Effects of Adrenal Sensitivity, Stress- and Cue-Induced Craving, and Anxiety on Subsequent Alcohol Relapse and Treatment Outcomes

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Context: Alcoholism is a chronic, relapsing illness in which stress and alcohol cues contribute significantly to relapse risk. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased anxiety, and high alcohol craving have been documented during early alcohol recovery, but their influence on relapse risk has not been well studied.

Objectives: To investigate these responses in treatment-engaged, 1-month–abstinent, recovering alcohol-dependent patients relative to matched controls (study 1) and to assess whether HPA axis function, anxiety, and craving responses are predictive of subsequent alcohol relapse and treatment outcome (study 2).

Design: Experimental exposure to stress, alcohol cues, and neutral, relaxing context to provoke alcohol craving, anxiety, and HPA axis responses (corticotropin and cortisol levels and cortisol to corticotropin ratio) and a prospective 90-day follow-up outcome design to assess alcohol relapse and aftercare treatment outcomes.

Setting: Inpatient treatment in a community mental health center and hospital-based research unit.

Participants: Treatment-engaged alcohol-dependent individuals and healthy controls.

Main Outcome Measures: Time to alcohol relapse and to heavy drinking relapse.

Results: Significant HPA axis dysregulation, marked by higher basal corticotropin level and lack of stress- and cue-induced corticotropin and cortisol responses, higher anxiety, and greater stress- and cue-induced alcohol craving, was seen in the alcohol-dependent patients vs the control group. Stress- and cue-induced anxiety and stress-induced alcohol craving were associated with fewer days in aftercare alcohol treatment. High provoked alcohol craving to both stress and to cues and greater neutral, relaxed–state cortisol to corticotropin ratio (adrenal sensitivity) were each predictive of shorter time to alcohol relapse.

Conclusions: These results identify a significant effect of high adrenal sensitivity, anxiety, and increased stress- and cue-induced alcohol craving on subsequent alcohol relapse and treatment outcomes. Findings suggest that new treatments that decrease adrenal sensitivity, stress- and cue-induced alcohol craving, and anxiety could be beneficial in improving alcohol relapse outcomes.

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(CRF) signaling in extrahypothalamic brain regions and altered hypothalamic-pituitary-adrenal (HPA) axis and autonomic responses have each been documented with long-term alcohol abuse.\textsuperscript{7-10} Blunted or unresponsive HPA axis responses to stress and CRF challenge in active and recently abstinent alcoholics are known.\textsuperscript{11-14} Early recovery from alcoholism involves an increased level of anxiety and alcohol craving, particularly with exposure to stressful or alcohol-related stimuli,\textsuperscript{14} a phenomenon that, in animal models, has been associated with stress-related CRF and noradrenergic mechanisms.\textsuperscript{15,16} Relapsing alcoholics show blunted cortisol responses to challenge,\textsuperscript{17-19} but concurrent assessment of stress-related measures, including HPA axis dysfunction and adrenal sensitivity, increased alcohol craving and anxiety during early alcohol recovery, and their possible effects on subsequent poor treatment engagement and alcohol relapse susceptibility have not been systematically investigated thus far, to our knowledge.

Using an experimental approach in an inpatient treatment research setting, combined with a prospective clinical outcome design (Figure 1), we conducted 2 related studies to test the hypotheses that HPA axis dysfunction accompanies high anxiety and alcohol craving during early recovery and that the level of subjective anxiety, alcohol craving, and HPA axis responses are predictive of subsequent alcohol relapse outcomes.

**METHODS**

**STUDY 1**

Objective

The objective of study 1 was to examine whether treatment-engaged, 1-month-abstinent, medication-free, recovering alcohol-dependent inpatients show HPA axis alterations, greater anxiety, and alcohol craving in response to stress and to alcohol cues relative to an active neutral, relaxing cue condition as compared with demographically matched, socially drinking healthy controls also admitted to a hospital research unit for a 3-night stay.

Participants

Men and women (aged between 21-50 years) seeking treatment for alcohol dependence and socially drinking healthy controls recruited from the community via local advertisements were evaluated for study participation. Individuals meeting DSM-IV criteria for current alcohol dependence were admitted to the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center for 4 to 6 weeks of inpatient treatment and research participation. Thirty-six of a total of 93 alcohol-dependent individuals studied were carefully matched to 36 healthy controls on age, race, sex, and years of education and composed the sample for study 1 (Table 1). The control

**Table 1. Demographic and Individual Characteristics of AD and HC Individuals in Study 1 and AD Sample in Study 2**

<table>
<thead>
<tr>
<th></th>
<th>HC (n=36)</th>
<th>AD (n=36)</th>
<th>AD (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>23 (63.89)</td>
<td>28 (77.78)</td>
<td>65 (69.89)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>27 (75)</td>
<td>30 (83.33)</td>
<td>61 (65.6)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>34.86 (9.41)</td>
<td>36.08 (8.07)</td>
<td>36.72 (7.76)</td>
</tr>
<tr>
<td>Education, y, mean (SD)</td>
<td>14.67 (1.97)</td>
<td>13.19 (1.70)</td>
<td>12.44 (1.75)</td>
</tr>
<tr>
<td>Prior alcohol/drug use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days used in last 30 d\textsuperscript{a}</td>
<td>6.03 (6.80)</td>
<td>17.47 (10.4)</td>
<td>16.27 (9.79)</td>
</tr>
<tr>
<td>No. of drinks/mo\textsuperscript{a}</td>
<td>10.61 (8.25)</td>
<td>365.29 (300.48)</td>
<td>315.66 (267.84)</td>
</tr>
<tr>
<td>Years of alcohol use\textsuperscript{a}</td>
<td>9.30 (8.93)</td>
<td>16.50 (8.21)</td>
<td>16.71 (8.62)</td>
</tr>
<tr>
<td>Age at onset of alcohol use</td>
<td>15.2 (4.52)</td>
<td>14.5 (3.13)</td>
<td>13.63 (3.39)</td>
</tr>
<tr>
<td>No. of days of drug use/mo</td>
<td>...</td>
<td>5.8 (12.22)</td>
<td>9.74 (13.7)</td>
</tr>
<tr>
<td>Regular smoker, No. (%)\textsuperscript{a}</td>
<td>5 (13.89)</td>
<td>32 (88.89)</td>
<td>83 (90.22)</td>
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<tr>
<td>Lifetime prevalence of psychiatric disorders, No. (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Major depressive disorders</td>
<td>3 (8.33)</td>
<td>6 (16.67)</td>
<td>20 (21.51)</td>
</tr>
<tr>
<td>PTSD</td>
<td>2 (5.56)</td>
<td>6 (16.67)</td>
<td>21 (22.58)</td>
</tr>
<tr>
<td>Anxiety disorders without PTSD</td>
<td>0</td>
<td>3 (8.33)</td>
<td>3 (4.17)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, alcohol dependent; ellipses, not applicable; HC, healthy control; PTSD, posttraumatic stress disorder.

\textsuperscript{a}Significant difference between HC and AD in study 1 (P<.05).
group reported drinking up to 25 drinks or less per month (<7 drinks/wk) and did not meet current or lifetime abuse or de-
pendence criteria for alcohol or any other illicit drug and had
documented multiple negative urine toxicology screen results
on admission. Individuals currently using opiates or who ever
met criteria for opiate dependence and those taking medica-
tions for any current psychiatric (including prescribed or un-
prescribed anxiolytics) or medical condition were excluded.

Women were excluded from the study if they were using hor-
monal contraceptives or were either perimenopausal or post-
menopausal. All subjects underwent a complete medical eval-
uation, including electrocardiography and laboratory tests of renal,
hepatic, pancreatic, hematopoietic, and thyroid functions, to
guarantee good physical health. All study procedures were
approved by the Human Investigation Committee of the Yale Uni-
versity School of Medicine and all participants signed a writ-
en informed consent.

Procedures

Alcohol-dependent patients were admitted to the Clinical Neu-
roscience Research Unit, a locked inpatient treatment re-
search facility with no access to alcohol or drugs and limited
access to visitors. Urine and breathalyzer testing was also con-
ducted regularly to ensure continued abstinence. All patients
participated in specialized treatment for 1 month prior to the
laboratory sessions that included weekly individual therapy pro-
vided by the psychiatry residents on the Clinical Neurosci-
eence Research Unit and twice-weekly 12-step–based group al-
cohol and drug counseling provided by an addiction specialist.
The group alcohol and drug treatment was part of the inpa-
tient treatment program that was initiated on admission and
included additional group programming from 9 AM to 3:30 PM
that covered daily life skills and other structured activities. The
laboratory study for alcohol patients was conducted 1 month
after admission to the inpatient unit to allow for normalization
of neurobiological changes associated with alcohol with-
drawal and to assess stress responses and craving in a con-
trolled early recovery period.

During the first week of the inpatient stay, subjects under-
grew an initial medical evaluation and provided demographic and
psychosocial history. In the second week, they were interviewed
using the Structured Clinical Interview for DSM-IV to assess psy-
chiatric and substance abuse diagnoses. Baseline alcohol-and drug-
related assessments, including alcohol use for the 90 days prior
to admission, were also completed. Social drinking controls com-
pleted demographic, diagnostic, and alcohol-related assess-
ments and script development sessions in 2 to 3 assessment ap-
pointments and were then admitted for a 3-day hospital stay to
the Hospital Research Unit at Yale–New Haven Hospital for par-
ticipation in the laboratory study. During this period, they were
required to stay on the unit, within a similar controlled environ-
ment as that of the alcohol patients.

All subjects participated in an imagery script development
session (week 3 of admission for alcohol-dependent individu-
als) during which they were asked to identify a highly stress-
ful event from their own lives (rated by the subject as ≥8 on a
10-point Likert scale for stressfulness): a personal alcohol cue–
related event that involved people, place, and objects related
to alcohol use and led to subsequent alcohol use; and a per-
sonal neutral, relaxing event. Examples of commonly re-
ported stressful situations included breakup with a significant
other, a verbal argument with a significant other or family mem-
ber, or unemployment-related stress, such as being fired or laid
off from work. Commonly reported alcohol cue situations were
buying alcohol, being at a bar, and watching others drink al-
cohol. Examples of neutral, relaxing situations included a sum-
mer afternoon at the beach, a fall day at the park, and taking a
bubble bath. Details of each elicited situation were described
using the Scene Construction Questionnaire, based on meth-
ods developed by Lang and colleagues and Miller and col-
leagues and further adapted in our previous studies that are
reviewed and summarized in Sinha. Scripts were developed
using a standardized format, based on specific stimulus and re-
ponse details of each situation, and then audiotaped for pre-
sentation in the laboratory sessions.

Laboratory Sessions

On a day prior to the laboratory sessions, subjects participated
in a habituation and imagery training procedure involving ex-
posure to the stress of intravenous catheter insertion and spe-
cific instructions on progressive relaxation and guided imag-
ery participation. This was followed by 3 experimental sessions
on consecutive days where subjects were exposed to 5-minute
audiotaped scripts of stress, alcohol-related, and neutral, re-
xivating scenarios, using a well-established and widely used, in-
dividually calibrated guided imagery procedure. Only 1 stimu-
lus script was presented per session on each day and condition
order was randomized and counterbalanced across partici-
pants by group. On each testing day, participants abstained from
breakfast and, after a smoke break at 7:30 AM, were brought to
the testing room at 7:45 AM and then prepared for intravenous
catheter insertion by the research nurse. After settling into a
sitting position in a hospital bed, a hepatic-injected catheter was
inserted by the research nurse in the antecubital region of the
subject’s nonpreferred arm to periodically obtain repeated blood
samples during the laboratory sessions. This was followed by a
1-hour adaptation and baseline period during which the sub-
jects were instructed to practice relaxation. At 9 AM, subjects
were provided headphones and an audio recording presented
the instructions for the imagery procedure and the script for
guided imagery. The subject’s task was to imagine the situa-
tion being described as if it were happening now. Research staff
conducting the experimental procedures and blood process-
ing remained blind to imagery condition and subjects were blind
to the order of the imagery condition until imagery induction
on each day.

Laboratory Assessments

Subjective Measures. Alcohol craving and anxiety were as-
essed using a 10-point visual analog scale in which 1 was an-
chored at “not at all” and 10 at “extremely high.” Subjects
rated their desire for an alcoholic drink and how anxious,
tense, and/or jittery they felt in that moment. All subjective
rating scales were administered at baseline (−5), immediately
following imagery (time 0), and at 5, 10, 15, 30, 45, 60, and 75
minutes after imagery.

HPA Axis Measures. To assess plasma levels of corticotropin
and cortisol, 4 mL of blood were collected at each point in a
heparinized tube that was placed on ice immediately after blood
drawing. Within 30 minutes of collection, the blood was cen-
trifuged at 4°C and the plasma was pooled and aliquoted for
corticotropin and cortisol assays. All tubes were stored at −70°C
and express shipped to Kreek Laboratories, Rockefeller Uni-
versity. Assay processing was conducted using standard radio-
imunoassay procedures at Kreek Laboratories under the su-
premision of one of us (M.J.K). Laboratory responses were
assessed at baseline prior to imagery (8:40 and 8:55 AM rep-
senting times −20 and −5) and immediately following imagery
(time 0) and at repeated recovery points every 15 minutes (15,
30, 45, 60, and 75 minutes) after imagery. Because cortisol se-
cretion from the adrenal glands occurs in response to circulat-
ing corticotropin released from the pituitary and may vary under rest and challenge conditions.\textsuperscript{25-27} we also assessed adrenal sensitivity as a ratio of cortisol to corticotropin. Furthermore, previous research on conditions with known HPA axis disturbances (eg, rheumatoid arthritis and posttraumatic stress disorder) have found the cortisol to corticotropin ratio as a measure of adrenal sensitivity to be an important marker of clinical symptoms and outcome.\textsuperscript{28,29} Cortisol and corticotropin are measured in mass concentrations and a ratio of cortisol to corticotropin was computed as in previous studies.\textsuperscript{27,28}

Data Analysis

Data were analyzed using mixed-effect models where group (control vs alcohol dependent), condition (stress, cues, and neutral, relaxing), and time (-20, -5, 0, 15, 30, 45, 60, and 75) were fixed effects and subject was the random effect. Baseline differences were accounted for as covariates in the model for each measure in which baseline differences were significant, with the exception of alcohol use measures. All HPA axis–provoked responses were assessed using baseline-adjusted measures. In addition, age and sex were included as covariates in all mixed-model analyses.

STUDY 2

Objective

The objective of study 2 was to assess whether alcohol craving, anxiety, corticotropin level, cortisol level, and adrenal sensitivity (cortisol to corticotropin ratio) in response to stress, alcohol cue, and neutral, relaxing imagery exposure were independently predictive of subsequent alcohol relapse and treatment outcomes in the 90-day period following discharge from inpatient treatment, after controlling for demographic and other individual history variables.

Participants

Ninety-three inpatient treatment–engaged, 1-month–abstinent, recovering alcohol-dependent individuals (Table 1) who participated in the inpatient and laboratory study procedures as described in study 1 were prospectively followed up with face-to-face interviews conducted at 14, 30, and 90 days postdischarge from inpatient treatment to assess relapse and treatment outcomes.

Prospective Follow-up Procedures

On discharge from the inpatient unit, all alcohol-dependent participants were given appointments for follow-up interviews on 14, 30, and 90 days postdischarge. Reminders were sent the week prior to each appointment. Follow-up assessments included breath alcohol and urine alcohol assessment (to assess for the alcohol metabolite ethyl glucuronide, detectable for approximately 80 hours after alcohol consumption) and daily retrospective reporting of alcohol use at each follow-up assessment using the timeline follow-back method.\textsuperscript{30-31} an instrument that has been validated in drug-abusing samples\textsuperscript{33} and widely used in assessing alcohol use outcomes in previous treatment research.\textsuperscript{33} Engagement in aftercare treatment was assessed using the Treatment Services Review.\textsuperscript{36} In addition, patients provided permission to contact 3 individuals close to them and with knowledge of their alcohol use to obtain collateral information in the event that the patients were lost to follow-up. Of the 93 patients who completed the laboratory and follow-up procedures in study 2, 3 attended the 14-day but not the 30- and 90-day interviews, 2 did not attend the 14-day but attended their 30- and 90-day interviews, an additional 2 attended the 14- and 30-day but not their 90-day interviews, and 1 patient only attended the 30-day interview. Overall, follow-up rates were 98% at day 14, 93% at day 30, and 89% at day 90.

Predictor Measures

Area under the curve for response in each condition, including baseline, was calculated using the trapezoid formula with the primary predictor variables of subjective anxiety, alcohol craving, corticotropin level, cortisol level, and adrenal sensitivity (cortisol to corticotropin ratio), a summary measure of HPA axis function commonly studied in stress-related mental and inflammatory conditions.\textsuperscript{25,26} in the stress, alcohol cue, and neutral, relaxing conditions (Table 2).

Primary Outcome Measures

Number of days of aftercare treatment participation (days of any outpatient treatment and self-help groups), time to alcohol relapse (first alcoholic drink), and time to heavy drinking (≥5 drinks/occasion for men; ≥4 drinks/occasion for women) were derived from follow-up assessments to assess aftercare treatment and relapse risk outcomes.

Data Analysis

Proportional hazards regression models were conducted to evaluate time to any alcohol use (alcohol relapse) and time to heavy drinking (heavy drinking relapse). Multiple regression was used to evaluate predictors of aftercare treatment engagement. Preliminary models assessed the contribution of sociodemographic variables (age, sex, race, IQ) and clinical characteristics (smoking status, baseline alcohol use prior to inpatient admission, and lifetime history of mood and anxiety disorders) and recent other drug use to assess their independent effects on relapse risk and treatment engagement. If any of these variables were predictive of outcome measures, they were included in the prediction models to assess the specific and independent effects of HPA axis responses, anxiety, and craving on relapse and treatment outcomes.

RESULTS

STUDY 1

Baseline Measures

Alcohol-dependent patients had significantly higher levels than controls of baseline corticotropin (t=2.22, P<.03), but neither anxiety, craving, nor other HPA axis measures were significantly different between groups. There were also no differences in baseline levels for any measure across the testing days, supporting the randomization of order manipulation across conditions.

Subjective Anxiety and Alcohol Craving Responses

As expected, stress and alcohol cue exposure significantly increased both subjective anxiety (condition:
As hypothesized, we found main effects of condition (corticotropin: $F_{2,136}=3.12; P<.05$; cortisol: $F_{2,136}=10.04; P<.001$; cortisol to corticotropin ratio: $F_{2,136}=5.33; P<.005$) and group $\times$ condition (corticotropin: $F_{2,135}=5.64; P=.004$; cortisol: $F_{2,136}=3.25; P=.04$; cortisol to corticotropin ratio: $P<.05$), time (corticotropin: $F_{6,420}=4.35; P<.001$; cortisol: $F_{6,420}=20.85; P<.001$; cortisol to corticotropin ratio: $F_{6,420}=12.6; P<.001$), and group $\times$ time interaction (corticotropin: $P<.07$; cortisol: $F_{6,420}=4.29; P<.001$; cortisol to corticotropin ratio: $P<.34$) for each measure. Condition main effects indicated greater responses in the stress (corticotropin: $P<.02$; cortisol: $P<.003$; cortisol to corticotropin ratio: $P<.007$) and alcohol cue (corticotropin: $P<.61$; cortisol: $P<.001$; cortisol to corticotropin ratio: $P<.007$) conditions relative to the neutral condition. Significant interactions were a result of higher corticotropin response in the neutral, relaxing condition in the alcohol-dependent patients relative to controls ($P<.01$), with no stress- and cue-induced corticotropin and cortisol responses to stress and to cues relative to the neutral condition in the patients relative to controls (Figure 4 highlights group $\times$ condition interactions showing baseline-adjusted mean responses of corticotropin and cortisol levels in the neutral, stress, and alcohol cue conditions for each group).

**Summary**

Treatment-engaged, 1-month–abstinent, recovering alcohol-dependent patients showed HPA axis dysfunction relative to controls. Alcohol-dependent patients showed higher basal levels of corticotropin and a lack of corticotropin and cortisol responses to stress and alcohol cues relative to neutral stimuli as compared with controls. Compared with controls, alcohol-dependent patients had increased anxiety in the neutral, relaxed state and in response to alcohol cues, along with significantly higher and persistent alcohol...
craving during stress and alcohol cue exposure. These data indicate increased neutral, relaxed–state anxiety and corticotropin levels, greater provoked alcohol craving, and HPA axis dysfunction that persists in alcohol-dependent patients even after 1 month of abstinence.

**STUDY 2**

**Relapse Rates**

Alcohol relapse rates were 47% (44 of 93 patients) at day 14, 59% (55 of 93 patients) at day 30, and 74% (69 of 93 patients) by day 90 of the follow-up period. For heavy drinking relapse, rates were 34% (32 of 93 patients) by
corticotropin and cortisol levels due to the circadian rhythm.) Effects varied by group (HC: S > C, and N imagery averaged across time indicated condition effects (healthy controls [HC]: S > N [P < .001] and C > N [P < .001]; alcohol-dependent [AD] patients: no differences across conditions; AD > HC in response of N [P < .01]). B, Baseline-adjusted plasma cortisol responses to S, C, and N imagery averaged across time indicated condition effects showing S greater than N (P < .003) and C greater than N (P < .001), but effects varied by group (HC: S > N [P < .001] and C > N [P < .001]; AD patients: C > N [P < .02] and no differences in S vs N). (Controls showed an increased response in S and C relative to N despite the diurnal drop in corticotropin and cortisol levels due to the circadian rhythm.)

day 14, 47% (44 of 93 patients) by day 30, and 67% (63 of 93 patients) by day 90 of follow-up.

**Aftercare Treatment Engagement**

Number of aftercare treatment days was positively associated with IQ (r = 0.22; P < .04), but no other covariate was significant. After accounting for IQ effects, aftercare treatment was negatively associated with increased anxiety in stress and cue conditions (stress: r = -0.26; P < .02; alcohol cue: r = -0.23; P < .04; neutral: r = -0.20; P < .06) and with stress-induced alcohol craving (r = -0.22; P < .05), but not with cortisol to corticotropin ratio.

**Alcohol Relapse Outcomes**

Among the demographic and clinical characteristics, only lower IQ (χ² = 4.67; P = .03; hazard ratio [HR] = 0.97; 95% confidence interval [CI], 0.95-0.998; heavy drinking relapse: χ² = 5.22; P = .02; HR = 0.97; 95% CI, 0.95-0.996), higher days of other drug use at baseline (time to relapse: χ² = 4.01; P = .05; HR = 1.01; 95% CI, 1.001-1.02), and female sex (heavy drinking relapse: χ² = 6.33; P = .01; HR = 0.51; 95% CI, 0.31-0.86) were predictive of shorter time to alcohol relapse. Other clinical history variables, such as lifetime prevalence of mood and anxiety disorders, were not predictive of alcohol relapse. These significant predictors were included as covariates for the time to alcohol relapse and time to heavy drinking relapse analyses whenever each contributed significantly to the respective proportional hazards model.

**Alcohol Craving and Subjective Anxiety**

Higher stress-induced (χ² = 4.37; P = .04; HR = 1.15; 95% CI, 1.01-1.31) and alcohol cue–induced alcohol craving (χ² = 4.82; P = .03; HR = 1.16; 95% CI, 1.02-1.32) were each significantly predictive of shorter time to alcohol relapse. The HRs indicated that for each point increase in alcohol craving during stress and alcohol cue exposure, there was a 15% and 16% increase in the likelihood of alcohol relapse in the sample (Figure 5). Alcohol craving was not predictive of time to heavy drinking relapse and subjective anxiety was not predictive of alcohol relapse outcomes.

**HPA Axis Responses**

Cortisol response in the stress condition was significantly predictive of time to alcohol relapse (χ² = 6.12; P = .01; HR = 1.10, 95% CI, 1.02-1.18), but not time to heavy drinking relapse. Cortisol to corticotropin ratio was a significant predictor of alcohol relapse, particularly in the neutral, relaxing condition (time to alcohol relapse: χ² = 7.38; P = .007; HR = 2.12; 95% CI, 1.23-3.63; time to heavy drinking: χ² = 10.4; P = .001; HR = 2.55; 95% CI, 1.29-4.1), but also in the stress condition (time to alcohol relapse: χ² = 3.74; P = .05; HR = 1.65; 95% CI, 1.10-2.49; time to heavy drinking: χ² = 4.04; P = .05; HR = 1.52; 95% CI, 1.02-2.42) and at baseline levels for time to alcohol relapse only (χ² = 4.49; P = .04; HR = 1.68; 95% CI, 1.04-2.71). In each case, higher cortisol levels and cortisol to corticotropin ratios were predictive of shorter time to alcohol relapse and shorter time to heavy drinking, with higher adrenal sensitivity during the neutral condition conferring a 2- to 2.5-fold greater risk of relapse for both time to alcohol relapse and time to heavy drinking (Figure 6). Corticotropin or cortisol responses at baseline or corticotropin responses during any condition were not predictive of alcohol relapse.

**Association Between Anxiety, Craving, and HPA Axis Measures**

Because study 1 showed significantly higher anxiety in alcohol-dependent patients in the neutral, relaxed condition relative to controls, we assessed whether higher neutral condition anxiety was associated with corticotropin level, cortisol level, cortisol to corticotropin ratio, and craving in study 2. Significant modest associations between anxiety in the neutral, relaxed condition
and alcohol craving (stress: $r = 0.39; P < .001$; cue: $r = 0.40; P < .001$; neutral: $r = 0.50; P < .001$), corticotropin (stress: $r = 0.36; P < .001$; cue: $r = 0.39; P < .001$; neutral: $r = 0.38; P < .001$) and cortisol (stress: $r = 0.30; P < .004$; cue: $r = 0.26; P < .01$; neutral: $r = 0.24; P < .02$) levels, but not cortisol to corticotropin ratio, were observed.

Using a controlled experimental approach combined with a prospective clinical outcomes design, the current results indicate high morning levels of corticotropin, a lack of stress- and cue-related cortisol and corticotropin response, increased neutral, relaxed- and cue-induced anxiety, and significantly increased stress- and alcohol cue–induced craving in 1-month–abstinent, treatment-engaged alcohol-dependent inpatients relative to matched social drinking controls. More importantly, cortisol to corticotropin ratios representing a marker of adrenal sensitivity and high alcohol craving were most significantly predictive of subsequent time to alcohol relapse outcomes while increased anxiety levels were associated with lower rates of aftercare treatment engagement. These findings provide direct evidence of stress-related pathophysiology during protracted alcohol abstinence as relevant to subsequent alcoholism relapse risk.

Previous basic science research indicates brain CRF and noradrenergic upregulation during protracted abstinence in alcohol-dependent animals. Preclinical and human studies have also shown blunted/lack of HPA axis.

**Figure 5.** Study 2: after holding covariates constant, estimated survival risk functions are shown for alcohol craving values for the mean (in red) and at 1, 2, and 3 SDs above the mean and at minimal craving levels (0 and 0.5) for stress-induced alcohol craving (S_CRV) (A) ($\chi^2 = 4.37; P < .04$; hazard ratio = 1.15; 95% confidence interval, 1.01-1.31) and alcohol cue–induced craving (C_CRV) (B) ($\chi^2 = 4.82; P < .03$; hazard ratio = 1.16, 95% confidence interval, 1.02-1.32). The proportion surviving 90-day relapse is shown on the y-axis and the time during the 90-day period when relapse occurred is shown on the x-axis. Hence, the estimated survival function at day 80 spans a 0.35 (35%) and 0.38 (38%) proportion of surviving relapse for those with an S_CRV and a C_CRV of 0, respectively, while there is only a 0.02 (0.02%) proportional chance of surviving relapse and 0.40 (40%) proportion surviving relapse and 0.48 (48%) surviving heavy drinking relapse for those at 3 SDs above the mean in S_CRV and C_CRV, respectively. Note: survival functions are cut off at day 80 instead of extending to day 90 because all alcohol-dependent patients with predictor values 3 SDs above the mean had relapsed by day 80.

**Figure 6.** Study 2: after holding covariates constant, estimated survival risk functions are shown for neutral, relaxing–condition cortisol to corticotropin ratio (N_C:C ratio) (adrenal sensitivity) values for the mean (in red) and at 1, 2, and 3 SDs above the mean and at minimal ratio values (0.1 and 0.05) for N_C:C ratio predicting time to alcohol relapse (A) ($\chi^2 = 7.38; P < .007$; hazard ratio = 2.12; 95% confidence interval, 1.23-3.63) and time to heavy drinking alcohol relapse (B) ($\chi^2 = 10.4; P < .001$; hazard ratio = 2.55; 95% confidence interval, 1.29-4.1). The proportion surviving 90-day relapse is shown on the y-axis and the time during the 90-day period when relapse occurred is shown on the x-axis. Hence, the estimated survival function at day 80 spans a 0.40 (40%) proportion surviving relapse and 0.48 (48%) surviving heavy drinking relapse for cortisol to corticotropin ratios at 0.05, respectively, while there is only a 0.02 (0.02%) proportional chance of surviving relapse and heavy drinking relapse for those at 3 SDs above the mean in N_C:C ratio. Note: survival functions are cut off at day 80 instead of extending to day 90 because all alcohol-dependent patients with predictor values 3 SDs above the mean had relapsed by day 80.
responses to stress challenge with long-term levels of alcohol consumption. Upregulation of central CRF and noradrenergic pathways would predict higher basal or resting-state HPA axis hormone levels, and this is consistent with higher morning basal corticotropin and higher neutral, relaxing–state corticotropin levels observed in alcohol-dependent patients compared with controls in study 1. On the other hand, unlike controls, there were no differences in corticotropin and cortisol responses to stress, cue, and neutral, relaxed conditions in alcohol-dependent patients. This lack of HPA axis response to challenge may represent a decreased physiological capacity of the HPA axis to recover to resting-state levels. Some evidence suggests that this lack of response to challenge in recovering alcohol-dependent patients may persist for at least 4 to 8 weeks’ abstinence, with documentation of partial recovery by 2 months. However, because a substantial number of alcoholics relapse within 2 months, an examination of whether such chronic alcohol-related effects on stress pathways contribute to relapse is of clinical significance.

Remarkably, after accounting for the effects of other significant demographic and clinical characteristics on outcome, we found that high adrenal sensitivity, particularly in the neutral, relaxing condition (but also at baseline and in the stress condition), increased relapse risk up to 2.5 times, suggesting that individuals who demonstrated the highest cortisol responsivity to corticotropin (adrenal sensitivity) during the neutral, relaxing condition showed the shortest time to alcohol relapse and return to heavy drinking. For example, as shown in Figure 6, alcohol-dependent patients with neutral-state cortisol to corticotropin ratios more than 1.5 had a less than 18% chance of surviving alcohol relapse on day 30, while those with a cortisol to corticotropin ratio at or less than 0.1 had a 60% chance of surviving relapse at day 30. With these significant differences in relapse risk on the basis of relaxed-state morning levels of adrenal sensitivity, it is possible that specific levels of resting-state adrenal sensitivity, and not provoked HPA axis response, could serve as a biomarker for identifying alcohol relapse risk during treatment.

Putting findings from study 1 and study 2 together, it appears that individuals with increased cortisol release (adrenal sensitivity) in response to high corticotropin levels were most susceptible to a shorter time to relapse and return to heavy drinking. This was most strongly observed in the neutral, relaxing condition, where controls showed significantly lower levels of corticotropin than alcohol-dependent patients. These data suggest that controls were able to relax and decrease their HPA axis reactivity during relaxing imagery, but alcohol-dependent patients, and particularly those who relapsed, were not able to relax and decrease their HPA axis responses in a relaxing imagery condition. Further support for the interpretation that alcohol-dependent patients had a lower ability to relax or decrease HPA axis function under relaxed conditions comes from their higher levels of reported anxiety in the neutral, relaxed condition relative to controls. Significant positive correlations between neutral-state anxiety levels and corticotropin and cortisol levels in each of the stress, cue, and neutral, relaxing conditions were also observed. These data are consistent with the notion of higher allostatic load in subjective, neuroendocrine, and motivational aspects of stress, anxiety, and craving processes during early alcohol recovery, and that such increased load contributes to relapse processes and poor treatment outcome.

Previous studies have shown lower cortisol levels in relapsed alcohol-dependent patients compared with those who remained abstinent in very early recovery and at a 6 months’ assessment. Although the current findings of higher neutral, relaxed–state cortisol to corticotropin ratios or cortisol levels in the stress condition predicting shorter time to alcohol relapse may seem contrary to previous work, it is important to consider the methodological differences between the previous studies and the current study. The previous studies used a stress challenge condition but no neutral or relaxing control condition. Thus, while baseline levels were considered, HPA axis responses during a controlled relaxed manipulation were not conducted. These studies also did not include a socially drinking control group to fully assess whether basal- or neutral, relaxed–state HPA axis measures were different from the control group. On the other hand, both relaxed- and challenge-state assessments were included in the current study and results specifically highlight 2 aspects of HPA axis dysfunction, namely, higher morning baseline corticotropin and neutral, relaxing–state corticotropin levels and lack of provoked HPA axis response to stress, the latter being consistent with previous work. The current study also expands on previous work to show that resting- or relaxed-state HPA axis function provides greater sensitivity and predictive power in terms of future alcohol relapse risk over the lack of reactivity in the provoked HPA axis responses. Therefore, consistent with preclinical research and expanding on previous clinical research, the current findings suggest high adrenal sensitivity as a potential marker of alcohol relapse risk and support the notion that normalizing of HPA axis function as a treatment target in alcoholism could have benefit in decreasing relapse risk.

At significant but more modest levels, stress- and cue-induced alcohol craving were also found to be predictive of time to alcohol relapse but not relapse to heavy drinking. These findings are consistent with previous research showing stress- and negative affect–related alcohol craving to be predictive of alcohol relapse. As shown in Figure 5, individuals with stress- and cue-induced craving levels higher than 6 of 10 had only a 16% chance of surviving relapse at day 30 compared with those with the mean area under the curve level of 1 of 10, showing about a 50% chance of surviving relapse at day 30. These results support previous research on the clinical importance of individual differences in craving responses and indicate that such variation is relevant to alcohol relapse risk and treatment outcome.

There are significant implications of the current findings for poor treatment retention and high rates of alcohol relapse observed in the treatment of alcohol dependence. First, the current results show specific levels of adrenal sensitivity and provoked alcohol craving that predict surviving subsequent relapse and those that suggest high relapse risk. If validated in future studies, these measures could serve as clinical markers of relapse risk to identify those...
alcohol-dependent individuals entering treatment who are most likely to relapse and drop out of alcohol treatment. Such assessments could inform clinicians of the need to tailor their interventions toward targeting reduction of stress and anxiety in relaxed and provoked states, which in turn could impact HPA axis responsivity and stress-induced cue-induced alcohol craving. Second, while there are several approved medications in the treatment of alcohol dependence, very few specifically address stress dysregulation, anxiety, and high levels of associated stress- or alcohol cue–induced alcohol craving. For example, while naltrexone hydrochloride decreases alcohol-induced craving, to our knowledge, its effects in decreasing stress-induced alcohol craving have not been shown in human studies. The current findings suggest that targeting the identified stress-related pathophysiology with medications that decrease anxiety and high provoked craving and normalize HPA axis function could be of benefit in improving relapse outcomes as well as increasing treatment engagement after inpatient alcohol treatment. Several potential pharmacologic targets have been identified in animal models of stress-induced alcohol relapse and in addressing alcohol relapse risk in humans.6,12 For example, nonpeptide CRF1 antagonists and noradrenergic agents have shown promise in reducing stress-induced relapse in animal models and would be an important class of agents to study in human laboratory models and with further clinical trials. Such strategies to decrease stress-related pathophysiology and provoked alcohol craving could ultimately reduce alcohol relapse risk, thereby decreasing the alcohol-related disease burden associated with high relapse rates in alcohol use disorders.

It is important to note study limitations. Because this was a prospective follow-up study, assessments of relapse were conducted at 3 points at follow-up and not weekly. While we obtained self-reported alcohol use data and urine alcohol assessments at day 14, 30, and 90 of the follow-up period, prospective daily or weekly assessments of drinking with objective drinking measures were not conducted. Despite these drawbacks, the current study used a well-controlled experimental study to assess alcohol craving, anxiety, and HPA axis function in response to stress, alcohol cue, and relaxing conditions, combined with a prospective follow-up design with an average 93% follow-up rate, to demonstrate that stress-related pathophysiology plays a significant role in motivation to drink and in alcohol relapse risk.

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