Alcohol use disorder relapse factors revisited

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Een kritische evaluatie van ‘terugval’ bij een Stoornis in het gebruik van Alcohol

Content

Introduction

Alcohol use disorder (AUD) is highly prevalent (Grant et al., 2015, 2017; Rehm et al., 2015), and accountable for substantial morbidity and mortality (Griswold et al., 2018; Leong et al., 2022; Rehm et al., 2017). However, most individuals with AUD do not get effective treatment. A very recent WHO initiated survey showed that, globally, only 11,8% of the respondents with lifetime AUD reported ever obtaining treatment and of those 44% reported that treatment was successful (Degenhardt et al., 2021). Importantly, defining treatment success remains notably difficult in the field of AUD. Outcome measures that have been used to evaluate treatment effectivity mostly refer to abstinence or different types of relapses into alcohol use. However, no international consensus has as yet been reached on definitions of relapse. Given the broad variety of these relapse types, comparisons between outcome studies in the AUD field has proven extremely difficult, warranting a clear need to sharpen the concept of relapse. In addition, next to the complexity of the concept of relapse many questions remain as to the different (clinical and cognitive) factors that play a role in the risk for relapse ("relapse factors"). From a clinical perspective, the relapse factors are of paramount importance, as a better understanding of these relapse factors can offer targets for treatment interventions.

In the current thesis, you will find the report of recent research investigating factors associated with relapse in Alcohol Use Disorder (AUD). This subject has already been studied for several decades, many publications on AUD relapse can be found in distinct journals, and over the years, several books on this topic have been published. However, the multitude and heterogeneity of identified relapse factors makes it difficult to get a meaningful overview (McKay et al., 2006; Miller, 1996).

It seems that research on this topic has peaked around the millennium and in these years also several 'relapse models' have been postulated (Connors et al., 1996; Hendershot et al., 2011; Witkiewitz and Marlatt, 2007, 2004). Nevertheless, the process leading to relapses or achieving recovery is still complex and very dynamic (Witkiewitz et al. 2020). To unravel this complex process of relapse takes a lot of patience and warrants further research. The topic is of utmost importance, while AUD and AUD relapse lead to considerable morbidity, social and economic damage, and sad enough substantial mortality.

Research goals

The main goal of this research was to reconsider the subject of AUD relapse factors. This research built on decennia of earlier research, but much in the dynamic process of relapse is still unknown. Moreover, from the existing literature dozens of distinct relapse factors can be identified. However, a recent systematic overview of current important relapse factors is lacking. In addition, it would be helpful if these relapse factors could also be ordered in a clear and meaningful way.

Furthermore, several distinct relapse factors still have not been thoroughly investigated. It is not always clear if there is any effect on relapse, and if so, in what direction (protective factor or promoting relapse). Reviewing the literature for relapse factors would definitely lead to identifying factors for which this effect is still not clear.

As noted, dozens of AUD relapse factors can be identified. Of these relapse factors, the rather scarcely investigated and new factors 'impulsivity' and 'meaning in life' seemed to deserve further attention (Copeland, 2020; Jentsch et al. 2015; Steger et al., 2006). To our knowledge, these were some of the factors that were apparently still not extensively investigated. For example, in earlier research 'meaning in life' seemed to be associated with more favorable AUD outcomes, but research on this relationship seemed to be rather sparse and additional research is therefore mandatory. During the research process, we were open in identifying and investigating other important relapse factors as well, like 'psychiatric co morbidity', 'craving' and 'AUD severity'.

Furthermore, in studying the relapse literature, we noted that it seems not to be clear what is actually meant by the term 'relapse'. In a 2016 review of some of the last decades AUD relapse literature, a semantic ambiguity in the use of the term was concluded (Maisto et al., 2016). Moreover, it is still unclear if and how many distinct relapse definitions are used throughout a longer period of AUD relapse literature.

Research Questions

Taking these considerations into account, and after 'pre reading' existing literature, we postulated the following research questions:

1. Which definitions are used for AUD relapse and how are these conceptualized?

2. Which clinical factors are associated with a heightened risk of AUD relapse?

3. What role plays the relapse factor 'impulsivity' in AUD relapse and what can be found about the specific effect size?

4. What can be said of craving in predicting AUD relapse?

5. Which is the role of 'meaning in life' in relation to AUD relapse?

Methods

Research Questions 1, 2 & 3: data were acquired by means of systematic literature reviews.

Research questions 4 & 5: data were acquired by means of a prospective cohort research in an inpatient sample of AUD patients.

Outline of the thesis

After a period (2014/2015) of extensive reading about AUD relapse, we identified a selection of potentially relevant research items. This eventually led to two PRISMA- based systematic reviews (the first to identify all known AUD relapse factors and another to focus on the factor 'impulsivity' in the context of AUD relapse). In addition, we also presented a narrative review on AUD relapse definitions.

Finally, we could present a research paper describing the outcomes of observational prospective patient cohort research, predominantly on the factors 'meaning in life', craving and relapse (inpatient setting de Hoop ggz, Dordrecht, The Netherlands).

Independent selection of papers and data extraction was mostly done by the first author (WS) as well as (and intensively supported by) Ranne de Waart. Statistical analyses were also performed by the author, supported by dr. Cis Vrijmoeth.

Of importance, the AUD relapse factors found, were ordered into biological, psychological, social and spiritual categories (BPS(S) model) (Wade & Halligan, 2017; Sulmasy, 2002). In this way, a logical and plain framework could be provided.

The current research –we trust- helps in further unravelling the complexity of the relapse process. The thesis is therefore entitled: **Alcohol Use Disorder relapse factors revisited**.

The main body of this thesis comprises of a (in 2019 in 'Psychiatry Research' published) systematic review of AUD relapse factors (Chapter 2), on which the research regarding AUD relapse definitions (Chapter 1) and 'Impulsivity and relapse' (Chapter 3) have been built. The fourth chapter describes research on relapse within an inpatient population, and predominantly investigates the 'meaning in life' concept.

We end this thesis with our main conclusions, discussion and suggestions for further research (Chapter 5) and an acknowledgements section (chapter 6). These chapters are followed by the distinct tables and figures. To promote the readability of the chapters 1-4, we placed them at the back of this thesis. Of note, to save space within this thesis we refer to the online references for consulting the supplemental material. All four studies have already been published and the references are provided at the beginning of each chapter.

The research and thesis were supervised by professors Witkiewitz and Roozen, under final supervision and responsibility of professor Dom.

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List of thesis related publications

2019:

Sliedrecht W, de Waart R, Witkiewitz K, Roozen HG. Alcohol use disorder relapse factors: A systematic review. Psychiatry Res. 2019 Aug; 278:97-115. doi:10.1016/j.psychres.2019.05.038. PMID: 31174033.

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Sliedrecht W, Roozen HG, Witkiewitz K, de Waart R, Dom G. The Association Between Impulsivity and Relapse in Patients With Alcohol Use Disorder: A Literature Review. Alcohol Alcohol. 2021 Oct 29;56(6):637-650. doi:10.1093/alcalc/agaa132. PMID: 33382416.

2022:

Sliedrecht W, Roozen H, de Waart R, Dom G, Witkiewitz K. Variety in Alcohol Use Disorder Relapse Definitions: Should the Term "Relapse" Be Abandoned? J Stud Alcohol Drugs. 2022 Mar;83(2):248-259. doi:10.15288/jsad.2022.83.248. PMID: 35254248.

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Summary

Alcohol Use Disorder (AUD) is a highly prevalent psychiatric disorder, which leads to substantial morbidity, economic damage and even mortality. Although many patients do recover (not seldom without any formal treatment), on the other hand a relapsing-remitting course is very common in patients with an AUD.

Chapter 1 gives an overview of 101 different relapse definitions that were used in last 2 decades of AUD relapse literature. Moreover, almost a quarter of included papers dealing with AUD relapse did not provide a definition of AUD relapse. Despite decades of research and discussion, there is still no widely accepted definition of AUD relapse. We propose to shift the focus from dichotomous AUD relapse terminology towards continuous outcome and quality of life related criteria. We suggest a future research panel to make a consensus decision on how to use the term 'AUD relapse', the possible use of an alternative term, or even abandoning the term.

Chapter 2 describes the findings of a systematic review of AUD relapse literature (2000-2019). The search yielded 4613 papers, from which 321 paper were eventually included. Thirty-seven subgroups of relapse determinants were identified, and ordered according to biopsychosocial and spiritual categories. An exploratory narrative review consequently provides a timely overview of the latest research on this topic.

In Chapter 3, we focus on one specific and seemingly relevant relapse determinant, namely 'impulsivity'. In this systematic review on impulsivity and AUD relapse, it surprisingly turned out that research on this subject is still relatively scarce. We identified two main impulsivity categories, namely 'behavioral' and 'trait' impulsivity, which both seemed to be associated with AUD relapse.

Chapter 4 describes the results of a small observational prospective cohort study, in which the factors dependence, craving and meaning in life were investigated in relation to AUD relapse. Contrary to our hypotheses and expectations, no protective effect of meaning in life in regard to AUD relapse was found, but the relapsed groups generally did have higher mean dependence and craving scores.

In Chapter 5 the findings are summarized and we provide a synthesis of the results. We discuss the main conclusions and add some extra discussion and suggestions for further research. We critically review some of our findings as well.

1. Variety in Alcohol Use Disorder Relapse Definitions: Should the Term 'Relapse' be Abandoned?

ABSTRACT: Objective: The definition of 'relapse' has been the subject of debate for decades and a semantic ambiguity highlighted in a 2016 paper in the Journal of Studies on Alcohol and Drugs remains. The current paper replicates and extends the 2016 findings on alcohol use disorder (AUD) relapse definitions.

Method: We conducted a systematic review of 321 papers that examined relapse in patients with AUD, published from 2000-2019. Relapse definitions were extracted and a narrative review of definitions was conducted.

Results: One hundred and one different definitions of relapse were used in 251 (78%) of the reviewed papers. In 70 (22%) of papers no definition of AUD relapse was provided. Fifty-three papers used diagnostic criteria (i.e., alcohol use after remission of AUD), whereas 99 papers defined relapse as 'any alcohol use' or 'any use of alcohol/drugs'. Additional papers defined relapse by alcohol outcomes (e.g., percent drinking days), alcohol-related problems, or hospitalizations (n=97). Only twelve papers described the time window of abstinence preceding a relapse. We observed relatively no meaningful intercontinental or time-related differences in relapse definitions, although the outcome 'percent heavy drinking days' was used more frequently in recent studies.

Conclusions: A wide variety of relapse definitions were identified. Despite decades of research and discussion, there is still no widely accepted consensus definition of AUD relapse. We propose to shift the focus towards clinical continuous outcomes, course specifiers based on the number of AUD symptoms present, and quality of life-related criteria instead of using current dichotomous AUD relapse terminology.

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1. INTRODUCTION

The definition of 'relapse' has been the subject of debate in research and practice of alcohol use disorder (AUD) for decades, and recent research has indicated semantic ambiguity in the use of the term (Maisto et al., 2016b). In medical terminology a relapse is commonly defined as the "return of a disease or the signs and symptoms of a disease after a period of improvement" (National Cancer Institute, 2015). This definition, when applied to AUD, would suggest that AUD was present, but then there was a period of improvement, followed by the return of AUD diagnosis or AUD symptoms.

The presence of an AUD can be diagnosed using the 5th edition of the Diagnostic and Statistical Manual of mental disorders (DSM 5) (Hasin et al., 2013; Robinson and Adinoff, 2016). Interestingly, the DSM 5 classification does not have the term relapse incorporated, nor defined, but it regards the disorder 'in remission', when no criteria (except 'craving') have been met for longer than a year. The term 'early remission' is used, when the symptoms have been absent between a 3- and 12-month period. In the World Health Organizations' (WHO) classification system of diseases, International Classification of Diseases (ICD-11), the terms 'alcohol dependence' and 'harmful alcohol use' do somewhat match DSM 5 AUD. Notably, the ICD-11 also does not mention 'relapse' (Saunders et al., 2019), and also has codes for remission, including 'early full remission', 'sustained partial remission', and 'sustained full remission'. Full remission is defined by abstinence of 1-12 months (early) or more than 12 months (sustained), whereas sustained partial remission is defined by a reduction in alcohol consumption for more than 12 months and not meeting criteria for alcohol dependence. Thus, remission refers to the lack of symptoms of the disorder, whereas 'relapse' is often used to indicate any alcohol use or related problems.

The term 'recovery' has also been used throughout the AUD literature. For example, a recent review defined recovery as "an ongoing dynamic process of behavior change characterized by relatively stable improvements in biopsychosocial functioning and purpose in life" (Witkiewitz, Montes, et al., 2020, p1). It must be noted that, by using this definition, the process of recovery is not dependent on the amount of alcohol consumption, and certainly not an antonym of 'relapse'.

However, 'relapse' in AUD has frequently been the focal point of past and present treatment research (Gorski, 1990; Hendershot et al., 2011; Hunter-Reel et al., 2009; McKay, 1999; Sliedrecht et al., 2019; Witkiewitz and Marlatt, 2004), and a frequently used outcome variable in clinical populations with AUD and substance use disorders (SUDs) (Hunt et al., 1971; Sinha, 2011). Numerous researchers have advocated, that given the frequent presentation with cycles of remission and relapse, AUD has to be seen and treated as a "chronic relapsing condition", highlighting the essential role of relapse in the conceptualization of addiction (McKay and Hiller-Sturmhofel, 2011). This has been supported by several neurobiological findings in animal models examining reinstatement of alcohol and other drug use and in human neuroimaging studies (Koob and Volkow, 2016; Seo, Dongju; Sinha et al., 2015; Uhl et al., 2019; Volkow et al., 2016). It must be noted, that the achievement of 'remission' or 'recovery' is defined by most clinicians as the ultimate

treatment goal, which frequently is associated with stable abstinence or reductions in drinking (Cranford et al., 2014; Rosenberg et al., 2020; Witkiewitz, Wilson, et al., 2019).

The occurrence and recurrence of relapse is also considered to be clinically important, and 'relapse prevention' interventions have been widely used in clinical practice (Donovan and Witkiewitz, 2012). Although given the chronic relapsing nature of the disorder (Volkow et al., 2016), stable abstinence might be very difficult to achieve. Owing to this perspective, Roozen & van de Wetering (2007) suggested to change the term 'relapse prevention' into 'relapse management', and consequently, they proposed a continuous assessment of relapse instead of a dichotomous approach (Roozen and van de Wetering, 2007).

Relapse Definitions across Studies

In the literature various terms have been used to describe the clinical course of AUD. Semantic terms encompass: 'slip', 'lapse', 'relapse', 'relapse to heavy drinking', 'recurrence', 'recovery' and 'remission'. For example, the relapse definitions used in alcohol literature varied from 'one drink' or 'any drinking' to 'drinking at least the former quantities'. Maisto and colleagues (2016) investigated the wide spectrum of definitions in the AUD treatment outcome literature, spanning the years 2010-2015 (Maisto et al., 2016b). They included 139 papers, and found 25 different definitions to characterize alcohol relapse. In addition, it was found that only six studies made notice of a required time-window of a period of improvement (defined as abstinence), after which a relapse could occur. Most studies made use of the cut-off point of 'any use' (alcohol or drugs) to define relapse. In four studies DSM symptom criteria were used to determine the occurrence of relapse. Furthermore, in this review only one of the included studies (Ramo et al., 2012) provided an empirical basis (referring to and building on earlier research) for the definition they had used to describe 'relapse' (Maisto et al., 2016b). This definitional ambiguity, however, is not unique to AUD relapse, and there is also ambiguity for the concept of relapse in schizophrenia (Olivares et al., 2013).

Relapse definitions reported by Maisto et al (2016b) were often derived from assessment instruments that measure daily use of alcohol, including the Timeline Follow-back (Sobell et al., 1996) and Form-90 (Miller and Del Boca, 1994). Daily drinking data is often summarized over specific time windows (e.g., past 30 days, past 3-months), such as percent heavy drinking days, percent days abstinent, drinks per drinking day, or drinks per day, and used as primary outcome variables in various studies reporting on the outcome of AUD interventions (Bach et al., 2019; Tonigan et al., 2017; Witkiewitz, 2011).

Moving Beyond Any Drinking

From a public health perspective for all-cause mortality and cardiovascular disease, the importance of reducing alcohol use is critical (Wood et al., 2018). Recent studies have advocated that favorable and acceptable outcome measures preferably should go beyond dichotomous (yes/ no drinking) outcomes and consider drinking reductions as the primary target for AUD treatment (Falk et al., 2019; Hasin et al., 2017; Mann et al., 2017; Roozen and

van de Wetering, 2007; Witkiewitz et al., 2017; Witkiewitz, Heather, et al., 2020). A recent meta-analysis of clinical trials of controlled drinking among patients with AUD found stable reductions in drinking are achievable, particularly if psychotherapy provides support for controlled drinking (Henssler et al., 2020). Further, binary definitions may actually be counterproductive in that they perpetuate the (partly self-imposed) stigma of AUD and also may reduce problem recognition and help seeking for AUD (Morris et al., 2020, 2021). Moreover, recent research suggested that the term 'relapse' is associated with a negative explicit and implicit bias; and it was proposed to instead use the more positive term 'recurrence of use' (Ashford et al., 2018). It must be noted that recent research suggested that non-abstinent treatment options are still deemed more acceptable in Europa and Australia, as compared to North America (Rosenberg et al., 2020). These findings suggest there could be geographical differences in relapse definitions, which has not previously been investigated.

Current Study

The current study is a narrative overview of current 'relapse' definitions, based on a systematic review on AUD relapse factors (Sliedrecht et al., 2019). The current paper is a replication and extension of the 2016 paper of Maisto et al. (Maisto et al., 2016b); using a span between the years 2000-2019, including studies that reported on 'relapse'. The current review extends the Maisto paper by examining relapse definitions in the decade prior to 2010 and in the four years following 2015. Furthermore, we examined the frequency of use on 'relapse' outcomes (i.e., from dichotomous towards continuous) in these two decades. In addition, we investigated whether there were differences in relapse definitions by geographic location.

2. Method

Search Strategy and Data Extraction

The original search algorithm is described in detail in a systematic review on AUD relapse factors (Sliedrecht et al., 2019). The Sliedrecht et al. (2019) review originally assessed AUD relapse determinants derived from two decades of AUD literature. Briefly, three databases were searched (PubMed, PsycINFO and the Cochrane database) with the dates of January 2000 to April 2019 for English language articles examining alcohol relapse in adult humans (18-65 years) with books and dissertations excluded. Both quantitative and qualitative research was included. Search terms included: 'alcohol use disorder' (AUD) and relevant synonyms (e.g., alcohol dependence), which were coupled with the terms 'relapse' or 'remission' using the Boolean search operators 'AND' and 'OR'. In the Sliedrecht et al. 2019 systematic review two reviewers (WS, RdW) extracted relapse determinants. For the current paper all full texts resulting from the expanded search were read by the first author (WS) who was also responsible for the extraction and coding (with KW) of relapse definitions. We also assessed the time-window of abstinence, after which a relapse could potentially take place. In addition, to explore any potential geographical difference, we analyzed the original papers and the results on any potential difference regarding binary versus continuous

outcomes among countries. More specific, and as an illustration, the outcomes 'any use' and daily drinking data were broken down by country of origin.

3. Results

Three hundred twenty-one papers were appraised on 'remission', 'recovery' or 'relapse' definitions. When no definition could be extracted, we assigned 'not applicable' (N/A). Papers were also appraised for an explanation of the given definition/description (Supplementary material S1). The relapse definitions were examined based on definitions that incorporated alcohol use outcomes, broken down by continuous and binary definitions, as well as alcohol-related problem measures. We also examined whether a period of improvement was considered, and whether diagnostic information based on the DSM was considered.

An overview of the grouped relapse definitions is displayed in Table 1. An additional overview of the 321 distinct analyzed papers, as well as a list with citations of the original research, can be found in the supplemental material. Hundred and one different definitions of relapse or remission were used in 251 (78%) of the reviewed papers. A total of 74 definitions concerned 'relapse', and 27 used the terms 'remission' or 'recovery'. In 70 papers (22%) no definition of AUD relapse was given or could be reconstructed from the content of the paper. Several of these original papers were reviews and in several cases no overarching relapse definition was given (Castaldelli-Maia and Bhugra, 2014; Foulds et al., 2017; Garcia and Salloum, 2015; Garfield et al., 2014; Gong and Minuk, 2018; Henkel, 2011; McKay et al., 2006; Tusa and Burgholzer, 2013; Walitzer and Dearing, 2006).

Dichotomous Drinking Outcomes

In 87 papers (27%) the 'any alcohol use' criterion was used to label a 'relapse'. In addition, in twelve papers 'any use' could also include the use of any illicit drugs. Thus, one-third of all papers defined relapse by any use.

Continuous Drinking Outcomes

In 26 papers one or more summary measures were used like 'percent drinking days', or 'days drinking'. Several papers explicitly used the '4 or more drinks per day for women and 5 or more drinks per day for men', or the equivalent '≥48 g/day for women and ≥60 g/day for men' criterion, from which the 'percent heavy drinking days' can be calculated (Tonigan et al., 1997).

Quantity and Time Frame

Twelve papers reported a time-window in which a relapse could take place given a period of improvement, but only five papers mentioned a specific number of abstinent days prior to relapse (Holt et al., 2012; Miller and Harris, 2000; Zywiak et al., 2003; Zywiak, Stout,

Longabaugh, et al., 2006; Zywiak, Stout, Trefry, et al., 2006). Another 12 papers only mentioned quantity of use, and another 17 articles combined quantity and time frame.

DSM/ ICD criteria, Recovery and Remission Definitions

In 53 papers (17%) that mostly had 'remission' as the outcome, authors made use of DSM related criteria. Six of these papers comprised 'recovery' as the outcome. In 2 papers ICD-criteria were used.

Various Definitions

In four papers readmission to a treatment service (e.g., detoxification clinic) or 'number of detoxifications', was used as outcome to define 'relapse'. Several papers used 'problem drinking' as outcome; but this term was not always explained. In some papers '(re) hospitalization' or 'medical harm' criteria were considered a characteristic of a problematic drinking pattern. The severity score of the Addiction Severity Index was used to define relapse in one paper (Strakowski et al., 2005).

In the rest of the papers, various other definitions were used. These definitions used for example 'use of former quantities', but the details of these quantities were not further specified.

Continuous vs. Dichotomous Outcomes and Results by Geographic Region

In order to examine time-effects on the application of 'relapse' outcomes, a division of papers reporting on dichotomous and continuous outcomes was also tabulated in Table 1. We found that 28 (9%) papers reported continuous outcomes; these papers were mostly published in more recent years (from 2011-2019). To assess potential differences in relapse definitions among countries and regions, we found all regions reported on a range of different definitions and did not find support for differences by region (see Supplement Table 2 for an overview).

4. Discussion

In line with earlier research (Maisto et al., 2016b), this study confirmed that relapse definitions varied substantially. As Maisto et al. found 25 different relapse definitions, our findings yielded a fourfold number of 101 different relapse definitions. As the original Sliedrecht et. al. systematic review aimed to investigate relapse determinants (and not relapse definitions), different from the Maisto et al. design, studies were included that did not provide a definition of relapse. Thus, in our research it became clear that in a sizeable proportion of papers no clear definition could be extracted from the papers nor an overarching 'relapse definition' (Castaldelli-Maia and Bhugra, 2014; Foulds et al., 2017; Garfield et al., 2014; Gong and Minuk, 2018; Henkel, 2011; McKay et al., 2006; Tusa and Burgholzer, 2013; Walitzer and Dearing, 2006). In the remaining papers the definition varied

substantially, with a range of outcomes from any use to percent days abstinent to amount of drinking to healthcare service utilization to DSM definitions of remission. Thus, we conclude that despite decades of AUD relapse research, no consensus has been reached to a uniform definition of 'relapse' (Maisto et al., 2016b; Miller, 1996; Sliedrecht et al., 2019). This semantic ambiguity complicates research synthesis of outcomes across studies, and prevents clinicians and researchers from speaking the same language on what is actually meant by using the term relapse.

The prevalence rate of reporting the dichotomous drinking outcome 'any drinking' versus 'abstinence' was common (Table 1). Approximately one-third of the papers defined relapse as any use of alcohol or drugs, without any consideration for a period of improvement preceding the relapse. However, the binary 'yes/no' drinking outcome has been shown to be inadequate and may not capture substantial improvements in patient functioning that occurs with reductions in drinking (Falk et al., 2019; Witkiewitz, Heather, et al., 2020). The 'any drinking' or 'any use' criteria may have some value within abstinent-only approaches (e.g., Twelve Step Facilitation, disulfiram), but it does not account for the complex and dynamic process of behavior change (Roozen and van de Wetering, 2007; Witkiewitz, Heather, et al., 2020; Witkiewitz, Pearson, et al., 2020; Witkiewitz, Wilson, et al., 2019).

Continuous measures, such as percent drinking days and percent heavy drinking days, attempt to capture a range of potential drinking outcomes and drinking practices. Yet, such measures were used in less than 10% of papers in the last two decades' research on relapse. Interestingly, 'heavy drinking' definitions generally better predict long-term outcomes, as compared with the 'any drinking' definition (Maisto et al., 2016a). These measures have been more frequently used in the last 5 years. It must be noted that the variation in relapse descriptions could impose difficulties in the interpretation and comparison of the results among studies. The criterion 'any use' after a period of abstinence was rarely reported, and in most cases the information on a preliminary abstinence period or other measure of improvement occurring prior to the relapse was not provided.

Interestingly, our research showed that DSM IV or 5 criteria were used in 53 papers (17 %) (compared to 2.9% in the 2016 Maisto paper), and in only two papers ICD-10 criteria were used. Consequently, more frequent use of DSM criteria emerged in more recent years as compared to earlier work (Maisto et al., 2016b). As the DSM 5 is prominent in classifying an AUD (Carvalho et al., 2019; Hasin et al., 2013; Robinson and Adinoff, 2016), it holds promise to employ the DSM related course specifier 'remission'. The outcome 'remission' minimally spans a timeframe of three months (early remission), where no AUD criteria (besides craving) are present (Hasin et al., 2013; Robinson and Adinoff, 2016). A remission period is not interrupted by just drinking one or more alcoholic beverages, but only when drinking leads to physical and/or psychosocial problems, as indicated by distinct DSM 5 criteria. In accordance with DSM 5 AUD course specifier definitions, the number of criteria present could indicate the severity of the reinstatement or impairment of the AUD. It seems that not only the remission criterion, but also the number of AUD symptoms could be used in the future. If patients exhibit a decrease in the number of AUD symptoms, this could be evaluated as indicating progress in treatment. On the other hand, clinicians should be alert

with any increase in the number of symptoms, even when full diagnostic disorder criteria are not met. However, with some individuals, considering their medical condition and quick deterioration after drinking any amount of alcohol, total abstinence, and not a reduction in symptoms could be discussed as a treatment goal. For some others, drinking reductions could be considered an alternative option (Ooms et al., 2021). Importantly, recent research has found reductions in World Health Organization (WHO) risk drinking levels are associated with better functioning (Witkiewitz, Heather, et al., 2020). The WHO risk drinking levels could be used by clinicians to demarcate increases or decreases in risk based on levels of consumption (very high risk: >101 gram for males/ >61 gram for females, high risk: 61–100 gram for males/41–60 gram for females, low risk: 1–40 gram for males/1–20 gram for females, medium risk: 41–60 gram for males/21–40 gram for females).

Furthermore, the term recovery was used in six papers, which was defined by abstinence OR meeting no DSM AUD criteria for a period that could vary between at least one and five years, and one author added 'risk drinking' and the "absence of severe headache when getting over drinking" to these criteria (Table 1). It has recently been advocated that besides consumption/abstinence, that measures like psychosocial functioning, employment, life satisfaction and mental health, should be taken into account when defining recovery (Witkiewitz, Wilson, et al., 2019). In those patients that persist in some heavy drinking in the year following treatment, nevertheless half of these patients appear to maintain high levels of psychosocial functioning; even up to 3 years following treatment (Pearson et al., 2021). It must be noted that in our study psychosocial functioning was incorporated in only 5 relapse definitions (Kelly et al., 2006; Mericle et al., 2018; Schutte et al., 2003, 2009; Wigg et al., 2017). Notably, in recent years a similar recovery/rehabilitation-based approach has been postulated in the broader context of psychiatry, appraising a broader perception of the distinct psychiatric disorder (Rössler, 2006; Rössler and Drake, 2017; Vita and Barlati, 2019).

Limitations

We used a systematic search strategy to include a broad array of relevant relapse factors. However, given the heterogeneity of included papers and number of different definitions, it was not possible to conduct a quantitative meta-analysis of different relapse definitions and how definitions may be associated with other measures. The extraction of relapse determinants in the 2019 systematic review was done by two reviewers, however in the current paper, the extraction of the relapse definitions was done by the first author, which could be regarded a limitation. As our review work covered only papers written in the English language, most research originated from the western world. Although we did not find differences among countries, other research suggested such difference in the acceptance of non-abstinent treatment outcomes, where by service providers non-abstinent outcomes are deemed more acceptable in Europa and Australia compared to Northern America (Rosenberg et al., 2020). Historically, this could be traced back to the dominance of abstinence-based approaches like Alcoholics Anonymous and Twelve Step Facilitation Treatment in the United States (US), which actually seem to favor dichotomous abstinence outcomes (Kelly et al., 2020). However, we did not find such dichotomy in our results, where for example 'any use' outcomes were not predominantly used in US research

(Supplement Table 2). It must be noted that most research was from German and US origin, indicating that the 'hotspots' of alcohol research might be situated in these countries. Broader inclusion of non-English language papers could provide more information about the range of relapse definitions used worldwide.

Definitions vary

A wide variety of relapse definitions were identified and consequently, and consistent with prior work by Maisto et al. (2016), we found lack of consensus in operationalization of AUD relapse in the AUD literature. This lack of consensus is further complicated by the use of the outcome terms 'remission' and 'recovery', but literature using these terms is also not always consistent, as for example a recent systematic review on SUD remission used the outcome '6 months without DSM symptoms' (instead of the 3- and 12-months' timeframe) (Fleury et al., 2016). Interestingly, the recovery definitions in our research also incorporated DSM remission criteria. For an overview of the use of 'recovery' in the literature we want to refer to a recent review by Witkiewitz and colleagues (Witkiewitz, Montes, et al., 2020). Actually, this could argue for using the 'medical' relapse definition ("return of a disease or the signs and symptoms of a disease after a period of improvement").

Leaving the Wagon?

Despite decades of research and discussion, there is still no widely accepted definition of AUD relapse. We propose to shift the focus from dichotomous AUD relapse terminology towards continuous outcome and quality of life related criteria. Outcomes like psychosocial functioning, life satisfaction and mental health, should also be taken into account. The clinical use of the DSM 5 criteria might be tempting, as one could distinguish AUD being present or being 'in (partial) remission'. The impact of treatment or the (natural) course of AUD could be monitored by the use of course specifiers (the number of AUD symptoms present), but also measures of functioning in different life areas. For example, recent research showed the usefulness of a health survey (to assess physical and mental health), and the World Health Organization Quality-of-Life Scale (Pearson et al., 2021; Witkiewitz, Pearson, et al., 2020).

Taken together, the great variability as shown in our review and its broad, negative, impact on the development of the AUD field, highlights the urgency for an international (Delphi-consensus) project in view of developing a general accepted and theoretically well embedded definition of relapse in AUD. As a preliminary suggestion a new AUD relapse definition could for example comprise: "Recurrence of AUD criteria after a period of 3-month remission (as for example has been employed in the DSM 5), accompanied with deterioration of health, mental well-being or life satisfaction". That said, we would suggest that a future expert panel might come to an evidence- and practice-based construct of AUD relapse, or any other related construct if this future panel would choose to rename 'relapse', and perhaps the panel would come to a consensus decision to stop using the term. This would probably provide the means of 'leaving the wagon' of over 40 years of semantic controversy (Miller, 1996).

Table can be found at the end of this publication. For this chapter Table 1 on page 107.

Supplementary materials associated with this article can be found in the online version, at doi: 10.15288/jsad.2022.83.248

References Chapter 1

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2. Alcohol Use Disorder relapse factors: A systematic Review

ABSTRACT:

A relapsing-remitting course is very common in patients with an Alcohol Use Disorder (AUD). Understanding the determinants associated with alcohol resumption remains a formidable task. This paper examines relapse determinants based on a systematic review of recent alcohol literature (2000–2019). Relevant databases were consulted for articles that contained information about specific relapse determinants and reported statistical significance of each relapse determinant in predicting relapse. Relapse was broadly defined based on the characterization in the included articles. From the initial identified 4613 papers, a total of 321 articles were included. Results encompass multiple relapse determinants, which were ordered according to biopsychosocial and spiritual categories, and presented, using a descriptive methodology. Psychiatric co-morbidity, AUD severity, craving, use of other substances, health and social factors were consistently significantly associated with AUD relapse. Conversely, supportive social network factors, self-efficacy, and factors related to purpose and meaning in life, were protective against AUD relapse. Despite heterogeneity in different methods, measures, and sample characteristics, these findings may contribute to a better therapeutic understanding in which specific factors are associated with relapse and those that prevent relapse. Such factors may have a role in a personalized medicine framework to improve patient outcomes.

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1. Introduction

Alcohol Use Disorder (AUD) is a highly prevalent psychiatric disorder. According to recent epidemiologic data, an estimated 23 million people have an AUD in the European Union (Rehm et al., 2015) and an estimated 32.6 million people have an AUD in the United States (Grant et al., 2017, 2015). Importantly, most people with AUD recover without any formal treatment (Cohen et al., 2007; Grant et al., 2015). Yet, for numerous individuals, having an AUD encompasses a chronic, recurring condition involving multiple cycles of treatment, abstinence, and relapse (McKay and Hiller-Sturmhofel, 2011). This is particularly common among individuals with AUD and psychiatric co-morbidity, where the course of AUD is typically chronic and disabling (Durazzo and Meyerhoff, 2017; Tuithof et al., 2014). For instance, AUD alone and in combination with psychiatric disorders is often associated with heightened suicide risk (Flensborg-Madsen et al., 2009; Kõlves et al., 2017).

1.1. Defining relapse

In AUD treatment and research, a semantic controversy exists, regarding the definition of "relapse". For instance, terms like 'slip' and 'lapse', indicating single instances of drinking, are commonly used in the literature. Despite a vast amount of research, the definition of relapse remains a semantic ambiguity (McKay et al., 2006; Miller, 1996), whereby "the heuristic value of AUD relapse as currently studied is low" (Maisto et al., 2016a).
Half a century ago Hunt, Barnett, and Branch (1971) found relapse rates (with relapse defined as any substance use) among multiple substances (alcohol, tobacco, and heroin) in addiction treatment were strikingly similar with most individuals returning to substance use within the first three months following treatment and less than 30% continuously abstinent at one year following treatment. A recent meta-analysis shows that at most 50% of people with an AUD, after a longer follow up period of several years, achieve remission (Fleury et al., 2016). To counteract the high relapse rates, Marlatt and Gordon (1985) proposed 'Relapse Prevention' skills to reduce relapse risk (Larimer et al., 1999; Roozen and van de Wetering, 2007), which is still a hallmark in addiction treatment (Hendershot et al., 2011). More recently, several psychological and psychobiological models have been postulated and tested for their validity in characterizing relapse (Connors et al., 1996; Hendershot et al., 2011; Witkiewitz, 2011; Witkiewitz and Marlatt, 2007, 2004).

1.2. Theories of relapse

Examining determinants that are frequently associated with relapse, as well as those factors that are protective in preventing relapse, is an important avenue for further research. Several studies have examined relapse determinants from a specific framework, such as social learning or cognitive behavioral framework (Witkiewitz and Marlatt, 2004), social factors (Hunter-Reel et al., 2009), neurobiological (Cui et al., 2015), and the 'disease concept' (McKay and Hiller-Sturmhofel, 2011).

In the last two decades, light has been shed on the neurobiology of addictive behaviors, including AUD (Koob and Volkow, 2016; Noël et al., 2013; Uhl et al., 2019), and heuristic neurobiological relapse models have been hypothesized. Dysfunctions in three major neurocircuits have been proposed: the basal ganglia (including the striatum), the extended amygdala, and the prefrontal cortex (Koob and Volkow, 2016), while other research has put an emphasis on the role of the insula (Noël et al., 2013). These theoretical frameworks have fostered the development of several behavioral and medical interventions (Volkow et al., 2016), but the 'translation' into clinical practice remains a challenge (Noël and Bechara, 2016). In addition, it must be noted that few studies have attempted to integrate social, psychological and neurobiological findings.

1.3. Current study

Engel's biopsychosocial (BPS) model (Engel, 1977) has proven validity (Wade and Halligan, 2017), and may be appropriate for examining determinants of AUD relapse that might foster translation into a clinical setting (Álvarez et al., 2012). Determinants leading to relapse, in the perspective of an integrative view like the BPS model, could be used as a practical clinical guide (Borrell-Carrio et al., 2004). Recently, this model has been expanded to the 'biopsychosocial-spiritual' (BPSS) model (Sulmasy, 2002), which may be particularly useful for characterizing relapse given the importance of spirituality in many AUD treatment and mutual help approaches. The objective of this exploratory narrative review is to provide an update on the latest research examining established relapse determinants, as well as to review the literature to identify novel relapse determinants. The BPSS model was used to catalog our results. As such, a general overview of identified relapse determinants will be provided. These relapse determinants could be integrated in the practice of current treatments and our findings could give rise to more extensive and systematic research on particular categories of the BPSS model.

2. Methods

2.1. Search strategy

Based on the Cochrane methodology, three databases (PubMed, PsycINFO and the Cochrane database) were consulted (January 2000–April 2019) for 'English' articles highlighting alcohol relapse in adult humans (18–65 years). The search was commenced on April 24th 2019. The search term 'Alcohol Use Disorder' (AUD) and relevant synonyms were coupled with the terms 'Relapse' or 'Remission' using the Boolean search operators 'AND' and 'OR'. The term 'recurrence' did not yield any relevant extra articles, so was discarded in the final search. In 'PICO' terms, the Population ('adults with an AUD'), the Intervention/determinant ('relapse determinants'), the Comparison ('remission determinants') and the Outcome ('AUD remission or relapse') could be formulated. The final search strategy used in PubMed is displayed in Table 1. For the two other databases, similar search terms were used.

The search in the Cochrane database yielded no articles describing AUD relapse factors. Books and dissertations were excluded.

Table 1 Search *details.*

(Alcoholism [MeSH Terms] OR Alcoholism [all] OR Alcohol Use Disorder [all] OR Alcohol Abuse [all] OR Alcohol Dependence [all]) AND (relapse [all] OR remission [all])
#1 Alcoholism (MesH and All Fields)
#2 Alcohol Use Disorder
#3 Alcohol Abuse
#4 Alcohol Dependence
#5 #1 OR #2 OR #3 OR #4
#6 Relapse
#7 Remission
#8 #6 OR #7 Combining: #5 AND #8
Filters added: Human/ English / Adult / Year 2000- (April) 2019

2.2. Study selection

The first author screened all abstracts on AUD, relapse or remittance terms. The retained abstracts were independently read by two individual reviewers (WS & RdW) to make a selection for considering full length articles.

2.2.1. Inclusion

We included studies describing relapse determinants, accounting for relapse or remission in AUD. All studies that described any specific determinant associated with relapse were included; for example, qualitative and quantitative reviews, randomized controlled trials, controlled clinical trials, uncontrolled studies, correlational, and descriptive studies. Based on abstract / full text reading, articles were identified that explicitly mentioned factors associated with remission or relapse of AUD.

2.2.2. Exclusion

Articles were excluded that described various unhealthy or problematic drinking patterns that did not meet DSM IV or DSM 5 AUD criteria. Also, case reports describing a theoretical effect on relapse were excluded. Of all 393 full-length articles assessed for eligibility, eventually 72 articles were excluded. Of these excluded articles, two studies were omitted, because they were duplicates. With respect to the final number of 393 articles, two studies were questioned whether they were eligible to include in this review (Bauer et al., 2007; Karriker-Jaffe et al., 2018) which was resolved by both reviewers, by eventually excluding one (Bauer et al., 2007). In case of non-consensus, a third reviewer (HR) could be consulted to make a final decision. Papers with a mixed drugs/alcohol use population, whereby data regarding alcohol samples could not be uniquely distinguished (White et al., 2013), were omitted. Furthermore, we excluded studies whereby the effect of the reported relapse factor was not further explained in

regard to AUD relapse (Sullivan and Covey, 2002), or despite our search terms only dealt with animal studies (Schank et al., 2012).
We also excluded articles describing a possible relapse hypothesis (Simioni et al., 2012), intervention studies (Sugaya et al., 2012), or in which no new determinants were described, but an adjusted model was tested on already known determinants (Witkiewitz and Marlatt, 2007).
Several studies describing treatment methods were excluded, if besides the treatment effect, no other independent risk factors for relapse were mentioned. In case the data of an original study was used more than once, for example as result of inclusion into a systematic review (Bottlender and Soyka, 2005a; Foulds et al., 2017; Gong and Minuk, 2018; Kelly et al., 2006), data on specific relapse determinants were used only a single time (Adamson et al., 2009; Henkel, 2011). For longitudinal studies that reported on multiple moments in time the sample size at baseline-only was reported (Moos et al., 2006; Moos and Moos, 2007, 2006). Eventually, 321 unique articles were included.
During the writing process, we checked the quality of our own review work by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method (Moher et al., 2009). A PRISMA checklist is provided in supplement 1 (*online available with original publication*).

2.3. Relapse definition

No uniform definition of relapse could be retrieved from the included articles, which is consistent with the findings of a recent systematic review of relapse definitions (Maisto et al., 2016a). The definitions varied largely across studies, varying from returning to any drinking, to the percentage of heavy drinking days, or the persistence of AUD over time. Associations that were examined focused on the relationship between each of the relapse factors and outcome, which was variably defined across the included studies. Thus, our “relapse” outcome was defined as it was defined in the original study. Roughly defined, relapse in our review can be seen as ‘an absence of abstinence’.

2.4. Data extraction

From the included articles, the following data were extracted and tabulated in terms of study design/population, follow-up period, study objective, sample size, results/statistics and the final conclusion (supplement 2; *online available*). Finally, the mentioned determinants of relapse/remission were tabulated according to Engel's biopsychosocial model expanded to the ‘biopsychosocial-spiritual’ (BPSS) model. Based on this model, 37 subgroups were composed, which are displayed in Table 2. These subgroups are partly known relapse categories from already existing and tested models (like ‘self-efficacy’ or ‘emotion(al states)’ (Witkiewitz and Marlatt, 2004), ‘psychiatric comorbidity’ or ‘stress’ (Blaine and Sinha, 2017). Determinants such as ‘genetics’ or ‘gender’ were considered biological. ‘Stress’, psychiatric and addiction related determinants were categorized psychological and ‘a supportive relationship’

was categorized as social. The determinant 'Living for a higher purpose in life' was categorized as spiritual.
Overall, we regarded a p-value <0.05 as statistically significant. Several papers only mentioned p-values and the clinical relevance was not made clear and very few studies reported effect sizes (Sullivan and Feinn, 2012). A few papers did not mention patient numbers or statistical analysis (McKay et al., 2006; Snelleman et al., 2018). Findings from these papers were categorized as 'statistically not significant', when these figures could not be retrieved after contacting the corresponding author. Quality assessment of included studies, identified 53 studies with a small sample size, eight studies where description of figures/ statistics was unclear or omitted. Of the 15 included reviews, only a few could be identified as 'systematic' and 5 were qualitative reviews not mentioning numerical data.
The most frequently reported determinants, or determinants found among a relatively large population are reported in Section 3. In cases where determinants were interrelated, we chose to report only the main findings and omitted the correlating determinant (Wiers et al., 2015).
To visualize the selection and data extraction process see the flow
chart in Fig. 1.

3. Results

3.1. Study selection

In PubMed, we obtained a total of 2689 references, 1915 in PsycINFO, and in the Cochrane database 9 (from which none described AUD relapse), thus making up a total of 4613 articles.
The two individual reviewers went through the abstracts and eventually 393 unique articles were marked as probably relevant to include in the actual review. From these, after comprehensive reading, another 72 were excluded. We included 321 articles in the actual review.
Because of the enormous diversity in described determinants, sample sizes and methodological quality and heterogeneity of the several studies, statistical analyses were not conducted and a narrative review was the focus of identifying those relapse determinants that consistently yielded statistically significant effects across studies.

3.2. Findings

Identified relapse determinants are reported in Tables 2 and 3. A complete overview of included articles can be found in Table 3. The results (number of studies and total sample size) are arranged using the BPSS model. The nature of each factor (in terms of relapse or remission) is described, as well as some relevant exemplary articles.

3.2.1. Biological factors

The factor 'age' was identified in 31 studies as having a statistically significant effect on relapse (aggregated sample size of 49,258 persons), whereas 15 studies found no

statistically significant effect of age on relapse (aggregated sample size of 2184 individuals). Generally, older age of onset of AUD was associated with a higher probability of remission (Abdin et al., 2014). A younger onset of AUD was associated with relapse (Vito Agosti, 2013).

The factor 'gender' was not a consistent predictor of relapse across studies. Some studies found that female gender was significantly associated with better prognosis (Boschloo et al., 2012; Dawson et al., 2005), whereas a greater number of studies found no statistically significant association between gender and relapse rates (Jakubczyk et al., 2013; Nalpas and Boulze-Launay, 2018; Spruyt et al., 2013).

'Brain' based determinants of relapse, measured via neuroimaging, were examined in 25 studies, however sample sizes tend to be smaller in neuroimaging studies. Generally, results are consistent with neurobiological models of addiction (Koob and Volkow, 2016; Noël et al., 2013) and studies have found dysfunction in the brain reward system, executive control network, and insula, among other regions were associated with significantly greater relapse rates. Only one study (Gross et al., 2013) failed to find an association between hippocampal volume and relapse risk among abstinent individuals with AUD.

The association between 'family history', reflecting genetic and shared environment variance, and 'genetic' factors (i.e., specific single nucleotide polymorphisms) and relapse has yielded mixed results. Generally, slightly more studies have identified family history and genetics to be associated with greater relapse risk, however a large number of studies have failed to find associations between family history or genetic factors and relapse risk.

The impact of 'health' as a relapse determinant was identified as statistically significant predictor of relapse or remission in nine studies with a total sample of 11,541 people. Across studies worse physical health was significantly associated with higher relapse risk (Satre et al., 2012) and only one study failed to find a significant association between health and relapse (Rus-Makovec and Cebasek-Travnik, 2008).

Eight studies with more than 400 patients found disturbed 'sleep' was associated with significantly greater relapse rates, and only one study found no effect of poor sleep on relapse (Jakubczyk et al., 2013).

'Hormonal' factors and specific 'biomarkers' of alcohol use (e.g., liver enzymes) have generally been less frequently studied and with smaller sample sizes, however most studies have found impaired hormone and elevated biomarkers are associated with relapse. For example, greater stress-induced craving was associated with a blunted cortisol response which predicted shorter time to relapse among outpatients with AUD (Higley et al., 2011).

3.2.2. Psychological determinants

In 44 studies (aggregated n = 24,889) 'psychiatric comorbidity', often diagnosed as affective disorder or attention deficit hyperactivity disorder (ADHD), was significantly related to an increased relapse risk (Schellekens et al., 2015; Trocchio et al., 2013). Conversely, in two studies, the presence of affective disorder was associated with remission (Terra et al., 2008; Tómasson and Vaglum, 2000). In 19 studies (n = 6819)

no statistically significant association between psychiatric disorders and relapse risk was found (Haller et al., 2014; Possemato et al., 2017; Sher et al., 2004).

'Severity of AUD' as a relapse factor was mentioned in 45 publications, with a total sample size of 34,160 persons. Generally, it was found that having more AUD symptoms was associated with relapse. A higher AUD severity is characterized by a chronic relapsing course (Chiappetta et al., 2014; Tuithof et al., 2014). However, ten studies (total n = 920) did not find that severity was associated with relapse.

In 29 studies (total n = 12,343) 'craving' was found to be a statistically significant predictor of relapse (McHugh et al., 2016; Roos et al., 2015; Weinland et al., 2019). In only six studies (total n = 384) craving was not found to be significantly associated with relapse (Charlet et al., 2014; McKay et al., 2006; Mo and Deane, 2016).

The factor 'abstinence duration' was significantly inversely related to relapse in 12 studies (6891 participants). For example, the influence of abstinence duration on relapse was shown in a US national epidemiologic three-year follow-up study (Dawson et al., 2007). Three studies did not find an association between abstinence duration and relapse (Bellamy et al., 2001; Junghanns et al., 2003; Kelly et al., 2006).

The factor 'emotion' (or 'negative affect') has shown a robust statistically significant effect on relapse in most studies (25 studies, n = 10,139), with more negative emotion associated with greater relapse risk (Moos et al., 2006). In eight studies (n = 724) the impact of emotion in predicting relapse was not statistically significant (Cooney et al., 2007).

The factor 'self-efficacy' is considered a protective factor (Witkiewitz and Marlatt, 2007), and data from 25 studies (n = 10,172) indicated a higher level of self-efficacy was significantly associated with lower relapse risk (Shaw and DiClemente, 2016). In three small studies, this association was not statistically significant (McKay et al., 2006; Sher et al., 2004; Trucco et al., 2007).

Comorbid 'Substance Use Disorder' (e.g., harmful use of cocaine, opiates or benzodiazepines) was significantly associated with relapse in 20 studies (total n = 45,382). In three studies (n = 310) the effect of comorbid substance use disorder on relapse was not statistically significant.

Similarly, fifteen studies (n = 20,092) reported on the influence of co-occurring 'smoking', accounting for a larger relapse risk. Only in one study (n = 557) the opposite was found, such that smoking predicted lower relapse risk (Schmidt and Smolka, 2007). Five other studies (total n = 456) did not find an association between smoking and relapse.

Although represented in fewer studies, 'treatment history', 'coping', and 'neurocognitive' factors were significantly associated with relapse risk in almost all studies, such that prior treatment, worse coping skills, and neurocognitive deficits predicted greater risk of relapse.

Seven studies (n = 14,508) found that having a 'personality disorder', increases the relapse risk. In five studies (n = 5083), this relationship was absent. A recent systematic review (with meta-analysis on a limited number of included studies) found that having personality disorders do not worsen AUD outcomes (Newton-Howes et al., 2017). In one paper, precise patient numbers could not be obtained and therefore

the paper was included in the 'not significant' column (Bradizza et al., 2006). Similarly, maladaptive 'personality traits' were significantly associated with greater risk of relapse in four (n = 5768) out of five studies.
'Life events', particularly trauma, and 'stress' were both associated with significantly higher relapse rates. For example, in a secondary analysis of COMBINE data (n = 1383), last weeks' perceived stress level was significantly associated with relapse (Witkiewitz, 2011). Only two studies of life events and two studies of stress did not provide support for a significant association between these determinants and relapse.
The findings about the determinant 'impulsivity' appear to be inconclusive, with nine studies (n = 554) showing a statistically significant association for several different measurement instruments used (Bernhardt et al., 2017; Rupp et al., 2016), and no statistically significant association in five other studies (n = 827). Most sample sizes of the included studies were small. Notably, one study (n = 20) showed a protective effect of higher impulsivity on relapse (Papachristou et al., 2014).
The 'number of prior detoxifications' was not strongly associated with relapse risk, with five out of ten studies finding that prior detoxification was significantly associated with relapse.
The remaining psychological factors, including 'insight', 'seeking help', 'drinking goals', 'outcome expectancies', 'motivation' and (negative) 'drinking consequences' were less widely studied and with fewer subjects per study. Yet, all of these factors were significantly associated with relapse, such that lower insight, less help seeking, non-abstinent goals, positive outcome expectancies, less alcohol-related negative consequences (Davis and Clifford, 2016), and lower motivation were associated with significantly greater relapse risk.

3.2.3. Social factors

Several studies showed that 'social' factors and the quality of social 'support' might be associated with diminished relapse risk. Consistently, it was found that having a positive social context and functioning (e.g., employment, greater socioeconomic status, education) was associated with reduced relapse risk in 43 publications (n = 47,866). On the other hand, in a systematic review (n = 5140) (Castaldelli-Maia and Bhugra, 2014), it was found, that living in a 'heavy drinking culture', is a strong risk factor for relapse. From a longitudinal cohort study, data showed that 'Alcohol availability' (neighborhood alcohol outlets) was a risk factor associated with an AUD, but not relapse (Karriker-Jaffe et al., 2018).
Living in a supportive relationship (e.g., marriage) was mentioned in 44 papers (n = 33,845). For example, in a follow-up study (n = 686), by McCutcheon et al. (2014), social support by friends, was associated with reduced relapse risk. However, in 17 articles (n = 11,136) no evidence for an effect of social factors on relapse were found. Furthermore, six articles (total N = 1155) did not find a statistically significant link between 'support' and relapse.
We also found in two studies, that having a (first-born) 'child', for women was related to reduce relapse risk (total sample size n = 6869).

3.2.4. Spiritual factors

Several articles examined the association between 'spiritual' concepts and relapse. Seven studies (n = 14,970) demonstrated a protective effect of spirituality on relapse rates and only three studies failed to confirm this association (n = 530). It should be noted that in one small study Muslim religion was significantly associated with greater risk of relapse (Sau et al., 2013).
A closely related concept is considered 'life purpose'. Six studies (n = 5415) reported on the positive effect of having a higher life purpose on reducing risk of relapse (Roos et al., 2015).

4. Discussion

Our systematic review delves into a broad array of relapse factors as described in recent literature. To our knowledge, no broad systematic review on AUD relapse factors has been conducted recently. The results give a timely update of significant relapse and protective factors covering almost twenty years of research.
Relapse and protective determinants were grouped by using the BPSS framework. Notably, biological factors such as having younger 'age' and poor 'health' seem to be important relapse predictors. So, more attention should be paid to prevention of alcohol use at younger ages (Kraus et al., 2018) and medical attention regarding co-existing health and somatic conditions.
In the last two decades the neurobiology of addiction (Koob and Volkow, 2016) has received increased attention, and neurobiological factors, mostly focused on the brain reward system, were identified in our search. Likewise, genetic factors, stress induced cortisol responses, and biomarkers were each unique predictors of relapse. Typically, research on neurobiological factors included smaller sample sizes limiting the generalizability. Future research with larger sample sizes is warranted to further identify biological predictors of relapse.
The effect of sleep disturbances on relapse has been previously substantiated in the literature (Miller et al., 2017), but seems not to be an area of extensive current research. Sleep management might be an important topic in addiction treatment (Miller et al., 2017).
The role of gender in relapse remains inconclusive, but warrants further research to specify segregated outcomes for males and females. Nonetheless, there is important pre-clinical work suggesting sex differences in relapse (Becker et al., 2017), and it is important to consider social and cultural factors when examining the association between gender and relapse (Becker et al., 2016). Some research suggest a 'telescoping effect' that suggests AUD in women may be followed by a more severe and progressive addiction course (Greenfield et al., 2010).
Results of the examination of psychological factors confirm prior findings that psychiatric comorbidity, addiction severity, craving and use of other substances are important relapse factors, as well as emotion, coping, and major life events. These factors were found in many studies with large sample sizes. Clinical treatment should take these factors into account, regarding relapse management, and treatment of co-occurring disorders (Bender et al., 2018; Tiet and Mausbach, 2007).

Our findings also confirm the necessity for offering help in smoking cessation (Castaldelli-Maia et al., 2018; Skelton et al., 2018).
Stress could be an interesting subject of further research, as it seems to be an important relapse factor (Blaine and Sinha, 2017; Kwako and Koob, 2017). Despite heterogeneity in stress-measures used, recent promising research focuses on neurobiological and hormonal factors and also points out the interrelationship with 'negative affect'.
Remarkably, we did not identify studies measuring 'positive affect' as a relapse or protective determinant; although this has been frequently studied in the past century (Larimer et al., 1999). This factor deserves renewed attention in future research.

Identifying different phenotypes of drinkers could be of clinical relevance (Helton and Lohoff, 2015), as recent work has suggested that individuals who drink alcohol to relieve negative emotions have a better treatment response to acamprosate (Roos et al., 2017), whereas those who drink for reward seeking have a better treatment response to naltrexone (Mann et al., 2018). Others have postulated different AUD 'typologies', each with a different probability regarding AUD course and treatment outcome (Weinland et al., 2017). Future pharmacogenetic treatment allocation might lead to improved personalized medicine for AUD (Sluiter et al., 2018).

Interestingly, many top-ranked treatments encompass 'motivational' interviewing / enhancement strategies (Miller and Moyers, 2017). However, only two studies delved into motivation as a relapse factor, so apparently a huge gap exists between this clinical practice and scientific findings that should be abridged in future research.
We could not confirm a clear link between impulsivity and relapse (Reyes-Huerta et al., 2018), since we found only a few studies. Difficulties in measurement of impulsivity, which is often considered a multidimensional construct (Dom et al., 2007; Herman et al., 2018; Stevens et al., 2014), could explain discrepancies across studies. For example, impulsivity measures were tested by using self-reports (Evren et al., 2012; Papachristou et al., 2014; Zikos et al., 2010), brain imaging correlates (Sorg et al., 2012) and neuropsychological tests (Fein et al., 2004; Quoilin et al., 2018). Recent research shows different aspects of impulsivity, including 'delay discounting', 'disinhibition' and 'decision making' (Reyes-Huerta et al., 2018; Stevens et al., 2014).

Previous studies have demonstrated that the cumulative amount of previous alcohol detoxifications may account for relapse (Duka and Stephens, 2014), but this was not confirmed in our review. Given the different definitions regarding supervised and unsupervised detoxification attempts, more research is needed on how the role of the number of detoxifications impacts relapse and the course of AUD.
Social factors seem to have a robust impact on relapse, whereby a positive social context and non-drinking social support appear to be protective. On the other hand, our results suggest that heavy drinking social network support is associated with greater relapse risk. So, clinically it is important to assess the characteristics of patients' social network to promote positive treatment outcomes (McKay, 2017). Having children could be a protective factor for women. Finally, factors concerning the

spiritual aspects and giving meaning to life were protective against relapse in a small number of studies.

Overall, the impact of impaired health, sleeping problems, psychiatric comorbidity, use of other substances (including nicotine), lack of coping skills, and addiction related factors like craving, diminished self- efficacy, AUD severity and the duration of abstinence, seem to have a more pronounced negative effect on the course of AUD.
Important protective factors seem to be 'spiritual' involvement, and a positive, supportive social environment.
Importantly, a number of the reviewed papers did not include standardized measures of effect sizes and only the most recent literature examined the impact of different relapse factors using effect size measures, such as odds- or hazard ratios. For example, in a national survey study (N=4828) it was found, that being physically active is associated with higher odds (OR:1.67, 95% CI: 1.28, 2.17) of 12-month AUD remission (Damian and Mendelson, 2017). In another recent study, the effect of smoking on alcohol relapse was quantified with a hazard ratio of 3.96 (Hufnagel et al., 2017).

Clinicians should assess those factors that are most strongly associated with relapse risk and offer treatment for psychiatric problems, use of other substances, and health and sleep- problems. Recommending mutual support group involvement, particularly for patients who are lacking a positive social environment that is supportive of recovery, may also be helpful.
As found in the 'Mesa Grande' study (Miller and Wilbourne, 2002), specific interventions (for example 'social skills training', 'marital therapy', case management, medication and the 'Community Reinforcement Approach/ Contingency Management' could aim at several of the relapse factors we found. At the behavioral level reinforcement-based interventions could help people link to other attractive reinforcers to compete with alcohol/drug use as a substitute for direct gratification tendencies (McKay, 2017).
Also, social skills training could help patients build up a positive social network. It must be noted, that given the role of stress sensitivity in addiction (Blaine and Sinha, 2017; Volkow et al., 2016), a stress- enhancing, confronting way of approaching those with an AUD should be avoided.

5. Strengths and limitations

We used a search strategy to include a broad array of relevant relapse factors. Data were obtained from multiple studies, often reporting on similar determinants. Conversely, sometimes just a few studies were identified mentioning relapse factors that have been understudied.
We limited our search to studies from the year 2000 and onwards to be able to make a synoptic overview of relapse determinants, but we realize a lot of important research was already done before (Becker, 1998; Marlatt, 1996; McKay, 1999), which has been summarized in prior reviews (Hendershot et al., 2011; Witkiewitz and Marlatt, 2004).

Unique in our review is the use of the BPSS model to arrange our findings. In comparison to earlier reviews some 'new' relapse determinants emerged, such as 'sleeping problems', 'impulsivity', 'health', 'smoking' and 'alcohol related negative consequences'. The amount of research for some other factors, like 'stress' and specific 'brain' areas, has increased in recent years.

As an integrative framework we chose the BPSS model to arrange our findings. In several cases, the allocation of factors to BPSS categories is open to multiple interpretations, as it can be argued that determinants could also be assigned to another category as well. In several cases categories are interrelated, as for example 'genetics' and 'receptor/ hormones' or 'psychiatric comorbidity' and 'personality disorder'. It should be noted that in several cases we could not ensure construct validity within one specific category, as in many cases the relapse factor was not consistently defined. This could lead to an observer bias. The number of publications in which a certain relapse factors was found, might also reveal a research or publication bias. On our part, we wanted to lower the risk of publication bias, by also mentioning statistically not significant outcomes. A large range of definitions for 'relapse' (Maisto et al., 2016a, b) also complicates a sound comparison among research results, preventing us from drawing firm conclusions. From this perspective, 'relapse' was considered an 'absence of abstinence'. Furthermore, in general, a wide range of follow up periods (weeks to years) in which a relapse could occur was used across studies.

Given the enormous heterogeneity in different methods, measures, and sample characteristics of the identified studies, we were unable to conduct a rigorous quality assessment of each study with respect to the identified relapse factor, and employed a descriptive methodology to summarize the findings. Statistical analyses (e.g., meta-analysis) were not possible given the extensive heterogeneity in our comprehensive assessment of relapse determinants. A narrower review within each category of determinants may be more amenable to meta-analytic investigation. However, where others conducted reviews and/or meta-analyses on -for example- the impact of 'personality disorder' on AUD relapse, only a few studies could be included for additional quantification (Newton-Howes et al., 2017).

We confirm the danger of a 'language bias' by limiting our search to the English language, mainly covering research from the western World. From this perspective, our findings may not be generalized to other parts of the World; although we also included several Asian studies.

Finally, it must be noted that most included research studies focused on abstinence-based approaches. In clinical practice, we encounter patient groups that are not able to achieve stable abstinence. As such, other treatment goals including moderation, harm-reduction and palliative care are considered complementary. Consequently, the label 'relapse' may be considered conflicting and may discount valuable clinical benefits that can be obtained in non-abstinent patient groups who achieve drinking reductions and improved quality of life (Hasin et al., 2017; Maisto et al., 2018; Mann et al., 2017; Palpacuer et al., 2018; Witkiewitz et al., 2019, 2017).

The definition of relapse has been the subject of debate for decades, and in the current paper we did not require a specific definition of relapse, remission, or recurrence to be included in the review. Yet, many empirical papers included in this

review did consider a return to any drinking or percent days abstinent as the definition of relapse. For many patients an abstinence-based drinking goal might be optimal, and abstinence is typically associated with better treatment outcome (Maisto et al., 2018; Witkiewitz and Masyn, 2008). At the same time, such a goal might not be attainable for everyone, and consequently, aiming at drinking reduction goals might be preferable and drinking reductions are also associated with improvements in functioning for some patient groups (Falk et al., 2019; Witkiewitz et al., 2019).

6. Conclusions

In this study, identified relapse factors encompassed psychiatric comorbidity, addiction severity, craving, negative emotion, use of other substances, health and social factors. Several supportive social factors, self-efficacy, and factors related to life purpose and spiritual involvement were recognized as protective. Many factors, including sleep, sex differences, neurobiological factors, genetics, impulsivity, positive affect, and motivation warrant further research.

Despite decades of research, the factors that lead to an AUD relapse are still highly variable and likely contextual. An integrative BPSS approach may help in gaining a better understanding of individual risk and protective factors in future studies. Future directions for applying our findings could be to consider specific interventions that may be most helpful for specific individual relapse risks (personalized medicine). Expansion of integrated treatment options for co-occurring psychiatric disorders seems to be a research area of particular interest. In addition, focusing on quality of life, in addition to reductions in alcohol consumption, should be taken into consideration.

Tables & Figure can be found at the end of this publication. For this chapter on page 113.

Supplementary materials associated with this article can be found in the online version, at doi: 10.1016/j.psychres.2019.05.038.

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3. The Association Between Impulsivity and Relapse in Patients with Alcohol Use Disorder: A Literature Review

ABSTRACT:

Aim: Impulsivity has been identified as a key relapse risk factor in patients with alcohol use disorder (AUD); however, the inherent characteristics of this relationship have been largely understudied. The heterogeneity of AUD and variation in impulsivity constructs require careful consideration to inform future work examining the relationship. This study sought to review empirical findings examining facets of impulsivity and AUD relapse.

Methods: A systematic search strategy was employed to capture studies on impulsivity measures related to AUD relapse. Impulsivity measures were qualitatively organized in terms of 'trait impulsivity'-typically measured by self-report questionnaires-and 'behavioral impulsivity', i.e., 'motor impulsivity', 'impulsive choice' and 'reflection impulsivity, assessed with cognitive-behavioral tasks.

Results: Seventeen peer-reviewed papers were identified. Relapse outcomes varied substantially in relation to impulsivity measures. Twelve papers included aspects of 'trait impulsivity', and nine studies included 'behavioral impulsivity' measures, from which five studies dealt with the 'impulsive choice' subcategory. The Barratt Impulsivity Scale was the self-report questionnaire that was most frequently used.

Conclusions: All three included facets of impulsivity ('trait-, motor- and impulsive choice impulsivity') were associated with AUD relapse, but none seemed to be superior to another. This study confirmed that research on the relation between impulsivity and AUD relapse is relatively scarce. Future research and treatment options are proposed.

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1. INTRODUCTION

Impulsivity construct

Alcohol use disorder (AUD) is a highly prevalent disorder (Rehm et al., 2015; Grant et al., 2017), frequently involving multiple cycles of treatment, abstinence and relapse (McKay and Hiller-Sturmhofel, 2011). For instance, such repeated abstinence–relapse cycles have been associated with intensified withdrawal and increased psychiatric symptoms (Ooms et al., 2021). Therefore, identifying distinct relapse factors is highly relevant (McKay et al., 2006). Impulsivity is one potentially relevant relapse determinant that remains relatively understudied (Reyes-Huerta et al., 2018; Sliedrecht et al., 2019).

The role of impulsivity in the initiation and progression of addictive behaviors remains an important topic (Noël et al., 2013; Noel et al., 2014; Koob and Volkow, 2016; Uhl et al., 2019). Yet, impulsivity may have an initiating role in the development and course of substance use disorder, suggesting an underlying vulnerability, or may also be a consequence of chronic substance use (Jentsch and Taylor, 1999; De Wit, 2009; Jentsch et al., 2015).

On a neurobiological level, deficits in response inhibition, leading to impulsive behaviors, could originate in both frontal cortex and striatal dysfunction. An overlap was found of impulsivity and addiction aspects that may have a common neurobiological origin, i.e., an abnormal frontostriatal connectivity (Galandra et al., 2018). On a neurochemical level, neurotransmitter dysfunctions, particularly decreased dopamine D2 receptor function and altered serotonin receptor function, seem to play a key role in promoting impulsive behaviors (Jentsch and Taylor, 1999; Jentsch et al., 2015). Recent research also found a role for dysfunctions in glutamate, gamma aminobutyric acid, dopamine, norepinephrine and serotonin signaling (Kozak et al., 2018).

On a cognitive level, impairments in executive function have been found related to several other psychiatric disorders, like borderline personality disorder (BPD) (Linhartová et al., 2021), suicidality (Liu et al., 2017) and attention deficit hyperactivity disorder (ADHD) (Adler et al., 2018; Linhartová et al., 2021). Furthermore, a vast body of research has investigated the impulsivity–gambling disorder association (Ioannidis et al., 2019). Recently, it has been advocated that impulsivity measures should be part of a standard neuropsychological assessment set to be used in research and treatment in addictive disorders— for instance— analogous to the MATRICS model, developed for schizophrenia (Yücel et al., 2019).

Impulsivity is frequently considered a multidimensional psychological construct, which is often seen as maladaptive inhibitory processes. These processes are characterized by an inability to withhold a response; often in the face of negative consequences, a preference for small immediate rewards at the expense of larger delayed rewards (i.e., delay discounting (DD)), acting without forethought, novelty/sensation seeking and an increased tendency to engage in risky behaviors (Bari and Robbins, 2013).

The impulsivity construct is an area of recent research interest. Over the past several years, several reviews on impulsivity and inhibition, impulsivity and

emotions/arousal and impulsivity and genetic factors have been published (Bari and Robbins, 2013; Kovács et al., 2017; Herman et al., 2018; Sanchez-Roige et al., 2019). Additionally, new research has emphasized emotional components of impulsivity in patients with substance use disorders (SUDs) (McHugh and Goodman, 2019). Importantly, the recently proposed Alcohol and Addiction Research Domain Criteria (Litten et al., 2015; Witkiewitz et al., 2019) has included impulsivity as a core construct within the executive function domain (Kwako et al., 2019), proposing that initiation and maintenance of AUD can be partially explained by neurobiological deficits and adaptations in executive function.

Recent advances have indicated that impulsivity is a broad umbrella construct (Dom et al., 2007; Broos et al., 2012; Stevens et al., 2014). Broos et al. (2012) have proposed the existence of three different aspects of impulsivity in humans: self-reported impulsivity, impulsive choice and impulsive action. Their impulsivity constructs were based on a principal component analysis on several commonly used assessment measures of impulsivity. Meda et al. also acknowledged the multidimensional aspect of impulsivity and, based on a factor analysis, identified five widely used impulsivity factors: 'Self-reported Behavioral Activation, Self-reported Compulsivity and Reward/Punishment, Self-reported Impulsivity, Behavioral Temporal Discounting and Behavioral Risk-Taking' (Meda et al., 2009, p. 390). In addition, Stevens et al. (2014) identified two aspects within the impulsivity construct, namely impulsive choice (subdivided into 'delay discounting' and 'decision-making') and 'impulsive action' (subdivided into 'motor disinhibition' and 'cognitive disinhibition').
Similar to Broos et al.'s (2012) definition, Herman et al. (2018) compared several existing impulsivity concepts and postulated an impulsivity subdivision in terms of 'trait impulsivity' and 'behavioral impulsivity'. 'Trait impulsivity' describes a somewhat stable pattern of impulsivity, grounded in the person's character, and is often assessed by the use of self-report questionnaires. 'Behavioral impulsivity' describes a behavioral pattern of impulsivity, which is often assessed by task-based measures of objective measures during variable circumstances. They also stated that the 'behavioral impulsivity' category could be further subcategorized into 'motor impulsivity', 'reflection impulsivity' and 'impulsive choice' categories (Herman et al., 2018).
As described in detail below, each of these categories can be measured by the use of a variety of self-report and behavioral task-based assessment instruments (Hamilton et al., 2015; Herman et al., 2018). Importantly, these subdivisions are also consistent with the definitions of impulsivity proposed by Meda et al. (2009) and Stevens et al. (2014), and thus, Herman et al.'s (2018) characterization incorporates aspects from multiple contemporary definitions of impulsivity (Meda et al., 2009; Broos et al., 2012; Stevens et al., 2014). As such, we have used this organizing framework from Herman et al. (2018) in the current study. Importantly, we have explicitly not included negative urgency, which is a unique dimension of impulsivity, in the current review, and we refer interested readers to a recent review on negative urgency and addiction relapse (Zorrilla and Koob, 2019).

Measuring impulsivity

Assessment of impulsivity

Previous research has shown that impulsivity can be captured by means of several self-report scales and behavioral tasks, but correlations were found to be generally weak (Reynolds et al., 2006; Dom et al., 2007; Broos et al., 2012; Stevens et al., 2014). Others, however, found a statistically significant overlap between several laboratory tasks and self-report measures (Meda et al., 2009). More recently, associations between behavioral performance, self-reported impulsivity and decision-making processes have been investigated (Portugal et al., 2018) and impulsiveness scores (but not decision-making) were associated with actual behavioral performance. Behavioral task measures of impulsivity have been shown to be reliably administered and may be used to assess various facets of impulsivity as intermediate phenotypes for SUD (Gottesmann and Gould, 2003; Weafer et al., 2013) and AUD (Kwako et al., 2019). While various self-report and behavioral measures measure different aspects of 'impulsivity', it seems none of these categories has better predictive value in regard to relapse (King et al., 2014). However, in a study of impulsivity in patients with BPD and SUD, behavioral measures were found to have a better predictive value in relation to actual behavior (Maraz et al., 2016).

Specific impulsivity measures

'Trait impulsivity' can be measured by several self-report scales. For example, the Barratt Impulsiveness Scale (BIS-11) is a commonly used self-report questionnaire to assess trait impulsivity (Patton et al., 1995). Other frequently used questionnaires are Zuckerman's Sensation Seeking Scale and the Urgency, Premeditation, Perseveration and Sensation-Seeking scale (Herman et al., 2018). 'Behavioral impulsivity' can be measured by several behavioral tasks, such as the stop-signal task (SST) and go/no-go (GNG) task, and several memory tasks, all measuring different aspects of 'motor impulsivity'. Also, tasks to measure 'reflection impulsivity' (whereby choices are made without consideration) have been developed. The 'behavioral impulsivity' subcategory 'impulsive choice' is often measured by using the DD task, the Iowa gambling task (IGT) and the balloon analogue risk task (BART) (Herman et al., 2018).

Impulsivity and relapse

An important question is whether cognitive deficits associated with impulsivity are relevant to clinical outcomes, i.e., treatment retention, relapse, reduction of substance use and/or craving, and quality of life (Verdejo-Garcia et al., 2019). A growing body of research suggests a potential link between impulsivity and relapse in substance use (Stevens et al., 2014, 2015; Barreno et al., 2019). In particular, impulsive choice and impulsive action are considered key relapse determinants in AUD (Reyes-Huerta et al., 2018). However, prospective studies exploring the relationship between relapse and impulsivity measures are scarce in patients with AUD. Courtney et al. (2012) tested several dimensions of impulsivity in a non-clinical

sample of problematic drinkers (majority having an AUD) and found impulsive decision-making to be related to the amount of alcohol use.
Although an association between relapse and impulsivity may exist, the nature of this relationship remains inconclusive (Sliedrecht et al., 2019). Of note, research on alcohol relapse is frequently complicated by the ambiguous and varying conceptualization of the concept of relapse. The definition of 'AUD relapse' remains a semantic indistinctness (Miller, 1996; McKay et al., 2006; Sliedrecht et al., 2019), whereby 'the heuristic value of AUD relapse as currently studied is low' (Maisto et al., 2016, p. 849). Taken together, impulsivity may seriously negatively impact the clinical outcome of patients. However, which dimensions of impulsivity are the drivers, the exact nature of the mechanisms involved, and the magnitude of these effects remain to be explored.

The present paper

The objective of this paper was to present the results of a systematic literature search on the relationship between impulsivity and relapse in patients with AUD, followed by a qualitative review of the results. The impulsivity subdivision of Herman et al. (2018) was used to provide an overview of the different aspects of impulsivity in terms of 'trait impulsivity' and 'behavioral impulsivity' (see Table 1).
The findings of the review will be categorized in terms of the aforementioned subdivision. We hypothesized that neurocognitive and behavioral measures of impulsivity would have a higher predictive value regarding AUD relapse over subjective self-report questionnaires (Gottesmann and Gould, 2003; Weafer et al., 2013; Salvatore, 2015; Stevens et al., 2015; Maraz et al., 2016; Kwako et al., 2019).

2. METHODS

Search strategy

The original search algorithm is described in a recent systematic review on AUD relapse factors (Sliedrecht et al., 2019). However, the search was updated and focused on the impulsivity–relapse association in patients with AUD, by means of using the broad MeSH search terms 'alcoholism' (which also includes terms AUD, alcohol dependence, alcohol abuse), 'recurrence' and 'impulsive behavior' (or synonyms compatible to the search engine used), which were coupled using the Boolean search operator 'AND'. The search was commenced in PubMed, PsycInfo, the Cochrane database of Systematic Reviews and the DARE database on June 24, 2020, and restricted to articles in the English language and were filtered on human studies.

Statistical analyses

The outcomes were tabulated in terms of the subdivision regarding impulsivity aspects. In those cases that the design of the included study permitted comparisons (control group), the impulsivity measures of the relapsed and those regarded as 'not relapsed' (i.e., in most cases abstinent patients) were extracted and compared. Complementary to the qualitative nature of this review, the associations between impulsivity measures and relapse, mean values and

standard deviation of the abstinent control group were collected from the original papers to calculate effect sizes, by dividing the mean value differences with the standard deviation of the abstinent control group. Effect sizes were calculated derived from 5 of the 16 included studies (31%) that comprised figures on the use of 9 measurement instruments.

3. RESULTS

Study selection

The search yielded 149 articles, from which titles and abstracts were screened by two authors (*W.S.* and *R.d.W.*). In order to be included, articles had to describe an association between AUD relapse and impulsivity in patients with AUD. Excluded were, for example, articles describing relapse in other substances, without measurement of impulsivity, as well as several articles that described 'craving'. Eventually, 35 full-text articles were read for eligibility assessment and added to this was one extra article from an earlier pilot search. Finally, 17 peer-reviewed articles describing AUD relapse in relation to impulsivity were included in this study.
The quality was guarded by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method (Moher et al., 2009). To visualize the selection and data extraction process, see the flow chart in Fig. 1.
From the included articles, the following data were extracted and tabulated in terms of study design/population, follow-up period, sample size, impulsivity measure used and the results/statistics. In addition, the AUD relapse definition that was used in each paper was tabulated. A relationship between impulsivity and AUD relapse with $P < 0.05$ was regarded as statistically significant.

Findings

General findings

Of the 17 included studies, 11 studies were European, 3 came from the United States, 1 from Canada, 1 from China and 1 from Turkey. Sample sizes varied between 20 and 473, and in all but two (Fein et al., 2004; Tucker et al., 2016) cases, the sample consisted of a clinically obtained research population. Follow-up period varied from several months to 8 years. Most research measured 'impulsivity' by using the Barratt Impulsiveness Scale (BIS11), which is a self-report measure (Patton et al., 1995). In half of the included studies, the impulsivity–relapse association was found to be statistically significant. An overview of included articles can be found in Table 1.

Relapse definitions

In all included articles, the definition for AUD relapse is provided in Table 1. Relapse definitions varied greatly, from any (substance) use to number of AUD-related problems. Therefore, no uniform relapse definition could be extracted from the included papers. In the current review, we examine the association between impulsivity and AUD relapse based on the impulsivity measures and AUD relapse definition as they were used in the original study.

Overview of included studies

Trait impulsivity.

Ten out of 16 studies reported on the relationship of BIS-11 or BIS-15 self-report measures and AUD relapse, whereby most frequently the BIS sum score was used in the analyses. In four studies, this association was found to be statistically significant (Bowden-Jones et al., 2005; Evren et al., 2012; Rubio et al., 2018; Wang et al., 2018). However, in one study, a more fine-grained analysis of the data was applied, whereas controlling for craving showed that the BIS score appeared to be indirectly associated with relapse via craving (Evren et al., 2012). In another study, an inverse relation was found, and lower trait impulsivity levels were associated with a higher probability of a lapse (Papachristou et al., 2014). In five studies, findings on the BIS/AUD relapse – association were not statistically significant (Charlet et al., 2013; De Wilde et al., 2013; Matheus-Roth et al., 2016; Bernhardt et al., 2017). Personality-based impulsivity measures were assessed by novelty seeking (NS) scores (Evren et al., 2012) and the 'Personality research form' (PRF) (Moos and Moos, 2003). Only the novelty seeking subcategory 3 (NS3) was significantly associated with relapse. Impulsivity in the PRF was not associated with relapse. Also, in one study, 'Trait impulsivity' was assessed by using the UPPS Impulsive Behavior scale (Quoilin et al., 2018), which was statistically significant associated with AUD relapse.

'*Behavioral impulsivity'— 'motor impulsivity'*.

In two studies, a GNG paradigm was used, testing the response inhibition performance. Response inhibition deficits were associated with AUD relapse (Czapla et al., 2016; Rupp et al., 2016). In one study, to assess 'motor impulsivity', the SST was used, but findings in relation to AUD relapse were not statistically significant (Jakubczyk et al., 2013). In a more recent study, measures of behavioral inhibition (visual reaction time (RT) task, SST, anti-saccade task, number–letter task) and neuronal motor inhibition (instructed-delay choice RT task) were all found to be statistically significant in relation to AUD relapse (Quoilin et al., 2018).

'*Behavioral impulsivity'— 'impulsive choice'*.

The outcomes on the IGT, the simulated gambling task and an unnamed gambling test (Bechara et al., 1994) were also investigated in relation to relapse. In two studies, a statistically significant association with relapse was found (Bowden-Jones et al., 2005; De Wilde et al., 2013), and in one study, this association was not statistically significant (Fein et al., 2004). DD was investigated in three studies. One study showed that DD was associated with AUD relapse (Bernhardt et al., 2017), and in another study, this association was not statistically significant (De Wilde et al., 2013). In an additional study (Tucker et al., 2016), no specific data regarding relapse could be extracted. Bernhardt et al. also investigated probability discounting for gain and mixed gambles, which were not associated with relapse. In this latter study, an association with probability discounting for loss (PDL) and AUD relapse was found (Bernhardt et al., 2017). In one study, the balloon analogue risk task (BART) was used and test performance was statistically significantly associated with relapse (Wang et al., 2018).

Effect sizes.
To give an impression of the strength of the impulsivity–relapse associations, we calculated effect sizes, which are displayed in Table 1. Effect sizes of 0.8 and more are considered as 'large', as effect sizes exceeding 1.2 are considered 'very large' (Sawilowsky, 2009). In the 'trait impulsivity' category, we calculated effect sizes of 0.7 (BIS-11 attention scores), 0.4 (BIS-11 total scores; Wang et al., 2018), 1.1 (NS3; Evren et al., 2012) and 1.7 (BIS; Bowden-Jones et al., 2005).
In the 'behavioral impulsivity' subcategory 'motor inhibition', we found an effect size of 1.1 for the GNG inhibition paradigm, accounting for an odds ratio of 1.55 (higher impulsivity scores associated with relapse) (Rupp et al., 2016). Finally, for the 'impulsive choice' subcategory, effect sizes of 0.4 (BART performance) (Wang et al., 2018), 0.2 (DD) and 0.7 (PDL) (Bernhardt et al., 2017) could be calculated. In addition, an effect size of 1.3 for an unnamed gambling task (Bowden-Jones et al., 2005) was calculated.

4. DISCUSSION

General overview

The role of impulsivity related to AUD and other SUDs is a growing area of research, but the current qualitative review on the empirical literature examining the association between impulsivity and AUD relapse suggests that this literature is relatively scarce and heterogenous. Our results add new elements to an earlier systematic review on a broader spectrum of factors associated with AUD relapse (Sliedrecht et al., 2019) and indicate some promising future directions for studying the association between AUD relapse and impulsivity, as outlined below. In the studies that used measures from the 'trait impulsivity' category, the BIS-11 was most frequently used. The results indicate a consistent association between 'trait impulsivity' and AUD relapse. However, the magnitude of this effect varied across studies. Among the other personality-based measurement instruments that have been used, we found less consistent associations between trait impulsivity and relapse. Together, the findings indicated a large variability in the association between AUD relapse and the construct of 'trait impulsivity'. For instance, although the BIS was the most frequently used measurement instrument, the effect sizes varied from small to large across studies of different research populations. To account for the impulsive reactions that may be elicited by different circumstances, it would be tempting to suggest that the use of objective 'behavioral impulsivity' tasks, would have a higher level of face validity and would be more preferable. With respect to the concept of 'behavioral impulsivity' multiple tasks, covering a wide range of aspects of this category has been employed. For example, the 'Go/No-Go' test is commonly used in measuring 'motor impulsivity', but even then accounts only for the 'inhibition' part (Herman et al., 2018; Vassileva and Conrod, 2019). For this 'behavioral impulsivity' subcategory, there seems to be an association with AUD relapse as well; but also in this category, various instruments are used and the strength of statistical outcomes varies. This prevents us from drawing firm conclusions. Finally, in the 'impulsive choice'

subcategory, different measurement instruments are used as well. In one of two studies, DD was associated with AUD relapse, and in another study, PDL was associated with relapse. The same was true for the BART, as was shown in one study. Relatively small effect sizes and highly varying statistical outcomes could indicate that the association of this category with AUD relapse is considered weak. As reported in Table 1, we also calculated effect sizes (based on difference of the means), which varied from small (DD) to very large (BIS). Because of heterogeneity in samples and definitions used, results should be interpreted with caution and a meta-analysis was not feasible. Based on the fraction of statistically significant findings within each category and the effect sizes found, our hypotheses were not supported and the behavioral measures and self-report measures of impulsivity were globally even strongly associated with AUD relapse. We would suggest the future use of well-defined and more semantically uniform sub-aspects of impulsivity constructs and AUD relapse definitions. The use of standardized impulsivity constructs and relapse definitions could help bridge key constructs in alcohol research to facilitate translational research (Ray et al., 2020).

It was recently hypothesized that AUD relapse can especially be seen as an inability to value delayed rewards (DD) and to inhibit prepotent responses (Reyes-Huerta et al., 2018). In a subset of patients with AUD, impulsivity might be associated with proneness on the rewarding effects of alcohol use (Westman et al., 2017) and higher levels of craving (Joos et al., 2012a). Alternatively, deficits in impulse control may impact treatment compliance and retention and via that way, indirectly, influence relapse in alcohol use for patients who engaged treatment.

Impulsivity may be considered a mediator of other factors that impact craving and relapse (e.g., stress or mood). It was recently found that the craving–relapse association can be mediated by impulsive decision-making ('rash impulsivity') (Coates et al., 2020).

Finally, the relation between stress and relapse might be mediated by impulsivity in the context of both cigarette smoking and alcohol use (Ansell et al., 2012; Hamilton et al., 2013). Other research on impulsivity has shown that the severity of AUDs is associated with impaired behavioral control (Claus et al., 2011), which may influence the risk of relapse. This imbalance in control abilities is caused by different developmental trajectories of distinct reward and regulatory brain circuitry during the maturing process (Van Leijenhorst et al., 2010). Yet, it has been shown that impulsivity fluctuates not only in adolescence, but also throughout the life span, suggesting state as well as trait aspects (Mayhew and Powell, 2014). Individual variation in decrease of impulsivity was found to be linked to alcohol consumption patterns (Littlefield et al., 2009; Littlefield and Sher, 2010), which could also imply reciprocal effects on the progression of addiction (Littlefield et al., 2009). According to the early Eysenck theoretical formulations, impulsivity was considered a prominent personality trait, originally included in the extraversion dimension, but later built-in the psychoticism dimension (Eysenck and Eysenck, 1977). Building upon Eysenck's work, psychobiological models that include impulsivity have been proposed and created by, e.g., Zuckerman and Neeb (1979), Zuckerman et al., 1991),

Cloninger et al. (1981), Cloninger (1994) and Babor et al. (1992), identifying impulsivity/disinhibition as an important risk factor for relapse and future substance abuse (Zuckerman and Neeb, 1979; Cloninger et al., 1981; Zuckerman et al., 1991; Babor et al., 1992; Cloninger, 1994). In general, such impulsivity concepts are typically applied to measure long-term trait-dependent features of impulsivity and frequently measured with the BIS-11, one of the most widely used self-report measures. In contrast, behavioral tasks are considered to be more sensitive to situation-specific changes in impulsivity that, e.g., encompass stressful situations, induced craving by cue-related stimuli such as alcohol and temporal impaired emotional functioning (Moeller et al., 2001; Dougherty et al., 2003, 2005). Furthermore, alcohol typology could be a useful framework in identifying future targeted medication options (Leggio et al., 2009), and to predict treatment retention and outcome (Foulds et al., 2017).

Limitations

Of importance, interpretation and generalization of the findings remain difficult, given that throughout the different studies impulsivity constructs, measurement instruments, patient numbers and follow-up periods varied widely. Also, the potential role of gender, age or psychiatric comorbidity (as a potential confounder) on the impulsivity–relapse association could not be deduced from the content of the included papers. This prevents us from drawing firm conclusions.

Being aware of a 'language bias', we limited our search to papers written in English. Nevertheless, research from various countries was included.

A meta-analysis of effect sizes was not feasible, given the heterogeneity in study designs, instruments used and relapse definitions. This was also found in a recent study on impulsivity and gambling, whereas meta-analyses could not be performed on impulsivity measures because of a lack of sufficient data in the included studies (Ioannidis et al., 2019).

It must be noted that in the last decades several perspectives on impulsivity have been postulated. Some components of frequently used inventories (like 'venturesomeness', 'positive urgency', 'inattention' and 'non-planning' impulsivity) can be categorized in the 'trait impulsivity' main category, whereas for example the 'behavioral impulsivity' sub category 'motor impulsivity' could be further subdivided into 'stopping' and 'waiting' impulsivity. In addition, some categories with different names throughout literature are actually synonyms, like 'insensitivity to consequences' and 'delay discounting', as well as 'impulsive choice' and 'decision-making'. We did not include measures of 'urgency' in the current review because negative urgency has recently been the focus of a similar review that was recently published (Zorrilla and Koob, 2019). Overall, the field of neurocognitive research in addictions is highly in need of the implementation of a widely accepted standard test battery probing well-defined cognitive dimensions relevant for addictive disorders (Verdejo-Garcia et al., 2019; Yücel et al., 2019).

Future research

Results from this review suggest that distinct aspects of impulsivity and AUD relapse are related. Experts in the field have indicated that impulsivity measures, i.e., impulse control, reward valuation and action selection, should be part of a standard neuropsychological assessment in addictive disorders (Yücel et al., 2019), and this would assist future research examining the impulsivity and AUD relapse association. The interpretation of the outcomes of self-report measures, like the BIS-11, should be done with caution. This accounts for distinct behavioral measures as well, such as reliability and predictive validity in relation to AUD relapse. More research is needed, as has for example been done recently in relation to success in quitting smoking (McCarthy et al., 2016). Our results show that we did not find evidence that behavioral measures have more predictive potential over self-report measures in relation to AUD relapse. As identified in many publications, there is no uniform concept of relapse being used in the literature. The use of a uniform definition of AUD relapse/remission would be critical for future comparative research.

Future treatment options

At this moment, the number of effective evidence-based treatment options specifically targeting impulsive behaviors is scant (Vassileva and Conrod, 2019). Novel treatment options are mostly experimental in nature (Vassileva and Conrod, 2019). A future step could be to initiate clinical trials that focus on potential therapeutic options for reducing impulsivity and increasing behavioral control in SUD/AUD patients. Psychological treatments can be used to strengthen top-down impulse control or weaken bottom-up drive (Verdejo-Garcia et al., 2019). A recent example of the former is Goal Management Training, which is a therapist-guided cognitive remediation training that instructs participants to implement a meta-cognitive strategy to decision-making (Levine et al., 2011), and has also been shown to improve executive function in alcohol and stimulant polysubstance users (Alfonso et al., 2011; Valls-Serrano et al., 2016) as well as in HIV+ participants with SUDs (Casaletto et al., 2016). However, in spite of the positive effects on cognitive measures, the effect on alcohol and substance use reduction could not be demonstrated. Treatment interventions can also aim at weakening the bottom-up substance use-oriented drive. An example of this approach is cognitive bias modification (CBM). In a recent meta-analysis, a cognitive bias–impulsivity relationship was demonstrated, supporting the need of further research on cognitive bias modification (Leung et al., 2017). In a recent review, however, a positive effect of CBM on AUD relapse rates could not be reliably confirmed (Boffo et al., 2019). The use of targeted repetitive transcranial magnetic stimulation (TMS) is an area of growing research interest. Several impulsivity-related brain areas have shown to be successfully targeted in TMS (Ibrahim et al., 2019; Vassileva and Conrod, 2019). Cognitive Enhancement Therapy may also be an effective treatment option for the 'impulsive AUD' population (Kozak et al., 2018). Finally, there is substantial evidence in preventing AUD relapse (McDonell et al., 2017) and SUD relapse (Davis et al., 2016) by employing contingency management. Furthermore, this was confirmed (Tomko et al., 2016) in a diagnostic group (smoking, cannabis) with impulsivity characteristics ('trait impulsivity' and 'impulsive choice' measures).

Based on 'impulsivity theoretical constructs', and their neurobiological basis, several pharmacological options ('cognitive enhancers') have recently been postulated and investigated. In a randomized placebo-controlled trial, the use of the 'cognitive enhancer' modafinil did not lead to higher abstinence rates, but there could be a positive effect in a subcategory of patients with baseline impaired response inhibition (Joos et al., 2012b). Modafinil also modulated impulsive decision-making (DD), as was shown in a small randomized, placebo-controlled study (Schmaal et al., 2014). Naltrexone is used as an anti-craving agent to prevent alcohol relapse but seems to have the potential to modulate the neural correlates of motor inhibition as well (Nestor et al., 2018). The same accounts for the anticonvulsant topiramate, which also showed some effects on 'behavioral impulsivity' (Rubio et al., 2009). In a placebo-controlled pilot study, the use of the antipsychotic medication quetiapine showed a significant effect on response inhibition, as measured by the SST (Moallem and Ray, 2012). Recent studies show a positive effect of high dosages of methylphenidate on amphetamine and cocaine use in stimulant dependent ADHD patients (Konstenius et al., 2014; Skoglund et al., 2017). Interestingly, also other associated substance use in these patients, e.g., alcohol and cannabis, diminished in these trials. This finding may indicate a substance 'transdiagnostic' effect of high-dose methylphenidate (Verdejo-Garcia et al., 2019). In a randomized, placebo-controlled, double-blind, crossover study with 87 healthy controls, the dopaminergic drug 'L-Dopa' attenuated risk seeking in the more impulsive individuals, but no effect on 'impulsive choice' was found (Petzold et al., 2019).
At last, the prescription of the aversive anti-relapse medication disulfiram is intuitively done with much precaution in 'impulsive' patients with AUD. However, the use of supervised disulfiram in a patient population known for impulsivity (BPD) was shown to be rather safe in a small case history study (Mutschler et al., 2010).

5. CONCLUSIONS

Both 'behavioral impulsivity' (with 'motor impulsivity' and 'impulsive choice' sub-categories) and 'trait impulsivity', as measured by distinct measurement instruments, seem to be associated with AUD relapse risk. Research on the relation between distinct measures of impulsivity and AUD relapse is still relatively scarce. We found that none of the impulsivity subcategories had greater predictive value in regard to AUD relapse. Treatment options are still largely experimental, so more research is needed. The use of standardized impulsivity constructs and relapse definitions could help bridge key constructs in alcohol research to facilitate translational research.

Table & Figure can be found at the end of this publication. For this chapter on page 120.

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4. Alcohol use disorder relapse factors: an exploratory investigation of craving, dependence severity, and meaning in life

ABSTRACT: For decades predictors of alcohol use disorder (AUD) relapse have been studied, and around 40 different clinical and demographic relapse determinants have been identified. This paper aims to investigate the relationship of two of these AUD relapse factors, namely craving and meaning in life. We hypothesized that greater meaning in life would be associated with lower craving and lower relapse rates.

An AUD subsample of 81 patients within a clinical population that participated in ongoing exploratory research on religious/spiritual factors related to substance use disorders was followed up to 1 year.

Craving (as measured with the Penn Alcohol Craving Scale) and meaning in life (as measured with the Meaning in Life Questionnaire- presence subscale) measures were assessed at baseline and relapse was assessed at 6- and 12-month follow up. Main effects and the interaction between craving and meaning in life in predicting alcohol relapse (with relapse defined as 'any alcohol use' and ≥ 3 consecutive days of drinking) were calculated/ subject of analyses. We also investigated the relation between relapse and alcohol dependence severity as measured with the Leeds Dependence Questionnaire.

Baseline craving and dependence severity were related with relapse, but there were no associations between meaning in life and levels of craving or alcohol relapse. Our findings suggest a need for additional research on characterizing the Meaning in Life concept.

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1. Introduction

Alcohol use disorder and relapse

Alcohol use disorder (AUD) is highly prevalent (Grant et al., 2015, 2017; Rehm et al., 2015), and accountable for substantial morbidity and mortality (Griswold et al., 2018; Leong et al., 2022; Rehm et al., 2017). Most individuals with AUD do not seek treatment (Tuithof et al., 2016), and a majority of people with AUD recover without any formal treatment (Cohen et al., 2007; Cutler & Fishbain, 2005; Fan et al., 2019; Grant et al., 2015; Tucker & Witkiewitz, 2020). Yet, for a sizeable number of patients, AUD encompasses a chronic, recurring condition (McKay & Hiller-Sturmhofel, 2011). Recent epidemiologic research showed a 1-year persistence of AUD of 34.2% within a national US population survey (Fan et al., 2019). Within this group with AUD, eventually 16% achieved abstinent recovery (Fan et al., 2019). Therefore, the prevention of relapse and promotion of recovery remain challenging and are the focus of most forms of psychological and pharmacological treatment (Ray et al., 2019).

Determinants frequently associated with relapse, as well as factors that are protective in preventing relapse, have already been well studied for several decades (Miller, 1996; Sliedrecht et al., 2019; Witkiewitz & Marlatt, 2004). Several psychological and psychobiological models have been postulated and tested for their validity in predicting relapse (Connors et al., 1996; Hendershot et al., 2011; Sliedrecht et al., 2019; Witkiewitz, 2011; Witkiewitz & Marlatt, 2004, 2007), and have generated therapeutic targets to prevent relapse (Donovan & Witkiewitz, 2012; Huebner & Kantor, 2010; Larimer et al., 1999). Craving is one of the most prominent targets for interventions (Donovan & Witkiewitz, 2012; Larimer et al., 1999) and a limited number of medications (Donoghue, 2021; Donoghue et al., 2015; Mann et al., 2018; Witkiewitz et al., 2019) within many treatment settings. 'Craving', as well as other determinants like 'severity of AUD', 'psychiatric comorbidity', 'emotions' and several social and spiritual factors have been identified as important factors in the achievement of remission or the occurrence of a relapse (Hendershot et al., 2011; Sliedrecht et al., 2019; Witkiewitz & Marlatt, 2004). Given the prominence of craving as risk factor in both AUD and substance use disorder (SUD), a recent meta- analysis suggested that in future research also examining mediating and moderating roles of different other neurocognitive functions should be considered (Cavicchioli et al., 2020).

One such potential moderator of the association between craving and relapse could be purpose or meaning in life (Cranford et al., 2014; Lyons et al., 2010; Roos et al., 2015; Waisberg & Porter, 1994). A recent paper stated that meaning in life "refers to the feeling that one's life and experiences make sense and matter", and purpose in life "is characterized by the extent to which one experiences life as being directed, organized, and motivated by important goals" (Salsman et al., 2020, p2299). It must be noted that the current concept of meaning in life is broader than the concept of purpose in life. A recent systematic review identified meaning to comprise of: 'comprehension/coherence, purpose, and existential mattering/significance' (King & Hicks, 2021).

Our main study goal was to examine the roles of craving and meaning in life (MiL) in AUD relapse.

Craving

Craving refers to the phenomenon of intense longing for alcohol, and is often seen as a multidimensional concept, consisting of emotional, cognitive, physiological and behavioral components (Rosenberg, 2009). Craving is currently one of the symptoms in the DSM 5 definition of AUD (Casey et al., 2012; Hasin et al., 2013; Robinson & Adinoff, 2016), as well as the description of Alcohol Dependence Syndrome in the International Classification of Diseases (ICD- 11) (Saunders et al., 2019). A neurobiological underpinning of craving with the 'incentive sensitization theory' was postulated (Robinson & Berridge, 1993, 2008); such that alcohol induced sensitization of mesocorticolimbic systems in the brain can lead to implicit 'wanting' or explicit cognitive craving (Kavanagh et al., 2005; Robinson & Berridge, 2008). Skinner and Aubin (2010) identified four different types of craving, namely conditioning-based-, cognitive-, psychobiological-, and motivation models (Skinner & Aubin, 2010). Recently, a metacognitive model of craving was postulated; integrating cognitive, automatic and physiological aspects of craving (Flaudias et al., 2019).

Although a number of behavioral tasks have been developed to measure craving (Kavanagh et al., 2013), craving is most commonly measured by various self-report questionnaires. The multi-item Penn Alcohol Craving Scale is one widely used measure, which has demonstrated excellent reliability, construct and concurrent validity (Kavanagh et al., 2013). Earlier research indicated that the Penn Alcohol Craving Scale (PACS) can be regarded a reliable prognostic measurement instrument (Flannery et al., 1999). The PACS measures self-reported craving via five different items in which scores can vary between 0-6. The PACS has now been used in a growing body of research as a craving measurement instrument (Evren et al., 2012; Hartwell et al., 2019; Hartwell & Ray, 2018; Schneekloth et al., 2012; Stohs et al., 2019). Higher PACS scores are associated with higher relapse risk during (Flannery et al., 2003) and within 12 months after treatment (Stohs et al., 2019). More specific, after dichotomizing to identify predictive cut off values, additional analysis showed that PACS scores of ≥ 6 were predictive of 12-month relapse (Stohs et al., 2019). This is in line with earlier research indicated PACS scores ≥ 7 measured at admission into an addiction clinic and PACS scores of ≥ 4 at discharge were predictive for relapse (Schneekloth et al., 2012).

Meaning in life

A number of MiL concepts have been used in previous research, with one well-known definition of MiL as "the sense made of, and significance felt regarding, the nature of one's being and existence" (Steger et al., 2006, p.81). In contrast to the well-studied concept of craving, the effect of various MiL- related issues in relation to AUD relapse seem to have been relatively understudied. In a recent systematic review on AUD relapse factors the MiL-related concept of 'purpose in life' (PiL) and likewise denominators like finding purpose in e.g., 'caregiving' were found mostly protective in relation to relapse (Sliedrecht et al., 2019), but it must be noted that in only two out of nine reviewed papers this factor had been

assessed by using the Purpose in Life test as a standardized assessment instrument (Cranford et al., 2014; Roos et al., 2015). It must be noted that 'purpose in life'(PiL) and 'meaning in life' (MiL) are related concepts, but are not synonyms (King & Hicks, 2021; Steger et al., 2006). MiL refers to how one appraises the meaningfulness of the world (consisting of the beliefs about self, the world, and relationships between self and the world) or one's life's goals and purposes, whereas PiL seems to encompass only the narrower, goal directed compound (Czekierda et al., 2017; Park & Folkman, 1997). In line with this, recent theoretical overviews postulated that MiL consists of three subconstructs, namely: coherence/ comprehension, purpose and significance/ mattering (George & Park, 2016; Martela & Steger, 2016). MiL has been shown to be positively associated with health and mental well-being (Aftab et al., 2019; Czekierda et al., 2017; Leamy et al., 2011; Steptoe et al., 2015), and lower suicide risk (Costanza et al., 2020). Moreover, meaning in life interventions have a clinical benefit in patients with advanced disease (Rubio et al., 2018).

However, in more recent research a frequently used measurement instrument to assess MiL is the "Meaning in Life Questionnaire" (MLQ) (Steger et al., 2006), which consists of the subscales 'presence of' and 'search for' MiL. The MLQ has produced valid scores in different age groups, cultures and clinical populations (Chika Chukwuorji et al., 2019; Hallford et al., 2018; Naghiyaee et al., 2020; Rose et al., 2017; Schulenberg et al., 2011; Schutte et al., 2016). Presence of meaning is associated with better health and mental well-being, but search for meaning shows an inverse relationship (Aftab et al., 2019). Moreover, it was recently found, that higher presence of meaning is associated with less alcohol use in a group of young adults (Csabonyi & Phillips, 2020).

Dependence, craving and meaning in life in association with AUD relapse

One prior study has examined the association between PiL with craving as related to alcohol relapse, and found craving and PiL were both associated with drinking outcomes (Roos et al., 2015). Higher PiL was related with lower craving and lower PiL was and higher craving were associated with more frequent and greater intensity drinking. In the same way, it seems plausible that the related concept of MiL could as well be related to drinking outcomes, and could potentially moderate the association between craving and relapse.

It was recently found that presence of MiL as measured with the MLQ is associated with less harmful drinking (Copeland et al., 2020). Interestingly, search for meaning showed an inverse relation (more harmful drinking). Moreover, these factors were mediated by trait self-control and how alcohol was valued, which however could be related to, but is not akin to craving. In line with this, other research within a group of undergraduate students suggested that a brief MiL intervention could lead to reduction in the 'incentive salience' of alcohol, which could potentially facilitate less drinking behavior (Ostafin & Feyel, 2019). As presence of meaning is associated with better health and mental well-being (Aftab et al., 2019), and perceived stress (Pulopulos & Kozusznik, 2018), it seems conceivable that presence of meaning could lead to less craving, eventually leading to less proneness to relapse. However, the association and interaction between MiL and craving with relapse outcomes in patients with AUD has still not been thoroughly investigated. Given the

importance of MiL in relation to other areas of mental and physical health and well-being, and being a potential therapeutic target, it may be the case that MiL may predict relapse outcomes and attenuate the association between craving and relapse.

In addition, 'Severity of AUD' or the level of 'dependence' has now been for decades been identified as a robust relapse factor (Sliedrecht et al., 2019). Measuring dependence levels over time, as for example often measured by the Leeds dependence questionnaire (LDQ), can be used to monitor the effects of treatment (Heather et al., 2008).

The current study

The objective of current study was to conduct a prospective cohort study within a clinical AUD population, in which we tested the association between MiL and craving with relapse outcomes at 6- and 12-month follow-ups. We hypothesized that higher baseline MiL would be associated with lower craving levels, and lower relapse. We also tested if this effect would run via a moderation effect, namely in that higher levels of meaning would attenuate the craving- relapse relation. In addition, we tested the association between MiL, severity of alcohol dependence (LDQ scores) and relapse.

2. Methods

Participants

The sample consisted of a clinical population that participated in ongoing longitudinal research study examining religious/spiritual factors related to substance use disorder. For our study, we included the subgroup with a diagnosed primary AUD. From this sample of 81 participants, we had 6-month follow up (FU) data from 78 patients (96%) available. In addition, from 51 participants (63%) 12- month FU data were available. In 3 patients the 6-month relapse data were not available, but nevertheless we had 12-month FU data of these patients. All participants were already detoxified at the baseline inclusion, mostly hospitalized within a specialized clinical psychotherapeutic treatment setting at the Hoop GGZ in Dordrecht, The Netherlands. This specific ward is predominantly overseen by psychologists, that are specialized in mental health, but also a psychiatrist and a doctor specialized in addiction medicine are part of the treatment staff. All patients received disorder specific treatment, which consisted of cognitive behavioral therapy for addiction as well as a 'schema therapy based' approach of comorbid personality disorders. Whenever needed, also additional pharmacotherapy or trauma therapy could be part of treatment. Besides the primary AUD, there were no other inclusion or exclusion criteria for our sample. However, the inpatient population consists of patients who despite their disorder can function within a group-therapy setting. Comorbid conditions were common in the inpatient population, including high rates of comorbid personality disorders, attention deficit hyperactivity disorder and posttraumatic stress disorder.

Procedure

Analyses were performed on data derived from patients who were included from February 2018 till December 2020.

From the group of 81 patients, 68% were male (n=55) and the mean age was 42.37 years (SD = 11.83). Most participants had one or more comorbid psychiatric disorders (78%). Comorbid substance use was rather common (38%; mostly cannabis- followed by cocaine use), and 45% was diagnosed with a tobacco use disorder. The smaller subgroup who provided the 12-month FU data were comparable to the total sample recruited at baseline (Table 1).

The ethical committee of the Universiteit van Amsterdam ethically approved the original larger research design (registration ID: 2017-DP-7969), and attested that as no interventions were conducted, an extensive assay was not required. Participants could voluntarily participate after they were on admission informed of the ongoing survey on 'spiritual and religious factors in treatment'.

A team of specialized clinicians clinically diagnosed the presence of substance use disorders or psychiatric comorbid disorders based on DSM 5 criteria. At the start of treatment, the 'Measurements in the Addictions for Triage and Evaluation' (MATE) (Schippers et al., 2010) was used to classify AUD and SUD's, and on indication the 'Structured Clinical Interview for DSM-5 Personality Disorders' (SCID-5-PD) was used to classify co- morbid personality disorders. Trained psychologists did the assessment of craving and meaning in life at baseline. Baseline measurements were mostly done during the hospitalization phase; several weeks after detoxification. Furthermore, a telephone interview was used to obtain follow up data at 1, 6, and 12 months. In addition, the LDQ was used at baseline and during follow up to assess for dependence on a variety of substances (Raistrick et al., 1994). We pre- registered our research at the Open Science Framework (OSF) database website (https://osf.io/yt8q5).

Measurement instruments and definitions

Craving

The PACS is a self- report questionnaire reporting on different aspects of craving covering the last week. Total scores on this 5-item assessment instrument could range from 0-30 (Flannery et al., 1999). An example item is: "How often have you thought about drinking or about how good a drink would make you feel during this period?".

In our reliability analysis, we found Cronbach's alpha of 0.92, which is consistent with former research that found a very high reliability value of 0.92 (Flannery et al., 1999).

Meaning in Life

The MLQ (5-item presence subscale) functions as a gauge to assess how patients judge their present life as being meaningful. Patients can rate on a scale from 1-7 ("absolutely untrue"-"absolutely true") how they experience present MiL. Consequently, total subscale scores could range from 5-35 (Steger et al., 2006). The statements are: 'I understand my life's meaning, 'My life has a clear sense of purpose', 'I have a good sense of what makes my life meaningful', 'I have discovered a satisfying life purpose', and 'My life has no clear purpose' (reverse-coded) (Steger et al., 2006). Former research found Cronbach alpha's varying from 0.81- 0.93 (Schulenberg et al., 2011), and in our own reliability analysis this value was .90 for the 'presence' subscale. In addition, we found Cronbach's alpha of .80 for the MLQ 'search' subscale (which also consists of 5 items). Also, MLQ scores showed good (1 month) to moderate (13 month) test- retest reliability (Schulenberg et al., 2011). We only used the presence subscale, and hypothesized that 'presence' of Mil, but not 'search' for meaning would moderate craving levels.

Dependence

Alcohol dependence severity levels at baseline, 6-month FU and 12-month FU were assessed with the LDQ. The LDQ is a 10-item, self-report questionnaire to asses dependence upon a variety of substances and monitor treatment outcome. Items are scored from 0-3, with higher scores pointing at higher levels of dependence. Cronbach's alpha was 0.94 and the test-retest reliability was found to be 0.95 (Raistrick et al., 1994). We found Cronbach alpha's of .90 for baseline LDQ, .91 at 6 months- and .93 at 1 year FU.

AUD relapse

AUD relapse was conservatively defined as 'any alcohol use' at 6 and 12 month follow up. This definition has been extensively used in AUD relapse research (Maisto et al., 2016; Sliedrecht et al., 2022). In addition, we examined ≥ 3 consecutive days of drinking as an alternative outcome measure, which has been used in former research (Demirbas et al., 2012; C. E. Wiers et al., 2015; R. W. Wiers et al., 2011).

Statistical Analyses

In June 2020 (well before data analyses) we performed a power analysis (considering main and interaction effects) within G*Power (alpha = 0.05, power = 0.8). Estimated relapse figures were conservatively set at 40% at six months and 75% at 12 months FU. The explaining variance for MiL was set at 0.09 for the 6-month FU (as Rubio et al. (2018) reported a 1-year coefficient of 0.17 (Rubio et al., 2018)). Based on these estimates we required 72 participants in assessing the relation between craving, MiL and relapse outcomes at 6-month FU. This matched with our inclusion of 81 patients with primary AUD from which we had 6 month and/or 1 year FU data. Statistical analyses were performed in SPSS v25. Moderation analyses were done by using Hayes' PROCESS v3.5.3 (version 11 February 2021; http://www.processmacro.org/download.html).

Statistical significance was considered to be at the level of $p < 0.05$. Assessing the 6 months relapse outcomes showed that, for unknown reasons, the outcome data of 3 patients were missing, whereas their data at 12-month FU were present.

Additionally, the PACS and MLQ scores were plotted to assess a normal distribution and to identify potential outliers. Descriptive statistics were performed for both the 6- and 12-month FU groups (Table 1). To test the association of baseline presence of MiL with craving levels and eventually relapse, univariate-, and multivariate analyses in SPSS were estimated. To test if MiL moderated the association between craving and relapse, we conducted a moderation analysis. As a side note, out of interest we also tested the possible effect of 'search for meaning' on craving and relapse.

3. Results

Descriptive statistics and correlational analyses

Percentages of relapse at 6- and 12-month FU and variables (craving, substance dependence and presence of MiL) for the total group and the groups based on relapse (yes or no) can be found in Table 2. In this clinical sample, the 6- and 12-month 'any alcohol use' relapse rates were 54% (42 of 78) and 63% (32 of 51), in which relapse conservatively was defined as 'any alcohol use'. When relapse was defined by ≥ 3 consecutive days of alcohol drinking, the relapse rates were 31% (24 of 78) and 39% (20 of 51), thus considerably lower. Mean baseline craving, baseline MiL-, and consecutive dependence scores of the 6- and 12-month FU groups are tabulated in Table 2. Sample t-tests indicated craving and dependence baseline scores were notably higher in the group of relapsed patients, statistically significant results are indicated in Table 2. Dependence scores at 6 months were generally lower than at baseline and 1 year follow up (Table 2).

Logistic regression analyses

To test our hypotheses, we performed univariate (see Supplemental table 1) and multivariate (see Table 3) logistic regression analyses, to examine the association of craving, substance dependence and presence of MiL with relapse rates. In the univariate and multivariate analyses, there were no significant relations between craving, dependence, and MiL with relapse defined as any alcohol use at 6 months, and no interaction between Mil and craving. Similarly, univariate and multivariate analyses showed no significant effects of craving, dependence and Mil on the outcome ≥ 3 consecutive days of alcohol drinking at 6-months, and no interaction with craving. At 12 months no effects were found for all univariate analyses for 'any alcohol use' and univariate and multivariate analyses for ≥ 3 consecutive days of alcohol drinking. In multivariate analyses there was a significant association between craving and relapse defined as any alcohol use at 12 months alcohol use' (B=.139, Wald (df=1) = 4.90, p=.03; OR: 1.15), but there was no interaction with MiL.

In addition, also no interaction effects of the search subscale of MiL on craving and relapse were found.

4. Discussion

As most of previous research has used cross-sectional designs, the prospective design of our study could be considered a strength. Our hypotheses, that higher baseline MiL would be associated with lower craving levels, and lower relapse, both directly and indirectly (moderation effect) via craving, were not confirmed within this research. However, although in most cases not statistically significant, the craving and dependence scores in the relapsed groups (both drinking outcomes) were higher as compared to the non- relapsed. This is in line with the findings in a recent systematic review that identified AUD severity and craving as robust relapse factors (Sliedrecht et al., 2019), and suggests a relation of these clinical parameters with our chosen relapse outcomes. Interestingly, dependence scores declined at 6-month FU; probably showing a treatment effect and indicating early recovery. At 12-month FU these scores were still lower than at baseline; but it must be noted that the sample size at 12-month FU was relatively small. In this relatively small clinical prospective cohort study, more than half of the patients had relapsed (outcome 'any alcohol use') at 6- and 12-months FU. This is in line with relapse rates mentioned in literature, depending on how 'relapse' had been defined. However, when we defined relapse as '≥ 3 consecutive days of drinking', which can be regarded a less strict outcome, these figures were considerably lower. In our univariate-, multivariate-, and moderation logistic regression analyses, we found no statistically significant effect of craving, meaning in life (MiL), or dependence scores on relapse, nor a moderating effect of MiL. MiL has in earlier research been shown to positively influence health and mental well-being in prior research, but this was not found in relation to craving and relapse within our sample of individuals receiving treatment for AUD. Out of interest we also tested the possible effect of 'search for meaning' on craving and relapse, which outcomes however were also not statistically significant. Presence of and search for meaning are not one to one related concepts. Empirical research suggested that people lacking meaning search for it, and the search for meaning did not appear to lead to presence of meaning (Steger et al., 2008). Moreover, understanding distinct meaning-related concepts and their interrelationship warrants more empirical research (Park, 2010).

In this exploratory research we examined craving, MiL, and drinking outcomes. Although the denominators MiL and PiL have been postulated to be equivalent (Steger et al., 2006), it seems that MiL is not synonymous with the more robust relapse factor 'having purpose in life', which has been shown to predict alcohol relapse and be associated with craving (Roos et al., 2015; Sliedrecht et al., 2019). It could be debated if these denominators are indeed identical as has been postulated in literature on this subject (Steger et al., 2006). Mil seems to point at a broader concept, whereas PiL refers to the goal- directed part of MiL, but also might fathom one's affective state (Steger et al., 2006). Moreover, according to recent research, MiL also consists of the constructs 'coherence/ comprehension' and 'significance/ mattering', from which the 'mattering' component partly accounts for the protective effect recently found (Sliedrecht et al., 2019). Moreover, as MiL seems to conflate 3 related concepts, potential future purer measures of an overall judgment of meaning might provide more useful information and should be examined in future research. However, as far as we know there is no earlier research that has explicitly investigated MLQ- scores in relation to relapse. However, also research investigating the PiL/ AUD relapse association, as measured

with the Purpose in Life test, seems to be relatively scarce, but has shown such a relation (Roos et al., 2015; Waisberg & Porter, 1994).

In our treatment settings one of the goals should still be to alleviate 'craving', while its association with relapse has been consistently shown in literature and clinical practice. Consequently, further research at possible moderators (Cavicchioli et al., 2020) could be an area of additional future research.

Limitations

Our research has several limitations. It must be noted that our number of patients was relatively small and the outcome 'any alcohol use' can be regarded somewhat strict. The less stringent relapse outcome ≥ 3 consecutive days of drinking, however, was also not associated with craving or MiL. In future research, it would be worthwhile to examine continuous outcome measures, such as percent heavy drinking days or reductions in drinking, as well as non-consumption outcomes such as drinking consequences and well-being. Furthermore, it also must be noted, that still no uniform relapse definition exists (Maisto et al., 2016; Sliedrecht et al., 2022), which makes it difficult to compare research outcomes.

The small sample size and rather heterogeneous patient population with high comorbidity may have reduced our ability to detect effects of interest. Furthermore, given the design of the study, which was still ongoing, the results of the smaller 12 month follow up group, might probably be underpowered. Especially for moderation analyses larger samples would be required. We did not apply any correction for multiple testing, but given the small number of tests and lack of statistically significant outcomes do not think this would have led to other outcomes. An additional sensitivity power analysis indicated that an effect size of 0.15 would be detectable, given the current samples size.

Another limitation is the use of self-report data, which could for example have led to underreporting of relapse. However, the use of self-report data has been commonplace in former relapse literature, and the reliability can be regarded acceptable (Cherrier et al., 2020; Schneekloth et al., 2012; Whitford et al., 2009). Nevertheless, last decades, a growing area of research has evolved on the 'near real time' assessment of craving (also in relation to relapse) via ecological momentary assessment (EMA) (Shiffman et al., 2008) and alcohol use (McKay et al., 2006; Morgenstern et al., 2014; Serre et al., 2015; Treloar Padovano & Miranda, 2020). Moreover, also EMA relies on self- report data.

Furthermore, it must be noted that craving and presence of MiL will fluctuate over time, although baseline MiL might be more stable over time and PACS measures craving over the last week period. However, higher PACS scores at admission have in earlier research indeed been related to higher relapses rates at 12 months (Stohs et al., 2019).

Finally, the Covid-19 pandemic may have influenced our research in several ways. The inpatient setting from 2020 on received less patients (Marsden et al., 2020), which led to

less than expected participants in our study. Furthermore, the pandemic and resulting 'lock downs' and 'social distancing' may have influenced the levels of stress and craving (Sallie et al., 2020) and experiencing lower meaning in life, eventually leading to less moderation effects of MiL on relapse.

However, in real life 'meaning' might actually be an important factor in the process of relapse, which is a finding we expected to see in this study. We think that despite statistically non-significant outcomes, this kind of research still deserves a place within the literature and requires additional research.

5. Conclusions

Craving has in earlier research been shown to be a robust predictor of AUD relapse, whereas the role of meaning in life as a predictor of relapse and potential moderator remains unclear. In other research, experiencing a 'purpose in life' has been found to be a protective factor in AUD relapse as well, but this denominator does not seem to equal the broader concept of experiencing MiL. In the current study, craving and alcohol dependence were more prominent in the relapsed groups. However, we did not find a meaningful statistical relationship of craving/ MiL and relapse in our study. As potential relapse determinants, the role of MiL and more specific religious factors might still be relevant to be investigated in future studies, that should encompass more participants.

Overview of frequently used acronyms:

AUD/ SUD= alcohol use disorder/ substance use disorder

MiL= Meaning in Life

MLQ= Meaning in Life Questionnaire

PiL= Purpose in Life

PACS= Penn Alcohol Craving Scale

LDQ= Leeds Dependence Questionnaire

Tables Chapter 4

Table 1 *Background characteristics of the participants with 6- and 12-month FU data*

	6-month FU (*N*=81)	**12-month FU (*N*=51)**
Mean age	42.37 (11.83)	42.90 (12.69)
Gender		
Male	55 (68%)	37 (72.5%)
Female	26 (32%)	14 (27.5%)
Co morbid smoking	36 (44%)	23 (45%)
Co morbid SUD	30 (37%)	21 (41%)
Co morbid psychiatric disorder	63 (78%)	38 (75%)

Table 2 *Percentages of relapse at 6- and 12-month FU and variables (craving, substance dependence and presence of MiL; mean & SD) for the total group and the groups based on relapse (yes or no)*

	Total group		**Relapse 'any alcohol use' at 6-month FU**		**Relapse '≥ 3 drinking days' at 6-month FU**		**Relapse 'any alcohol use' at 12-month FU**		**Relapse '≥ 3 drinking days' at 12-month FU**	
	6-month FU (*N*=81)	**12-month FU** (*N*=51)	**Yes*** (*N*=42) (54%)	**No** (*N*=36)	**Yes*** (*N*=24) (31%)	**No** (*N*=54**)**	**Yes** (*N*=32) (63%)	**No** (*N*=19)	**Yes** (*N*=20) (39%)	**No** (31)
baseline Craving *(Mean/SD)*	7,37 (6,66)	7,18 (6,60)	8.24 (7.39)	6.08 (5.61)	8.25 (7.28)	6.80 ** (6.75)	8.47 (7.27)	5.00 (4.69)	**8.90** (8.34)	**6.06** (5.03)
baseline Presence of MiL *(Mean/SD)*	22,90 (7,82)	22,57 (8,07)	22.95 (7.29)	22.78 (8.62)	25.00 (6.45)	21.74 (9.03)	23.41 (7.27)	21.16 (9.29)	23.00 (8.22)	22.29 (8.08)
baseline Substance dependence *(Mean/SD)*	8,42 (7,64)	8,39 (7,42)	9.62 (7.67)	6.39 (6.70)	9.71 (7.95)	7.80 (6.68)	9.72 (7.26)	6.16 (6.94)	8.80 (5.93)	8.13 (8.12)
6-month FU Substance dependence	4.43 (6.19)	N/A	6.05 (7.15)	2.47 (4.07)	**7.75** (8.46)	**2.00** (1.78)	**5.55** (6.37)	**1.68** (1.56)	5.55 (6.15)	3.10 (4.66)
12-month FU Substance dependence	N/A	N/A	N/A	N/A	N/A	N/A	**7.61** (8.07)	**1.06** (1.31)	**9.11** (8.58)	**2.73** (4.73)

*At 6-month FU 3 patients had missing relapse data

** with 9 patients missing variables LDQ/PACS/MLQ meaning

Craving > PACS at baseline, presence of MiL > MLQ presence at baseline, Substance Dependence> LDQ at baseline, 6-month FU & 12-month FU

Bold*:* statistically significant difference in means (*t*-test) at the $p<0.05$ level

Table 3 Multivariate *logistic regression of craving or substance dependence with presence of MiL associated with relapse*

	B	SE	*Z*	*p*-value	Odds ratio	95% CI odds ratio
Any use at 6-month FU						
Craving	.06	.039	2.28	.13	1.06	0.98-1.15
Presence of MiL	.02	.032	0.37	*.54*	1.02	0.96-1.09
Substance dependence	.06	.034	3.65	.06	1.07	1.00-1.14
Presence of MiL	.01	.030	0.10	.76	1.01	0.95-1.07
≥ 3 consecutive days use at 6-month FU						
Craving	.06	.041	2.15	.14	1.06	0.98-1.15
Presence of MiL	.07	.036	3.73	.05	1.073	1.00-1.15
Substance dependence	.05	.035	2.13	.15	1.05	0.98-1.13
Presence of MiL	.06	.035	3.01	.08	1.06	0.99-1.14
Any use at 12-month FU						
Craving	.14	.063	4.90	**.03***	1.15	1.02-1.30
Presence of MiL	.08	.044	3.18	.07	1.08	0.99-1.18
Substance dependence	.08	.046	3.24	.07	1.09	0.99-1.19
Presence of MiL	.05	.039	1.58	.21	1.05	0.97-1.13
≥ 3 consecutive days use at 12-month FU						
Craving	.09	.051	2.94	.09	1.09	0.99-1.20

Presence of MiL	.04	.041	0.95	.33	1.04	0.96-1.13
Substance dependence	.02	.040	0.14	.71	1.02	0.94-1.10
Presence of MiL	.01	.037	0.14	.71	1.01	0.94-1.09

* Significant at the $p<0.05$ level

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References Chapter 4

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5. Conclusions, discussion and future research

"**What's in a name? That which we call a rose**

By any other name would smell as sweet."

– William Shakespeare, *Romeo and Juliet*, Act II, Scene II

Relapse definitions

In our research we studied the clinically and empirically well-known concept of alcohol use disorder (AUD) relapse. But what do we really mean when talking about relapse in the context of an AUD? Relapse is often viewed as a setback and subsequently used to indicate a failure to reach or maintain a pre-defined therapeutic goal.

We found that there is still no widely accepted definition of AUD relapse, and a striking new finding was that a large body of previous outcome research did not include clear definitions regarding the term relapse. As over one hundred different relapse definitions have been identified, the goal to provide a comprehensive overview of AUD relapse definitions, seemed to be an impossible task. These findings are in line with recent research on the concepts of substance use disorder relapse (Moe et al., 2021), and recovery in AUD (Witkiewitz et al., 2020). Despite the various differences in relapse definitions, we were able to capture and structure relapse definitions, and provide a substantial amount of context to characterize the concept of relapse.

Interestingly, a substantial amount of research placed relapse in the context of an 'abstinence only' based approach. In the context of AUD treatment, it is important to determine treatment goals that are within reach and attainable for the patient. Reaching the goal of stable abstinence may be valuable for certain patient groups. However, putting a disproportionate weight on reaching abstinence during treatment might impose a risk in devaluing other meaningful and crucial aspects of treatment progress (Sliedrecht et al., 2022). The use of the term relapse as a return to any level of drinking could easily set the stage for failure in many cases, causing more harm than good (Morris et al., 2020, 2022).

Of note, since AUD is classified by a subset of DSM criteria, the use of official DSM remission criteria was infrequently and inconsistently applied throughout literature. A 'medical' relapse definition ("return of a disease or the signs and symptoms of a disease after a period of improvement") was also uncommon. In addition, we have proposed to shift the focus

from dichotomous AUD relapse terminology towards continuous outcome- and quality of life related criteria. More specifically, outcomes like psychosocial functioning, life satisfaction and mental health, should in future (research) also be taken into account. It should also be monitored if these changes would have a positive impact on the (experienced) stigmatization of AUD patients (Rundle et. al. 2021). It would be interesting to further investigate the presumably negative impact of 'relapse' on motivation, self- efficacy and subsequent treatment outcomes, like AUD symptoms or number of (heavy) drinking days. However, at the very least, future outcome measures as used throughout literature need to be uniform. Provocatively, the pejorative term relapse (Miller, 1996) could better be abandoned, as the Babylonian confusion surrounding the word does not help us to resolve this issue, and it no longer "smells as sweet" (Sliedrecht et al., 2022).

As a preliminary suggestion for a new AUD relapse definition, we suggested: "Recurrence of AUD criteria after a period of 3-month remission (as for example has been employed in the DSM 5), accompanied with deterioration of health, mental well-being or life satisfaction" (Sliedrecht et al., 2022).

In changing the focus from an 'abstinence only' based approach to the usage of more continuous measures and integrating a broader perspective on recovery and satisfaction/well-being as well, we could alternatively give credit to an interwoven Bio-Psycho-Social- Spiritual based approach of AUD (see Chapter 2). This would further challenge our current treatment approach, as an abstinence-focused paradigm seems to be limited with respect to a broad array of human life-facets. That's why addiction therapists should focus on social-, health- and client's personal (quality of) life related goals. In our national- and international context it deserves consideration to revise the content and maybe even a call to omit the term "relapse prevention" without a well-defined treatment context of recovery.

In light of "better safe than sorry", we would like to add that we encourage the growing national and international attention for 'prevention' (Evers et al., 2022; Sánchez-Puertas et al., 2022), and given the toxic properties of alcohol we agree that "the safest level of drinking is none" (Griswold et al., 2018).

Alcohol Use Disorder Relapse factors

In our comprehensive systematic review, we identified several previously known, but also some new relapse factors. We specified and structured multiple (37) relapse factors according to Bio – Psycho- Social, and Spiritual (BPSS) categories. Some of these factors seem to be understudied or the interaction with AUD is rather complex, while further research of factors like sleep problems, impulsivity and motivation could give rise to specific treatment options that may lead to better AUD treatment outcomes. Given that factors that lead to an AUD relapse are still highly variable and likely contextual; an integrative Bio-Psycho-Social-Spiritual approach may help in gaining a better understanding of individual risk and protective factors in future studies. Furthermore, as we identified as many as 37 distinct relapse factors, it could be that earlier models of relapse -often over 20 years old-

and relapse management/ relapse prevention interventions need to be revised and updated. 'New' relapse factors should be incorporated, but their clinical relevance needs additional research. Clinicians should reckon with these relapse factors, identify some patients' unique possible strengths or vulnerabilities, and when relevant also integrate them in treatment. We propose that also other outcome measures, like psychosocial functioning, deserve a more prominent place within 'relapse' models.

Several factors and findings warrant careful interpretation. First, the weight or impact of these different factors remain unclear, making it hard to prioritize their importance and clinical relevance. Next, it remains unclear as to how these factors cluster and influence each other, i.e., what are direct effects and associations or which factors have a predominantly triggering role or might be consequences of alcohol use. Finally, the exploration to what extent specific types of treatment might be more effective and match specific relapse factors should be embraced. However, despite these caveats we think that our findings, in bringing systematically together a large number of clinical relapse factors, are important for future clinical and research work. It must be noted, that most of the identified factors have a small or modest impact on the occurrence of relapse and cannot be prioritized based on the data. However, many of these factors are situated in the client's constitution, direct life-sphere, and/or environment/community. Yet it seems viable that the presence of multiple relapse factors may have an amplified effect and cause more severe disadvantaged life circumstances. That said, such a perspective set the stage for addiction treatments that account for a wide variety of important BPSS related life domains. In this respect, it seems appealing to depart from narrowly and briefly (protocolized) interventions that are directly focused on substance use/non-use to treatment that is more broadly oriented in which the patient should be situated in the 'driver's seat' in identifying and prioritizing treatment goals. Treatment modalities that acknowledge a wide life scope, like the Community Reinforcement Approach (CRA) (Roozen & Smith, 2021, 2022), should receive more attention in this regard.

Taken together the findings of our review revealed a wealth of different (clinical) factors that are related to an increased risk of relapse within the context of AUD treatment. Potentially, these could be helpful in identifying patients at increased risk for relapse and offer a multitude of relevant treatment targets, like sleeping problems, craving, meaning in life, impulsivity and co-morbid smoking. Our research will hopefully add scientific information that could lead to the development of more diverse treatment options for the heterogenous AUD (Litten et al., 2015, Witkiewitz et al., 2019). Of these, impulsivity, craving and meaning in life have in our view a special relevance. Future directions for applying our findings could be to consider specific interventions that may be most helpful for specific individual relapse risks (personalized medicine) (Kuhlemeier et al., 2021; Lohoff, 2020; Votaw et al., 2022).

1. Impulsivity: In our literature overview we found that, in contrast to the theoretical importance within the pathogenic models of addiction, the relapse factor '*impulsivity*' seemed to be relatively understudied. In our research on impulsivity measures, we found that both 'behavioral impulsivity' (with 'motor impulsivity' and

'impulsive choice' sub-categories) and 'trait impulsivity', as measured by distinct measurement instruments, seem to be associated with increased AUD relapse risk. However, the underlying mechanisms that link impulsivity dimensions with an increased risk of relapse and the possible clinical-therapeutical translation of this finding, remain as yet to be determined. Indeed, as demonstrated consistently throughout neurobiological studies brain regions and neurocircuitries that are involved in top-down regulation (impulse control) of behavior and emotions show impairments of functionality in groups of SUD patients (e.g., Dom et al., 2005, 2006; Noel et al., 2013; Verdejo-Garcia et al., 2019; Volkow et al., 2016; Koob et al., 2021). Nevertheless, many treatments are typically focused on self- control interventions, while the executive functions appear to be disrupted (Volkow et al., 2004). This may often lead to less favorable outcomes.

On a behavioral level this translates in impulsive behaviors with among others an increased risk of relapse. This line of thinking has been confirmed in our literature review, showing considerable effect-sizes (up to 1.7) of distinct impulsivity measures. Impulsivity was measured by behavioral tasks and/or self-report questionnaires ("trait" impulsivity). However, in spite of these significant indications regarding the role of impulsivity in relation to AUD relapse risk, the exact nature of the different aspects/ dimensions of impulsivity on this risk remains yet unclear. For example, which dimensions of impulsivity directly affect processes of self-control with respect to relapse in substance use? Or, alternatively, does impulsivity acts as a mediating factor enhancing the craving-relapse association (Coates et al., 2020)?

Answers to these questions are important when formulating and implementing treatment interventions aiming to target these specific vulnerabilities. Indeed, from a theoretical stance and as an example, it can be hypothesized that AUD patients with impairments in delay discounting, one of the main dimensions of behavioral impulsivity, might be specifically sensitive to interventions including fast rewards associated with short tile abstinence (the behavior to be stimulated). Evidence is accumulating that these kinds of interventions, e.g., Contingency Management or Community Reinforcement Approach do prove to be effective in the treatment of patients with complex SUD (Roozen & Smith, 2021, 2022; Destoop et al., 2021). However, whether they specifically are effective for patients with specific impulsivity impairments remains to be explored. In the same line of thinking, a limit number of studies points to the effect of cognitive training programs, aiming to improve cognitive control and executive functioning (Verdejo-Garcia et al., 2019).

Another strategy that is focused on training the prefrontal cortex is Goal Management Training; in which patients learn to periodically stop ongoing behavior to monitor and adjust their goals (Anderson, et al., 2022; Levine et al., 2011; Stamenova & Levine, 2019).

Interestingly and somewhat counter-intuitive, also the usage of the aversive medication Disulfiram, could have a place within treatment of the 'impulsive patient

population' (Mutschler et al., 2010; Ralevski et al., 2007), but current research is scarce and future clinical trials mandatory.

Recent research again highlighted the importance of reducing impulsivity, while impulsivity was found to be related to reduced quality of life and well-being after alcohol withdrawal treatment (Reichl et al., 2022). In this field the exact impulsivity dimensions (and importantly how to measure them) remains to be elucidated.

However, and despite the many remaining questions, our findings overall highlight the importance of impulsivity as a central construct in the process of relapse and as such gives an extra strong incentive for more research in this area.

2. Craving: In many earlier research, *craving* has been identified to be a robust predictor of AUD relapse. Craving refers to the phenomenon of intense longing for alcohol and is often seen as a multidimensional concept, consisting of emotional, cognitive, physiological and behavioral components (Rosenberg, 2009). Research at the complex nature of craving is still ongoing and recently several models, integrating cognitive, automatic and physiological aspects of craving, have been postulated (Flaudias et al. 2019; Skinner & Aubin, 2010) Interestingly, it was recently found that craving mediates the impulsivity-associated relapse risk in AUD (Coates et al., 2020). Other research found, next to impulsivity, also the catechol-O-methyltransferase (COMT) genotype is involved in the craving- relapse association (Padula et al., 2021). In our research the craving- AUD relapse association was less convincing. We measured baseline craving with the Penn Alcohol Craving Scale (PACS), which has demonstrated excellent reliability, construct and concurrent validity (Kavanagh et al., 2013). Higher PACS scores were found to be associated with AUD relapse (Flannery et al., 2003; Schneekloth et al., 2012; Stohs et al., 2019). Assessment of craving via 'near real time' methods/ ecological momentary assessment (EMA) will deliver data that probably enable us to discover more direct relationships between craving and alcohol use (McKay et al., 2006; Treloar Padovano & Miranda, 2021).

Despite our limited findings within a relatively small observational study, the craving-relapse association seems to be above any suspicion, but given the multidimensional concept and the many ways in which craving is measured, more research and a uniform 'craving-concept' is also needed.

3. Meaning in Life: The role of *meaning in life* (MiL) as a predictor of relapse and potential moderator remains unclear. In other research, experiencing a 'purpose in life' has been found to be a protective factor in AUD relapse as well, but this denominator does not seem to equal the broader concept of experiencing MiL. In our patient study, we found that craving and alcohol dependence were more prominent in the relapsed groups. However, we did not find a meaningful statistical relationship of craving/ MiL and relapse in our study. One important reason could be

that the number of patients included was relatively small, and the population was rather heterogeneous. This could have hindered the detection of relevant associations. It must be noted that MiL seems to conflate 3 related concepts, and furthermore does not seem to be equal to the concept of 'Purpose in Life', that in some earlier research has been found to be associated with lower relapse rates. The findings from our small patient study are somehow disappointing, as we expected to find at least some protective effect of MiL in relation to AUD relapse. Partly, because of getting less clinical admissions as part of the Covid situation at the time of this research, we also had less study inclusions than we expected. This does not take away that this exploratory prospective research was rather unique in addressing the MiL concept in relation to AUD relapse, and will hopefully be followed by more research on this topic. It is promising that also very recent research has investigated the role of MiL in relation to harmful alcohol use (Copeland et al., 2022).

As potential (protective) relapse determinants, the role of MiL and more specific religious factors might still be relevant to be investigated in future larger patient studies. As MiL seems to conflate related concepts, such as life purpose, well-being, and valued living, and it would be useful to develop a measure of MiL that disambiguates these different constructs and could be examined in future research. Surprisingly, also research investigating the Purpose in Life/ relapse association seems to be scarce, and might deserve further attention.

Finally, our research aimed to give a broad, timely overview of AUD relapse factors, and also focused on some seemingly interesting ones, like meaning in life and impulsivity. We also detected a great variety in the use of AUD relapse definitions and questioned the use of the term 'relapse'. Has in 2023 the time come to 'leave the wagon' (Miller, 1996)?

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Meanwhile we investigated the possibility of combining our research with a PhD trajectory. We contacted Professor Dom (Antwerp University), who was willing to serve as promotor, together with professors Witkiewitz and Roozen.

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7. Tables & figures

Table Chapter 1

Table 1 *Relapse Definitions used Across Reviewed Papers (n=321)*

Relapse Definition	Citing Papers	Number of studies
Continuous Drinking Outcomes		28
Days drinking, drinks per day **past 28 days**	Brower, 2003	
Percent days alcohol consumed, average daily number of drinks	Prisciandaro, 2012	
Percent days drinking (PDD)	Gillihan, 2011; Zandberg, 2016	
Percent heavy drinking days (PHDD), defined as **≥ 4** drinks per day for women and **≥ 5** drinks per day for men OR **≥48 g/day** for women and **≥60 g/day** for men	Witkiewitz, 2011; Janu, 2012; Bujarski, 2013; Witkiewitz, 2015; Possemato, 2017/ Jorde, 2014, Bach, 2015; Zois, 2016; Field, 2017; Zois, 2017; Bach, 2019a; Bach, 2019b	12
Average number of drinks per day	Lehavot, 2014	
Drinks per drinking day (DDD), PDD and PHDD	Witkiewitz, 2009; Witkiewitz, 2013; Maisto, 2018	
Percent days abstinent (PDA), mean number of DDD or PHDD	Davis, 2016	
PDD and DDD	Roos, 2015; Karpyak, 2016; Maisto, 2017	
PDA and DDD	Tonigan, 2017	
DDD	Adinoff, 2017	
Number of drinking days and number of heavy drinking days	Conroy, 2006	
Time to first day of heavy drinking, defined **≥ 6** drinks for men or **≥ 5** for women, PDD and DDD	Gelernter, 2007	
Dichotomous Drinking Outcomes		
	Any Use	102
Any alcohol use	Curran, 2000; Gulliver, 2000; Tómasson, 2000; Bellamy, 2001; Brower, 2001; Driessen, 2001; Gann, 2001; Gish, 2001; Schmidt, 2001; Vielva, 2001; Gann, 2002; Lucht, 2002; Junghanns, 2003; Schadé, 2003; Walton, 2003; Wiesbeck, 2003; Bottlender, 2004; Mann, 2004; Miguet, 2004; Pfefferbaum, 2004; Bottlender, 2005a; Friend, 2005a; Björnsson, 2005; Junghanns, 2005a; Bottlender, 2005b; Friend, 2005b; Junghanns, 2005b; Bowden- Jones, 2005; Jorge, 2005; Perney, 2005; Turkcapar, 2005; Verheul, 2005; Walter, 2006a; Walter, 2006b; Demmel, 2006; Gordon, 2006; Sander, 2006; Terra, 2006; Bartels, 2007; Diehl, 2007; Feige, 2007; Schmidt, 2007; Sterling, 2007; Edens, 2008; Krampe, 2008; Müller, 2008; Pinto, 2008; Rus- Makovec, 2008; Terra, 2008; Witkiewitz, 2008; Wojnar, 2008; Oslin, 2009; Pitel, 2009; Wojnar, 2009; Farren, 2010; Müller, 2010; Berking, 2011; Cardenas, 2011; Costa, 2011; Dahlgren, 2011; Durazzo, 2011; Lejoyeux, 2011; Rando, 2011; Sinha, 2011; Suter, 2011; Garland, 2012; Schneekloth, 2012; Deruytter, 2013; Dolan, 2013; Jakubczyk, 2013; Oberleitner, 2013; Smith, 2014; Weinberger, 2015; Budzyński, 2016; Engel, 2016; Law, 2016; Manning, 2016; McHugh,	87

	2016; Mo, 2016; Shaw, 2016; Durazzo, 2017a; Durazzo, 2017b; Hufnagel, 2017; Wang, 2018; Wu, 2018; Zou, 2018; Ledda, 2019	
Any use of alcohol or illicit drugs	Strowig, 2000; Walton, 2000; Bauer, 2001; McKay, 2006; Tate, 2008; Heffner, 2011; McKee, 2011; Bauer, 2012; Camchong, 2013; De Wilde, 2013; Sau, 2013; Trocchio, 2013;	12
Alcohol or substance use, excluding caffeine and tobacco, but including the intake of "nonalcoholic beer"	Rupp, 2016; Rupp, 2017	2
Any drinking, a drinking binge, **3 consecutive days** of drinking	Kushner, 2005	1
	Quantity of use	12
≥5 drinks on one occasion	Aguiar, 2012	
≥3 standard drinks women, **≥ 5**standard drinks men	Greenfield, 2000; Greenfield, 2002; Greenfield, 2003; Trucco, 2007	
Consumption of **>60 grams** of alcohol in men or **>40 grams** of alcohol in women	Wrase, 2008; Charlet, 2013; Charlet, 2014; Garbusow, 2016; Sebold, 2017; Quoilin, 2018	
Relapse to heavy drinking: consumption of **≥60/48** (male/female) grams of alcohol in **1** drinking occasion	Bernhardt, 2017	
Relapse Defined by Timeframe		12
Time to first drink	Pagano, 2004; Ludwig, 2013; Seo, 2013; Zakiniaeiz, 2017	
Drinking lapse: the first drink recorded after a period of **≥7** days of abstinence	Holt, 2012	
Consumption of any alcohol on **≥3** consecutive days	Demirbas, 2012; Wiers, 2015	
Heavy drinking after **≥4** days abstinence	Miller, 2000	
A day of drinking preceded by **≥4** days of abstinence	Zywiak, 2003b; Zywiak, 2006b	
Alcohol consumption after **≥2** weeks abstinence	Zywiak, 2006a	
≥ 1 weeks of substance use after the **26th week** of remission from use	Aharonovich, 2005	
Relapse Defined by Quantity and Timeframe		17
21 units (12 gram per unit) of alcohol per week **≥ 1 week** and/or any use of illegal provided drugs and/or any use of benzodiazepines (prescribed or illegal)	Pedersen, 2009	
≥3 consecutive **days** of drug use and/or heavy drinking operationalized **≥6** drinks per day for men and **≥4** drinks per day for women	Tate, 2005	
> 4 standard drinks (1 standard drink = 10 g of pure alcohol) on 1 day/ **≥ 5 drinks** on 1 day	Nieva, 2011/ Oslin, 2002	
drinking **>30 grams** of ethanol (**2** standard drinks) **in 24 h**	Haver, 2001	
≥31 standard drinks in ≤**3 days**	Allsop, 2000	
≥4 standard drinks for women and **≥5** standard drinks for men **at least once in the past 30 days**	Mojarrad, 2014	
Relapse spectrum: minor lapse (**1 use**) - very heavy relapse (**> 4 uses/week, > 6 weeks**)	Humke, 2005	
≥5 standard drinks of alcohol **≥3 days a week**	Marquenie, 2006	
>3 drinks per day for **at least 1 month**	Sorg, 2012	
Heavy drinking (i.e. consumption of **≥5 alcoholic beverages on one day**), or intoxication with alcohol during **2 consecutive days** a week	Schellekens, 2015	
Relapsers to alcohol abuse: women consuming **≥4 drinks daily for 1 day**, men consuming **≥5 drinks daily for 1 day**, or any adult consuming **≥3 drinks** daily for **≥7 consecutive days**	Wilens, 2011	
Consumption of **≥5 units** of alcohol on one occasion and **≥4** such occasions **in 1 week**, or **≥12 units** on **≥1** occasions	Willinger, 2002	
≥3 consecutive days of drinking operationalized as **≥6** drinks per day for men and **≥4** drinks per day for women	Durazzo, 2010a; Durazzo, 2010b	
≥5 drinks per day for men and **≥4** drinks for women; or **≥5** consecutive days of slips for men and **≥4** days for women	Zikos, 2010	

≥1 drink (0.5 ounces of ethanol) **a month for a year**	Vaillant, 2003	
Relapse Defined by Return to Previous Levels of Drinking		4
Resumption of frequent use or a return to previous levels of alcohol use	Pelc, 2002	
Return to drinking, consuming alcohol regularly at least in the amount of prior use	Evren, 2012	
Return to alcohol consumption rates at or near the level of their pre-detoxification use	Matheus-roth, 2016	
Relapse into pre-treatment drinking levels	Snelleman, 2018	
Readmission and Detoxification Measures		4
Re-admission detox unit	Callaghan, 2002	
Number of previous detoxifications	Baars, 2013	
Number of alcohol-related hospital readmissions and the days to first readmission	Weinland, 2017; Weinland, 2019	
Qualitative Definitions, Alternative Measures of Severity, and Problem Drinking		19
Not occasional, but continuous re-drinking	Haraguchi, 2009	
Drinking -but improved-or drinking unimproved	Long, 2000	
Any episode of problematic drinking, however brief or limited	Ercan, 2003	
Problem drinking: (1) drinking **≥5** drinks per day at least once a month for men or **≥3** drinks per day weekly for women, (2) **≥1** alcohol-related social consequences in the past year (from a list of eight), and/or (3) **≥1** alcohol dependence symptoms in the past year (from a list of nine)	Mericle, 2018	
Excessive drinking (regularly **>70 g of pure ethanol**); hospitalization (reinstitutionalized primarily for alcohol-related problems); unable to drink due to illness (remained abstinent at home because of illness)	Noda, 2001	
>4 drinks/ day, >**4 days** drinking/ week, situations requiring detoxification	Noël, 2002	
Recurrence of a drinking pattern which results in a premature termination of treatment or cessation of post-treatment follow-up visits	Wagner, 2004; Krampe, 2006	
(1) Need for hospitalization, or emergency department attendance, due to alcohol consumption (2) Positivity of a urine screening. (3) Clinical detection, according to patient's medical record, of any alcohol consumption	Barrio, 2017	
Recurrence of "alcoholic disease"	Platz, 2000	
Harmful drinking with recorded medical or social harm, or drinking **>140 g** ethanol/week / harmful relapse: associated with medical or social harm or a return to daily consumption of alcohol or in excess of **140 g** of ethanol/week	Kelly, 2006; Wigg, 2017	
Relapse to problem use	Mertens, 2012	
Repeated drinking after initial lapse/ repeated alcohol consumption	Papachristou, 2014; Nalpas, 2018	
Experiencing one or more items of the 'Drinking Problems Index'	Schutte, 2003; Schutte, 2009	
Drug- or alcohol-related problems at both follow-up and over the preceding year	Landheim, 2006	
≥1 week of new symptom severity scores greater than 3 (no dependence criteria, but the ASI rater severity score greater than 3)	Strakowski, 2005	
DSM/ ICD criteria, Recovery and Remission Definitions		53
	DSM	11
Recurrence of any DSM-IV AUD symptoms	Dawson, 2007	
Reinstatement of a state of alcohol dependence according to DSM-IV criteria	Spruyt, 2013	

Returning to drinking after a period of abstinence accompanied by reinstatement of dependence symptoms	Paulino, 2017	
Two or more DSM-5 AUD symptoms following remission	Tuithof, 2014	
Fulfilling DSM-III-R criteria for alcohol dependence 3 months after hospital admission	Tatsuzawa, 2002	
Problem drinkers > reported any criteria for a diagnosis of ''alcohol abuse'' or ''dependence'' during 12 months	Russell, 2001	
DSM-IV, ICD-10 and CWM criteria at 1 and 3 year follow up (relapse to abuse of dependence)	De Bruijn, 2006	
≥ 1 week with any DSM-IV dependence or abuse symptom after 26 weeks of remission	Samet, 2013	
Recurrence, defined number of assessment ages at which a DSM (III, III-R, IV) AUD was diagnosed	Milne, 2009	
Recurrence, defined as presence of a CIDI diagnosis of Alcohol Dependence (DSM-IV) at any time during the **2-year** follow-up	Boschloo, 2012	
Persistence, defined as maintaining full criteria for DSM-IV alcohol dependence (i.e. chronicity/persistence) throughout **3 years**	Elliott, 2016	
	Recovery	6
Recovery: abstinent or no **last year** DSM-IV criteria abuse/ dependence, no risk drinker	Dawson, 2005; Dawson, 2006	
Recovery: abstinent or no **last year** DSM-IV criteria abuse/ dependence, no severe headaches when getting over drinking, no risk drinker	Dawson, 2012	
Recovery: past **3-year** interval of no diagnosis, characterizing *securely* abstinent former abusers	McAweeney, 2005	
Recovery: no DSM-III-R abuse and dependence criteria over at least the final **5-year** follow up period	Schuckit, 2011; Haller, 2014	
	Remission	36
Remission: at least **six months** without evidence of abuse or dependence	Brunette, 2003	
Remission: did not meet criteria for any substance use disorder in the **past year**	Karno, 2008	
Remission: either past-year abstinence from both alcohol and drug use, or **past-year** non-problem substance use	Tsoh 2011; Satre, 2012	
Remission: no criteria for dependence or abuse during the last year but reported using drugs or alcohol during the past year at least once; or abstinent, no longer criteria for dependence or abuse and reported no substance use during the **last year**	Arndt, 2010	
Remission: absence of full criteria for abuse or dependence (**DSM-III**-R)	Xie, 2010	
Remission: a minimum of **6 months** with either no use of alcohol or some use of alcohol but no symptoms of dependence or abuse (DSM-III-R), and the criteria for dependence (or abuse) not met	Knop, 2007; Penick, 2010	
Remission: no DSM-III-R criteria dependence for **6 months** or more	Gilder, 2008	
Remission: no DSM-III criteria abuse/ dependence for **12 months**	Sher, 2004	
Remission: no longer meeting **DSM-IV** criteria for an alcohol or drug dependence disorder (**past 12 months**)	Grella, 2013	
Remission: no DSM-IV criteria abuse/ dependence for **12 months**	Ojesjö, 2000; Bischof, 2001; Bischof 2005; Bischof, 2007; Damian, 2017	
Remission: cessation of alcohol use and the absence of any pre-existing DSM-IV abuse or dependence symptoms for **at least 1 year** before the interview	Silveira, 2011	
Remission: no DSM-IV criteria dependence for **12 months**	Pirkola, 2006	
Remission: no DSM-IV or ICD-10 criteria last **12 months**	Rumpf, 2002; Degenhardt, 2018	
Remission: cessation of alcohol use and the absence of any pre-existing DSM-IV abuse or dependence symptoms for **at least 1 year**	Silviera, 2011	
Remission: the cessation of alcohol use and the absence of any symptoms (DSM-IV) for **at least two years**	Kalaydjian, 2009; Lee, 2009; Suliman, 2010; Abdin, 2014	

Remission: did not meet DSM-IV criteria for AUD in any subsequent follow-up	Trim, 2013	
Remission: no DSM-IV criteria dependence	Lopez-Quintero, 2011	
Remission: **at least 1 year** none of **DSM-5** AUD criteria/ symptoms	McCutcheon, 2012; McCutcheon, 2014; McCutcheon, 2017	
Remission: one or none of: (1) drinking five or more drinks a day at least once a month for men (three or more drinks a day for women); (2) one or more alcohol-related social consequences (from a list of eight); and (3) one or more alcohol dependence symptoms (from a list of nine)	Matzger, 2005	
Remission: abstinence, **≤3 ounces** on a drinking day, no alcohol related problems	Moos, 2003	
Remission: abstinence or moderate drinking in each of the **past 6 months**, no intoxication and consumption of no more than 3 oz. of ethanol on drinking days in the past month, and no drinking problems in the past **6 months**	Moos, 2005; Moos, 2006a; Moos, 2006b; Moos, 2007	
No Relapse Definition		70
No definition	Markianos, 2001; Schutte, 2001; Zywiak, 2003a; Hufford, 2003; Fein, 2004; Tapert, 2004; Garbutt, 2005; Ilgen, 2005; Krahn, 2005; McKay, 2005; Bradizza, 2006; Brady, 2006; Hammerbacher, 2006; Hingson, 2006; Jackson, 2006; Rask, 2006; Walitzer, 2006; Arnedt, 2007; Cooney, 2007; Di Sclafani, 2007; Levin, 2007; Waldrop, 2007; Becker, 2008; Tucker, 2008; Hunter- Reel, 2009; Mattoo, 2009; Romo, 2009; Udo, 2009; Borders, 2010; Dom, 2010; Gamble, 2010; Kalman, 2010; Loeber, 2010; North, 2010; Henkel, 2011; Higley, 2011; Kelly, 2011; Schepis, 2011; Copeland, 2012; Dakwar, 2012; Fein, 2012; Kelly, 2012; O'Daly, 2012; Abulseoud, 2013; Connolly, 2013; Farren, 2013; Gross, 2013; Khan, 2013; Preuss, 2013; Schepis, 2013; Tuithof, 2013; Vito Agosti, 2013; Castaldelli-Maia, 2014; Chiappetta, 2014; Cosgrove, 2014; Cranford, 2014; Garfield, 2014; Huntley, 2014; Jessup, 2014; Segobin, 2014; Flórez, 2015; Garcia, 2015; Conde, 2016; Czapla, 2016; Weinberger, 2016; Zahr, 2016; Blaine, 2017; Foulds, 2017; Gong, 2018; Karriker-Jaffe, 2018	

Tables and Figures Chapter 2

Figure 1

Figure 1. Flowchart (Prisma based)

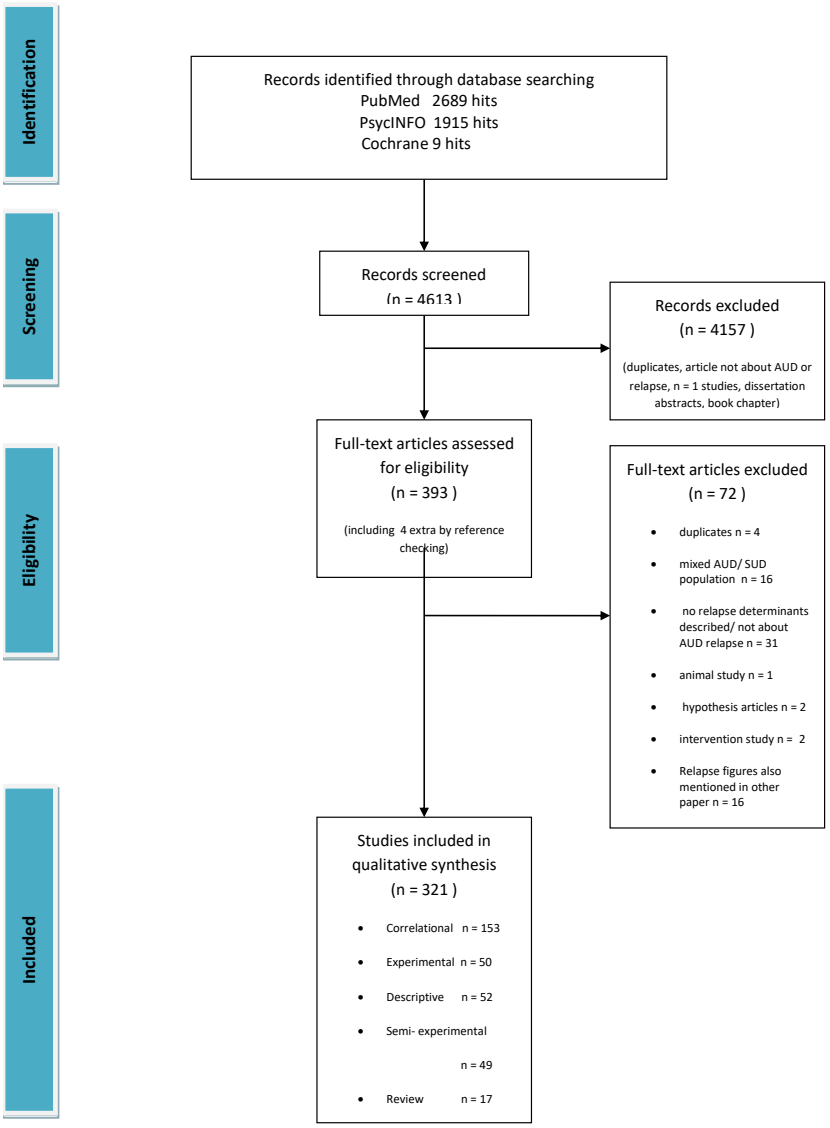

Table 2 *Search results per category (BPSS model).*

Determinant category	Statistically significant factor Number of studies (total n across studies)	Statistically non-significant factor Number of studies (total n across studies)	Number and percentage of significant studies (within relapse factor category)
BIOLOGICAL			
Age	31 (n=49258)	15 (n=2184)	31/46 = 67%
Gender	14 (n=14212)	20 (n=13850)	14/34 = 41%
Brain (*Thalamus, Vermis†, Frontal white Matter*, *Mesolimbic, Brain Reward System, Amygdala, Basal ganglia, Rostral ACC †, Medial frontal gyrus, brain-injury, Gray Matter Volumes, Gray matter volume Cuneus & connectivity, Gray matter volume in medial orbito frontal cortex, impaired medial prefrontal cortex function, cingulate cortex functional connectivity, volumes of: the right caudal anterior cingulate cortex (ACC), right rostral ACC, and total right frontal gray matter, bilateral frontal Gray Matter, Gray Matter volume caudate/ amygdala, ventral medial prefrontal cortex (VmPFC) dysfunction*, *White matter microstructure deficits: corpus callosum/ stria terminalis/fornix/left anterior corona radiata, Nucleus accumbens (NAcc) activation*)	25 (n=1388)	2 (n=49) (*hippocampus, Thalamic N-acetylaspartate (NAA) deficits*)	25/27 = 93%
Family history	8 (n=1921)	6 (n=552)	8/14 = 57%
Genetics (*PDYN rs2281285, HTR2A, GABRA2, KIBRA, DRD2, BDNF, 5-HTTLPR*, rs1789891)	7 (n=1136)	4 (n=517) (*OPRM1, TPH2, SLC6A4, HTR1A, HTR2A, CHRM2, ANKK1, BDNF. COMT, DAD2, DAD3*)	7/11 = 64%
Health	7 (n=6530) 2 (n=5011) †	1 (n=222)	7/10 = 70% 2/10 = 20% †
Sleep	8 (n=404)	1 (n=254)	8/9 = 89%
Receptor/hormones (*GATA4>ANP, BDNF, Cortisol in CSF, Cortisol response, D2 Dopamine receptor responsivity on Prolactin, basal cortisol:ACTH,Leptin levels*)	8 (n=351) 2 (n=148) †	1 (n=38) (*DAT methylation*)	8/11 = 73% 2/11 = 18% †
Biological markers (*liver enzymes, MCV, baseline urine ethyl glucuronide (EtG), Body Mass Index (men)*)	5 (n=866)	2 (n=121) (*Body Mass Index, blood glucose/ lipids*)	5/7= 71%
PSYCHOLOGICAL			

Psychiatric (*Anxiety, Depression, Suicidality, ADHD, Social phobia, Dysthymia, Panic disorder, Bipolar disorder , mood disorder*)	44 (n=24889) 2 (n=384) †	19 (n=6819)	44/65 = 68% 2/65 = 3% †
Severity AUD	45 (n=34160)	10 (n=920)	45/55 = 82%
Craving	29 (n=12343)	6 (n=384)	29/35 = 83%
Abstinence duration	12 (n=6891)	3 (n=249)	12/15 = 80%
Emotion	25 (n=10139)	8 (n=724)	25/33 = 76%
Self-efficacy	25 (n=10172)	3 (n=163)	25/28 = 89%
Comorbid SUD	20 (n=45382)	3 (n=310)	20/23 = 87%
Smoking	15 (n=20092) 1 (n=557) †	5 (n=456)	15/21 = 71% 1/21 = 5% †
Treatment history	20 (n=8660)	2 (n=213)	20/22= 91%
Coping	17 (n=6241)	2 (n=130)	17/19 = 89%
Neurocognitive	18 (n=2521)	4 (n=120)	18/21= 82%
Personality disorder	7 (n=14508)	5 (n=5083)	7/12 = 58%
Life events (*trauma, 'rock bottom'*†)	9 (n=8155) 1 (n= 659) †	2 (n=148)	9/12 = 75% 1/12 = 8% †
Stress	12 (n=4470)	2 (n=34)	12/14 = 86%
Impulsivity	9 (n=554) 1 (n=20) †	5 (n=827)	9/15 = 60% 1/15= 7% †
Number of prior detoxifications	5 (n=930)	5 (n=1976)	5/10 = 50%
Insight	6 (n=2272)	-	6/6 = 100%
Personality traits	4 (n=5768)	1 (n=61)	4/5 = 80%
Seeking help	1 (n=168) 4 (n=7332) †	-	1/5 = 20% 4/5 = 80% †
Drinking goal	4 (n=2308)	-	4/4 = 100 %
Outcome expectancies	3 (n=334)	-	3/3 = 100%
Motivation	2 (n=689)	-	2/2 = 100 %
Drinking consequences	1 (n=952) †	-	1/1 = 100 %
SOCIAL			
Social ‡ (*cultural, education, employment, -economic, -pressure, non drinking*)	43 (n=47866)	18 (n= 85013)	43/61 = 70 % ‡
Support ‡	44 (n=33845)	6 (n=1155)	44/50 = 88% ‡
Child	1 (n=300) 2 (n=6869) †	-	1/3 = 33% 2/3 = 66% †
SPIRITUAL			
Social spiritual	1 (n=102) 7 (n=14970) †	3 (n=530)	1/11 = 9 % 7/11 = 64% †
Life purpose	6/5415†	1 (n= 48)	6/7 = 86% †

† protective

‡ direction of social factors on relapse/ remission is context dependent (see paragraph 3.2.3)

Table 3 *Cross references per category (BPSS model)*

Determinant category	Studies where factor is statistically significant predictor of relapse/remission	Studies where factor is not a statistically significant predictor of relapse/remission
BIOLOGICAL		
Age	(Gong, 2018), (Abdin, 2014), (Sau, 2013), (Tuithof, 2013), (Agosti, 2013), (Trim, 2013), (Farren, 2013), (Mertens, 2012), (Satre, 2012), (Demirbas, 2012), (Heffner, 2011), (Silveira, 2011), (Lopez-Quintero, 2011), (Suliman, 2010), (Mattoo, 2009), (Kalaydjian, 2009), (Lee, 2009), (Gilder, 2008), (Dawson, 2007), (Gelernter, 2007), (Hingson, 2006), (Demmel, 2006), (Perney, 2005), (Bowden-Jones, 2005), (Junghanns, Aug 2005), (Dawson, 2005), (Moos, 2003), (Pelc, 2002), (Russell, 2001), (Schutte, 2001), (Ojesjö, 2000)	(Cranford, 2014), (Jakubczyk, 2013), (Spruyt, 2013), (Evren, 2012), (Milne, 2009), (Müller, 2008), (Landheim, 2006), (Krampe, 2006), (Sander, 2006), (Jorge, 2005), (Björnsson, 2005), (Miguet, 2004), (Oslin, 2002), (Tómasson, 2000), (Platz, 2000)
Gender	(Gong, 2018), (Farren, 2013), (Satre, 2012), (Boschloo, 2012), (Heffner, 2011), (Lopez-Quintero, 2011), (Gilder, 2008), (Edens, 2008), (Moos, Sep 2006) , (Bottlender, Oct 2005), (Dawson, 2005), (Garbutt, 2005), (Moos, 2003), (Schutte, 2001)	(Nalpas, 2018), (Khan, 2013), (Gross, 2013), (Jakubczyk, 2013), (Spruyt, 2013), (Berking, 2011), (Suliman, 2010), (Müller, 2010), (Müller, 2008), (Diehl, 2007), (Krampe, 2006), (Sander, 2006), (Walitzer, 2006), (Jorge, 2005), (Björnsson, 2005), (Miguet, 2004), (Callaghan, 2002), (Willinger, 2002), (Tómasson, 2000), (Greenfield, 2000)
Brain	(Zou, 2018), (Wu, 2018), (Wang, 2018), (Zois, 2017), (Sebold, 2017), (Zakiniaeiz, 2017), (Durazzo, 2017a), (Durazzo, 2017b), (Blaine, 2017), (Zois, 2016), (Garbusow, 2016), (Segobin, 2014), (Charlet, 2014), (Charlet, 2013), (Janu, 2012), (Sorg, 2012), (Cardenas, 2011), (Durazzo, 2011), (Rando, 2011), (Durazzo, Mar 2010), (Durazzo, May 2010), (Wojnar, 2009), (Wrase, 2008), (Jorge, 2005), (Noël, 2002)	(Zahr, 2016), (Gross, 2013)
Family history	(Gong, 2018), (McCutcheon, 2017), (Deruytter, 2013), (Farren, 2010), (Mattoo, 2009), (Milne, 2009), (Perney, 2005), (Hufford, 2003)	(Trim, 2013), (Knop, 2007), (Junghanns, Aug 2005), (Miguet, 2004), (Junghanns, 2003), (Russell, 2001)
Genetics	(Bach, 2019b), (Preuss, 2013), (Jakubczyk, 2013), (Bauer, 2012), (Dahlgren, 2011), (Wojnar, 2009), (Pinto, 2008)	(Bach, 2015), (Bauer, 2012), (Wojnar, 2009), (Wiesbeck, 2003)
Health	(Damian, 2017), (Gong, 2018), (Jakubczyk et al., 2016), (Dakwar, 2012), (Satre, 2012), (Penick, 2010), (Pedersen, 2009), (Moos, 2007), (Pelc, 2002)	(Rus-Makovec, 2008)
Sleep	(Garcia, 2015), (Smith, 2014), (Arnedt, 2007), (Feige, 2007), (Conroy, 2006), (Gann, 2002), (Gann, 2001), (Brower, 2001)	(Jakubczyk, 2013)
Receptor/hormones	(Bach, 2019a), (Adinoff, 2017), (Zois, 2016), (Jorde, 2014), (Higley, 2011), (Costa, 2011), (Walter, Jul 2006), (Junghanns, Jan 2005), (Junghanns, 2003), (Markianos, 2001)	(Wiers, 2015)
Biological markers	(Weinland, 2019), (Barrio, 2017), (Flórez, 2015), (Aguiar, 2012), (Pfefferbaum, 2004)	(Bach, 2019a), (Budzyński 2016)
PSYCHOLOGICAL		
Psychiatric	(Gong, 2018), (Durazzo, 2017a), (Schellekens, 2015), (Chiappetta, 2014), (Tuithof, 2013), (Trocchio, 2013), (Jakubczyk, 2013), (Samet, 2013), (Boschloo, 2012), (Bauer, 2012), (Prisciandaro, 2012), (Copeland, 2012), (Wilens, 2011), (Suter, 2011), (Witkiewitz, 2011), (McKee, 2011), (Lejoyeux, 2011), (Farren, 2010),	(Possemato, 2017), (Haller, 2014), (Huntley, 2014), (Berking, 2011), (Lopez-Quintero, 2011), (Müller, 2010), (Rus-Makovec, 2008), (Pinto, 2008), (Di Sclafani, 2007), (Terra, 2006), (Krampe, 2006), (Bradizza, 2006),

	(Gamble, 2010), (Dom, 2010), (Xie, 2010), (Pedersen, 2009), (Wojnar, 2008), (Gilder, 2008), (Terra, 2008), (Landheim, 2006), (Moos, Sep 2006), (Gordon, 2006), (Waldrop, 2007), (Sander, 2006), (Pirkola, 2006), (Kushner, 2005), (Bottlender, Jun 2005), (Ilgen, 2005), (Strakowski, 2005), (Greenfield, 2003), (Moos, 2003), (Ercan, 2003), (Hufford, 2003), (Schadé, 2003), (Lucht, 2002), (Pelc, 2002), (Greenfield, 2002), (Driessen, 2001), (Tómasson, 2000), (Curran, 2000)	(Marquenie, 2006), (Kelly, 2006), (Bischof, 2005), (Sher, 2004), (Mann, 2004), (Junghanns, 2003), (Russell, 2001)
Severity AUD	(Gong, 2018), (Weinland, 2017), (Conde, 2016), (Zandberg, 2016), (Chiappetta, 2014), (Tuithof, 2014), (Sau, 2013), (Tuithof, 2013), (Jakubczyk, 2013), (McCutcheon, 2012), (Boschloo, 2012), (Bauer, 2012), (Copeland, 2012), (Witkiewitz, 2011), (Rando, 2011), (Mattoo, 2009), (Pedersen, 2009), (Udo, 2009), (Witkiewitz, 2008), (Dawson, 2007), (Knop, 2007), (Diehl, 2007), (Gelernter, 2007), (Walter, Feb 2006), (Jackson, 2006), (Krampe, 2006), (De Bruijn, 2006), (Garbutt, 2005), (Turkcapar, 2005), (Moos, Feb 2006), (Perney, 2005), (Bottlender, June 2005), (McAweeney, 2005), (Moos, 2005), (Dawson, 2005), (Ilgen, 2005), (Greenfield, 2003), (Moos, 2003), (Vaillant, 2003), (Schutte, 2003), (Hufford, 2003), (Haver, 2001), (Russell, 2001), (Bischof, 2001), (Schutte, 2001)	(Charlet, 2013), (Spruyt, 2013), (Pinto, 2008), (Sander, 2006), (Kelly, 2006), (Miguet, 2004), (Junghanns, 2003), (Tómasson, 2000), (Platz, 2000), (Allsop, 2000)
Craving	(Weinland, 2019), (Ledda, 2019), (McHugh, 2016), (Roos, 2015), (Flórez, 2015), (Papachristou, 2014), (Preuss, 2013), (Abulseoud, 2013), (Schneekloth, 2012), (Witkiewitz, 2013), (Connolly, 2013), (Prisciandaro, 2012), (Copeland, 2012), (Higley, 2011), (Witkiewitz, 2011), (Farren, 2010), (Oslin, 2009), (Wrase, 2008), (Krampe, 2008), (Zywiak, Dec 2006) , (Gordon, 2006), (Brady, 2006), (Turkcapar, 2005), (Junghanns, Aug 2005), (Bottlender, June 2005), (Verheul, 2005), (Bottlender, 2004), (Zywiak, Dec 2003), (Tatsuzawa, 2002)	(Mo, 2016), (Charlet, 2013), (Spruyt, 2013), (Cooney, 2007), (McKay, 2006), (Krahn, 2005)
Abstinence duration	(Maisto, 2018), (Gong, 2018), (Farren, 2013), (Ludwig, 2013), (Farren, 2010), (Dom, 2010), (Witkiewitz, 2008), (Dawson, 2007), (Cooney, 2007), (Perney, 2005), (Vielva, 2001), (Platz, 2000)	(Kelly, 2006), (Junghanns, 2003), (Bellamy, 2001)
Emotion	(Karpyak, 2016), (Engel, 2016), (Witkiewitz, 2015), (Abulseoud, 2013), (Oberleitner, 2013), (Trocchio, 2013), (Baars, 2013), (Berking, 2011), (Gillihan, 2011), (Witkiewitz, 2011), (Witkiewitz, 2009), (Zywiak, Dec 2006) , (Moos, Sep 2006), (Zywiak, June 2006), (Walitzer, 2006), (Hammerbacher, 2006), (Sher, 2004), (Verheul, 2005), (Zywiak, Dec 2003), (Hufford, 2003), (Lucht, 2002), (Strowig, 2000), (Platz, 2000), (Miller, 2000), (Long, 2000)	(Snelleman, 2018), (Mo, 2016), (Garfield, 2014), (Gross, 2013), (Connolly, 2013), (Oslin, 2009), (Cooney, 2007), (McKay, 2006)
Self-efficacy	(Shaw, 2016), (Kelly, 2012), (Witkiewitz, 2011), (Mattoo, 2009), (Romo, 2009), (Krampe, 2008), (Tate, 2008), (Cooney, 2007), (Levin, 2007), (Moos, 2007), (Moos, Sep 2006), (Gordon, 2006), (Demmel, 2006), (Moos, Feb 2006), (McKay, 2005), (Humke, 2005), (Moos, 2003), (Hufford, 2003), (Walton, 2003), (Russell, 2001), (Vielva, 2001), (Miller, 2000), (Long, 2000), (Greenfield, 2000), (Allsop, 2000)	(Trucco, 2007), (McKay, 2006), (Sher, 2004)
Comorbid SUD	(Gong, 2018), (Weinberger, 2016), (Mojarrad, 2014), (Chiappetta, 2014), (Vito Agosti, 2013), (Schepis, 2013), (Aguiar, 2012), (Bauer, 2012), (Copeland, 2012), (Schepis, 2011), (Lopez-Quintero, 2011), (Farren, 2010), (Xie, 2010), (Borders, 2010), (Karno, 2008), (Aharonovich,	(Björnsson, 2005), (Sher, 2004), (Brunette, 2003)

	2005), (Hufford, 2003), (Pelc, 2002), (Haver, 2001), (Russell, 2001)	
Smoking	(Gong, 2018), (Hufnagel, 2017), (Durazzo, 2017a), (Weinberger, 2015), (Cosgrove, 2014), (Chiappetta, 2014), (Holt, 2012), (Tsoh, 2011), (Kalman, 2010), (Dawson, 2007), (Cooney, 2007), (Schmidt, 2007), (Pirkola, 2006), (Friend, Oct 2005), (Junghanns, Aug 2005), (Friend, Apr 2005)	(Nieva, 2010), (Müller, 2010), (Sher, 2004), (Schmidt, 2001), (Gulliver, 2000)
Treatment history	(Nalpas, 2018), (Gong, 2018), (Possemato, 2017), (Wigg, 2017),(Cranford, 2014), (Mertens, 2012), (Witkiewitz, 2011), (Henkel, 2011), (Pedersen, 2009), (Schutte, 2009), (Terra, 2008), (Schmidt, 2007), (Dawson, 2007), (Bottlender, Jun 2005), (McAweeney, 2005), (Bottlender, Oct 2005), (Wagner, 2004) , (Moos, 2003), (Haver, 2001), (Tómasson, 2000)	(Trucco, 2007), (Krampe, 2006)
Coping	(Lehavot, 2014), (Dolan, 2013), (Demirbas, 2012), (Mattoo, 2009), (Witkiewitz, 2008), (Krampe, 2008), (Levin, 2007), (Moos, 2007), (Moos, Sep 2006), (Rask, 2006), (Moos, Feb 2006), (Walitzer, 2006), (Tapert, 2004), (Moos, 2003), (Russell, 2001), (Miller, 2000), (Walton, 2000)	(McKay, 2006), (Walter, Feb 2006)
Neurocognitive	(Rupp, 2017), (Field, 2017), (Charlet, 2014), (Seo, 2013), (De Wilde, 2013), (Camchong, 2013), (Spruyt, 2013), (Garland, 2012), (Sorg, 2012), (Penick, 2010), (Loeber, 2010), (Bowden-Jones, 2005), (Junghanns, Jan 2005), (Verheul, 2005), (Zywiak, Dec 2003), (Noël, 2002), (Bauer, 2001), (Allsop, 2000)	(Manning, 2016), (Pitel, 2009), (Becker, 2008), (Bartels, 2007)
Personality disorder	(Elliott, 2016), (Chiappetta, 2014), (Lopez-Quintero, 2011), (Penick, 2010), (Dawson, 2005), (Wagner, 2004), (Gish, 2001)	(Fein, 2012), (Bradizza, 2006), (Sher, 2004), (Russell, 2001)
Life events	(Zandberg, 2016), (McCutcheon, 2012), (Heffner, 2011), (North, 2010), (Mattoo, 2009), (Waldrop, 2007), (Walitzer, 2006), (Matzger, 2005), (Bottlender, Oct 2005), (Zywiak, June 2003)	(Jessup, 2014), (Greenfield, 2002)
Stress	(Gong, 2018), (Maisto, 2017), (Possemato, 2017), (Law, 2016), (Grella, 2013), (O'Daly, 2012), (Sinha, 2011), (Witkiewitz, 2011), (Tate, 2008), (Moos, Sep 2006), (Walter, Jul 2006), (Tate, 2005)	(Gross, 2013), (Becker, 2008)
Impulsivity	(Quoilin, 2018), (Wang, 2018), (Bernhardt, 2017), (Rupp, 2016), (Czapla, 2016), (Papachristou, 2014), (Sorg, 2012), (Evren, 2012), (Zikos, 2010), (Bowden-Jones, 2005)	(Matheus-roth, 2016), (Charlet, 2013), (Jakubczyk, 2013), (Fein, 2004) , (Moos, 2003)
Number detoxifications	(Weinland, 2017), (Czapla, 2016), (Müller, 2010), (Perney, 2005), (Pelc, 2002)	(Loeber, 2010), (Pinto, 2008), (Krampe, 2006), (Sander, 2006), (Callaghan, 2002)
Insight	(Gong, 2018), (Gilder, 2008), (Krampe, 2008), (Moos, 2005), (McKay, 2005), (Moos, 2003)	-
Personality traits	(Foulds, 2017), (Schuckit, 2011), (Schmidt, 2007), (Willinger, 2002)	(Paulino, 2017)
Seeking help	(Grella, 2013), (Dawson, 2012), (Farren, 2010), (Dawson, 2006), (Moos, Feb 2006)	-
Drinking goal	(Haller, 2014), (Bujarski, 2013), (Ludwig, 2013), (Mertens, 2012)	(Pitel, 2009), (Becker, 2008), (Bartels, 2007)
Outcome expectancies	(Humke, 2005), (Sher, 2004), (Miller, 2000)	(Jessup, 2014), (Greenfield, 2002)
Motivation	(Gong, 2018), (Pedersen, 2009)	-
Drinking consequences	(Davis, 2016)	-
SOCIAL		
Social	(Degenhardt, 2018), (Mericle, 2018), (Gong, 2018), (Durazzo, 2017a), (Zandberg, 2016), (Castaldelli-Maia, 2014), (Sau, 2013), (Abdin, 2014), (Trocchio, 2013), (Dawson, 2012), (Trim, 2013), (Aguiar, 2012), (Mertens, 2012), (Boschloo, 2012), (Demirbas, 2012), (Henkel,	(Karriker-Jaffe, 2018), (Connolly, 2013), (Evren, 2012), (Arndt, 2010), (Suliman, 2010), (Hunter-Reel, 2009), (Müller, 2008), (Krampe, 2006), (Sander, 2006), (Kelly, 2006), (McKay, 2006),

	2011), (Silveira, 2011), (Kelly, 2011), (Penick, 2010), (Xie, 2010), (Pedersen, 2009), (Kalaydjian, 2009), (Lee, 2009), (Tucker, 2008), (Moos, 2007), (Walter, Feb 2006), (Zywiak, June 2006), (Pirkola, 2006), (Jorge, 2005), (McAweeney, 2005), (Moos, 2005), (McKay, 2005), (Zywiak, Dec 2003), (Greenfield, 2003), (Schutte, 2003), (Hufford, 2003), (Walton, 2003), (Pelc, 2002), (Greenfield, 2002), (Bischof, 2001), (Schutte, 2001), (Platz, 2000), (Walton, 2000)	(Jorge, 2005), (Björnsson, 2005), (Moos, 2003), (Brower, 2003), (Russell, 2001), (Tómasson, 2000), (Platz, 2000)
Support	**(Gong, 2018),** (Wigg, 2017), (Schellekens, 2015), (McCutcheon, 2014), (Sau, 2013), (Trocchio, 2013), (Grella, 2013), (Dolan, 2013), (Satre, 2012), (McCutcheon, 2012), (Demirbas, 2012), (Kelly, 2012), (Witkiewitz, 2011), (McKee, 2011), (Dom, 2010), (Haraguchi, 2009), (Kalaydjian, 2009), (Rus-Makovec, 2008), (Terra, 2008), (Krampe, 2008), (Müller, 2008), (Bischof, 2007), (Trucco, 2007), (Moos, 2007), (Walter, Feb 2006), (Zywiak, Dec 2006) , (Moos, Sep 2006), (Demmel, 2006), (Pirkola, 2006), (Walitzer, 2006), (McAweeney, 2005), (Moos, 2005), (Dawson, 2005), (Sher, 2004), (Greenfield, 2003), (Hufford, 2003), (Walton, 2003), (Pelc, 2002), (Greenfield, 2002), (Rumpf, 2002), (Noda, 2001), (Russell, 2001), (Bischof, 2001), (Schutte, 2001)	(Evren, 2012), (Krampe, 2006), (Sander, 2006), (Björnsson, 2005), (Miguet, 2004), (Moos, 2003)
Child	(Gong, 2018), (McCutcheon, 2014), (McCutcheon, 2012)	-
SPIRITUAL		
Social spiritual	(Tonigan, 2017), (Castaldelli-Maia, 2014), (Tusa, 2013), (Sau, 2013), (Dawson, 2012), (Kelly, 2012), (Sterling, 2007), (Matzger, 2005)	(Borders, 2010), (Gordon, 2006), (Sher, 2004)
Life purpose	(Roos, 2015), (Cranford, 2014), (McCutcheon, 2014), (Dawson, 2012), (Pagano, 2004), (Walton, 2000)	(Jessup, 2014)

Tables and Figures Chapter 3

Figure 1 Flowchart literature review

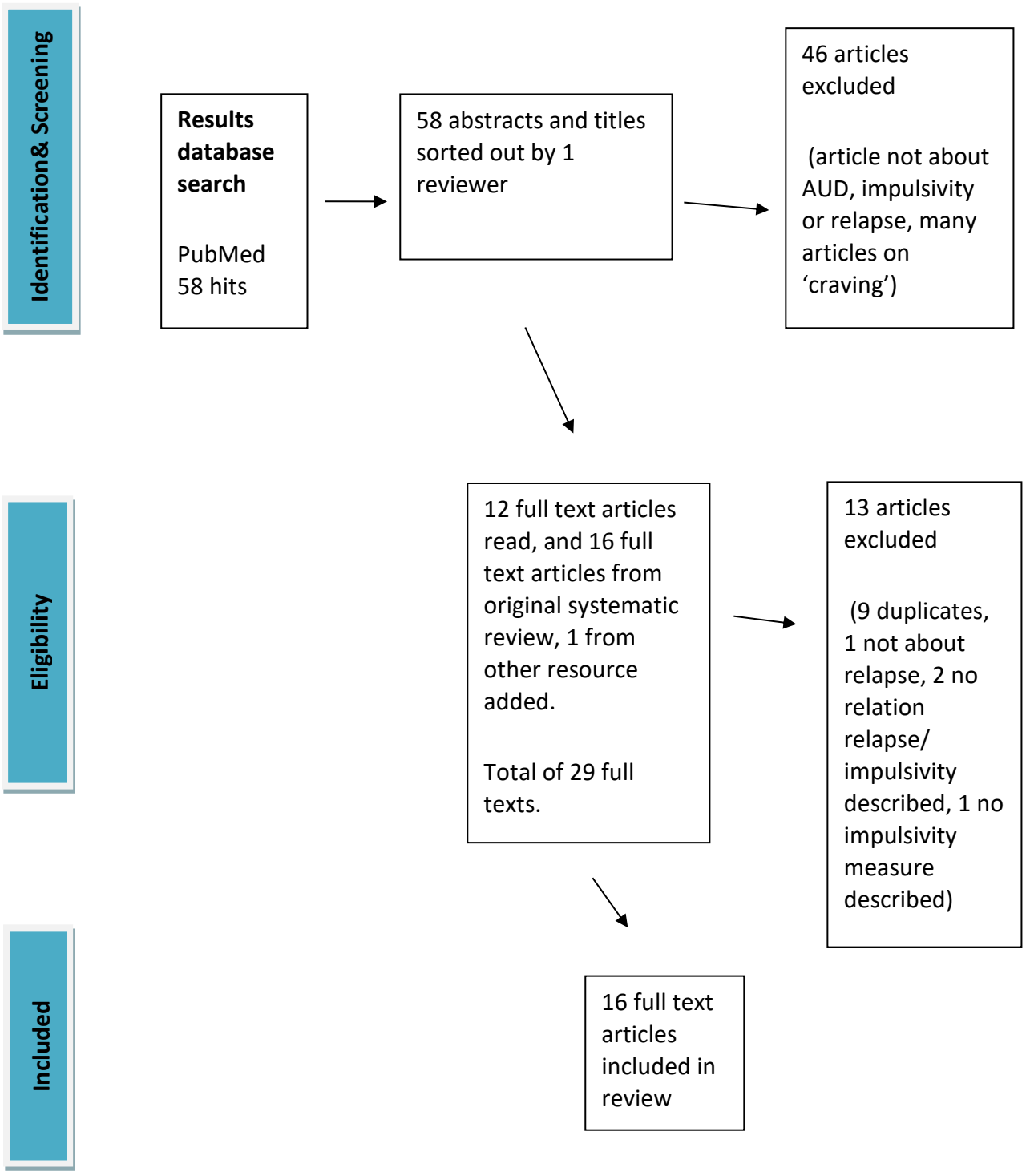

Table 1 *Overview studies*

Study Author, year	Design	Sample size	Study objective	AUD relapse definition & relapse figures	Impulsivity measures, statistical significance and impulsivity category (**TI** (trait)**,** or **BI** (behavioural)/ subcategory **MI** (motor) **or IC** (choice))	Effect sizes
Quoilin, 2018	Prospective study, experiment, Belgium.	N= 20 Alcohol Dependent patients	evaluate the potential relationship between the level of neural motor inhibition and the propensity to relapse within the following year. Also assessed trait impulsivity and behavioural inhibition	60 gram alcohol for males; 40 grams for a female on a single occasion during past year 11 relapse, 9 abstinent/ non relapse Relapse rate: 55%	**TI:** **trait impulsivity** (UPPS), F2,37 = 10.52; $p <$ **0.001** **BI/ MI:** **behavioural inhibition** (visual reaction time (RT) task, Stop-Signal, Anti-Saccade, Number-Letter task), F2,35 = 8.99; $p <$ **0.001** **neural motor inhibition** (instructed-delay choice RT task), F2,35 = 6.53; $p <$ **0.01**	**N/A**

Wang, 2018	Prospective study, brain imaging, China	N= 58 Alcohol Dependent male patients	identify biomarkers of relapse vulnerability by investigating persistent brain abnormalities in abstinent alcohol-dependent patients	At least one drink during the 3 month follow up period 35 relapse, 21 abstinent Relapse rate: 60%	**TI:** **BIS-11 total** score, *p* **=0.006** (relapsers vs. healthy controls (HC)) **BIS-11 attention** scores, *p* **<0.001** (relapsers vs. HC) **BI/ IC:** **BART** performance **(**Balloon analogue risk test**),** *p* **=0.013** (relapsers vs. abstainers) *p* **=0.007** (relapsers vs. HC)	BIS-11 total scores: **0.4** BIS-11 attention scores: **0.7** BART performance: **0.4**

Rubio, 2018	Randomized study, Spain	N= 207 Alcohol depended patients	investigate whether inclusion of self-help groups into the hospital treatment program improves the prognosis of alcohol dependence through the treatment period; and to examine therapeutic adherence and prognosis during continuing care	Any at- risk drinking day, 6 year follow up 93 relapse, 116 abstinent Relapse rate: 45%	**TI:** **BIS- 11** score, *p* **=0.008 (**less accumulated months of abstinence)	**N/A**

Bernhardt, 2017	Behavioural data choice impulsivity, Germany	N= 85 detoxified AUD patients	assess the predictive value of choice impulsivity for relapse to heavy alcohol use in patients during	heavy drinking: consumption of ≥60/48 (male/female) grams of alcohol in 1 drinking occasion and the amount of alcohol consumption, 48 weeks follow up 58 relapse, 27 abstinent Relapse rate: 68%	**TI:** Barratt Impulsiveness Scale BIS- 15 sum, *p* =0.242 (*NS*) (Subscales also *NS*) **BI/ IC:** **Delay Discounting** (DD), *p* **=0.029** **probability discounting for losses** (PDL), *p* **=0.008** probability discounting for gains (PDG), *p* =0.282 (*NS*) Mixed Gambles = MG,	Delay Discounting: **0.2** Probability discounting for losses (PDL): **0.7**

					p =0.491 (*NS*) (Cox proportional hazards)	
Tucker, 2016	Prospective community study. Hypothetical money DD task, USA.	N= 175, problem drinkers	compare the predictive utility of "Alcohol-Savings Discretionary Expenditure" (ASDE) index with measures of behavioral impulsivity and self-control, to predict outcomes of natural recovery attempts	Abstinent or drinking below risky drinking thresholds without problems. 6 & 12 month follow up N=103: 'resolved abstinent'	**BI/IC:** Log k DD parameter (*NS*)	N/A
Matheus-Roth, 2016	Go, No Go assessment, ERP, interview at F- up, Germany	N= 23 detoxified alcohol dependent patients	Asses occipital Event Related Potentials (ERPs) to alcohol- and non-alcohol-related stimuli in recently detoxified patients and controls & ERPs significance for relapse research	return to alcohol consumption rates at or near the level of their pre-detoxification use, 3 month follow up 12 relapse, 11 abstinent Relapse rate: 52%	**<u>TI:</u>** Barratt Impulsivity Scale BIS- total mean score *p* =.866 (*NS*) (no difference relapsers vs. abstainers)	**<u>N/A</u>**

Rupp, 2016	Prospective study, Austria Clinical population	N= 43 alcohol dependent inpatients	prospectively investigate the impact of neurocognitive impulsivity at treatment onset on treatment completion	Any alcohol or substance use, follow up 8 weeks Relapse figures of total 43 not mentioned in paper, only relapse figures mentioned from treatment dropouts (10 out of 14)	**BI/ MI & IC:** Go/No-Go Stop Signal Test Delay Discounting Iowa Gambling Task > **GNG response inhibition performance** *p* **=0.023**	Go/ No Go response inhibition performance: **1.1**
Czapla, 2016	Prospective study, Germany Clinical population	N= 81 alcohol dependent in-patients	identify which particular cognitive functions are impaired in ADP. Furthermore, we analysed the association between cognitive deficits and relapse rates and the reversibility of cognitive deficits under abstinence in a 6-month follow-up period	any alcohol use, 6 month follow up 63 relapse, 18 abstinent Relapse rate: 78%	**BI/ MI & IC:** Alcohol Go/No-Go task Cambridge Gambling Task BIS-11 **> Response inhibition deficits** *(factor 3 of the principal components analysis)*, *p* **=0.033**	**N/A**

Papachristou, 2014	Prospective follow up study, Netherlands	N= 20 (19 alcohol dependent, 1 alcohol abuse)	Investigate whether cue-elicited craving, impulsivity, and their interaction term predict a lapse in problem drinkers	Lapse: one drink during 3 month follow up, all considered to have relapsed 6 lapse, 14 abstinent Relapse rate: 30%	**TI:** BIS-11 **higher trait impulsivity score** > **less relapse,** *p* **<0.05**	**N/A**
De Wilde, 2013	Naturalistic outcome, follow up study, Belgium	N= 37 PSA= poly substance dependent alcoholics	Investigate whether deficits in decision-making in polysubstance-dependent alcoholics (PSA) are critical risk factors predicting relapse	Relapse: any substance use, 10 week follow up 23 non abstinent, 14 abstinent Relapse rate: 62%	**TI:** BIS *NS* **BI/ IC:** **Iowa Gabling Task** (IGT), *p* **=0.028** Delay Discounting Task, *p* =0.520 (*NS*)	**N/A**

Charlet, 2013	Functional Brain Imaging study, Germany	N= 29 recently detoxified right-handed alcohol depended inpatients.	functional brain imaging was used to examine the hypothesis that neural activation elicited by a cue-comparison paradigm presenting aversive faces versus neutral shapes is diminished in Alcohol Dependent Patients compared with healthy control subjects (HC)	Relapse: Subsequent alcohol consumption versus abstinent, 6 month follow up 15 relapse, 14 abstinent Relapse rate: 52%	**TI:** Barratt Impulsivity Scale BIS sum score, *p* =0.55 (*NS*) (see Table S3 in original paper)	**N/A**
Jakubczyk, 2013	Prospective Follow up study, Poland	N=254.	to assess the contribution of T102C polymorphism (rs6313) in the type 2A serotonin receptor (HTR2A) gene as a predictor of relapse in relation to other previously identified predictors	Any drinking during follow up period (12 months) 145 relapse, 109 abstinent Relapse rate: 57%	**BI/ MI:** Stop Signal Test; motor impulsivity/ stop reaction time, *p* =0.2 (*NS*)	**N/A**

Evren, 2012	Follow up study, face to face interviews, Turkey	N= 102 inpatient alcohol dependent	evaluate the relationship of relapse with impulsivity, novelty seeking (NS) and craving during 12 month follow up after inpatient treatment in male alcohol dependents	Relapse: return to drinking during 12 month follow up 63 relapse, 39 abstinent Relapse rate: 62%	**TI:** Novelty Seeking NS (subcategories 1,2,3,4) **NS-3**, *p* **=0.002** BIS-11 not after forward logistic regression analysis.	Novelty seeking 3: **1.1**

Zikos, 2010	Follow up study, interviews, Canada	N= 138	determine the prevalence of concurrent personality disorders (PDs) among alcoholic men and women seeking outpatient treatment, and to examine their effect on the course of alcohol treatment	Relapse: 5 or more drinks per day for men and 4 or more drinks for women; or 5 or more consecutive days of slips for men and 4 or more days for women slip: any drinking 12 week follow up period No relapse figures mentioned	**TI:** BIS-11 at intake & 12 weeks F- up Impulsivity via BIS-11/ BPD association, *NS*	**N/A**

Bowden-Jones, 2005	Pilot study, UK	N= 21	Testing effect of risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction on relapse in alcohol dependency	Relapse: non abstinent, 3 month follow up 6 relapse, 15 abstinent Relapse rate: 29%	**TI:** **BIS-11**, ***U* =8.0, *p* =0.016** **BI/ IC:** **Gambling Task**, ***U* =13.5, *p* =0.014**	Barratt Impulsiveness Scale: **1.7** Gambling task: **1.3**
Fein, 2004	Gambling task in abstinent alcoholics, USA	N= 44	using the simulated gambling task (SGT) to examine decision making in long-term abstinent alcoholics (mean of 6.6 years' abstinence) who do not have antisocial personality disorder or a history of conduct disorder	Retrospective abstinence duration (varied from at least 6 months- 6.6 years) 44 abstinent,	**BI/ IC:** SGT / simulated gambling task, *NS*	**N/A**

Moos, 2003	Naturalistic, longitudinal follow up study, USA	N= 473 AUD patients without former treatment	identify risk factors for 1-year and 8-year nonremission among initially untreated individuals with alcohol use disorders & examine whether a longer duration of professional treatment or Alcoholics Anonymous (AA) increased the likelihood of remission, moderated the influence of risk factors on remission status and reduced modifiable risk factors	Non remission: one or more alcohol-related problem, consuming> 3 ounces on a drinking day, 1,3 & 8 years of follow up At 1 Year: 255 non remitted 218 remitted Relapse rate: 54%	**TI:** Impulsivity from Personality Research Form (PRF), *NS*	**N/A**

Categories:

TI: Trait Impulsivity, BI: Behavioural Impulsivity, IC: Impulsive Choice, MI: Motor Impulsivity

Bold: statistically significant findings

Abbreviations:

AD: Alcohol Dependent, AUD: Alcohol Use Disorder

BIS: Barratt Impulsivity Scale, BPD: Borderline Personality Disorder

DD: Delay Discounting

HC: Healthy Controls

N/A: Not Applicable, NS: Not Significant

RT: reaction time

UPSS: Urgency, Premeditation, Perseveration and Sensation-Seeking

Vormgeving en druk verzorgd door:

De Hoop Drukkerij
ontwerpstudio | drukwerk | direct mail

Alcohol Use Disorder (AUD) is a highly prevalent psychiatric disorder, which leads to substantial morbidity, economic damage and mortality. For a sizeable number of patients AUD is characterized by a chronic relapsing course.
However, from a clinical and research view, the concept of relapse remains ill defined. This thesis unravels the concept of relapse as it has been used the last two decades in the scientific literature on AUD and aims to contribute to the development of a more consistent definition.
In addition, the thesis explores the role of important clinical elements such as impulsivity, meaning in life and craving, as underlying drivers in relapse.

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