The American Journal on Addictions, 26: 838–844, 2017

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12641

Buprenorphine-Naloxone Treatment Responses Differ Between Young Adults With Heroin and Prescription Opioid Use Disorders

Mauricio Romero-Gonzalez, MD, MPH,[1,2] Abtin Shahanaghi, MD,[1,3] Gregory J. DiGirolamo, PhD,[1,4,5] Gerardo Gonzalez, MD [1,2,6]

[1]Division of Addiction Psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts
[2]MAYU of New England, New Haven, Connecticut
[3]Department of Psychiatry, Boston University, Boston, Massachusetts
[4]College of the Holy Cross, Worcester, Massachusetts
[5]Department of Radiology, University of Massachusetts Medical School, Worcester, Massachusetts
[6]VA Central Western Massachusetts Healthcare System, Leeds, Massachusetts

Background and Objectives: Opioid use disorder among young adults is rising sharply with an increase in morbidity and mortality. This study examined differences in treatment response to a fixed dose of buprenorphine-naloxone between heroin (HU) and prescriptions opioids (POU) users.
Methods: Eighty opioid dependent young adults ($M = 22$ years) were treated with buprenorphine-naloxone 16–4 mg/day for 8 weeks. Differences between HU ($N = 17$) and POU ($N = 63$) on changes in weekly opioid use, opioid craving, withdrawal, and depression symptoms were analyzed with mixed-effects regression models.
Results: The HU had an overall mean proportion of weekly opioid use of .32 (SD = .14) compared to POU's weekly mean of .24 (SD = .15) showing a significant main effect ($Z = 2.21$, $p = .02$). Depressive symptoms (CES-D scores) were elevated at baseline for both groups (HU: $M = 23.1$, SD = 11.9; PO: $M = 22.2$, SD = 9.4), but only POU improved significantly to a score of 9.88 (SD = 7.4) compared to HU's score of 18.58 (SD = 10.3) at week 8 ($Z = 2.24$, $p = .02$). There were no significant differences in treatment retention, craving, or withdrawal symptoms.
Discussion and Conclusions: Treatment response to 16-4 mg/day of buprenorphine–naloxone was significantly diminished for heroin users relative to opioid prescription users in weekly opioid use. Heroin users also had persistent depressive symptoms suggesting the need for close monitoring.
Scientific Significance: These data suggest that young heroin users might require higher doses of buprenorphine. (Am J Addict 2017;26:838–844)

Received March 24, 2017; revised September 15, 2017; accepted October 22, 2017.
Clinicaltrials.gov Identifier: NCT01052662
Address correspondence to: Dr. Gonzalez, Division of Addiction Psychiatry, University of Massachusetts Medical School, 55 North Lake Avenue, Rm S3-426, Worcester, MA 01655.
E-mail: gerardo.gonzalez@umassmed.edu

INTRODUCTION

Opioid use disorders are a serious public health problem associated with increased morbidity and mortality.[1–3] A 2010 global analysis estimated that 15.5 million people over 15 years who had opioid use disorder contributed 9.2 million of disability adjusted life years to the global burden of disease.[4] Heroin use in the general population in the US has increased after a relative stable period.[5] Moreover, heroin (~.7%, MTF) and prescription opioid use (8.8%, NSDUH) among young adults is disproportionately elevated.[6,7] In addition, the percentage of injection drug use-related infective endocarditis hospitalizations among young adults (15–34 years) in the US increased from 27.7% in 2008 to 42% in 2013.[2] There has been also an increase of the age-adjusted rates of deaths by drug overdose from 6.1 per 100,000 on 1999 to 16.3 per 100,000 in 2015, with a significant trend for younger adults (15–24 years) to increase but growing at slower rates compared to older adults.[8] With this increase of deaths by opioid overdose and endocarditis associated with increase of heroin and opioid usage, optimization of medication assisted treatment for young adults is necessary.[9] Currently, medication-assisted treatment with μ-opioid agonists continues to be the most effective treatment for opioid use disorders.[10] However, there is evidence in adults that prescription opioid users (POU) have better treatment response than heroin users (HU) or combined (heroin and prescription opioid) users.[11,12] In addition, Weiss et al.[13,14] have shown that current oral POUs with a history of heroin use have worse treatment response and more unfavorable long-term outcome with buprenorphine treatment.

However, it is not clear if young adults (18–25 years-old) who have less years of opioid use and a developing brain may

respond differently to treatment. The population of young adults allows us to investigate the potential deleterious effects of heroin usage on treatment outcomes compared to other young adults who have similar years of opioid use but no heroin usage. While heroin use may be of less duration in younger adults, it also may be even more harmful than older adults as their brains are still developing; particularly, within the frontal cortex.[15] Opioid use may drastically alter the early developmental processes of motivational and reward circuits that may impair function/development of the frontal control mechanisms.[16,17] Hence, younger adults may be more impulsive, and less committed to treatment. Additionally, they are predominantly using prescription opioids, may have less years of heroin use and could respond differently to buprenorphine treatment compared to the adult population who have fully matured brains, and whose years of drug usage are frequently confounded with heroin usage.

A retrospective study indicated that buprenorphine treatment was effective for young adults but most of the sample were IV HU and they did not compare them with POU.[18] It is still uncertain if there are any significant differences in the treatment response to buprenorphine-naloxone when comparing young adults that are only POU to those who have already begun using heroin. This current study evaluated the extent to which a fixed dose of 16-4 mg/day of buprenorphine-naloxone treatment with weekly Group Cognitive Behavioral Therapy during an 8-week outpatient treatment period improved opioid usage, opioid craving, and withdrawal, and depression symptoms in HU, and POU young adults. The combination buprenorphine–naloxone tablet was used as the addition of naloxone is considered a deterrent to intravenous use of buprenorphine. The use of the same behavioral counseling intervention in both groups was important because it delivers enhanced treatment to all participants, and was used to facilitate treatment retention. Based on the adult literature, we predicted that the HU would improve less than POU on opioid use, but that the 16 mg of buprenorphine treatment would be sufficient to suppress opioid withdrawal and craving equally among the two groups. In addition, since we had excluded patients with major depressive disorders and those receiving or needing pharmacotherapy for any depressive disorder, we expected that any depressive symptoms at baseline would improve equally for both groups. This improvement in depressive symptoms was expected as they reduced their opioid use, became abstinent, regained psychosocial functioning, and benefit from any potential anti-depressant effects of buprenorphine.[19]

METHOD

Participants

A 63 POU and 17 HU between the ages of 18–25 years old were included in this study. Details of recruitment and selection for the parent study that evaluated the combination of memantine and buprenorphine-naloxone for young adults with opioid use disorder are included elsewhere.[9] The main findings of the parent study showed that memantine 30 mg/day improved short-term treatment with buprenorphine/naloxone for opioid dependent young adults by reducing relapse and opioid use after buprenorphine discontinuation on week 9. Subjects provided written informed consent after receiving a complete description of the study. Following the consent process, participants were screened for DSM-IV criteria for opioid dependence (Structured Clinical Interview for DSM-IV, SCID),[20] assessed with physical and psychiatric evaluations, urine drug tested and completed the Addiction Severity Index (ASI).[21,22] These opioid-dependent subjects were actively using opioids or heroin as evidenced by self-report and having a positive urine drug test for opioids or oxycodone at intake, but negative for buprenorphine and benzodiazepines. Participants were all educated about HIV and Hepatitis C, counseled about the importance and meaning of screening for these disorders and they were offered onsite screening with referral to their PCP when needed. In addition, they all completed a Brief HIV Risk Questionnaire[23] to help with the risk assessment and counseling. All the subjects who met DSM-IV criteria for Opioid Dependence determined by SCID and confirmed by psychiatric evaluation, and were part of the intent-to-treat (ITT) sample of the parent study were included in the current study. The group assignment was determined by their reported primary drug used at entry into the parent study. Potential participants were excluded if they were diagnosed with other drug or alcohol dependence (except nicotine and cannabis), had Major Depressive disorder, displayed severe depressive symptoms defined as needing treatment with anti-depressants or were receiving any psychotropic medications. The study was approved by the University of Massachusetts Institute Review Board.

Study Design

This 8-week treatment period inducted participants onto a fixed dose of buprenorphine-naloxone (16-4 mg/day) on week 1 after they had stopped all opioid use and displayed mild to moderate opioid withdrawal symptoms (Clinical Opiate Withdrawal Scale (COWS) ≥ 8[24]). Buprenorphine-naloxone treatment was continued at this fixed dose until the end of week 8. All participants received group cognitive-behavioral therapy on a weekly basis delivered by a clinical psychologist trained in CBT and relapse prevention. Baseline assessments were performed during the first week of study participation. Each week subjects provided supervised urine samples, performed assessments, received study medications and participated in group therapy.

Medications

Buprenorphine–naloxone tablets (Suboxone; Rieckett Benkkiser Pharmaceuticals) was given on day 1 at bup/nal 8/2 mg, increased to bup/nal 12/3 mg on day 2, and then increased to bup/nal 16/4 mg on day 3 where it remained until the last day of week 8. Participants were observed for 1 hour on

the first day of induction and received a 7-day supply of medication each week thereafter.

Group Cognitive Behavioral Therapy

The cognitive-behavioral treatment was delivered by an experienced psychologist using the 90 minute sessions "Group Drug Counseling Manual" by Daley and co-workers."[25] The session topics focused on understanding substance use disorders and the recovery process, establishing a support system, managing feelings, coping with high-risk situations, and preventing relapses. Each session followed the procedures to enhance motivation and emphasize commitment to practicing acquired skills. As this group therapy was given to all patients, it was not a factor of analysis in our study and was used solely to enhance treatment and was used to facilitate treatment retention.

Assessments

Opioid use was measured as the mean proportion of weekly opioid use determined by self-report and urine drug screen. Self-reported days of opioid use during the previous week for opioid analgesics and/or heroin use was assessed using the time-line followed-back method (TLFB).[26] A urine drug screen for opiates, oxycodone, methadone, cocaine, benzodiazepines, amphetamines, buprenorphine, and phencyclidine results at the end of each week was used to verify the self-reported use of the previous week. Participants scored 100% opioid use if they reported using any opioid each day of the previous week and had a positive urine for opiate, oxycodone, or methadone at the end of that week. Participants were given a score of 1 for each day of reported opioid use, and a score of 1 for a positive opioid urine for that week. Hence, Participants scored 100% if they reported 7 days of use and had a positive opioid urine, totaling a score of 8. All other scores less than a 100% were the total score divided by the eight potential points. In addition, the other outcomes were treatment retention, treatment compliance with weekly buprenorphine urine testing and change from baseline to week 8 on repeated measures of opioid withdrawal symptoms measured by the Clinical Opiate Withdrawal Scale (COWS),[24] opioid craving measured by Heroin Craving Questionnaire-Short Form-14 (HCQ-SF-14),[27,28] and depression symptoms measured by the Center for Epidemiologic Studies Depression Scale (CES-D).[29]

Statistical Analyses

The analyses were conducted on the intent-to-treat sample that participated in the parent study.[9] The group variable was the POU or HU conditions. Baseline differences were determined by using Pearson chi-square tests for categorical variables and *t*-test for continuous variables. The HU group had 13 of 17 subjects, and the POU had 38 of 67 subjects that had received memantine treatment. While during the short stabilization period (week 1–8) in the parent study there were no significant differences between groups, the assignment to study arm (memantine 0, 15, and 30 mg) was used as covariate in all subsequent analyses to control for potential effects of memantine. Treatment retention was determined by using Kaplan–Meier estimates[30] and differences by group using Mantel–Cox log rank tests.[31] Change of opioid use was evaluated by modeling the mean proportion of opioid use using a mixed-effect linear regression approach to assess the time effect, group effect, and the interaction of time x group effect while adjusting for baseline opioid use as covariate.[32] Missing data was handled by inclusion in all these models capable of dealing with missing data without being imputed. The effect of the group across time on outcomes was evaluated by performing mixed-effect regression models on COWS, HCQ-SF-14, and CES-D. All analyses were two-tail and statistical significance was set at a p-value $<.05$.

RESULTS

Baseline Demographics and Clinical Characteristics

Participants were on average 22 years old, predominately single Caucasian males (66%) with a high school degree or GEDs (40%), and working part or full-time (51%) (Table 1). The HU ($n = 17$) had been using heroin on average for 3.7 years and used on average 25 days of the previous month. The POU group ($n = 63$) had been using prescription opioids on average for 3 years and were using prescription opioids on average 25 days of the previous month. The reported average heroin use was 8.29 small bags (SD = 5.02 small bags) per day and the reported average morphine equivalent dose used for prescription opioids was 153.5 mg (SD = 119.5 mg) per day the week prior to treatment. However, there were no other demographic or clinical significant differences between groups on any other measures at baseline. This group of young adults were likely to be depressed (CES-D; mean = 22.4; SD = 9.9), and reported substantial problems on the ASI composite scores on drug use (mean = .34; SD = .08), and employment (mean = .49; SD = .28). While all participants were negative for HIV at screening, 82% of the HU were IVDUs and 12% of participants admitted to sharing needles and syringes the month prior to entering treatment compared to 6% of the POU were IVDUs and none had shared paraphernalia.

Treatment Retention and Compliance

The retention during the 8 weeks of treatment was numerically better for POU with 82.5% (52/63) remaining in treatment compared to 64.7% (11/17) of HU (log rank = 2.3; $p = .13$). In addition, the verification of buprenorphine–naloxone by weekly urine toxicology showed that the POU was significantly more compliant with 99% of urine screen positive for buprenorphine compared to HU that had 96% compliance ($X^2 = 4.4$, $p < .04$).

Group Effect on Treatment Response

Weekly Opioid Use

Both groups had a sharp reduction in opioid use after induction onto bup/nal on the first week that continued over the

TABLE 1. Demographics and baseline characteristics

	Total		Heroin		Prescription			
	($N = 80$)		($N = 17$)		($N = 67$)			
Variables	Mean	SD	Mean	SD	Mean	SD	t	p value
Age (years)	22.65	1.917	23.06	1.784	22.54	1.95	−0.991	0.325
Gender	N	%	N	%	N	%	x^2	p value
Male	53	66.3	11	64.7	42	66.7	0.023	0.879
Female	27	33.8	6	35.3	21	33.3		
Marital status								
Never married	78	97.5	16	94.1	62	98.4	1.013	0.314
Divorced	2	2.5	1	5.9	1	1.6		
Etnicity								
Caucacian	73	91.3	14	82.4	59	93.7	2.14	0.143
Hispanic	7	8.8	3	17.6	4	6.3		
Education								
High school degree and GED.	32	40	8	47.1	24	38.1	2.038	0.565
Some college	35	43.8	8	47.1	27	42.9		
College	5	6.3	0	0	5	7.9		
Others	8	10	1	5.9	7	11.1		
Employment								
Full time	26	32.5	4	23.5	22	34.9	3.771	0.287
Part time	15	18.8	5	29.4	10	15.9		
Unemployed	26	32.5	7	41.2	19	30.2		
Student	13	16.3	1	5.9	12	19		
Opioid use severity								
Baseline Oxy positive urines	62	77.5	8	47.1	54.0	85.7	11.5	0.001
Baseline opiate positive urines	40	50.0	17	100.0	23.0	36.5	21.6	<0.0001
	Mean	SD	Mean	SD	Mean	SD	t	p value
Opioid analgesic use (7 days TLFB)	4.45	2.79	0.65	1.32	5.51	2.08	9.12	<0.0001
Opioid analgesic use (last 30 days)	20.40	11.06	3.35	5.48	25.00	6.85	12.01	<0.0001
Opioid analgesic use (years)	3.20	1.98	3.82	2.43	3.03	1.83	−1.47	0.15
Heroin use (7 days TLFB)	1.47	2.71	6.35	1.32	0.11	0.55	−29.21	<0.0001
Heroin use (last 30 days)	5.78	11.08	25.65	6.60	0.15	0.52	−30.09	<0.0001
Heroin use (years)	1.08	2.19	3.76	2.77	0.32	1.20	−7.54	<0.0001
Current clinical status								
COWS	4.70	4.03	4.18	3.19	4.84	4.24	0.60	0.55
Heroin craving	4.37	1.08	4.52	0.77	4.33	1.16	−0.62	0.54
CES-D scores	22.41	10.00	23.53	12.20	22.11	9.41	−0.52	0.61
ASI composite scores								
Drug	0.34	0.08	0.34	0.07	0.34	0.08	0.20	0.84
Alcohol	0.05	0.07	0.04	0.06	0.05	0.07	0.39	0.70
Legal	0.13	0.19	0.15	0.18	0.13	0.19	−0.36	0.72
Family	0.14	0.17	0.17	0.17	0.14	0.17	−0.53	0.60
Employment	0.49	0.28	0.54	0.29	0.47	0.28	−0.99	0.33
Medical	0.05	0.18	0.00	0.00	0.06	0.20	1.29	0.20
Psychiatric	0.19	0.17	0.26	0.16	0.18	0.18	−1.63	0.11

8 weeks. As shown in Figure 1, treatment with bup/nal reduced the mean proportion of weekly opioid use of the HU from an average of .87 (SD = .21) on week 1–.27 (SD = .18) at week 2 and to .22 (SD = .22) by week 8. The POU had an initial mean proportion of weekly opioid use of .71 (SD = .26) on week 1 that was reduced to .14 (SD = .14) on week 2 and to .18 (SD = .17) by week 8. The mixed-effect model showed a significant main effect of group with POU reducing their usage more than the HU ($Z = 2.21$, $p = .02$) and a significant time effect ($Z = -9.85$, $p < 0001$), but there was no significant

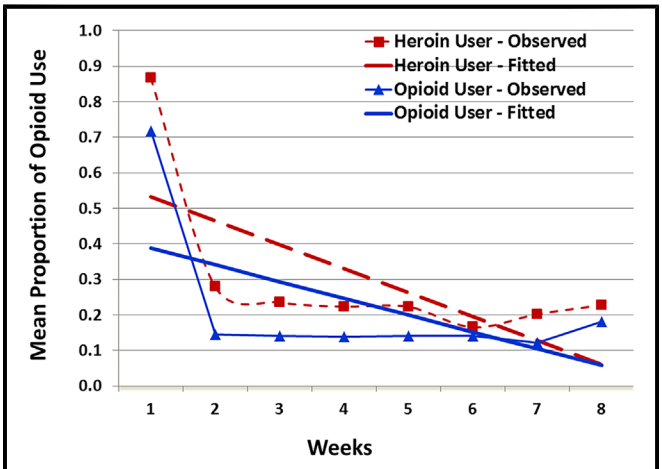

FIGURE 1. Change of weekly opioid use between heroin users ($N = 17$) and prescription opioid users ($N = 67$) treated with fixed dose of buprenorphine–naloxone (16-4 mg/day). The figure shows observed and fitted trend lines of weekly mean proportion of opioid use for heroin users and prescription opioid users. The fitted trend lines are based on the results of mixed-effect linear regression model that controlled for baseline opioid use. There is a significant main effect difference ($Z = 2.21$, $p = .02$) and a significant time effect ($Z = -9.85$, $p < 0.001$), but there is no significant group x time interaction ($Z = 1.83$, $p = .06$).

group x time interaction ($Z = 1.83$, $p = .06$). The main effect showed that HU had an overall mean proportion of weekly opioid use of .32 (SD = .14) compared to POU's weekly mean of .24 (SD = .15).

Craving for Opioids

Both groups reduced their weekly craving for opioids (HCQ-SF-14, scale range 1–7) from an average for the HU of 4.5 (SD = .77) and for POU of 4.3 (SD = 1.1) on the week 1 to an average of 3.2 (SD = 1.2) and 2.7 (SD = 1.1) by week 8, respectively. The mixed-effect model showed the significant time effect ($Z = -10.0$, $p < .0001$); however, there were no group effect ($Z = 1.62$, $p = .1$) nor a group x time interaction effect ($Z = .15$, $p = .8$).

Opioid Withdrawal Symptoms

Clinical opioid withdrawal symptoms (COWS) scores were initially mild for both groups (range 8–12), with HU scoring 8.4 (SD = 3.5) and POU scoring at 9.4 (SD = 3). Both groups attenuated their opioid withdrawal scores to an average of 3.2 (SD = 1.2) and to 2.7 (SD = 1.1) by week 8, respectively, showing a time effect ($Z = -12.4$, $p < .0001$) with no group or group by time interaction differences.

Depressive Symptoms

As shown in Figure 2, both the HU and POU groups had elevated baseline depressive symptoms (CES-D >16, scale range 0–60) at baseline scoring an average of 23.1 (SD = 12.1) and of 22.2 (SD = 9.4), respectively, but only the POU improved significantly after starting treatment with buprenorphine–naloxone compared to the HU. The POU reduced their score to an average of 12.6 (SD = 7.8) on week 2 and then to an average score of 9.88 (SD = 7.3) by week 8. Compared to the HU that remained with scores over 16 throughout the 8 weeks with another peak of 22.1 (SD = 12.4) on week 6 and then with an average score of 19 (SD = 10) by week 8. The mixed effect models showed a significant group effect ($Z = 1.95$, $p = .05$), time effect ($Z = -11.3$, $p < .001$), and a group by time interaction ($Z = 2.24$, $p = .02$).

DISCUSSION AND CONCLUSIONS

These findings support our predictions that young adults with heroin use disorders improved significantly less than prescription opioid use disorders with buprenorphine-naloxone (16-4 mg) treatment on their weekly opioid use. Also, an unexpected treatment outcome was observed with the HU group not improving on depressive symptoms as the POU group in spite of the exclusion of participants that had Major Depressive Disorder, severe depressive symptoms or those who were taking antidepressants.

Diminished reductions of opioid use and treatment retention for HU in our young adults are consistent with data on older adults.[11,12] In these studies, adult HU provided more positive urines and had worse retention in treatment than POU. Also, a history of heroin use in primarily POU treated with buprenorphine and counseling had a negative prognostic impact on

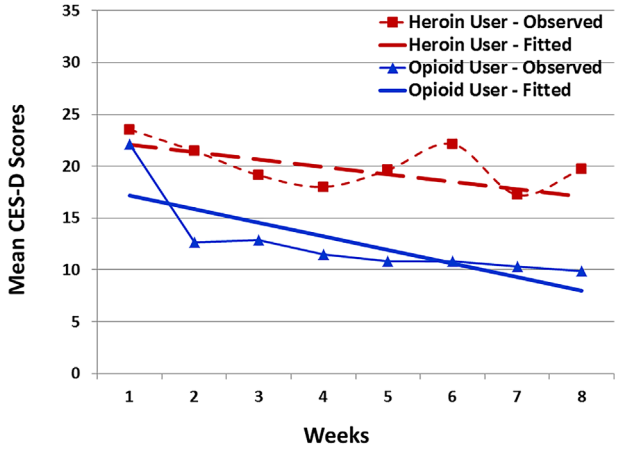

FIGURE 2. Change of weekly depressive symptoms (CES-D scores) between heroin users ($N = 17$) and prescription opioid users ($N = 67$) treated with fixed dose of buprenorphine-naloxone (16-4 mg/day). The figure shows observed and fitted trend lines of weekly depressive symptoms as measures by CES-D[29] for heroin users and prescription opioid users. The fitted trend lines are based on the results of mixed-effect linear regression model that controlled for baseline score of depressive symptoms. There is a significant group effect ($Z = 1.95$, $p = .05$), time effect ($Z = -11.3$, $p < .001$), and a group by time interaction ($Z = 2.24$, $p = .02$).

treatment response[13] and on long-term outcomes.[14] A multi-site study evaluating pre-treatment characteristics in POU also showed that older age, no prior treatment attempts, and diagnoses of depression were associated with better outcome.[33]

A potential factor associated with reduced improvement of the HU in the present study may have been the use of a fixed dose of buprenorphine at 16 mg/day. Buprenorphine is a high affinity partial mu- receptor (MOR) agonist that at a 16 mg dose has the ability to reduce the brain MOR availability by 80% when compared to 0 mg dose.[34] A daily dose of buprenorphine of 4 mg has the ability to suppress opioid withdrawal symptoms when brain MOR availability is $\leq$50%. However, a dose of buprenorphine higher than 16 mg/day may be needed to reduce the reinforcing and subjective effects of opioids with MOR availability of less than 20%.[35] Taken together this data suggests that HU in this study may have needed a higher dose of buprenorphine.

The elevated depression scores at baseline for both groups are likely to be substance-induced depressive symptoms rather than dysphoric mood related to opioid withdrawal symptoms given the low COWS score that were measured at the same time as the CES-D. The finding that the HU did not improve at all on depressive symptoms as expected with abstinence and the potential antidepressant-like effect of buprenorphine treatment[19] is remarkable. Studies that have evaluated depression with treatment response in HU have mixed results showing either worse[36] or better outcomes.[33] However, to the best of our knowledge, this is the first study to evaluate the pattern of depressive symptoms during a fixed dose of buprenorphine in a sample of young HU and POU that excluded Major Depressive Disorder or those with severe symptoms of depression needing antidepressants. Possible hypotheses for this different pattern of change of depressive symptoms between HU and POU is the emerging concept of "biased agonism" where unique opioid ligands may have a different ability to signal on G protein coupled receptors with different responses or consequences.[37] Thus heroin and prescription opioids may have induced depressive symptoms differently by interacting in different ways with kappa opioid receptors (KOR) that mediates dysphoria, and/or with the delta opioid receptors (DOR) that is considered to decrease levels of anxiety and reduce depressive-like behaviors.[38] Likewise, the antidepressant-like effect of buprenorphine that is mediated by its antagonist effect at KOR[19] may have acted differently based on different profile changes effects of heroin versus prescription opiates on the different opioid receptors.

Another possible explanation of the different pattern of depressive symptoms in HU may be related to potential differences in brain structures between HU and POU. A study evaluating the left nucleus accumbens in HU, found it to be reduced in size when compared to healthy controls and this reduction correlated with worse depressive symptoms.[39] However, a comparison of the left nucleus accumbens of HU with POU is unknown. Lastly, the results of a rodent study that used knockout MOR in the dorsal raphe nucleus of the mice prior to heroin exposure displayed protective features in social withdrawal, and treatment with fluoxetine prevented low sociability in these animals.[38] While these human and rodent findings support the potential of adding an SSRI antidepressant to improve HU with depressive symptoms, the results of controlled studies evaluating SSRIs for depressed opioid dependent populations have had mixed results.[40]

The clinical implications of these findings are that young adult HU may have worse treatment response with buprenorphine-naloxone at 16-4 mg/day and may need higher dose. The persistent depressive symptoms of this group of young adults with heroin use disorder is concerning, but further investigation is necessary to better understand this pattern, and to assess whether adding an SSRI to buprenorphine treatment would be beneficial. There are a few limitations that need to be considered. One potential limitation of this study was the small number in the heroin group. However, the magnitude of the effects allowed for significant statistical differences between our groups. Another potential limitation is the difference in the reported amount of opioids used between groups that could have impacted the results and was not controlled in our analysis due to the small sample size. The variation in concentration between bags of heroin is usually large and this factor cannot be included calculating amount of heroin use. Another limitation is a lack of generalizability to patients with opioid dependence and co-occurring diagnoses, which are usually the high-risk population in specialty treatment settings. Lastly, the lack of follow-up data at 3 months or more after the study completion reduces the findings for generalization.

In summary, both heroin and prescription opioid groups improved during this 8 week treatment period with buprenorphine/naloxone on the outcomes evaluated, but the HU improved significantly less than the POU group on weekly opioid use and depressive symptoms. These results suggest that young adults with heroin use disorder appear to improve less with fixed dose of buprenorphine (16-4 mg) and may need higher dosage. Also, careful monitoring of depressive symptoms in HU is recommended. Further research into this pattern of persistent depressive symptoms with evaluation of efficacy of SSRI treatment in this situation is needed before the recommendation of adding of SSRI to buprenorphine treatment.

This study was supported by the National Institute on Drug Abuse (NIDA) Grant R01DA027138 to Gerardo Gonzalez, MD. The results of this manuscript were previously presented at the 76th Annual Meeting of the College of Problems on Drug Dependence in Puerto Rico, June14–19, 2014.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

REFERENCES

1. Yokell MA, Delgado MK, Zaller ND, et al. Presentation of prescription and nonprescription opioid overdoses to US emergency departments. *JAMA Intern Med*. 2014;174:2034–2037.

2. Wurcel AG, Anderson JE, Chui KK, et al. Increasing infectious endocarditis admissions among young people who inject drugs. *Open Forum Infect Dis* 2016;3:ofw157.
3. Hsu DJ, McCarthy EP, Stevens JP, et al. Hospitalizations, costs, and outcomes associated with heroin and prescription opioid overdoses in the United States 2001–2012. *Addiction*. 2017;112:1558–1564.
4. Degenhardt L, Charlson F, Mathers B, et al. The global epidemiology and burden of opioid dependence: Results from the global burden of disease 2010 study. *Addiction*. 2014;109:1320–1333.
5. Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med*. 2016;374: 154–163.
6. Johnston LD, O'Malley PM, Bachman JG, et al. *Demographic Subgroup Trends Among Young Adults in the Use of Various Licit and Illicit Drugs 1989-2013 (Monitoring the Future Occasional Paper 80)*. Ann Arbor: MI Institute for Social Research; 2014.
7. SAMHSA. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. HHS Publication No. (SMA) 14–4863. 2014. Rockville, MD, Substance Abuse and Mental Health Services Administration. NSDUH Series H-48.
8. Hedegaard H, Warner M, Minino AM. Drug overdose deaths in the United States, 1999-2015. *NCHS Data Brief*. 2017;273:1–8.
9. Gonzalez G, DiGirolamo G, Romero-Gonzalez M, et al. Memantine improves buprenorphine/naloxone treatment for opioid dependent young adults. *Drug Alcohol Depend*. 2015;156:243–253.
10. Gonzalez G, Oliveto A, Kosten TR. Combating opiate dependence: A comparison among the available pharmacological options. *Expert Opin Pharmacother*. 2004;5:713–725.
11. Nielsen S, Hillhouse M, Mooney L, et al. Buprenorphine pharmacotherapy and behavioral treatment: Comparison of outcomes among prescription opioid users, heroin users and combination users. *J Subst Abuse Treat*. 2015;48:70–76.
12. Moore BA, Fiellin DA, Barry DT, et al. Primary care office-based buprenorphine treatment: Comparison of heroin and prescription opioid dependent patients. *J Gen Intern Med*. 2007;22:527–530.
13. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68:1238–1246.
14. Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the national drug abuse treatment clinical trials network prescription opioid addiction treatment study. *Drug Alcohol Depend*. 2015;150:112–119.
15. Casey BJ, Jones RM, Hare TA. The adolescent brain. *Ann N Y Acad Sci*. 2008;1124:111–126.
16. Belin D, Jonkman S, Dickinson A, et al. Parallel and interactive learning processes within the basal ganglia: Relevance for the understanding of addiction. *Behav Brain Res*. 2009;199:89–102.
17. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nat Neurosci*. 2005;8: 1458–1463.
18. Vo HT, Robbins E, Westwood M, et al. Relapse prevention medications in community treatment for young adults with opioid addiction. *Subst Abus*. 2016;37:392–397.
19. Falcon E, Browne CA, Leon RM, et al. Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. *Neuropsychopharmacology*. 2016;41:2344–2351.
20. First MB, Spitzer RL, Gibbon M. *Structured Clinical Interview for DSM-IV*. Washington, DC: American Psychiatric Association Press; 1995.
21. McLellan AT, Luborsky L, Woody GE, et al. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *J Nerv Ment Dis*. 1980;168:26–33.
22. McLellan AT, Kushner H, Metzger D, et al. The fifth edition of the addiction severity index. *J Subst Abuse Treat*. 1992;9:199–213.
23. Copersino ML, Meade CS, Bigelow GE, et al. Measurement of self-reported HIV risk behaviors in injection drug users: Comparison of standard versus timeline follow-back administration procedures. *J Subst Abuse Treat*. 2010;38:60–65.
24. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). *J Psychoactive Drugs*. 2003;35:253–259.
25. Daley DC, Mercer D, Carpenter G. Group drug counseling manual, 2nd Edn. *Export*. PA: Daley Publications; 2004.
26. Ehrman RN, Robbins SJ. Reliability and validity of 6-month timeline reports of cocaine and heroin use in a methadone population. *J Consult Clin Psychol*. 1994;62:843–850.
27. Heinz AJ, Epstein DH, Schroeder JR, et al. Heroin and cocaine craving and use during treatment: Measurement validation and potential relationships. *J Subst Abuse Treat*. 2006;31:355–364.
28. Singleton E. *HCQ-Now-SF-14r: Revised Version of the Heroin Craving Questionnaire—Brief*. Baltimore, MD: Johns Hopkins University; 1998.
29. Radloff LS. A CES-D scale: A self-reported depression scale for reaserch in the general population. *Appl Psychol Meas I*. 1977;1:385–401.
30. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc*. 1958;53:457–481.
31. Peto R, Peto J. Asymptomatically efficient rank invariant test procedures. *J R Stat Soc [A]*. 1972;135:185–207.
32. Hedeker D, Gibbons RD. MIXREG: A computer program for mixed-effects regression analysis with autocorrelated errors. *Comput Methods Programs Biomed*. 1996;49:229–252.
33. Dreifuss JA, Griffin ML, Frost K, et al. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug Alcohol Depend*. 2013;131:112–118.
34. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*. 2003;28:2000–2009.
35. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: Implications for clinical use and policy. *Drug Alcohol Depend*. 2014; 144:1–11.
36. Teesson M, Marel C, Darke S, et al. Long-term mortality, remission, criminality and psychiatric comorbidity of heroin dependence: 11-year findings from the Australian Treatment Outcome Study. *Addiction*. 2015;110:986–993.
37. Dogra S, Yadav PN. Biased agonism at kappa opioid receptors: Implication in pain and mood disorders. *Eur J Pharmacol*. 2015;763:184–190.
38. Lutz PE, Ayranci G, Chu-Sin-Chung P, et al. Distinct mu, delta, and kappa opioid receptor mechanisms underlie low sociability and depressive-like behaviors during heroin abstinence. *Neuropsychopharmacology*. 2014;39:2694–2705.
39. Seifert CL, Magon S, Sprenger T, et al. Reduced volume of the nucleus accumbens in heroin addiction. *Eur Arch Psychiatry Clin Neurosci*. 2015;265:637–645.
40. Pani PP, Vacca R, Trogu E, et al. Pharmacological treatment for depression during opioid agonist treatment for opioid dependence. *Cochrane Database Syst Rev*. 2010;CD008373.