

Alcohol use disorder relapse factors revisited



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Alcohol Use Disorder relapse revisited

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

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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.

References

- Connors GJ, Maisto SA, Donovan DM. Conceptualizations of relapse: a summary of psychological and psychobiological models. *Addiction*. 1996 Dec;91 Suppl:S5-13.
- Copeland A, Jones A, Field M. The association between meaning in life and harmful drinking is mediated by individual differences in self-control and alcohol value. *Addict Behav Rep*. 2020 Jan 27;11:100258.
- Degenhardt L, Bharat C, Chiu WT, Harris MG, Kazdin AE, Vigo DV, Sampson NA, Alonso J, Andrade LH, Bruffaerts R, Bunting B, Cardoso G, de Girolamo G, Florescu S, Gureje O, Haro JM, Hu C, Karam AN, Karam EG, Kovess-Masfety V, Lee S, Makanjuola V, McGrath JJ, Medina-Mora ME, Moskalewicz J, Navarro-Mateu F, Posada-Villa J, Rapsley C, Stagnaro JC, Tachimori H, Ten Have M, Torres Y, Williams DR, Zarkov Z, Kessler RC; WHO World Mental Health Survey collaborators. Perceived helpfulness of treatment for alcohol use disorders: Findings from the World Mental Health Surveys. *Drug Alcohol Depend*. 2021 Dec 1;229(Pt B):109158.
- Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, Venkateswaran V, Tapp AD, Forouzanfar MH, Salama JS, et al. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018 Sep 22;392(10152):1015-1035
- Hendershot CS, Witkiewitz K, George WH, Marlatt GA. Relapse prevention for addictive behaviors. *Subst. Abuse Treat. Prev. Policy*. 2011; 6, 17.
- Jentsch J, Ashenurst J, Cervantes M et al. Dissecting impulsivity and its relationships to drug addictions. *Ann N Y Acad Sci* 2015;1327:1–26.
- Leong C, Bolton JM, Ekuma O, Prior HJ, Singal D, Nepon J, Konrad G, Paille M, Finlayson G, Nickel N. Association of alcohol use disorder on alcohol-related cancers, diabetes, ischemic heart disease and death: a population-based, matched cohort study. *Addiction*. 2022;117(2):368–381.
- Maisto, S. A., Witkiewitz, K., Moskal, D., & Wilson, A. D. Is the construct of relapse heuristic, and does it advance alcohol use disorder clinical practice? *Journal of Studies on Alcohol and Drugs*. 2016;77, 849–858.
- McKay JR, Franklin TR, Patapis N, Lynch KG. Conceptual, methodological, and analytical issues in the study of relapse. *Clin Psychol Rev*. 2006 Mar;26(2):109-27.
- Miller WR. What is a relapse? Fifty ways to leave the wagon. *Addiction*. 1996 Dec;91 Suppl:S15-27.
- Rehm J, Gmel GE, Gmel G, Hasan OSM, Imtiaz S, Popova S, Probst C, Roerecke M, Room R, Samokhvalov AV, et al. The relationship between different dimensions of alcohol use and the burden of disease-an update. *Addiction*. 2017; 112(6):968–1001.
- Steger MF, Frazier P, Kaler M, Oishi S. The meaning in life questionnaire: assessing the presence of and search for meaning in life. *J Couns Psychol*. 2006;53(1):80–93.
- Sulmasy DP. A biopsychosocial-spiritual model for the care of patients at the end of life. *Gerontologist* 2002;42 Spec No, 24–33.
- Wade DT, Halligan PW. The biopsychosocial model of illness: a model whose time has come. *Clin Rehabil*. 2017 Aug;31(8):995-1004
- Witkiewitz K, Marlatt GA. Modeling the complexity of post-treatment drinking: it's a rocky road to relapse. *Clin Psychol Rev*. 2007 Jul;27(6):724-38
- Witkiewitz K, Marlatt GA. Relapse prevention for alcohol and drug problems: that was zen, this is tao. *Am Psychol*. 2004 May-Jun;59(4):224-35.
- Witkiewitz K, Montes KS, Schwebel FJ, Tucker JA. What Is Recovery? *Alcohol Res*. 2020 Sep 24;40(3):01.

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.

2021:

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.

Sliedrecht W, Seesink HJ, Vrijmoeth C, de Waart R, Wiers RW, Ostafin B, Schaap-Jonker H, Roozen HG, Witkiewitz K, Dom G. Alcohol use disorder relapse factors: an exploratory investigation of craving, alcohol dependence severity, and meaning in life. *Addiction Research & Theory.* 2022;30:5, 351-359, doi:10.1080/16066359.2022.2040488

Sliedrecht W, Roozen HG, Dom G, Witkiewitz K. Alcohol use disorder 'relapse' definitions revisited: With no standard definition in the literature, is it time to abandon the term? *JSAD FastTakes.* 2022;no. 10. doi:10.15288/jsad-FT.07.26.2022-10

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](https://doi.org/10.15288/jsad.2022.83.248)

References Chapter 1

- Ashford, R. D., Brown, A. M., and Curtis, B. (2018). Substance use, recovery, and linguistics: The impact of word choice on explicit and implicit bias. *Drug and Alcohol Dependence*, 189(June), 131–138. Elsevier.
- Bach, P., Bumb, J. M., Schuster, R., Vollstädt-Klein, S., Reinhard, I., Rietschel, M., Witt, S. H., et al. (2019). Effects of leptin and ghrelin on neural cue-reactivity in alcohol addiction: Two streams merge to one river? *Psychoneuroendocrinology*, 100(July 2018), 1–9.
- Carvalho, A. F., Heilig, M., Perez, A., Probst, C., & Rehm, J. (2019). Alcohol use disorders. *Lancet*, 394(10200), 781–792.
- Castaldelli-Maia, J. M., & Bhugra, D. (2014). Investigating the interlinkages of alcohol use and misuse, spirituality and culture - Insights from a systematic review. *International Review of Psychiatry (Abingdon, England)*, 26(3), 352–367.
- Cranford, J. A., Krentzman, A. R., Mowbray, O., & Robinson, E. A. R. (2014). Trajectories of alcohol use over time among adults with alcohol dependence. *Addictive Behaviors*, 39(5), 1006–1011.
- Donovan, D., & Witkiewitz, K. (2012). Relapse prevention: From radical idea to common practice. *Addiction Research and Theory*, 20(3), 204–217.
- Falk, D. E., O'Malley, S. S., Witkiewitz, K., Anton, R. F., Litten, R. Z., Slater, M., et al., & the Alcohol Clinical Trials Initiative (ACTIVE) Workgroup. (2019). Evaluation of Drinking Risk Levels as Outcomes in Alcohol Pharmacotherapy Trials: A Secondary Analysis of 3 Randomized Clinical Trials. *JAMA Psychiatry*, 76(4), 374–381.
- Fleury, M. J., Djouini, A., Huỳnh, C., Tremblay, J., Ferland, F., Ménard, J. M., & Belleville, G. (2016). Remission from substance use disorders: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, 168, 293–306.
- Foulds, J., Newton-Howes, G., Guy, N. H., Boden, J. M., & Mulder, R. T. (2017). Dimensional personality traits and alcohol treatment outcome: a systematic review and meta-analysis. *Addiction*, 112(8), 1345–1357.
- Garcia, A. N., & Salloum, I. M. (2015). Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: A focused review. *The American Journal on Addictions*, 24(7), 590–598.
- Garfield, J. B. B., Lubman, D. I., & Yücel, M. (2014). Anhedonia in substance use disorders: a systematic review of its nature, course and clinical correlates. *The Australian and New Zealand Journal of Psychiatry*, 48(1), 36–51.
- Gong, A., & Minuk, G. Y. (2018). Predictors of alcohol relapse following liver transplantation for alcohol-induced liver failure. Consideration of “A–D” selection criteria. *Annals of Transplantation*, 23, 129–135.
- Gorski, T. T. (1990). The Cenaps model of relapse prevention: basic principles and procedures. *Journal of Psychoactive Drugs*, 22(2), 125–133.
- Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., et al. (2013). DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry*, 170(8), 834–851.
- Hasin, D. S., Wall, M., Witkiewitz, K., Kranzler, H. R., Falk, D., Litten, R., et al., & the Alcohol Clinical Trials Initiative (ACTIVE) Workgroup. (2017). Change in non-abstinent WHO drinking risk levels and alcohol dependence: a 3 year follow-up study in the US general population. *The Lancet. Psychiatry*, 4(6), 469–476.
- Hendershot, C. S., Witkiewitz, K., George, W. H., and Marlatt, G. A. (2011). Relapse prevention for addictive behaviors. *Substance Abuse Treatment, Prevention, and Policy*, 6(1747–597X, 1747–597X), 17.
- Henkel, D. (2011). Unemployment and substance use: a review of the literature (1990-2010). *Current Drug Abuse Reviews*, 4(1), 4–27.

Henssler, J., Müller, M., Carreira, H., Bschor, T., Heinz, A., & Baethge, C. (2021). Controlled drinking – non-abstinent versus abstinent treatment goals in alcohol use disorder: A Systematic Review, Meta-Analysis and Meta-Regression. *Addiction*, 116(8):1973-1987.

Holt, L. J., Litt, M. D., & Cooney, N. L. (2012). Prospective analysis of early lapse to drinking and smoking among individuals in concurrent alcohol and tobacco treatment. *Psychol Addict Behav*, 26(3), 561–572.

Hunt, W. A., Barnett, L. W., & Branch, L. G. (1971). Relapse rates in addiction programs. *Journal of Clinical Psychology*, 27(4), 455–456.

Hunter-Reel, D., McCrady, B., & Hildebrandt, T. (2009). Emphasizing interpersonal factors: an extension of the Witkiewitz and Marlatt relapse model. *Addiction (Abingdon, England)*, 104(8), 1281–1290.

Kelly, J. F., Abry, A., Ferri, M., & Humphreys, K. (2020). Alcoholics Anonymous and 12-Step Facilitation Treatments for Alcohol Use Disorder: A Distillation of a 2020 Cochrane Review for Clinicians and Policy Makers. *Alcohol and Alcoholism*, 55(6), 641–651.

Kelly, M., Chick, J., Gribble, R., Gleeson, M., Holton, M., Winstanley, J., et al. (2006). Predictors of relapse to harmful alcohol after orthotopic liver transplantation. *Alcohol and Alcoholism*, 41(3), 278–283.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, 3(8):760-773.

Maisto, S. A., Roos, C. R., Hallgren, K. A., Moskal, D., Wilson, A. D., & Witkiewitz, K. (2016a). Do Alcohol Relapse Episodes During Treatment Predict Long-Term Outcomes? Investigating the Validity of Existing Definitions of Alcohol Use Disorder Relapse. *Alcoholism, Clinical and Experimental Research*, 40(10), 2180–2189.

Maisto, S. A., Witkiewitz, K., Moskal, D., & Wilson, A. D. (2016b). Is the Construct of Relapse Heuristic, and Does It Advance Alcohol Use Disorder Clinical Practice? *Journal of Studies on Alcohol and Drugs*, 77(6), 849–858.

Mann, K., Aubin, H.-J., & Witkiewitz, K. (2017). Reduced Drinking in Alcohol Dependence Treatment, What Is the Evidence? *European Addiction Research*, 23(5), 219–230.

McKay, J. R. (1999). Studies of factors in relapse to alcohol, drug and nicotine use: a critical review of methodologies and findings. *Journal of Studies on Alcohol*, 60(4), 566–576.

McKay, J. R., Franklin, T. R., Patapis, N., & Lynch, K. G. (2006). Conceptual, methodological, and analytical issues in the study of relapse. *Clinical Psychology Review*, 26(2), 109–127.

McKay, J. R., & Hiller-Sturmhofel, S. (2011). Treating alcoholism as a chronic disease: approaches to long-term continuing care. *Alcohol Res Health*, 33(4), 356–370.

Mericle, A. A., Kaskutas, L. A., Polcin, D. L., & Karriker-Jaffe, K. J. (2018). Independent and Interactive Effects of Neighborhood Disadvantage and Social Network Characteristics on Problem Drinking after Treatment. *Journal of Social and Clinical Psychology*, 37(1), 1–21.

Miller, W. R. (1996). What is a relapse? Fifty ways to leave the wagon. *Addiction (Abingdon, England)*, 91(s12, Suppl), S15–S27.

Miller, W. R., & Del Boca, F. K. (1994). Measurement of drinking behavior using the Form 90 family of instruments. *J Stud Alcohol Suppl*, 12(s12), 112–118.

Miller, W. R., & Harris, R. J. (2000). A simple scale of Gorski’s warning signs for relapse. *Journal of Studies on Alcohol*, 61(5), 759–765.

Morris, J., Albery, I. P., Heather, N., & Moss, A. C. (2020). Continuum beliefs are associated with higher problem recognition than binary beliefs among harmful drinkers without addiction experience. *Addictive Behaviors*, 105, 106292.

Morris, J., Moss, A. C., Albery, I. P., & Heather, N. (2022). The “alcoholic other”: harmful drinkers resist problem recognition to manage identity threat. *Addictive Behaviors*, 124:107093.

Olivares, J. M., Sermon, J., Hemels, M., & Schreiner, A. (2013). Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. *Annals of General Psychiatry*, 12(1), 32.

Ooms M, Roozen HG, Willering JH, Zijlstra WP, de Waart R, Goudriaan AE. Effects of Multiple Detoxifications on Withdrawal Symptoms, Psychiatric Distress and Alcohol-Craving in Patients with an Alcohol Use Disorder. *Behav Med*. 2021 Jul-Sep;47(4):296-310.

Pearson, M. R., Wilson, A. D., Richards, D. K., & Witkiewitz, K. (2021). Reconsidering alcohol treatment non-responders: psychosocial functioning among heavy drinkers 3 years following treatment. *Addiction*, 116(5), 1262–1269.

Ramo, D. E., Prince, M. A., Roesch, S. C., & Brown, S. A. (2012). Variation in substance use relapse episodes among adolescents: a longitudinal investigation. *Journal of Substance Abuse Treatment*, 43(1), 44–52.

Robinson, S. M., & Adinoff, B. (2016). The classification of substance use disorders: Historical, contextual, and conceptual considerations. *Behavioral Sciences (Basel, Switzerland)*, 6(3), 18.

Roozen, H. G., & van de Wetering, B. J. M. (2007). Neuropsychiatric insights in clinical practice: from relapse prevention toward relapse management. *The American Journal on Addictions*, 16(6), 530–531.

Rosenberg, H., Grant, J., and Davis, A. K. (2020). Acceptance of Non-Abstinence as an Outcome Goal for Individuals Diagnosed With Substance Use Disorders: A Narrative Review of Published Research. *Journal of Studies on Alcohol and Drugs*, 81(4), 405–415.

Rössler, W. (2006, October). Psychiatric rehabilitation today: an overview. *World Psychiatry; Official Journal of the World Psychiatric Association (WPA)*, 5(3), 151–157 .

Rössler, W., & Drake, R. E. (2017). Psychiatric rehabilitation in Europe. *Epidemiology and Psychiatric Sciences*, 26(3), 216–222.

Saunders, J. B., Degenhardt, L., Reed, G. M., & Poznyak, V. (2019). Alcohol Use Disorders in ICD-11: Past, Present, and Future. *Alcoholism, Clinical and Experimental Research*, 43(8), 1617–1631.

Schutte, K. K., Brennan, P. L., & Moos, R. H. (2009). Treated and untreated remission from problem drinking in late life: post-remission functioning and health-related quality of life. *Drug and Alcohol Dependence*, 99(1-3), 150–159.

Schutte, K. K., Nichols, K. A., Brennan, P. L., & Moos, R. H. (2003). A ten-year follow-up of older former problem drinkers: risk of relapse and implications of successfully sustained remission. *Journal of Studies on Alcohol*, 64(3), 367–374.

Seo, D., & Sinha, R. (2015). Neuroplasticity and Predictors of Alcohol Recovery. *Alcohol Research : Current Reviews*, 37(1), 143–152 .

Sinha, R., Fox, H. C., Hong, K. I., Hansen, J., Tuit, K., & Kreek, M. J. (2011). Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. *Archives of General Psychiatry*, 68(9), 942–952.

Sliedrecht, W., de Waart, R., Witkiewitz, K., & Roozen, H. G. (2019). Alcohol use disorder relapse factors: A systematic review. *Psychiatry Research*, 278, 97–115.

Sobell, L. C., Brown, J., Leo, G. I., & Sobell, M. B. (1996). The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug and Alcohol Dependence*, 42(1), 49–54.

Strakowski, S. M., DelBello, M. P., Fleck, D. E., Adler, C. M., Anthenelli, R. M., Keck, P. E., et al. (2005). Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch Gen Psychiatry*, 62(8), 851–858.

Tonigan, J. S., Miller, W. R., & Brown, J. M. (1997). The reliability of Form 90: an instrument for assessing alcohol treatment outcome. *Journal of Studies on Alcohol*, 58(4), 358–364.

Tonigan, J. S., McCallion, E. A., Frohe, T., & Pearson, M. R. (2017). Lifetime Alcoholics Anonymous attendance as a predictor of spiritual gains in the Relapse Replication and Extension Project (RREP). *Psychol Addict Behav*, 31(1), 54–60.

Tusa, A. L., & Burgholzer, J. A. (2013). Came to believe: spirituality as a mechanism of change in alcoholics anonymous: a review of the literature from 1992 to 2012. *Journal of Addictions Nursing*, 24(4), 237–246.

Uhl, G. R., Koob, G. F., & Cable, J. (2019). The neurobiology of addiction. *Annals of the New York Academy of Sciences*, 1451(1), 5–28.

Vita, A., & Barlati, S. (2019). The implementation of evidence-based psychiatric rehabilitation: Challenges and opportunities for mental health services. *Frontiers in Psychiatry*, 10(MAR), 147.

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic Advances from the Brain Disease Model of Addiction. *The New England Journal of Medicine*, 374(4), 363–371.

Walitzer, K. S., & Dearing, R. L. (2006). Gender differences in alcohol and substance use relapse. *Clinical Psychology Review*, 26(2), 128–148.

Wigg, A. J., Mangira, D., Chen, J. W., & Woodman, R. W. (2017). Outcomes and predictors of harmful relapse following liver transplantation for alcoholic liver disease in an Australian population. *Internal Medicine Journal*, 47(6), 656–663.

Witkiewitz, K. (2011). Predictors of heavy drinking during and following treatment. *Psychol Addict Behav*, 25(3), 426–438.

Witkiewitz, K., Heather, N., Falk, D. E., Litten, R. Z., Hasin, D. S., Kranzler, H. R., et al. (2020). World Health Organization risk drinking level reductions are associated with improved functioning and are sustained among patients with mild, moderate and severe alcohol dependence in clinical trials in the United States and United Kingdom. *Addiction*, 115(9), 1668–1680.

Witkiewitz, K., & Marlatt, G. A. (2004). Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. *The American Psychologist*, 59(4), 224–235.

Witkiewitz, K., Montes, K. S., Schwebel, F. J., & Tucker, J. A. (2020). What is recovery? *Alcohol Research : Current Reviews*, 40(3), 01.

- Witkiewitz, K., Pearson, M. R., Wilson, A. D., Stein, E. R., Votaw, V. R., Hallgren, K. A., et al. (2020). Can Alcohol Use Disorder Recovery Include Some Heavy Drinking? A Replication and Extension up to 9 Years Following Treatment. *Alcoholism, Clinical and Experimental Research*, 44(9), 1862–1874.
- Witkiewitz, K., Wilson, A. D., Pearson, M. R., Hallgren, K. A., Falk, D. E., Litten, R. Z., et al. (2017). Temporal Stability of Heavy Drinking Days and Drinking Reductions Among Heavy Drinkers in the COMBINE Study. *Alcoholism, Clinical and Experimental Research*, 41(5), 1054–1062.
- Witkiewitz, K., Wilson, A. D., Pearson, M. R., Montes, K. S., Kirouac, M., Roos, C. R., et al. (2019). Profiles of recovery from alcohol use disorder at three years following treatment: can the definition of recovery be extended to include high functioning heavy drinkers? *Addiction*, 114(1), 69–80.
- Wood, A. M., Kaptoge, S., Butterworth, A. S., Willeit, P., Warnakula, S., Bolton, T., et al., & the Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. (2018). Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet*, 391(10129), 1513–1523.
- Zywiak, W. H., Stout, R. L., Longabaugh, R., Dyck, I., Connors, G. J., & Maisto, S. A. (2006). Relapse-onset factors in Project MATCH: the Relapse Questionnaire. *Journal of Substance Abuse Treatment*, 31(4), 341–345.
- Zywiak, W. H., Stout, R. L., Trefry, W. B., Glasser, I., Connors, G. J., Maisto, S. A., & Westerberg, V. S. (2006). Alcohol relapse repetition, gender, and predictive validity. *Journal of Substance Abuse Treatment*, 30(4), 349–353.
- Zywiak, W. H., Westerberg, V. S., Connors, G. J., & Maisto, S. A. (2003). Exploratory findings from the Reasons for Drinking Questionnaire. *Journal of Substance Abuse Treatment*, 25(4), 287–292.

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 (Flensburg-Madsen et al., 2009; Kölves 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.

| |
|---|
| <p><i>(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])</i></p> <p><i>#1 Alcoholism (MeSH and All Fields)</i></p> <p><i>#2 Alcohol Use Disorder</i></p> <p><i>#3 Alcohol Abuse</i></p> <p><i>#4 Alcohol Dependence</i></p> <p><i>#5 #1 OR #2 OR #3 OR #4</i></p> <p><i>#6 Relapse</i></p> <p><i>#7 Remission</i></p> <p><i>#8 #6 OR #7 Combining: #5 AND #8</i></p> <p><i>Filters added: Human/ English / Adult / Year 2000- (April) 2019</i></p> |
|---|

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 factor 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.

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References Chapter 2

- Abdin, E., Subramaniam, M., Vaingankar, J.A., Chong, S.A., 2014. The role of sociodemographic factors in the risk of transition from alcohol use to disorders and remission in Singapore. *Alcohol Alcohol* 49, 103–108.
- Abulseoud, O.A., Karpyak, V.M., Schneckloth, T., Hall-Flavin, D.K., Loukianova, L.L., Geske, J.R., Biernacka, J.M., Mrazek, D.A., Frye, M.A., 2013. A retrospective study of gender differences in depressive symptoms and risk of relapse in patients with alcohol dependence. *Am. J. Addict.* 22, 437–442.
- Adamson, S.J., Sellman, J.D., Frampton, C.M.A., 2009. Patient predictors of alcohol treatment outcome: a systematic review. *J. Subst. Abuse Treat.* 36, 75–86.
- Adinoff, B., Leonard, D., Price, J., Javors, M., Walker, R., Brown, E., Xiao, H., Rao, U., 2017. Adrenocortical Sensitivity, Moderated by Ongoing Stress, Predicts Drinking Intensity in Alcohol-Dependent Men. *Psychoneuroendocrinology* 76, 67–76.
- Aguiar, P., Neto, D., Lambaz, R., Chick, J., Ferrinho, P., 2012. Prognostic factors during outpatient treatment for alcohol dependence: cohort study with 6 months of treatment follow-up. *Alcohol Alcohol* 47, 702–710.
- Aharonovich, E., Liu, X., Samet, S., Nunes, E., Waxman, R., Hasin, D., 2005. Postdischarge cannabis use and its relationship to cocaine, alcohol, and heroin use: a prospective study. *Am. J. Psychiatry* 162, 1507–1514.
- Allsop, S., Saunders, B., Phillips, M., 2000. The process of relapse in severely dependent male problem drinkers. *Addiction* 95, 95–106.
- Álvarez, A.S., Pagani, M., Meucci, P., 2012. The clinical application of the biopsychosocial model in mental health: a research critique. *Am. J. Phys. Med. Rehabil.* 91, 173–180.
- Arndt, S., Vélez, M.B., Segre, L., Clayton, R., 2010. Remission from substance dependence in U.S. Whites, African Americans, and Latinos. *J. Ethn. Subst. Abuse* 9, 237–248.
- Arnedt, J.T., Conroy, D.A., Brower, K.J., 2007. Treatment options for sleep disturbances during alcohol recovery. *J. Addict. Dis.* 26, 41–54.
- Baars, M.Y., Müller, M.J., Gallhofer, B., Netter, P., 2013. Relapse (Number of Detoxifications) in abstinent male alcohol-dependent patients as related to personality traits and types of tolerance to frustration. *Neuropsychobiology* 67, 241–248.
- Bach, P., Bumb, J.M., Schuster, R., Vollstädt-Klein, S., Reinhard, I., Rietschel, M., Witt, S.H., Wiedemann, K., Kiefer, F., Koopmann, A., 2019a. Effects of leptin and ghrelin on neural cue-reactivity in alcohol addiction: two streams merge to one river? *Psychoneuroendocrinology* 100, 1–9.
- Bach, P., Vollstädt-Klein, S., Kirsch, M., Hoffmann, S., Jorde, A., Frank, J., Charlet, K., Beck, A., Heinz, A., Walter, H., Sommer, W.H., Spanagel, R., Rietschel, M., Kiefer, F., 2015. Increased mesolimbic cue-reactivity in carriers of the mu-opioid-receptor gene OPRM1 A118G polymorphism predicts drinking outcome: a functional imaging study in alcohol dependent subjects. *Eur. Neuropsychopharmacol.* 25, 1128–1135.
- Bach, P., Zois, E., Vollstädt-Klein, S., Kirsch, M., Hoffmann, S., Jorde, A., Frank, J., Charlet, K., Treutlein, J., Beck, A., Heinz, A., Walter, H., Rietschel, M., Kiefer, F., 2019b. Association of the alcohol dehydrogenase gene polymorphism rs1789891 with gray matter brain volume, alcohol consumption, alcohol craving and relapse risk. *Addict. Biol.* 24, 110–120.
- Barrio, P., Mondon, S., Teixidor, L., Ortega, L., Vieta, E., Gual, A., 2017. One year clinical correlates of ETG positive urine screening in alcohol-dependent patients: a survival analysis. *Alcohol Alcohol* 52, 460–465.
- Bartels, C., Kunert, H.J., Stawicki, S., Kröner-Herwig, B., Ehrenreich, H., Krampe, H., 2007. Recovery of hippocampus-related functions in chronic alcoholics during monitored long-term abstinence. *Alcohol Alcohol* 42, 92–102.

Bauer, L.O., 2001. Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. *Neuropsychopharmacology* 25, 332–340.

Bauer, L.O., Covault, J., Gelernter, J., 2012. GABRA2 and KIBRA genotypes predict early relapse to substance use. *Drug Alcohol Depend.* 123, 154–159.

Bauer, L.O., Covault, J., Harel, O., Das, S., Gelernter, J., Anton, R., Kranzler, H.R., 2007. Variation in GABRA2 predicts drinking behavior in project MATCH subjects. *Alcohol Clin. Exp. Res.* 31, 1780–1787.

Becker, H.C., 2008. Alcohol dependence, withdrawal, and relapse. *Neurobiol. Alcohol Depend.* 31, 377–410.

Becker, H.C., 1998. Kindling in alcohol withdrawal. *Alcohol Health Res. World* 22, 25–33.

Becker, J.B., McClellan, M., Reed, B.G., 2016. Sociocultural context for sex differences in addiction. *Addict. Biol.* 21, 1052–1059.

Becker, J.B., McClellan, M.E., Glover Reed, B., 2017. Sex differences, gender and addiction. *J. Neuropsych. Res.* 95, 136–147.

Bellamy, C., DiMartini, A., Ruppert, K., Jain, A., Dodson, F., Torbenson, M., Starzl, T., Fung, J., Demetris, A., 2001. Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. *Transplantation* 72, 619–626.

Bender, S., Specka, M., Buchholz, A., Hölscher, S., Rist, F., Heinz, T.W., Schifano, F., Scherbaum, N., 2018. Joint versus separate inpatient rehabilitation treatment for patients with alcohol use disorder or drug use disorder: an observational study. *Subst. Abuse Rehabil.* 9, 23–29.

Berking, M., Margraf, M., Ebert, D., Wupperman, P., Hofmann, S.G., Junghanns, K., 2011. Deficits in emotion-regulation skills predict alcohol use during and after cognitive-behavioral therapy for alcohol dependence. *J. Consult. Clin. Psychol.* 79, 307–318.

Bernhardt, N., Nebe, S., Pooseh, S., Sebold, M., Sommer, C., Birkenstock, J., Zimmermann, U.S., Heinz, A., Smolka, M.N., 2017. Impulsive decision making in young adult social drinkers and detoxified alcohol-dependent patients: a cross-sectional and longitudinal study. *Alcohol. Clin. Exp. Res.* 41, 1794–1807.

Bischof, G., Rumpf, H.J., Hapke, U., Meyer, C., John, U., 2001. Factors influencing remission from alcohol dependence without formal help in a representative population sample. *Addiction* 96, 1327–1336.

Bischof, G., Rumpf, H.J., Meyer, C., Hapke, U., John, U., 2007. Stability of subtypes of natural recovery from alcohol dependence after two years. *Addiction* 102, 904–908.

Bischof, G., Rumpf, H.J., Meyer, C., Hapke, U., John, U., 2005. Influence of psychiatric comorbidity in alcohol-dependent subjects in a representative population survey on treatment utilization and natural recovery. *Addiction* 100, 405–413.

Björnsson, E., Olsson, J., Rydell, A., Fredriksson, K., Eriksson, C., Sjöberg, C., Olausson, M., Bäckman, L., Castedal, M., Friman, S., 2005. Long-term follow-up of patients with alcoholic liver disease after liver transplantation in Sweden: impact of structured management on recidivism. *Scand. J. Gastroenterol.* 40, 206–216.

Blaine, S.K., Seo, D., Sinha, R., 2017. Peripheral and prefrontal stress system markers and risk of relapse in alcoholism. *Addict. Biol.* 22, 468–478.

Blaine, S.K., Sinha, R., 2017. Alcohol, stress, and glucocorticoids: from risk to dependence and relapse in alcohol use disorders. *Neuropharmacology* 122, 136–147.

Borders, T.F., Curran, G.M., Mattox, R., Booth, B.M., 2010. Religiousness among at-risk drinkers: is it prospectively associated with the development or maintenance of an alcohol-use disorder? *J. Stud. Alcohol Drugs* 71, 136–142.

Borrell-Carrio, F., Suchman, A., Epstein, R., 2004. The biopsychosocial model 25 years later. *Ann. Fam. Med.* 2, 576–582.

Boschloo, L., Vogelzangs, N., Van den Brink, W., Smit, J.H., Beekman, A.T.F., Penninx, B.W.J.H., 2012. Predictors of the 2-year recurrence and persistence of alcohol dependence. *Addiction* 107, 1639–1640.

Bottlender, M., Soyka, M., 2005a. Impact of different personality dimensions (NEO FiveFactor Inventory) on the outcome of alcohol-dependent patients 6 and 12 months after treatment. *Psychiatry Res.* 136, 61–67.

Bottlender, M., Soyka, M., 2005b. Outpatient alcoholism treatment: predictors of outcome after 3 years. *Drug Alcohol Depend.* 80, 83–89.

Bottlender, M., Soyka, M., 2005c. Efficacy of an intensive outpatient rehabilitation program in alcoholism: predictors of outcome 6 months after treatment. *Eur. Addict. Res.* 11, 132–137.

Bottlender, M., Soyka, M., 2004. Impact of craving on alcohol relapse during, and 12 months following, outpatient treatment. *Alcohol Alcohol.* 39, 357–361.

Bowden-Jones, H., McPhillips, M., Rogers, R., Hutton, S., Joyce, E., 2005. Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *J. Neuropsychiatry Clin. Neurosci.* 17, 417–420.

Bradizza, C.M., Stasiewicz, P.R., Paas, N.D., 2006. Relapse to alcohol and drug use among individuals diagnosed with co-occurring mental health and substance use disorders: a review. *Clin. Psychol. Rev.* 26, 162–178.

Brady, K.T., Back, S.E., Waldrop, A.E., McRae, A.L., Anton, R.F., Upadhyaya, H.P., Saladin, M.E., Randall, P.K., 2006. Cold pressor task reactivity: predictors of alcohol use among alcohol-dependent individuals with and without comorbid posttraumatic stress disorder. *Alcohol. Clin. Exp. Res.* 30, 938–946.

Brower, K.J., Aldrich, M.S., Robinson, E.A., Zucker, R.A., Greden, J.F., 2001. Insomnia, self-medication, and relapse to alcoholism. *Am. J. Psychiatry* 158, 399–404.

Brower, K.J., Carey, T.L., 2003. Racially related health disparities and alcoholism treatment outcomes. *Alcohol. Clin. Exp. Res.* 27, 1365–1367.

Brunette, M., Noordsy, D., Xie, H., Drake, R.E., 2003. Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. *Psychiatr. Serv.* 54, 1395–1401.

Budzyński, J., Ziółkowski, M., Kłopotka, M., Czarnecki, D., 2016. Blood glucose and lipid concentrations after overload are not associated with the risk of alcohol relapse. *Drug Alcohol Depend.* 161, 356–362.

Bujarski, S., O'Malley, S.S., Lunny, K., Ray, L.A., 2013. The effects of drinking goal on treatment outcome for alcoholism. *J. Consult. Clin. Psychol.* 81, 13–22.

Callaghan, R.C., Cunningham, J.A., 2002. Gender differences in detoxification: predictors of completion and re-admission. *J. Subst. Abuse Treat.* 23, 399–407.

Camchong, J., Stenger, A., Fein, G., 2013. Resting-state synchrony during early alcohol abstinence can predict subsequent relapse. *Cereb. Cortex* 23, 2086–2099.

Cardenas, V.A., Durazzo, T.C., Gazdzinski, S., Mon, A., Studholme, C., Meyerhoff, D.J., 2011. Brain morphology at entry into treatment for alcohol dependence is related to relapse propensity. *Biol. Psychiatry* 70, 561–567.

Castaldelli-Maia, J.M., Bhugra, D., 2014. Investigating the interlinkages of alcohol use and misuse, spirituality and culture - Insights from a systematic review. *Int. Rev. Psychiatry* 26, 352–367.

Castaldelli-Maia, J.M., Loreto, A.R., Guimarães-Pereira, B.B.S., Carvalho, C.F.C., Gil, F., Frallonardo, F.P., Ismael, F., Andrade, A.G.de, Ventriglio, A., Richter, K.P., Bhugra, D., 2018. Smoking cessation treatment outcomes among people with and without mental and substance use disorders: an observational real-world study. *Eur. Psychiatry* 53, 22–28.

Charlet, K., Beck, A., Jorde, A., Wimmer, L., Vollstädt-Klein, S., Gallinat, J., Walter, H., Kiefer, F., Heinz, A., 2014. Increased neural activity during high working memory load predicts low relapse risk in alcohol dependence. *Addict. Biol.* 19, 402–414.

Charlet, K., Schlagenhaut, F., Richter, A., Naundorf, K., Dornhof, L., Weinfurter, C.E.J., König, F., Walaszek, B., Schubert, F., Müller, C.A., Gutwinski, S., Seissinger, A., Schmitz, L., Walter, H., Beck, A., Gallinat, J., Kiefer, F., Heinz, A., 2013. Neural activation during processing of aversive faces predicts treatment outcome in alcoholism. *Addict. Biol.* 19, 439–451.

Chiappetta, V., García-Rodríguez, O., Jin, C.J., Secades-Villa, R., Blanco, C., 2014. Predictors of quit attempts and successful quit attempts among individuals with alcohol use disorders in a nationally representative sample. *Drug Alcohol Depend.* 141, 138–144.

Cohen, E., Feinn, R., Arias, A., Kranzler, H.R., 2007. Alcohol treatment utilization: findings from the national epidemiologic survey on alcohol and related conditions. *Drug Alcohol Depend.* 86, 214–221.

Conde, K., Lichtenberger, A., Satángelo, P., Cremonte, M., 2016. Natural recovery from alcohol use disorders in argentinean university students. *J. Subst. Use* 21, 537–542.

Connolly, J.M., Kavanagh, D.J., Baker, A.L., Kay-Lambkin, F.J., Lewin, T.J., Davis, P.J., Quek, L.H., 2013. Craving as a predictor of treatment outcomes in heavy drinkers with comorbid depressed mood. *Addict. Behav.* 38, 1585–1592.

Connors, G.J., Maisto, S.A., Donovan, D.M., 1996. Conceptualizations of relapse: a summary of psychological and psychobiological models. *Addiction* 91, S5–S13.

Conroy, D.A., Todd Arnedt, J., Brower, K.J., Strobbe, S., Consens, F., Hoffmann, R., Armitage, R., 2006. Perception of sleep in recovering alcohol-dependent patients with insomnia: relationship with future drinking. *Alcohol. Clin. Exp. Res.* 30, 1992–1999.

Cooney, N.L., Litt, M.D., Cooney, J.L., Pilkey, D.T., Steinberg, H.R., Oncken, C.A., 2007. Alcohol and tobacco cessation in alcohol-dependent smokers: analysis of real-time reports. *Psychol. Addict. Behav.* 21, 277–286.

Copeland, W.E., Angold, A., Shanahan, L., Dreyfuss, J., Dlamini, I., Costello, E.J., 2012. Predicting persistent alcohol problems: a prospective analysis from the Great Smoky Mountain Study. *Psychol. Med.* 42, 1925–1935.

Cosgrove, K.P., McKay, R., Esterlis, I., Kloczynski, T., Perkins, E., Bois, F., Pittman, B., Lancaster, J., Glahn, D.C., O'Malley, S., Carson, R.E., Krystal, J.H., 2014. Tobacco smoking interferes with GABAA receptor neuroadaptations during prolonged alcohol withdrawal. *Proc. Natl. Acad. Sci. U. S. A.* 111, 18031–18036.

Costa, M.-A., Girard, M., Dalmay, F., Malauzat, D., 2011. Brain-derived neurotrophic factor serum levels in alcohol-dependent subjects 6 months after alcohol withdrawal. *Alcohol. Clin. Exp. Res.* 35, 1966–1973.

Cranford, J.A., Krentzman, A.R., Mowbray, O., Robinson, E.A.R., 2014. Trajectories of alcohol use over time among adults with alcohol dependence. *Addict. Behav.* 39, 1006–1011.

Cui, C., Noronha, A., Warren, K.R., Koob, G.F., Sinha, R., Thakkar, M., Matochik, J., Crews, F.T., Chandler, L.J., Becker, H.C., Lovinger, D., Everitt, B.J., Egli, M., Chitra, D., Fein, G., Potenza, M.N., Harris, R.A., Grant, K.A., Meyerhoff, D.J., Sullivan, E.V., Pfefferbaum, A., Becker, H.C., Lovinger, D., Everitt, B.J., Egli, M., Mandym, C.D., Fein, G., Potenza, M.N., Harris, R.A., Grant, K.A., Roberto, M., Meyerhoff, D.J., Sullivan, E.V., 2015. Brain pathways to recovery from alcohol dependence. *Alcohol* 49, 435–452.

Curran, G.M., Flynn, H.A., Kirchner, J., Booth, B.M., 2000. Depression after alcohol treatment as a risk factor for relapse among male veterans. *J. Subst. Abuse Treat.* 19, 259–265.

Czapla, M., Simon, J.J., Richter, B., Kluge, M., Friederich, H.C., Herpertz, S., Mann, K., Herpertz, S.C., Loeber, S., 2016. The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: implications for psychotherapeutic treatment. *Addict. Biol.* 21, 873–884.

Dahlgren, A., Wargelius, H.L., Berglund, K.J., Fahlke, C., Blennow, K., Zetterberg, H., Oreland, L., Berggren, U., Balldin, J., 2011. Do Alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study. *Alcohol Alcohol* 46, 509–513.

Dakwar, E., Blanco, C., Lin, K., Liu, S., Warden, D., Trivedi, M., Nunes, E.V., 2012. Exercise and mental illness: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J. Clin. Psychiatry* 73, 960–966.

Damian, A., Mendelson, T., 2017. Association of physical activity with alcohol abuse and dependence in a nationally-representative U.S. sample. *Subst. Use Misuse* 52, 1744–1750.

Davis, C.M., Clifford, P.R., 2016. Ascertaining the relationships between the trajectories of specific categories of alcohol-related negative consequences and subsequent drinking behavior. *Psychol. Addict. Behav.* 30, 648–658.

Dawson, D.A., Grant, B.F., Stinson, F.S., Chou, P.S., Huang, B., Ruan, W.J., 2005. Recovery from DSM-IV alcohol dependence: United States, 2001–2002. *Addiction* 100, 281–292.

Dawson, D.A., Goldstein, R.B., Grant, B.F., 2007. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: a 3-year follow-up. *Alcohol. Clin. Exp. Res.* 31, 2036–2045.

Dawson, D.A., Goldstein, R.B., Ruan, W.J., Grant, B.F., 2012. Correlates of recovery from alcohol dependence: a prospective study over a 3-year follow-up interval. *Alcohol. Clin. Exp. Res.* 36, 1268–1277.

Dawson, D.A., Grant, B.F., Stinson, F.S., Chou, P.S., 2006. Estimating the effect of helpseeking on achieving recovery from alcohol dependence. *Addiction* 101, 824–834.

De Bruijn, C., Van Den Brink, W., De Graaf, R., Vollebergh, W.A.M., 2006. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the Craving Withdrawal Model. *Addiction* 101, 385–392.

De Wilde, B., Verdejo-García, A., Sabbe, B., Hulstijn, W., Dom, G., 2013. Affective decision-making is predictive of three-month relapse in polysubstance-dependent alcoholics. *Eur. Addict. Res.* 19, 21–28.

Degenhardt, L., Glantz, M., Bharat, C., Peacock, A., Lago, L., Sampson, N., Kessler, R.C., 2018. The impact of cohort substance use upon likelihood of transitioning through stages of alcohol and cannabis use and use disorder: findings from the Australian National Survey on Mental Health and Wellbeing. *Drug Alcohol Rev.* 37, 546–556.

Demirbas, H., Ilhan, I.O., Dogan, Y.B., 2012. Ways of problem solving as predictors of relapse in alcohol dependent male inpatients. *Addict. Behav.* 37, 131–134.

Demmel, R., Nicolai, J., Jenko, D., 2006. Self-efficacy and alcohol relapse: concurrent validity of confidence measures, self-other discrepancies, and prediction of treatment outcome. *J. Stud. Alcohol.* 67, 637–641.

Deruytter, E., van Steenkiste, C., Trépo, E., Geerts, A., van Vlierberghe, H., Berrevoet, F., de Hemptinne, B., Rogiers, X., Troisi, R., Colle, I., 2013. Liver transplantation for alcoholic liver disease: a retrospective analysis of recidivism, survival and risk factors predisposing to alcohol relapse. *Acta Gastroenterol. Belg.* 76, 282–290.

Di Sclafani V, Finn P, Fein G., 2007. Psychiatric comorbidity in long-term abstinent alcoholic individuals. *Alcohol Clin Exp Res.* 31(5):795-803.

Diehl, A., Croissant, B., Batra, A., Mundle, G., Nakovics, H., Mann, K., 2007. Alcoholism in women: is it different in onset and outcome compared to men? *Eur. Arch. Psychiatry Clin. Neurosci.* 257, 344–351.

Dolan, S.L., Rohsenow, D.J., Martin, R.A., Monti, P.M., 2013. Urge-specific and lifestyle coping strategies of alcoholics: relationships of specific strategies to treatment outcome. *Drug Alcohol Depend.* 128, 8–14.

Dom, G., De Wilde, B., Hulstijn, W., Sabbe, B., 2007. Dimensions of impulsive behaviour in abstinent alcoholics. *Pers. Individ. Dif.* 42, 465–476.

Dom, G., Francque, S., Michielsen, P., 2010. Risk for relapse of alcohol use after liver transplantation for alcoholic liver disease: a review and proposal of a set of risk assessment criteria. *Acta Gastroenterol. Belg.* 73, 247–251.

Driessen, M., Meier, S., Hill, A., Wetterling, T., Lange, W., Junghanns, K., 2001. The course of anxiety, depression and drinking behaviours after completed detoxification in alcoholics with and without comorbid anxiety and depressive disorders. *Alcohol* 36, 249–255

Duka, T., Stephens, D.N., 2014. Repeated detoxification of alcohol-dependent patients impairs brain mechanisms of behavioural control important in resisting relapse. *Curr. Addict. Rep.* 1–9.

Durazzo, T.C., Gazdzinski, S., Mon, A., Meyerhoff, D.J., 2010a. Cortical perfusion in alcohol-dependent individuals during short-term abstinence: relationships to resumption of hazardous drinking after treatment. *Alcohol* 44, 201–210.

Durazzo, T.C., Meyerhoff, D.J., 2017. Psychiatric, demographic, and brain morphological predictors of relapse after treatment for an alcohol use disorder. *Alcohol Clin. Exp. Res.* 41, 107–116.

Durazzo, T.C., Mon, A., Gazdzinski, S., Meyerhoff, D.J., 2017. Regional brain volume changes in alcohol-dependent individuals during early abstinence: associations with relapse following treatment. *Addict. Biol.* 22, 1416–1425.

Durazzo, T.C., Pathak, V., Gazdzinski, S., Mon, A., Meyerhoff, D.J., Rer Nat, D., 2010b. Metabolite levels in the brain reward pathway discriminate those who remain abstinent from those who resume hazardous alcohol consumption after treatment for alcohol dependence. *Stud. Alcohol Drugs* 71, 278–289.

Durazzo, T.C., Tosun, D., Buckley, S., Gazdzinski, S., Mon, A., Fryer, S.L., Meyerhoff, D.J., 2011. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. *Alcohol. Clin. Exp. Res.* 35, 1187–1200.

Edens, E.L., Glowinski, A.L., Grazier, K.L., Bucholz, K.K., 2008. The 14-year course of alcoholism in a community sample: do men and women differ? *Drug Alcohol Depend.* 93, 1–11.

Elliott, J.C., Stohl, M., Wall, M.M., Keyes, K.M., Skodol, A.E., Eaton, N.R., Shmulewitz, D., Goodwin, R.D., Grant, B.F., Hasin, D.S., 2016. Childhood maltreatment, personality disorders and 3-year persistence of adult alcohol and nicotine dependence in a national sample. *Addiction* 111, 913–923.

Engel, G., 1977. The need for a new medical model: a challenge for biomedicine. *Science.* Engel, K., Schaefer, M., Stickel, A., Binder, H., Heinz, A., Richter, C., 2016. The role of psychological distress in relapse prevention of alcohol addiction. Can high scores on the SCL-90-R predict alcohol relapse? *Alcohol Alcohol* 51, 27–31.

Ercan, E.S., Coşkunol, H., Varan, A., Toksöz, K., 2003. Childhood attention deficit/hyperactivity disorder and alcohol dependence: a 1-year follow-up. *Alcohol Alcohol* 38, 352–356.

Evren, C., Durkaya, M., Evren, B., Dalbudak, E., Cetin, R., 2012. Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. *Drug Alcohol Rev.* 31, 81–90.

Falk, D.E., O'Malley, S.S., Witkiewitz, K., Anton, R.F., Litten, R.Z., Slater, M., Kranzler, H.R., Mann, K.F., Hasin, D.S., Johnson, B., Meulien, D., Ryan, M., Fertig, J., 2019. Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials.

JAMA Psychiatry 76, 374–381.

Farren, C.K., McElroy, S., 2010. Predictive factors for relapse after an integrated inpatient treatment programme for unipolar depressed and bipolar alcoholics. *Alcohol Alcohol* 45, 527–533.

Farren, C.K., Snee, L., Daly, P., McElroy, S., 2013. Prognostic factors of 2-year outcomes of patients with comorbid bipolar disorder or depression with alcohol dependence: importance of early abstinence. *Alcohol Alcohol* 48, 93–98.

Feige, B., Scaal, S., Hornyak, M., Gann, H., Riemann, D., 2007. Sleep electroencephalographic spectral power after withdrawal from alcohol in alcohol-dependent patients. *Alcohol. Clin. Exp. Res.* 31, 19–27.

Fein, G., Klein, L., Finn, P., 2004. Impairment on a simulated gambling task in long-term abstinent alcoholics. *Alcohol Clin. Exp. Res.* 28, 1487–1491.

Fein, G., Nip, V., 2012. Borderline personality symptoms in short-term and long-term abstinent alcohol dependence. *Alcohol. Clin. Exp. Res.* 36, 1188–1195.

Field, M., Di Lemma, L., Christiansen, P., Dickson, J., 2017. Automatic avoidance tendencies for alcohol cues predict drinking after detoxification treatment in alcohol dependence. *Psychol. Addict. Behav.* 31, 171–179.

Flensburg-Madsen, T., Knop, J., Mortensen, E.L., Becker, U., Sher, L., Grønbaek, M., 2009. Alcohol use disorders increase the risk of completed suicide — irrespective of other psychiatric disorders. A longitudinal cohort study. *Psychiatry Res.* 167, 123–130.

Fleury, M.J., Djouini, A., Huynh, C., Tremblay, J., Ferland, F., Ménard, J.M., Belleville, G., 2016. Remission from substance use disorders: a systematic review and meta-analysis. *Drug Alcohol Depend.* 168, 293–306.

Flórez, G., Saiz, P.A., García-Portilla, P., De Cos, F.J., Dapía, S., Álvarez, S., Nogueiras, L., Bobes, J., 2015. Predictors of posttreatment drinking outcomes in patients with alcohol dependence. *Eur. Addict. Res.* 21, 19–30.

Foulds, J., Newton-Howes, G., Guy, N.H., Boden, J.M., Mulder, R.T., 2017. Dimensional personality traits and alcohol treatment outcome: a systematic review and metaanalysis. *Addiction* 112, 1345–1357.

Friend, K.B., Pagano, M.E., 2005a. Changes in cigarette consumption and drinking outcomes: findings from Project MATCH. *J. Subst. Abuse Treat.* 29, 221–229.

Friend, K.B., Pagano, M.E., 2005b. Smoking cessation and alcohol consumption in individuals in treatment for alcohol use disorders. *J. Addict. Dis.* 24, 61–75.

Gamble, S.A., Conner, K.R., Talbot, N.L., Yu, Q., Tu, X.M., Connors, G.J., 2010. Effects of pretreatment and posttreatment depressive symptoms on alcohol consumption following treatment in Project MATCH. *J. Stud. Alcohol Drugs* 71, 71–77.

Gann, H., Feige, B., Fasihi, S., Van Calker, D., Voderholzer, U., Riemann, D., 2002. Periodic limb movements during sleep in alcohol dependent patients. *Eur. Arch. Psychiatry Clin. Neurosci.* 252, 124–129.

Gann, H., Feige, B., Hohagen, F., Van Calker, D., Geiss, D., Dieter, R., 2001. Sleep and the cholinergic rapid eye movement sleep induction test in patients with primary alcohol dependence. *Biol. Psychiatry* 50, 383–390.

Garbusow, M., Schad, D.J., Sebold, M., Friedel, E., Bernhardt, N., Koch, S.P., Steinacher, B., Kathmann, N., Geurts, D.E.M., Sommer, C., Müller, D.K., Nebe, S., Paul, S., Wittchen, H.U., Zimmermann, U.S., Walter, H., Smolka, M.N., Sterzer, P., Rapp, M.A., Huys, Q.J.M., Schlagenhauf, F., Heinz, A., 2016. Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence. *Addict. Biol.* 21, 719–731.

Garbutt, J.C., Kranzler, H.R., O'Malley, S.S., Gastfriend, D.R., Pettinati, H.M., Silverman, B.L., Loewy, J.W., Ehrlich, E.W., Vivitrex Study, G., 2005. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 293, 1617–1625.

Garcia, A.N., Salloum, I.M., 2015. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: a focused review. *Am. J. Addict.* 24, 590–598.

Garfield, J.B.B., Lubman, D.I., Yücel, M., 2014. Anhedonia in substance use disorders: a systematic review of its nature, course and clinical correlates. *Aust. New Zeal. J. Psychiatry* 48, 36–51.

Garland, E.L., Franken, I.H.A., Howard, M.O., 2012. Cue-elicited heart rate variability and attentional bias predict alcohol relapse following treatment. *Psychopharmacology* 222, 17–26.

Gelernter, J., Gueorguieva, R., Kranzler, H.R., Zhang, H., Cramer, J., Rosenheck, R., Krystal, J.H., 2007. Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the va cooperative study. *Alcohol. Clin. Exp. Res.* 31, 555–563.

Gilder, D.A., Lau, P., Linda Corey, M., Cindy Ehlers, M.L., 2008. Factors associated with remission from alcohol dependence in an American Indian Community Group. *Am. J. Psychiatry* 165, 1172–1178.

Gillihan, S.J., Farris, S.G., Foa, E.B., 2011. The effect of anxiety sensitivity on alcohol consumption among individuals with comorbid alcohol dependence and posttraumatic stress disorder. *Psychol. Addict. Behav.* 25, 721–726.

Gish, R.G., Lee, A., Brooks, L., Leung, J., Lau, J.Y., Moore 2nd, D.H., 2001. Long-term follow-up of patients diagnosed with alcohol dependence or alcohol abuse who were evaluated for liver transplantation. *Liver Transpl.* 7, 581–587.

Gong, A., Minuk, G.Y., 2018. Predictors of alcohol relapse following liver transplantation for alcohol-induced liver failure. Consideration of “A–D” selection criteria. *Ann. Transplant.* 23, 129–135.

Gordon, S., Sterling, R., Siatkowski, C., Raively, K., Weinstein, S., Hill, P., 2006. Inpatient desire to drink as a predictor of relapse to alcohol use following treatment. *Am. J. Addict.* 15, 242–245.

Grant, B.F., Chou, S.P., Saha, T.D., Pickering, R.P., Kerridge, B.T., Ruan, W.J., Huang, B., Jung, J., Zhang, H., Fan, A., Hasin, D.S., 2017. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: results from the national epidemiologic survey on alcohol and related conditions. *JAMA Psychiatry* 74, 911–923.

Grant, B.F., Goldstein, R.B., Saha, T.D., Chou, S.P., Jung, J., Zhang, H., Pickering, R.P., Ruan, W.J., Smith, S.M., Huang, B., Hasin, D.S., 2015. Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiatry* 72, 757–766.

Greenfield, S.F., Back, S.E., Lawson, K., Brady, K.T., 2010. Substance abuse in women. *Psychiatr. Clin. North Am.* 33, 339–355.

Greenfield, S.F., Hufford, M.R., Vagge, L.M., Muenz, L.R., Costello, M.E., Weiss, R.D., 2000. The relationship of self-efficacy expectancies to relapse among alcohol dependent men and women: a prospective study. *J. Stud. Alcohol* 61, 345–351.

Greenfield, S.F., Kolodziej, M.E., Sugarman, D.E., Muenz, L.R., Vagge, L.M., He, D.Y., Weiss, R.D., 2002. History of abuse and drinking outcomes following inpatient alcohol treatment: a prospective study. *Drug Alcohol Depend.* 67, 227–234.

Greenfield, S.F., Sugarman, D.E., Muenz, L.R., Patterson, M.D., He, D.Y., Weiss, R.D., 2003. The relationship between educational attainment and relapse among alcohol-dependent men and women: a prospective study. *Alcohol Clin. Exp. Res.* 27, 1278–1285.

Grella, C.E., Stein, J.A., 2013. Remission from substance dependence: differences between individuals in a general population longitudinal survey who do and do not seek help. *Drug Alcohol Depend.* 133, 146–153.

Gross, C.M., Spiegelhalter, K., Mercak, J., Feige, B., Langosch, J.M., 2013. Predictability of alcohol relapse by hippocampal volumetry and psychometric variables. *Psychiatry Res. - Neuroimaging* 212, 14–18.

Gulliver, S., Kalman, D., Rohsenow, D., Colby, S., Eaton, C., Monti, P., 2000. Smoking and drinking among alcoholics in treatment: cross-sectional and longitudinal relationships. *J. Stud. Alcohol* 61, 157–163.

Haller, M., Wang, F., Bountress, K., Chassin, L., 2014. The interactive effects of effort to regulate alcohol use, anxiety disorders and affective disorders on long-term remission from alcohol dependence. *Addict. Res. Theory* 22, 371–379.

Hammerbacher, M., Lyvers, M., 2006. Factors associated with relapse among clients in Australian substance disorder treatment facilities. *J. Subst. Use* 11, 387–394.

Haraguchi, A., Ogai, Y., Senoo, E., Saito, S., Suzuki, Y., Yoshino, A., Ino, A., Yanbe, K., Hasegawa, M., Murakami, M., Murayama, M., Ishikawa, T., Higuchi, S., Ikeda, K., 2009. Verification of the Addiction Severity Index Japanese Version (ASI-J) as a treatment-customization, prediction, and comparison tool for alcohol-dependent individuals. *Int. J. Environ. Res. Public Health* 6, 2205–2225.

Hasin, D.S., Wall, M., Witkiewitz, K., Kranzler, H.R., Falk, D., Litten, R., Mann, K., O'Malley, S.S., Scodes, J., Robinson, R.L., Anton, R., Fertig, J., Isenberg, K., McCann, D., Meulien, D., Meyer, R., O'Brien, C., Ryan, M., Silverman, B., Trinquet, F., Wong, C., Zakine, B., 2017. Change in non-abstinent WHO drinking risk levels and alcohol dependence: a 3 year follow-up study in the US general population. *Lancet Psychiatry* 4, 469–476.

Haver, B., Dahlgren, L., Willander, A., 2001. A 2-year follow-up of 120 Swedish female alcoholics treated early in their drinking career: prediction of drinking outcome. *Alcohol. Clin. Exp. Res.* 25, 1586–1593.

Heffner, J.L., Blom, T.J., Anthenelli, R.M., 2011. Gender differences in trauma history and symptoms as predictors of relapse to alcohol and drug use. *Am. J. Addict.* 20, 307–311.

Helton, S.G., Lohoff, F.W., 2015. Pharmacogenetics of alcohol use disorders and comorbid psychiatric disorders. *Psychiatry Res* 230, 121–129.

Hendershot, C.S., Witkiewitz, K., George, W.H., Marlatt, G.A., 2011. Relapse prevention for addictive behaviors. *Subst. Abuse Treat. Prev. Policy* 6, 17.

Henkel, D., 2011. Unemployment and substance use: a review of the literature (1990–2010). *Curr. Drug Abuse. Rev* 4, 4–27.

Herman, A.M., Critchley, H.D., Duka, T., 2018. The role of emotions and physiological arousal in modulating impulsive behaviour. *Biol. Psychol.* 133, 30–43.

Higley, A.E., Crane, N.A., Spadoni, A.D., Quello, S.B., Goodell, V., Mason, B.J., 2011. Craving in response to stress induction in a human laboratory paradigm predicts treatment outcome in alcohol-dependent individuals. *Psychopharmacology* 218, 121–129.

Hingson, R.W., Heeren, T., Winter, M.R., 2006. Age of alcohol-dependence onset: associations with severity of dependence and seeking treatment. *Pediatrics* 118, 755–763.

Holt, L.J., Litt, M.D., Cooney, N.L., 2012. Prospective analysis of early lapse to drinking and smoking among individuals in concurrent alcohol and tobacco treatment. *Psychol. Addict. Behav.* 26, 561–572.

Hufford, M.R., Witkiewitz, K., Shields, A.L., Kodya, S., Caruso, J.C., 2003. Relapse as a nonlinear dynamic system: application to patients with alcohol use disorders. *J. Abnorm. Psychol.* 112, 219–227.

Hufnagel, A., Frick, U., Ridinger, M., Wodarz, N., 2017. Recovery from alcohol dependence: do smoking indicators predict abstinence? *Am. J. Addict.* 26, 366–373.

Humke, C., Radnitz, C.L., 2005. An instrument for assessing coping with temptation: psychometric properties of the alcohol abuse coping response inventory. *Subst. Use Misuse* 40, 37–62.

Hunt, W.A., Barnett, L.W., Branch, L.G., 1971. Relapse rates in addiction programs. *J. Clin. Psychol.* 27, 455–456.

Hunter-Reel, D., McCrady, B., Hildebrandt, T., 2009. Emphasizing interpersonal factors: an extension of the Witkiewitz and Marlatt relapse model. *Addiction* 104, 1281–1290.

Huntley, Z., Young, S., 2014. Alcohol and substance use history among ADHD adults. *J. Atten. Disord.* 18, 82–90.

Ilgen, M., Moos, R., 2005. Deterioration following alcohol-use disorder treatment in project MATCH. *J. Stud. Alcohol* 66, 517–525.

Jackson, K.M., O'Neill, S.E., Sher, K.J., 2006. Characterizing alcohol dependence: transitions during young and middle adulthood. *Exp. Clin. Psychopharmacol.* 14, 228–244.

Jakubczyk, A., Ilgen, M.A., Kopera, M., Krasowska, A., Klimkiewicz, A., Bohnert, A., Blow, F.C., Brower, K.J., Wojnar, M., 2016. Reductions in physical pain predict lower risk of relapse following alcohol treatment. *Drug Alcohol Depend.* 158, 167–171.

Jakubczyk, A., Klimkiewicz, A., Kopera, M., Krasowska, A., Wrzosek, M., Matsumoto, H., Burmeister, M., Brower, K.J., Wojnar, M., 2013. The CC genotype in the T102C HTR2A polymorphism predicts relapse in individuals after alcohol treatment. *J. Psychiatr. Res.* 47, 527–533.

Janu, L., Rackova, S., Horacek, J., 2012. Regional cerebellar metabolism (18FDG PET) predicts the clinical outcome of the short-term inpatient treatment of alcohol addiction. *Neuroendocrinol. Lett.* 33, 419–424.

Jessup, M.A., Ross, T.B., Jones, A.L., Satre, D.D., Weisner, C., Chi, F., Mertens, J.R., 2014. Significant life events and their impact on alcohol and drug use: a qualitative study. *J. Psychoact. Drugs* 46, 450–459.

Jorde, A., Bach, P., Witt, S.H., Becker, K., Reinhard, I., Vollstädt-Klein, S., Kirsch, M., Hermann, D., Charlet, K., Beck, A., Wimmer, L., Frank, J., Treutlein, J., Spanagel, R., Mann, K., Walter, H., Heinz, A., Rietschel, M., Kiefer, F., 2014. Genetic variation in the atrial natriuretic peptide transcription factor GATA4 modulates amygdala responsiveness in alcohol dependence. *Biol. Psychiatry* 75, 790–797.

Jorge, R.E., Starkstein, S.E., Arndt, S., Moser, D., Crespo-Facorro, B., Robinson, R.G., 2005. Alcohol misuse and mood disorders following traumatic Brain Injury. *Arch. Gen. Psychiatry* 62, 742–749.

Junghanns, K., Backhaus, J., Tietz, U., Lange, W., Bernzen, J., Wetterling, T., Rink, L., Driessen, M., 2003. Impaired serum cortisol stress response is a predictor of early relapse. *Alcohol Alcohol* 38, 189–193.

Junghanns, K., Backhaus, J., Tietz, U., Lange, W., Rink, L., Wetterling, T., Driessen, M., 2005a. The consumption of cigarettes, coffee and sweets in detoxified alcoholics and its association with relapse and a family history of alcoholism. *Eur. Psychiatry* 20, 451–455.

Junghanns, K., Tietz, U., Dibbelt, L., Kuether, M., Jurth, R., Ehrenthal, D., Blank, S., Backhaus, J., 2005b. Attenuated salivary cortisol secretion under cue exposure is associated with early relapse. *Alcohol Alcohol* 40, 80–85.

Kalaydjian, A., Swendsen, J., Chiu, W.T., Dierker, L., Degenhardt, L., Glantz, M., Merikangas, K.R., Sampson, N., Kessler, R., 2009. Sociodemographic predictors of transitions across stages of alcohol use, disorders, and remission in the National Comorbidity Survey Replication. *Compr. Psychiatry* 50, 299–306.

Kalman, D., Kim, S., Digirolamo, G., Smelson, D., Ziedonis, D., 2010. Addressing tobacco use disorder in smokers in early remission from alcohol dependence: the case for integrating smoking cessation services in substance use disorder treatment programs. *Clin. Psychol. Rev.* 30, 12–24.

Karno, M.P., Grella, C.E., Niv, N., Warda, U., Moore, A.A., 2008. Do substance type and diagnosis make a difference? A study of remission from alcohol-versus drug-use disorders using the national epidemiologic survey on alcohol and related conditions. *J. Stud. Alcohol Drugs* 69, 491–495.

Karpyak, V.M., Biernacka, J.M., Geske, J.R., Abulseoud, O.A., Brunner, M.D., Chauhan, M., Hall-Flavin, D.K., Lewis, K.A., Loukianova, L.L., Melnyk, G.J., Onsrud, D.A., Proctor, B.D., Schneekloth, T.D., Skime, M.K., Wittkopp, J.E., Frye, M.A., Mrazek, D.A., 2016. Gender-specific effects of comorbid depression and anxiety on the propensity to drink in negative emotional states. *Addiction* 111, 1366–1375.

Karriker-Jaffe, K.J., Ohlsson, H., Kendler, K.S., Cook, W.K., Sundquist, K., 2018. Alcohol availability and onset and recurrence of alcohol use disorder: examination in a longitudinal cohort with cosibling analysis. *Alcohol. Clin. Exp. Res.* 42, 1105–1112.

Kelly, J.F., Hoepfner, B., Stout, R.L., Pagano, M., 2012. Determining the relative importance of the mechanisms of behavior change within Alcoholics Anonymous: a multiple mediator analysis. *Addiction* 107, 289–299.

Kelly, J.F., Stout, R.L., Magill, M., Tonigan, J.S., 2011. The role of Alcoholics Anonymous in mobilizing adaptive social network changes: a prospective lagged mediational analysis. *Drug Alcohol Depend.* 114, 119–126.

Kelly, M., Chick, J., Gribble, R., Gleeson, M., Holton, M., Winstanley, J., McCaughan, G.W., Haber, P.S., 2006. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. *Alcohol Alcohol* 41, 278–283.

Khan, S., Okuda, M., Hasin, D.S., Secades-Villa, R., Keyes, K., Lin, K.H., Grant, B., Blanco, C., 2013. Gender differences in lifetime alcohol dependence: results from the national epidemiologic survey on alcohol and related conditions. *Alcohol. Clin. Exp. Res.* 37, 1696–1705.

Knop, J., Penick, E.C., Nickel, E.J., Mednick, S.A., Jensen, P., Manzardo, A.M., Gabrielli, W.F., 2007. Paternal alcoholism predicts the occurrence but not the remission of alcoholic drinking: a 40-year follow-up. *Acta Psychiatr. Scand.* 116, 386–393.

Kölves, K., Draper, B., Snowdon, J., De Leo, D., 2017. Alcohol-use disorders and suicide: results from a psychological autopsy study in Australia. *Alcohol* 64, 29–35.

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry.* 3(8), 760–773.

Krahn, D., Bohn, M., Henk, H., Grossman, J., Gosnell, B., 2005. Patterns of urges during early abstinence in alcohol-dependent subjects. *Am. J. Addict.* 14, 248–255.

Krampe, H., Stawicki, S., Ribbe, K., Wagner, T., Bartels, C., Kroener-Herwig, B., Ehrenreich, H., 2008. Development of an outcome prediction measure for alcoholism therapy by multimodal monitoring of treatment processes. *J. Psychiatr. Res.* 43, 30–47.

Krampe, H., Wagner, T., Stawicki, S., Bartels, C., Aust, C., Kroener-Herwig, B., Kuefner, H., Ehrenreich, H., 2006. Personality disorder and chronicity of addiction as independent outcome predictors in alcoholism treatment. *Psychiatr. Serv.* 57, 708–712.

Kraus, L., Seitz, N.N., Piontek, D., Molinaro, S., Siciliano, V., Guttormsson, U., Arpa, S., Monshouwer, K., Leifman, H., Vicente, J., Griffiths, P., Clancy, L., Feijão, F., Florescu, S., Lambrecht, P., Nociar, A., Raitasalo, K., Spilka, S., Vyshinskiy, K., Hibell, B., 2018. “Are the Times A-Changin’?” Trends in adolescent substance use in Europe. *Addiction.* 1317–1332.

Kushner, M.G., Abrams, K., Thuras, P., Hanson, K.L., Brekke, M., Sletten, S., 2005. Followup study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. *Alcohol. Clin. Exp. Res.* 29, 1432–1443.

Kwako, L.E., Koob, G.F., 2017. Neuroclinical framework for the role of stress in addiction. *Chronic Stress* 1, 1–14.

Landheim, A.S., Bakken, K., Vaglum, P., 2006. Impact of comorbid psychiatric disorders on the outcome of substance abusers: a six year prospective follow-up in two Norwegian counties. *BMC Psychiatry* 6, 44.

Larimer, M.E., Palmer, R.S., Marlatt, G.A., 1999. Relapse prevention: an overview of marlatt's cognitive-behavioral model. *Alcohol Res. Heal.* 23, 151–160.

Law, B., Gullo, M.J., Daghli, M., Kavanagh, D.J., Feeney, G.F.X., Young, R.M., Connor, J.P., 2016.

Craving mediates stress in predicting lapse during alcohol dependence treatment. *Alcohol. Clin. Exp. Res.* 40, 1058–1064.

Ledda, R., Battagliese, G., Attilia, F., Rotondo, C., Pisciotta, F., Gencarelli, S., Greco, A., Fiore, M., Ceccanti, M., Attilia, M.L., 2019.

Drop-out, relapse and abstinence in a cohort of alcoholic people under detoxification. *Physiol. Behav.* 198, 67–75.

Lee, S., Guo, W.J., Tsang, A., He, Y.L., Huang, Y.Q., Zhang, M.Y., Liu, Z.R., Shen, Y.C., Kessler, R.C., 2009. Associations of cohort and socio-demographic correlates with transitions from alcohol use to disorders and remission in metropolitan China. *Addiction* 104, 1313–1323.

Lehavot, K., Stappenbeck, C.A., Luterek, J.A., Kaysen, D., Simpson, T.L., 2014. Gender differences in relationships among PTSD severity, drinking motives, and alcohol use in a comorbid alcohol dependence and PTSD sample. *Psychol. Addict. Behav.* 28, 42–52.

Lejoyeux, M., Lehert, P., 2011. Alcohol-use disorders and depression: results from individual patient data meta-analysis of the acamprosate-controlled studies. *Alcohol Alcohol* 46, 61–67.

Levin, C., Ilgen, M., Moos, R., 2007. Avoidance coping strategies moderate the relationship between self-efficacy and 5-year alcohol treatment outcomes. *Psychol. Addict. Behav.* 21, 108–113.

Loeber, S., Duka, T., Márquez, H.W., Nakovics, H., Heinz, A., Mann, K., Flor, H., 2010. Effects of repeated withdrawal from alcohol on recovery of cognitive impairment under abstinence and rate of relapse. *Alcohol Alcohol* 45, 541–547.

Long, C.G., Williams, M., Midgley, M., Hollin, C.R., 2000. Within-program factors as predictors of drinking outcome following cognitive-behavioral treatment. *Addict. Behav.* 25, 573–578.

Lopez-Quintero, C., Hasin, D.S., De Los Cobos, J.P., Pines, A., Wang, S., Grant, B.F., Blanco, C., 2011. Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction* 106, 657–669.

Lucht, M., Jahn, U., Barnow, S., Freyberger, H., 2002. The use of a symptom checklist (SCL-90-R) as an easy method to estimate the relapse risk after alcoholism detoxification. *Eur. Addict. Res.* 8, 190–194.

Ludwig, F., Tadayon-Mansuri, E., Strik, W., Moggi, F., 2013. Self-efficacy as a predictor of outcome after residential treatment programs for alcohol dependence: simply ask the patient one question! *Alcohol. Clin. Exp. Res.* 37, 663–667.

Maisto, S.A., Hallgren, K.A., Roos, C.R., Witkiewitz, K., 2018. Course of remission from and relapse to heavy drinking following outpatient treatment of alcohol use disorder. *Drug Alcohol Depend.* 187, 319–326.

Maisto, S.A., Roos, C.R., Hallgren, K.A., Moskal, D., Wilson, A.D., Witkiewitz, K., 2016a. Do alcohol relapse episodes during treatment predict long-term outcomes? Investigating the validity of existing definitions of alcohol use disorder relapse. *Alcohol. Clin. Exp. Res.* 40, 2180–2189.

Maisto, S.A., Witkiewitz, K., Moskal, D., Wilson, A., 2016b. Is the construct of relapse heuristic, and does it advance alcohol use disorder clinical practice? *J. Stud. Alcohol Drugs* 77, 849–858.

Maisto, S.A., Xie, F.C., Witkiewitz, K., Ewart, C.K., Connors, G.J., Zhu, H., Elder, G., Ditmar, M., Chow, S.-M., 2017. How chronic self-regulatory stress, poor anger regulation, and momentary affect undermine treatment for alcohol use disorder: integrating social action theory with the dynamic model of relapse. *J. Soc. Clin. Psychol.* 36, 238–263.

Mann, K., Aubin, H.-J., Witkiewitz, K., 2017. Reduced drinking in alcohol dependence treatment, what is the evidence? *Eur. Addict. Res.* 23, 219–230.

Mann, K., Hintz, T., Jung, M., 2004. Does psychiatric comorbidity in alcohol-dependent patients affect treatment outcome? *Eur. Arch. Psychiatry Clin. Neurosci.* 254, 172–181.

Mann, K., Roos, C.R., Hoffmann, S., Nakovics, H., Leménager, T., Heinz, A., Witkiewitz, K., 2018. Precision medicine in alcohol dependence: a controlled trial testing pharmacotherapy response among reward and relief drinking phenotypes. *Neuropsychopharmacology* 43, 891–899.

- Manning, V., Teo, H.C., Guo, S., Wong, K.E., Li, T.K., 2016. Neurocognitive functioning and treatment outcome following detoxification among asian alcohol-dependent inpatients. *Subst. Use Misuse* 51, 193–205.
- Markianos, M., Lykouras, L., Moussas, G., Hatzimanolis, J., 2001. Changes in dopamine receptor responsivity during alcohol detoxification may predict relapse. *Drug Alcohol Depend* 64, 363–365.
- Marlatt, G.A., Gordon, J.R. (Eds.), 1985. *Relapse prevention: maintenance strategies in the treatment of addictive behaviors*. Guilford Press, New York.
- Marlatt, A.G., 1996. Taxonomy of high-risk situations for alcohol relapse: evolution and development of a cognitive-behavioral model. *Addiction* 91.
- Marquenie, L.A., Schadé, A., Van Balkom, A.J.L.M., Koeter, M., Frenken, S., Van Den Brink, W., Van Dyck, R., 2006. Comorbid phobic disorders do not influence outcome of alcohol dependence treatment. Results of a naturalistic follow-up study. *Alcohol Alcohol* 41, 168–173.
- Matheus-roth, C., Schenk, I., Wiltfang, J., Scherbaum, N., Müller, B.W., 2016. Occipital event-related potentials to addiction-related stimuli in detoxified patients with alcohol dependence, and their association with three-month relapse. *BMC Psychiatry* 1–12.
- Mattoo, S.K., Chakrabarti, S., Anjaiah, M., 2009. Psychosocial factors associated with relapse in men with alcohol or opioid dependence. *Indian J. Med. Res.* 130, 702–708.
- Matzger, H., Kaskutas, L.A., Weisner, C., 2005. Reasons for drinking less and their relationship to sustained remission from problem drinking. *Addiction* 100, 1637–1646.
- McAweeney, M.J., Zucker, R.A., Fitzgerald, H.E., Puttler, L.I., Wong, M.M., 2005. Individual and partner predictors of recovery from alcohol-use disorder over a nineyear interval: findings from a community sample of alcoholic married men. *J. Stud. Alcohol* 66, 220–228.
- McCutcheon, V.V., Kramer, J.R., Edenberg, H.J., Nurnberger, J.I., Kuperman, S., Schuckit, M.A., Heath, A.C., Bucholz, K.K., 2014. Social contexts of remission from DSM-5 alcohol use disorder in a high-risk sample. *Alcohol. Clin. Exp. Res.* 38, 2015–2023.
- McCutcheon, V.V., Schuckit, M.A., Kramer, J.R., Chan, G., Edenberg, H.J., Smith, T.L., Bender, A.K., Hesselbrock, V., Hesselbrock, M., Bucholz, K.K., 2017. Familial association of abstinent remission from alcohol use disorder in first-degree relatives of alcohol-dependent treatment-seeking probands. *Addiction* 112, 1909–1917.
- McCutcheon, V.V., Grant, J.D., Heath, A.C., Bucholz, K.K., Sartor, C.E., 2012. Environmental influences predominate in remission from alcohol use disorder in young adult twins"Environmental influences predominate in remission from alcohol use disorder in young adult twins. *Psychol. Med.* 42 (11), 2421–2431.
- McHugh, R.K., Fitzmaurice, G.M., Griffin, M.L., Anton, R.F., Weiss, R.D., 2016. Association between a brief alcohol craving measure and drinking in the following week. *Addiction* 111, 1004–1010.
- McKay, J.R., 2017. Making the hard work of recovery more attractive for those with substance use disorders. *Addiction* 112, 751–757.
- McKay, J.R., 1999. Studies of factors in relapse to alcohol, drug and nicotine use: a critical review of methodologies and findings. *J. Stud. Alcohol* 60, 566–576.
- McKay, J.R., Foltz, C., Stephens, R.C., Leahy, P.J., Crowley, E.M., Kissin, W., 2005. Predictors of alcohol and crack cocaine use outcomes over a 3-year follow-up in treatment seekers. *J. Subst. Abuse Treat.* 28, S73–S82.
- McKay, J.R., Franklin, T.R., Patapis, N., Lynch, K.G., 2006. Conceptual, methodological, and analytical issues in the study of relapse. *Clin. Psychol. Rev.* 26(2), 109-127
- McKay, J.R., Hiller-Sturmhofel, S., 2011. Treating alcoholism as a chronic disease. *Alcohol Res. Heal.* 33, 356–370.
- McKee, L.G., Bonn-Miller, M.O., Moos, R.H., 2011. Depressive symptoms, friend and partner relationship quality, and posttreatment abstinence. *J. Stud. Alcohol Drugs* 72, 141–150.
- Mericle, A.A., Kaskutas, L.A., Polcin, D.L., Karriker-Jaffe, K.J., 2018. Independent and interactive effects of neighborhood disadvantage and social network characteristics on problem drinking after treatment. *J. Soc. Clin. Psychol.* 37, 1–21.
- Mertens, J.R., Kline-Simon, A.H., Delucchi, K.L., Moore, C., Weisner, C.M., 2012. Ten year stability of remission in private alcohol and drug outpatient treatment: nonproblem users versus abstainers. *Drug Alcohol Depend* 125, 67–74.

Miguet, M., Monnet, E., Vanlemmens, C., Gache, P., Messner, M., Hruskovsky, S., Perarnau, J., Pageaux, G., Duvoux, C., Minello, A., Hillon, P., Bresson-Hadni, S., Mantion, G., Miguet, J., 2004. Predictive factors of alcohol relapse after orthotopic liver transplantation for alcoholic liver disease. *Gastroenterol. Clin. Biol.* 28, 845–851

Miller, M.B., Donahue, M.L., Carey, K.B., Scott-Sheldon, L.A.J., 2017. Insomnia treatment in the context of alcohol use disorder: a systematic review and meta-analysis. *Drug Alcohol Depend* 181, 200–207.

Miller, W.R., 1996. What is a relapse? Fifty ways to leave the wagon. *Addiction*. 91, Suppl:S15-27.

Miller, W.R., Harris, R., 2000. A simple scale of Gorski's warning signs for relapse. *J. Stud. Alcohol* 61, 759–765.

Miller, W.R., Moyers, T.B., 2017. Motivational interviewing and the clinical science of Carl Rogers. *J. Consult. Clin. Psychol.* 85, 757–766.

Miller, W.R., Wilbourne, P.L., 2002. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 97, 265–277.

Milne, B.J., Caspi, A., Harrington, H., Poulton, R., Rutter, M., Moffitt, T.E., 2009. Predictive value of family history on severity of illness: the case for depression, anxiety, alcohol dependence, and drug dependence. *Arch. Gen. Psychiatry* 66, 738–747.

Mo, C., Deane, F.P., 2016. Reductions in craving and negative affect predict 3-month postdischarge alcohol use following residential treatment. *Int. J. Ment. Health Addict.* 14, 761–774.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J.A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J.J., Devereaux, P.J., Dickersin, K., Egger, M., Ernst, E., Gøtzsche, P.C., Grimshaw, J., Guyatt, G., Higgins, J., Ioannidis, J.P.A., Kleijnen, J., Lang, T., Magrini, N., McNamee, D., Moja, L., Mulrow, C., Napoli, M., Oxman, A., Pham, B., Rennie, D., Sampson, M., Schulz, K.F., Shekelle, P.G., Tovey, D., Tugwell, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6.

Mojarrad, M., Samet, J.H., Cheng, D.M., Winter, M.R., Saitz, R., 2014. Marijuana use and achievement of abstinence from alcohol and other drugs among people with substance dependence: a prospective cohort study. *Drug Alcohol Depend* 142, 91–97.

Moos, R.H., Moos, B.S., 2007. Protective resources and long-term recovery from alcohol use disorders. *Drug Alcohol Depend* 86, 46–54.

Moos, R.H., Moos, B.S., 2006. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 101, 212–222.

Moos, R.H., Moos, B.S., 2005. Sixteen-year changes and stable remission among treated and untreated individuals with alcohol use disorders. *Drug Alcohol Depend.* 80, 337–347.

Moos, R.H., Moos, B.S., 2003. Risk factors for nonremission among initially untreated individuals with alcohol use disorders. *J. Stud. Alcohol* 64, 555–563.

Moos, R.H., Moos, B.S., Timko, C., 2006. Gender, treatment and self-help in remission from alcohol use disorders. *Clin. Med. Res.* 4, 163–174.

Müller, C.A., Schäfer, M., Schneider, S., Heimann, H.M., Hinzpeter, A., Volkmar, K., Förg, A., Heinz, A., Hein, J., 2010. Efficacy and safety of levetiracetam for outpatient alcohol detoxification. *Pharmacopsychiatry* 43, 184–189.

Müller, S.E., Weijers, H.G., Böning, J., Wiesbeck, G.A., 2008. Personality traits predict treatment outcome in alcohol-dependent patients. *Neuropsychobiology* 57, 159–164.

Nalpas, B., Boulze-Launay, I., 2018. Maintenance of abstinence in self-help groups. *Alcohol Alcohol* 53, 89–94.

Newton-Howes, G.M., Foulds, J.A., Guy, N.H., Boden, J.M., Mulder, R.T., 2017. Personality disorder and alcohol treatment outcome: systematic review and metaanalysis. *Br. J. Psychiatry* 211, 22–30.

Nieva, G., Ortega, L.L., Mondon, S., Ballbè, M., Gual, A., 2010. Simultaneous versus delayed treatment of tobacco dependence in alcohol-dependent outpatients. *Eur. Addict. Res.* 17, 1–9.

Noda, T., Imamichi, H., Kawata, A., Hirano, K., Ando, T., Iwata, Y., Yoneda, H., 2001. Long-term outcome in 306 males with alcoholism. *Psychiatry Clin. Neurosci.* 55, 579–586.

Noël, X., Bechara, A., 2016. Bridging the gap between the lab and the clinic: psychopathology's grand challenge. *Front. Psychol.* 7, 1–3.

Noël, X., Brevers, D., Bechara, A., 2013. A triadic neurocognitive approach to addiction for clinical interventions. *Front. Psychiatry* 4, 1–14.

Noël, X., Sferrazza, R., Van Der Linden, M., Paternot, J., Verhas, M., Hanak, C., Pelc, I., Verbanck, P., 2002. Contribution of frontal cerebral blood flow measured by (99m)Tc-Bicisate spect and executive function deficits to predicting treatment outcome in alcohol-dependent patients. *Alcohol Alcohol* 37, 347–354.

North, C., Ringwalt, C., Danadowns, D., Jimderzon, D., 2010. Postdisaster course of alcohol use disorders in systematically studied survivors of 10 disasters. *Arch. Gen. Psychiatry* 68, 173–180.

O'Daly, O.G., Trick, L., Scaife, J., Marshall, J., Ball, D., Phillips, M.L., Williams, S.S., Stephens, D.N., Duka, T., 2012. Withdrawal-associated increases and decreases in functional neural connectivity associated with altered emotional regulation in alcoholism. *Neuropsychopharmacology* 3777, 2267–2276.

Oberleitner, L.M.S., Mandel, D.L., Easton, C.J., 2013. Treatment of co-occurring alcohol dependence and perpetration of intimate partner violence: the role of anger expression. *J. Subst. Abuse Treat.* 45, 313–318.

Ojesjö, L., Hagnell, O., Otterbeck, L., 2000. The course of alcoholism among men in the Lundby Longitudinal Study, Sweden. *J. Stud. Alcohol* 61, 320–322.

Oslin, D.W., Cary, M., Slaymaker, V., Collieran, C., Blow, F.C., 2009. Daily ratings measures of alcohol craving during an inpatient stay define subtypes of alcohol addiction that predict subsequent risk for resumption of drinking. *Drug Alcohol Depend.* 103, 131–136.

Oslin, D.W., Pettinati, H., Volpicelli, J.R., 2002. Alcoholism treatment adherence older age predicts better adherence and drinking outcomes. *Am. J. Geriatr. Psychiatry* 10, 740–747.

Pagano, M.E., Friend, K.B., Tonigan, J.S., Stout, R.L., 2004. Helping other alcoholics in alcoholics anonymous and drinking outcomes: findings from project MATCH. *J. Stud. Alcohol* 65, 766–773.

Palpacuer, C., Duprez, R., Huneau, A., Locher, C., Boussageon, R., Laviolle, B., Naudet, F., 2018. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. *Addiction* 113, 220–237.

Papachristou, H., Nederkoorn, C., Giesen, J.C.A.H., Jansen, A., 2014. Cue reactivity during treatment, and not impulsivity, predicts an initial lapse after treatment in alcohol use disorders. *Addict. Behav.* 39, 737–739.

Paulino, S., Pombo, S., Ismail, F., Figueira, M.L., Lesch, O., 2017. The role of affective temperament as a predictor of relapse in alcohol dependence. *Personal. Ment. Health* 11, 278–289.

Pedersen, M.U., Hesse, M., 2009. A simple risk scoring system for prediction of relapse after inpatient alcohol treatment. *Am. J. Addict.* 18, 488–493.

Pelc, I., Ansoms, C., Lehert, P., Fischer, F., Fuchs, W., Landron, F., Pires Preto, A., 2002. The European NEAT program: an integrated approach using acamprosate and psychosocial support for the prevention of relapse in alcohol-dependent patients with a statistical modeling of therapy success prediction. *Alcohol. Clin. Exp. Res.* 26, 1529–1538.

Penick, E.C., Knop, J., Nickel, E.J., Jensen, P., Manzardo, A.M., Lykke-Mortensen, E., Gabrielli, W.F., 2010. Do premorbid predictors of alcohol dependence also predict the failure to recover from alcoholism? *J. Stud. Alcohol Drugs* 71, 685–694.

Perney, P., Bismuth, M., Sigaud, H., Picot, M.C., Jacquet, E., Puche, P., Jaber, S., Rigole, H., Navarro, F., Eledjam, J.J., Blanc, F., Larrey, D., Pageaux, G.P., 2005. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease? *Transpl. Int.* 18, 1296–1297.

Pfefferbaum, A., Rosenbloom, M.J., Serventi, K.L., Sullivan, E.V., 2004. Brain volumes, RBC status, and hepatic function in alcoholics after 1 and 4 weeks of sobriety: predictors of outcome. *Am. J. Psychiatry* 161, 1190–1196.

Pinto, E., Reggers, J., Gorwood, P., Boni, C., Scantamburlo, G., Pitchot, W., Anseau, M., 2008. The short allele of the serotonin transporter promoter polymorphism influences relapse in alcohol dependence. *Alcohol Alcohol* 43, 398–400.

Pirkola, S.P., Poikolainen, K., Lönnqvist, J.K., 2006. Currently active and remitted alcohol dependence in a nationwide adult general population - results from the Finnish Health 2000 study. *Alcohol Alcohol* 41, 315–320.

Pitel, A.L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B., Eustache, F., 2009. Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. *Alcohol. Clin. Exp. Res.* 33, 490–498.

Platz, K., Mueller, A., Spree, E., Schumacher, G., Nüssler, N., Rayes, N., Glanemann, M., Bechstein, W., Neuhaus, P., 2000. Liver transplantation for alcoholic cirrhosis. *Transpl. Int.* 13, S127–S130.

Possemato, K., Maisto, S.A., Wade, M., Barrie, K., Johnson, E.M., Ouimette, P.C., 2017. Natural course of co-occurring PTSD and alcohol use disorder among recent combat veterans. *J. Trauma. Stress* 30, 279–287.

Preuss, U.W., Winham, S.J., Biernacka, J.M., Geske, J.R., Bakalkin, G., Koller, G., Zill, P., Soyka, M., Karpyak, V.M., 2013. PDYN rs2281285 variant association with drinking to avoid emotional or somatic discomfort. *PLoS One* 8.

Prisciandaro, J.J., Desantis, S.M., Chiuhan, C., Brown, D.G., Brady, K.T., Tolliver, B.K., 2012. Impact of depressive symptoms on future alcohol use in patients with co-occurring bipolar disorder and alcohol dependence: a prospective analysis in an 8-week randomized controlled trial of acamprosate. *Alcohol. Clin. Exp. Res.* 36, 490–496.

Quoilin, C., Wilhelm, E., Maurage, P., De Timary, P., Duque, J., 2018. Deficient inhibition in alcohol-dependence: let's consider the role of the motor system! *Neuropsychopharmacology* 43, 1851–1858.

Rando, K., Hong, K.-I., Bhagwagar, Z., Ray, C.-S., Bergquist, K., Guarnaccia, J., Sinha, R., 2011. Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: a prospective study. *Am. J. Psychiatry* 168, 183–192.

Rask, M.B., Jørgensen, T., Jensen, J.P., Jørgensen, K.B., Madsen, M., Nielsen, B., Andersen, A.M.N., Nielsen, A.S., Grønbaek, M., 2006. Influence of pretreatment coping strategies on the outcome of outpatient treatment of danish alcohol abusers. *Eur. Addict. Res.* 12, 83–90.

Rehm, J., Anderson, P., Barry, J., Dimitrov, P., Elekes, Z., Feijão, F., Frick, U., Gual, A., Gmel, G., Kraus, L., Marmet, S., Raninen, J., Rehm, M.X., Scafato, E., Shield, K.D., Trapencieris, M., Gmel, G., 2015. Prevalence of and potential influencing factors for alcohol dependence in europe. *Eur. Addict. Res.* 21, 6–18.

Reyes-Huerta, H.E., dos Santos, C., Martínez, K., 2018. Impulsive mechanisms influencing relapse in alcohol drinking. *Med. Hypotheses* 112, 27–29.

Romo, L., Le Strat, Y., Bichat, X., Aubry, C., Marquez, S., Houdeyer, K., Batel, P., Adès, J., Gorwood, P., 2009. The role of brief motivational intervention on self-efficacy and abstinence in a cohort of patients with alcohol dependence. *Int'l. J. Psychiatry Med.* 39, 313–323.

Roos, C., Kirouac, M., Pearson, M., Fink, B., Witkiewitz, K., 2015. Examining temptation to drink from an existential perspective: associations among temptation, purpose in life, and drinking outcomes. *Psychol. Addict. Behav.* 29, 716–724.

Roos, C.R., Mann, K., Witkiewitz, K., 2017. Reward and relief dimensions of temptation to drink: construct validity and role in predicting differential benefit from acamprosate and naltrexone. *Addict. Biol.* 22, 1528–1539.

Roozen, H.G., van de Wetering, B.J.M., 2007. Neuropsychiatric insights in clinical practice: from relapse prevention toward relapse management. *Am. J. Addict.* 16, 530–531.

Rumpf, H., Bischof, G., Hapke, U., Meyer, C., John, U., 2002. The role of family and partnership in recovery from alcohol dependence: comparison of individuals remitting with and without formal help. *Eur. Addict. Res.* 8, 122–127.

Rupp, C.I., Beck, J.K., Heinz, A., Kemmler, G., Manz, S., Tempel, K., Fleischhacker, W.W., 2016. Impulsivity and alcohol dependence treatment completion: is there a neurocognitive risk factor at treatment entry? *Alcohol. Clin. Exp. Res.* 40, 152–160.

Rupp, C.I., Derntl, B., Osthaus, F., Kemmler, G., Fleischhacker, W.W., 2017. Impact of social cognition on alcohol dependence treatment outcome: poorer facial emotion recognition predicts relapse/dropout. *Alcohol. Clin. Exp. Res.* 41, 2197–2206.

Rus-Makovec, M., Cebasek-Travnik, Z., 2008. Co-occurring mental and somatic diagnoses of alcohol dependent patients in relation to long-term aftercare alcohol abstinence and well-being. *Psychiatr Danub* 20, 194–207.

Russell, M., Peirce, R.S., Chan, A.W.K., Wieczorek, W.F., Moscato, B.S., Nochajski, T.H., 2001. Natural recovery in a community-based sample of alcoholics: study design and descriptive data. *Subst. Use Misuse* 36, 1417–1441.

Samet, S., Fenton, M.C., Nunes, E., Greenstein, E., Aharonovich, E., Hasin, D., 2013. Effects of independent and substance-induced major depressive disorder on remission and relapse of alcohol, cocaine and heroin dependence. *Addiction* 108, 115–123.

Sander, W., Jux, M., 2006. Psychological distress in alcohol-dependent patients. Evaluating inpatient treatment with the symptom checklist (SCL-90-R). *Eur. Addict. Res.* 12, 61–66.

Satre, D.D., Chi, F.W., Mertens, J.R., Weisner, C.M., 2012. Effects of age and life transitions on alcohol and drug treatment outcome over nine years. *J. Stud. Alcohol Drugs* 73, 459–468.

Sau, M., Mukherjee, A., Manna, N., Sanyal, S., 2013. Sociodemographic and substance use correlates of repeated relapse among patients presenting for relapse treatment at an addiction treatment center in Kolkata, India. *Afr. Health Sci.* 13, 791–799.

Schadé, A., Marquenie, L.A., Van Balkom, A.J.L.M., De Beurs, E., Van Dyck, R., Van Den Brink, W., Schadé, A., Marquenie, L.A., Balkom, A.J.L.M.V.A.N., Beurs, E.D.E., 2003. Do comorbid anxiety disorders in alcohol-dependent patients need specific treatment to prevent relapse? *Alcohol Alcohol* 38, 255–262.

Schank, J.R., Ryabinin, A.E., Giardino, W.J., Ciccocioppo, R., Heilig, M., 2012. Stress-related neuropeptides and addictive behaviors: beyond the usual suspects. *Neuron* 76, 192–208.

Schellekens, A.F.A., de Jong, C.A.J., Buitelaar, J.K., Verkes, R.J., 2015. Co-morbid anxiety disorders predict early relapse after inpatient alcohol treatment. *Eur. Psychiatry* 30, 128–136.

Schepis, T.S., Hakes, J.K., 2013. Dose-Related effects for the precipitation of psychopathology by opioid or tranquilizer/sedative nonmedical prescription use. *J. Addict. Med.* 7, 39–44.

Schepis, T.S., Hakes, J.K., 2011. Non-medical prescription use increases the risk for the onset and recurrence of psychopathology: results from the national epidemiological survey on alcohol and related conditions. *Addiction* 106, 2146–2155.

Schmidt, L.G., Smolka, M.N., 2007. Results from two pharmacotherapy trials show alcoholic smokers were more severely alcohol dependent but less prone to relapse than alcoholic non-smokers. *Alcohol Alcohol* 42, 241–246.

Schmidt, L.G., Smolka, M.N., 2001. Relapse prevention in alcoholics by cigarette smoking? Involvement of nicotinic-dopaminergic mechanisms. *Alcohol* 24, 111–115.

Schneekloth, T.D., Biernacka, J.M., Hall-Flavin, D.K., Karpyak, V.M., Frye, M.A., Loukianova, L.L., Stevens, S.R., Drews, M.S., Geske, J.R., Mrazek, D.A., 2012. Alcohol craving as a predictor of relapse. *Am. J. Addict.* 21, S20–S26.

Schuckit, M.A., Smith, T.L., 2011. Onset and course of alcoholism over 25 years in middle class men. *Drug Alcohol Depend* 113, 21–28.

Schutte, K., Nichols, K., Brennan, P., Moos, R., 2003. A ten-year follow-up of older former problem drinkers: risk of relapse and implications of successfully sustained remission. *J. Stud. Alcohol* 64, 367–374.

Schutte, K.K., Brennan, P.L., Moos, R.H., 2009. Treated and untreated remission from problem drinking in late life: post-remission functioning and health-related quality of life. *Drug Alcohol Depend* 99, 150–159.

Schutte, K.K., Byrne, F., Brennan, P., Moos, R., 2001. Successful remission of late-life drinking problems: a 10-year follow-up. *J. Stud. Alcohol* 62, 322–334.

Sebold, M., Nebe, S., Garbusow, M., Guggenmos, M., Schad, D.J., Beck, A., Kuitunen-Paul, S., Sommer, C., Frank, R., Neu, P., Zimmermann, U.S., Rapp, M.A., Smolka, M.N., Huys, Q.J.M., Schlagenhauf, F., Heinz, A., 2017. When habits are dangerous: alcohol expectancies and habitual decision making predict relapse in alcohol dependence. *Biol. Psychiatry* 82, 847–856.

Segobin, S.H., Chételat, G., Le Berre, A.P., Lannuzel, C., Boudehent, C., Vabret, F., Eustache, F., Beaunieux, H., Pitel, A.L., 2014. Relationship between brain volumetric changes and interim drinking at six months in alcohol-dependent patients. *Alcohol. Clin. Exp. Res.* 38, 739–748.

Seo, D., Lacadie, C.M., Tuit, K., Hong, K.I., Todd Constable, R., Sinha, R., 2013. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry* 70, 727–739.

Shaw, M.A., DiClemente, C.C., 2016. Temptation minus self-efficacy in alcohol relapse: a project MATCH follow-up. *J. Stud. Alcohol Drugs* 77, 521–525.

Sher, K., Gotham, H., Watson, A., 2004. Trajectories of dynamic predictors of disorder: their meanings and implications. *Dev. Psychopathol.* 16, 825–856.

Silveira, C.M., Viana, M.C., Siu, E.R., de Andrade, A.G., Anthony, J.C., Andrade, L.H., 2011. Sociodemographic correlates of transitions from alcohol use to disorders and remission in the São Paulo megacity mental health survey, Brazil. *Alcohol Alcohol* 46, 324–332.

Simioni, N., Cottencin, O., Guardia, D., Rolland, B., 2012. Early relapse in alcohol dependence may result from late withdrawal symptoms. *Med. Hypotheses* 79, 894–895.

Sinha, R., 2011. Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. *Arch. Gen. Psychiatry* 68, 942.

Skelton, E., Tzelepis, F., Shakeshaft, A., Guillaumier, A., McCrabb, S., Bonevski, B., 2018. Integrating smoking cessation care in alcohol and other drug treatment settings using an organisational change intervention: a systematic review. *Addiction*. 113(12), 2158–2172

Sluiter, R.L., Kievit, W., Van Der Wilt, G.J., Schene, A.H., Teichert, M., Coenen, M.J.H., Schellekens, A., 2018. Cost-effectiveness analysis of genotype-guided treatment allocation in patients with alcohol use disorders using naltrexone or acamprosate, using a modeling approach. *Eur. Addict. Res.* 24, 245–254.

Smith, N., Hill, R., Marshall, J., Keane, F., Wanigaratne, S., 2014. Sleep related beliefs and their association with alcohol relapse following residential alcohol detoxification treatment. *Behav. Cogn. Psychother.* 42, 593–604.

Snelleman, M., Schoenmakers, T.M., van de Mheen, D., 2018. Relapse and craving in alcohol-dependent individuals: a comparison of self-reported determinants. *Subst. Use Misuse* 53, 1099–1107.

Sorg, S.F., Taylor, M.J., Alhassoon, O.M., Gongvatana, A., Theilmann, R.J., Frank, L.R., Grant, I., 2012. Frontal white matter integrity predictors of adult alcohol treatment outcome. *Biol. Psychiatry* 71, 262–268.

Spruyt, A., De Houwer, J., Tibboel, H., Verschuere, B., Crombez, G., Verbanck, P., Hanak, C., Brevers, D., Noël, X., 2013. On the predictive validity of automatically activated approach/avoidance tendencies in abstaining alcohol-dependent patients. *Drug Alcohol Depend* 127, 81–86.

Sterling, R., Weinstein, S., Losardo, D., Raively, K., Hill, P., Petrone, A., Gottheil, E., 2007. A retrospective case control study of alcohol relapse and spiritual growth. *Am. J. Addict.* 16, 56–61.

Stevens, L., Verdejo-García, A., Goudriaan, A.E., Roeyers, H., Dom, G., Vanderplasschen, W., 2014. Impulsivity as a vulnerability factor for poor addiction treatment outcomes: a review of neurocognitive findings among individuals with substance use disorders. *J. Subst. Abuse Treat.* 47, 58–72.

Strakowski, S.M., DelBello, M.P., Fleck, D.E., Adler, C.M., Anthenelli, R.M., Keck, P.E., Arnold, L.M., Amicone, J., 2005. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch. Gen. Psychiatry* 62, 851–858.

Strowig, A.B., 2000. Relapse determinants reported by men treated for alcohol addiction: the prominence of depressed mood. *J. Subst. Abuse Treat.* 19, 469–474.

Sugaya, N., Ogai, Y., Kakibuchi, Y., Senoo, E., Ikeda, K., 2012. Influence of GIRK channel inhibition on relapse risk in Japanese alcohol-dependent inpatients. *Nihon Shinkei Seishin Yakurigaku Zasshi* 32, 165–167.

Suliman, S., Seedat, S., Williams, D.R., Stein, D.J., 2010. Predictors of transitions across stages of alcohol use and alcohol-use disorders in South Africa. *J. Stud. Alcohol Drugs* 71, 695–703.

Sullivan, G.M., Feinn, R., 2012. Using effect size - or why the P value is not enough. *J. Grad. Med. Educ.* 4, 279–282.

Sullivan, M., Covey, L., 2002. Current perspectives on smoking cessation among substance abusers. *Curr. Psychiatry Rep.* 4, 388–396.

Sulmasy, D.P., 2002. A biopsychosocial-spiritual model for the care of patients at the end of life. *Gerontologist* 42 Spec No, 24–33.

Suter, M., Strik, W., Moggi, F., 2011. Depressive symptoms as a predictor of alcohol relapse after residential treatment programs for alcohol use disorder. *J. Subst. Abuse Treat.* 41, 225–232.

Tapert, S.F., Ozyurt, S.S., Myers, M.G., Brown, S.A., 2004. Neurocognitive ability in adults coping with alcohol and drug relapse temptations. *Am. J. Drug Alcohol Abuse* 30, 445–460.

Tate, S.R., McQuaid, J.R., Brown, S.A., 2005. Characteristics of life stressors predictive of substance treatment outcomes. *J. Subst. Abuse Treat.* 29, 107–115.

Tate, S.R., Wu, J., McQuaid, J.R., Cummins, K., Shriver, C., Krenek, M., Brown, S.A., 2008. Comorbidity of substance dependence and depression: role of life stress and self-efficacy in sustaining abstinence. *Psychol. Addict. Behav.* 22, 47–57.

Tatsuzawa, Y., Yoshimasu, H., Moriyama, Y., Furusawa, T., Yoshino, A., 2002. Validation study of the Japanese version of the obsessive-compulsive drinking scale. *Psychiatry Clin. Neurosci.* 56, 91–95.

Terra, M.B., Barros, H.M.T., Stein, A.T., Figueira, I., Athayde, L.D., Ott, D.R., De Azambuja, R.D.C.S., Da Silveira, D.X., 2008. Predictors of relapse in 300 Brazilian alcoholic patients: a 6-month follow-up study. *Subst. Use Misuse* 43, 403–411.

Terra, M.B., Barros, H.M.T., Stein, A.T., Figueira, I., Athayde, L.D., Spanemberg, L., de Aguiar Possa, M., Filho, L.D., da Silveira, D.X., 2006. Does co-occurring social phobia interfere with alcoholism treatment adherence and relapse? *J. Subst. Abuse Treat.* 31, 403–409.

Tiet, Q.Q., Mausbach, B., 2007. Treatments for patients with dual diagnosis: a review. *Alcohol. Clin. Exp. Res.* 31, 513–536.

Tómasson, K., Vaglum, P., 2000. Antisocial addicts: the importance of additional axis I disorders for the 28-month outcome.

Eur. Psychiatry 15, 443–449.

Tonigan, J., McCallion, E., Frohe, T., Pearson, M., 2017. Lifetime Alcoholics Anonymous attendance as a predictor of spiritual gains in the Relapse Replication and Extension Project (RREP). *Psychol. Addict Behav.* 31, 54–60.

Trim, R.S., Schuckit, M.A., Smith, T.L., 2013. Predictors of initial and sustained remission from alcohol use disorders: findings from the 30-Year follow-up of the san diego prospective study. *Alcohol. Clin. Exp. Res.* 37, 1424–1431.

Trocchio, S., Chassler, D., Storbjörk, J., Delucchi, K., Witbrodt, J., Lundgren, L., 2013. The association between self-reported mental health status and alcohol and drug abstinence 5 years post-assessment for an addiction disorder in U.S. and Swedish samples. *J. Addict. Dis.* 32, 180–193.

Trucco, E.M., Connery, H.S., Griffin, M.L., Greenfield, S.F., 2007. The relationship of self-esteem and self-efficacy to treatment outcomes of alcohol-dependent men and women. *Am. J. Addict.* 16, 85–92.

Tsoh, J.Y., Chi, F.W., Mertens, J.R., Weisner, C.M., 2011. Stopping smoking during first year of substance use treatment predicted 9-year alcohol and drug treatment outcomes. *Drug Alcohol Depend* 114, 110–118.

Tucker, J.A., Foushee, H.R., Black, B.C., 2008. Behavioral economic analysis of natural resolution of drinking problems using IVR self-monitoring. *Exp. Clin. Psychopharmacol.* 16, 332–340.

Tuithof, M., ten Have, M., van den Brink, W., Vollebergh, W., de Graaf, R., 2014. Alcohol consumption and symptoms as predictors for relapse of DSM-5 alcohol use disorder. *Drug Alcohol Depend.* 140, 85–91.

Tuithof, M., ten Have, M., van den Brink, W., Vollebergh, W., de Graaf, R., 2013. Predicting persistency of DSM-5 alcohol use disorder and examining drinking patterns of recently remitted individuals: a prospective general population study. *Addiction* 108, 2091–2099.

Turkcapar, H., Kose, S., Ince, A., Myrick, H., 2005. Beliefs as a predictor of relapse in alcohol-dependent Turkish men. *J. Stud. Alcohol* 66, 848–851.

Tusa, A.L., Burgholzer, J.A., 2013. Came to Believe. *J. Addict. Nurs.* 24, 237–246.

Udo, T., Clifford, P.R., Davis, C.M., Maisto, S.A., 2009. Alcohol use post treatment initiation as a predictor of later functioning. *Am. J. Drug Alcohol Abuse* 35, 128–132.

Uhl, G.R., Koob, G.F., Cable, J., 2019. The neurobiology of addiction. *Ann. N.Y. Acad. Sci.* 1451(1), 5–28

Vaillant, G.E., 2003. A 60-year follow-up of alcoholic men. *Addiction* 98, 1043–1051.

Verheul, R., Lehert, P., Geerlings, P.J., Koeter, M.W.J., Van Den Brink, W., 2005. Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. *Psychopharmacology (Berl.)* 178, 167–173.

Vielva, I., Iraurgi, I., 2001. Cognitive and behavioural factors as predictors of abstinence following treatment for alcohol dependence. *Addiction* 96, 297–303.

Vito Agosti, M., 2013. Predictors of alcohol dependence relapse during recurrence of major depression. *J. Addict. Dis.* 32, 79–84.

Volkow, N.D., Koob, G.F., McLellan, A., 2016. Neurobiologic advances from the brain disease model of addiction. *N. Engl. J. Med.* 374, 363–371.

Wade, D.T., Halligan, P.W., 2017. The biopsychosocial model of illness: a model whose time has come. *Clin. Rehabil.* 31, 995–1004.

Wagner, T., Krampe, H., Stawicki, S., Reinhold, J., Jahn, H., Mahlke, K., Barth, U., Sieg, S., Maul, O., Galwas, C., Aust, C., Kröner-Herwig, B., Brunner, E., Poser, W., Henn, F., Rütger, E., Ehrenreich, H., 2004. Substantial decrease of psychiatric comorbidity in chronic alcoholics upon integrated outpatient treatment - results of a prospective study. *J. Psychiatr. Res.* 38, 619–635.

Waldrop, A.E., Back, S.E., Verduin, M.L., Brady, K.T., 2007. Triggers for cocaine and alcohol use in the presence and absence of posttraumatic stress disorder. *Addict. Behav.* 32, 634–639.

Walitzer, K.S., Dearing, R.L., 2006. Gender differences in alcohol and substance use relapse. *Clin. Psychol. Rev.* 26, 128–148.

Walter, M., Gerhard, U., Duersteler-MacFarland, K.M., Weijers, H.G., Boening, J., Wiesbeck, G.A., 2006a. Social factors but not stress-coping styles predict relapse in detoxified alcoholics. *Neuropsychobiology* 54, 100–106.

Walter, M., Gerhard, U., Gerlach, M., Weijers, H.G., Boening, J., Wiesbeck, G.A., 2006b. Cortisol concentrations, stress-coping styles after withdrawal and long-term abstinence in alcohol dependence. *Addict. Biol.* 11, 157–162.

Walton, M.A., Blow, F.C., Bingham, C.R., Chermack, S.T., 2003. Individual and social/ environmental predictors of alcohol and drug use 2 years following substance abuse treatment. *Addict. Behav.* 28, 627–642.

Walton, M.A., Blow, F.C., Booth, B.M., 2000. A comparison of substance abuse patients' and counselors' perceptions of relapse risk - Relationship to actual relapse. *J. Subst. Abuse Treat.* 19, 161–169.

Wang, J., Fan, Y., Dong, Y., Ma, M., Dong, Y., Niu, Y., Jiang, Y., Wang, H., Wang, Z., Wu, L., Sun, H., Cui, C., 2018. Combining gray matter volume in the cuneus and the cuneus-prefrontal connectivity may predict early relapse in abstinent alcohol-dependent patients. *PLoS One* 13, 1–18.

Weinberger, A.H., Platt, J., Goodwin, R.D., 2016. Is cannabis use associated with an increased risk of onset and persistence of alcohol use disorders? A three-year prospective study among adults in the United States. *Drug Alcohol Depend.* 161, 363–367.

Weinberger, A.H., Platt, J., Jiang, B., Goodwin, R.D., 2015. Cigarette smoking and risk of alcohol use relapse among adults in recovery from alcohol use disorders. *Alcohol Clin Exp Res.* 39, 1989–1996.

Weinland, C., Braun, B., Mühle, C., Kornhuber, J., Lenz, B., 2017. Cloninger type 2 score and lesch typology predict hospital readmission of female and male alcohol-dependent inpatients during a 24-month follow-up. *Alcohol. Clin. Exp. Res.* 41, 1760–1767

Weinland, C., Mühle, C., Kornhuber, J., Lenz, B., 2019. Body mass index and craving predict 24-month hospital readmissions of alcohol-dependent in-patients following withdrawal. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 90, 300–307.

White, W.L., Weingartner, R.M., Levine, M.W., Evans, A.C., Lamb, R., 2013. Recovery prevalence and health profile of people in recovery: results of a southeastern pennsylvania survey on the resolution of alcohol and other drug problems. *J. Psychoactive Drugs* 45, 287–296.

Wiers, C.E., Shumay, E., Volkow, N.D., Freling, H., Kotsiari, A., Lindenmeyer, J., Walter, H., Bermpohl, F., 2015. Effects of depressive symptoms and peripheral DAT methylation on neural reactivity to alcohol cues in alcoholism. *Transl. Psychiatry* 5, e648.

Wiesbeck, G.A., Weijers, H.-G., Wodarz, N., Herrmann, M.J., Johann, M., Keller, H.K., Michel, T.M., Böning, J., 2003. Dopamine D2 (DAD2) and dopamine D3 (DAD3) receptor gene polymorphisms and treatment outcome in alcohol dependence. *J. Neural Transm.* 110, 813–820.

Wigg, A.J., Mangira, D., Chen, J.W., Woodman, R.W., 2017. Outcomes and predictors of harmful relapse following liver transplantation for alcoholic liver disease in an Australian population. *Intern. Med. J.* 47, 656–663.

Wilens, T.E., Adler, L.A., Tanaka, Y., D'souza, D.N., Gutkin, S.W., Sherwood, A.C., Baker, L., Upadhyaya, H.P., 2011. Correlates of alcohol use in adults with ADHD and comorbid alcohol use disorders: exploratory analysis of a placebo- controlled trial of atomoxetine. *Curr. Med. Res. Opin.* 27, 2309–2320.

Willinger, U., Lenzinger, E., Hornik, K., Fischer, G., Schönbeck, G., Aschauer, H., Meszaros, K., 2002. Anxiety as a predictor of relapse in detoxified alcohol-dependent patients. *Alcohol Alcohol* 37, 609–612.

Witkiewitz, K., 2011. Predictors of heavy drinking during and following treatment. *Psychol. Addict. Behav.* 25, 426–438.

Witkiewitz, K., Marlatt, G.A., 2007. Modeling the complexity of post-treatment drinking: it's a rocky road to relapse. *Clin. Psychol. Rev.* 27, 724–738.

Witkiewitz, K., Marlatt, G.A., 2004. Relapse prevention for alcohol and drug problems: that was zen, this is tao. *Am. Psychol.* 59, 224–235.

Witkiewitz, K., Masyn, K.E., 2008. Drinking trajectories following an initial lapse. *Psychol. Addict. Behav.* 22, 157–167.

Witkiewitz, K., Villarroel, N.A., 2009. Dynamic association between negative affect and alcohol lapses following alcohol treatment. *J. Consult. Clin. Psychol.* 77, 633–644.

Witkiewitz, K., Vowles, K.E., McCallion, E., Frohe, T., Kirouac, M., Maisto, S.A., 2015. Pain as a predictor of heavy drinking and any drinking lapses in the COMBINE study and the UK alcohol treatment trial. *Addiction* 110, 1262–1271.

Witkiewitz, K., Wilson, A.D., Pearson, M.R., Hallgren, K.A., Falk, D.E., Litten, R.Z., Kranzler, H.R., Mann, K.F., Hasin, D.S., O'Malley, S.S., Anton, R.F., 2017. Temporal stability of heavy drinking days and drinking reductions among heavy drinkers in the COMBINE study. *Alcohol. Clin. Exp. Res.* 41, 1054–1062.

Witkiewitz, K., Wilson, A.D., Pearson, M.R., Montes, K.S., Kirouac, M., Roos, C.R., Hallgren, K.A., Maisto, S.A., 2019. Profiles of recovery from alcohol use disorder at three years following treatment: can the definition of recovery be extended to include

high functioning heavy drinkers? *Addiction* 114, 69–80.

Wojnar, M., Brower, K.J., Strobbe, S., Ilgen, M., Matsumoto, H., Nowosad, I., Sliwerska, E., Burmeister, M., 2009. Association between Val66Met brain-derived neurotrophic factor (BDNF) gene polymorphism and post-treatment relapse in alcohol dependence. *Alcohol. Clin. Exp. Res.* 33, 693–702.

Wojnar, M., Ilgen, M.A., Jakubczyk, A., Wnorowska, A., Klimkiewicz, A., Brower, K.J., 2008. Impulsive suicide attempts predict post-treatment relapse in alcohol-dependent patients. *Drug Alcohol Depend* 97, 268–275.

Wrase, J., Makris, N., Braus, D., Mann, K., Smolka, M., Kennedy, D., Caviness, V., Hodge, S., Tang, L., Albaugh, M., Ziegler, D., Davis, O., Kissling, C., Schumann, G., Breiter, H., Heinz, A., 2008. Amygdala volume associated with alcohol abuse relapse and craving. *Am. J. Psychiatry.* 165, 1179–1184.

Wu, G.R., Baeken, C., Van Schuerbeek, P., De Mey, J., Bi, M., Herremans, S.C., 2018. Accelerated repetitive transcranial magnetic stimulation does not influence grey matter volumes in regions related to alcohol relapse: an open-label exploratory study. *Drug Alcohol Depend* 191, 210–214.

Xie, H., Drake, R.E., McHugo, G.J., Xie, L., Mohandas, A., 2010. The 10-year course of remission, abstinence, and recovery in dual diagnosis. *J. Subst. Abuse Treat.* 39, 132–140.

Zahr, N., Carr, R., Rohlfing, T., Mayer, D., Sullivan, E., Colrain, I., Pfefferbaum, A., 2016. Brain metabolite levels in recently sober individuals with alcohol use disorder: relation to drinking variables and relapse. *Psychiatry Res.* 250, 42–49.

Zakiniacz, Y., Scheinost, D., Seo, D., Sinha, R., Constable, R.T., 2017. Cingulate cortex functional connectivity predicts future relapse in alcohol dependent individuals. *NeuroImage Clin.* 13, 181–187.

Zandberg, L., Rosenfield, D., McLean, C., Powers, M., Asnaani, A., Foa, E., 2016. Concurrent treatment of posttraumatic stress disorder and alcohol dependence: predictors and moderators of outcome. *J. Consult. Clin. Psychol.* 84, 43–56.

Zikos, E., Gill, K.J., Charney, D.A., 2010. Personality disorders among alcoholic outpatients: prevalence and course in treatment. *Can. J. Psychiatry* 55, 65–73.

Zois, E., Vollstädt-Klein, S., Hoffmann, S., Reinhard, I., Bach, P., Charlet, K., Beck, A., Treutlein, J., Frank, J., Jorde, A., Kirsch, M., Degenhardt, F., Walter, H., Heinz, A., Kiefer, F., 2016. GATA4 variant interaction with brain limbic structure and relapse risk: a voxel-based morphometry study. *Eur. Neuropsychopharmacol.* 26, 1431–1437.

Zois, E., Vollstädt-Klein, S., Hoffmann, S., Reinhard, I., Charlet, K., Beck, A., Jorde, A., Kirsch, M., Walter, H., Heinz, A., Kiefer, F., 2017. Orbitofrontal structural markers of negative affect in alcohol dependence and their associations with heavy relapse-risk at 6 months post-treatment. *Eur. Psychiatry* 46, 16–22.

Zou, Y., Murray, D.E., Durazzo, T.C., Schmidt, T.P., Murray, T.A., Meyerhoff, D.J., 2018. White matter microstructural correlates of relapse in alcohol dependence. *Psychiatry Res. - Neuroimaging* 281, 92–100.

Zywiak, W.H., Stout, R., Trefry, W., LaGrutta, J., Lawson, C., Khan, N., Swift, R., Schneider, R., 2003a. Alcohol relapses associated with September 11, 2001: a case report. *Subst. Abuse.* 24, 123–128.

Zywiak, W.H., Stout, R.L., Longabaugh, R., Dyck, I., Connors, G.J., Maisto, S.A., 2006a. Relapse-onset factors in Project MATCH: the Relapse Questionnaire. *J. Subst. Abuse Treat.* 31, 341–345.

Zywiak, W.H., Stout, R.L., Trefry, W.B., Glasser, I., Connors, G.J., Maisto, S.A., Westerberg, V.S., 2006b. Alcohol relapse repetition, gender, and predictive validity. *J. Subst. Abuse Treat.* 30, 349–353.

Zywiak, W.H., Westerberg, V.S., Connors, G.J., Maisto, S.A., 2003b. Exploratory findings from the Reasons for Drinking Questionnaire. *J. Subst. Abuse Treat.* 25, 287–292.

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 (McDonnell 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.

References Chapter 3

- Adler LA, Faraone SV, Spencer TJ et al. (2018) The structure of adult ADHD. *Int J Methods Psychiatr Res* 26:e1555.
- Alfonso JP, Caracuel A, Delgado-Pastor LC et al. (2011) Combined goal management training and mindfulness meditation improve executive functions and decision-making performance in abstinent polysubstance abusers. *Drug Alcohol Depend* 117:78–81.
- Ansell EB, Gu P, Tuit K et al. (2012) Effects of cumulative stress and impulsivity on smoking status. *Hum Psychopharmacol Clin Exp* 27:200–8.
- Babor TF, Hofmann M, DelBoca FK et al. (1992) Types of alcoholics, I: evidence for an empirically derived typology based on indicators of vulnerability and severity. *Arch Gen Psychiatry* 49:599–608.
- Bari A, Robbins TW (2013) Progress in neurobiology inhibition and impulsivity: behavioral and neural basis of response control. *Prog Neurobiol* 108:44–79.
- Barreno EM, Domínguez-Salas S, Díaz-Batanero C et al. (2019) Specific aspects of cognitive impulsivity are longitudinally associated with lower treatment retention and greater relapse in therapeutic community treatment. *J Subst Abuse Treat* 96:33–8.
- Bechara A, Damasio A, Damasio H et al. (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50:7–15.
- Bernhardt N, Nebe S, Poese S et al. (2017) Impulsive decision making in young adult social drinkers and detoxified alcohol-dependent patients: a cross-sectional and longitudinal study. *Alcohol Clin Exp Res* 41:1794–807.
- Boffo M, Zerhouni O, Gronau QF et al. (2019) Cognitive bias modification for behavior change in alcohol and smoking addiction: Bayesian metaanalysis of individual participant data. *Neuropsychol Rev* 29:52–78.
- Bowden-Jones H, McPhillips M, Rogers R et al. (2005) Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *J Neuropsychiatry Clin Neurosci* 17:417–20.
- Broos N, Schmaal L, Wiskerke J et al. (2012) The relationship between impulsive choice and impulsive action: a cross-species translational study. *PLoS One* 7:e36781.
- Casaleto KB, Moore DJ, Woods SP et al. (2016) Abbreviated goal management training shows preliminary evidence as a neurorehabilitation tool for HIV-associated neurocognitive disorders among substance users. *Clin Neuropsychol* 30:107–30.
- Charlet K, Schlagenhauf F, Richter A et al. (2013) Neural activation during processing of aversive faces predicts treatment outcome in alcoholism. *Addict Biol* 19:439–51.
- Claus ED, Kiehl KA, Hutchison KE (2011) Neural and behavioral mechanisms of impulsive choice in alcohol use disorder. *Alcohol Clin Exp Res* 35:1209–19.
- Cloninger CR (1994) Temperament and personality. *Curr Opin Neurobiol* 4:266–73.
- Cloninger CR, Bohman M, Sigvardsson S (1981) Inheritance of alcohol abuse: cross-fostering analysis of adopted men. *Arch Gen Psychiatry* 38:861–8.
- Coates JM, Gullo MJ, Feeney GFX et al. (2020) Craving mediates the effect of impulsivity on lapse-risk during alcohol use disorder treatment. *Addict Behav* 105:106286.
- Courtney KE, Arellano R, Barkley-Levenson E et al. (2012) The relationship between measures of impulsivity and alcohol misuse: an integrative structural equation modeling approach. *Alcohol Clin Exp Res* 36:923–31.
- Czapla M, Simon JJ, Richter B et al. (2016) The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: implications for psychotherapeutic treatment. *Addict Biol* 21:873–84.
- Davis DR, Kurti AN, Skelly JM et al. (2016) A review of the literature on contingency management in the treatment of substance use disorders, 2009–2014. *Prev Med (Baltim)* 92:36–46.
- Dom G, De Wilde B, Hulstijn W et al. (2007) Dimensions of impulsive behaviour in abstinent alcoholics. *Personal Individ Differ* 42:465–76.

Dougherty DM, Bjork JM, Harper RA et al. (2003) Behavioral impulsivity paradigms: a comparison in hospitalized adolescents with disruptive behavior disorders. *J Child Psychol Psychiatry Allied Discip* 44:1145–57.

Dougherty DM, Mathias CW, Marsh DM et al. (2005) Laboratory behavioral measures of impulsivity. *Behav Res Methods* 37:82–90.

Evren C, Durkaya M, Evren B et al. (2012) Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. *Drug Alcohol Rev* 31:81–90.

Eysenck SBG, Eysenck HJ (1977) The place of impulsiveness in a dimensional system of personality description. *Br J Soc Clin Psychol* 16:57–68.

Fein G, Klein L, Finn P (2004) Impairment on a simulated gambling task in long-term abstinent alcoholics. *Alcohol Clin Exp Res* 28:1487–91.

Foulds J, Newton-Howes G, Guy NH et al. (2017) Dimensional personality traits and alcohol treatment outcome: a systematic review and metaanalysis. *Addiction* 112:1345–57.

Galandra C, Basso G, Cappa S et al. (2018) The alcoholic brain: neural bases of impaired reward-based decision-making in alcohol use disorders. *Neurol Sci* 39:423–35.

Gottesmann I, Gould T (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 160:636–45.

Grant BF, Chou SP, Saha TD et al. (2017) Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiat* 74:911–23.

Hamilton KR, Ansell EB, Reynolds B et al. (2013) Self-reported impulsivity, but not behavioral choice or response impulsivity, partially mediates the effect of stress on drinking behavior. *Stress* 16:3–15.

Hamilton KR, Mitchell MR, Wing VC et al. (2015) Choice impulsivity: definitions, measurement issues, and clinical implications. *Personal Disord Theory Res Treat* 6:182–98.

Herman AM, Critchley HD, Duka T (2018) The role of emotions and physiological arousal in modulating impulsive behaviour. *Biol Psychol* 133:30–43.

Ibrahim C, Rubin-Kahana DS, Pushparaj A et al. (2019) The insula: a brain stimulation target for the treatment of addiction. *Front Pharmacol* 10:1–18.

Ioannidis K, Hook R, Wickham K et al. (2019) Impulsivity in gambling disorder and problem gambling: a meta-analysis. *Neuropsychopharmacology* 44:1354–1361.

Jakubczyk A, Klimkiewicz A, Kopera M et al. (2013) The CC genotype in the T102C HTR2A polymorphism predicts relapse in individuals after alcohol treatment. *J Psychiatr Res* 47:527–33.

Jentsch J, Ashenhurst J, Cervantes M et al. (2015) Dissecting impulsivity and its relationships to drug addictions. *Ann N Y Acad Sci* 1327:1–26.

Jentsch JD, Taylor JR (1999) Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* 146:373–90.

Joos L, Goudriaan AE, Schmaal L et al. (2012a) The relationship between impulsivity and craving in alcohol dependent patients. *Psychopharmacology* 226:273–83.

Joos L, Sabbe BGC, Dom G et al. (2012b) Effect of modafinil on impulsivity and relapse in alcohol dependent patients: a randomized, placebo-controlled trial. *Eur Neuropsychopharmacol* 23:948–55.

King KM, Patock-Peckham JA, Dager AD et al. (2014) On the mismeasurement of impulsivity: trait, behavioral, and neural models in alcohol research among adolescents and young adults. *Curr Addict Rep* 1:19–32.

Konstenius M, Jayaram-Lindström N, Guterstam J et al. (2014) Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. *Addiction* 109:440–9.

Koob GF, Volkow ND. (2016) Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3:760–73.

Kozak K, Lucatch AM, Lowe DJE et al. (2018) The neurobiology of impulsivity and substance use disorders: Implications for treatment. *Ann N Y Acad Sci* 1451:71–91.

Kovács I, Richman MJ, Janka Z et al. (2017) Decision making measured by the Iowa Gambling Task in alcohol use disorder and gambling disorder: a systematic review and meta-analysis. *Drug Alcohol Depend* 181:152–61.

Kwako LE, Schwandt ML, Ramchandani VA et al. (2019) Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *Am J Psychiatry* 176:744–53.

Leggio L, Kenna GA, Fenton M et al. (2009) Typologies of alcohol dependence. From Jellinek to genetics and beyond. *Neuropsychol Rev* 19:115–29.

Van Leijenhorst L, Moor BG, Op de Macks ZA et al. (2010) Adolescent risky decision-making: neurocognitive development of reward and control regions. *Neuroimage* 51:345–55.

Leung D, Staiger PK, Hayden M et al. (2017) Meta-analysis of the relationship between impulsivity and substance-related cognitive biases. *Drug Alcohol Depend* 172:21–33.

Levine B, Schweizer TA, O'Connor C et al. (2011) Rehabilitation of executive functioning in patients with frontal lobe brain damage with goal management training. *Front Hum Neurosci* 5:1–9.

Linhartová P, Širůček J, Ejova A, Barteček R, Theiner P, Kašpárek T. Dimensions of Impulsivity in Healthy People, Patients with Borderline Personality Disorder, and Patients with Attention-Deficit/Hyperactivity Disorder. *J Atten Disord*. 2021 Feb;25(4):584-595.

Litten RZ, Ryan ML, Falk DE et al. (2015) Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. *Alcohol Clin Exp Res* 39:579–84.

Littlefield AK, Sher KJ (2010) The multiple, distinct ways that personality contributes to alcohol use disorders. *Soc Personal Psychol Compass* 4:767–82.

Littlefield AK, Sher KJ, Wood PK (2009) Is 'maturing out' of problematic alcohol involvement related to personality change? *J Abnorm Psychol* 118:360–74.

Liu RT, Trout ZM, Hernandez EM et al. (2017) A behavioral and cognitive neuroscience perspective on impulsivity, suicide, and non-suicidal self-harm: meta-analysis and recommendations for future research. *Neurosci Biobehav Rev* 83:440–50.

Maisto SA, Roos CR, Hallgren KA et al. (2016) Do alcohol relapse episodes during treatment predict long-term outcomes? Investigating the validity of existing definitions of alcohol use disorder relapse. *Alcohol Clin Exp Res* 40:2180–9.

Maraz A, Andó B, Rigó P et al. (2016) The two-faceted nature of impulsivity in patients with borderline personality disorder and substance use disorder. *Drug Alcohol Depend* 163:48–54.

Matheus-Roth C, Schenk I, Wiltfang J et al. (2016) Occipital event-related potentials to addiction-related stimuli in detoxified patients with alcohol dependence, and their association with three-month relapse. *BMC Psychiatry* 16:1–12.

Mayhew MJ, Powell JH (2014) The development of a brief self-report questionnaire to measure 'recent' rash impulsivity: a preliminary investigation of its validity and association with recent alcohol consumption. *Addict Behav* 39:1597–605.

McCarthy D, Bold K, Minami H et al. (2016) Reliability and validity of measures of impulsive choice and impulsive action in smokers trying to quit. *Exp Clin Psychopharmacol* 24:120–30.

McDonnell MG, Skalisky J, Leickly E et al. (2017) Pilot investigation of a phosphatidylethanol-based contingency management intervention targeting alcohol use. *Psychol Addict Behav* 31:608–13.

McHugh RK, Goodman FR (2019) Are substance use disorders emotional disorders? Why heterogeneity matters for treatment. *Clin Psychol Sci Pract* 26:1–4.

McKay JR, Franklin TR, Patapis N, & Lynch KG. (2006) Conceptual, methodological, and analytical issues in the study of relapse. *Clin Psychol Rev* 26:109–27.

McKay JR, Hiller-Sturmhofel S (2011) Treating alcoholism as a chronic disease. *Alcohol Res Health* 33:356–70.

Meda SA, Stevens MC, Potenza MN et al. (2009) Investigating the behavioral and self-report constructs of impulsivity domains using principal component analysis. *Behav Pharmacol* 20:390–9.

Miller WR (1996) What is a relapse? Fifty ways to leave the wagon. *Addiction* 91 Suppl:S15–S27.

Moallem N, Ray LA (2012) Quetiapine improves response inhibition in alcohol dependent patients: a placebo-controlled pilot study. *Pharmacol Biochem Behav* 100:490–3.

Moeller FG, Barratt ES, Dougherty DM et al. (2001) Psychiatric aspects of impulsivity. *Am J Psychiatry* 158:1783–93.

Moher D, Liberati A, Tetzlaff J et al. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6:e1000097.

Moos RH, Moos BS (2003) Risk factors for nonremission among initially untreated individuals with alcohol use disorders. *J Stud Alcohol* 64:555–63.

Mutschler J, Grosshans M, Koopmann A et al. (2010) Supervised disulfiram in relapse prevention in alcohol-dependent patients suffering from comorbid borderline personality disorder—a case series. *Alcohol Alcohol* 45:146–50.

Nestor LJ, Paterson LM, Murphy A et al. (2018) Naltrexone differentially modulates the neural correlates of motor impulse control in abstinent alcohol-dependent and polysubstance-dependent individuals. *Eur J Neurosci* 50:2311–21.

Noel X, Brevers D, Bechara A (2014) A neurocognitive approach to understanding the neurobiology of addiction. *Curr Opin Neurobiol* 23:632–8.

Noël X, Brevers D, Bechara A (2013) A triadic neurocognitive approach to addiction for clinical interventions. *Front Psych* 4:1–14.

Ooms M, Roozen HG, Willering JH, Zijlstra WP, de Waart R, Goudriaan AE. Effects of Multiple Detoxifications on Withdrawal Symptoms, Psychiatric Distress and Alcohol-Craving in Patients with an Alcohol Use Disorder. *Behav Med*. 2021 Jul-Sep;47(4):296-310.

Papachristou H, Nederkoorn C, Giesen JCAH et al. (2014) Cue reactivity during treatment, and not impulsivity, predicts an initial lapse after treatment in alcohol use disorders. *Addict Behav* 39:737–9.

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* 51:768–74.

Petzold J, Kienast A, Lee Y et al. (2019) Baseline impulsivity may moderate L-DOPA effects on value-based decision-making. *Sci Rep* 9:5652.

Portugal AC, Afonso AS Jr, Caldas AC et al. (2018) Inhibitory mechanisms involved in Stroop-matching and stop-signal tasks and the role of impulsivity. *Acta Psychol (Amst)* 191:234–43.

Quoilin C, Wilhelm E, Maurage P et al. (2018) Deficient inhibition in alcohol dependence: let's consider the role of the motor system! *Neuropsychopharmacology* 43:1851–1858.

Ray LA, Grodin EN, Leggio L et al. (2021) The future of translational research on alcohol use disorder. *Addict Biol* 26(2):e12903.

Rehm J, Anderson P, Barry J et al. (2015) Prevalence of and potential influencing factors for alcohol dependence in Europe. *Eur Addict Res* 21: 6–18.

Reyes-Huerta HE, dos Santos C, Martínez K (2018) Impulsive mechanisms influencing relapse in alcohol drinking. *Med Hypotheses* 112:27–9.

Reynolds B, Ortengren A, Richards JB et al. (2006) Dimensions of impulsive behavior: personality and behavioral measures. *Personal Individ Differ* 40:305–15.

Rubio G, Marín M, Arias F et al. (2018) Inclusion of alcoholic associations into a public treatment programme for alcoholism improves outcomes during the treatment and continuing care period: a 6-year experience. *Alcohol Alcohol* 53:78–88.

Rubio G, Martínez-Gras I, Manzanares J (2009) Modulation of impulsivity by topiramate. *J Clin Psychopharmacol* 29:584–9.

Rupp CI, Beck JK, Heinz A et al. (2016) Impulsivity and alcohol dependence treatment completion: is there a neurocognitive risk factor at treatment entry? *Alcohol Clin Exp Res* 40:152–60.

Salvatore JE, Gottesman II, Dick DM (2015) Endophenotypes for alcohol use disorder: an update on the field. *Curr Addict Rep* 2:76–90.

Sanchez-Roige S, Fontanillas P, Elson SL, Gray JC, de Wit H, MacKillop J, & Palmer AA. (2019) Genome-wide association studies of impulsive personality traits (BIS-11 and UPPSP) and drug experimentation in up to 22,861 adult research participants identify loci in the CACNA1I and CADM2 genes. *J Neurosci* 39:2562–72.

Sawilowsky SS (2009) New effect size rules of thumb. *J Mod Appl Stat Methods* 8:597–9.

Schmaal L, Goudriaan AE, Joos L et al. (2014) Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients. *Psychol Med* 44:2787–98.

Skoglund C, Brandt L, D'Onofrio B et al. (2017) Methylphenidate doses in attention deficit/hyperactivity disorder and comorbid substance use disorders. *Eur Neuropsychopharmacol* 27:1144–52.

Sliedrecht W, de Waart R, Witkiewitz K et al. (2019) Alcohol use disorder relapse factors: a systematic review. *Psychiatry Res* 278:97–115.

Stevens L, Goudriaan AE, Verdejo-Garcia A et al. (2015) Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychol Med* 45:2083–93.

Stevens L, Verdejo-García A, Goudriaan AE et al. (2014) Impulsivity as a vulnerability factor for poor addiction treatment outcomes: a review of neurocognitive findings among individuals with substance use disorders. *J Subst Abuse Treat* 47:58–72.

Tomko RL, Bountress KE, Gray KM (2016) Personalizing substance use treatment based on pre-treatment impulsivity and sensation seeking: a review. *Drug Alcohol Depend* 167:1–7.

Tucker JA, Cheong JW, Chandler SD et al. (2016) Prospective analysis of behavioral economic predictors of stable moderation drinking among problem drinkers attempting natural recovery. *Alcohol Clin Exp Res* 40:2676–84.

Uhl GR, Koob GF, Cable J (2019) The neurobiology of addiction. *Ann N Y Acad Sci* 1451:5–28.

Valls-Serrano C, Caracuel A, Verdejo-García A (2016) Goal management training and mindfulness meditation improve executive functions and transfer to ecological tasks of daily life in polysubstance users enrolled in therapeutic community treatment. *Drug Alcohol Depend* 165:9–14.

Vassileva J, Conrod PJ (2019) Impulsivities and addictions: a multidimensional integrative framework informing assessment and interventions for substance use disorders. *Philos Trans R Soc B Biol Sci* 374:20180137.

Verdejo-García A, García-Fernández G, Dom G (2019) Cognition and addiction. *Dialogues Clin Neurosci* 21:281–90.

Wang J, Fan Y, Dong Y et al. (2018) Combining gray matter volume in the cuneus and the cuneus-prefrontal connectivity may predict early relapse in abstinent alcohol-dependent patients. *PLoS One* 13:1–18.

Weafer J, Baggott MJ, De Wit H (2013) Test-retest reliability of behavioral measures of impulsive choice, impulsive action, and inattention. *Exp Clin Psychopharmacol* 21:475–81.

Westman JG, Bujarski S, Ray LA (2017) Impulsivity moderates subjective responses to alcohol in alcohol-dependent individuals. *Alcohol Alcohol* 52:249–55.

De Wilde B, Verdejo-García A, Sabbe B et al. (2013) Affective decisionmaking is predictive of three-month relapse in polysubstance-dependent alcoholics. *Eur Addict Res* 19:21–8.

De Wit H (2009) Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addict Biol* 14:22–31.

Witkiewitz K, Litten RZ, Leggio L (2019) Advances in the science and treatment of alcohol use disorder. *Sci Adv* 5:eaax4043.

Yücel M, Oldenhof E, Ahmed SH et al. (2019) A transdiagnostic dimensional approach towards a neuropsychological assessment for addiction: an international Delphi consensus study. *Addiction* 114:1095–109.

Zorrilla EP, Koob GF (2019) Impulsivity derived from the dark side: neurocircuits that contribute to negative urgency. *Front Behav Neurosci* 13:1–15.

Zuckerman M, Michael Kuhlman D, Thornquist M et al. (1991) Five (or three) robust questionnaire scale factors of personality without culture. *Personal Individ Differ* 12:929–41.

Zuckerman M, Neeb M (1979) Sensation seeking and psychopathology. *Psychiatry Res* 1:255–64.

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 assess 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 | 7,37 | 7,18 | 8.24 | 6.08 | 8.25 | 6.80 ** | 8.47 | 5.00 | 8.90 | 6.06 |
| Craving | (6,66) | (6,60) | (7.39) | (5.61) | (7.28) | (6.75) | (7.27) | (4.69) | (8.34) | (5.03) |
| <i>(Mean/SD)</i> | | | | | | | | | | |
| baseline | 22,90 | 22,57 | 22.95 | 22.78 | 25.00 | 21.74 | 23.41 | 21.16 | 23.00 | 22.29 |
| Presence of MiL | (7,82) | (8,07) | (7.29) | (8.62) | (6.45) | (9.03) | (7.27) | (9.29) | (8.22) | (8.08) |
| <i>(Mean/SD)</i> | | | | | | | | | | |
| baseline | 8,42 | 8,39 | 9.62 | 6.39 | 9.71 | 7.80 | 9.72 | 6.16 | 8.80 | 8.13 |
| Substance dependence | (7,64) | (7,42) | (7.67) | (6.70) | (7.95) | (6.68) | (7.26) | (6.94) | (5.93) | (8.12) |
| <i>(Mean/SD)</i> | | | | | | | | | | |
| 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 | 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) |
| Substance dependence | | N/A | | | | | | | | |

*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*

| | <i>B</i> | <i>SE</i> | <i>Z</i> | <i>p</i> -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

- Aftab, A., Lee, E. E., Klaus, F., Daly, R., Wu, T. C., Tu, X., Huege, S., & Jeste, D. V. (2019). Meaning in life and its relationship with physical, mental, and cognitive functioning: A study of 1,042 community-dwelling adults across the lifespan. *Journal of Clinical Psychiatry*, *81*(1), 1–18.
- Casey, M., Adamson, G., Shevlin, M., & McKinney, A. (2012). The role of craving in AUDs: Dimensionality and Differential Functioning in the DSM-5. *Drug and Alcohol Dependence*, *125*(1–2), 75–80.
- Cavicchioli, M., Vassena, G., Movalli, M., & Maffei, C. (2020). Is craving a risk factor for substance use among treatment-seeking individuals with alcohol and other drugs use disorders? A meta-analytic review. *Drug and Alcohol Dependence*, *212*(1 July), 108002.
- Cherrier, M. M., Shireman, L. M., Wicklander, K., Yeung, W., Kooner, P., Saxon, A. J., Simpson, T., Terman, G., & Shen, D. (2020). Relationship of Phosphatidylethanol Biomarker to Self-Reported Alcohol Drinking Patterns in Older and Middle-Age Adults. *Alcoholism: Clinical and Experimental Research*, *44*(12), 2449–2456.
- Chika Chukwuorji, J. B., Ekpedoho, E. A., Ifeagwazi, C. M., Iorfa, S. K., & Nwonyi, S. K. (2019). Psychometric properties of the Meaning in Life Questionnaire – Hausa version among internally displaced persons in Nigeria. *Transcultural Psychiatry*, *56*(1), 103–122.
- Cohen, E., Feinn, R., Arias, A., & Kranzler, H. R. (2007). Alcohol treatment utilization: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence*, *86*(2–3), 214–221.
- Connors, G. J., Maisto, S. A., & Donovan, D. M. (1996). Conceptualizations of relapse: A summary of psychological and psychobiological models. *Addiction*, *91*(SUPPL.), S5-13.
- Copeland, A., Jones, A., & Field, M. (2020). The association between meaning in life and harmful drinking is mediated by individual differences in self-control and alcohol value. *Addictive Behaviors Reports*, *11*(January), 100258.
- Costanza, A., Baertschi, M., Richard-Lepouriel, H., Weber, K., Pompili, M., & Canuto, A. (2020). The presence and the search constructs of meaning in life in suicidal patients attending a psychiatric emergency department. *Frontiers in Psychiatry*, *11*(April), 1–7.
- Cranford, J. A., Krentzman, A. R., Mowbray, O., & Robinson, E. A. R. (2014). Trajectories of alcohol use over time among adults with alcohol dependence. *Addictive Behaviors*, *39*(5), 1006–1011.
- Csabonyi, M., & Phillips, L. J. (2020). Meaning in Life and Substance Use. *Journal of Humanistic Psychology*, *60*(1), 3–19.
- Cutler, R. B., & Fishbain, D. A. (2005). Are alcoholism treatments effective? The Project MATCH data. *BMC Public Health*, *5*, 1–11.
- Czekierda, K., Banik, A., Park, C. L., & Luszczynska, A. (2017). Meaning in life and physical health: systematic review and meta-analysis. *Health Psychology Review*, *11*(4), 387–418.
- Demirbas, H., Ilhan, I. O., & Dogan, Y. B. (2012). Ways of problem solving as predictors of relapse in alcohol dependent male inpatients. *Addictive Behaviors*, *37*(1), 131–134.
- Donoghue, K. (2021). The correlates and extent of prescribing of medications for alcohol relapse prevention in England. *Addiction*, *116*(11), 3019–3026.
- Donoghue, K., Elzerbi, C., Saunders, R., Whittington, C., Pilling, S., & Drummond, C. (2015). The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: A meta-analysis. *Addiction*, *110*(6), 920–930.
- Donovan, D., & Witkiewitz, K. (2012). Relapse prevention: From radical idea to common practice. *Addiction Research and Theory*, *20*(3), 204–217.
- Evren, C., Durkaya, M., Evren, B., Dalbudak, E., & Cetin, R. (2012). Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. *Drug and Alcohol Review*, *31*(1), 81–90.
- Fan, A. Z., Chou, S. P., Zhang, H., Jung, J., & Grant, B. F. (2019). Prevalence and Correlates of Past-Year Recovery From DSM-5 Alcohol Use Disorder: Results From National Epidemiologic Survey on Alcohol and Related Conditions-III. *Alcoholism: Clinical and Experimental Research*, *43*(11), 2406–2420.
- Flannery, B. A., Poole, S. A., Gallop, R. J., & Volpicelli, J. R. (2003). Alcohol craving predicts drinking during treatment: An analysis of three assessment instruments. *Journal of Studies on Alcohol*, *64*(1), 120–126.
- Flannery, B. A., Volpicelli, J. R., & Pettinati, H. M. (1999). Psychometric properties of the Penn Alcohol Craving Scale. *Alcoholism: Clinical and Experimental Research*, *23*(8), 1289–1295.

- Flaudias, V., Heeren, A., Brousse, G., & Maurage, P. (2019). Toward a Triadic Approach to Craving in Addictive Disorders: The Metacognitive Hub Model. *Harvard Review of Psychiatry*, 27(5), 326–331.
- George, L. S., & Park, C. L. (2016). Meaning in life as comprehension, purpose, and mattering: Toward integration and new research questions. *Review of General Psychology*, 20(3), 205–220.
- Grant, B. F., Chou, S. P., Saha, T. D., Pickering, R. P., Kerridge, B. T., Ruan, W. J., Huang, B., Jung, J., Zhang, H., Fan, A., & Hasin, D. S. (2017). Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*, 74(9), 911–923.
- Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., Pickering, R. P., Ruan, W. J., Smith, S. M., Huang, B., & Hasin, D. S. (2015). Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry*, 72(8), 757–766.
- Griswold, M. G., Fullman, N., Hawley, C., Arian, N., Zimsen, S. R. M., Tymeson, H. D., Venkateswaran, V., Tapp, A. D., Forouzanfar, M. H., Salama, J. S., Abate, K. H., Abate, D., Abay, S. M., Abbafati, C., Abdulkader, R. S., Abebe, Z., Aboyans, V., Abrar, M. M., Acharya, P., ... Gakidou, E. (2018). Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, 392(10152), 1015–1035.
- Hallford, D. J., Mellor, D., Cummins, R. A., & McCabe, M. P. (2018). Meaning in Life in earlier and later older-adulthood: Confirmatory factor analysis and correlates of the meaning in life questionnaire. *Journal of Applied Gerontology*, 37(10), 1270–1294.
- Hartwell, E. E., Bujarski, S., Green, R. J., & Ray, L. A. (2019). Convergence between the Penn Alcohol Craving Scale and diagnostic interview for the assessment of alcohol craving. *Addictive Behaviors Reports*, 10(June), 100198.
- Hartwell, E. E., & Ray, L. A. (2018). Craving as a DSM-5 symptom of alcohol use disorder in non-treatment seekers. *Alcohol and Alcoholism*, 53(3), 235–240.
- Hasin, D., O'Brien, C., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W., Crowley, T., Ling, W., Petry, N., Schuckit, M., & Grant, B. (2013). DSM-5 Criteria for Substance Use Disorders: Recommendations and Rationale. *American Journal of Physical Medicine & Rehabilitation*, 170(8), 834–851.
- Heather, N., Copello, A., Godfrey, C., Hodgson, R., Orford, J., Raistrick, D., Russell, I., Tober, G., Slegg, G. P., & Morton, V. (2008). UK Alcohol Treatment Trial: Client-treatment matching effects. *Addiction*, 103(2), 228–238.
- Hendershot, C. S., Witkiewitz, K., George, W. H., & Marlatt, G. A. (2011). Relapse prevention for addictive behaviors. *Substance Abuse Treatment, Prevention, and Policy*, 6, 17.
- Huebner, R. B., & Kantor, L. W. (2010). Advances in alcoholism treatment. *Alcohol Research and Health*, 33(4), 295–299.
- Kavanagh, D. J., Andrade, J., & May, J. (2005). Imaginary relish and exquisite torture: The elaborated intrusion theory of desire. *Psychological Review*, 112, 446–467.
- Kavanagh, D. J., Statham, D. J., Feeney, G. F. X., Young, R. M. D., May, J., Andrade, J., & Connor, J. P. (2013). Measurement of alcohol craving. *Addictive Behaviors*, 38(2), 1572–1584.
- King, L. A., & Hicks, J. A. (2021). The Science of Meaning in Life. *Annual Review of Psychology*, 72, 561–584.
- Larimer, M. E., Palmer, R. S., & Marlatt, G. A. (1999). Relapse prevention: An overview of Marlatt's Cognitive-Behavioral Model. *Alcohol Research & Health*, 23(2), 151–160.
- Leamy, M., Bird, V., Le Boutillier, C., Williams, J., & Slade, M. (2011). Conceptual framework for personal recovery in mental health: Systematic review and narrative synthesis. *British Journal of Psychiatry*, 199(6), 445–452.
- Leong, C., Bolton, J. M., Ekuma, O., Prior, H. J., Singal, D., Nepon, J., Konrad, G., Paillé, M., Finlayson, G., & Nickel, N. (2022). Association of alcohol use disorder on alcohol-related cancers, diabetes, ischemic heart disease and death: a population-based, matched cohort study. *Addiction*, 117(2), 368–381.
- Lyons, G. C. B., Deane, F. P., & Kelly, P. J. (2010). Forgiveness and purpose in life as spiritual mechanisms of recovery from substance use disorders. *Addiction Research and Theory*, 18(5), 528–543.
- Maisto, S. A., Witkiewitz, K., Moskal, D., & Wilson, A. (2016). Is the Construct of Relapse Heuristic, and Does It Advance Alcohol Use Disorder Clinical Practice? *Journal of Studies on Alcohol and Drugs*, 77(6), 849–858.

- Mann, K., Roos, C. R., Hoffmann, S., Nakovics, H., Leménager, T., Heinz, A., & Witkiewitz, K. (2018). Precision Medicine in Alcohol Dependence: A Controlled Trial Testing Pharmacotherapy Response among Reward and Relief Drinking Phenotypes. *Neuropsychopharmacology*, 43(4), 891–899.
- Marsden, J., Darke, S., Hall, W., Hickman, M., Holmes, J., Humphreys, K., Neale, J., Tucker, J., & West, R. (2020). Mitigating and learning from the impact of COVID-19 infection on addictive disorders. *Addiction*, 115(6), 1007–1010.
- Martela, F., & Steger, M. F. (2016). The three meanings of meaning in life: Distinguishing coherence, purpose, and significance. *Journal of Positive Psychology*, 11(5), 531–545.
- McKay, J. R., Franklin, T. R., Patapis, N., & Lynch, K. G. (2006). Conceptual, methodological, and analytical issues in the study of relapse. In *Clinical Psychology Review* (Vol. 26, Issue 2, pp. 109–127).
- McKay, J. R., & Hiller-Sturmhofel, S. (2011). Treating Alcoholism As a Chronic Disease. *Alcohol Research & Health*, 33(4), 356–370.
- Miller, W. R. (1996). What is a relapse? Fifty ways to leave the wagon. *Addiction*, 91(SUPPL.).
- Morgenstern, J., Kuerbis, A., & Muench, F. (2014). Ecological momentary assessment and alcohol use disorder treatment. *Alcohol Research: Current Reviews*, 36(1), 101–110.
- Naghiyae, M., Bahmani, B., & Asgari, A. (2020). The Psychometric Properties of the Meaning in Life Questionnaire (MLQ) in Patients with Life-Threatening Illnesses. *Scientific World Journal*.
- Ostafin, B. D., & Feyel, N. (2019). The effects of a brief meaning in life intervention on the incentive salience of alcohol. *Addictive Behaviors*, 90(October), 107–111.
- Park, C. L. (2010). Making Sense of the Meaning Literature: An Integrative Review of Meaning Making and Its Effects on Adjustment to Stressful Life Events. *Psychological Bulletin*, 136(2), 257–301.
- Park, C. L., & Folkman, S. (1997). Meaning in the context of stress and coping. *Review of General Psychology*, 1(2), 115–144.
- Pulopulos, M. M., & Kozusznik, M. W. (2018). The moderating role of meaning in life in the relationship between perceived stress and diurnal cortisol. *Stress*, 21(3), 203–210.
- Raistrick, D., Bradshaw, J., Tober, G., Weiner, J., Allison, J., & Healey, C. (1994). Development of the Leeds Dependence Questionnaire (LDQ): a questionnaire to measure alcohol and opiate dependence in the context of a treatment evaluation package. *Addiction*, 89(5), 563–572.
- Ray, L. A., Bujarski, S., Grodin, E., Hartwell, E., Green, R. J., Venegas, A., Lim, A. C., Gillis, A., & Miotto, K. (2019). State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. *American Journal of Drug and Alcohol Abuse*, 45(2), 124–140.
- Rehm, J., Anderson, P., Barry, J., Dimitrov, P., Elekes, Z., Feijão, F., Frick, U., Gual, A., Gmel, G., Kraus, L., Marmet, S., Raninen, J., Rehm, M. X., Scafato, E., Shield, K. D., Trapencieris, M., & Gmel, G. (2015). Prevalence of and potential influencing factors for alcohol dependence in europe. *European Addiction Research*, 21(1), 6–18.
- Rehm, J., Gmel, G. E., Gmel, G., Hasan, O. S. M., Imtiaz, S., Popova, S., Probst, C., Roerecke, M., Room, R., Samokhvalov, A. V., Shield, K. D., & Shuper, P. A. (2017). The relationship between different dimensions of alcohol use and the burden of disease—an update. *Addiction*, 112(6), 968–1001.
- Robinson, S. M., & Adinoff, B. (2016). The classification of substance use disorders: Historical, contextual, and conceptual considerations. *Behavioral Sciences*, 6(3).
- Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*, 18(3), 247–291.
- Robinson, T. E., & Berridge, K. C. (2008). The incentive sensitization theory of addiction: Some current issues. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1507), 3137–3146.
- Roos, C., Kirouac, M., Pearson, M., Fink, B., & Witkiewitz, K. (2015). Examining temptation to drink from an existential perspective: Associations among temptation, purpose in life, and drinking outcomes. *Psychology of Addictive Behaviors*, 29(3), 716–724.
- Rose, L. M., Zask, A., & Burton, L. J. (2017). Psychometric properties of the Meaning in Life Questionnaire (MLQ) in a sample of Australian adolescents. *International Journal of Adolescence and Youth*, 22(1), 68–77.
- Rosenberg, H. (2009). Clinical and laboratory assessment of the subjective experience of drug craving. *Clinical Psychology Review*, 29(6), 519–534.

Rubio, G., Marín, M., Arias, F., López-Trabada, J. R., Iribarren, M., Alfonso, S., Prieto, R., Blanco, A., Urosa, B., Montes, V., Jurado, R., Jiménez-Arriero, M. Ángel, & de Fonseca, F. R. (2018). Inclusion of alcoholic associations into a public treatment programme for alcoholism improves outcomes during the treatment and continuing care period: A 6-year experience. *Alcohol and Alcoholism*, 53(1), 78–88.

Sallie, S. N., Ritou, V., Bowden-Jones, H., & Voon, V. (2020). Assessing international alcohol consumption patterns during isolation from the COVID-19 pandemic using an online survey: Highlighting negative emotionality mechanisms. *BMJ Open*, 10(11), 1–10.

Salsman, J. M., Schalet, B. D., Park, C. L., George, L., Steger, M. F., Hahn, E. A., Snyder, M. A., & Cella, D. (2020). Assessing meaning & purpose in life: development and validation of an item bank and short forms for the NIH PROMIS®. *Quality of Life Research*, 29(8), 2299–2310.

Saunders, J. B., Degenhardt, L., Reed, G. M., & Poznyak, V. (2019). Alcohol Use Disorders in ICD-11: Past, Present, and Future. *Alcoholism: Clinical and Experimental Research*, 43(8), 1617–1631.

Schippers, G. M., Broekman, T. G., Buchholz, A., Koeter, M. W. J., & Van Den Brink, W. (2010). Measurements in the Addictions for Triage and Evaluation (MATE): An instrument based on the World Health Organization family of international classifications. *Addiction*, 105(5), 862–871.

Schneekloth, T. D., Biernacka, J. M., Hall-Flavin, D. K., Karpyak, V. M., Frye, M. A., Loukianova, L. L., Stevens, S. R., Drews, M. S., Geske, J. R., & Mrazek, D. A. (2012). Alcohol Craving as a Predictor of Relapse. *American Journal on Addictions*, 21, S20–S26.

Schulenberg, S. E., Strack, K. M., & Buchanan, E. M. (2011). The meaning in life questionnaire: psychometric properties with individuals with serious mental illness in an inpatient setting. *Journal of Clinical Psychology*, 67(12), 1210–1219.

Schutte, L., Wissing, M. P., Ellis, S. M., Jose, P. E., & Vella-Brodrick, D. A. (2016). Rasch analysis of the Meaning in Life Questionnaire among adults from South Africa, Australia, and New Zealand. *Health and Quality of Life Outcomes*, 14(1), 1–15.

Serre, F., Fatseas, M., Swendsen, J., & Auriacombe, M. (2015). Ecological momentary assessment in the investigation of craving and substance use in daily life: A systematic review. In *Drug and Alcohol Dependence* (Vol. 148, pp. 1–20).

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, 4(February), 1–32.

Skinner, M. D., & Aubin, H. J. (2010). Craving's place in addiction theory: Contributions of the major models. *Neuroscience and Biobehavioral Reviews*, 34(4), 606–623.

Sliedrecht, W., de Waart, R., Witkiewitz, K., & Roozen, H. G. (2019). Alcohol use disorder relapse factors: A systematic review. *Psychiatry Research*, 278, 97–115.

Sliedrecht, W., Roozen, H., de Waart, R., Dom, G., & Witkiewitz, K. (2022). Variety in alcohol use disorder relapse definitions: Should the term “relapse” be abandoned? *Journal of Studies on Alcohol and Drugs*, 83, 248–259.

Steger, M. F., Frazier, P., Kaler, M., & Oishi, S. (2006). The meaning in life questionnaire: Assessing the presence of and search for meaning in life. *Journal of Counseling Psychology*, 53(1), 80–93.

Steger, M. F., Kashdan, T. B., Sullivan, B. A., & Lorentz, D. (2008). Understanding the search for meaning in life: Personality, cognitive style, and the dynamic between seeking and experiencing meaning. *Journal of Personality*, 76(2), 199–228.

Steptoe, A., Deaton, A., & Stone, A. A. (2015). Subjective wellbeing, health, and ageing. *Lancet*. 385(9968):640-648.

Stohs, M. E., Schneekloth, T. D., Geske, J. R., Biernacka, J. M., & Karpyak, V. M. (2019). Alcohol craving predicts relapse after residential addiction treatment. *Alcohol and Alcoholism*, 54(2), 167–172.

Treloar Padovano, H., & Miranda, R. (2021). Incubation of alcohol craving as it naturally occurs in a developmentally diverse sample of dependent and nondependent drinkers. *Addiction Biology*, May;26(3):e12934

Tucker, J., & Witkiewitz, K. (2020). Epidemiology of Recovery from Alcohol Use Disorder. *Alcohol Research: Current Reviews*, 40(3).

Tuithof, M., Ten Have, M., Van Den Brink, W., Vollebergh, W., & De Graaf, R. (2016). Treatment Seeking for Alcohol Use Disorders: Treatment Gap or Adequate Self-Selection? *Eur Addict Res*, 22, 277–285.

Waisberg, J. L., & Porter, J. E. (1994). Purpose in life and outcome of treatment for alcohol dependence. *British Journal of Clinical Psychology*, 33(1), 49–63.

Whitford, J. L., Widner, S. C., Mellick, D., & Elkins, R. L. (2009). Self-report of drinking compared to objective markers of alcohol consumption. *American Journal of Drug and Alcohol Abuse*, 35(2), 55–58.

- Wiers, C. E., Shumay, E., Volkow, N. D., Frieling, H., Kotsiari, A., Lindenmeyer, J., Walter, H., & Berman, F. (2015). Effects of depressive symptoms and peripheral DAT methylation on neural reactivity to alcohol cues in alcoholism. *Translational Psychiatry*, 5(9), e648.
- Wiers, R. W., Eberl, C., Rinck, M., Becker, E. S., & Lindenmeyer, J. (2011). Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome. *Psychological Science*, 22(4), 490–497.
- Witkiewitz, K., Litten, R. Z., & Leggio, L. (2019). Advances in the science and treatment of alcohol use disorder. *Science Advances*, 5(9).
- Witkiewitz, Katie. (2011). Predictors of heavy drinking during and following treatment. *Psychology of Addictive Behaviors*, 25(3), 426–438.
- Witkiewitz, Katie, & Marlatt, G. A. (2004). Relapse prevention for alcohol and drug problems: That was zen, this is tao. In *American Psychologist* (Vol. 59, Issue 4, pp. 224–235).
- Witkiewitz, Katie, & Marlatt, G. A. (2007). Modeling the complexity of post-treatment drinking: It's a rocky road to relapse. *Clinical Psychology Review*, 27(6), 724–738.

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 term 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)?

References

- Anderson AC, Robinson AH, Lubman DI, Verdejo-Garcia A. Protocol for a cluster randomised crossover pilot trial of Goal Management Training+ (GMT+) for methamphetamine use disorder. *Contemp Clin Trials Commun.* 2022 Aug 11;29:100969. doi: 10.1016/j.conctc.2022.100969.
- Coates JM, Gullo MJ, Feeney GFX, McD Young R, Dingle GA, Clark PJ, Connor JP. Craving mediates the effect of impulsivity on lapse-risk during alcohol use disorder treatment. *Addict Behav.* 2020 Jun;105:106286
- Copeland A, Jones A, Acuff SF, Murphy JG, Field M. (2022) Meaning in life: investigating protective and risk factors for harmful alcohol consumption, *Addiction Research & Theory.* 2022. DOI: 10.1080/16066359.2022.2134991
- Destoop M, Docx L, Morrens M, Dom G. Meta-Analysis on the Effect of Contingency Management for Patients with Both Psychotic Disorders and Substance Use Disorders. *J Clin Med.* 2021 Feb 6;10(4):616
- Dom G, Sabbe B, Hulstijn W, van den Brink W. Substance use disorders and the orbitofrontal cortex: systematic review of behavioural decision-making and neuroimaging studies. *Br J Psychiatry.* 2005 Sep;187:209-20.
- Dom G, Hulstijn W, Sabbe B. Differences in impulsivity and sensation seeking between early- and late-onset alcoholics. *Addict Behav.* 2006 Feb;31(2):298-308.
- Evers et al. Gedragsexpertise is de sleutel tot effectief leefstijlbeleid, 2022.
<https://lifestyle4health.nl/onderzoek/gedragsexpertise-de-sleutel-tot-effectief-leefstijlbeleid/>
- Flannery BA, Poole SA, Gallop RJ, Volpicelli JR. 2003. Alcohol craving predicts drinking during treatment: an analysis of three assessment instruments. *J Stud Alcohol.* 64(1):120–126.
- Flaudias V, Heeren A, Brousse G, Maurage P. 2019. Toward a triadic approach to craving in addictive disorders: the metacognitive hub model. *Harv Rev Psychiatry.* 27(5):326–331.
- Griswold et al. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2018 Sep 22;392(10152):1015-1035. doi: 10.1016/S0140-6736(18)31310-2.
- Kavanagh DJ, Statham DJ, Feeney GFX, Young RMD, May J, Andrade J, Connor JP. 2013. Measurement of alcohol craving. *Addict Behav.* 38(2):1572–1584.
- Koob GF. Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development. *Pharmacol Rev.* 2021 Jan;73(1):163-201.
- Kuhlemeier A, Desai Y, Tonigan A, Witkiewitz K, Jaki T, Hsiao YY, Chang C, Van Horn ML. Applying methods for personalized medicine to the treatment of alcohol use disorder. *J Consult Clin Psychol.* 2021 Apr;89(4):288-300. doi: 10.1037/ccp0000634.
- Levine B, Schweizer TA, O'Connor C, Turner G, Gillingham S, Stuss DT, Manly T, Robertson IH. Rehabilitation of executive functioning in patients with frontal lobe brain damage with goal management training. *Front Hum Neurosci.* 2011 Feb 17;5:9. doi: 10.3389/fnhum.2011.00009.
- Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF. Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. *Alcohol Clin Exp Res.* 2015 Apr;39(4):579-84.
- Lohoff FW. Pharmacotherapies and personalized medicine for alcohol use disorder: a review. *Pharmacogenomics.* 2020 Oct;21(15):1117-1138. doi: 10.2217/pgs-2020-0079
- McKay JR, Franklin TR, Patapis N, Lynch KG. Conceptual, methodological, and analytical issues in the study of relapse. *Clin Psychol Rev.* 2006 Mar;26(2):109-27.
- Miller, W. R. (1996). What is a relapse? Fifty ways to leave the wagon. *Addiction*, 91, Supplement 12, S15–S27. doi:10.1111/j.1360-0443.1996.tb02324.x

- Moe FD, Moltu C, McKay JR, Nesvåg S, Bjornestad J. Is the relapse concept in studies of substance use disorders a 'one size fits all' concept? A systematic review of relapse operationalisations. *Drug Alcohol Rev.* 2022 May;41(4):743-758.
- Morris, J., Albery, I. P., Heather, N., & Moss, A. C. (2020). Continuum beliefs are associated with higher problem recognition than binary beliefs among harmful drinkers without addiction experience. *Addictive Behaviors*, 105, 106292.
- Morris, J., Moss, A. C., Albery, I. P., & Heather, N. (2022). The "alcoholic other": harmful drinkers resist problem recognition to manage identity threat. *Addictive Behaviors*, 124:107093.
- Mutschler J, Grosshans M, Koopmann A et al. (2010) Supervised disulfiram in relapse prevention in alcohol-dependent patients suffering from comorbid borderline personality disorder-a case series. *Alcohol Alcohol* 45:146–50.
- Noël X, Brevers D, Bechara A. A neurocognitive approach to understanding the neurobiology of addiction. *Curr Opin Neurobiol.* 2013 Aug;23(4):632-8.
- Padula CB, Hansen A, Hughes RL, McNerney MW. Dimensions of Craving Interact with COMT Genotype to Predict Relapse in Individuals with Alcohol Use Disorder Six Months after Treatment. *Brain Sci.* 2021 Jan 6;11(1):62.
- Ralevski E, Ball S, Nich C, Limoncelli D, Petrakis I. The impact of personality disorders on alcohol-use outcomes in a pharmacotherapy trial for alcohol dependence and comorbid Axis I disorders. *Am J Addict.* 2007 Nov-Dec;16(6):443-9. doi: 10.1080/10550490701643336.
- Reichl D, Enewoldsen N, Weisel KK, Fuhrmann L, Lang C, Saur S, Berking M, Zink M, Ahnert A, Falkai P, Kraus T, Hillemecher T, Müller FN, Kornhuber J, Bönsch D, Kerkemeyer L, Steins-Loeber S. Association of impulsivity with quality of life and well-being after alcohol withdrawal treatment. *J Clin Psychol.* 2022 Jul;78(7):1451-1462.
- Rosenberg H. 2009. Clinical and laboratory assessment of the subjective experience of drug craving. *Clin Psychol Rev.* 29(6):519–534.
- Roozen H.G., Smith J.E. (2021) CRA and CRAFT: Behavioral Treatments for Both Motivated and Unmotivated Substance-Abusing Individuals and Their Family Members. In: el-Guebaly N., Carrà G., Galanter M., Baldacchino A.M. (eds) *Textbook of Addiction Treatment*. Springer Cham.
- Rundle SM, Cunningham JA, Hendershot CS. Implications of addiction diagnosis and addiction beliefs for public stigma: A cross-national experimental study. *Drug Alcohol Rev.* 2021 Jul;40(5):842-846. doi: 10.1111/dar.13244.
- Sánchez-Puertas R, Vaca-Gallegos S, López-Núñez C, Ruisoto P. Prevention of Alcohol Consumption Programs for Children and Youth: A Narrative and Critical Review of Recent Publications. *Front Psychol.* 2022 Mar 16;13:821867. doi: 10.3389/fpsyg.2022.821867.
- Skinner MD, Aubin HJ. 2010. Craving's place in addiction theory: contributions of the major models. *Neurosci Biobehav Rev.* 34(4): 606–623.
- Sliedrecht W, de Waart R, Witkiewitz K, Roozen HG. Alcohol use disorder relapse factors: A systematic review. *Psychiatry Res.* 2019 Aug;278:97-115.
- 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.
- 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.
- Sliedrecht W, Seesink HJ, Vrijmoeth, C, de Waart R, Wiers RW, Ostafin BD, Schaap H, Roozen H, Witkiewitz K, Dom G. (2022) Alcohol use disorder relapse factors: an exploratory investigation of craving, dependence severity, and meaning in life. *Addiction Research & Theory*, 30:5, 351-359.
- Sliedrecht, W., Roozen, H., Dom, G., & Witkiewitz, K. (2022). Alcohol use disorder 'relapse' definitions revisited: With no standard definition in the literature, is it time to abandon the term? *JSAD FastTakes*, no. 10. doi:10.15288/jsad-FT.07.26.2022-10
- Schneekloth TD, Biernacka JM, Hall-Flavin DK, Karpyak VM, Frye MA, Loukianova LL, Stevens SR, Drews MS, Geske JR, Mrazek DA. 2012. Alcohol craving as a predictor of relapse. *Am J Addict.* 21: S20–S26.
- Stohs ME, Schneekloth TD, Geske JR, Biernacka JM, Karpyak VM. 2019. Alcohol craving predicts relapse after residential addiction treatment. *Alcohol Alcohol.* 54(2):167–172.

Treloar Padovano H, Miranda R Jr. Incubation of alcohol craving as it naturally occurs in a developmentally diverse sample of dependent and nondependent drinkers. *Addict Biol.* 2021 May;26(3):e12934.

Verdejo-Garcia A, Garcia-Fernandez G, Dom G. Cognition and addiction. *Dialogues Clin Neurosci.* 2019 Sep;21(3):281-290.

Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology.* 2004;47 Suppl 1:3-13.

Stamenova V, Levine B. Effectiveness of goal management training in improving executive functions: A meta-analysis. *Neuropsychol Rehabil.* 2019 Dec;29(10):1569-1599. doi: 10.1080/09602011.2018.1438294.

Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med.* 2016 Jan 28;374(4):363-71.

Votaw VR, Mann K, Kranzler HR, Roos CR, Nakovics H, Witkiewitz K. Examining a brief measure and observed cutoff scores to identify reward and relief drinking profiles: Psychometric properties and pharmacotherapy response. *Drug Alcohol Depend.* 2022 Mar 1;232:109257. doi: 10.1016/j.drugalcdep.2021.109257.

Witkiewitz K, Litten RZ, Leggio L. Advances in the science and treatment of alcohol use disorder. *Sci Adv.* 2019 Sep 25;5(9):eaax4043.

Witkiewitz K, Montes KS, Schwebel FJ, Tucker JA. What Is Recovery? *Alcohol Res.* 2020 Sep 24;40(3):01.

6. Acknowledgements

The research plan was born around the year 2014, when the author (then still working at an alcohol detoxification ward in Delft, The Netherlands) met Professor Roozen (at that moment Tilburg University, from 2016 University of New Mexico) and after discussing the subject of relapse decided to contact a leading researcher on this subject: professor Witkiewitz (University of New Mexico). Of note, Katie Witkiewitz (together with Alan Marlatt) in 2004 has published the very useful and important 'Witkiewitz- Marlatt- relapse model'. Together with co-author Ranne de Waart, several important topics were identified, and systematic research on AUD relapse factors was the first project taken at hand. Also, some distinct relapse factors were identified that seemed eligible for further research, like gender, impulsivity, meaning in life, but also a need was identified to investigate what is actually meant with the term 'relapse' in the literature.

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.

I am thankful that the process that already started in 2014, and has led to four peer-reviewed papers in authoritative journals, and now in 2023 the process has ended with the current thesis. I hope that researchers, professionals and above all the patients will benefit from this research.

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eventually has led to taking up this challenge. The circle is round in that together with professor Schellekens he was willing to serve as external assessor. Interestingly, I met professor Schellekens for the first time around the year 2006 on our way to a scientific congress in Paris. At that moment I think he was at the start of his own PhD traject and I was still convinced that this was no future way for me to go. It is a honour to me that both professors could now play this role at the end of my PhD process.

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My admiration goes to those patients that sometimes for years or even decades struggle with AUD and strive after recovery. I dedicate this work to them!

I owe a lot to my dear family; my parents that have laid the primary foundation, and especially my wife Elizabeth, my children Channah, Salomé, Rachelle, Elias and Thirza had at times really to endure my absence (in practice or in mind), when I was occupied with this research.

Lastly, I want to end with the creed: *Soli Deo Gloria*.

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; Turckapar, 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; Zakiniaez, 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 <i>securely</i> 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 | Silveira, 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; Czaplá, 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)

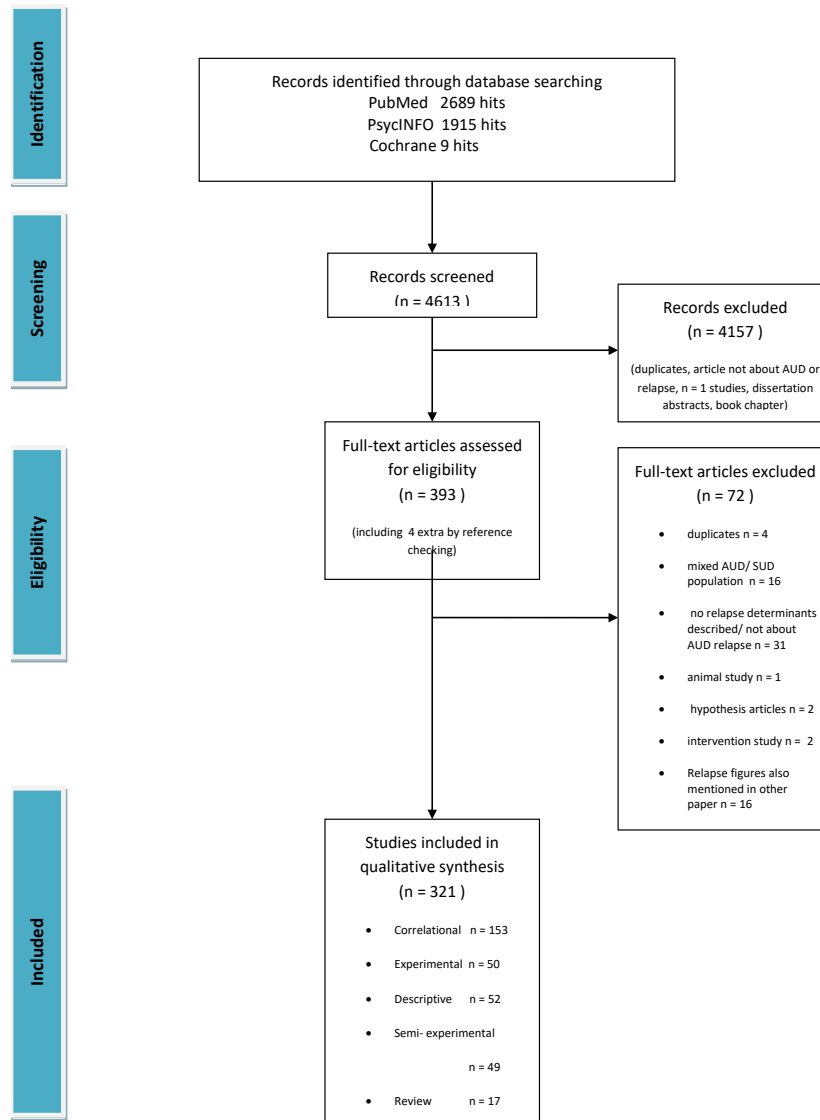


Table 2 Search results per category (BPSS model).

| 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) |
|---|--|---|--|
| <u>BIOLOGICAL</u> | | | |
| Age | 31 (n=49258) | 15 (n=2184) | 31/46 = 67% |
| Gender | 14 (n=14212) | 20 (n=13850) | 14/34 = 41% |
| Brain <i>(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)</i> | 25 (n=1388) | 2 (n=49) <i>(hippocampus, Thalamic N-acetylaspartate (NAA) deficits)</i> | 25/27 = 93% |
| Family history | 8 (n=1921) | 6 (n=552) | 8/14 = 57% |
| Genetics <i>(PDYN rs2281285, HTR2A, GABRA2, KIBRA, DRD2, BDNF, 5-HTTLPR, rs1789891)</i> | 7 (n=1136) | 4 (n=517) <i>(OPRM1, TPH2, SLC6A4, HTR1A, HTR2A, CHRM2, ANKK1, BDNF, COMT, DAD2, DAD3)</i> | 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 <i>(GATA4>ANP, BDNF, Cortisol in CSF, Cortisol response, D2 Dopamine receptor responsivity on Prolactin, basal cortisol:ACTH, Leptin levels)</i> | 8 (n=351) 2 (n=148) † | 1 (n=38) <i>(DAT methylation)</i> | 8/11 = 73% 2/11 = 18% † |
| Biological markers <i>(liver enzymes, MCV, baseline urine ethyl glucuronide (EtG), Body Mass Index (men))</i> | 5 (n=866) | 2 (n=121) <i>(Body Mass Index, blood glucose/ lipids)</i> | 5/7 = 71% |
| <u>PSYCHOLOGICAL</u> | | | |

| | | | |
|---|-----------------------------|---------------|----------------------------|
| 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 % |
| <u>SOCIAL</u> | | | |
| 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% † |
| <u>SPIRITUAL</u> | | | |
| 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), (Tuihof, 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), (Zakiniiez, 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), (Tuihof, 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 Scalfani, 2007), (Terra, 2006), (Krampe, 2006), (Bradizza, 2006), |

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| | (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 | (Karpayak, 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), (Aguaiar, 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) |

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| | 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) | - |
| <u>SOCIAL</u> | | |
| 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), |

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| | 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) | - |
| <u>SPIRITUAL</u> | | |
| 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

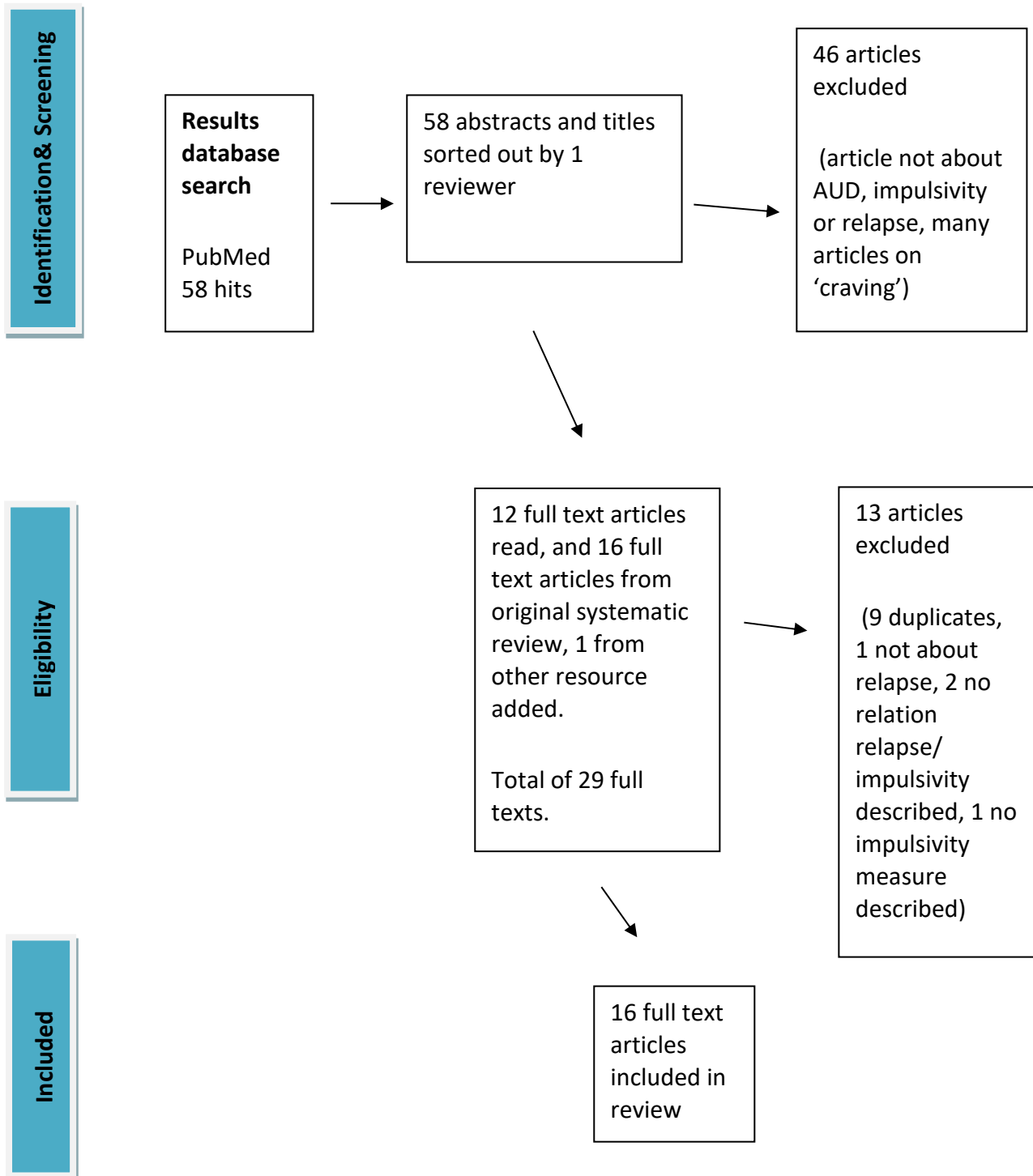


Table 1 *Overview studies*

| 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), $F_{2,37} = 10.52; p < 0.001$ BI/ MI: behavioural inhibition (visual reaction time (RT) task, Stop- Signal, Anti- Saccade, Number-Letter task), $F_{2,35} = 8.99; p < 0.001$ neural motor inhibition (instructed-delay choice RT task), $F_{2,35} = 6.53; p < 0.01$ | N/A |

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| 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% | <u>TI:</u> BIS-11 total score, <i>p =0.006</i> (relapsers vs. healthy controls (HC)) BIS-11 attention scores, <i>p <0.001</i> (relapsers vs. HC) <u>BI/ IC:</u> BART performance (Balloon analogue risk test), <i>p =0.013</i> (relapsers vs. abstainers) <i>p =0.007</i> (relapsers vs. HC) | BIS-11 total scores: 0.4 BIS-11 attention scores: 0.7 BART performance: 0.4 |
|------------|---|--|--|---|--|--|

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|--------------------|-------------------------|-------------------------------------|--|---|---|-------------------|
| 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% | <u>TI:</u> BIS- 11 score, $p =0.008$ (less accumulated months of abstinence) | <u>N/A</u> |
|--------------------|-------------------------|-------------------------------------|--|---|---|-------------------|

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|-------------------------------|---|--------------------------------------|--|--|---|--|
| <p>Bernhardt, 2017</p> | <p>Behavioural data choice impulsivity, Germany</p> | <p>N= 85 detoxified AUD patients</p> | <p>assess the predictive value of choice impulsivity for relapse to heavy alcohol use in patients during</p> | <p>heavy drinking: consumption of $\geq 60/48$ (male/female) grams of alcohol in 1 drinking occasion and the amount of alcohol consumption, 48 weeks follow up</p> <p>58 relapse, 27 abstinent</p> <p>Relapse rate: 68%</p> | <p>TI:</p> <p>Barratt Impulsiveness Scale BIS- 15 sum, $p = 0.242$ (NS)</p> <p>(Subscales also NS)</p> <p>BI/ IC:</p> <p>Delay Discounting (DD), $p = 0.029$</p> <p>probability discounting for losses (PDL), $p = 0.008$</p> <p>probability discounting for gains (PDG), $p = 0.282$ (NS)</p> <p>Mixed Gambles = MG,</p> | <p>Delay Discounting: 0.2</p> <p>Probability discounting for losses (PDL): 0.7</p> |
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|--------------------|--|---|---|--|---|------------|
| | | | | | $p = 0.491$ (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% | TI: Barratt Impulsivity Scale BIS- total mean score $p = .866$ (NS) (no difference relapsers vs. abstainers) | N/A |

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|---------------------|---|-------------------------------------|---|--|---|--|
| 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 <i>p =0.023</i> | 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 <i>(factor 3 of the principal components analysis),</i> <i>p =0.033</i> | N/A |

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

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| 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 |

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| <p>Evren, 2012</p> | <p>Follow up study, face to face interviews, Turkey</p> | <p>N= 102 inpatient alcohol dependent</p> | <p>evaluate the relationship of relapse with impulsivity, novelty seeking (NS) and craving during 12 month follow up after inpatient treatment in male alcohol dependents</p> | <p>Relapse: return to drinking during 12 month follow up</p> <p>63 relapse, 39 abstinent</p> <p>Relapse rate: 62%</p> | <p>TI:</p> <p>Novelty Seeking NS (subcategories 1,2,3,4)</p> <p>NS-3,</p> <p>$p = 0.002$</p> <p>BIS-11 not after forward logistic regression analysis.</p> | <p>Novelty seeking 3: 1.1</p> |
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| 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 | <u>TI:</u> BIS-11 at intake & 12 weeks F- up Impulsivity via BIS-11/ BPD association, <i>NS</i> | <u>N/A</u> |
|-------------|-------------------------------------|--------|---|---|---|-------------------|

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|----------------------------------|---|--------------|--|--|---|---|
| <p>Bowden-Jones, 2005</p> | <p>Pilot study, UK</p> | <p>N= 21</p> | <p>Testing effect of risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction on relapse in alcohol dependency</p> | <p>Relapse: non abstinent, 3 month follow up</p> <p>6 relapse, 15 abstinent</p> <p>Relapse rate: 29%</p> | <p><u>TI:</u></p> <p>BIS-11,</p> <p><i>U</i> = 8.0, <i>p</i> = 0.016</p> <p><u>BI/ IC:</u></p> <p>Gambling Task,</p> <p><i>U</i> = 13.5, <i>p</i> = 0.014</p> | <p>Barratt Impulsiveness Scale: 1.7</p> <p>Gambling task: 1.3</p> |
| <p>Fein, 2004</p> | <p>Gambling task in abstinent alcoholics, USA</p> | <p>N= 44</p> | <p>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</p> | <p>Retrospective abstinence duration (varied from at least 6 months- 6.6 years)</p> <p>44 abstinent,</p> | <p><u>BI/ IC:</u></p> <p>SGT / simulated gambling task,</p> <p><i>NS</i></p> | <p><u>N/A</u></p> |

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|------------|---|---|---|--|---|------------|
| 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% | <u>TI:</u> Impulsivity from Personality Research Form (PRF), NS | <u>N/A</u> |
|------------|---|---|---|--|---|------------|

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:

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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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