

Comprehensive assessment of impulsivity in alcohol use and gambling disorders

Summary of Ph.D. Thesis

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I. Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) introduced a novel approach in the classification of addictive disorders, since Gambling Disorder (GD) was reclassified from *Impulse Control Disorders* into *Substance-Related and Addictive Disorders* as the first and yet the only non-substance-related addiction. Scientific literature indicates that from substance-related addictions, alcohol use disorder (AUD) shows the highest comorbidity with GD. It is also highlighted that GD displays similar features to substance-related disorders, thus AUD, in terms of clinical expression, comorbidity, physiology, brain origin and treatment prognosis. Although the background and characteristics of these disorders separately have been assessed for decades, data on features of concomitant AUD and GD are scarce, which underlines the paramount importance of examining the two disorders jointly. For this purpose, our aim was firstly to review the similarities of AUD and GD, from which higher impulsiveness was pointed out as a core feature in both disorders. Then, in the framework of a systematic review-based meta-analysis, aggregated clinical data was analysed concerning cognitive impulsivity in AUD and GD patients contrasted with healthy controls. Moreover, different aspects of impulsivity were investigated in AUD patients with or without comorbid GD symptoms to assess whether the comorbidity of these two disorders are accompanied by more severe impulse control deficits.

The main goals of the studies comprising the present thesis were the following:

- I. To assess similarities and differences between alcohol use disorder and gambling disorder.
- II. To differentiate patients diagnosed with alcohol use disorder, gambling disorder and healthy matched controls in terms of cognitive impulsivity measured by the Iowa Gambling Task.
- III. To evaluate the comorbidity of gambling disorder symptoms in alcohol use disorder patients receiving inpatient treatment.
- IV. To investigate whether concomitant gambling disorder symptoms in chronic alcohol use disorder patients is accompanied by more severe impulse control deficiencies.

II. Background

II.1 Similarities in the symptomatology of AUD and GD and the role of impulsivity

GD shows a significant overlap with the diagnostic criteria of AUD; they share the aspects of decreased work performance, existential problems and interpersonal disadvantages, craving, withdrawal symptoms, tolerance, frequent relapse episodes, disfunctions in inhibitory control and higher impulsivity. Multiple studies have pinpointed that impulsivity is simultaneously present as a symptom and an aetiological factor and is regarded as a core feature in addictive disorders, thus AUD and GD, since many of the diagnostic criteria of both disorders may also be interpreted in the framework of impulsivity or may be related to it. Defining the concept of impulsivity is actually quite difficult, since it is regarded as a manifold, multifaceted construct consisting of several related subdomains and is regularly grasped as the repeated performing of maladaptive behavioural actions resulting in probable negative consequences. In this sense, impulsive actions may be considered as rapid and unplanned reactions to internal or external stimuli with the aim of achieving immediate pleasure and/or gratification. Recent understandings of impulsiveness underline the importance of not just the behavioural aspects of impulsivity, but also their underlying neurobiological and neuropsychological components.

II.2 Aspects of impulsivity in AUD and GD and its assessment

AUD and GD not only share elevated levels of impulsiveness as a common symptom, but it is demonstrated that higher impulsivity is a common underlying genetic vulnerability and is considered to be an endophenotypic indicator in both disorders. Endophenotypes can be defined as measurable components that are not visible explicitly along the pathways in between distal genotypes and the disease itself. Concerning AUD and GD, impulsivity is not regarded as a unitary construct, consequently it is not likely to be traceable in studies as an endophenotype as a whole, but specific aspects like the ability to delay rewards as a form of cognitive impulsivity has been proposed as a cognitive endophenotype. Impulsivity in case of both AUD and GD has been linked to negative accompanying features like the increase in addictive symptom severity, thus more alcohol intake and higher gambling activity, poor clinical outcomes and the increase of relapse risk, which underscores the need for the comprehensive assessment of impulsivity in these disorders.

Despite having an agreement in the scientific literature regarding impulsivity as a complex, multifaceted construct, there is still no consensus on the exact classification of the subdimensions comprising its multifactorial nature. On this notion, current measurements of the different aspects of impulsivity range from self-assessment, measures and electrophysiological neurocognitive assessments of impulsiveness. The numerous assessment

approaches can be subordinated to four major conceptual categories: trait impulsivity, impulsive aggression, choice impulsivity/delay discounting and impulsive decision making/risk preference, i.e. cognitive impulsivity.

The classical trait concept of impulsivity can be defined as a component of personality, which involves a tendency towards displaying such behaviour that is characterized by little or even no reflection, forethought or consideration of consequences. It has traditionally been characterized as an enduring and stable personality trait, which can be measured by a range of self-reported assessment scales. Another dimension of impulsiveness is impulsive (unplanned) aggression, which can be defined as an unpredictable or sudden use of force or action without taking into consideration of the consequences of this behaviour. From a physiological aspect, impulsive aggression is hypothesized as a partially biologically-based construct, where cortical inhibitory mechanisms and the results of the interactions of serotonin, the prefrontal cortex, the amygdala and the limbic system play essential roles in the emergence of aggressive impulses. A mainly neurocognitively-investigated component of impulsivity is choice impulsivity/delay discounting, which can be defined as making haste choices and having tendencies of preferring smaller but instant gratifications over later but larger rewards. That aspect is directly connected to the inability to exert self-control or delay gratifications, which are important elements of addictive behaviour. Additionally, impulsive decision-making as a form of cognitive impulsivity is defined as a complex cognitive process allowing individuals to choose the most optimal course of action, which is preceded by reasoned consideration of possible existing alternatives. In case of addictive disorders, the assessment of decision-making dominantly focuses on neurocognitive performance tasks assessing inhibitory control. In the present thesis, these four subdimensions of impulsivity are evaluated utilizing both self-assessment and computerized neuropsychological measurements.

III. Aims and hypotheses

It has been well documented that AUD and GD show similarities in symptomatology, aetiology, epidemiology and comorbidity with other psychiatric disorders. From these, higher impulsivity is of key importance, since it has not only been proved to be a comorbid symptom, but has been established to characterize both disorders as a common vulnerability marker, with one aspect of impulsivity, cognitive impulsivity serving as a potential cognitive endophenotype in AUD and GD. Based on these and the theoretical background detailed above, the present thesis centres around two empirical studies with the following aims:

Aim 1: Scientific literature points out that AUD and GD are both characterized by higher levels of impulsivity, although in terms of the different aspects of impulsivity, exact findings are inconclusive; one aspect, cognitive impulsivity is proposed as a potential endophenotype in both disorders. Based on this, in the first part of the thesis (in Study I), this facet of impulsivity, impulsive decision-making, i.e. cognitive impulsivity was chosen to be examined closely in the framework of a systematic review-based quantitative meta-analysis. For this purpose, one assessment tool was selected to measure the dimension of impulsive decision-making: the Iowa Gambling Task (IGT), which is considered to be the most commonly used and ecologically valid computerized neuropsychological task for measuring real-life impulsive decision-making in laboratory circumstances. On this notion, (i) it was hypothesized that both AUD and GD patient groups showed impaired decision-making measured with the IGT compared to matched HC group, and (ii) AUD and GD patient groups could also be differentiated in terms of decision-making measured by the IGT net scores.

Aim 2: Higher impulsivity both in AUD and in GD has been associated with negative concomitant features like higher addiction-related symptom severity, i.e. more severe alcohol consumption and more intensive gambling activity or the elevated risk of relapse. However, despite the high documented comorbidity, these studies were only conducted in cases of sole diagnoses of either AUD or GD. Based on these, in the second part of the present thesis (in Study II), the occurrence of concomitant GD symptoms in a chronic, long-term AUD patients were evaluated, with a more comprehensive assessment of impulsivity in patients with and without comorbid GD symptom. In Study II, the multifaceted nature of impulsivity was also taken into consideration, a complex set of test battery was utilized covering four different aspects of impulsivity: trait, choice and cognitive impulsivity and impulsive aggression. Based on these, (iii) it was hypothesized that the prevalence of comorbid GD symptoms with AUD would fit in with international trends in an inpatient treatment unit for AUD. Additionally, (iv) it was theorized that long-term AUD patients with comorbid GD symptoms expressed higher symptom severity of substance use and psychopathological symptoms, and (v) long-term AUD patients with comorbid GD symptoms presented higher levels of trait impulsivity, choice impulsivity, impulsive aggression and impulsive decision-making.

IV. Methods, materials and data analysis

IV.1 Study I

In Study I, a single domain of impulsivity, namely cognitive impulsivity in the form of impulsive decision-making measured with the Iowa Gambling Task (IGT) was selected for

comparison between patients with DSM or ICD diagnoses of either AUD or GD and matched healthy controls. In the present systematic review and meta-analysis three scientific databases were thoroughly searched to determine empirical studies concerning alcohol use disorder and gambling disorder and the IGT. After applying all exclusion criteria, from the total of 1,198 potential findings, 17 empirical studies remained and met the criteria to be included for qualitative analysis of aggregated empirical data, from which 23 contrasts were obtained from AUD/GD groups compared to HCs, which was the unit of data analysis. All analyses were calculated using the Comprehensive Meta-Analysis (CMA) 3.0 with the use of random-effects model, including the estimation of publication bias, calculations of effect sizes, subgroup analysis, moderator analyses, and meta-regression was also conducted to examine potential mediators like the proportion of males, mean years of education and age. To determine AUD and GD group differences, the two groups' sampling variances were calculated and be compared with the standard normal z test statistics.

IV.2 Study II

The focus of Study II was to assess the comorbidity of AUD and GD with addressing impulsivity from a broader perspective. For this purpose, 103 patients without clinically significant intellectual disability (IQ above 70 in each case, measured by the fourth edition of the Weschler's Adult Intelligence Scale – WAIS-IV) were enrolled, receiving inpatient treatment for AUD and were estimated with a test battery assessing the severity of both addictions measured with the Alcohol Use Disorder Identification Test (AUDIT) and the South Oaks Gambling Scale (SOGS), psychopathological symptom severity evaluated with the Symptom Checklist-90-R (SCL-90-R). The different aspects of impulsivity was evaluated by the incorporation of both objective and subjective measurements of the following five impulsivity tasks covering four domains of impulsivity: trait impulsivity measured by Barratt Impulsivity Scale (BIS), impulsive aggression assessed by the Buss-Perry Aggression Questionnaire (BPAQ), choice impulsivity evaluated with the Delay Discounting Task (DDT) and impulsive decision-making measured by the Wisconsin Card Sorting Task (WCST) and the Iowa Gambling Task (IGT). Patients were enrolled into AUD and AUD+ Gambling groups based on the presence of GD symptoms. Independent-samples t -tests and Chi-square tests were utilized to determine group differences and demographic parameters. Partial correlation analysis was calculated to reveal the relationship between the different facets of impulsivity and gambling symptom severity. The effect of demographic variables, psychopathological symptoms and measures of impulsivity on the likelihood that patients have problem gambling

symptoms was examined with binary logistic regressions with forward stepwise regression method, and effect sizes were calculated using Cohen's d values.

V. Results

V.1 Study I

A total of 792 AUD or GD patients were compared to 568 HCs. The random effects estimate indicated impaired IGT performance in both AUD patients ($N = 500$; $d = -0.581$, CI: $-89.5 < \delta < -26.6\%$) and GD patients ($N = 292$; $d = -1.034$, CI: $-156.1 < \delta < 50.7\%$). It is also evident, that AUD patients display less advantageous decision making than controls and the same is true for GD patients. In order to compare the two groups' results, sampling variances were calculated for both AUD ($v_1 = 0.0056$) and GD groups ($v_2 = 0.0061$), from which z-score was calculated ($z = -21.0785$). This indicates statistically significant difference between AUD and GD groups, meaning that the overall deficit is more expressed in GD as compared to AUD. Publication bias and heterogeneity was assessed with funnel plots depicting standard errors, which appeared to be symmetric for both AUD and GD, Egger's test for intercept indicated symmetry (intercept = 0.796, P -value = 0.745). Similarly, the Begg and Mazumdar test could not detect evidence of publication bias (Kendall's tau = 0.05929, $p = 0.672$) either. It was estimated that there was a high likelihood of contextual and methodological heterogeneity because of the differing health service contexts regarding each study; therefore, a random effects model was utilized to calculate the summary effect estimates. There was significant heterogeneity in the sample ($Q_w = 131.217$, $df = 22$, $p < 0.001$) but the two subgroups (AUD: $Q_w = 81.72$, $df = 15$, $p < 0.001$; GD: $Q_w = 30.62$, $df = 6$, $p < 0.001$) did not differ from each other in terms of heterogeneity ($Q_w = 2.097$, $df = 1$, $p = 0.149$). Since significant heterogeneity was detected, we conducted moderator and covariate analyses on the sample. Based on the model that incorporated the differences between patient groups and HCs regarding age (coefficient: 0.0270, $p = 0.48$) the proportion of males (coefficient: 0.0049, $p = 0.46$) and level of education in the sample (coefficient: 0.0521, $p = 0.50$) and the age of the treatment groups (coefficient: 0.0164, $p = 0.39$), none of the moderator variables had a significant effect on decision making deficit indicated by the p -value. We also tested each moderator separately: age difference between patient groups and HCs had no significant p -value (coefficient: 0.0098, $p = 0.72$); age of the patient groups had no significant p -value either (coefficient: 0.0202, $p = 0.24$); the proportion of gender in the sample was also tested and did not differ significantly (coefficient: 0.0048, $p = 0.41$); and the level of education showed no significant p -value either (coefficient: 0.0236, $p = 0.67$).

V.2 Study II

The AUD and AUD+Gambling group did not differ in gender, age, education, IQ, start of alcohol consumption or abstinence during the last 30 days, but the AUD+Gambling group was characterised by more severe alcohol use ($t(100) = -2.489, p = 0.014$) and longer lifetime alcohol consumption ($t(100) = -2.109, p = 0.037$). Partial correlation with age, lifetime alcohol consumption and SCL-90-R Global Severity Index (GSI) as covariates were conducted to explore the associations between test variables, where the severity of gambling symptoms (SOGS score) showed significant correlation with the BIS Total Score ($r = 0.278, p = 0.006$), while other variables did not show significant connection with SOGS score. Based on this, independent sample t -tests were conducted to explore group differences in the subscales of the BIS. The AUD+Gambling group had higher scores in the BIS Nonplanning ($t(100) = -3.024, p = 0.003$, Cohen's $d = -0.634$) and the BIS Total scores ($t(100) = -2.635, p = 0.010$, Cohen's $d = -0.555$), and a tendency toward significance in the BIS Motor Impulsivity ($t(100) = -1.767, p = 0.080$, Cohen's $d = -0.371$).

To explore the effect of demographic variables, psychopathological symptoms and measures of impulsivity on gambling symptoms, we performed two binary logistic regressions with forward stepwise regression method with AUD vs. AUD+Gambling as dependent variable. The first binary logistic regression was performed with age, gender, IQ measured by the WAIS-IV and SCL-90-R GSI as covariates. The BPAQ Total score, the BIS Total score, the number of correct responses in the WCST, the number of total errors in the WCST, the number of perseverative errors in the WCST, the DDT score, the total win on the IGT, the number of advantageous choices on the IGT, the number of disadvantageous choices on the IGT and the IGT net score on the likelihood that patients have problem gambling symptoms were entered as predictors. Assumption of collinearity was tested and resulted in no indication of multicollinearity (Tolerance below 0.865 and VIF below 3.645 for every variable in the model). The baseline model ($B = -0.895$, S.E. = 0.220, Wald $\chi^2(1) = 16.507, p \leq 0.001$, OR = 0.408) had an accuracy of 71.0% overall percentage. The binary logistic regression model was statistically significant ($\chi^2(1) = 7.324, p = 0.007$; $R^2 = 0.101$; Hosmer-Lemeshow goodness-of-fit test: $\chi^2(8) = 2.703, p = 0.958$). Increasing BIS Total score was associated with the increased likelihood of having problem gambling symptoms ($B = 0.057$, S.E. = 0.022, Wald $\chi^2(1) = 6.631, p = 0.010$, OR = 1,059, 95% CI = 1.014 – 1.105) while all the other variables had a non-significant effect in the final model.

In the second binary logistic regression the BIS and BPAQ subscales were also included besides the total scores, namely: BIS Motor Impulsivity Score, BIS Cognitive Impulsivity Score, BIS Nonplanning Score, BPAQ Verbal Aggression Score, BPAQ Physical Aggression, BPAQ Hostility score and BPAQ Anger score. Additionally, the number of correct responses in the WCST, the number of total errors in the WCST, the number of perseverative errors in the WCST, the DDT, the total win on the IGT, the number of advantageous choices on the IGT, the number of disadvantageous choices on the IGT and the IGT net score were included as predictors with age, gender, IQ measured by the WAIS-IV and SCL-90-R GSI as covariates. Assumption of collinearity was tested and resulted in no indication of multicollinearity (Tolerance below 0.819 and VIF below 3.808 for every variable in the model). The baseline model ($B = -0.895$, $S.E. = 0.220$, $Wald \chi^2(1) = 16.507$, $p \leq 0.001$, $OR = 0.408$) had an accuracy of 70.0% overall percentage. The binary logistic regression model was statistically significant ($\chi^2(1) = 8.914$, $p = 0.003$; $R^2 = 0.122$; Hosmer-Lemeshow goodness-of-fit test: $\chi^2(7) = 9.121$, $p = 0.244$). Increasing BIS Nonplanning score was associated with the increased likelihood of having problem gambling symptoms ($B = 0.143$, $S.E. = 0.051$, $Wald \chi^2(1) = 7.844$, $p = 0.005$, $OR = 1.154$, $95\% CI = 1.044 - 1.275$), while all the other variables had a non-significant effect in the final model.

VI. Discussion of the results

AUD and GD show similarities concerning their clinical picture, aetiology, comorbidity, physiology, treatment prognosis and symptomatology, from which higher impulsivity is a core feature in both disorders. The present thesis aimed to focus on the comprehensive evaluation of the different aspects of impulsivity and their expression in sole diagnoses and comorbid occurrence of AUD and GD. Firstly, aggregated clinical data were analysed in a systematic-review based quantitative meta-analysis, concentrating on the comparison of diagnosed GD and AUD patients compared to matched HCs on a neurocognitive task (the IGT) measuring one dimension of cognitive impulsivity: impulsive decision-making. Then clinical data was evaluated to assess the differences in terms of the different aspects of impulsivity examined with a range of objective and subjective measurement tests to determine whether the co-occurrence of GD symptoms in chronic AUD patients show more severe deficits in impulse control.

The (*i*) first hypothesis, that both AUD and GD patients show impaired decision-making measured with the IGT compared to matched HC group was confirmed. In a systematic literature search-based meta-regression of AUD and GD patients' decision-making

characteristics measured by a computerized neuropsychological task, the IGT, deficits were detected in both patient groups compared to matched HC participants. The reason behind the focus on the IGT was that this neurocognitive task is one of the most widely accepted and clinically used computerized neurocognitive measurement option that models real-life decision-making under laboratory circumstances. This impairment may be linked to the disturbance of global executive functions in AUD and GD that is strongly associated with relapse, which is imminent during the recovery processes. Relapse prevention is a key factor in the maintenance of long-term abstinence, although many AUD and GD patients fail to succeed in sustaining prolonged abstinence. This might be reasoned with dysfunctional decision-making presented in choosing disadvantageous long-term strategies by favouring immediate rewards accompanied by the disregard of future negative consequences.

The (ii) second hypothesis that AUD and GD patient groups can be differentiated in terms of decision-making measured by the IGT net scores was also confirmed, since both patient groups showed deficits in decision-making; moreover, the presence of impaired decision-making was even larger in the case of GD patients than in the AUD group. Analysis of aggregated clinical data suggest that not the substance itself might lie in the background of the deficit detected in decision-making, but rather other dysfunctions of cognitive and personality traits that are associated with addictive disorders. Despite literature indicating differences in age, gender and education in the course and patterns of AUD and GD, in the present aggregated clinical data, moderator and covariate analysis of these variables did not yield results for sufficiently supporting their impact in the detected deficit of decision-making. The presence of significant heterogeneity might be the reason for that across and within the samples. Besides age, gender and education, several other factors, such as intellect, the length of abstinence and other psychopathological characteristics like the levels of depressive symptoms or anxiety may contribute to the emergence and understanding of the characteristics of cognitive impulsivity in AUD and GD. The present meta-analysis corroborates previous scientific literature that impairment in decision-making, as a core symptom in addictive disorders, may not be directly connected to the substance consumption itself, since it is not only present, but is independently and more characteristically displayed in a non-substance-related, behavioural disorder (GD), than in a substance-related dependence (AUD). This supports the recent re-placement in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) where GD was moved from *Impulse control disorders* to *Substance-related and addictive disorders*.

The (iii) third hypothesis that the prevalence of comorbid GD symptoms with AUD fits in with international trends in inpatient treatment unit for AUD was also confirmed, since 31.1%

of chronic AUD patients reported concomitant GD symptoms. Several large, population-based studies conducted in English-speaking regions of the world and in Western Europe reported a huge overlap (17-33%, depending on the exact study) between alcohol and gambling addictions and vice versa, and these numbers greatly exceed the prevalence data of 0.5-2% reported in studies of general populations.

The (iv) fourth hypothesis that long-term AUD patients with comorbid GD symptoms express higher symptom severity of substance use and psychopathological symptoms was partially confirmed. In the clinical sample evaluated in this thesis, patients with comorbid AUD and GD symptoms reported more severe alcohol use and longer lifetime alcohol consumption, but psychopathological symptom severity was only significant on the level of tendency. The reason for the significance on the level of tendency in the present study might lie in the fact that both patient groups were chronic, long-term AUD patients, in which case higher psychopathological symptom severity is a documented aspect both in case of subclinical and clinically diagnosed samples.

The (v) fifth hypothesis that long-term AUD patients with comorbid GD symptoms present higher levels of trait impulsivity, choice impulsivity, impulsive aggression and impulsive decision-making was partially confirmed, since only higher trait impulsivity proved to be present in chronic AUD comorbid with GD symptoms. Patients with chronic AUD receiving inpatient treatment for their alcohol dependence were assessed with or without GD symptoms on an extensive battery comprising of objective and subjective measurements of four sub-dimensions of impulsivity. Regardless of intelligence, age, gender and psychopathological symptom severity, solely higher trait impulsivity and its non-planning subdimension were linked to the co-occurrence of concomitant GD symptoms in chronic AUD.

The lack of difference between the AUD and AUD with GD symptoms groups may be reasoned with the consequences of prolonged alcohol consumption on those cortical regions that play central roles in decision-making and response inhibition, which in the present case did not result in an even more predominant decline in neurocognitive performance of AUD patients with comorbid GD symptoms contrasted with patients with sole AUD. Concerning the lack of differences besides trait impulsivity, but not in other facets of impulsivity evaluated in this thesis, meta-analyses highlight that impulsivity is not a unitary construct, but has a multifaceted nature with distinct manifestations in AUD and GD, demonstrating a general deficit in inhibitory control, thus impulsive cognitive dysfunction.

VII. Summary of the results and conclusion

Impulsivity is regarded as a key concept in AUD and GD as well, that provided the basis of the empirical research on which the present thesis is based on. Firstly, the two disorders were separately assessed in one aspect of impulsivity, decision-making as a form of cognitive impulsivity measured by the IGT to determine differences between the two disorders compared to HC groups. Additionally, although in scientific literature impulsivity is regarded as a multidimensional construct, no previous studies have incorporated a comprehensive assessment of impulsivity in chronic AUD patients with or without comorbid GD symptoms before.

Based on these, novel findings of the present thesis are the following:

- I. Decision-making deficit is apparent in both alcohol use disorder (AUD) and gambling disorder (GD).
- II. Impaired decision-making is not linked to substance use itself, but rather to addictive behaviour, since the decision-making deficit is more expressed in GD than in AUD.
- III. The prevalence of comorbid GD symptoms in AUD was 31.1%, which fits in with international trends.
- IV. Chronic AUD patients with GD symptoms exhibited more severe alcohol use and longer lifetime alcohol consumption.
- V. Gambling symptom severity was associated with higher trait impulsivity in chronic AUD.
- VI. Higher trait impulsivity increased the risk of problem gambling in chronic AUD.

The establishment of a link between comorbid GD and AUD in a given population might enhance clinicians' ability to make therapies more personalized and could lead to the enhancement of treatment efficacy as well, resulting in the lowering of treatment costs and the reduce of relapse rates. Future research could benefit from the longitudinal evaluation of the distinct dimensions of impulsivity in chronic AUD populations. Taking special attention to its different presentations in AUD comorbid with GD symptoms may contribute to clearing directions for providing target-specific and effective treatment approaches. Integrating the comprehensive assessment of GD symptoms into the treatment regime of AUD patients might help in reducing the additive adverse effects of comorbid AUD and GD related problems.

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