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Antidepressants and alcohol use disorder: A multicenter study on the mediating role of depression symptom changes

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Abstract

Background: Alcohol use disorder (AUD) and depression are highly prevalent and tied to significant psychological, physiological, social and economic consequences. Their co-occurrence presents a complex clinical challenge, as the impact of antidepressant medication on AUD outcomes remains equivocal. In this multicenter, longitudinal study we investigated the relationship between antidepressant medication and changes in depression symptoms and alcohol use in AUD patients.

Methods: We analyzed data from 153 detoxified AUD patients who attended a 12-week residential treatment program between 2015 and 2019. Within a mediation analysis, adopting a bootstrapping approach and a quasi-Bayesian framework, we estimated the total, direct, and mediated effects of antidepressants on the percentage of days abstinent to assess the role of changes in depression symptoms as a mediating factor.

Results: The mediation analysis revealed a dual impact pathway model with a negative direct effect of antidepressants on abstinence ($p = 0.004$) and a positive indirect effect, mediated through the reduction of depression symptoms ($p = 0.002$).

Conclusions: The findings of the mediation analysis show that patients treated with antidepressants and whose depression symptoms do not improve over time show more relapses, while patients treated with antidepressants who achieve a reduction in depression symptoms show fewer relapses over time. Thus, to optimize treatment outcome, depression symptoms should be vigilantly monitored when antidepressants are prescribed during AUD treatment.

KEYWORDS
alcohol use disorder, antidepressants, depressive symptoms, mediation analysis, percent days of abstinence

Trial registration: ClinicalTrials.gov, ID: NCT02968537. Registered on November 18th, 2016.

INTRODUCTION

Alcohol use disorder (AUD) and major depressive disorder (MDD) are both among the most prevalent mental disorders and entail significant psychological, physiological, social and economic consequences (Grant et al., 2021; Rehm, 2011). The two disorders share common genetic, environmental and behavioral risk factors, which contribute to the explanation of their frequent co-occurrence (Kuria et al., 2012; McHugh & Weiss, 2019) and reciprocal influence (Boden & Fergusson, 2011). Next to genetic and biological shared factors, there are two main models explaining the linkage between AUD and MDD. Some studies suggest that the development of AUD may possibly be the result of self-medication as a dysfunctional coping strategy to deal with depressive symptoms (e.g. Kuo et al., 2006). However, the current state of the literature suggests that the associations between AUD and depressive symptoms were best explained by a model in which problems with alcohol led to increased risk of depressive symptoms (Boden & Fergusson, 2011), and in some cases eventually to MDD due to sociopsychological factors and mechanisms based on alcohol use-dependent metabolic and neurobiological changes, e.g. structural and functional changes in the reward system (Boden & Fergusson, 2011; Bracht et al., 2021; Soravia et al., 2022). Furthermore, many patients with AUD develop depression symptoms, which often occur during and/or after withdrawal due to the patient's excessive alcohol use, but the symptoms usually dissipate untreated with medium- to long-term abstinence (remission within 3–4 weeks) (Farré et al., 2020; McHugh & Weiss, 2019). Various pharmacological treatments are available to address these symptoms independently of each other (Alsheikh et al., 2020; Burnette et al., 2022). However, the entanglement of the two disorders introduces a cause-and-effect relationship between pharmacological agent, depression symptoms and AUD that is notably difficult to examine (Alsheikh et al., 2020).

Antidepressants are often prescribed in patients with AUD with co-occurring depression symptoms (Torrens et al., 2005). In fact, antidepressants are one of the most prescribed medications in patients with AUD (Foulds et al., 2016; Knudsen et al., 2007; Mark et al., 2003). Trials on pharmacological treatment for the co-occurrence of AUD and depression symptoms have focused mainly on antidepressant agents (Agabio et al., 2018; Burnette et al., 2022; Iovieno et al., 2011; Nunes & Levin, 2004). In the population of patients with AUD and co-occurring depression symptoms, antidepressants have been shown to be on average more effective in reducing depression symptoms than placebos (McHugh & Weiss, 2019). However, meta-analyses have shown that antidepressants only contribute to the reduction of depression symptoms in the case of a moderate-to-severe manifestation of the MDD (Fournier et al., 2010), whereas patients with mild depression symptoms do not necessarily profit from antidepressant treatment (Farré et al., 2020; Gelenberg & Chesen, 2000; McHugh & Weiss, 2019).

Another meta-analysis by Zhou et al. (2015) including five trials with 290 adolescents and young adults with co-occurring depression and substance use disorder found antidepressant medication effective for the treatment of depressive syndrome, but it did not improve substance abuse. The authors suggest that emphasis needs to be placed on treatment of the addiction, independent of antidepressant treatment (Zhou et al., 2015). This is partly in line with a review by Yoon and Petrakis (2018) who evaluated pharmacological and psychological interventions for patients with comorbid AUD and depressive disorder. Results showed that antidepressants were efficacious only in some trials in improving alcohol use outcomes (Yoon & Petrakis, 2018).

About half of patients with AUD reporting depression symptoms during withdrawal treatment are prescribed antidepressants, even though it is not necessarily indicated, as they may not respond to antidepressants beyond the remission that is achieved with alcohol abstinence (Ballesta, Orio, et al., 2019). In those cases, the prescription of antidepressants is unnecessary, costly and burdensome to those patients (Pary et al., 2017; Pettinati et al., 2013).

Summarized, there are inconsistent findings regarding the effects of antidepressants on AUD symptoms, e.g. alcohol use and craving. Thus, there is some supporting evidence for a beneficial effect of antidepressants on AUD symptoms, particularly when evaluating populations that simultaneously present AUD symptoms and at least moderate depression symptom manifestation (Chan et al., 2015; Li et al., 2020; McHugh & Weiss, 2019; Ostacher, 2007; Pettinati, 2004). However, in the absence of significant depression symptoms, studies show heterogeneous results and a trend toward no evidence of antidepressants on AUD symptoms (Iovieno et al., 2011; Nunes & Levin, 2004; Torrens et al., 2005). Importantly, some findings even indicate a negative effect of antidepressants on AUD symptoms, such as provoking premature relapse (Ballesta, Alén, et al., 2019; Brookwell et al., 2014; Dundon et al., 2004).

One likely solution for the heterogeneous findings on the effects of on alcohol use may be that they are a result of a latent mediation effect—i.e., improvement in depression symptoms due to antidepressants leads to improvement in AUD outcome (Nunes et al., 1998). Under this mediation hypothesis, a synthesis of the conflicting literature may be plausible: (1) antidepressants-induced reduction of depression symptoms leads to a reduction of alcohol use; (2) in the absence of depression symptoms no or even a negative effect on alcohol use may be observed; (3) the indirect effect of antidepressants on alcohol use through altered depression symptoms may mask a null or negative direct effect of antidepressants on alcohol use.

Evidence in favor of or opposing such a mediation hypothesis and the subsequent assumptions could be highly important for the treatment of patients with AUD since antidepressants medication is often part of the AUD treatment in clinical routine care (Agabio et al., 2018; Hillemacher & Frieling, 2019; Mark et al., 2003). However, to the best of our knowledge the associations of antidepressants, AUD and depression symptoms have not been adequately addressed for patients attending residential treatment. Therefore, the aim of the present study is to narrow this gap. Based on previous studies (Alén et al., 2013; Ballesta, Alén, et al., 2019; Brookwell et al., 2014; Dundon et al., 2004; Iovieno et al., 2011; Nunes &

Levin, 2004), we assume antidepressants to have an overall positive impact on depression symptoms and alcohol use. We expect a decrease in depression symptoms to be associated with a decrease in alcohol use as well and that the direct effect of antidepressants on alcohol use diminishes when accounting for the change in depression symptoms (Nunes et al., 1998).

METHODS

Participants

All participants were part of a multicenter, double-blind randomized controlled trial (for detailed information see, Tschuemperlin et al., 2019). We extend upon the previous work and data of Stein et al. (2023), which conducted a comprehensive double-blind, randomized clinical trial on alcohol-specific inhibition training among patients with AUD, conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. For a full understanding of the methodology and broad findings from that study, we direct readers to the original publication.

Patients were detoxified, attended an approximately 12-week abstinence-oriented residential treatment program for AUD between 2015 and 2019 in one of three specialized treatment centers in Switzerland (Suedhang Clinic Bern, Forel Clinic Zuerich, and Psychiatric Hospital Muensingen). The relevant time points to the present study are the assessment at treatment admission (T1), discharge (T2), and 3-month follow-up (T3) after residential treatment discharge.

Inclusion criteria consisted of a diagnosis of AUD according to DSM-5 (assessed with DIA-X, adapted to DSM-5 criteria (World Health Organization, 1993)) and 18–60 years of age. Exclusion criteria were as follows: (1) a primary psychiatric diagnosis other than AUD (psychiatric comorbidity was permitted in patients for whom AUD was considered the primary diagnosis); (2) additional severe substance use disorders (with the exception of nicotine; as determined by a score of 25 or greater per substance on the Drug Use Identification Test (Berman et al., 2005)); (3) neurological conditions (e.g., Korsakoff syndrome); (4) existing medical conditions that precluded participation (e.g., acute infectious disease); or (5) an inability to read and understand the study details. Possible reasons for exclusion during the study were voluntary discontinuations and deterioration of either physical or mental health. Table 1 presents sociodemographic and clinical characteristics of the sample including 42 females (27.5%) and 111 males with an average age of 45.4 (SD = 9.60) years. Twenty-four patients were diagnosed with a moderate to severe MDD according to the DIA-X interview at treatment admission and 65 patients received antidepressants medication during residential treatment.

All patients provided written informed consent and the study was approved by the local ethics committee (KEK-number: 2016-00988) and registered at Clinicaltrials.gov (NCT02968537) and the Swiss National Clinical Trials Portal (SNCTP000002043).

Measurements

Relevant measurements were obtained at admission (baseline), discharge, and 3-month follow-up treatment (for a detailed description, see Tschuemperlin et al., 2019). AUD and MDD diagnoses were validated using the Diagnostic Expert System for Psychiatric Disorders (DIA-X (Wittchen & Pfister, 1997), adapted to DSM-5). General, clinically significant, symptoms were assessed by the global severity index (GSI) of the Brief-Symptom-Checklist (BSCL; Derogatis, 1993).

Assessment of AUD and alcohol use

Evaluating alcohol use, and its intrapersonal change between pre- (baseline) and post-inpatient treatment, was based on estimating the difference in the percentage of days abstinent (PDA, i.e., days without alcohol consumption). PDA was calculated, for the respective 90-day period, by averaging the estimated assessed with a timeline follow-back interview (TLFB (Sobell & Sobell, 1992)), within the Health and Daily Living Form questionnaire (HDL (Moos et al., 1990)), and a short telephone interview (only at 3-month follow-up). To account for bias related to inpatient stays in a protected environment (defined as psychiatric, substance-related, or somatic inpatient facility) PDA was adjusted and calculated as: PDA = ((days abstinent − days inpatient treatment)/(90 − days in inpatient treatment) × 100). Since the expected difference of PDA at baseline—between patients receiving antidepressants medication and patients who do not—was not zero, we opted for the best practice of computing walkera change-score model. Intrapersonal change was thus calculated as $PDA_{\Delta} = PDA_{post} - PDA_{pre}$. Additionally, AUD symptom severity was assessed with the Alcohol Use Disorders Identification Test at treatment admission (AUDIT (Saunders et al., 1993)).

Assessment of depression symptoms

The depression subscale of the Brief-Symptom-Checklist (BSCL (Derogatis, 1993)) was used to assess depression symptom severity at treatment admission (baseline; Cronbach's alpha = 0.885), discharge (Cronbach's alpha = 0.894), and 3-month follow-up. At baseline, those were validated with the Beck Depression Inventory (BDI-II (Beck et al., 2006); Cronbach's alpha = 0.913). To estimate the intrapersonal change of depression symptoms between baseline and discharge, the within-patient difference was calculated as: $DS_{\Delta} = DS_{post} - DS_{pre}$.

Assessment of antidepressant medication

Antidepressant medication was assessed at treatment admission and discharge. Antidepressant medication was categorized according to the classification system of the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC – ATC/DDD Index, n.d.) into

TABLE 1 Sociodemographic and clinical sample characteristics.

	Total sample		No-AD		AD		
Variable	***N***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	**Test**
Clinic	153		88		65		$\chi^2 = 3.31$
Suedhang Clinic	95	62.10%	60	68.20%	35	53.80%	
Forel Clinic	47	30.70%	23	26.10%	24	36.90%	
Psychiatric Hospital Muensingen	11	7.20%	5	5.70%	6	9.20%	
Age	153	45.371 (9.6)	88	44.15 (10.44)	65	47.02 (8.11)	$F = 3.41$
Gender	153		88		65		$\chi^2 = 5.95$
Male	111	72.50%	71	80.70%	40	61.50%	
Female	42	27.50%	17	19.30%	25	38.50%	
Marital status	153		88		65		$\chi^2 = 3.65$
Single	64	41.80%	36	40.90%	28	43.10%	
Married, living together	31	20.30%	18	20.50%	13	20%	
Married, living separately	12	7.80%	5	5.70%	7	10.80%	
Divorced	43	28.10%	26	29.50%	17	26.20%	
Concubinage	1	0.70%	1	1.10%	0	0%	
Widowed	2	1.30%	2	2.30%	0	0%	
Years of education	151	13.709 (3.03)	87	13.97 (2.57)	64	13.36 (3.55)	$F = 1.49$
Employment	153		88		65		$\chi^2 = 2.01$
Unemployed	69	45.10%	39	44.30%	30	46.20%	
Part-time position	20	13.10%	9	10.20%	11	16.90%	
Full-time position	58	37.90%	36	40.90%	22	33.80%	
Protected employment	6	3.90%	4	4.50%	2	3.10%	
Duration of inpatient treatment	150	107.96 (49.39)	86	103.28 (41.76)	64	114.25 (57.84)	$F = 1.82$
No. of prior detoxifications	153	2.17 (3.58)	88	1.94 (3.52)	65	2.492 (3.66)	$F = 0.65$
Age of problematic drinking	153	32.10 (11.52)	88	31.17 (10.98)	65	33.35 (12.18)	$F = 1.35$
AUDIT	114	22.64 (5.63)	65	22.71 (5.91)	49	22.55 (5.28)	$F = 0.02$
BSCL GSI	153	0.735 (0.54)	88	0.574 (0.46)	65	0.952 (0.57)	$F = 20.77^*$
BSCL depr. baseline	153	0.978 (0.88)	88	0.733 (0.81)	65	1.31 (0.88)	$F = 17.76^*$
BSCL depr. discharge	137	0.482 (0.73)	81	0.38 (0.73)	56	0.63 (0.73)	$F = 3.63$
Δ BSCL depr.	137	−0.381 (0.68)	81	−0.27 (0.67)	56	−0.55 (0.67)	$F = 5.72^*$
BDI-II							
No depression (0–8)	58		45	51.1%	13	20%	$\chi^2 = 17.9^{**}$
Minimal depression (8–13)	30		17	19.3%	13	20%	
Mild depression (14–19)	23		10	11.4%	13	20%	
Moderate depression (20–28)	29		11	12.5%	18	27%	
Severe depression (29–63)	13		5	5.7%	8	12.3%	
M-to-S-MDD DIA-X	153		88		65		$\chi^2 < 0.01$
No	138	90.20%	79	89.80%	59	90.80%	
Yes	15	9.80%	9	10.20%	6	9.20%	
PDA baseline	153	22.81 (26.91)	88	23.12 (28.22)	65	22.39 (25.26)	$F = 0.03$
PDA 3-month follow-up	153	86.70 (27.23)	88	90.69 (24.16)	65	81.30 (30.28)	$F = 4.55^*$
Δ PDA	153	63.892 (27.94)	88	67.57 (27.62)	65	58.91 (27.81)	$F = 3.66$

Abbreviations: AD, antidepressant medication group; AUDIT, Alcohol Use Disorders Identification Test; BDI II, Beck Depression Inventory with severity categorization; BSCL depr., Depression Subscale of the Brief Symptom Check List; BSCL GSI, Global severity index of the Brief Symptom Check List; m-to-s-MDD DIA-X, moderate-to-severe depression diagnosis according to the diagnostic expert system for psychiatric disorders; No. Detox, number of prior detoxifications; No-AD, no antidepressant medication group; PDA, percentage of days abstinent; ΔDS, the average difference from baseline to discharge of the severity of depressive symptoms; ΔPDA, the average difference from baseline to 3-month follow-up of the percentage of days abstinent.

$^*p < 0.05$.

$^{**}p < 0.01$.

the following groups: nonselective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), other antidepressants (N06AX). The group of selective serotonin reuptake inhibitors was the most used antidepressantmedication in the present sample, with escitalopram as the dominant agent (see Table S1). At treatment admission nine patients received a combination of two antidepressants, with the majority receiving an atypical antidepressantas a supplement. Furthermore, only antidepressants used to treat explicitly depressive symptoms were included. Other antidepressant medication, (which are selectively administered in subtherapeutic dosages as a sleep inducement therapy) were excluded. Patients were subsequently divided into two groups: the group receiving antidepressant medication (AD group; $n=65$) and the group without antidepressantmedication (No-AD group; $n=88$).

Statistics

This study follows the "AGReMA" Statement Guidelines for Reporting Mediation Analyses of Observational Studies (Lee et al., 2021). We analyzed the data for potential missingness patterns with little's MCAR-test and by testing for inter- antidepressant-group differences. Missing data were treated with multiple-imputations and sensitivity analyses were conducted with complete-cases and last-observation-carried-forward (see Table 2 and Appendix S1).

To investigate the association between antidepressant medication, depression symptoms, and alcohol use, we conducted a mediation analysis (Rijnhart et al., 2021) based on change-score models (Valente et al., 2021). The mediation analysis is grounded in the theoretical underpinning that antidepressants do not simply have a direct effect on alcohol use outcomes, but rather exert an effect through the improvement of depression symptoms, which in turn affects alcohol use outcomes. This is consistent with the cascade model of intervention effects by Stice et al. (2009, 2010), which posits that treatment affects an intermediate variable (e.g., depression symptoms), and this variable then influences the primary outcome (e.g., alcohol use). Antidepressant medication was therein the predictor, DS_{Δ} the proposed mediator, and PDA_{Δ} the outcome. The mediation analysis was performed using the R package "mediation" (Racine, 2012; Tingley et al., 2014). The regression coefficients of the mediation model were first calculated in separate regression models. Equations (1) and (2) constitute the equations utilizing change scores for the mediator and the outcome variable, respectively.

$$DS_{\Delta} = i_1 + \beta_1 AD + e_1, \quad (1)$$

$$PDA_{\Delta} = i_2 + c'AD + \beta_2 DS_{\Delta} + e_2. \quad (2)$$

We estimated the mediation effect by calculating the product of β_1 from Equation (1) and β_2 from Equation (2), which represents the indirect effect of antidepressants on PDA_{Δ} through its effect on DS_{Δ}. We then tested these relationships in a single model using a bootstrapping approach relying on a quasi-Bayesian framework (using the standard method of the package MBESS v. 4.9.3 in R) to assess the effects credible-intervals in a full model. The unstandardized effects were calculated for 1000 bootstrap samples, and the 95%-credible interval was calculated by determining the effects at the 2.5th and 97.5th percentile. We additionally performed a comprehensive examination of the covariates sex, age and clinic site and their potential impact on our model. Because of the nonsignificance of these covariates the statistical analysis are only reported in the supplements.

In addition, the presence or absence of a moderate-to-severe MDD diagnosis assessed with the DIA-X at baseline was evaluated as a dichotomous variable. This was intended to address the following analytic objectives: (1) to determine whether the presence of such a diagnosis correlates with the prescription of antidepressant medication; (2), to estimate a possible interaction of such a diagnosis with the effect of antidepressants on PDA_{Δ}.

RESULTS

Participants

The two patient groups, patients with AUD and an antidepressant medication (AD) or without an antidepressant medication (No-AD) did not differ significantly in any sociodemographic, alcohol specific or clinical characteristics except of depression symptoms und general symptom severity (GSI BSCL) at treatment admission (see Table 1); little's MCAR-test was not statistically significant ($p=0.51$). Variables of interest were balanced across the group AD and group No-AD at baseline, necessitating no adjustment for potential confounders.

TABLE 2 Effect of antidepressant medication on the change of percentage of days abstinent mediated by the change of depression symptoms based on multiple imputation, complete-cases, and LOCF.

	Multiple imputations			Complete-cases			LOCF		
Effect	**Est.**	**95% CI**	***p***	**Est.**	**95% CI**	***p***	**Est.**	**95% CI**	***p***
ACME	3.60	1.07 to 7.28	0.002	2.90	0.27 to 6.62	0.026	1.96	0.064 to 4.67	0.038
ADE	−12.40	−21.71 to −3.05	0.004	−13.18	−22.01 to −3.58	0.008	−10.62	−19.85 to −1.68	0.018
Total Effect	−8.80	−17.93 to 0.41	0.064	−10.28	−19.58 to 0.86	0.040	−8.66	−17.56 to 0.62	0.064

Abbreviations: ACME, average causal mediated effect; ADE, average direct effect; CI, credible interval; Est., estimate; LOCF, last observation carried forward.

Analysis

Figure 1 presents the estimated effect of *antidepressant* medication on PDA_{Δ}: direct, indirect through the mediation of DS_{Δ}, and in total. No evidence ($p > 0.05$) for a total effect was found. However, indications for an effect significantly different from zero imply that patients in the AD group, compared to the No-AD group, showed a conditional mean reduction of 12.4 PDA_{Δ}—i.e., when the mediation effect of DS_{Δ} is controlled, patients receiving *antidepressants* during residential treatment show fewer days abstinent in the 3 months following treatment. Further, the average mediation (i.e., indirect) effect of the bootstrap sample was 3.60 (95% CI [1.07, 7.28], $p = 0.002$). Hence in the present sample, DS_{Δ} is considered a significantly relevant mediator for the effect of AD on PDA_{Δ}, in the way that patients who improved in depression symptoms due to *antidepressant* medication reported an increased PDA_{Δ}, while patients with *antidepressants* without improvement in depression symptoms reported decreased PDA_{Δ}.

Table 2 presents the estimated effects of the full mediation models, relying on quasi-Bayesian bootstrapping. While regarding the models based on multiple-imputations as main results, under all three data missingness assumptions, the same pattern of effects is evident.

There was no indication for a correlation between antidepressant and a moderate-to-severe MDD diagnosis statistically significantly different from zero ($\chi^2(1153) = 0.001$, $p = 0.99$). However, a significant effect of antidepressant medication while controlling for the diagnosis of moderate-to-severe MDD has been observed, suggesting that patients receiving antidepressant medication experience −10.35 lower PAD_{Δ} ($t(151) = -2.17$, $p = 0.032$, SE = 4.77; see Table S2).

DISCUSSION

In the context of a limited understanding surrounding the effects of antidepressant medication in the treatment of AUD, we aimed to disentangle the multifaceted relationship between antidepressant medication, co-occurring depression symptoms, and post-discharge alcohol use in patients attending residential AUD treatment. Our findings advocate for a dual pathway framework in which antidepressants concomitantly are negatively and positively associated with alcohol use. Specifically, our findings revealed statistically a negative direct effect of antidepressants on abstinence three-month post-discharge and a positive indirect effect mediated by reduced depression symptoms. However, these contrasting effect pathways counterbalanced each other in the studied patients with AUD, indicated by a nonsignificant average total effect of antidepressants on abstinence in the mediation model. Taking into account the relationship of antidepressants to alcohol use within the context of the proposed dual-pathway framework hypothesis offers a substantial contribution to the existing literature, emphasizing that antidepressants may hinder and may promote days of abstinence (MacKinnon et al., 2000). The potential advantages of antidepressants for the abstinence of patients' with AUD seem to be closely tied to the alleviation of depression symptoms.

While prior studies have investigated the relationship between antidepressant medication and AUD outcomes in patients with AUD and comorbid depression (Chan et al., 2015; Li et al., 2020; McHugh & Weiss, 2019; Ostacher, 2007; Pettinati, 2004), they predominantly examined the overarching average total effect of antidepressant medications on alcohol use. Using a mediation model suggests a more nuanced understanding of the mechanisms of change. Thereby, the identified dual pathway framework may echo the inconsistent findings in previous research. For instance, some studies have reported that antidepressants may improve AUD treatment outcomes (Chan et al., 2015; Li et al., 2020; McHugh & Weiss, 2019; Ostacher, 2007; Pettinati, 2004), while others have found little or no benefit (Iovieno et al., 2011; Nunes & Levin, 2004; Torrens et al., 2005), or even a negative effect (Ballesta, Alén, et al., 2019; Brookwell et al., 2014; Dundon et al., 2004; Muhonen et al., 2008; Yoon & Petrakis, 2018; Zhou et al., 2015). Our findings might help to reconcile some of these conflicting results by suggesting that the benefits of antidepressants for patients with AUD hinge on their potential to alleviate depression symptoms. Particularly our proposed framework suggests that antidepressants may prove beneficial for patients with AUD only when depression symptoms improve concurrently; otherwise, antidepressants may exacerbate alcohol use. It both emphasizes that antidepressants may have a negative impact on alcohol use and acknowledges that when antidepressants are expected to improve

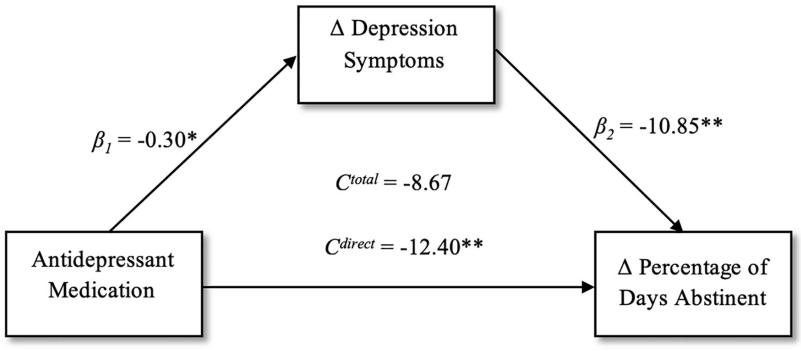

FIGURE 1 Effect of antidepressant medication during residential treatment on the change of percentage of days abstinent mediated by the change of depression symptoms. *Note*: The values shown are the unstandardized regression weights. *$p < 0.05$; **$p < 0.01$.

depression symptoms—a benefit that has shown to be only evident in patients with at least moderate to severe depression symptoms (Fournier et al., 2010)—they may reduce alcohol use. There are several studies showing that antidepressants significantly reduce depression symptoms in patients with AUD and comorbid depression but have no effect on alcohol-related outcomes (Zhou et al., 2015). However, our results support that in the absence of moderate-to-severe depression symptoms and when no improvement of those symptoms occur, a negative association of antidepressants and post-treatment alcohol use is likely to occur and may outweigh a positive (mediated) effect.

Our study highlights the importance of personalized clinical decision-making based on vigilant monitoring of depression symptoms during AUD treatment. This aligns with recommendations from previous studies that have emphasized the need for tailored treatment approaches to address the heterogeneity in patients with AUD (Knox et al., 2019; Litten et al., 2016). Furthermore, our findings support the notion that drinking as an AUD treatment outcome may be optimized by targeting both AUD and co-occurring depression symptoms (Mann et al., 2004; Riper et al., 2014).

Several notable limitations of this study warrant discussion: Firstly, our mediation analysis is a secondary data analysis of a multicenter, double-blind randomized controlled trial with repeated measures examining another research question and as such relies for this study on an observational design and not a randomized controlled double-blind study experimentally manipulating the antidepressant medication. Although the observed effects suggest important interactions, our findings should not be mistaken for causal relationships. To establish causality, future research should utilize experimental designs, such as randomized controlled trials, which enable causal inferences to be drawn. Secondly, it is worth considering that our sample size was arguably small, which could have potentially limited the power to detect smaller effect sizes and increased the risk of Type II errors. Larger samples in future studies could help to further validate our findings and provide more reliable estimates of the true effect size. Third, the generalizability of our results may be limited by the specific patient population included in the study, as participants were recruited from residential AUD treatment programs. Future research should aim to investigate the dual pathway framework in more diverse settings and populations, such as outpatient treatment programs and those with varying levels of depression severity. Fourth, we recognize the importance of separating out classes of antidepressants due to their varying mechanisms of action and potential differences in their effects on AUD. In our study, we treated antidepressant medication use as a binary variable (yes/no) rather than differentiating between specific classes and dosages (Pettinati, 2001). While this may introduce some variability in the observed effects, our main message remains focused on the aggregated mediating role of depression symptoms. Fifth, the residential treatment program included next to regularly psychotherapy sessions, various group therapies focusing on addiction but also on general emotion and stress regulation, behavioral activation, meditation, art- and music therapy. The skills attained in these treatment approaches do not only target addiction but also depressive symptoms, which was not systematically assessed nor included in the mediational model. Finally, our primary hypothesis investigated the indirect effect of antidepressants on alcohol use through changes in depression symptoms. However, it should be noted that the patients in our sample showed a great variability regarding depression symptoms at baseline, thus the effects may differ in other samples.

In conclusion, our study provides a rationale to characterize the relationship between antidepressant medication, post-discharge alcohol use, and depression symptoms in patients attending residential AUD treatment, by proposing a dual effect pathway framework. This framework highlights the potential benefits and drawbacks—i.e., a negative association of antidepressants and alleviation of depressive symptoms, respectively with abstinence at three-month follow-up. Our findings call for personalized clinical decision-making based on vigilant monitoring of depression symptoms, and adopting tailored treatment approaches to optimize AUD treatment outcomes. Although our study is limited by its observational design, it contributes to the existing literature by reconciling previously conflicting results. Given the frequent co-occurrence of AUD and depression symptoms and their treatment with antidepressant medication, our study offers potential implications for everyday clinical practice and calls for further investigation of the dual pathway hypothesis in diverse settings and populations.

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CONFLICT OF INTEREST STATEMENT

The authors report no financial or other relationship relevant to the subject of this article.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed for the present study are not publicly available but are available from the corresponding author at reasonable request. Code, and additional analyses are publicly available via the Open Science Framework: https://osf.io/4fc6q and Github: https://github.com/Joshuajaeger.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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