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Sex-based differences in psychiatric symptoms and opioid abstinence during buprenorphine/naloxone treatment in adolescents with opioid use disorders

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ABSTRACT

Background: Recent studies indicate that sex-based differences exist in co-occurring psychiatric symptoms and disorders among individuals with opioid use disorders (OUD). Whether these associations are present in adolescent samples and change during OUD treatment is poorly understood.
Objectives: In the current study, we examined sex-based differences in psychiatric symptoms and relationships among sex, psychiatric symptoms, and opioid use outcomes in youth with OUD receiving buprenorphine/naloxone (Bup/Nal) and psychosocial treatment.
Methods: The study randomly assigned one hundred and fifty-two youth (15–21 years old) diagnosed with OUD to either 12 weeks of treatment with Bup/Nal or up to 2 weeks of Bup/Nal detoxification with both treatment arms receiving weekly drug counseling as part of a multisite clinical trial (NIDA-CTN-0010). We compared psychiatric symptoms, assessed via the Youth Self Report (YSR) at baseline and week 12, across male and female OUD participants. The study used logistic regression models to identify sex and psychiatric symptom variables that were predictors of opioid positive urine (OPU) at week 12.
Results: Compared to males, females with OUD had higher mean psychiatric symptom scores at baseline across broad-band and narrow-band symptom domains. The study observed significant reductions in psychiatric symptom scores in both males and females during treatment, and by week 12, females only differed from males on anxious-depressive symptom scores. Females, in general, and youth of both sexes presenting to treatment with higher anxious depression scores were less likely to have a week-12 OPU.
Conclusions: Clinically significant sex-based differences in psychiatric symptoms are present at baseline among youth with OUD receiving Bup/Nal-assisted treatment and mostly resolve during treatment.

1. Introduction

American youth have suffered substantial negative sequelae from the opioid epidemic. Prescription opioids are the second most commonly misused illicit drug among adolescents living in the United States, and U.S. young adults have the highest rates of opioid misuse of any age group (Johnston et al., 2019; SAMSHA, 2019). According to U.S. prevalence rates, 3.3 million American youth reported past-year prescription opioid misuse in 2017, including 3.6% of adolescents ages 12–17 years and 7.5% of young adults ages 18–25 years (Hudgins et al., 2019; SAMSHA, 2019). Opioid use during adolescence is associated with many adverse health outcomes, including opioid use disorders (OUD), medical and psychiatric comorbidities, socioeconomic challenges, legal problems, academic and occupational failure, high-risk sexual behavior, and elevated risk for sexually transmitted infections (hepatitis C and HIV) and opioid-related overdose and death (Bahorik et al., 2017; Curtin et al., 2017; Subramaniam & Stitzer, 2009). During the current opioid epidemic, opioid-related emergency department visits, overdoses, and deaths have increased among adolescents and young adults (Curtin et al., 2017; Gaither et al., 2016; Tadros et al., 2016). Further study of

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adolescent-specific burden of disease is crucial as adolescents may be at elevated risk for negative outcomes related to opioid use and as adolescent opioid use remains elevated (Curtin et al., 2017; Osborne et al., 2019).

Comorbid psychiatric symptoms and disorders are frequent with opioid use and OUD, and this comorbidity is associated with increased all-cause mortality (Bogdanowicz et al., 2015; Han, Compton, Blanco, & Colpe, 2017; Han, Compton, Blanco, Crane, et al., 2017; Richardson et al., 2012; Rounsaville et al., 1986). Adults who misuse opioids or who have OUD have higher lifetime prevalence of psychiatric disorders compared to the general population and are more likely to experience concurrent psychiatric symptoms and disorders during periods of opioid use (Han, Compton, Blanco, & Colpe, 2017; Richardson et al., 2012; Rounsaville et al., 1986). A recent population-wide sample of U.S. adults found that 64% of adults diagnosed with OUD had one or more concurrent psychiatric disorder, and 27% of adults with OUD met criteria for having a severe mental illness (Jones & McCance-Katz, 2019). While comorbidity between opioid use and psychiatric disorders is well established, whether opioid-psychiatric symptom relationships represent generalized "nonspecific" psychopathology associations versus distinct substance-psychiatric symptom "specific" associations is less clear. Some studies have reported associations between adult opioid use and related disorders with all psychiatric symptom domains suggesting general psychopathology relationships (Mason et al., 1998). Conversely, other studies have reported unique relationships between adult opioid use and distinct psychiatric symptom domains or disorders, with affective symptoms being the most consistently reported co-occurring psychiatric symptoms in opioid using or dependent adults (Rounsaville et al., 1986). Further work is needed to clarify the generality vs. specificity of these relationships as well as their temporal characteristics and prognostic significance.

While less studied, young people who use opioids and who meet criteria for OUD also have higher lifetime and concurrent psychiatric symptoms and disorders than youth without OUD in the general population, including hopelessness, major depression, and suicide (Edlund et al., 2015; Zullig & Divin, 2012). Prevalence rates of comorbid psychiatric disorders are higher in clinical samples of adolescents with OUD, at rates up to 80%, which may exceed the prevalence of comorbidity observed in adolescents treated for non–opioid substance use disorders (SUDs) (Subramaniam & Stitzer, 2009). Compared to youth, far more is known about psychiatric comorbidities in opioid-using adult populations (Jones & McCance-Katz, 2019).

Accumulating empirical evidence indicates that men and women with OUD exhibit different patterns of co-occurring psychiatric and medical comorbidity, respond differently to opioids, and have different opioid use and OUD-related health correlates, risk factors, and prognostic-factors that influence treatment outcomes (Greenfield et al., 2010; Jones & McCance-Katz, 2019; Kennedy et al., 2013). Sex-based differences in co-occurring psychiatric symptoms and disorders in adults with OUD have been reported in population-wide survey samples, OUD clinical samples, and pain clinic samples (Campbell et al., 2018; Osborne et al., 2019; Yarborough et al., 2016; Zilberman et al., 2003). Across studies, women who misuse prescription opioids or who meet diagnostic criteria for OUDs generally show higher severity of psychiatric symptoms and increased rates of co-occurring psychiatric disorders; medical conditions; chronic pain; and family, social, and employment difficulties than their male counterparts. While good evidence exists for sex-based differences in co-occurring/comorbid psychiatric disorders in adults, we know little about sex-specific correlates of opioid use in adolescents. Of the few studies published to date, all have used general population survey data and have focused on specific associations between opioid use and depression (Chan & Marsack-Topolewski, 2019; Edlund et al., 2015). These studies collectively show stronger relationships between opioid use and depression in adolescent females compared to males in the general population. We do not know whether opioid use is associated with psychiatric symptoms/disorders aside from depression in adolescents, and, if present, whether these associations are sex-specific or shared.

Co-occurring psychiatric disorders in individuals with OUD may affect treatment retention and treatment response for both opioid use and psychiatric outcomes via sex-specific and shared pathways. A recent review of the adult literature found that women are more likely than men to present to OUD treatment with co-occurring psychiatric conditions such as depression and that women with OUD may respond better to buprenorphine-naloxone (BUP-NAL)-assisted treatment (Huhn et al., 2019). Women presenting for OUD treatment tend to have higher rates of psychiatric comorbidities than men and may seek treatment for different reasons, such as to address ongoing psychological distress or pain (Chatham et al., 1999). Results from studies in treatment-seeking adults examining sex-based differences in OUD treatment retention and outcomes have been mixed. Some studies have reported that women receiving treatment for OUD have better retention rates and reduced risk for opioid relapse compared to men, while other studies reported no sex-based differences in treatment outcomes. In parallel, studies examining the influence of concurrent psychiatric comorbidity on adult OUD treatment outcomes have also shown mixed findings, with some studies reporting no association (Krawczyk et al., 2017), while others report a negative impact of psychiatric comorbidity or a protective effect of psychiatric comorbidity on OUD treatment outcomes (Maremmani et al., 2008). Some of the variance in the relationships between psychiatric disorders and OUD treatment outcomes may be attributable to sex-specific individual differences in response to evidence-based OUD treatment modalities and pharmacologically distinct medications to treat OUD (Herbeck et al., 2016).

Despite growing research in adult populations, little is known about how sex and co-occurring psychiatric symptoms across different domains relate to treatment response in youth receiving medication for addiction treatment for OUDs. Given the lack of information in adolescent samples and growing evidence for clinical relevance of sex differences from the adult literature, the current study examines data from a large multisite clinical trial of adolescents with OUD receiving bup/nal-assisted psychosocial treatment to identify sex-based differences in psychiatric symptoms and treatment outcomes, to provide further insights into potential sex-specific and sex-shared mechanisms of treatment response that relate to concurrent psychiatric symptomatology. The current report draws data from the National Institute on Drug Abuse Clinical Trials Network (CTN) 0010 trial, a study that investigated the efficacy of short-term bup/nal detoxification ("Detox") versus extended-term bup/nal-assisted treatment ("bup-nal") on opioid abstinence outcomes in a large sample of adolescents seeking treatment for OUD (Woody et al., 2008). Importantly, the NIDA-CTN-0010 trial comprehensively assessed psychiatric symptoms across domains using empirically based youth and young adult self-report questionnaires (Achenbach, 1997; Achenbach & Rescorla, 2001) at different time points. This assessment allowed for us to characterize in our analyses the relative influence of both "generalized" psychiatric symptoms via broad-band hierarchical multiple-domain scores (e.g., total psychological problems) and specific psychiatric symptom domains via narrow-band syndrome scores (e.g., anxious/depression). The aims of this secondary analysis were to (1) test for sex-based differences in the severity of psychiatric symptoms across domains at the pretreatment baseline visit (termed BSL throughout), (2) to determine if changes in psychiatric symptoms and opioid use over the course of the 12-week trial differed in sex-specific ways, and (3) to identify whether the BSL severity and during-treatment course of general vs. domain-specific psychiatric symptoms were associated with lower opioid use, and, if present, whether these associations differed in sex-specific ways.

2. Methods

2.1. Participants and study procedures

Adolescent and young adult males and females aged 15–21 years who met DSM-IV-TR diagnostic criteria for opioid dependence with physiological features, who were free of serious medical or psychiatric disorders that would make participation hazardous, and who were seeking outpatient substance use treatment were recruited from six community treatment programs for the NIDA-CTN-0010 trial between July 2003 and December 2005. The study excluded from participation subjects who the screening assessment identified as being acutely suicidal, homicidal, psychotic, or otherwise seriously impaired and incapable of giving informed consent. Details on the rationale, design, full assessment battery, and primary outcomes for NIDA-CTN-0010 are described elsewhere (Subramaniam & Stitzer, 2009; Woody et al., 2008). The study team obtained written assent and written parental consent from all participants under 18 years, and written consent from all participants aged 18 years and older. The institutional review boards from all participating sites approved the parent study.

2.2. Study treatment

Medication dosing was flexible and the treating clinician determined the dosing based on safety parameters and response to medication. Participants randomized to bup/nal followed a dosing schedule that involved a 1–2 week induction phase followed by a stable dosing phase from weeks 3 to 8, and ending with a slow dose taper beginning in week 9 and ending by week 12. Target dose of bup/nal during the stable dosing phase was 12–18 mg/day up to a maximum dose of 24 mg/day. The study asked all participants to participate in manual-guided psychosocial treatment in the form of individual and group drug counseling sessions based on cognitive behavioral, relapse prevention, and twelve-step facilitation approaches, offered on a weekly basis throughout the 12-week study. In the event that participants discontinued study medication during the trial, the study staff encouraged them to continue with the weekly psychosocial treatment.

2.3. Assessments

2.3.1. Demographics, and baseline and during treatment clinical characteristics

At screening and/or BSL visits, the study used the NIDA-CTN-0010 baseline demographics form to collect information on age, sex, race/ethnicity, years of education, employment, and use of various drug types (alcohol, cannabis, cocaine, etc.) in the past 30 days and lifetime (years). All participants also received a medical examination during which the study obtained medical and psychiatric history and participants completed a physical examination and urine drug testing. The study assessed receipt of ancillary treatments at BSL and during active study treatment. We also collected information on prescribed and over the counter medications at BSL and on a weekly basis, and assessed non-study medical and psychiatric services monthly. The study recorded in weekly logs attendance at individual, group, family, and ancillary other drug counseling sessions during weeks 1 through 12.

2.3.2. Psychiatric symptom scales

The Youth Self Report (YSR) and Young Adult Self-report (YASR) are self-report questionnaires developed to assess psychiatric symptoms and behavioral problems in adolescents ages 11–18 years (YSR) and young adults 18–30 years (YASR), respectively (Achenbach, 1997; Achenbach & Rescorla, 2001). Each YSR and YASR item is rated on a 3-point scale, including 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). Both checklists include validated broad-band scales assessing symptoms of internalizing problems, externalizing problems, and total problem scores, as well as narrow-band syndrome scales assessing specific psychiatric syndromes of anxious depression, withdrawn depression, somatic complaints, thought problems, attentional problems, aggressive behaviors, and delinquent behaviors. Most YSR and YASR items overlap; some variation exists in item content on some of the subscales. The YSR also includes a social problem subscale not included in the YASR, and the YASR includes an intrusive problem subscale not included in the YSR. Studies on the validity and reliability of the YSR and YASR broad-band scales and narrow-band syndrome scales have been extensively documented (Ferdinand & Verhulst, 1994; Liu et al., 1997).

The NIDA-CTN-0010 study administered the YSR and YASR at BSL and week 12 to participants ages 15–17 years and 18–21 years, respectively. This study used raw scores in all analyses, consistent with prior studies using the YSR and YASR to predict health outcomes (Achenbach & Rescorla, 2001). We calculated a change score for each participant on each YSR/YASR scale by subtracting the week-12 raw score from the BSL.

2.3.3. Primary opioid use outcome

Opioid positive urine tests (OPU) assessed at week 12 was the primary outcome that the NIDA-CTN-0010 study used and the main outcome of interest in our analyses.

2.4. Statistical analysis

Research staff conducted analyses using IBM SPSS Statistics Analytic software V25.0 (IBM, Armonk, NY). The study used self-reported sex based upon a dichotomous question from the demographics form to categorize participants into male vs. female for the current analyses. The main analytic sample included 141 participants (93% of the randomized sample) who had available YSR/YASR data collected at BSL. From that group, week-12 YSR/YASR data was available on 85 participants. Participants without available week-12 YSR/YASR data did not differ from those with available week-12 YSR/YASR data on age, sex, race/ethnicity, education, or on any YSR/YASR psychiatric symptom scores at BSL (all p's > 0.05) but were significantly more likely to be in the detox group ($t_{(85)} = 2.23$, $p = 0.03$). Missing item data from participants who completed the YSR/YASR was minimal (1–3%) and were multiply imputed. The study imputed missing urine drug testing data from the week-12 visit (40%) as a positive, a method that does not make the missing-at-random assumption and has been employed in other substance use treatment studies, consistent with an intent-to-treat approach (Avants et al., 2000; Bickel et al., 1988; Budney et al., 2006; Schmidt et al., 2007; Trivedi et al., 2017; Winhusen et al., 2013). The study examined descriptive statistics on demographics and BSL and during treatment clinical characteristics in the total sample and compared across sexes. Our primary analyses focused on group differences in YSR/YASR broad and narrow band scores at BSL and week 12 between male and female OUD participants, with exploratory analyses examining changes in YSR/YASR scores from BSL to week 12. The study team calculated these comparisons using independent sample t-tests. No correction for multiple comparisons occurred due to the hypothesis generating nature of the study. For prediction analyses, we conducted preliminary bivariate analyses on variables of interest (sex and psychiatric symptoms), comparing youth stratified by week 12 OPU status in the ITT sample. Study staff then entered variables identified as significant predictors of week 12 OPU in these analyses into binary logistic and multivariate regression models to determine whether those factors were associated with week-12 OPU while controlling for other significant factors. In all models, the study entered YSR/YASR scores as predictors with week-12 OPU ("1" = positive, "0" = negative) serving as the dependent variable, and age, race/ethnicity, and education included as covariates. Given the focus on sex-based differences, the stud also conducted exploratory analyses, stratifying the sample by sex. The study team performed four sensitivity analyses: First, we reran variables identified as significant predictors of week 12 OPU, including treatment

covariates. The study team conducted supplemental analyses paralleling the primary ITT sample analyses in the completer sample. In the third sensitivity analysis, the study conducted parallel prediction models using sex and psychiatric symptoms as IVs and treatment completion status ("1" = treatment completer, "0" = non-completer) as the DV to determine if significant predictors identified in the primary analyses were specific to week 12 OPU or alternatively were predictive of both treatment completion status and week 12 OPU in the sample. Last, we performed a fourth sensitivity analysis rerunning our primary analyses but excluding participants who received ancillary psychotropic medication treatment during the study.

3. Results

3.1. Study sample characteristics

Table 1 presents demographic and clinical information from the analytic sample stratified by sex. The study randomly assigned one hundred and forty-one participants, including 84 adolescent males and 57 adolescent females, to 12 weeks of bup/nal ($n = 74$, 57% male) or up to 2 weeks of bup/nal as part of a detoxification protocol ($n = 78$, 63% male). The mean age for the male sample was 19.7 (SD = 1.5) and 19.6 (SD = 1.5) for the female sample. Male and female OUD participants did not differ on age, race/ethnicity, years of education, employment status, marital status, or treatment arm assignment. The study did not observe any significant differences between male and female participants in pretreatment substance use behaviors, including the type of opioid used (heroin vs. non–medical prescription opioid use); and past 30-day opioid, alcohol, cannabis, tobacco, and other drug use at BSL.

Table 1
Demographics and baseline clinical characteristics of study sample, by sex.

Variable	Male OUD participants ($N = 84$)	Female OUD participants ($N = 57$)	Test statistic	*P*
Treatment assignment, n (%)			−0.72	0.47
Bup-Nal	45 (54%)	27 (47%)		
Detox	39 (46%)	30 (53%)		
Age (years)	19.8 (1.5)	19.6 (1.5)	0.48	0.63
Race/ethnicity, n (%)			−1.30	0.20
Caucasian	58 (69%)	45 (79%)		
Non-Caucasian	27 (31%)	16 (28%)		
Employment in past 30 days	45 (53%)	32 (56%)	0.43	0.51
Years of education	11.1 (1.5)	11.2 (1.5)	−0.44	0.66
Married, n (%)	5 (6%)	3 (5%)	0.15	0.70
Heroin use in past 30 days	19.4 (13.1)	19.7 (13.0)	−0.15	0.88
Non-medical prescription opioid use in past 30 days	1.1 (3.8)	1.3 (3.5)	−0.26	0.80
Alcohol use in past 30 days	1.7 (3.9)	1.9 (3.9)	−0.36	0.71
Alcohol intoxication in past 30 days	0.5 (1.4)	0.9 (2.5)	−1.13	0.26
Cannabis use in past 30 days	9.4 (11.4)	7.6 (11.2)	0.94	0.35
Tobacco product use in past 30 days	26.0 (8.9)	27.1 (8.4)	−0.74	0.46
Other drugs use in 30 days	12.1 (11.0)	12.1 (11.5)	0.02	0.98

Note: Test statistic was Chi squared test for categorical variables and independent *t*-tests for continuous variables. Variables: Substance use characteristics for opioid and other drug use were from the baseline assessment and represent the mean days of use in the past 30 days for each respective drug. Abbreviations: OUD = opioid use disorder.

3.2. Sex-based differences in baseline and week-12 psychiatric symptoms

In the total ITT sample across treatment arms, female OUD participants had increased mean YSR/YASR psychiatric symptom scores at BSL on *broad-band* total problems, externalizing problems, and internalizing problems scales and on *narrow-band* anxious depression, withdrawn depression, somatic complaints, thought problems, attention problems, aggressive behavior, and delinquent behavior scales compared to males (see Table 2 and Fig. 1). Male and female OUD participants both showed significant BSL to week-12 reductions in YSR/YASR psychiatric symptom scores across all broad-band and narrow-band scales. Compared to males, female OUD participants had greater BSL to week-12 reductions in internalizing problems (−8.6 vs. −3.5, $t_{(84)} = 2.74$, $p = 0.007$) and anxious depression (−5.8 vs. −2.6, $t_{(85)} = 2.43$, $p = 0.02$) scores. At week 12, female OUD participants (compared to male) had higher anxious depression scores (10.6 vs. 7.5, $t_{(85)} = -2.20$, $p = 0.03$).

3.3. Sex and psychiatric symptoms as predictors of opioid use following treatment

In both preliminary bivariate analyses (Table 3) and confirmatory logistic regression models using the ITT sample (supplemental data Tables S1 and S2), female sex (adj. odds ratio [*aOR*] = 0.43, 95% CI: 0.02–0.90, $p = 0.025$) and increased anxious depression scores at BSL (*aOR* = 0.94, 95% CI: 0.89–0.98, $p = 0.010$) were associated with lower rates of OPU at week 12. Given these results, we conducted exploratory post-hoc analyses to test for treatment-level and individual-level factors that might explain variance in the identified relationships between sex, anxious depression scores, and OPU at week 12. In these analyses, female sex and anxious depression scores at BSL remained significant predictors of week-12 OPU after individually and collectively controlling for treatment assignment (Bup-Nal vs. Detox), number of therapy sessions, and total psychiatric problem scores at BSL. The final multivariate regression model was significant and found that combining sex and anxious depression scores increased the overall predictive value (suppl. data Table S3) but resulted in sex and anxious depression scores at BSL no longer being independently associated with week-12 OPU. A subsequent model testing for interactive effects found that a sex-by-anxious depression interaction was associated with week-12 OPU (suppl. data Table S4). Exploratory regression analyses stratified by sex identified one predictor unique to male OUD participants and no predictors unique to female OUD participants. In male OUD participants, greater BSL to week-12 reductions in somatic complaint scores ($t_{(83)} = 3.85$, $p = 0.05$) was predictive of negative week-12 OPU.

3.4. Sensitivity analyses

Results from the four sensitivity analyses were not substantively different from the primary analyses we just described. For analyses using the completer sample, group differences between male and female OUD participants in psychiatric symptoms at BSL and week 12 largely paralleled the outcomes observed in the ITT analyses with a few exceptions. For example, in contrast to the ITT sample, female and male OUD participants in the completer sample did not differ on mean withdrawn depression (4.6 vs. 3.7, $t_{(81)} = -1.56$, $p = 0.12$), somatic complaints (8.3 vs. 7.3, $t_{(81)} = -1.01$, $p = 0.31$), and thought problem (4.6 vs. 3.5, $t_{(81)} = -1.66$, $p = 0.10$) *narrow-band* subscale scores at BSL. In prediction analyses using the completer sample, results paralleled the ITT findings but were less robust, with female sex (*aOR* = 0.45, 95% CI: 0.18–1.09, $p = 0.077$) and anxious depression scores at BSL (*aOR* = 0.95, 95% CI: 0.89–1.01, $p = 0.094$) being predictive of a lower likelihood of week-12 OPU at the trend level of significance. In exploratory analyses examining sex and psychiatric symptoms as predictors of treatment completion, increased anxious depression scores at BSL (*aOR* = 1.06, 95% CI: 1.01–1.11, $p = 0.028$) but not female sex (*aOR* = 1.63, 95% CI: 0.83–3.29, $p = 0.178$) was predictive of a higher likelihood of treatment

Table 2
Changes in psychiatric symptom scores from baseline to week-12 in male and female OUD participants.

Psychiatric symptom scores, by domain	Female OUD participants				Male OUD participants				Females vs. males			
	Baseline ($n = 56$)	Week 12 ($n = 37$)	Test statistics	*P*	Baseline ($n = 83$)	Week 12 ($n = 48$)	Test statistics	*P*	Baseline Test statistics	*P*	Week 12 Test statistics	*P*
Broad-band scales												
Total problem score	66.5 (25.8)	42.9 (23.8)	**5.19**	**<0.001**	45.4 (26.4)	34.7 (23.3)	**4.75**	**<0.001**	**−4.65**	**<0.001**	−1.58	0.12
Externalizing problem score	21.3 (9.7)	14.5 (8.9)	**5.42**	**0.001**	15.5 (10.0)	11.7 (8.4)	**3.82**	**<0.001**	**−3.42**	**0.001**	−1.48	0.14
Internalizing problem score	22.3 (9.8)	14.0 (8.6)	**3.53**	**<0.001**	13.6 (9.9)	10.4 (8.1)	**3.56**	**0.001**	**−5.1**	**<0.001**	−1.94	0.06
Narrow-band scales												
Anxious/depressed prob	15.7 (6.5)	10.6 (7.0)	**5.04**	**0.001**	9.5 (7.3)	7.5 (6.3)	**3.41**	**0.001**	**−5.14**	**<0.001**	**−2.20**	**0.03**
Withdrawn/depressed prob	4.8 (3.3)	2.6 (2.5)	**3.67**	**0.001**	3.3 (2.8)	2.7 (2.4)	**2.41**	**0.02**	**−2.92**	**0.004**	0.12	0.90
Somatic complaints	8.5 (4.4)	5.0 (4.4)	**4.17**	**<0.001**	6.5 (5.0)	4.5 (4.5)	**3.92**	**<0.001**	**−2.49**	**0.014**	−0.57	0.57
Thought problems	5.0 (4.2)	3.0 (2.5)	**2.91**	**0.006**	3.3 (3.1)	3.1 (2.6)	**2.15**	**0.04**	**−2.64**	**0.009**	0.16	0.87
Attention problems	9.8 (3.9)	6.6 (3.9)	**4.83**	**<0.001**	6.8 (3.8)	5.2 (4.0)	**4.09**	**<0.001**	**−4.48**	**<0.001**	−1.60	0.11
Aggressive behavior	10.6 (5.5)	7.2 (5.1)	**3.46**	**0.001**	7.2 (5.4)	5.5 (4.6)	**3.00**	**0.004**	**−3.72**	**<0.001**	−1.60	0.11
Delinquent behavior	7.5 (5.1)	4.4 (3.3)	**4.09**	**<0.001**	5.5 (4.7)	4.1 (4.2)	**2.86**	**0.006**	**−2.45**	**0.015**	−0.31	0.76

Note: Test statistic was paired *t*-tests for within group comparison of baseline to week 12 psychiatric symptom scores in OUD male and female participant groups. Test statistic was independent *t*-test for comparison of female versus male OUD participants on psychiatric symptom scores at baseline and week 12. *P* values in bold indicate statistical significance. Variables: Psychiatric symptom scores were from YSR and YASR self-report questionnaires administered at baseline and week 12. Abbreviations: OUD = opioid use disorder.

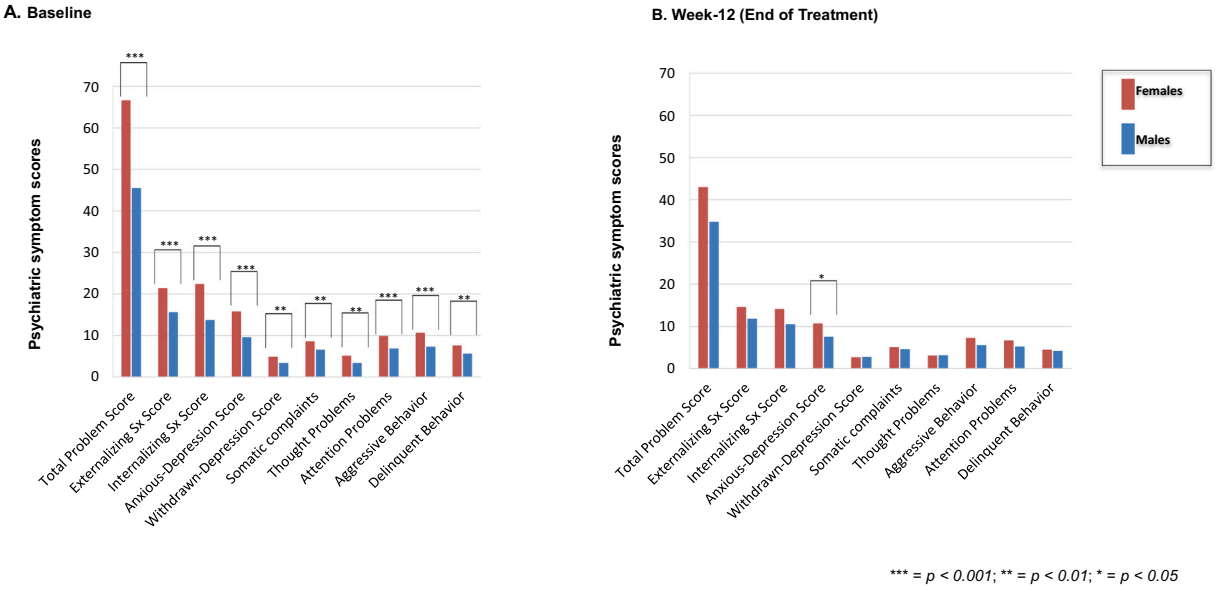

Fig. 1. Psychiatric symptom scores at baseline and week-12 in male and female OUD participants.

completion. Last, two participants reported taking neuroleptic medications, and six participants reported taking other psychiatric medications throughout the active treatment period. Rerunning the main analyses excluding these participants did not impact the study's findings.

4. Discussion

This secondary analysis of data from the NIDA-CTN-0010 study examined sex-based differences in psychiatric symptoms among adolescents receiving bup-nal treatment for OUD and their associations with opioid use following treatment. To our knowledge, this study is the first to examine sex-based differences in psychiatric symptoms and their relationship with treatment outcomes in an adolescent sample. We found that female OUD participants had increased psychiatric symptom scores at BSL across broad-band and narrow-band syndrome domains. Both male and female OUD participants showed significant during-treatment reductions in psychiatric symptoms from BSL to week 12, and by week 12, only anxious depression scores remained increased in female compared to male OUD participants. Female sex and increased anxious depression scores at BSL were associated with a lower likelihood of opioid use at the end of active treatment. These results suggest that sex-based differences in psychiatric symptoms are present in adolescents

Table 3
Relationship of sex and baseline and week-12 psychiatric symptom scores with week-12 opioid positive urine tests.

Variable	Intent-to-treat sample		Test statistic	*P*
	Urine negative at 12 wk (*N* = 43)	Urine positive at 12 wk (*N* = 98)		
Age	19.6 (1.4)	19.7 (1.5)	0.42	0.73
Male sex, n (%)	19 (44%)	65 (66%)	**−2.50**	**0.01**
Education, years	11.2 (1.5)	11.1 (1.5)	−0.35	0.67
12-wk Bup-Nal treatment arm, n (%)	28 (65%)	41 (42%)	**−2.59**	**0.01**
Baseline psychiatric symptoms				
Total problem score	58.3 (22.1)	51.9 (30.2)	−1.25	0.22
Externalizing problem score	18.1 (8.5)	17.7 (11.0)	−0.20	0.84
Internalizing problem score	16.0 (11.0)	19.6 (9.7)	−1.84	0.07
Anxious/depressed problem score	14.5 (6.8)	10.9 (7.7)	**−2.67**	**0.008**
Withdrawn/ depressed problem score	4.2 (3.4)	3.8 (3.0)	−0.75	0.45
Somatic complaints	8.1 (4.4)	6.9 (5.1)	−1.34	0.18
Thought problems	4.0 (2.8)	4.0 (4.0)	−0.08	0.94
Attention problems	8.6 (3.8)	7.8 (4.3)	−1.13	0.26
Aggressive behavior	8.5 (5.0)	8.6 (5.9)	0.12	0.90
Delinquent behavior	6.2 (5.3)	6.5 (4.0)	0.13	0.68
Week-12 psychiatric symptoms				
Total problem score	40.2 (23.5)	36.4 (24.3)	−0.74	0.64
Externalizing problem score	13.6 (8.8)	12.3 (8.6)	−0.66	0.51
Internalizing problem score	12.8 (8.7)	11.2 (8.2)	−0.86	0.39
Anxious/depressed problem score	9.6 (7.0)	8.1 (6.5)	−1.03	0.31
Withdrawn/ depressed problem score	2.7 (2.7)	2.6 (2.2)	−0.30	0.77
Somatic complaints	4.7 (4.4)	4.7 (4.5)	0.01	0.99
Thought problems	2.8 (2.3)	3.3 (2.8)	0.86	0.39
Attention problems	6.4 (4.2)	5.2 (3.8)	−1.42	0.16
Aggressive behavior	6.8 (5.1)	5.6 (4.6)	−1.17	0.25
Delinquent behavior	3.9 (3.0)	4.6 (4.5)	0.03	0.91

Note: Test statistic was Chi squared test for categorical variables and independent *t*-tests for continuous variables. P values in bold indicate statistical significance. Variables: Psychiatric symptom scores were from YSR and YASR self-report questionnaires administered at baseline and week 12. Abbreviations: 12-wk Bup-Nal treatment arm = 12-week extended buprenorphine/naloxone therapy assisted treatment assignment with this variable indexing the number and percentage of participants who had a negative urine for opioids at week 12 and a positive urine for opioids at week 12.

with OUD and may be relevant to OUD treatment response in youth. We discuss the implications of these findings here.

We found that female OUD participants (compared to males) had increased psychiatric symptoms across all domains at BSL, with symptoms in one domain (anxious-depression) persisting into week 12. Female and male OUD participants also differed in the magnitude of decrease of their internalizing and anxious depression symptoms following study treatment, with females, compared to males, showing a greater reduction in the severity of their psychiatric symptoms. These findings indicate that sex-based differences in psychiatric symptoms exist in adolescents receiving OUD treatment. Further, they suggest that sex-based differences in general psychopathology and affective symptom domains exhibit differential patterns of persistence following bup-nal treatment. Our results are consistent with prior studies in adults with OUD that have shown that women have higher rates of comorbid/co-occurring psychiatric disorders and distress than men and may be more motivated to initiate opioid treatment because of these psychiatric problems (Chatham et al., 1999; Huhn et al., 2018). They also align with studies showing sex-based differences in internalizing disorders in the general population of adolescents (Eaton et al., 2012; Hankin et al., 1998). In conjunction with the adult literature, our findings suggest that sex-based differences in psychiatric symptoms among individuals with OUD show a similar pattern of expression across developmental stages (e.g., adolescence vs. adulthood). Despite potential prognostic implications, few longitudinal studies have examined how psychiatric symptoms change during OUD treatment. Our findings largely parallel the results of prior studies (Brooner et al., 2013; Kidorf et al., 2015; King et al., 2014). For example, King and colleagues found that adults with OUD and comorbid psychiatric disorders exhibited sex-based differences in global distress at treatment initiation that resolved following methadone maintenance treatment (King et al., 2014). Our findings are also consistent with the only study published to date that investigates changes in psychiatric symptoms during youth OUD treatment. Moore and colleagues conducted secondary analyses on data from 36 adolescents enrolled in a 28-day medication for addiction treatment withdrawal intervention trial (Marsch et al., 2005) and found that youth who remained in OUD treatment, regardless of assigned withdrawal medication (buprenorphine or clonidine), showed a significant reduction in psychiatric symptom severity across domains (Moore et al., 2011). Our findings suggest that female youth present for OUD treatment with higher severity of psychiatric symptoms across all symptom domains, and that sex-based differences in the severity of these symptoms, with the exception of anxiety and depression symptoms, resolve following bup-nal treatment. The “transient” nature of these sex differences in general psychopathology and most domain categories and their resolution following a treatment with bup-nal medication and psychotherapy that did not specifically target co-occurring psychiatric conditions, suggests that many of these symptoms may emerge as a consequence of opioid use. In contrast, the persistence of sex-based differences in anxious-depression symptomatology suggests possible independent syndromic psychiatric disorder diagnoses or interdependent symptoms that recover along a protracted time scale. The current data cannot determine these explanations. Regardless of their origin, the lack of resolution of anxious-depression symptomatology in female youth receiving OUD treatment suggests that they may require separate targeted treatment. The timing of onset, temporal dynamics, independence versus interdependence, and generality versus specificity of these associations warrant further investigation. The etiology of these psychiatric symptoms and whether they represent substance-induced versus independent conditions may carry implications for treatment sequencing and intervention selection.

A main objective of the study was to investigate the effects of sex and psychiatric symptoms on opioid abstinence following bup-nal treatment in youth. Our results identified three patient-level characteristics that were associated with a lower likelihood of OPU at week 12: female sex, increased anxious depression scores at BSL; and in men, greater BSL to week-12 reduction in somatic complaint scores. Our results regarding sex-based differences in treatment outcomes are consistent with prior studies in adult OUD samples that have shown that women receiving bup-nal-based medication treatment for OUD have lower relapse rates than men (Huhn et al., 2018). Furthermore, our sex-based findings were robust to sensitivity testing, remaining significant even after controlling for total psychiatric symptoms, treatment assignment, and therapy dose. A number of possible factors could explain the presence of sex-based differences in treatment outcomes in the sample. One explanation may be that women have different motives for using opioids (e.g., opioid use to cope with negative affect) (McHugh et al., 2013) and different motives for entering into opioid treatment than men (e.g., pain or psychiatric distress) (Chatham et al., 1999). In addition, women may respond differently from a physiological standpoint than men to medications for OUD (Huhn et al., 2018; Lynch et al., 2002; Niesters et al., 2010). This sex-specific sensitivity to medications may be more pronounced in individuals with co-occurring affective disorders and may be particularly

relevant for agonist-based treatment of OUD in women (Huhn et al., 2019; Levine et al., 2015). Emerging literature on buprenorphine's antidepressant properties (Falcon et al., 2016; Serafini et al., 2018) may have implications for treatment matching strategies in young females. Our results also indicated that increased anxious-depression scores at BSL in all participants and during treatment reductions in somatic complaints in men were predictive of opioid abstinence at week 12. Prior studies suggest that comorbidity and severity of mood and anxiety disorders and symptoms may portend poorer substance use and health outcomes across drug classes (Baker et al., 2007; Lubman et al., 2007). Specific to OUD, studies have observed complex relationships between affective and somatic symptoms and opioid use during and following treatment (Rounsaville et al., 1986). For example, co-occurring depression has been associated with both worse (Rounsaville et al., 1986) and better (Peckham et al., 2020) opioid treatment outcomes in previous OUD clinical trials. Some of the variance across studies in this association may be due to individual differences in response to medications for OUD treatment. Alternatively, our affect-treatment outcome findings could be the result of different adherence rates, treatment motives, or utilization of ancillary services in youth who self-report higher anxious-depressive symptoms. Utilization of ancillary services has been associated with better retention and outcomes in prior studies, including in a previously published secondary analysis of the NIDA-CTN-0010 study (Subramaniam et al., 2011). That higher anxious depressive symptoms at BSL were also associated with a greater likelihood of treatment completion in our sample are consistent with this explanation. Last, it is important to note that in our final multivariate analysis, combining sex and anxious depression scores improved the predictive value of the model, but, interestingly, also led to sex and anxious depression scores no longer being significant independent predictors of week 12 OPU. Thus, some of the variance in the relationship between sex and week-12 OPU can be explained by anxious depressive symptoms at BSL and vice-versa. This finding suggests that sex and anxious depressive symptoms interact to influence the likelihood of opioid use following bup-nal treatment (as opposed to independently influencing opioid outcomes). Future work building on these findings should seek to clarify how psychiatric symptoms and general and specific treatment factors independently and interactively contribute to positive treatment outcomes through sex-specific and shared pathways.

Collectively, the findings presented here lend further support to a growing literature suggesting additional burden of disease and unmet clinical needs in women with substance use disorders, including OUDs (Greenfield et al., 2010). Women are quicker to escalate from first use to disordered use of drugs ("telescoping phenomena") (Greenfield et al., 2007). They enter into treatment earlier than men, but despite this positive prognostic factor, are underrepresented in substance use treatment (Campbell et al., 2018; Hernandez-Avila et al., 2004). Men and women have different drug treatment needs and carry risk for different opioid and psychiatric outcomes (Greenfield et al., 2007). For example, adolescent females with OUD are at greater risk for having nonfatal opioid overdoses than adolescent males with OUD (Chatterjee et al., 2019), and higher rates of mood/anxiety and stress-related disorders in females appears to contribute to this sex-based difference on NFOD risk (Bagley et al., 2020). Given the higher rates of co-occurring psychiatric and medical problems in women with OUD, concurrent treatment for those problems during OUD treatment may help to increase overall treatment success. Further, compared to men, women with OUD are more likely to be victims of physical and sexual violence (Vigna-Taglianti et al., 2016), which research has also shown plays a role in substance use treatment response (Leone et al., 2017). Deficient sex-specific services in drug treatment programs may lead to barriers to care that impact treatment participation and retention (McCaul et al., 2001). Furthermore, preliminary studies suggest that sex-specific substance use interventions that focus on the presenting problems common to substance-using women are effective (Greaves & Poole, 2008; Greenfield et al., 2007). These sex-specific interventions have yet to be adapted to or tested in substance-using youth. Additional should help to clarify which psychiatric symptoms, environmental factors, and treatment components (e.g., medications, psychosocial interventions, ancillary services, etc.) and contexts (mixed vs. sex-specific group settings) are most relevant to treatment outcomes in male and female youth receiving OUD treatment; and apply these findings to inform the development of age-appropriate sex-specific therapies.

This study has several relevant limitations and some notable strengths. As the study was a secondary analysis, the clinical trial was not designed or powered to answer specific research questions about sex-based differences and psychiatric symptoms, and we were reliant on the assessments that the primary study team chose. The restriction of eligibility to subjects without serious psychiatric disorders and symptoms (e.g., suicidality, homicidality, and psychosis) may have limited the range of psychopathology in the sample, making it less generalizable to youth seeking OUD treatment, which could have affected the prognostic findings. The use of self-report as opposed to multi-informant assessments of psychiatric symptoms could have led to inflation or underreporting of certain psychiatric symptoms, especially in externalizing domains. Additionally, we define our primary variable of interest, *sex*, by self-report and was not confirmed via genetic karyotyping, and the study did not query gender identity and other sex and gender-related variables. This is problematic as a growing literature suggests that sociological gender and biological sex may independently and interactively contribute to substance use risk (Becker et al., 2016). Furthermore, without a true nonintervention control condition, we cannot directly attribute the reduction in psychiatric symptoms during treatment to the common psychosocial interventions received since this could be due to a regression to the mean. Another major limitation is participant attrition, and the effect of attrition on the availability of psychiatric assessments at week 12. While attrition rates for the current study parallel those seen in other buprenorphine studies (Borodovsky et al., 2018; Marsch et al., 2005), they led to follow-up YSR/YASR data only being available in 61% of participants in the analytic sample. To address concerns about dropout effects, we tested for differences between completers and noncompleters on baseline characteristics and ran our primary analyses using both ITT and completer samples, finding no completer vs. noncompleter group differences and negligible effect on the results. Still, given the limited sample with follow-up data, our findings on changes in psychiatric symptoms are likely underpowered and should be interpreted cautiously. Additionally, a small number of participants (~5%) were receiving ancillary psychotropic medication treatment during the study, but excluding these participants did not alter our findings. Last, data collection for the NIDA-CTN-0010 study occurred from 2003 to 2006, and thus, may not reflect more recent trends in sex or comorbidity relationships in youth receiving OUD treatment. Despite these limitations, the study also has many strengths. The analysis presented here relies on data from the largest clinical trial conducted in youth diagnosed with OUDs to date. Our study's use of well-established empirically validated psychiatric rating scales and its fine-grained analytic approach allowing for a comparative analysis of general and domain-specific psychiatric symptoms and exploratory characterization of treatment-level factors that influence the expression of these symptoms is a major strength. Applying these approaches, this study has identified key treatment targets for male and female youth with OUD. Further, it has preliminarily characterized how different psychiatric symptoms change in sex-specific and shared ways during treatment, offering insight into the treatment efficacy of buprenorphine medication in combination with psychosocial treatment.

4.1. Conclusion

In conclusion, in this secondary analysis of the NIDA-CTN-0010 study, we identified clinically meaningful sex-based differences in psychiatric symptoms among youth with OUD presenting for bup-nal assisted treatment. Sex-specific and shared psychiatric-symptom

correlates with opioid use during treatment may reflect distinct prognostic subgroups. Associations among opioid abstinence, sex, and affective and somatic symptoms suggest that sex-specific interventions and interventions tailored to youth with OUD with and without co-occurring affective disorders may improve outcomes.

CRediT authorship contribution statement

Christopher Hammond: Conceptualization, Data curation, Methodology, Investigation, Formal Analysis, Validation, Visualization, Writing – Original Draft, Writing-Review & Editing, Supervision; **Grace Park**: Formal Analysis, Data Curation, Visualization, Writing-Review & Editing; **Annabel Kady**: Conceptualization, Data curation, Formal Analysis, Visualization, Writing – Original Draft, Writing-Review & Editing; **Krutika Rathod**: Conceptualization, Data curation, Methodology, Writing-Review & Editing; **Naisa Rahman**: Conceptualization, Data curation, Methodology, Writing-Review & Editing; **Carol Vidal**: Formal Analysis, Writing-Review & Editing; **Kevin Wenzel**: Conceptualization, Formal Analysis, Writing-Review & Editing; **Marc Fishman**: Conceptualization, Investigation, Formal Analysis, Writing-Review & Editing, Supervision.

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Declaration of competing interest

Dr. Hammond serves as a scientific advisor for the National Courts and Science Institute and as a subject matter expert for the Substance Abuse Mental Health Services Administration (SAMHSA) related to co-occurring substance use disorders and severe emotional disturbance in youth. Dr. Fishman serves as a consultant/advisory board member for Alkermes, Mid Atlantic ATTC, and US World Meds and receives research grant funding from Alkermes. The other authors report no disclosures or conflicts of interest related to the information presented in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsat.2021.108495.

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