FIGURE S1. Study Flow Diagram

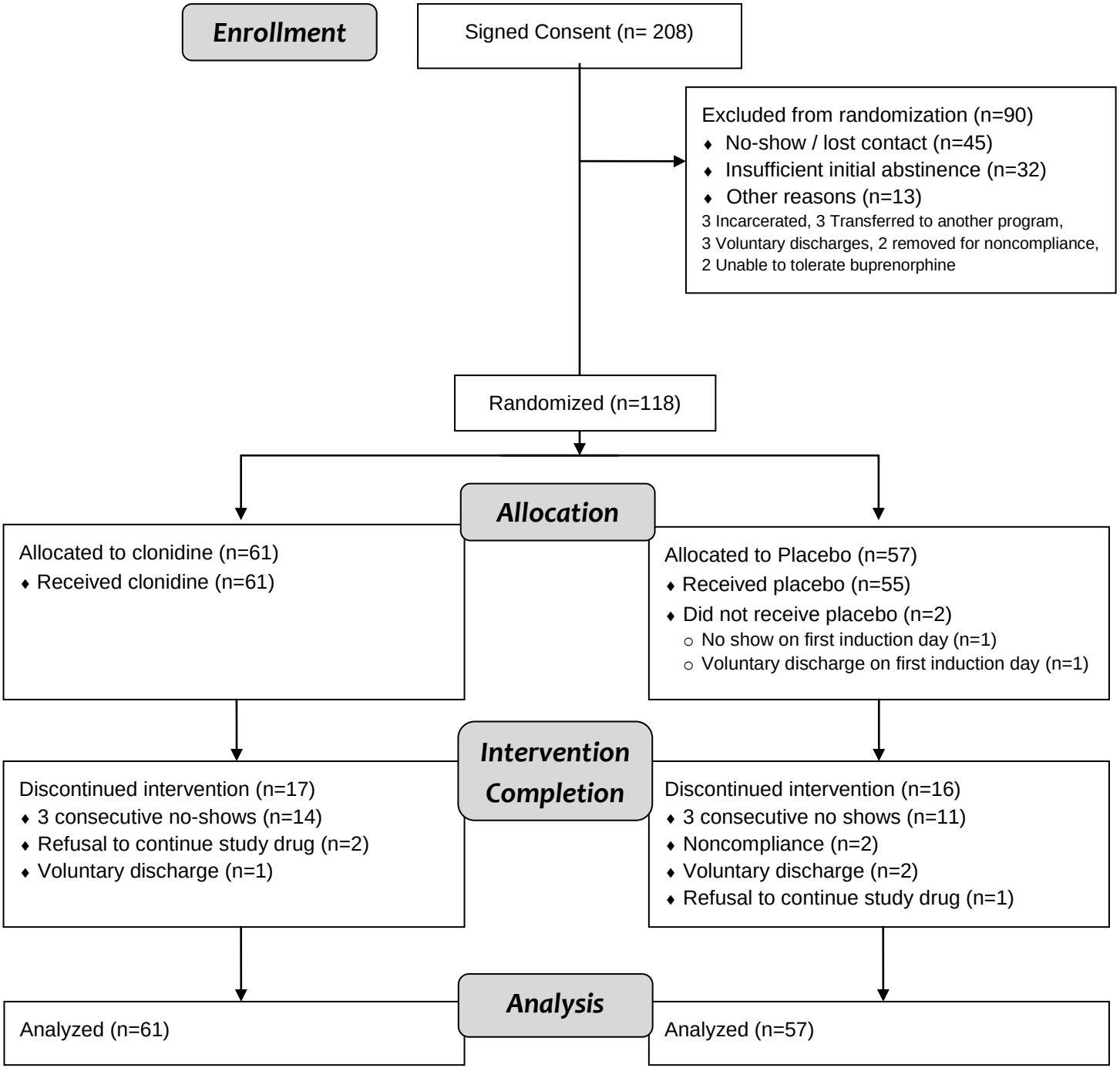


TABLE S1. Bivariate Comparisons Between Randomized and Non-Randomized Participants

	Not Randomized (N = 90)		Randomized (N = 118)	
	Mean	SD	Mean	SD
Age (years)	36.3*	8.7	38.8*	8.1
Education (years)	11.8	1.8	12.0	1.6
Employment (days paid for work in the last 30)	9.1	9.9	8.7	9.1
Heroin/Rx Opioid use (days in the last 30)	26.8*	6.8	24.7*	7.9
Heroin/Rx Opioid use (years)	11.3	8.6	12.0	7.6
Cocaine use (days in the last 30)	3.2	7.3	3.4	7.4
Cocaine use (years)	3.1	5.8	3.8	5.9
# of drug treatments	2.0	1.9	1.7	1.6
Money spent on Drugs ($ per month)	1335	1121	1106	1183
	N	%	N	%
Gender				
male	66	73.3	92	78.0
female	24	26.7	26	22.0
Race				
black	53	58.9	71	60.2
white	35	38.9	44	37.3
other	2	2.2	3	2.5
Major Substance Problem				
Heroin	70	77.8	87	73.7
Polysubstance	15	16.7	20	16.9
Rx Opioids	5	5.6	11	9.3
Heroin/Rx Opioid route				
IN	49	54.4	71	60.2
IV	38	42.2	35	29.7
oral	2	2.2	8	6.8
smoked	1	1.1	4	3.4
Cocaine route				
smoked	22	40.7	40	56.3
IN	17	31.5	16	22.5
IV	15	27.8	15	21.1

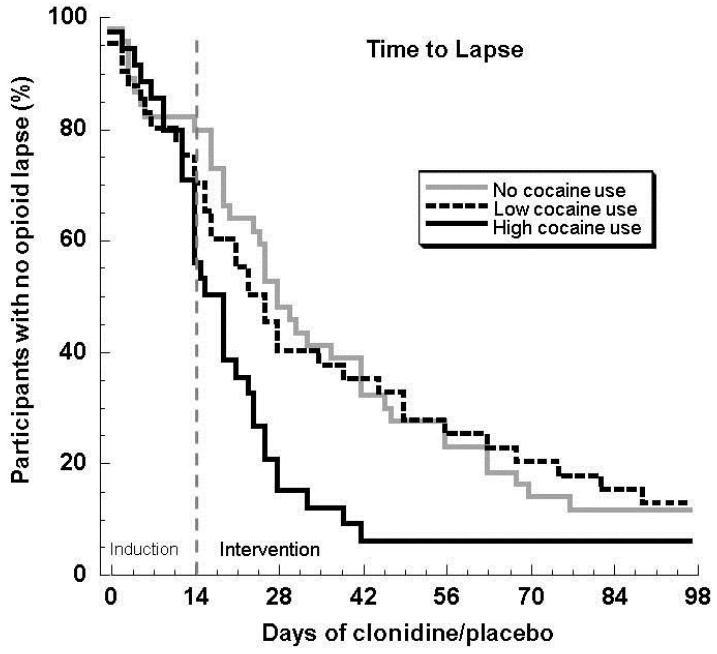
These analyses used independent-samples t-tests, χ-squares, or Fisher exact tests, as appropriate. Differences between randomized and non-randomized participants at $p \leq 0.05$ indicated by *.

TABLE S2. Adverse Events

Category	Symptom	Placebo		Clonidine		
		N	%	N	%	p
Any	Any	48	84.2	58	95.1	.05*
CNS	Sedation	8	14.0	17	27.9	.07
	Lightheaded	3	5.3	7	11.5	.33
Cardiovascular	Hypotension	3	5.3	8	13.3	.14
Dermatological	Rash	1	1.8	5	8.2	.21
	Lesion	2	3.5	4	6.6	.68
ENT	URI	16	28.1	13	21.3	.39
	Sore Throat	4	7.0	0	0.0	.05*
General	Fatigue	6	10.5	10	16.4	.35
	Trauma	8	14.0	3	4.9	.09
	Dizziness	1	1.8	5	8.2	.21
	Dry Mouth	0	0.0	6	9.8	.03*
	Dental	10	17.5	13	21.3	.61
Gastrointestinal	Vomiting	6	10.5	6	9.8	.90
	Nausea	3	5.3	7	11.5	.35
	Diarrhea	2	3.5	4	6.6	.68
	Constipation	6	10.5	11	18.0	.25
Musculoskeletal	Joint Pain	9	15.8	4	6.6	.11
	Back Pain	6	10.5	7	11.5	.87
Neurological	Headache	11	19.3	15	24.6	.49

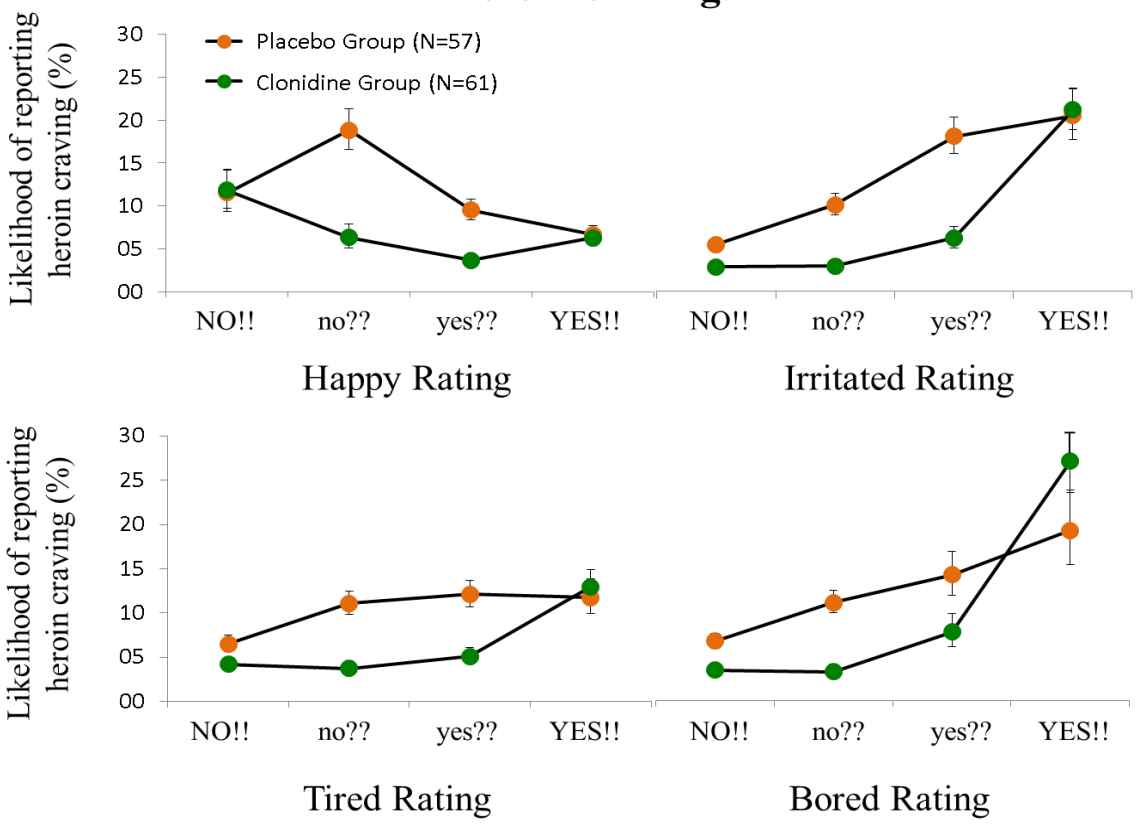
These analyses used χ-squares or Fisher exact tests, as appropriate. Group differences in reported rates of adverse events during the Induction and Intervention phases at $p \leq 0.05$ indicated by *.

FIGURE S2. Survival Curve for Time Until Lapse to Opioid Use: Differences by Cocaine Use



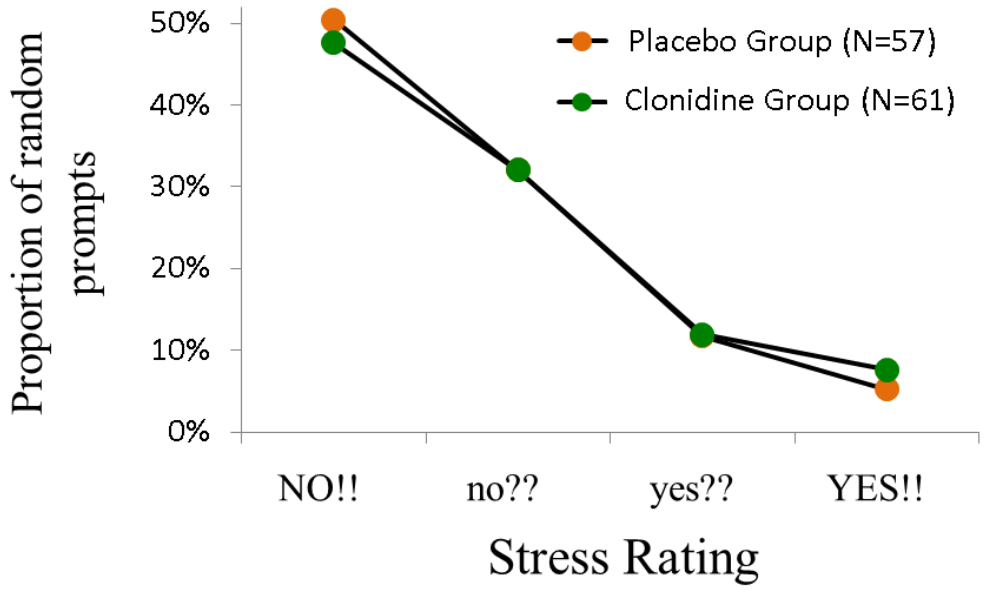
Cocaine use during the 8-week Baseline phase was associated with increased likelihood of a subsequent lapse to opioid use during the Intervention phase (Wald χ^2 =7.02, p≤0.05). Participants with greater than 25% cocaine-positive urines during Baseline were at greater risk than participants with fewer Baseline cocaine positives (HR=1.96, CI95:3.34-1.15, p≤0.05) or none (HR=2.48, CI95:5.35-1.14, p≤0.05).

Figure S3. The relationship between mood captured with EMA and heroin craving.



Heroin craving was significantly associated with concomitant ratings of both positive and negative moods (with the direction of the effect depending on the valence of the mood variable), but moods also interacted with clonidine/placebo group, reflecting, in the clonidine group, the same decoupling of mood from craving as was seen with stress and craving. Main effects and interaction effects were as follows: happy, (main: $F_{(3,257)}=42.3$, $p\leq0.001$, interaction: $F_{(3,257)}=28.3$, $p\leq0.001$), irritated (main: $F_{(3,257)}=210.7$, $P\leq0.001$, interaction: $F_{(3,257)}=29.4$, $p\leq0.001$), tired (main: $F_{(3,257)}=54.7$, $p\leq0.001$, interaction: $F_{(3,257)}=24.9$, $p\leq0.001$), and bored (main: $F_{(3,257)}=123.0$, $p\leq0.001$, interaction: $F_{(3,257)}=24.9$, $p\leq0.001$).

Figure S4. Stress responding across groups



Participants in the clonidine group seemed somewhat more likely to report "YES!!" stress than those in the placebo group. To assess that, we created a SAS GLIMMIX model using the logit function in which we compared the likelihood of a "YES!!" vs. all other responses. Controlling for the number of responses each participant made, there was an effect of group, such that those in the clonidine group were more likely to report extreme stress (clonidine: 7.6%, 95% CI=6.9%-8.3%, placebo: 5.3%, 95% CI=4.6%-5.9%, $F(1,105)=25.63$, $p \leq 0.001$, Cohen's $d=0.95$). We have no *a priori* reason to conclude that clonidine actually caused an increase in stress. The conclusion we can draw, however, is that clonidine's effect was to decouple stress from craving, rather than simply to decrease stress.