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Original article

Young Adults Have Worse Outcomes Than Older Adults: Secondary Analysis of a Medication Trial for Opioid Use Disorder

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A B S T R A C T

Purpose: Young adults are disproportionately affected by the current opioid crisis. Although medications for opioid use disorder are broadly effective, with reductions in morbidity and mortality, the particular effectiveness of medications for opioid use disorder among young adults is less well understood.

Methods: This secondary analysis compared young adults (aged 18–25 years) with older adults (aged ≥26 years) in a large comparative effectiveness trial ("XBOT") that randomized subjects to extended-release naltrexone or sublingual buprenorphine–naloxone for 6 months. Opioid relapse was defined by opioid use over four consecutive weeks or seven consecutive days, using urine testing and self-report.

Results: Among subjects in the intention-to-treat sample (n = 570, all randomized participants), a main effect of age group was found, with higher relapse rates among young adults (70.3%) compared with older adults (58.2%), with an odds ratio of 1.72 (95% confidence interval = 1.08–2.70), $p = .02$. In the per-protocol sample (n = 474, only participants who started medication), relapse rates were higher among young adults (66.3%) compared with older adults (50.8%), with an odds ratio of 1.91 (95% confidence interval = 1.19–3.06). Among the intention-to-treat sample, survival analysis revealed a significant time-by-age group interaction ($p = .01$) with more relapse over time in young adults. No significant interactions between age and medication group were detected.

Conclusions: Young adults have increased rates of relapse compared with older adults, perhaps because of vulnerabilities that increase their risk for treatment dropout and medication nonadherence, regardless of medication assignment. These results suggest that specialized, developmentally informed interventions may be needed to improve retention and successful treatment of opioid use disorder among young adults.

IMPLICATIONS AND CONTRIBUTION

This study examined the effectiveness of medications for opioid use disorder (extended-release naltrexone and buprenorphine–naloxone) in young adults (aged 18–25 years) compared with older adults. Young adults had significantly higher rates of relapse at 6 months, regardless of medication. Although medications for opioid use disorder are effective for youth, improvement is needed for this developmentally vulnerable population that is disproportionately affected by the current opioid crisis.

Young adults in the U.S. are disproportionately affected by the current opioid crisis, with 1.1% (392,000) diagnosed with opioid use disorder (OUD) in 2016 and the highest per capita rates of misuse of both prescription opioids and heroin [1]. Furthermore, approximately two thirds of all overdose deaths among young

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adults in recent years involved opioids. With the recent availability of high purity heroin and especially of very high potency, illicitly manufactured fentanyl analogs, the rates of increases in overdose deaths have outstripped the rates of increase in use and OUD [2]. Assessment of effective treatments for OUD in this vulnerable population is a top public health priority.

Medications for opioid use disorder (MOUD) include an opioid agonist (methadone), partial agonist (buprenorphine), and antagonist (naltrexone). These pharmacologically distinct approaches have demonstrated effectiveness and are the standard of care for adults with OUD. Although these treatments are well established in older adults, there is less available data on MOUD in youth [3]. The existing small body of research on MOUD in young adults provides evidence of efficacy, and MOUD is endorsed by the American Academy of Pediatrics as the recommended standard for adolescents and young adults [4–7].

A recent review of buprenorphine treatment in adolescents and young adults concluded that buprenorphine should be considered a first-line treatment in youth as it is for older adults [8], as it consistently produces improved outcomes compared with treatment without MOUD. Data on extended-release naltrexone (XR-NTX) in young adults is even sparser than for buprenorphine; although, observational studies provide support [9] and suggest treatment effects comparable to buprenorphine [10].

Despite the growing body of evidence that MOUD is effective for youth, including a large-scale study of claims data demonstrating that it considerably improves treatment retention for youth [11], youth tend to have poorer engagement in and response to MOUD. For example, in a naturalistic study of adolescents in buprenorphine treatment, retention rates were approximately 25% at 6 months and 10% at 1 year [6]. Another study found that emerging adults (aged 18–25 years) in buprenorphine treatment were retained in treatment at a lower rate and were more likely to use opioids and drop out during treatment, compared with the older adults in the clinic [12]. Reasons for overall poorer outcomes in youth may include features of their substantial and special developmental vulnerability, including lack of economic and social independence from their families, early onset of SUD, limited engagement in clinical care or low motivation to change [13–15], subjective sense of invincibility, immature executive function, high rates of psychiatric comorbidity [16], OUD and MOUD-related stigma, misinformation about OUD risk and the potential benefits of MOUD, biases against medication, difficulties with enduring medication adherence, and insurance and regulatory restrictions [17–23].

Despite calls for more use of and research on MOUD in the vulnerable youth population, scientists and practitioners have been slow to respond. In addition, access to and engagement of adolescents and young adults in MOUD treatment has been alarmingly low [11,24,25]. For example, a recent retrospective cohort study of 2.4 million youth determined that only 23.5% of youth with identified OUD received medication within 3 months of diagnosis [11], and XR-NTX is especially underutilized in youth [5]. There is a dearth of research examining how age and developmental vulnerability comparatively impact treatment matching and outcome. No study with an experimental design has compared the effectiveness of different MOUDs in youth.

The XBOT study is, to date, the largest comparative effectiveness trial of daily sublingual buprenorphine (BUP-NX) versus monthly extended-release injection naltrexone (XR-NTX) [26–28]. Its main findings were more patients had success initiating buprenorphine than XR-NTX (induction failure); among the intention-to-treat (ITT) sample (all randomized participants), relapse rates were modestly lower among the buprenorphine patients because of early relapse in those who did not successfully initiate XR-NTX; and among the per-protocol sample (only those who successfully initiated either medication), there was no difference in relapse rates.

The XBOT study offers the opportunity to examine outcomes of MOUD in the young adult subgroup. We, therefore, conducted a secondary analysis of the XBOT trial to compare the effectiveness of MOUD treatment in the young adult subgroup versus the older adult participants and to examine whether the two medication treatments differ in their outcomes in the younger subgroup. We hypothesized that prior findings of poorer treatment response would be confirmed and that XR-NTX would confer an advantage because of its potential benefit for adherence.

Methods

Brief characteristics of parent study

The methods and design [26–28] of the parent multisite trial are presented elsewhere. For the parent study, participants (aged ≥18 years) seeking acute care for OUD were recruited during an index residential treatment episode from the routine patient flow at eight different specialty SUD treatment sites. Subjects were randomized in a 1:1 allocation ratio to either daily sublingual BUP-NX or monthly injectable XR-NTX, having agreed that they would accept either as a randomized assignment. Patients were inducted onto the assigned medication through the study and then continued through the study in outpatient medication treatment for 24 weeks. During the study intervention, assigned medications were provided for up to 24 weeks. For the purposes of the parent study, those subjects that did not start assigned medication, discontinued assigned medication, or met relapse criteria were considered to have discontinued study treatment. Patients were followed weekly during study treatment for 24 weeks and then again at 28 and 36 weeks post end of treatment. All sites obtained local institutional review board approval, and all participants provided written informed consent.

Present study and sample

This secondary analysis included all randomized participants from the ITT sample (N = 570). Participants were divided into two groups based on age: young adults (aged 18–25 years) versus older adults (aged ≥26 years). This age cut-off was used based on common definitions in the existing literature [29]. A number of patients (96/570, 16.8%) failed to initiate the medication to which they were assigned, largely because of failure to complete detoxification required to begin naltrexone. Thus, we also examine the “per-protocol” sample of patients (n = 474) who successfully initiated, that is, received at least one dose of assigned study medication.

Outcome measures

The first outcome, induction status, was defined as failing to initiate the study medication (yes/no) the participant was randomized to receive. A participant failed to initiate if they never received a single dose of the medication. The second outcome,

Table 1
Baseline demographic, clinical, and substance use measures by age group for the intention-to-treat sample (n = 570)

Measure	Youth ≤25 years (n = 111)		Adults >25 years (n = 459)		Difference between groups
	N	% or M (SD)	N	% or M (SD)	*p*-value
Gender					.0051
Male	66	59.5%	335	73.0%	
Female	45	40.5%	124	27.0%	
Hispanic ethnicity (% Hispanic)	20	18.0%	79	17.2%	.8404
Marital status					<.0001
Have been married	10	9.0%	181	39.4%	
Never narried	101	91.0%	275	59.9%	
Unknown	0	.0%	3	.7%	
Employment (% not employed)	71	64.0%	289	63.0%	.8445
IV use (% yes)	78	70.3%	282	61.4%	.0834
Primary opioid					.4009
Buprenorphine	2	1.8%	6	1.3%	
Opioid analgesics	14	12.7%	76	16.6%	
Methadone	0	.0%	7	1.5%	
Heroin	94	85.5%	369	80.6%	
Primary opioid cost ($/day)	110	92.4 (66.6)	458	93.8 (77.7)	.8535
Age at onset of opioid use	111	17.1 (2.7)	459	22.3 (7.4)	<.0001
Duration of opioid use (years)	111	6.0 (2.6)	459	14.1 (9.3)	<.0001
First treatment episode (% yes)	43	38.7%	166	36.2%	.6137
Stimulant use (30 days before adm) (% yes)	62	55.9%	234	51.0%	.3562
Sedative use (30 days before adm) (% yes)	34	30.6%	130	28.3%	.6298
Heavy alcohol use (30 days before adm) (% yes)	25	22.5%	122	26.6%	.3806
Cannabis use (30 days before adm) (% yes)	67	60.4%	187	40.7%	.0002
HAM-D score (range: 0–52)	111	8.3 (6.2)	458	9.1 (6.6)	.2726
Any psych disorders (% yes)	79	71.2%	302	65.8%	.2803
SOWS (range: 0–64)	111	15.0 (12.5)	459	15.7 (13.4)	.6096
Severity					.9646
Low	67	60.4%	276	60.1%	
High	44	39.6%	183	39.9%	

adm = administration; HAM-D = Hamilton Depression scale; IV = intravenous; M = mean; SD = standard deviation; SOWS = subjective opioid withdrawal scale.

relapse (yes/no), was defined as relapsing at any point after Day 20 postrandomization over 24-week follow-up, indicating either a return to regular opioid use or dropout from treatment. Relapse was operationalized as four or more consecutive weeks of any nonstudy opioid use (by urine toxicology, or self-report, or failure to provide a urine sample) or seven or more consecutive days of self-reported nonstudy opioid use. Self-reported substance use was collected with the Timeline Followback [30]. Urine toxicology was done on weekly urine samples that were tested for opioids (buprenorphine, methadone, morphine [heroin, codeine, and morphine], and oxycodone). The third outcome, time to relapse (in days), which was the primary outcome of the parent trial, was defined as the time from randomization to the start of relapse. Participants who did not relapse were censored at the end of the 24 weeks.

Statistical analyses

Among the ITT sample, baseline differences in demographic, clinical, and substance use measures between age groups were assessed using *t* tests for continuous measures and chi-square tests for categorical measures. To assess whether age moderated the effect of treatment on failure to induct onto study medication and/or the effect of treatment on relapse, a logistic regression model estimating the probability of each of these outcomes was fit including the effects of age (younger vs. older), treatment (XR-NTX vs. BUP-NX), and their interaction. If the interaction was not significant, it was omitted from the model, and only the main effects were assessed.

Furthermore, to assess whether the effects of treatment and age remained constant over follow-up time, Cox proportional hazard models were fit including treatment-by-time and age-by-time interactions. Both the logistic models on relapse and Cox proportional hazard model for time to relapse were fit using the ITT sample (n = 570) and then the per-protocol sample (n = 474). The per-protocol sample was defined as all participants who were randomized and were inducted onto study medication.

All models controlled for site as a random effect and were fit using SAS version 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided with a significance level of 5%.

Results

Baseline characteristics

Table 1 shows baseline characteristics by age group. Overall, most participants in the parent study (n = 570) were white men, aged 25–45 years (mean = 34 years), had a primary heroin use disorder, were using by injection, were single, unemployed, and Medicaid insured. There were 111 (19.5%) young adults aged 18–25 years versus 459 (80.5%) older adults (aged >25 years). Compared with the older adults, young adults were more likely to be female (40.5% vs. 27.0%) and less likely to have ever been married (9.0% vs. 39.4%). Other baseline differences compared with the older adults include an earlier age of onset of opioid use among young adults (17.1 years vs. 22.3 years), higher rates of past 30-day cannabis use among young adults (60.4% vs. 40.7%), and somewhat higher rates of injection use among young adults, although not significantly different (70.3% vs. 61.4%, $p = .08$). No significant differences were found between young adults and older adults on baseline depression symptom severity,

prevalence of psychiatric disorders, withdrawal symptoms, or severity of OUD.

Induction onto MOUD

Age did not significantly moderate the effect of treatment on failure to induct onto study medication (age-by-treatment interaction: $F(1,559) = .63$; $p = .427$). This suggests that there are no significantly different effects of treatment between the two age groups on failure to initiate medication. Similar to findings from the parent study, a main effect of treatment on medication induction was found such that participants randomized to XR-NTX had significantly higher odds of induction failure compared with those randomized to BUP-NX (odds ratio [OR] = 6.51, 95% confidence interval [CI] = 3.69, 11.48; $p < .001$). But there were no significantly different effects of treatment between the two age groups on failure to initiate medication. The rates of failure to initiate assigned XR-NTX were 18.37% for young adults versus 29.91% for older adults, whereas the rates of failure to initiate BUP-NX were 6.45% for young adults versus 5.78% for older adults. The main effect of age group on initiation was not significant ($p = .230$).

Relapse (ITT sample)

The unadjusted relapse rates are presented in Table 2. For the ITT sample, the unadjusted 24-week relapse rate in the young adult group was 70.3% overall (compared with 58.8% for older adults), 72.6% for those assigned to BUP-NX (compared with 52.4% for older adults), and 67.3% for those assigned to XR-NTX (compared with 65.0% for older adults). However, the age-by-treatment interaction was not significant ($F(1,559) = 2.29$; $p = .131$). Similar to the parent study ITT analysis, the odds of relapse were significantly greater among those assigned to XR-NTX, compared with those assigned to BUP-NX (OR = 1.48, 95% CI = 1.05, 2.09; $p = .026$). In addition, there was a significant main effect of age such that the odds of relapse were higher among young adults compared with older adults (OR = 1.71, 95% CI = 1.08, 2.72; $p = .022$).

Relapse (per-protocol sample)

For the per-protocol sample, the unadjusted relapse rate in the young adult group was 66.3% overall (compared with 50.8% for older adults), 70.7% for those assigned to BUP-NX (compared with 51.4% for older adults), and 60.0% for those assigned to XR-NTX (compared with 50.0% for older adults). The age group-by-treatment interaction was not significant ($F(1,463) = .67$; $p = .414$). As in the parent study, the odds of relapse were not significantly different among those randomized and inducted onto XR-NTX, compared with those randomized and inducted onto BUP-NX ($p = .508$). There was a main effect of age, such that the odds of relapse were significantly higher among young adults who initiated medication compared with older adults who initiated medication (OR = 1.91, 95% CI = 1.19, 3.06; $p = .008$).

Time to relapse

Among the ITT sample, Figure 1A shows the relapse-free survival curves by age group, and Figure 2A shows the model estimated hazard ratios (HRs) of age over time. In the ITT analysis, the constancy of the relative hazard assumption was violated for both treatment and age, as evidenced by a significant treatment-by-time interaction ($p = .005$) and a significant age-by-time interaction ($p = .012$). The risk of relapse was significantly lower in the BUP-NX group than the XR-NTX group earlier in the study period but by Week 8, this difference was no longer significant. For age groups, the risk of relapse did not differ significantly by age group at the start of the study period, but by Week 8, the risk of relapse is significantly and progressively higher in the young adult group compared with older adults through Week 24.

Figure 3A shows the relapse survival curves for the ITT sample among the young adults by treatment, with no significant interaction, that is, no significant difference from the sample as a whole (which showed an advantage in the ITT sample for BUP-NX).

Among the per-protocol sample, Figure 1B shows the relapse-free survival curves by age group, and Figure 2B shows the model estimated HRs of treatment and age over time. For the per-protocol sample, the proportional hazards assumption was not violated (treatment-by-time interaction: $p = .776$; age-by-time interaction: $p = .119$), with the HR estimates for treatment and for age remaining constant over time. That is, there was no variation over time in the relative hazards of relapse related to either the treatment group or age group. There was no significant difference in the risk of relapse between treatment groups ($p = .488$), but there was a significant difference in the risk of relapse between age groups. Younger adults had a higher risk of relapse over time compared with older adults (HR = 1.43, $p = .013$).

Figure 3B shows the relapse survival curves among the young adults in the per-protocol sample by treatment, with no significant interaction, that is, no significant difference from the sample as a whole (which showed no significant difference in the per-protocol sample between BUP-NX and XR-NTX).

Discussion

This study examined the association of age group with MOUD treatment outcomes in a secondary analysis comparing young

Table 2
Unadjusted 24-week relapse rates of the overall sample and by randomized treatment assignment for the intention-to-treat and per-protocol samples

Sample	Overall				Naltrexone				Buprenorphine			
	N	% not relapsed	N	% relapsed	N	% not relapsed	N	% relapsed	N	% not relapsed	N	% relapsed
ITT	(N = 570)				(N = 283)				(N = 287)			
≤25	33	29.7	78	70.3	16	32.7	33	67.3	17	27.4	45	72.6
>25	189	41.2	270	58.8	82	35.0	152	65.0	107	47.6	118	52.4
Per-protocol	(N = 474)				(N = 204)				(N = 270)			
≤25	33	33.7	65	66.3	16	40.0	24	60.0	17	29.3	41	70.7
>25	185	49.2	191	50.8	82	50.0	82	50.0	103	48.6	109	51.4

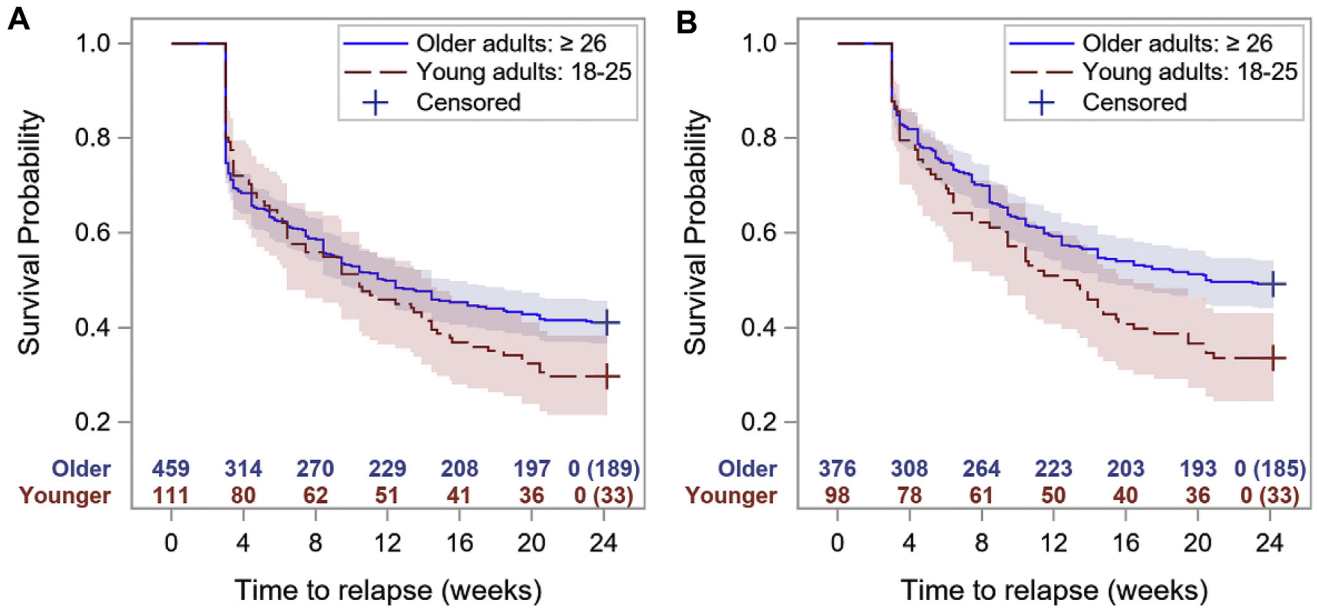

Figure 1. Relapse-free survival curves with 95% confidence intervals by age group among the intention-to-treat sample (A: left panel) and among the per-protocol sample (B: right panel). Corresponding number of subjects at risk are presented along x-axis along with number censored at Week 24.

adult participants (aged 18–25 years; n = 111) versus older adults (aged ≥26 years; n = 459) from the XBOT comparative effectiveness trial of XR-NTX versus BUP-NX [26]. Three outcomes were examined: rates of successful induction onto medication, rates of relapse at 24 weeks, and relapse-free survival over time. Age group did not have a significant impact on rates of medication induction success/failure. Age group did have a significant impact on treatment effectiveness, for both treatment effectiveness outcomes examined (rates of relapse at 24 weeks and relapse-free survival over time) and for both analysis samples examined (the ITT group and the per-protocol group). Young adults had significantly worse outcomes in all four of these treatment effectiveness analyses (24-week relapse ITT, 24-week per-protocol, relapse-free survival ITT, and relapse-free survival per-protocol).

Our results are consistent with previous findings that younger age generally confers worse treatment prognosis in OUD treatment [6,12]. Poorer treatment response in young adults presumably reflects various features of the well-known developmental

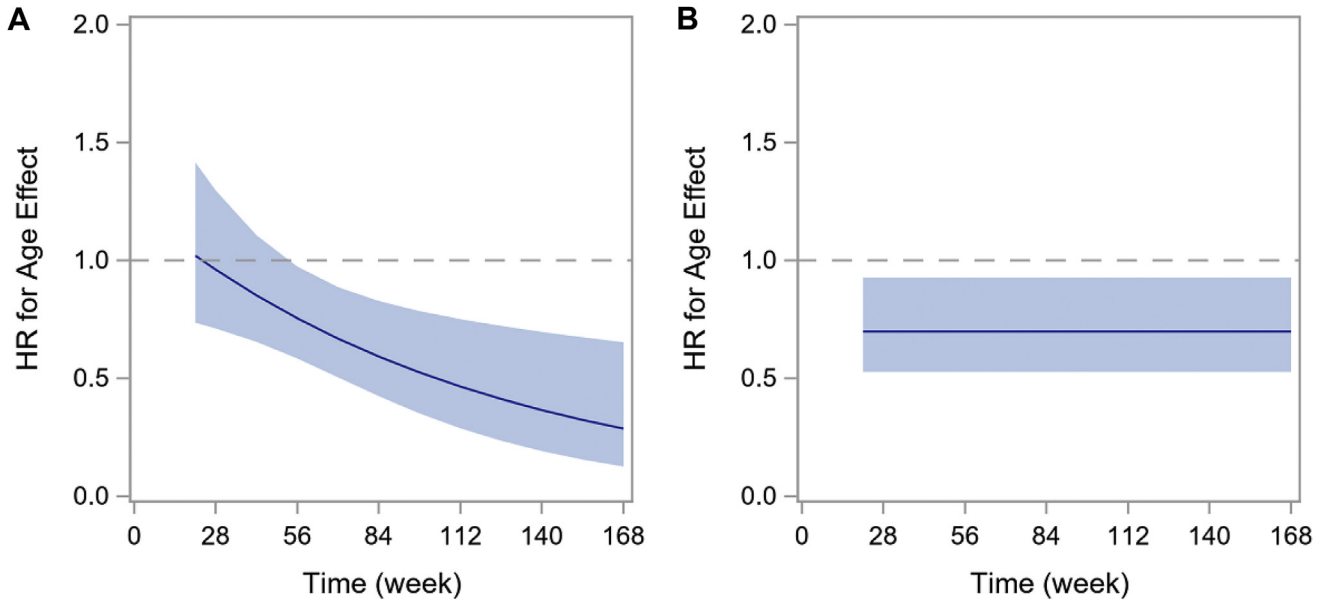

Figure 2. Model estimated hazard ratio along with corresponding 95% confidence interval over time for the effect of age group on risk of relapse among the intention-to-treat sample (A: left panel) and the per-protocol sample (B: right panel; HR > 1 favors young adults, HR < 1, favors older adults.). HR = hazard ratio.

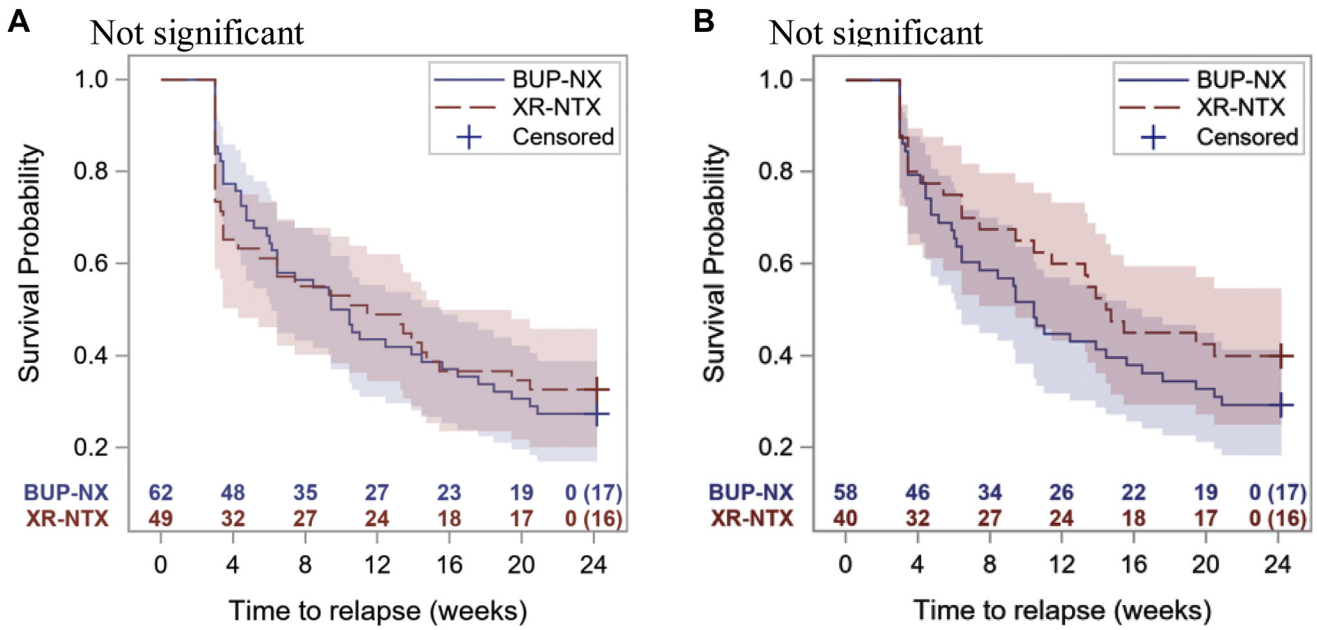

Figure 3. Relapse-free survival curves with 95% confidence intervals in young adults by treatment among the intention-to-treat sample (A: left panel) and among the per-protocol sample (B: right panel). Corresponding number of subjects at risk are presented along x-axis along with number censored at Week 24.

vulnerability of young adults. As there is no evidence of any lesser direct biological efficacy of MOUD based on age, differential response is more likely to involve aspects of medication adherence, motivation for change, treatment engagement and retention, and possibly comorbidities. Little, if any, research has directly addressed these factors in youth OUD treatment response. Immature executive function would be an intuitive candidate for exploration, although these issues of potential mechanism are beyond the scope of the present study.

There was no significant interaction with the age group on success/failure to initiate medications. The finding of a significant "induction hurdle" for naltrexone compared with buprenorphine occurred in both age groups and was consistent with the parent study. As in the parent study, the difference between rates of relapse events in the ITT and per-protocol samples was largely accounted for by the occurrence of early relapse among XR-NTX induction failures. Just as for older adults, the impediments to naltrexone induction in young adults leave considerable room for improvement, highlighting the importance of the body of work that seeks to identify strategies for reducing barriers to naltrexone initiation. One such strategy might be the facilitation of longer lengths of stay in residential treatment to allow more sufficient time for an opioid-free washout period without anxieties over the risk of precipitated withdrawal, perhaps particularly relevant for young adults who may be especially distress intolerant. Another strategy is the use of accelerated induction protocols [31–33]. This might have particular relevance to youth because of impatience and impulsiveness that can be aspects of developmental vulnerability.

Although younger age was associated with worse outcomes for both medications, there was no significant impact of age on the comparative effectiveness of the two medications. Although the model did not show a significant moderation by age group, the unadjusted raw numbers were in the direction of greater relapse rates for BUP-NX than for XR-NTX. In the ITT analysis, 24-week young adult relapse rates were 72.6% for those assigned to BUP-NX, and 67.3% for those assigned to XR-NTX (a minor difference but in the opposite direction as the older adults and the parent study), and in the per-protocol analysis, 24-week young adult relapse rates were 70.7% for those assigned to BUP-NX and 60.0% for those assigned to XR-NTX. It is possible that a sample with larger numbers of young adults could help with further exploration of the question of differential medication response. One might speculate that a long-acting formulation medication such as XR-NTX would be particularly useful for youth, given difficulties with adherence, although there was no advantage shown in this study. The same speculation might also pertain to newly developed extended-release buprenorphine formulations [34,35].

The strengths of this study include largest young adult sample to date in a study examining the role of age in MOUD outcomes, largest young adult sample and first study with experimental design to examine treatment outcomes in young adults with more than one type of MOUD, and first study to examine the role of age on initiation of either XR-NTX or BUP-NX.

The limitations include relatively small young adult sample size compared with older adult sample, limiting power to test interactions, secondary analysis with post-hoc hypotheses, and lack of exploration of potential co-factors that may have served as mechanisms, moderators, or mediators of the effect of age group (such as cognitive function and others).

Future research should focus on development of models of care that attempt to overcome the treatment outcome gap in the younger age group, targeting barriers to treatment engagement and retention, and especially medication adherence. Additional investigation should also include larger young adult sample sizes, exploration of possible mediators such as age of onset, medication adherence, executive function measures, motivation measures, psychiatric comorbidities, nonopioid substance use, and others. Such explorations may be partially informed by the

differential baseline characteristics of the young adults in this sample, that is, greater proportion female, younger age of onset, greater rates of cannabis use, and lower rates of ever having been married (and likely more dependent on family of origin). Based on the finding that the ITT sample survival curves of the two age groups start to diverge progressively at 8 weeks, it may be fruitful to explore within-treatment phenomena at or preceding that time point.

Despite having lower overall effectiveness compared with older adults, this analysis also serves to highlight that young adults *do* respond positively to both of these medications, reinforcing the emerging body of work and consensus that MOUD should be incorporated into the standard of care as first line. Although many of the young adult participants did relapse, many did not—29.7% in the ITT sample and 33.7% in the per-protocol sample. And although those rates are 11.5% and 15.5% below the unadjusted numbers for the older adults, they still represent a vast improvement over treatment without MOUD. Both buprenorphine and XR-NTX are available in SUD specialty and, increasingly, in primary care settings. The effectiveness gap conferred by age further reminds us of the particular vulnerabilities and special needs of youth, and the imperative to develop and implement developmentally informed strategies to improve engagement, retention, and medication adherence in youth with OUD. Such strategies, for further future exploration, could include family involvement, home delivery of medications [36], electronic reminders and other messaging, age-specific engagement approaches, young adult specialty programs [10], lower barrier delivery models [37], phased treatment with higher intensity early on, and others.

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