Intravenous Ghrelin Administration Increases Alcohol Craving in Alcohol-Dependent Heavy Drinkers: A Preliminary Investigation

Supplemental Information

Study Population Inclusion/Exclusion Criteria

Inclusion Criteria:

- 18-70 years old
- DSM-IV diagnosis of alcohol dependence
- Heavy drinking, which in this study was defined as consuming on average ≥4 standard drinks/day for women, or ≥5 standard drinks/day for men, during the 90-day period before screening, as assessed by the Timeline Followback (TLFB). Consistent with the NIH/NIAAA definition, a standard drink was considered any drink that contains about 0.6 fluid ounces or 14 grams of "pure" alcohol.
- Willingness to receive an intravenous line.

Exclusion Criteria:

- Current DSM-IV diagnosis of dependence on any psychoactive substance other than alcohol and nicotine (a urine drug screen was also performed)
- DSM-IV Axis I criteria for a lifetime diagnosis of schizophrenia, bipolar disorder, or other psychoses
- Current DSM-IV diagnosis of major depressive or anxiety disorder
- Risk of suicide
- History of alcohol intoxication delirium, alcohol withdrawal delirium or seizure
- Clinical Institute Withdrawal Assessment for Alcohol revised score ≥10

- Having received any behavioral and/or pharmacological treatment for alcohol dependence within the past 30 days and/or being interested in receiving treatment
- Current use of psychotropic medications that could not be discontinued
- Clinically significant medical conditions
- Diabetes or obesity (body mass index ≥ 30 kg/m^2)
- History of clinically significant hypotension
- History of adverse reactions to needle puncture
- Potentially fertile women were admitted only if practicing an effective birth control method (a urine pregnancy test was also performed at each visit).

Table S1. Mean and standard deviation for alcohol and juice urge increases and baseline (pre-infusion) levels in the three study groups.*

	Alcohol Urge Increase	**Juice Urge Increase**
Placebo	1.851 (2.987)	1.379 (2.996)
Ghrelin 1 mcg/kg	2.469 (2.982)	2.670 (2.989)
Ghrelin 3 mcg/kg	4.578 (3.012)	2.855 (3.020)
	Alcohol Urge Pre-Infusion†	**Juice Urge Pre-Infusion†**
Placebo	3.111 (3.160)	2.611 (2.118)
Ghrelin 1 mcg/kg	4.308 (3.591)	2.077 (2.629)
Ghrelin 3 mcg/kg	2.429 (3.413)	3.000 (2.882)

*Dependent variables are collapsed across trials of the same type.
† *p*'s = .35 and .64 respectively.

Table S2. Adverse events (AEs; number/group) assessed via the Systematic Assessment for Treatment Emergent Events (SAFTEE)*

AE Description	Placebo (*n* = 18)	Ghrelin 1 mcg/kg (*n* = 13)	Ghrelin 3 mcg/kg (*n* = 14)
Dizziness	3	1	4
Decrease in Appetite	2	1	1
Increase in Appetite	11	11	11
Changes in Vision	2	1	1
Slowness, Sleepiness, Fatigue	5	0	1
Difficulty with Coordination or Balance	1	0	0
Difficulty with Concentration or Attention	2	1	0
Tingling in Fingers or Toes	2	0	0
Word Finding Difficulties	3	0	0
Memory Difficulties	1	1	1
Change in Taste	2	1	2
Tremor	2	0	1
Constipation	1	0	0
Diarrhea	1	0	0
Headache	7	3	1
Restlessness	5	1	4
Nervousness or Anxiety	3	2	2
Irritability	2	0	2
Depression or Mood Disturbances	2	0	2
Changes in Libido	0	1	1
Slowed Breathing	0	0	1
Hyperventilation	1	0	0
Difficult Breathing	0	0	1
Stupor	2	0	0
Fast Heart Beat	2	1	0
Flushing of Face	2	1	1
Muscle Aches	4	1	0
Eye Pain	1	0	0
Any of 20 through 23	6	2	4

*no significant differences in AEs were found across groups (p's > 0.05). AEs listed in the table are only those for which at least 1 case was reported.

Table S3. Mean and standard deviation for mean arterial pressure (MAP; expressed in mmHg) and heart rate (HR; expressed in beats per minute) for each trial.*

		1st Alcohol Cue Trial	2nd Alcohol Cue Trial	1st Juice Cue Trial	2nd Juice Cue Trial
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
MAP	Placebo	98.6 (5.5)	101.5 (7.7)	98.4 (7.1)	99.2 (5.6)
	Ghrelin 1 mcg/kg	93.7 (5.4)	94.9 (7.4)	92.7 (6.8)	93.8 (5.4)
	Ghrelin 3 mcg/kg	89.9 (5.3)	89.3 (7.5)	89.1 (6.8)	88.5 (5.3)
HR	Placebo	69.7 (6.1)	69.1 (4.8)	72.7 (5.6)	70.2 (5.4)
	Ghrelin 1 mcg/kg	67.0 (5.9)	66.8 (4.8)	69.0 (5.6)	65.4 (5.4)
	Ghrelin 3 mcg/kg	67.9 (6.1)	65.0 (4.8)	70.1 (5.7)	65.9 (5.5)

* Multiple measurements were taken during each trial in the 3 study groups.

Table S4. Mean and standard deviation for saliva mass, in the three study groups.*

	Alcohol Trials	Juice Trials
	Saliva Mass (grams)	Saliva Mass (grams)
Placebo	3.2 (1.4)	3.3 (1.1)
Ghrelin 1 mcg/kg	1.8 (1.4)	1.9 (1.1)
Ghrelin 3 mcg/kg	1.9 (1.4)	1.9 (1.1)

*Dependent variables are collapsed across trials of the same type.

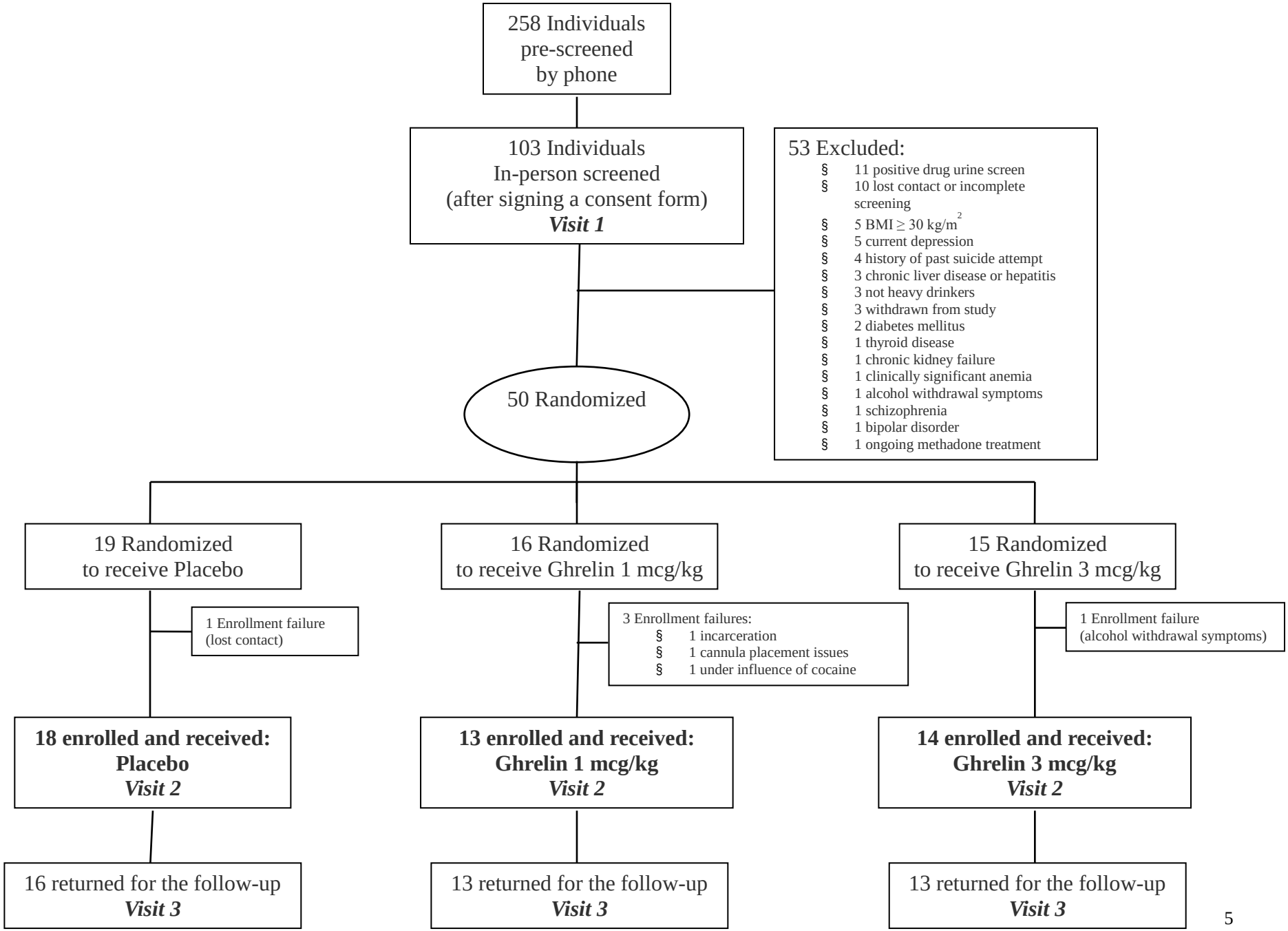
258 Individuals pre-screened by phone
103 Individuals In-person screened (after signing a consent form) Visit 1
53 Excluded:
§ 11 positive drug urine screen
§ 10 lost contact or incomplete screening
§ 5 BMI ≥ 30 kg/m2
§ 5 current depression
§ 4 history of past suicide attempt
§ 3 chronic liver disease or hepatitis
§ 3 not heavy drinkers
§ 3 withdrawn from study
§ 2 diabetes mellitus
§ 1 thyroid disease
§ 1 chronic kidney failure
§ 1 clinically significant anemia
§ 1 alcohol withdrawal symptoms
§ 1 schizophrenia
§ 1 bipolar disorder
§ 1 ongoing methadone treatment
50 Randomized
19 Randomized to receive Placebo
16 Randomized to receive Ghrelin 1 mcg/kg
15 Randomized to receive Ghrelin 3 mcg/kg
1 Enrollment failure (lost contact)
3 Enrollment failures:
§ 1 incarceration
§ 1 cannula placement issues
§ 1 under influence of cocaine
1 Enrollment failure (alcohol withdrawal symptoms)
18 enrolled and received: Placebo Visit 2
13 enrolled and received: Ghrelin 1 mcg/kg Visit 2
14 enrolled and received: Ghrelin 3 mcg/kg Visit 2
16 returned for the follow-up Visit 3
13 returned for the follow-up Visit 3
13 returned for the follow-up Visit 3

Figure S1. Trial flow-chart and profile. After screening (Visit 1), the 50 eligible individuals were urn randomized to ghrelin 1 mcg/kg, 3 mcg/kg, or 0 mcg/kg (placebo) based on the urn variables assessed at screening, i.e., gender, severity of alcohol-dependence (measured with the alcohol dependence scale), and alcohol craving (Alcohol-Visual Analogue Scale). As expected, the three groups did not differ significantly on the three urn variables. Randomization took place between Visit 1 and Visit 2. Five of the 50 participants failed enrollment on Visit 2, while 45 participants did receive the study drug, specifically 18 (95%) of the placebo subjects, 13 (81%) of the low dose ghrelin subjects, and 14 (93%) of the high dose ghrelin subjects. These attrition rates were not significantly different [$X^2(1,N = 50) = 2.02$, $p = .36$]. Analyses included all participants ($n = 45$) who were randomized and received at least one dose of study drug (which, in this case, was equivalent to receiving the whole study drug, given that this was a single-administration drug study).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5, 9-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	21
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	21
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	21
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	21

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5-6
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	9, Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-17
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17