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# Does Comorbid Anxiety or Depression Moderate Effects of Approach Bias Modification in the Treatment of Alcohol Use Disorders?

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**Objective:** Approach bias modification (ApBM) is a promising new add-on training intervention for patients with alcohol use disorder (AUD). Given that comorbid anxiety and major depressive disorders are very common in AUD, and that such comorbidity affects psychological treatments negatively, the primary aim of the present study was investigating whether ApBM training is moderated by anxiety/major depressive disorder comorbidity. The secondary aim was to examine whether ApBM's relapse-preventive effect can be replicated. **Method:** We conducted a large-scale randomized controlled trial (RCT) in a clinical sample of AUD inpatients ($n = 729$) with a follow-up assessment after 1 year. All patients received 12 weeks of inpatient treatment as usual (TAU). On top of that, patients were randomized to a 12-session ApBM (TAU + ApBM), and a no-training control condition (TAU-only). Treatment success was defined as either no relapse or a single lapse shorter than 3 days in duration, ended by the patient and followed by at least 4 weeks of abstinence. Failure was defined as relapse, passed away, no contact, or refusal to provide information. **Results:** We found that TAU + ApBM had significantly higher success rates than TAU-only at 1-year follow-up. Importantly, anxiety/depressive comorbidity moderated ApBM's effects: Adding ApBM to TAU increased success rates more for patients with a comorbid anxiety and/or depressive disorder than for patients without such comorbidity. **Conclusions:** Our data suggest that adding ApBM to TAU works better in patients with a comorbid anxiety and/or depressive disorder; a promising finding gave the high rates of comorbidity in clinical practice.

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### Public Health Significance Statement
This study indicates that patients with an alcohol use disorder (AUD) who received standard care plus training to avoid alcohol cues had less relapse into drinking about a year later compared to patients who only received standard care. This study indicates that among patients with an AUD, it is particularly those who have an additional anxiety or major depressive disorder, who benefit from the alcohol-avoid training.

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In 2010, approximately 11 million Europeans (3.4%) between the ages of 18 and 64 met the criteria for alcohol dependence (Rehm et al., 2015). A more general estimate, accounting for age and less severe forms of alcohol abuse, yielded 23 million affected people in Europe. These prevalence rates are alarming as problematic alcohol consumption has been identified as one of the leading avoidable risk factors for illness, disability, and mortality (Rehm et al., 2009). To make matters worse, co-occurring anxiety and/or depressive disorders are very common in alcohol use disorder (AUD: Lai et al., 2015; Stapinski et al., 2015). Life-time AUD is for example associated with persistent depression, panic disorder, specific phobia, and generalized anxiety disorder (Grant et al., 2015). Moreover, the estimated prevalence of anxiety disorders in substance abuse treatment settings is very high, with estimates as high as 80% (Bakken et al., 2007; see also Wolitzky-Taylor et al., 2011).

There are evidence-based psychological treatments for AUD, however, data are accumulating that a comorbid anxiety disorder or depressive disorder negatively impacts such treatments. Curran et al. (2002), for example, found that severe depressive symptomatology is a risk factor for early attrition from a substance use treatment. In addition, Driessen et al. (2001) reported that 60.5% of their noncomorbid AUD patients succeeded in staying abstinent at 6-months follow-up after Cognitive Behavior Therapy (CBT), while only 26.7% of the comorbid patients (AUD plus anxiety and/or depressive disorder) succeeded (see also Kushner et al., 2005). There is some inconsistency in the literature because some studies did not observe a greater risk of relapse for AUD patients with anxiety/depressive comorbidity compared to AUD patients without such comorbidity after treatment (e.g., see Marquenie et al., 2006 for anxiety comorbidity), but overall, it is suggested that comorbid anxiety disorders/major depressive disorders (ANX-DEP) are associated with more relapse and poorer treatment outcome for AUD (Sliedrecht et al., 2019; Stapinski et al., 2015; Wolitzky-Taylor et al., 2011).

Recently, new methods have been developed in the context of AUD treatment. Cognitive Bias Modification paradigms (CBM, reviews: Wiers et al., 2013, 2018) have been designed to retrain cognitive biases which are assumed to play an important role in addictive behaviors (Stacy & Wiers, 2010; Strack & Deutsch, 2004). In a computerized joystick task, many heavy drinkers and AUD patients have an approach bias for alcohol stimuli; they have a stronger tendency to pull alcohol-related stimuli closer than to push them away (Wiers et al., 2009, 2011). A training paradigm has been designed to reduce this maladaptive action tendency bias, the so-called alcohol Approach Bias Modification (ApBM). Individuals are trained to make avoidance movements (pushing a joystick) in response to alcohol-related pictures, with the pictures also shrinking in size (zooming effect). Studies in students and alcohol-dependent patients have shown that action tendencies can be changed by the computerized ApBM training with effects on drinking behavior (review: Kakoschke et al., 2017). Wiers et al. (2011), for instance, showed that ApBM combined with treatment as usual (TAU) in abstinent alcohol-dependent inpatients changed implicit alcohol-approach tendencies into avoidance tendencies and, most importantly, in clinical terms, treatment outcome improved. At 1-year follow-up, 13% fewer patients relapsed in the TAU + ApBM group compared to the TAU + Control group. This pattern of findings has been replicated (Eberl et al., 2013; Manning et al., 2016, 2021; Rinck et al., 2018), and in one of these studies, the changed approach bias mediated the effect on relapse rates at 1-year follow-up (Eberl et al., 2013).

CBM training, including ApBM, appears to be a promising new approach that could supplement existing treatments for AUD. However, a recent meta-analysis on CBM in addiction is critical about CBM's utility (Cristea et al., 2016) and there is notable variability in CBM's effectiveness (Boffo et al., 2019). Variability in findings could be related to differences in the populations studied (patients vs. community volunteers), the format (stand-alone vs. addition to TAU; online vs. offline), the type of study (experimental vs. clinical) (Wiers et al., 2018), and success in bias change (Grafton et al., 2017). Given that ANX-DEP comorbidity impacts upon CBT's effectiveness, such comorbidity could equally impact upon CBM's effectiveness, explaining the observed variety in CBM effects. Up to now, however, ANX-DEP comorbidity as a potential moderator of CBM's effectiveness has never been tested.

Therefore, the primary aim of the present study was to investigate whether the presence of additional anxiety and/or major depressive disorder moderates the effectiveness of ApBM, and whether the preventive effects of ApBM on relapse rates can be replicated in currently abstinent AUD inpatients. To test this, a large-scale randomized controlled trial (RCT) was conducted in a clinical sample of currently abstinent AUD inpatients with a 1-year follow-up assessment. All AUD patients received treatment as usual (TAU). On top of that, patients were randomized to an additional 12-session ApBM (i.e., TAU + ApBM) or to a no-training control condition (i.e., TAU-only, note that earlier studies found no difference in outcomes between sham-trainings and no training, Rinck et al., 2018; Wiers et al., 2011). To modify alcohol-approach bias, an ApBM task was used to train patients to push away (avoid) alcohol-related pictures. The primary, clinical outcome variable was relapsed at 1-year follow-up (Eberl et al., 2013; Rinck et al., 2018; Wiers et al., 2011).

## Method

### Participants

Participants were currently abstinent AUD patients receiving a 12-week inpatient treatment at the salus clinic in Lindow, Germany. Patients were informed about the study and their option to withdraw from it, without incurring any disadvantages regarding their treatment. Included patients signed informed consent. The patient's information letters and informed consent form are included in the Supplemental Materials section. The study was approved by the

**Table 1**
*Participant Characteristics of TAU + ApBM and TAU-Only Group: Means (SDs) and Significance of Group Difference Tests*

| Characteristics | TAU + ApBM group | TAU-only group | Statistics | *p* value |
|---|---|---|---|---|
| $N^a$ | 304 | 425 | — | — |
| Age, mean (*SD*), years | 46.5 (9.0) | 46.1 (8.4) | $t(727) = 0.58$ | .56 |
| Sex (% male) | 76.3% | 72.2% | $\chi^2(1) = 1.53$ | .22 |
| Education level, mean (*SD*) | 3.1 (0.8) | 3.0 (0.8) | $t(727) = 1.66$ | .10 |
| AUDIT score, mean (*SD*) | 25.4 (7.0) | 24.7 (7.3) | $t(697) = 1.16$ | .25 |
| ANX-DEP comorbidity (%) | 21.1% | 19.5% | $\chi^2(1) = 0.26$ | .61 |
| Smoking: Fagerström score, mean (*SD*) | 4.6 (2.7) | 4.8 (2.7) | $t(604) = 1.10$ | .27 |
| Depression: BDI score, mean (*SD*) | 12.8 (10.6) | 12.5 (10.6) | $t(712) = 0.39$ | .70 |
| Mental burden: SCL-90 score, mean (*SD*) | 59.2 (10.9) | 59.1 (10.9) | $t(685) = 0.14$ | .89 |

*Note.* ApBM = approach bias modification; TAU = Treatment as Usual; For education level, each score means successfully finished that level with 1 = primary school, 2 = basic school (9 years), 3 = intermediate school (10 years), 4 = high school (12 years), and 5 = university. AUDIT = Alcohol Use Disorders Identification Test; ANX-DEP = anxiety disorder and/or major depressive disorder; BDI = Beck Depression Inventory; SCL-90 = Symptom Checklist-90.
[a] Sample sizes vary per analysis due to missing values.

ethics committee of the German Pension Fund (8011-106-31/31.96) and registered in the ISRCTN registry with number ISRCTN 97173360. The study was a continuation of the procedure described by Eberl et al. (2013). The patients in the present study did not participate in the study by Eberl et al. (2013) nor in the Rinck et al. (2018); it is a new data set and there is no overlap. The recruitment for the study started in September 2009 and was finished in September 2010. Every patient had a primary diagnosis of alcohol dependence International Classification of Diseases (ICD-10), assessed with the computerized version of the Composite International Diagnostic Interview (CIDI; Robins et al., 1988). This was complemented by a diagnostic interview based on the "German Manual for Documentation in Addiction Help" published by the German "Hauptstelle für Suchtfragen, DHS." Both the CIDI and the interview formed the basis for clinical psychologists to formulate the final diagnoses. Exclusion criteria were nonnative speakers of German, history of schizophrenia or psychotic disorders, visual or hand-motoric handicaps, strong withdrawal symptoms, neurocognitive problems, or participation in the Eberl et al. study. None of the patients received anticraving medication.

The sample consisted of 729 patients (mean age 46.3 years, $SD = 8.7$; 539 males) who were randomly allocated to the TAU + ApBM ($N = 304$) or the TAU-only group ($N = 425$). The TAU + ApBM group completed on average 9.2 training sessions ($SD = 4.4$). The two groups did not differ significantly in age, sex distribution, education level, severity and duration of alcohol dependence, nicotine dependence, depression, or level of distress and mental burden (Symptom Check List-90, SCL-90, Franke & Stacker, 1995; see Table 1 for the sample characteristics). ANX-DEP comorbidity is defined as having a comorbid anxiety disorder (panic disorder, agoraphobia, generalized anxiety disorder, social anxiety disorder, specific anxiety disorder, unspecified anxiety disorder) and/or a comorbid major depressive disorder (single episode moderate, severe, or reactive; or recurrent in nature).[1] Based on the CIDI and diagnostic interview, 147 patients (20.2%) were part of the ANX-DEP group (see Supplemental Materials, Table 1 for frequencies). These patients with ANX-DEP comorbidity did not differ significantly in Alcohol Use Disorders Identification Test (AUDIT) scores from the 582 patients without such comorbidity ($p = .11$). The TAU + ApBM and TAU-only group did not differ significantly in the distribution of patients with versus without

ANX-DEP comorbidity (TAU + ApBM: $n = 64$ vs 240; TAU-only: $n = 83$ vs 342; see Table 1).

## Materials

### ApBM

The ApBM consisted of 12 sessions of training (see also Eberl et al., 2013). Each session took approx. 15 min and was designed to train avoidance movements as the response to pictures of alcoholic beverages, and approach movements as the response to pictures of nonalcoholic beverages. All pictures were presented in landscape or portrait format, which served as the cue for the correct response: Patients had to push the joystick in response to landscape pictures, and pull the joystick in response to portrait pictures. Pushing the joystick away was accompanied by a zoom-out effect (the picture decreased in size), whereas pulling the joystick resulted in a zoom-in effect (the picture increased in size). This dynamic zoom effect created the subjective impression of pushing the pictures away or pulling them closer. After moving the joystick completely in the correct direction, the picture disappeared. The joystick then had to be moved back to the central position. Upon pressing the fire button of the joystick, the next picture appeared. The stimuli set consisted of 10 different pictures of alcoholic beverages and 10 different pictures of nonalcoholic beverages.

Each training session consisted of 200 training trials. Here, 100 alcohol pictures were always presented in the push-away format (each of the 10 different pictures 10 times), and 100 nonalcohol pictures always in the pull-closer format (each of the 10 different pictures 10 times). The trials were presented in a quasirandomized order, such that pictures of the same format were not presented more than three times in a row.

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[1] There were $n = 29$ AUD patients (4.0%) who were in-between cases. These patients had no anxiety disorder, and only a bipolar disorder ($n = 4$), dysthymia (persistent mood disorder, $n = 7$), or major depressive disorder, single episode, mild subtype ($n = 11$). As such, they did not belong to the comorbid ANX-DEP group. However, as they also do not fully belong to the noncomorbid group either, we have analyzed the data with these $n = 29$ patients excluded. This does not change any of the results, including the significant interaction between Training group and ANX-DEP comorbidity in the second step of the regression analysis, $p = .04$, Exp(B) = 2.23.

### Follow-Up Assessment Relapse

Relapse was evaluated at 1-year follow-up (FU) using a binary outcome variable (successful outcome or not), following conservative intention-to-treat (ITT) principles. As defined by the DGSS-4 (Deutsche Gesellschaft für Suchforschung und Suchttherapie) standard of the German Addiction Society, successful outcomes consisted of either no relapse at all or a single lapse shorter than 3 days in duration, ended by the patient without further negative consequences and followed by at least 4 weeks of abstinence until FU. Failure was defined as relapse, passed away, no contact, or refusal to provide information (as in Eberl et al., 2013; Rinck et al., 2018; Wiers et al., 2011).

### Questionnaires

To assess drinking amount, frequency, and negative consequences, the German version of the AUDIT (Saunders et al., 1993) was used. The questionnaire consists of 10 items and has high test–retest reliability ($r = .95$; Dybek et al., 2006).

The German version of the Fagerström Test for Nicotine Dependence (FTND; Bleich et al., 2002) was used as a self-report measure of the degree of nicotine dependence. The test–retest reliability of the German version is high ($r = .88$; Bleich et al., 2002).

We assessed the level of depressive symptoms with the German version of the Beck Depression Inventory (BDI; Hautzinger et al., 1994). It is a 21-item self-report questionnaire with high internal consistency (Cronbach's $\alpha = .80$) and test–retest reliability ($r = .92$; Hautzinger et al., 1994).

The German version of the SCL-90 (Franke & Stacker, 1995) was used to measure physical and psychological impairment. It consists of 90 items, and answers are given on a five-point scale. A global severity index indicates the overall level of distress and mental burden and has excellent internal consistency (Cronbach's $\alpha = .97$; Franke & Stacker, 1995).

### Procedure

During the first week of treatment, AUD patients completed the CIDI, a diagnostic interview, and the questionnaires described above. All patients had finished detoxification before entering the clinic. After the first week, participating patients were randomly assigned to the TAU + ApBM or the TAU-only group. ApBM training is conducted on a PC. As the present study provided 12 sessions of ApBM training compared to four sessions in an earlier study (Wiers et al., 2011), the single room with three PCs was not sufficient to train patients with 12 sessions each. Therefore, the randomization to the conditions was based on 40% of the patients being allocated to the TAU + ApBM and 60% of the patients to the TAU-only, from the first participant onwards. An excel program generated a random number between 1 and 100 (inclusive). Anybody with a number of 40 or below was allocated to the TAU + ApBM training, and the rest was allocated to the TAU-only group. The training sessions started approximately 6 weeks before the patients' planned discharge, to ensure a standardized amount of time between the last training session and discharge. Patients allocated to the TAU + ApBM group were scheduled to complete 12 sessions of training, preferably within 4 weeks. Independently of the training group, all patients received treatment

as usual (TAU). TAU consisted of an inpatient abstinence-oriented, multidisciplinary program including individual and group sessions of CBT, social work, relaxation training, and physical exercises. As part of the routine clinical procedure, participants received a standard follow-up questionnaire 1 year after treatment discharge. It was asked whether patients had been continuously abstinent during the past year. If they denied, additional questions addressed the type of drugs consumed, the duration of abstinence after treatment discharge, the duration of the current abstinence (if currently abstinent), the number and duration of the relapse(s), and the way the last relapse was ended (if it was ended). Patients who did not return the questionnaire were reminded by mail once, and finally an attempt was made to reach them by phone. As a result, the interval period between the end of treatment and the follow-up assessment varied between 12 and approximately 13 months, depending on when the patient responded to the contact attempts. The patients were contacted by therapists or interns who did not know which experimental group the patient belonged to.

### Data Analysis Plan

To examine whether ApBM yields higher success rates than TAU-only, and explore whether ANX-DEP comorbidity moderates the effect of ApBM on clinical success, we used a hierarchical logistic regression analysis. Training group (TAU + ApBM vs. TAU-only), ANX-DEP comorbidity (yes vs. no), and Sex (given sex differences in success rates, Wiers et al., 2011) were entered in the first step of the hierarchical logistic regression analysis, and the interaction between Training group and ANX-DEP comorbidity was entered in the second step of the analysis.[2] Clinical success at 1-year follow-up (yes vs. no) was the dependent variable. All analyses were conducted following conservative ITT principles (including patients with incomplete training sessions),[3] using two-sided tests with $p = .05$. To further test the replicability of ApBM preventive effects at 1-year follow-up, we also conducted a Chi-square test comparing the number of successes and failures in the TAU + ApBM and TAU-only groups, given that previous studies also reported Chi-square tests.

### Results

In the first step of the hierarchical logistic regression analysis (see Table 2), only Training group was a significant predictor of clinical success. AUD patients who had followed the ApBM training on top

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[2] As Eberl et al. (2013) found that age moderated the efficacy of ABM, we examined whether ANX-DEP comorbidity was related to age. In the current data set, the comorbid and non-comorbid groups did not differ significantly in age, $t(727) = 1.36$, $p = 0.174$. It thus seems unlikely that age may have confounded the present analyses.

[3] The analyses were also conducted using a "completers" approach, including only patients with a complete training (defined as ten or more sessions, cf. Eberl et al., 2013); $n = 207$ in the TAU + ApBM group. Results were comparable to the ITT-approach with Training group being a significant predictor in the first step of the hierarchical logistic regression analysis, $p < .001$, Exp(B) = 1.86, and a significant Chi-square test, $\chi^2(1) = 12.27$, $p \leq .001$, $\phi = .14$, again indicating higher success rates in the TAU + ApBM compared to the TAU-only group. Furthermore, the interaction between Training group and ANX-DEP comorbidity was again significant in the second step of the regression analysis, $p = .03$, Exp(B) = 2.63. For all details, see Supplemental Materials, Results Completers Analyses.

**Table 2**
*Hierarchical Logistic Regression Analysis Results for Predicting Treatment Success at 1-Year Follow-Up*

| Step | Variable | $b$ | SE $b$ | Wald $z$ | $p$ | Exp(B) | 95% CI for Exp(B) |
|---|---|---|---|---|---|---|---|
| 1 | Sex | −0.21 | .17 | 1.46 | .23 | 0.81 | 0.58—1.14 |
| 1 | Training group | 0.42 | .15 | 7.67 | .01 | 1.53 | 1.13—2.06 |
| 1 | ANX-DEP comorbidity | −0.30 | .19 | 2.58 | .11 | 0.74 | 0.51—1.07 |
| 2 | Sex | −0.18 | .18 | 1.09 | .30 | 0.83 | 0.59—1.17 |
| 2 | Training group | 0.26 | .17 | 2.30 | .13 | 1.30 | 0.93—1.81 |
| 2 | ANX-DEP comorbidity | −0.65 | .25 | 6.51 | .01 | 0.52 | 0.32—0.86 |
| 2 | Training group × ANX-DEP comorbidity | 0.81 | .39 | 4.38 | .04 | 2.24 | 1.05—4.77 |

*Note.* Sex: 0 = female and 1 = male; Training group: 0 = TAU-only and 1 = TAU + ApBM, TAU = Treatment as usual, ApBM = approach bias modification; ANX-DEP = anxiety disorder and/or major depressive disorder; ANX-DEP comorbidity: 0 = no comorbidity and 1 = comorbid anxiety disorder or major depressive disorder.

of TAU (TAU + ApBM) were significantly more likely to have a successful outcome at 1-year follow-up compared to AUD patients in the TAU-only condition. Similarly, the significant Chi-square test indicated that the TAU + ApBM group yielded significantly higher success rates than the TAU-only group at 1-year follow-up, $\chi^2(1) = 7.23$, $p = .007$, $\phi = .10$. Of the patients in the TAU + ApBM group, 58.6% (178 out of 304) had a successful outcome at 1-year follow-up, compared to only 48.5% in the TAU-only group (206 out of 425; See Supplemental Materials, Table 2 for more details and frequencies of the follow-up assessment outcomes). Thus, we replicated the finding that adding ApBM to TAU increases success rates about 1 year later.

In the second step of the hierarchical logistic regression analysis (see Table 2), there were two significant predictors of clinical success. ANX-DEP comorbidity was a significant predictor with lower success rates for AUD patients with ANX-DEP comorbidity (compared to patients without such comorbidity) in the TAU-only group, as well as the interaction between Training group and ANX-DEP comorbidity. This highlights the role of comorbidity and indicates that the impact of the ApBM differed for patients with versus without ANX-DEP comorbidity (see Figure 1). To better understand the interaction effect, additional logistic regression analyses were conducted, separately for patients with versus without

**Figure 1**
*Illustration of the Interaction Between Training Group (TAU + ApBM vs. TAU-Only) and ANX-DEP Comorbidity (With vs. Without Comorbid Anxiety/Major Depressive Disorder) in Understanding Success at Follow-Up*



*Note.* TAU = Treatment as usual, ApBM = approach bias modification; ANX-DEP = anxiety disorder and/or major depressive disorder. See the online article for the color version of this figure.

ANX-DEP comorbidity (see Table 3). In patients with comorbid ANX-DEP, training group was a significant predictor of clinical success, with higher success rates in the TAU + ApBM group (62.5%) than in the TAU-only group (36.1%). In patients without ANX-DEP comorbidity, training group was not a significant predictor (TAU + ApBM: success rate = 57.5%, TAU-only = 51.5%). Overall, having a comorbid ANX-DEP reduced the likelihood of success after TAU: However, it increased the advantage of TAU + ApBM over TAU-only, suggesting that patients with ANX-DEP comorbidity especially benefitted from the added ApBM.

## Discussion

In a large sample of AUD patients, we found that the presence of a comorbid anxiety disorder/major depressive disorder diagnosis impacted upon ApBM's effectiveness. However, contrary to what might have been expected, AUD patients with a comorbid anxiety or major depressive disorder profited more rather than less from ApBM being added to TAU compared to AUD patients without such comorbidity. In general, having an anxiety or major depressive disorder in addition to an AUD is "bad news" because it is associated with more severe and chronic AUD (Wolitzky-Taylor et al., 2011) and lower treatment success rates (Sliedrecht et al., 2019; Stapinski et al., 2015; Wolitzky-Taylor et al., 2011). The present study also brings some "positive news" because ApBM was successful in the comorbid ANX-DEP sample. This shows that ApBM is not a training that is only effective for the milder cases without comorbidity. Instead, ApBM is actually very helpful for the disadvantaged patients who have an AUD and an anxiety and/or major depressive disorder.

This is the first study examining the moderating role of ANX-DEP comorbidity on ApBM's effects on relapse prevention, and clearly replication is necessary to examine the robustness of this finding. It is an open question why ApBM seems to work well, while CBT seems to work less well in AUD patients with a comorbid ANX-DEP. A possible explanation might be that the emotional symptoms in AUD patients with comorbid ANX-DEP interfere with fully engaging in a cognitively and emotionally demanding psychological treatment such as CBT, while they perform better in less demanding interventions such as ApBM. Another explanation might be the generally lower success rates in AUD patients with comorbidity, which leave more room for improvement in that group. Another possibility might be that ApBM results in broader changes in cognitive control with effects on the emotional symptoms of AUD
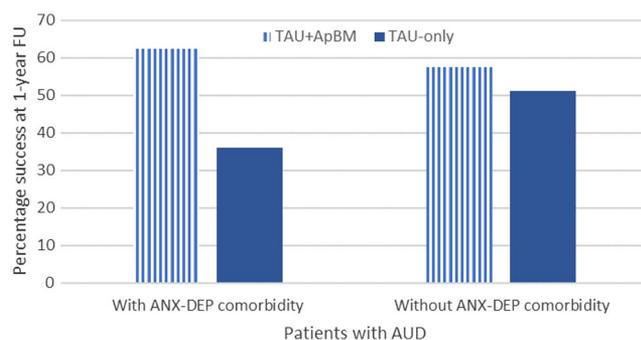
**Table 3**

*Logistic Regression Results for Predicting Treatment Success, Separately for Patients With and Without Anxiety/Major Depressive Disorder Comorbidity*

| Patients | Variable | $b$ | $SE\ b$ | Wald $z$ | $p$ | Exp(B) | 95% CI for Exp(B) |
|---|---|---|---|---|---|---|---|
| Comorbid | $N = 147$ | | | | | | |
| | Sex | 0.12 | .35 | 0.12 | .73 | 1.13 | 0.57—2.24 |
| | Training group | 1.09 | .35 | 9.90 | .01 | 2.98 | 1.51—5.88 |
| Noncomorbid | $N = 582$ | | | | | | |
| | Sex | −0.28 | .20 | 1.95 | .16 | 0.75 | 0.51—1.12 |
| | Training group | 0.27 | .17 | 2.44 | .12 | 1.31 | 0.93—1.82 |

*Note.* Comorbid patients = AUD patients with a co-occurring anxiety disorder and/or major depressive disorder; Noncomorbid patients = AUD patients without a co-occurring anxiety disorder and/or major depressive disorder; Sex: 0 = female and 1 = male; Training group: 0 = TAU-only and 1 = TAU + ApBM, TAU = Treatment as usual, ApBM = approach bias modification.

patients with ANX-DEP comorbidity. In ApBM, patients learn to respond differently to relevant stimuli, and this may result in a general increase in the ability to control and regulate responses (see Wiers, Stelzel, et al., 2015, for a comparable suggestion). Such increased regulatory control has been shown to affect the processing of emotional stimuli (Salemink & Wiers, 2012) and could result in less anxiety and depressive symptoms. Given the role of negative emotions and stress in relapse (Sinha, 2007), the increased cognitive control and reduced emotions might be an additional mechanism through which ApBM reduces relapse rates, specifically in AUD patients with ANX-DEP comorbidity. By including measures of cognitive control and emotional symptoms, future research could test the latter explanation of ApBM's increased effectiveness in AUD patients with comorbid ANX-DEP.

With respect to the aim of replicating the relapse-preventing effect of ApBM, we found that adding ApBM to TAU resulted in a 10.1% increase in success rate at about 1-year follow-up. That is, more patients in the TAU + ApBM group were abstinent at follow-up than patients in the TAU-only group. These findings replicate previous ApBM effects in clinical samples (Eberl et al., 2013; Manning et al., 2021; Rinck et al., 2018; Wiers et al., 2011) and add to the accumulating evidence of the added value of ApBM on top of TAU in AUD. Given that ApBM is low in cost, involves no therapist and only minimal time from the patient, it is a promising and cost-effective new add-on intervention in the treatment of AUD. These results of ApBM as an add-on to TAU in a clinical setting are in contrast to the less promising results of stand-alone ApBM offered online (Wiers, Houben, et al., 2015). There are several differences between those sets of studies, and more research is needed to identify which of these differences are crucial for the variability in ApBM effectiveness (Bratti-van der Werf et al., 2018). The current results might offer a tentative explanation: If the percentage of AUD patients with ANX-DEP comorbidity is higher in clinical samples than in online samples (many participants of online alcohol interventions are first-time help seekers (Riper et al., 2014)) and ApBM works better in patients with ANX-DEP comorbidity (this study), that might (partly) explain the diverging results between RCTs in clinical samples and online RCTs.

The present study is, as any study, not without limitations. First, a no-training condition was used as the control condition (TAU-only). While it reflects standard care, it is suboptimal from a research perspective because the two groups (TAU + ApBM vs. TAU-only) are not comparable in terms of exposure to alcoholic and nonalcoholic pictures, time behind a computer, time receiving an intervention, and other nonspecific factors. However, previous clinical trials with ApBM have included well-matched placebo-control conditions (Rinck et al., 2018; Wiers et al., 2011). None of these studies yielded significant differences between the placebo and the no-training control conditions, and all of them yielded comparable effects of ApBM on success rates at 1-year follow-up. Therefore, it seems unlikely that the effects observed here are entirely due to nonspecific factors, though that could not be tested in the present study. Moreover, for the present study about the influence of comorbidity, this problem (if it is one) is less relevant as it applies to both comorbid and noncomorbid patients. A second limitation of the present study is the absence of a measure of change in approach tendencies due to the limited amount of data. This is related to the practicalities of the clinical setting of this study. The clinic's policy regarding privacy and data security for example requires nightly removal of all data saved on the computers and this unfortunately interfered with the saving of the research data. Only one study found that ApBM effects on relapse prevention were mediated by the change in approach tendencies (Eberl et al., 2013). It therefore remains important to identify the working mechanism of ApBM specifically and CBM in general (Grafton et al., 2017). A third limitation is the lack of a biological confirmation of abstinence at follow-up. Fourth, it is unknown how the comorbid anxiety and depression diagnoses of the current patients changed over the course of treatment and during the follow-up period. Therefore, we do not know whether patients still fulfilled diagnostic criteria for those disorders, and whether ApBM had an impact on those disorders. Finally, the manuscript describes the analyses of data collected in 2009 and 2010. A limitation of the study is that the number of patients that were excluded by the exclusion criteria was not registered at that time. Also, registering a study was not yet a requirement and still very unusual for studies with an experimental-cognitive focus in clinical practice. Thus, while the study is registered, it was, unfortunately, not preregistered, which is a limitation of the study.

Summing up, this large-scale RCT replicated ApBM effects on success rates in currently abstinent AUD inpatients when adding it to TAU. AUD patients who completed TAU and ApBM training had higher success rates after about 1 year than AUD patients who had completed TAU-only. Furthermore, a comorbid anxiety and/or major depressive disorder moderated ApBM effectiveness: Adding ApBM to TAU increased success rates more for AUD patients with

ANX-DEP comorbidity than for AUD patients without such comorbidity. As comorbidity is frequent in AUD, this is a promising finding for clinical practice. We may also conclude that ApBM need not be reserved for AUD patients with no comorbidity: It has significant effects even in disadvantaged AUD patients who suffer from comorbid disorders such as anxiety or major depressive disorder.

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