital she was taking over 100 mg of amphetamine and Dexedrine daily. The author concluded that addiction to amphetamines was possible but extremely rare.

Opinion: This article presents one patient who met only one criterion of addiction: preoccupation with the behavior. Specific details were lacking, preventing a determination

of whether the others were met. Therefore, this is a possible but not a definitive case of DEX addiction.

This is a possible single case of addiction.

The evidence rating for this study is level IV: this is a case-series study with no comparator group.

Paper 2: Amphetamine addiction Bell and Threthowan, 1961 [62].

This observational cohort study included 14 cases of amphetamine abuse, including amphetamines, DEX, and methamphetamines. Over 70% of the cohort presented with poly-amphetamine use, with an average maximum daily dosage of 230 mg and a median dosage of 150 mg. Only two of the fourteen individuals had solely used DEX. All 14 had underlying personality disorders, and it was noted that amphetamine use led to feelings of elevated self-esteem and delusions of omnipotence. All 14 individuals apparently suffered drug withdrawal symptoms. All had experienced a disturbed childhood, and many had a family history of alcoholism and other mental illnesses. An important limitation of the study was that addiction to amphetamines was based solely on self-reporting rather than the systematic application of specific criteria. The authors concluded that widespread amphetamine use led to the occurrence of addiction; however, they noted that underlying personality instability may have contributed to the impressions of addiction rather than the drug alone.

Opinion: This paper hinted at a drug withdrawal syndrome, but this was not supported with any descriptive details. Although the effects of stimulants were mentioned, two elements from Sussman's definition of addiction (one and five: suffering negative consequences and a preoccupation with the behavior were met in the form of withdrawal). The authors only suggested the continued use of amphetamines led to a reduced occupational level but did not specify how the varying quantities and doses of stimulants affected each individual patient to a level to be able to determine whether the features of addiction were met. Therefore, we cannot conclude that addiction had occurred in two out of the fourteen cases with individuals solely taking DEX.

Addiction to DEX is possible but was not definitive in the two individuals solely using DEX.

The evidence rating for this study is level IV: this is a retrospective case series with no comparator group.

Paper 3: Habituation and Addiction to Amphetamines, Kiloh and Brandon, 1962 [23].

In this case-series study, the authors reported on amphetamine prescriptions at two hospitals in Newcastle, UK. Of the 40 different amphetamine formulations prescribed, drinamyl (a combination of DEX and a barbiturate) accounted for 53% of all prescriptions. The authors presented two cases as examples of presumed amphetamine addiction in individuals using very high doses. Case 1 involved a woman in her 30s with a history of DEX use of up to 200 mg. After being caught by the police, she was confined to a bed and was showing symptoms of hypersomnia. This event was preceded by several years of phenmetrazine use with the associated withdrawal symptoms ("feeling depressed and flat"). Prior to being caught, she was said to be restless, overactive, doing her housework in spurts, and unable to settle. She suffered additional withdrawal symptoms after hospitalization as well as hallucinations, sleepiness, and depression.

Case 2 was a woman in her 20s believed to be addicted to Drinamyl (a combination of amobarbital and DEX). Again, much of the relevant clinical details were lacking. The paper also suggested that 20% of amphetamine users were taking "moderate" doses and were habituated or addicted to the drug, showing a dependence on it and being resistant to its withdrawal. However, this was based on a survey of general practitioners' subjective estimates. The paper used the WHO definition of addiction in use at the time: an over-

powering desire or need to continue taking the substance and obtain it by any means; a tendency to increase the dose; a psychological and physical dependence on the effects of the substance; and a detrimental effect on the individual and on society [63].

Opinion: This paper suggests that at least some individuals might be consuming excessive quantities of amphetamines which fulfil the WHO definition of addiction from 1957 [63]. It is important to note that the WHO definition at the time, unlike that of the ICD-11 and DSM 5, solely listed the characteristics of addiction without providing a definitive set of criteria for diagnosis. Case 1 satisfies the minimum requirement for an ICD-11 diagnosis of addiction to DEX (dose escalation and withdrawal syndrome) and meets two of Sussman's five elements of addiction (one and five: a preoccupation with the behavior and suffering negative consequences). However, case 2 lacks sufficient information to infer addiction. Furthermore, the patient took drinamyl, of which DEX is only one component. In conclusion, the paper highlights the potential for abuse and describes a single case meeting two requirements for addiction to DEX taken at massive doses.

Therefore, there is one possible case of DEX addiction.

The evidence rating of this study is level IV: the authors utilized a case-series approach to illustrate habituation and addiction to amphetamines, including DEX, based on subjective estimates.

Paper 4: Dextroamphetamine, an evaluation of psychomimetic properties in man, Griffith et al., 1972 [64].

In this interventional cohort study, DEX was given to nine adult men with a history of drug abuse. DEX was initially administered intravenously and then orally every hour across several days. The cumulative doses ranged from 100 mg to 800 mg over up to 6 days. The effects of DEX were monitored via recorded interviews, narrative descriptions obtained by psychiatrists, a symptom checklist, retrospective descriptions by the participants, and psychological tests. After 50 mg of a cumulative dosage had been reached, all the participants displayed characteristics of depression; six went on to develop psychosis. All psychotic behavior ceased upon the discontinuation of DEX, and there was no mention of any withdrawal syndrome, cravings, or tolerance.

Opinion: In this carefully monitored experimental study, giving large doses of DEX over a few days was sufficient to cause psychosis in some; however, there was no mention of addiction to DEX according to the ICD-11 guidelines or Sussman's five elements. It is perhaps of significance that addiction was neither described nor apparently even considered a risk during this experiment.

There was no evidence of DEX addiction.

The evidence rating of this study is level III C: the authors included a control period of this single arm study. It lacked a placebo arm or randomization but was conducted at a level higher than level IV.

Paper 5: Addictiveness of central stimulants Dackis and Gold, 1990 [65]

This review, which is a chapter in the book *Addiction Potential of Abused Drugs and Drug Classes*, discusses the addictive potential of amphetamines (specifically DEX and methamphetamine) and cocaine. Cocaine addiction was a major focus due to the cocaine epidemic at the time of publishing. The authors' hypothesis was that stimulant addiction is mainly driven by cravings and drug-induced euphoria. The authors cited data from a cocaine hotline indicating that a significant number of cocaine users (74%) were addicted. They noted that while the stimulants methylphenidate and DEX are widely used for ADHD treatment, there is potential for abuse in young patients. However, the authors considered the therapeutic doses as typically being too low to promote euphoria or cravings, the presumed major drivers of dependence.

Opinion: This review, while discussing the features of addiction, did not present data from human studies that met the ICD-11 criteria for substance addiction or any of the features of addiction. The primary focus of the author was on the abuse of stimulants with a focus mainly on cocaine. Not only is convincing evidence of DEX addiction lacking, but the authors put forward the opinion that low doses that do not induce euphoria should not be addictive.

There was no evidence of DEX addiction.

An evidence rating for this study is not possible: the NHMRC levels of evidence only rate review studies that are to the level of a systematic review, which this is not.

Paper 6: America's first amphetamine epidemic 1929–1971: a quantitative and qualitative retrospective with implications for the present, Rasmussen, 2008 [24].

This historical review paper was included as it has been frequently cited (258 citations in Google Scholar) and the powerful message that it conveys is that there is a problem of increasing amphetamine abuse. This is mainly due to increased illicit methamphetamine production, but increased amphetamine prescription rates have allegedly contributed as well.

This author suggested prescribed amphetamines may lead to addiction, citing data from four sources. The first was from the Substance Abuse and Mental Health Services Administration 2002–2006, from which the author asserted that during 2004 "Some 3 million Americans consumed amphetamine-type stimulants of all kinds non-medically" and that "250,000 to 350,000 of them were addicted". However, DEX addiction cannot be inferred because the dataset would have included methamphetamine [66].

The second source was Kiloh and Brandon [23] (Paper 3 above). Rasmussen reported this as evidence of a "significant dependency on prescribed amphetamines", based on the primary care physician survey.

The third source was a GP survey by Brandon and Smith in 1962 [67]. This was a cohort study of data collected prospectively by GPs on consecutive patients prescribed amphetamines in general practice. Of their sample of 620 patients, 20.5% were considered habituated to amphetamines. Any differentiation between habituation and addiction is unclear. The paper uses the term "habituation" throughout, apart from one mention of addiction: "Of the total addiction 24.5% occurred in the over 65 years age group". Rasmussen apparently combined the findings of the studies by Brandon and Smith, 1962 [67], and Kiloh and Brandon, 1962 [23], inferring a "dependency rate among past-year medical amphetamine users of 6.7 to 10%."

The fourth reference was another British study, which found that one-third of people taking Dexamyl (similar to Drinamyl, it contains DEX and a barbiturate) were either habituated or dependent on the medication [68]. However, this could have been due to the barbiturate component.

Opinion: This historical review did not present any novel human data. The sources cited do not contribute to the case for the addictive properties of DEX.

This paper did not contribute any new or convincing evidence to support the claim that the use of DEX leads to addiction.

An evidence rating for this study is not possible: the NHMRC level of evidence only rates review studies that are to the level of a systematic review, which this is not.

Paper 7: The potential for misuse and abuse of medications for ADHD: a review by Clemow and Walker, 2014 [6].

This review paper was included as it discussed ADHD medications including DEX and spoke towards dependence. It explored the evidence for misuse, abuse, dependence, and a diversion of ADHD medications, specifically methylphenidate and amphetamines. The authors defined addiction as a physical and psychological dependence and noted that an

individual may be psychologically dependent on a substance without being truly addicted. The authors noted that misuse and diversion to other users to whom the medication has not been prescribed is common, with the prevalence rates of illicit use ranging from 5 to 10% in high school students and 5% to 35% in tertiary education students [69].

While there was evidence of non-medical use of stimulants for performance enhancement and recreational use, there was no clear evidence presented to support any natural progression from stimulant use to the development of a true stimulant dependence.

Opinion: This literature review addresses concerns regarding the misuse and diversion of ADHD medications, including amphetamines. However, it points out that there is no clear association between the long-term use of these medications and addiction. This paper presents no definitive link between DEX usage and addiction.

An evidence rating is not possible: the NHMRC level of evidence only rates review studies that are to the level of a systematic review, which this is not.

From our secondary search, a total of four RCTs [70–73] looked at DEX therapy in ADHD patients with a total of 205 participants. In these studies, there was no mention of addiction as adverse effect of the use of DEX for ADHD management.

5. Discussion

The seven studies reviewed were of poor design and gave low quality evidence. Only four studies presented original data. Three were rated level IV, and one study was rated level III C. The three reviews were not systematic reviews and, therefore, did not qualify for the NHMRC evidence grade criteria.

Our comprehensive literature review on DEX addiction yielded a total of only four possible, but not definitive cases, which met either one or two criteria for addiction to DEX. These cases were poorly documented, with insufficient clinical details for a full evaluation.

We found a notable lack of recent studies, with only two published this century and the majority dating back to the 1950s to 1980s. While the early research was more specific in identifying the type of stimulant leading to addiction, recent evidence has failed to differentiate between different amphetamine-based compounds, simply inferring a similar addiction potential. The design of the older studies was weak, including three observational cohort studies with a limited number of participants ranging from 9 to 32. Three studies were literature reviews. One was a historical review spanning from the 1930s to the 1970s [24]. The second lacked evidence from studies in humans linking DEX to addiction [65], while the third only briefly discussed DEX and addiction, noting a lack of conclusive evidence for long-term non-medical use leading to addiction [6]. While there is evidence of the addiction potential of psychostimulants such as methamphetamine [74,75] or cocaine [76,77], our comprehensive review yielded minimal evidence of DEX addiction.

The main limitation of this review is the lack of available evidence. After excluding the studies that combined DEX under the umbrella term “amphetamines”, there were no recent or good quality studies that could answer the research question. As a result, our review was based on a pitifully small number of studies (n = 7), almost entirely from the twentieth century. A meta-analysis of these studies was not possible.

6. Conclusions

The review underscores the need for a more nuanced approach when considering DEX addiction, emphasizing the importance of evaluating specific types of amphetamines, doses, and the circumstances of use. In this literature review, spanning 77 years, only four possible cases of addiction to DEX were found. The papers were cited in evidence of prescription amphetamine addiction [24], but did not stand up to scrutiny. In conclusion, the definitive evidence that DEX is addictive is severely lacking. Given the large amount of research on

the use of stimulant medication for treating ADHD, the failure to report specifically on the presence or absence of instances of addiction represents a missed opportunity for updating the evidence on this important question. This should be included in all future studies. Overall, the evidence that DEX is addictive is limited and inconclusive, highlighting the need for more rigorous research and relevant reporting to clarify its true addiction risk.

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