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Physical Alteration of Prescription Opioids Prior to Ingestion: An Under-Recognized Risk of Prescription Opioid Nonmedical Use

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Abstract

Background: To examine the role of physical alteration of prescription opioids prior to ingestion (PAPO) as part of the current opioid public health crisis, this study compared biopsychosocial characteristics and behaviors among individuals who reported prescription opioid nonmedical use (NMU) via oral INTACT only, PAPO, and NONORAL routes of administration.

Methods: A YouGov survey of the United States (US) general adult population (n = 24,000) captured demographics, polysubstance use, motivations for NMU, source of drug, age of first use, and environmental factors that influenced route of administration. Four mutually exclusive groups based on prescription opioid NMU routes of administration were compared.

Results: Of the 4,590 that reported prescription opioid NMU: 3,477 (75.8%) reported prescription opioid NMU via oral INTACT only; 438 (9.5%) PAPO; 390 (8.5%) NONORAL; and 285 (6.2%) PAPO + NONORAL. Compared to the INTACT only group, PAPO and NONORAL groups reported higher prevalence of lifetime diagnosis of behavioral/mental health comorbidities, polysubstance use, and abuse-related motivations for NMU, as well as earlier age of substance use initiation and higher likelihood of obtaining drugs through illicit channels.

Conclusions: PAPO group characteristics were highly consistent with NONORAL group and significantly different than INTACT group, therefore, PAPO should be considered a high-risk behavior and a potentially critical transition in substance use trajectories. This study cannot determine causality yet suggests a greater likelihood of additional high-risk behaviors in those that engage in PAPO. These findings highlight why PAPO should be as concerning as NONORAL use, as both are associated with underlying behavioral/mental health issues, polysubstance use, and associated high-risk behaviors.

Keywords

Substance-related disorders, Opioid-related disorders, Nonmedical use, drug abuse, Route of administration, Illicit drugs

Introduction

The latest data regarding overall substance use in the US reflect higher morbidity and mortality than ever, further exacerbated by the collision of the opioid epidemic and the COVID-19 pandemic [1-6]. Overdose deaths have increased (primarily from illicit drugs like fentanyl and heroin), compounded by rising co-use with cocaine and methamphetamine [2-4]. Numerous interventions have

been employed to mitigate the role of prescription opioid medications in the opioid epidemic, such as educational programs for providers and patients required under the Opioid Analgesics Risk Evaluation and Mitigation Strategy [7], opioid prescribing guidelines (Center for Disease Control; CDC) [8, 9], expansion of access to medications to treat opioid use disorder [10], state-level prescription drug monitoring programs [11], prescription drug take-back (safe disposal) events organized by the Drug Enforcement Agency [12], development of abuse-deterrent formulations [13], expansion of harm reduction services such as naloxone distribution [14], and other government legislation [15].

Despite strategies specific to deterrence of prescription opioid NMU, overdose, and death, 20.7% of drug overdose deaths in 2021 still involved prescription opioids either alone or in combination with another drug [4]. According to the 2021 National Survey on Drug Use and Health, among people aged ≥12 years, an estimated 1.8 million people initiated prescription opioid NMU in the past year and 8.7 million people reported prescription opioid NMU in the past year [5]. Prescription opioid NMU can lead to serious adverse consequences such as substance use disorders, emergency department visits, and overdose deaths [6]. Furthermore, recent studies have focused on closing the knowledge gap regarding the substance use trajectories, or individual transitions and progressive patterns of drug use and related behaviors [16-22], specifically the role of prescription opioid NMU and associated behavioral profiles contributing to this ongoing public health crisis. While there are multiple substance use trajectories, several studies have reported initiation with prescription opioid NMU prior to transitioning to illicit drugs [17-22], however most did not study the trajectory of routes of administration used with prescription opioid NMU which may contribute to the understanding of related behaviors along the substance use trajectory.

Prescription opioid NMU often involves physical alteration of the medication (e.g., crushing or dissolving) to facilitate intranasal or intravenous use, which are considered nonoral routes of administration. This is typically done for the purpose of changing the user experience through alteration of the bioavailability of the active ingredient, for example to increase the speed and intensity of a psychotropic effect or for a more rapid release of the active ingredient to get quicker pain relief [23]. Factors that influence prescription opioid NMU via nonoral routes are drug characteristics (fillers, dosage strength, immediate- versus extended-release formulation, size of pill/tablet, active ingredient; ease of tampering; high-seeking behavior), motivations for use, and the setting in which they are using [22]. The impact of nonoral routes of prescription opioid administration on the severity of outcomes was studied by Green et al. [24], who found the relative risk of an exposure resulting in a life-threatening event or death was 2.43 (95% CI 1.97, 2.99) if nonoral routes were reported compared to exposures involving oral route only. When evaluating the specific nonoral routes, a relative risk of 2.24 (95% CI 1.67, 3.01) was associated with snorting and 2.60 (95% CI 1.99, 3.40) with injection. The increased risk associated with nonoral routes of administration of a prescription opioid is important and targeted interventions, namely the development of abuse-deterrent formulations of prescription opioids [25-28], have sought to reduce rates of nonoral NMU.

While the risks and potential interventions to deter nonoral NMU are well studied, most prescription opioid NMU occurs via the oral route of administration. One limitation of most published work to date is that the study designs did not allow for distinction between use of an intact prescription opioid medication (oral intact or swallowing whole; no physical alteration prior to use) and use of a prescription opioid that has been physically altered prior to oral use (PAPO). Examples of PAPO include chewing, crushing, cutting, or dissolving the prescription opioid medication before ingesting or swallowing. PAPO prevalence estimates are sparse and vary by population, active ingredient, and formulation. For instance, chewing among recreational users was estimated at 20 - 40% in one study [29] and chewing among college students was estimated at 64% in another study [23]. In a study of individuals evaluated for substance use treatment, the prevalence of prescription opioid NMU via PAPO ranged from 31.8 (95% CI 26.6 - 37.4) to 41.5 (95% CI 40.2 - 42.8) depending on the opioid product involved [30].

To date, no published study addressed the clinical risks associated with PAPO or the role it plays in substance use trajectories. Hence, it is unknown if those who engage in PAPO are at an increased risk of transition to prescription opioid NMU via nonoral routes of administration, initiation of illicit drugs, or development of a substance use disorder. If so, then additional interventions to prevent seemingly benign PAPO could disrupt a substance use trajectory. The objective of this study was to utilize data from a general population study in the US to compare biopsychosocial and behavioral characteristics among those reporting prescription opioid NMU via oral intact route only, PAPO, and nonoral routes of administration.

Materials and Methods

This was an observational study that collected data using an online survey conducted with a nationally representative sample of the US adult general population. Data collection was conducted from 27 July 2018 through 02 September 2018 and then again from 20 September 2020 through 17 October 2020. Participants were recruited via email through YouGov, a survey panel company that has an established participant registry as well as a validated sampling methodology to ensure representativeness of the target population. The study sample was drawn from the YouGov panelists using sample-matching methods to represent a target population of US adults ages 18 to 49 years. Sample matching is a methodology for selection of representative samples from non-randomly selected pools of respondents. The YouGov sampling frame is based upon the 2019 American Community Survey public use microdata file. The Pew Research Center conducted a study in which an identical 56-item questionnaire was administered to nine samples supplied by eight different online panel vendors, including YouGov. YouGov performed the best on all 20 benchmarks, on the 8 civic benchmarks, and among Black and Latino populations. Additionally, the regression models from the YouGov online sample did the best job of predicting outcomes

on benchmark samples.

Inclusion criteria for this study was a history of prescription opioid NMU during one's lifetime. Prescription opioid NMU included ANY of the following: use for any reason, even once, without your own prescription; use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason or way than prescribed); and use for the feeling or experience the medication caused (such as a feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms, or other feelings). Four mutually exclusive groups were studied (Table 1): (1) *INTACT*: those who only reported prescription opioid NMU via oral intact route of administration only, (2) *PAPO*: those who reported any PAPO and no nonoral routes of administration, (3) *NONORAL*: those who reported any nonoral route of administration but no PAPO, and (4) *PAPO + NONORAL*: those who reported PAPO and at least one nonoral route of administration. Prescription opioid NMU via oral intact route of administration may have also been reported in groups 2, 3, and 4. The route referenced as PAPO was defined as physical alteration of a prescription opioid prior to ingesting (e.g., chewing, crushing, cutting, or dissolving then swallowing). Hence, if a medication is only intended to be used by swallowing an intact pill or tablet, then PAPO is considered NMU, regardless of intent.

Data were collected on demographics (age, sex, race, ethnicity, education, college enrollment, employment, etc.), select co-morbidities (diagnosis of anxiety, depression, alcohol use disorder, substance use disorder, etc.), age of initiation of illicit drug use, history and age of initiation of prescription medication NMU, routes of administration, sources of drug procurement, primary reason for use, situational factors influencing use of nonoral routes of administration, and concomitant use of other substances with prescription opioid NMU. Prescription opioid product names, active ingredients, and photos were used to aid in selection of substances previously used. Selected products were then presented in subsequent questions to inquire about route of administration, reason for use, and source of drug procurement.

Statistical analyses included the generation of contingency tables to calculate prevalence estimates of prescription medication NMU among the four mutually exclusive study groups according to population characteristics (i.e., age, sex, race, education level, geography, etc.). Select co-morbidities, substances used concomitantly with prescription opioid NMU, motivations for NMU, source of drug procurement, age of first use of illicit drugs, age of first prescription drug NMU, and environmental factors that influence route of administration were also compared among the study groups. Statistical significance was assessed using Chi square tests where statistical significance was determined when $p < 0.05$. Unadjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated for the association between prescription opioid NMU via specific routes (PAPO, NONORAL, and PAPO + NONORAL; reference group = INTACT) and lifetime diagnosis of select behavioral and mental health conditions using Poisson regression models without an offset. This analysis was repeated for the association between NMU via specific routes and concomitant use of other substances. Distributions were used to illustrate comparisons of the age of first use and situational factors that influenced substance use decisions. This study was approved by the Western Institutional Review Board.

Results

Of the 24,000 study participants, 4,590 reported a history of prescription opioid NMU and met inclusion criteria for analysis: 3,477 (75.8%) reported prescription opioid NMU via oral INTACT only; 438 (9.5%) reported PAPO; 390 (8.5%) reported NONORAL; and 285 (6.2%) reported PAPO + NONORAL. Oral intact use was reported in 38.1% of the PAPO group, 62.1% of the NONORAL group, and 65.6% of the PAPO + NONORAL group (Table 2). When compared to INTACT users, the PAPO group was significantly different ($p < 0.05$) in all characteristics evaluated apart from level of educational and annual family income. Compared to INTACT users, the NONORAL group was significantly different ($p < 0.05$) in all characteristics apart from current college/university enrollment, employment status, and annual family income. Compared to INTACT users, the PAPO + NONORAL group was significantly different ($p < 0.05$) on all characteristics apart from race, educational attainment, and employment status. In general, compared to INTACT users, those who reported PAPO and/or NONORAL were more likely to be male, be younger in age, and cover their healthcare costs through Medicare and/or Medicaid. These respondents were also more likely to have been arrested compared to INTACT users. Those who reported PAPO (with or without nonoral routes) were more likely to be currently enrolled in a college or university than those who reported prescription opioid NMU via INTACT route only.

The prevalence of lifetime diagnosis of select behavioral and mental health comorbidities was significantly higher for all PAPO or NONORAL study groups when compared to the INTACT group (Table 3). The prevalence of anxiety, ADHD, bipolar, and alcohol use disorder did not differ between those

Table 1: Study group definitions.

INTACT	*Oral Intact Only*: reported prescription opioid NMU via oral intact route of administration only
PAPO	*PAPO (no nonoral routes)*: reported prescription opioid NMU via any physical alteration prior to oral use (PAPO), such as chewing, crushing, cutting or dissolving then swallowing; no nonoral routes of administration reported; may have also reported INTACT use
NONORAL	*Nonoral Route (no PAPO)*: reported prescription opioid NMU via any nonoral route of administration, such as intranasal or intravenous use; no PAPO reported; may have also reported INTACT use
PAPO+NONORAL	*PAPO plus Nonoral Route*: reported prescription opioid NMU via PAPO and at least one nonoral route of administration, such as intranasal or intravenous; may have also reported INTACT use

Table 2: Demographics and characteristics of respondents who reported lifetime prescription opioid NMU by study group: Oral INTACT Only, PAPO, NONORAL, and PAPO+NONORAL.

Routes**		INTACT (N = 3,477)		PAPO (N = 438)		NONORAL (N = 390)		PAPO + NONORAL (N = 285)		INTACT vs. PAPO	INTAC vs. NONRAL	INTACT vs. PAPO + NONORAL	PAPO vs. NONORAL
		n	%	n	%	n	%	n	%	p-value*	p-value*	p-value*	p-value*
Oral Intact Use of Prescription Opioid	**Oral intact use in lifetime**	3,477	100	170	38.9	242	62.1	184	64.6	N/A	N/A	N/A	*<0.01*
	No oral intact use in lifetime	---	---	268	61.2	148	37.9	101	35.4				
Sex	**Male**	1,450	41.7	245	55.9	196	50.3	168	58.9	*<0.01*	*<0.01*	*<0.01*	*0.10*
	Female	2,027	58.3	193	44.1	194	49.7	117	41.1				
Age distribution	**18-24 years**	405	11.6	102	23.3	52	13.3	49	17.2	*<0.01*	*<0.01*	*<0.01*	*<0.01*
	25-34 years	1,232	35.4	161	36.8	179	45.9	119	41.8				
	35-44 years	1,232	35.4	126	28.8	134	34.4	101	35.4				
	45-49 years	608	17.5	49	11.2	25	6.4	16	5.6				
Spanish, Latino, or Hispanic origin or descent	**Yes**	724	20.8	117	26.7	60	15.4	84	29.5	*<0.01*	*0.01*	*<0.01*	*<0.01*
	No	2,752	79.1	321	73.3	330	84.6	201	70.5				
	Missing	1	0.0	0	0.0	0	0.0	0	0.0				
Race¤	**White**	2,294	66.0	230	52.5	294	75.4	191	67.0	*<0.01*	*<0.01*	0.09	*<0.01*
	Black	430	12.4	89	20.3	26	6.7	22	7.7				
	Hispanic	495	14.2	64	14.6	36	9.2	44	15.4				
	Asian	117	3.4	38	8.7	10	2.6	15	5.3				
	Native American	26	0.7	6	1.4	6	1.5	5	1.8				
	Mixed	82	2.4	4	0.9	12	3.1	5	1.8				
	Other	30	0.9	2	0.5	6	1.5	3	1.1				
	Middle Eastern	3	0.1	5	1.1	0	0.0	0	0.0				
Highest level of education	**No high school degree**	151	4.3	17	3.9	26	6.7	17	6.0	0.08	*<0.01*	0.36	*<0.01*
	High school graduate	968	27.8	115	26.3	122	31.3	78	27.4				
	Some college, but no degree (yet)	913	26.3	96	21.9	118	30.3	60	21.1				
	2-year college degree	421	12.1	50	11.4	41	10.5	37	13.0				
	4-year college degree	707	20.3	110	25.1	52	13.3	63	22.1				
	Postgraduate degree	317	9.1	50	11.4	31	7.9	30	10.5				
Currently enrolled in a college/ university	**Yes**	514	14.8	160	36.5	71	18.2	114	40.0	*<0.01*	0.07	*<0.01*	*<0.01*
	No	2,963	85.2	278	63.5	319	81.8	171	60.0				

Marital status	**Married, living with spouse**	1,486	42.7	213	48.6	143	36.7	142	49.8	*0.01*	*0.04*	*<0.01*	*<0.01*
	Separated	82	2.4	16	3.7	16	4.1	7	2.5				
	Divorced	236	6.8	19	4.3	23	5.9	21	7.4				
	Widowed	29	0.8	5	1.1	6	1.5	7	2.5				
	Single, never married	1,367	39.3	163	37.2	164	42.1	84	29.5				
	Domestic partnership	277	8.0	22	5.0	38	9.7	24	8.4				
Employment status	**Working full-time now**	1,670	48.0	219	50.0	180	46.2	149	52.3	*<0.01*	0.09	0.13	*0.04*
	Working part time now	459	13.2	74	16.9	46	11.8	40	14.0				
	Temporarily laid off	62	1.8	12	2.7	15	3.8	10	3.5				
	Unemployed	382	11.0	45	10.3	55	14.1	27	9.5				
	Retired	28	0.8	2	0.5	2	0.5	3	1.1				
	Permanently disabled	252	7.2	15	3.4	23	5.9	15	5.3				
	Taking care of home or family (homemaker)	393	11.3	27	6.2	40	10.3	20	7.0				
	Student	188	5.4	39	8.9	25	6.4	16	5.6				
	Other	43	1.2	5	1.1	4	1.0	5	1.8				
Family annual income	**Less than $30,000**	1,012	29.1	146	33.3	122	31.3	84	29.5	0.16	0.37	*<0.01*	0.24
	$30,000 – $49,999	689	19.8	75	17.1	86	22.1	49	17.2				
	$50,000 – $69,999	557	16.0	63	14.4	52	13.3	42	14.7				
	$70,000 – $99,999	516	14.8	64	14.6	46	11.8	43	15.1				
	$100,000 – $149,999	355	10.2	48	11.0	38	9.7	35	12.3				
	$150,000 or more	171	4.9	28	6.4	23	5.9	28	9.8				
	Prefer not to say	177	5.1	14	3.2	23	5.9	4	1.4				
How do you cover healthcare costs	**Medicaid/Medicare**	987	28.4	198	45.2	142	36.4	119	41.8	*<0.01*	*<0.01*	*<0.01*	*<0.01*
	Medicare (ONLY)	186	5.3	43	9.8	30	7.7	33	11.6				
	Commercial Payer (insurance through employer or open market)	1,615	46.4	127	29.0	131	33.6	70	24.6				
	Uninsured/ exhausted benefits	263	7.6	15	3.4	34	8.7	21	7.4				
	Self-Pay	314	9.0	41	9.4	43	11.0	33	11.6				
	Other	112	3.2	14	3.2	10	2.6	9	3.2				

Have you ever been arrested and charged in your lifetime (Multiple responses allowed) [€]	**Any Arrest**	**531**	**15.3**	**162**	**37.0**	**180**	**46.2**	**166**	**58.2**	*<0.01*	*<0.01*	*<0.01*	*<0.01*
	Shoplifting or vandalism	192	5.5	45	10.3	67	17.2	56	19.6				
	Parole or probation violations	85	2.4	44	10.0	60	15.4	56	19.6				
	Drug charges or possession	242	7.0	69	15.8	102	26.2	85	29.8				
	Forgery	35	1.0	23	5.3	17	4.4	35	12.3				
	Failure to pay alimony or child support	26	0.7	25	5.7	21	5.4	31	10.9				
	Weapons offense	31	0.9	25	5.7	10	2.6	26	9.1				
	Burglary, larceny, breaking or entering	45	1.3	14	3.2	28	7.2	33	11.6				
	Robbery	20	0.6	19	4.3	11	2.8	24	8.4				
	Assault	100	2.9	18	4.1	31	7.9	28	9.8				
	Arson	14	0.4	10	2.3	7	1.8	19	6.7				
	Rape	6	0.2	8	1.8	4	1.0	18	6.3				
	Homicide or manslaughter	6	0.2	13	3.0	7	1.8	20	7.0				
	Prostitution	9	0.3	6	1.4	5	1.3	12	4.2				
	Contempt of court	37	1.1	10	2.3	9	2.3	18	6.3				
	Other (Do not include misdemeanors)	45	1.3	4	0.9	9	2.3	9	3.2				
	None	**2,946**	**84.7**	**276**	**63.0**	**210**	**53.8**	**119**	**41.8**				

[†]Italics indicate significance as determined by p-value <0.05. **Study groups are mutually exclusive.

[¶] Statistical testing for race was conducted among the collapsed race categories of White, Black, Hispanic, Asian, and Other (which includes Native American, Mixed, Other, and Middle Eastern). [€]Any arrest versus no arrest for statistical comparison groups.

who reported PAPO and those in the NONORAL group. The prevalence of substance use disorder significantly increased from the PAPO group to the NONORAL group to the PAPO + NONORAL group. Substance use disorder diagnosis was 3.92 times (95% CI 3.22, 4.76), 5.04 times (95% CI 4.18, 6.08), and 7.18 times (95% CI 5.97, 8.64) more prevalent among the PAPO group, NONORAL group, and PAPO + NONORAL group, respectively, compared to the INTACT group. The prevalence of a learning disability, conduct disorder, and oppositional defiant disorder increased from the NONORAL group to the PAPO group to the PAPO + NONORAL group; prevalence was significantly higher for those who reported PAPO compared to those in the NONORAL group. Compared to the INTACT group, a learning disability was reported 2.27 times (95% CI 1.76, 2.93) more often in the NONORAL group, 3.47 times (95% CI 2.81, 4.27) more often in the PAPO group, and 4.44 times (95% CI 3.56, 5.55) more often in the PAPO + NONORAL group. Conduct disorder was 4.60 times (95% CI 3.24, 6.55), 9.77 times (95% CI 7.41, 12.88), and 13.27 times (95% CI 9.98, 17.64) more prevalent in the NONORAL group, PAPO group, and PAPO + NONORAL group, respectively, compared to the INTACT group. Oppositional defiant disorder diagnosis was 5.73 times (95% CI 4.07, 8.07) more prevalent in the NONORAL group, 10.21 times (95% CI 7.67, 13.57) in the PAPO group, and 13.51 times (95% CI 10.06, 18.14) in the PAPO + NONORAL group compared to the INTACT group.

The age of first prescription medication NMU and illicit drug use are illustrated for each study group in figure 1. The age of initiation for most substances was younger for those in the PAPO and NONORAL groups compared to the INTACT group. First prescription opioid NMU before the age of 21 was reported by 36.7% of the INTACT group, 56.9% of the PAPO group, 62.3% of the NONORAL group, and 76.5% of the PAPO + NONORAL group. Similar progressive patterns are seen for age of first NMU of prescription diet aids, muscle relaxants, sleep aids, and tranquilizers/sedatives. Prescription stimulant NMU age of initiation in the INTACT group was similar to that of the other study groups. Less distinct patterns were seen for age of first use for the illicit drugs when stratified by the study groups.

In relation to polysubstance use, the prevalence of concomitant use of almost all other substances was significantly higher for those reporting PAPO compared to those who reported INTACT only (Table 4), the one exception being caffeine. In turn, the prevalence of concomitant use of almost all other substances was significantly higher for the NONORAL group compared to those who reported PAPO. The exceptions were tranquilizers or sedatives, gabapentin, and street fentanyl. Those who reported PAPO were 3.19 times (95% CI 2.35, 4.33) more likely to concurrently use methamphetamine, 3.46 times (95% CI 2.61, 4.59) more likely to concurrently use cocaine, 3.67 times (95% CI 2.76, 4.88) more likely to concurrently use prescription stimulants for NMU, 9.50 times (95%

Table 3: Lifetime diagnosis by a healthcare professional among those who reported prescription opioid NMU by study group: Oral INTACT Only, PAPO, NONORAL, and PAPO+NONORAL.

Lifetime Diagnosis[€]	INTACT (N = 3,477)		PAPO (N = 438)		NONORAL (N = 390)		PAPO + NONORAL (N = 285)		INTACT vs. PAPO	INTACT vs. NONORAL	INTACT vs. PAPO + NONORAL	PAPO vs. NONORAL
	n	%	n	%	n	%	n	%	p-value*	p-value*	p-value*	p-value*
Any diagnosis of the conditions listed	2,363	68.0	345	78.8	339	86.9	262	91.9	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		1.16 (1.04-1.30)		1.27 (1.14-1.43)		1.35 (1.19-1.54)					
Anxiety	1,816	52.2	269	61.4	263	67.4	219	76.8	*<0.01*	*<0.01*	*<0.01*	0.07
PR (95% CI)	ref		1.18 (1.03-1.34)		1.29 (1.13-1.47)		1.47 (1.28-1.69)					
Depression	1,805	51.9	267	61.0	265	67.9	216	75.8	*<0.01*	*<0.01*	*<0.01*	*0.04*
PR (95% CI)	ref		1.17 (1.03-1.34)		1.31 (1.15-1.49)		1.46 (1.27-1.68)					
ADHD	466	13.4	144	32.9	116	29.7	147	51.6	*<0.01*	*<0.01*	*<0.01*	0.33
PR (95% CI)	ref		2.45 (2.03-2.96)		2.22 (1.81-2.72)		3.85 (3.20-4.63)					
Bipolar	454	13.1	141	32.2	126	32.3	143	50.2	*<0.01*	*<0.01*	*<0.01*	0.97
PR (95% CI)	ref		2.47 (2.04-2.98)		2.47 (2.03-3.01)		3.84 (3.18-4.64)					
Alcohol Use Disorder	330	9.5	145	33.1	116	29.7	137	48.1	*<0.01*	*<0.01*	*<0.01*	0.30
PR (95% CI)	ref		3.49 (2.87-4.24)		3.13 (2.54-3.87)		5.07 (4.15-6.18)					
Substance Use Disorder (other than Alcohol)	304	8.7	150	34.2	172	44.1	179	62.8	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		3.92 (3.22-4.76)		5.04 (4.18-6.08)		7.18 (5.97-8.64)					
Learning disability	291	8.4	127	29.0	74	19.0	106	37.2	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		3.47 (2.81-4.27)		2.27 (1.76-2.93)		4.44 (3.56-5.55)					
Conduct disorder	91	2.6	112	25.6	47	12.1	99	34.7	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		9.77 (7.41-12.88)		4.60 (3.24-6.55)		13.27 (9.98-17.64)					
Oppositional defiant disorder	84	2.4	108	24.7	54	13.8	93	32.6	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		10.21 (7.67-13.57)		5.73 (4.07-8.07)		13.51 (10.06-18.14)					
Other	377	10.8	77	17.6	54	13.8	47	16.5	*<0.01*	0.07	*<0.01*	0.14
PR (95% CI)	ref		1.62 (1.27-2.07)		1.28 (0.96-1.70)		1.52 (1.12-2.06)					

PR = prevalence ratio. *Italics indicate significance as determined by p-value <0.05. €Multiple diagnoses could be reported.

CI 6.07, 14.88) more likely to concurrently use heroin, and 12.00 times (95% CI 7.63, 18.89) more likely to concurrently use street fentanyl than those in the INTACT group.

Therapeutic intent (to treat pain) was a significantly more common reason for prescription opioid NMU among those who reported INTACT use compared to all other study groups (Table 5). The prevalence of NMU to treat or prevent withdrawal (opioid or other) did not differ between the PAPO and NONORAL groups. Interestingly, those who reported PAPO were significantly more likely to do so to treat pain, for energy/stimulation, or to enhance the effect of other drugs than those who in the NONORAL group.

Those in the INTACT group most often obtained the medication from their own prescription (71.4%) or from a family member/friend (37.7%), as did those who reported PAPO (64.6% and 52.1%, respectively) (Table 6). These sources were also frequently reported among the NONORAL group. However, compared to the INTACT group (4.3%), obtaining the prescription opioid from a dealer was reported by a significantly higher proportion of those who reported PAPO (14.2%), NONORAL (40.8%), and PAPO + NONORAL (56.8%). Obtaining from a family member/friend, online, trading for it, faking a prescription, and stealing were also reported significantly more often in the PAPO and NONORAL groups compared to the INTACT group. When sources of procurement were compared between the PAPO and nonoral groups, own prescription and buying online without a doctor's visit were reported significantly more frequently among those who reported PAPO, while obtaining from a family member/friend, a dealer, and trading for it was more frequently reported in the NONORAL group.

The impact of a variety of situational factors were studied in relation to their influence on how an individual decided to use a prescription opioid for NMU (e.g., route of adminis-

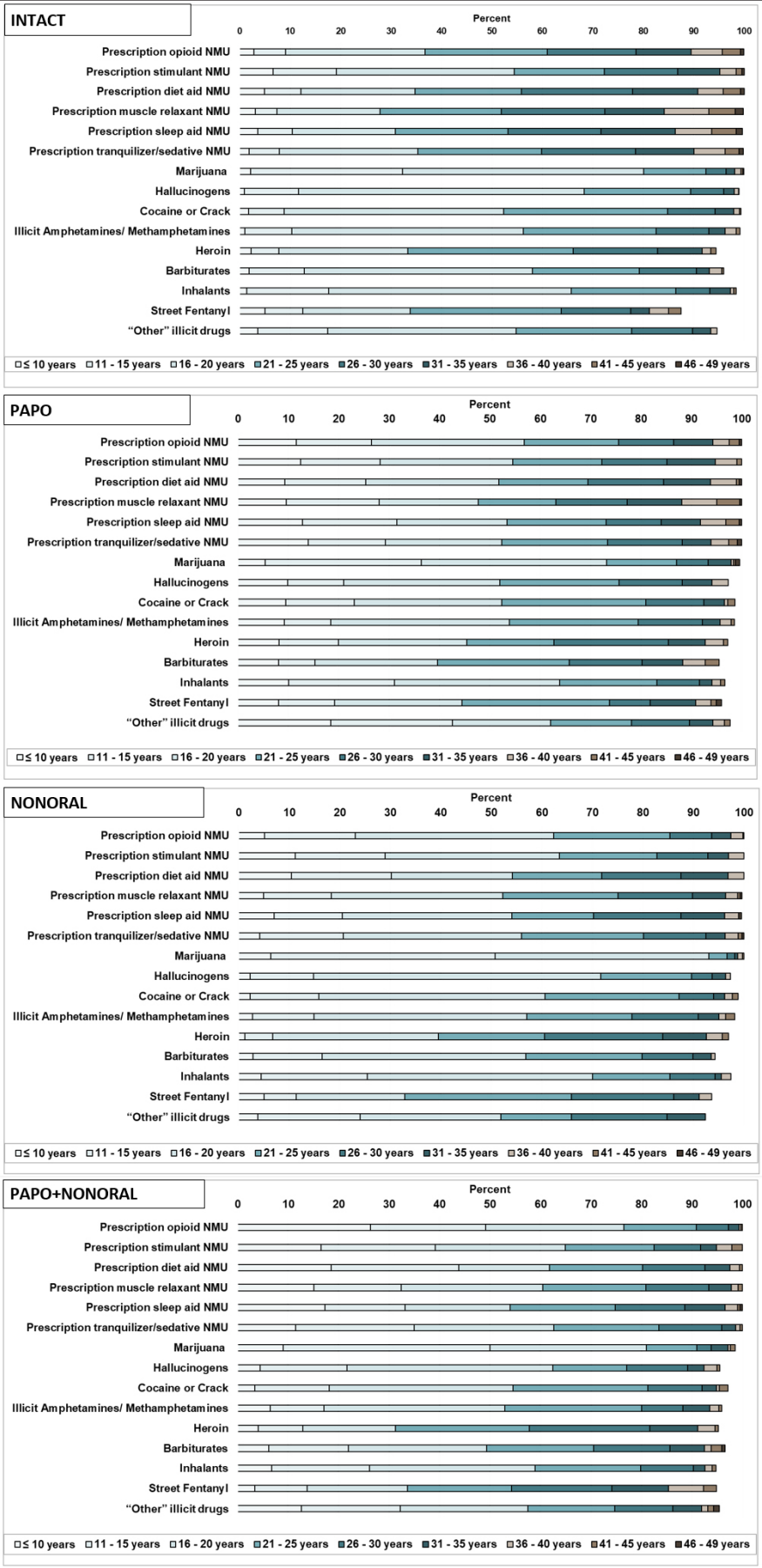

Figure 1: Age of prescription medication NMU and illicit drug initiation by study group*: Oral INTACT Only, PAPO, NONORAL, and PAPO+NONORAL.
*Percentages may not add to 100% as some respondents were missing an age at initiation.

Table 4: Other drugs used at the same time as prescription opioid NMU by study group: Oral INTACT Only, PAPO, NONORAL, and PAPO+NONORAL.

Other Drugs Used Concomitantly[¢]	INTACT (N = 3,477)		PAPO (N = 438)		NONORAL (N = 390)		PAPO + NONORAL (N = 285)		INTACT vs. PAPO	INTACT vs. NONORAL	INTACT vs. PAPO + NONORAL	PAPO vs. NONORAL
	n	%	n	%	n	%	n	%	p-value*	p-value*	p-value*	p-value*
Caffeine	1,765	50.8	230	52.5	240	61.5	194	68.1	0.52	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		1.03 (0.90-1.18)		1.21 (1.06-1.39)		1.34 (1.16-1.56)					
Tobacco	1,243	35.8	199	45.4	284	72.8	195	68.4	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		1.26 (1.09-1.47)		2.04 (1.79-2.32)		1.92 (1.65-2.23)					
Alcohol	1,019	29.3	171	39.0	228	58.5	163	57.2	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		1.33 (1.13-1.56)		1.99 (1.73-2.30)		1.95 (1.66-2.30)					
Marijuana	848	24.4	130	29.7	240	61.5	137	48.1	*0.02*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		1.21 (1.01-1.46)		2.52 (2.19-2.91)		1.97 (1.65-2.36)					
Cocaine	158	4.5	69	15.8	126	32.3	112	39.3	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		3.46 (2.61-4.59)		7.11 (5.63-8.98)		8.66 (6.79-11.03)					
Tranquilizers or sedatives	198	5.7	71	16.2	77	19.7	108	37.9	*<0.01*	*<0.01*	*<0.01*	0.18
PR (95% CI)	ref		2.84 (2.17-3.72)		3.47 (2.66-4.51)		6.66 (5.27-8.42)					
Methamphetamine	144	4.1	58	13.2	100	25.6	107	37.5	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		3.19 (2.35-4.33)		6.19 (4.80-7.99)		9.07 (7.07-11.65)					
Gabapentin	202	5.8	65	14.8	56	14.4	85	29.8	*<0.01*	*<0.01*	*<0.01*	0.86
PR (95% CI)	ref		2.55 (1.93-3.37)		2.47 (1.84-3.32)		5.14 (3.99-6.62)					
Prescription stimulants	149	4.3	69	15.8	86	22.1	100	35.1	*<0.01*	*<0.01*	*<0.01*	*0.02*
PR (95% CI)	ref		3.67 (2.76-4.88)		5.15 (3.95-6.71)		8.20 (6.36-10.56)					
Heroin	35	1.0	42	9.6	76	19.5	81	28.4	*<0.01*	*<0.01*	*<0.01*	*<0.01*
PR (95% CI)	ref		9.50 (6.07-14.88)		19.36 (12.98-28.89)		28.26 (19.01-42.01)					
Street fentanyl	31	0.9	47	10.7	30	7.7	66	23.2	*<0.01*	*<0.01*	*<0.01*	0.14
PR (95% CI)	ref		12.00 (7.63-18.89)		8.63 (5.22-14.25)		26.00 (16.97-39.84)					
Other drugs	49	1.4	26	5.9	16	4.1	28	9.8	*<0.01*	*<0.01*	*<0.01*	0.23
PR (95% CI)	ref		4.20 (2.61-6.76)		2.91 (1.66-5.12)		6.98 (4.39-11.10)					

PR = prevalence ratio. *Italics indicate significance as determined by p-value <0.05. [¢]Responses are not mutually exclusive and do not necessarily add to 100%.

tration) (Figure 2). Among those who reported PAPO, the factors that were most often rated as "high impact" included whether using alone or with at least one other person (15.1%), the reason for use (15.1%), how easy the product is to crush, chew, or dissolve (13.9%), access to clean needles or supplies (13.7%), and upcoming deadlines or exams (13.2%). The most common "high impact" situations among the NONORAL group were the reason for use (29.0%), the type of medication used (23.3%), how easy the product is to crush, chew, or dissolve (20.3%), where used (16.9%), and access to clean needles or other supplies (14.9%). In the PAPO + NONORAL group, the factors that were most often rated as "high impact" included the reason for use (31.6%), the type of medication used (26.3%), where used (25.6%), how easy the product is to crush, chew, or dissolve (23.5%), and access to clean needles or supplies (21.8%).

Discussion

This study highlights the biopsychosocial characteristics and behaviors of participants who have engaged in prescription opioid NMU via different routes of administration (oral INTACT only, PAPO, NONORAL, and PAPO + NONORAL). Consistent with previously published studies, prescription opioid NMU was predominantly (75.8%) via oral INTACT route of administration yet 1 in 4 participants reported PAPO and/or nonoral routes. Prescription opioid NMU via nonoral routes of administration presents significantly higher risk of life-threatening events and death [13]. By establishing the similarities between individuals who engage in PAPO and those who use via nonoral routes, the dangers of PAPO and their potential role in substance use pathways can be better understood.

Those who reported PAPO were more likely to be male, younger, Spanish/Latino/Hispanic descent, currently enrolled in a college/university, covered by Medicaid/Medicare, and have a history of arrest than those in the INTACT group. These characteristics were more consistent with those of NONORAL users, suggesting target groups that are most at risk.

Table 5: Primary reasons for prescription opioid NMU by study group: Oral INTACT Only, PAPO, NONORAL, and PAPO+NONORAL.

Primary Motivations for NMU[¢]	INTACT (N = 3,477)		PAPO (N = 438)		NONORAL (N = 390)		PAPO + NONORAL (N = 285)		INTACT vs. PAPO	INTACT vs. NONORAL	INTACT vs. PAPO + NONORAL	PAPO vs. NONORAL
	n	%	n	%	n	%	n	%	p-value*	p-value*	p-value*	p-value*
To treat my pain	2,730	78.5	222	50.7	140	35.9	116	40.7	*<0.01*	*<0.01*	*<0.01*	*<0.01*
To get high	490	14.1	123	28.1	253	64.9	163	57.2	*<0.01*	*<0.01*	*<0.01*	*<0.01*
For energy or stimulation	139	4.0	99	22.6	39	10.0	112	39.3	*<0.01*	*<0.01*	*<0.01*	*<0.01*
To enhance effect of other drugs	64	1.8	64	14.6	30	7.7	91	31.9	*<0.01*	*<0.01*	*<0.01*	*<0.01*
To treat or prevent opioid-related withdrawal	40	1.2	52	11.9	53	13.6	121	42.5	*<0.01*	*<0.01*	*<0.01*	0.46
By mistake (such as forgot you already took it)	128	3.7	8	1.8	6	1.5	33	11.6	*0.046*	*0.03*	*<0.01*	0.75
To treat or prevent withdrawal from alcohol or other drugs (NOT opioid-related)	30	0.9	20	4.6	21	5.4	84	29.5	*<0.01*	*<0.01*	*<0.01*	0.59
Other reason	102	2.9	12	2.7	11	2.8	11	3.9	0.82	0.90	0.38	0.94

*Italics indicate significance as determined by p-value <0.05. [¢]Responses are not mutually exclusive and do not necessarily add to 100%.

Table 6: Source of procurement of prescription opioids used for NMU by study group: Oral INTACT Only, PAPO, NONORAL, and PAPO+NONORAL.

Source[¢]	INTACT (N = 3,477)		PAPO (N = 438)		NONORAL (N = 390)		PAPO + NONORAL (N = 285)		INTACT vs. PAPO	INTACT vs. NONORAL	INTACT vs. PAPO + NONORAL	PAPO vs. NONORAL
	n	%	n	%	n	%	n	%	p-value*	p-value*	p-value*	p-value*
My own prescription from one doctor or several doctors	2,482	71.4	283	64.6	180	46.2	198	69.5	*<0.01*	*<0.01*	0.49	*<0.01*
Bought/given/stole it from family or friend	1,311	37.7	228	52.1	275	70.5	249	87.4	*<0.01*	*<0.01*	*<0.01*	*<0.01*
Bought it from a dealer (a known seller)	148	4.3	62	14.2	159	40.8	162	56.8	*<0.01*	*<0.01*	*<0.01*	*<0.01*
Bought it online without a doctor's visit	52	1.5	87	19.9	36	9.2	119	41.8	*<0.01*	*<0.01*	*<0.01*	*<0.01*
Traded for it	39	1.1	14	3.2	39	10.0	46	16.1	*<0.01*	*<0.01*	*<0.01*	*<0.01*
Wrote or bought a fake prescription	19	0.6	24	5.5	12	3.1	59	20.7	*<0.01*	*<0.01*	*<0.01*	0.09
Stole them (from someone I did not know)	20	0.6	14	3.2	16	4.1	50	17.5	*<0.01*	*<0.01*	*<0.01*	0.49
Other source	60	1.7	8	1.8	6	1.5	6	2.1	0.88	0.79	0.64	0.75

*Italics indicate significance as determined by p-value <0.05. [¢]Responses are not mutually exclusive and do not necessarily add to 100%.

The prevalence of any mental or behavioral health diagnosis significantly increased from the INTACT group (68.0%) to the PAPO group (78.8%), to the NONORAL group (86.9%), to the PAPO + NONORAL group (91.9%). The PAPO, NONORAL, and PAPO + NONORAL groups were significantly more likely than the INTACT group to report all mental health comorbidities studied, including being diagnosed with a substance use disorder. The prevalence of several mental and behavioral health issues did not differ among the PAPO and NONORAL groups, namely anxiety, ADHD, bipolar and alcohol use disorder. The prevalence of learning disability, conduct disorder and oppositional defiant disorder were actually significantly higher in the PAPO group compared to the NONORAL group. These data align with the association between underlying mental illness and substance use disorders recently highlighted by the National Institute on Drug Abuse (NIDA) [31]. The NIDA report estimates 43% of people in treatment for prescription opioid NMU have a diagnosis or symptoms of mental health disorders (particularly depression and anxiety). This study found even higher rates of depression and anxiety, particularly in the PAPO (61.0%, 61.4%), NONORAL (67.9%, 67.4%), and PAPO + NONORAL (75.8%, 76.8%) groups. The NIDA report identifies three main pathways that further support the links between

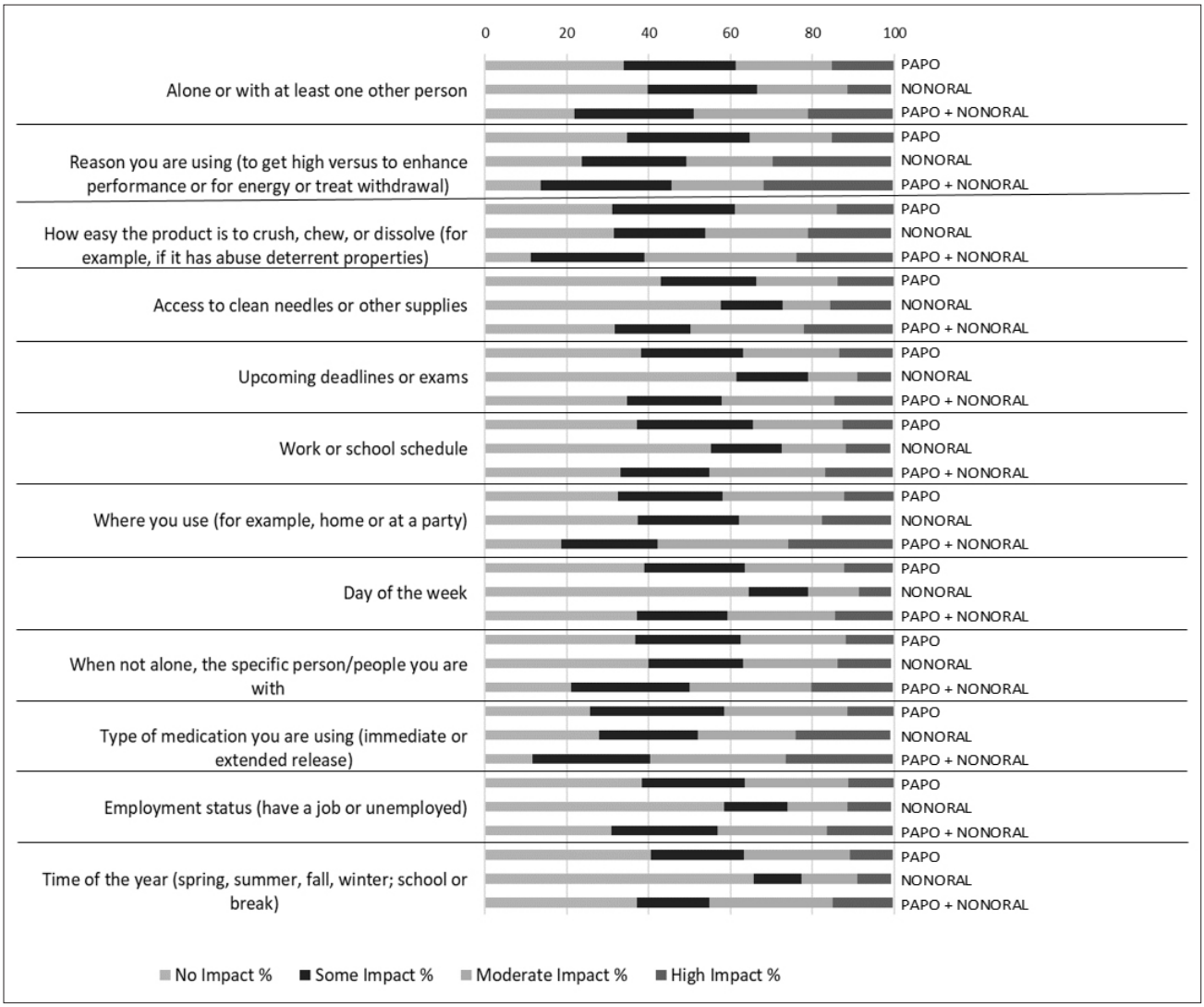

Figure 2: Impact assessment of situational factors that influence decisions on how to use prescription opioids for NMU by study group: PAPO, NONORAL, and PAPO+NONORAL.

mental illness and substance use disorders: 1) common risk factors can contribute to mental illness, substance use, and addiction, 2) mental illness may contribute to substance use and addiction, and 3) substance use and addiction can contribute to the development of mental illness.

The age of first use of other prescription medication NMU and illicit drug use illustrated additional distinctions between the study groups. The distribution of age of first NMU for all prescription medications except prescription stimulants skewed younger for the PAPO and NONORAL route groups as compared to the INTACT group, suggesting a more rapid acceleration of polysubstance use for those engaging in PAPO and/or nonoral routes. Polysubstance use of all other drugs studied was significantly higher for the PAPO and NONORAL groups as compared to the INTACT group. The association between polysubstance use and prescription opioid NMU via nonoral routes is not a new finding. However, this study is the first to establish an association between polysubstance use and PAPO. Alarmingly, those who reported PAPO were at least 3 times more likely to concurrently use cocaine, methamphetamine, or prescription stimulants for NMU, 9.5 times more likely to concurrently use heroin, and 12 times more likely to concurrently use street fentanyl than those who reported prescription opioid NMU via INTACT only. The increased risk of mortality when these drugs are used in combination has been highlighted in recent publications from the CDC [1, 3] and others [2]. These data demonstrate the elevated risks associated with PAPO; risks which have previously only been associated with prescription opioid NMU via nonoral routes.

Patterns in motivations for prescription opioid NMU and diversion are also suggestive of closer similarities between the PAPO and NONORAL groups than those in the INTACT group. The PAPO group was twice as likely to report "to get high" and ten times as likely to report "to treat or prevent opioid-related withdrawal" as a primary reason for NMU and over three times as likely to report procurement of prescription opioids through a dealer than the INTACT group. The 'reason for use' was noted as having the highest impact on how one used prescription opioids for NMU. Other moderate to high

impact factors were 'how easy the product is to crush, chew or dissolve' and 'type of medication you are using'. Prescription opioid medications with abuse deterrent formulations are designed to increase the time and effort required to physically alter the medication, in turn reducing abuse via NONORAL routes [13]. These formulations have primarily focused on extended-release products which contain larger amounts of the active ingredient. To date, only one immediate-release prescription opioid has been granted Food and Drug Administration labeling related to abuse deterrence, yet immediate-release opioids account for roughly 90% of prescribed opioids. Immediate-release formulations are also the most preferred for NMU, reportedly due to the perceived immediacy and quality of the high from immediate-release products and the ease of use compared to extended-release products, particularly when manipulated for nonoral use [22]. The ease of use applies to PAPO as well, with immediate-release products readily available to chew, crush, cut, or dissolve prior to ingestion, accelerating the release of the active drug.

This is the first study to contextualize the role of prescription opioid NMU via PAPO in the substance use trajectory among the general US adult population. All previous studies sampled individuals with significant substance use history or who were in substance use treatment [8-13]. While there is not just one trajectory, one common trajectory among published studies is initiation with prescription opioid medications (typically via oral route) prior to initiation of illicit drugs. While our study does not address the order of initiation, polysubstance use is an indicator of severity of drug use. The PAPO group reported significantly higher polysubstance use than the INTACT group, and in turn the NONORAL groups reported significantly higher polysubstance use than the PAPO group. This suggests PAPO could be a critical transition regarding substances used along the trajectory. Along with substance transitions, route transitions can also be indicative of the severity of drug use. Oral use is the most reported route for prescription opioid NMU initiation [22], this would include oral INTACT as well as PAPO. In our study, 61.2% of PAPO, 37.9% of NONORAL, and 35.4% of PAPO + NONORAL never used prescription opioids for NMU via INTACT route. This suggests that one type of trajectory involves initiation of prescription opioid NMU via a higher-risk route of administration.

The strengths of this study include a large representative sample from a general population and granular stratification of prescription opioid NMU routes of administration (oral INTACT only, PAPO, and NONORAL). This is the first study to date to establish the elevated risks associated with PAPO. As with all observational studies, these data are subject to limitations that accompany self-report of historical behaviors. This study was not able to determine causality or influence of one's experience on future experiences or behavior. The frequency of prescription opioid NMU by route of administration was not measured in this study nor were the participants followed longitudinally to know if the INTACT group engaged in further transitions, presenting additional limitations in understanding the full trajectory of use within the study groups. However, by comparing the groups in this snapshot of data, we can identify those who may be at higher risk for transitioning to higher risk behaviors.

Conclusion

The profile of the PAPO group was highly consistent with that of the NONORAL group and significantly different than the INTACT group, and as such, PAPO should be considered a high-risk behavior and a potentially critical transition in substance use trajectories. This study did not allow for determination of causation yet suggests a greater likelihood of additional high-risk behaviors in those that engage in PAPO. These conclusions may be surprising to those who view nonoral routes (intranasal or intravenous use) as the first sign of problematic (or aberrant) behavior. However, these findings highlight why PAPO is not to be ignored and should be as concerning as nonoral use, with both PAPO and nonoral routes associated with underlying behavioral/mental health issues, polysubstance use, and other high-risk behaviors.

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