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Escalation of drug use in persons dually diagnosed with opioid and cocaine dependence: Gender comparison and dimensional predictors

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ABSTRACT

Background: Persons dually diagnosed with opioid and cocaine dependence (OD + CD) present a clinical challenge and are at risk of morbidity and mortality. The time of escalation of heroin and cocaine exposure in persons with OD + CD remain understudied, and the influence of gender and other variables have not been examined. This observational study focused on the time of escalation of heroin and cocaine in volunteers with OD + CD, examining gender and exposure to other drugs (e.g., cannabis or alcohol) as predictors. Ages of first use and of onset of heaviest use of each drug were collected (in whole years). Time of escalation was defined as the interval between age of first use and onset of heaviest use.

Volunteers: sequentially ascertained adult volunteers recruited from the New York Metropolitan area, of which n = 297 were diagnosed with OD + CD.

Methods: Instruments administered were the SCID-I diagnostic interview (DSM-IV criteria), BIS-11 impulsiveness scale, and KMSK scales, dimensional measures of maximal exposure to specific drugs.

Results: In volunteers with OD + CD, ages of onset of heaviest use of cannabis (median age = 15) and alcohol (median age = 19) were in adolescence or emerging adulthood and preceded those for heroin and cocaine (median ages = 26 and 25, respectively). Maximal levels of cannabis and alcohol exposure were high, in volunteers with OD + CD. In adjusted Cox regressions, gender was not a significant predictor of time of heroin or cocaine escalation. However, more rapid time of alcohol escalation was a predictor of more rapid time of escalation of both heroin and cocaine, in volunteers with OD + CD.

1. Introduction

Persons with dual opioid and cocaine use disorders present complex clinical and prognostic challenges. Dual use of heroin (and other mu-opioid agonists, including illicit prescription opioids) and cocaine, is linked to negative effects on health and elevated risk of drug overdose (Hedegaard et al., 2018; Kandel et al., 2017; Leri et al., 2004; Lorvick et al., 2018; Rodriguez-Cintas et al., 2016). The most recent data from the Centers of Disease Control and Prevention indicate that approximately one third of all opioid overdose deaths in 2018 also involved cocaine (Gladden et al., 2019). Therefore, study of dual exposure to mu-opioid agonists and cocaine continues to be important.

Few studies have explored the processes of escalation of heroin and cocaine use in persons with dual opioid and cocaine dependence (OD + CD) diagnoses. This dual diagnosis could be considered the most severe clinical presentation resulting from this pattern of poly-drug use (Rodriguez-Cintas et al., 2016). Other studies have examined, more broadly, persons with dual heroin and cocaine ***use***, which could encompass a broader range of severity (Bandettini Di Poggio et al., 2006; Leeman et al., 2016; Leri et al., 2004; Woodcock et al., 2015).

Escalation of drug intake has been examined extensively in preclinical studies (Zernig et al., 2007). Some operant self-administration studies in rodents found that females escalated intake of drugs faster than males (Becker, 2016; Roth and Carroll, 2004). Some, but not all, clinical studies indicate that females escalate their use of heroin more rapidly than males (also known as “telescoping”) (Anglin et al., 1987; Hernandez-Avila et al., 2004; Hines et al., 2017; Stoltman et al., 2015). Data on gender effects in escalation of cocaine are mixed (Haas and Peters, 2000; McCance-Katz et al., 1999; Wagner and Anthony, 2007), possibly due to differences in methodologies used to examine escalation

Abbreviations: 95%CL, 95% confidence limits; CB1-r, cannabinoid-1 receptor; CD, cocaine dependence diagnosis; IQR, inter-quartile range; KMSK score, Kreek-McHugh-Schluger-Kellogg score to measure maximal exposure to specific drugs; NS, non-significant; NV, normal volunteers; OD, opioid dependence diagnosis; OD + CD, volunteers with dual opioid and cocaine dependence diagnoses; OUD, opioid use disorder; SUD, substance use disorders

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and in the disease severity in the clinical populations studied. However, the relationship of gender with escalation of drug use in persons dually diagnosed with OD + CD has not been examined, to our knowledge.

Trait impulsivity has been examined for its association to opioid or cocaine use disorders, and persons with these SUD typically exhibit greater impulsivity than controls (Coffey et al., 2003; Moeller et al., 2001; Nielsen et al., 2012). Trait impulsivity has also been examined preclinically as a predictor of rapid escalation of heroin or cocaine intake (Anker et al., 2009; McNamara et al., 2010). However, there is only limited information on the association of trait impulsivity with escalation of drug use in persons with dual opioid and cocaine use disorders (Rodriguez-Cintas et al., 2016).

Exposure to mu-opioid agonists and cocaine can affect similar downstream systems (including dopaminergic and dynorphin/kappa-opioid receptor systems) (Becker et al., 2017; Di Chiara and Imperato, 1988; Martinez et al., 2019; Unterwald et al., 1994). Even so, rodent studies show that even within the same subject, sensitivity to the rewarding effects of mu-opioid agonists and cocaine can differ (Lenoir et al., 2012). Therefore, it is important to examine escalation of drug use in persons with dual opioid and cocaine use disorders (Kariisa et al., 2019).

Longitudinal studies show that cannabis or alcohol use disorders can be predictors of opioid or cocaine use disorders as categorical outcomes (Blanco et al., 2018; Florez-Salamanca et al., 2013; Olfson et al., 2018). One current emphasis of SUD research is to examine dimensional variables (i.e., variables that are studied along some form of a continuum) (Kwako et al., 2018; Yucel et al., 2018). However, little is known about the dimensional relationship between the use of cannabis and alcohol, and escalation of heroin and cocaine use, in persons diagnosed with OD + CD. The main goal of this study was therefore to examine the above variables as predictors of times of heroin and cocaine escalation, in volunteers with dual opioid and cocaine dependence diagnoses.

2. Materials and methods

This was an observational study of adult volunteers examined sequentially as outpatients in a research hospital in the greater New York City area. This was a secondary analysis of volunteers originally recruited and ascertained for genetic association studies of opioid and cocaine use disorders (see examples) (Bond et al., 1998; Levran et al., 2014).

2.1. Volunteers

Volunteers were recruited from the community in the New York City metropolitan area and from several local SUD treatment clinics. Ethnicity was obtained from a family history questionnaire (categorized as African American, Hispanic, Caucasian and "Other"). Gender (Male/Female) was categorized by self-report. The main outcome studied here was the presence of DSM-IV diagnoses of both opioid and cocaine dependence (i.e., OD + CD), which can be considered a "composite" endpoint (de Mutsert et al., 2009).

2.1.1. Recruitment, inclusion and exclusion criteria

This study follows the recommendations for Human Subjects Policies and Guidance of the National Institutes of Health. The Rockefeller University Hospital Institutional Review Board (IRB) approved the study protocol. In accordance with the Declaration of Helsinki, written informed consent was collected from all volunteers. Recruitment of male and female volunteers (≥ 18 years of age) was carried out through IRB-approved postings in community newspapers and in local SUD treatment centers. **Inclusion Criteria:** Volunteers were required to be able to understand study procedures and understand and sign the IRB-approved informed consent in English. **Exclusion criteria:** If there were acute or chronic conditions that prevented the individual from actively and accurately participating in the interview (e.g., psychotic symptoms, or signs of intoxication), they were excluded.

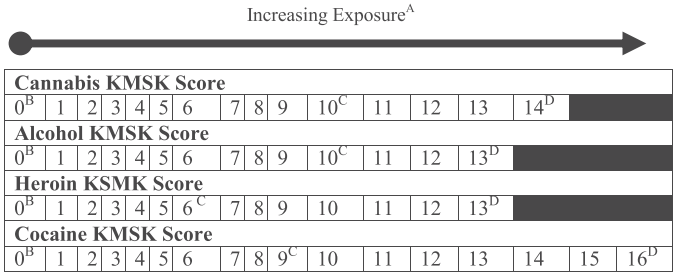
2.2. Instruments administered during clinical interviews

Each volunteer underwent a standardized in-person private interview with a trained clinician (e.g., physician, clinical psychologist, nurse practitioner or registered nurse), with all instruments and verbal communication in English. During the interview, the following instruments were administered:

The **SCID-I/P structured interview** (Version 2.0; DSM-IV criteria) (First et al., 2002) was used for categorical diagnoses. The main diagnostic categories studied here (i.e., opioid and cocaine dependence) were based on this instrument. The SCID-I instrument did not have a module for tobacco/nicotine dependence; therefore, tobacco data was not analyzed herein.

The BIS-11 trait impulsivity scale (Patton et al., 1995) was used to measure self-reported trait impulsivity. Scores in the BIS-11 scale range from 30 to 120 (low to high trait impulsivity).

The **Kreek-McHugh-Schluger-Kellogg (KMSK)** scales provide dimensional measures of maximal self-exposure to specific drugs



[A] The overall KMSK score is the composite of three sub-scores (measuring the *frequency*, *amount* and *duration* of drug use). The scales were constructed with specific adaptations for each drug (e.g., due to the different frequencies of use that can occur for heroin versus cocaine). Therefore, the overall range of KMSK scores is not identical among drugs.

[B] Score 0 = No exposure; never used

[C] Optimal "cutpoint" for drug dependence diagnosis, by DSM-IV criteria

[D] Maximal score for each scale

Fig. 1. Description of cannabis, alcohol, heroin and cocaine KMSK scales. KMSK scores are on an ordinal integer scale and focus on the time in a volunteer's life when use is the heaviest.
[A]The overall KMSK score is the composite of three sub-scores (measuring the *frequency*, *amount* and *duration* of drug use). The scales were constructed with specific adaptations for each drug (e.g., due to the different frequencies of use that can occur for heroin versus cocaine). Therefore, the overall range of KMSK scores is not identical among drugs.
[B]Score 0 = No exposure; never used.
[C]Optimal "cutpoint" for drug dependence diagnosis, by DSM-IV criteria.
[D]Maximal score for each scale.

(cannabis, alcohol, heroin and cocaine, in this study). KMSK scales can be completed rapidly ($\leq$5 min per drug) and characterize exposure to a drug at the point in the volunteer's life when use was at its heaviest. The KMSK score for each drug is on an ordinal integer scale, with "0" denoting no exposure (never used) and increasing up to a maximum (i.e., 14 for cannabis, 13 for alcohol and heroin, and 16 for cocaine; see Fig. 1 for a brief description) (Butelman et al., 2018a; Kellogg et al., 2003; Tang et al., 2011). The overall KMSK score is the composite of three sub-scores measuring the *frequency*, *amount* and *duration* of drug use. The KMSK scale was constructed with specific adaptations for each drug (e.g., due to the different frequencies of use that can occur for heroin versus cocaine). Therefore, the overall range of KMSK scores is not identical among drugs (Fig. 1). The high concurrent validity of KMSK scores with the respective DSM-IV dependence diagnoses was recently confirmed (Butelman et al., 2018a). This instrument also collects two age-related "milestones": **age of first use** of a drug, and **age of onset of heaviest use** (in whole years). We then calculated **time of escalation** as: the age of onset of heaviest use minus the age of first use. The full text of the KMSK scales is available at http://lab.rockefeller.edu/kreek/kmsk, and also in a recent publication (Butelman et al., 2018a).

2.3. Statistical analyses

If there were missing data for a within-subject analysis, all data for the volunteer were removed. The p-value for significance was set at the $p \leq 0.05$ level.

2.3.1. Univariate unadjusted analyses

GraphPad Prism software (v. 8) was used for univariate analyses. Demographic variables (age at ascertainment, gender and ethnicity) and other measures were analyzed non-parametrically (i.e., Mann-Whitney U tests, χ^2 analyses, Kruskal-Wallis ANOVA, Friedman's ANOVA). Times of escalation were analyzed with unadjusted survival analyses (log-rank tests) comparing males and females. Preliminary analyses also included Spearman correlations of the potential predictors (i.e., BIS-11 impulsiveness scores, cannabis and alcohol KMSK scores, and cannabis and alcohol times of escalation) to the two outcomes, times of heroin or cocaine escalation. Based on these preliminary results, we then examined time of alcohol escalation data as tertiles, defined as "fast," "medium" and "slow". These tertiles for time of alcohol escalation (in whole years) were designed to avoid overlap, and thus deviate slightly in their "n".

2.3.2. Multivariate adjusted analyses

Two multivariate Cox regressions with a time-varying covariate were carried out with SPSS software. The outcomes for these two regressions were: 1) time of heroin escalation (years), and 2) time of cocaine escalation (years). Based on the demographics and preliminary analyses, each of these regressions examined the following predictors: a) age of ascertainment (years; time-varying covariate), b) gender (females as the reference category), c) ethnicity (Caucasian as reference category), d) time of alcohol escalation (years).

3. Results

3.1. Demographics

We present demographic data for all volunteers with OD + CD (n = 297), stratified by gender (Table 1a). The age at ascertainment for males (mean = 44.43) was not significantly different from that of females (mean = 43.50; Mann-Whitney U = 9738; N.S.). A contingency analysis of ethnicity ($\chi^2 = 10.16$, $p = 0.0173$) was significant. Table 1b shows other measures for the volunteers with OD + CD. BIS-11 trait impulsivity scores (Mann-Whitney U = 3963; N.S.) did not differ across gender.

3.1.1. Exposure to cannabis and alcohol

Volunteers with OD + CD had high median cannabis KMSK scores (Table 1b), with a majority having scores above the optimal "cutpoint" for a DSM-IV cannabis dependence diagnosis (Fig. 1) (Butelman et al., 2018a). Males had significantly higher cannabis KMSK scores than females (U = 7,440, $p < 0.001$). The median alcohol KMSK scores in volunteers with OD + CD were also high (Table 1b), with a majority having scores above the optimal "cutpoint" for a DSM-IV alcohol dependence diagnosis (Fig. 1) (Butelman et al., 2018a), without a significant gender difference. Times of escalation of cannabis and alcohol did not differ across gender (Table 1b).

3.1.2. Exposure to heroin and cocaine

As expected, volunteers with OD + CD diagnoses had high heroin (median = 11; IQR:9-13) and cocaine (median = 16; IQR:13-16) KMSK scores (not shown; see scale ranges in Fig. 1) (Butelman et al., 2018a). There were no gender differences in heroin or cocaine KMSK scores in volunteers with OD + CD (not shown). Times of escalation of heroin and cocaine are further analyzed below (3.3).

3.2. Ages of first use and onset of heaviest use of drugs in volunteers with OD + CD

Age of first use of drugs: A Friedman's ANOVA was significant for age of first use across the four drugs, in each gender (Table 2). The median ages of first use of cannabis and alcohol were in adolescence and did not differ from each other (Table 2). Ages of first use of heroin and cocaine occurred significantly later (Table 2). Ages of first use of heroin and cocaine did not differ from each other. Males had an earlier age of first use of cannabis than females (Log-rank test; $\chi^2 = 6.51$, $p = 0.011$). By contrast, there were no gender differences in age of first use of alcohol, heroin or cocaine.

Ages of onset of heaviest use of drugs: A Friedman's ANOVA was significant for age of onset of heaviest use across the four drugs in each gender (see Fig. 2). Dunn's post-hoc tests showed that the onset of heaviest use of cannabis preceded that for alcohol. Age of onset of heaviest use of both cannabis and alcohol preceded those for cocaine and heroin. The ages of onset of heaviest use of cocaine and heroin did not differ from each other. No gender differences were observed in this sequence.

3.3. Escalation of drug use in volunteers with OD + CD

3.3.1. Univariate analyses of time of escalation

Time of escalation of each drug was defined as: age of onset of heaviest use minus age of first use (in years). Thus, the most rapid possible time of escalation with this measure was "0" years; indicating that first use and onset of heaviest use of cannabis occurred within the same year (see Table 1b and Fig. 3).

We first carried out a univariate analysis of times of escalation of the four drugs under study, stratified by gender. In males, a Friedman's ANOVA was significant ($F = 47.04$; $p < 0.0001$; all data available from n = 91). Dunn's post-hoc tests in males indicate that the time of cannabis escalation was more rapid than those of alcohol, heroin or cocaine. In females, a Friedman's ANOVA was also significant ($F = 38.48$; $p < 0.0001$; all data available from n = 41). Dunn's post-hoc tests in females indicate that the time of cannabis escalation was more rapid than those of alcohol or cocaine; also the time of escalation of heroin was faster than that of alcohol.

We also compared the time of heroin and cocaine escalation across gender. An unadjusted survival analysis showed a significantly faster escalation of heroin use in females (Log-rank test; $p = 0.011$) (Fig. 3). By contrast, a similar analysis did not detect a gender difference in time of escalation of cocaine use (Fig. 3).

In preliminary analyses, we found that of the variables under study (i.e., in Table 1b), only time of alcohol escalation was correlated with

Table 1
Demographics (Volunteers with OD + CD, ascertained sequentially from April 2002 to July 2018).

Table 1a. Basic Demographic Data

		Male (Total n = 184)	Female (Total n = 113)	Mann-Whitney U or χ^2 [df]; p-value
Mean Age at Ascertainment (95% CI)		44.43 (42.84-46.02)	43.50 (41.88-45.13)	U = 9738, N.S.
Ethnicity n (% of total)	**African American**	76 (41.3%)	59 (52.2%)	χ^2 = 10.16 [3], p = 0.0173
	Caucasian	45 (24.5%)	25 (22.1%)	
	Hispanic	53 (28.8%)	17 (15.0%)	
	Other	10 (5.4%)	12 (10.6%)	

Table 1b.[A] Behavioral measures: Median (IQR)

BIS-11 trait impulsivity score	64.5 (58.8-72.0)	n = 114	67.0 (58.0-72.5)	n = 72	U = 3963, N.S.
Cannabis KMSK score (Range 0-14)[B]	13 (11-14)	n=176	11.5 (3-14)	n = 110	U = 7440, p < 0.001
Time of Cannabis Escalation (years)[C]	0 (0-2)	n = 110	0 (0-0)	n = 60	Log-rank test = 3.16; N.S.
Alcohol KMSK score (Range 0-13)[B]	12 (9-13)	n=182	12 (9-13)	n = 112	U = 9840, N.S.
Time of Alcohol Escalation (years)[C]	6 (1-14)	n = 158	8 (0-17)	n = 87	Log-rank test = 0.990; N.S.

[A] "n" values do not match the totals in Table 1a, due to missing data for specific measures.
[B] KMSK scales measure maximal drug exposure and are described in Fig. 1.
[C] Time of escalation is defined as: Age of onset of heaviest use of a drug – age of first use (in whole years).

Table 2
Ages of first use of cannabis, alcohol, heroin and cocaine in volunteers with OD + CD[a].

	Males (n = 110) Median age of first use (IQR)	Females (n = 54) Median age of first use (IQR)	Log-rank test (p-value)
Cannabis	14.0 (12-15)	14.5 (13-16)	p = 0.011
Alcohol	13.0 (12-15)	13.0 (12-15)	N.S.
Heroin	19.0 (17-25)	21.0 (18-28)	N.S.
Cocaine	18.0 (16-22)	19.5 (17-24.25)	N.S.
Friedman's ANOVA; p-value	214.5; p < 0.0001	77.2; p < 0.0001	
Dunn's Tests	Cannabis < Heroin Cannabis < Cocaine Alcohol < Heroin Alcohol < Cocaine	Cannabis < Heroin Cannabis < Cocaine Alcohol < Heroin Alcohol < Cocaine	

[a] Volunteers were excluded from this repeated measures analysis if their age of first use was not available for all four substances.

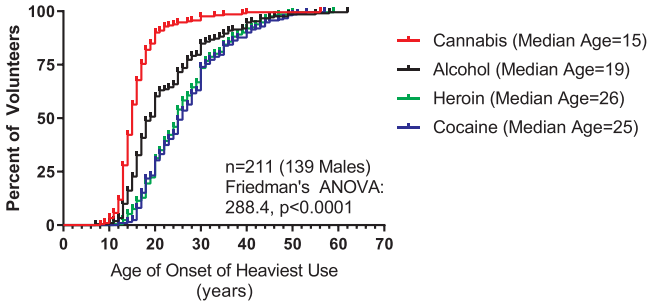


Fig. 2. Survival curves for ages of onset of heaviest use of cannabis, alcohol, heroin and cocaine, in volunteers with OD + CD (males and females; upper and lower panels, respectively). Data were analyzed with Friedman's ANOVAs. Volunteers were excluded from this repeated measures analysis if their age of onset of heaviest use was not available for all four substances.

the outcomes of the study. Thus, time of alcohol escalation was positively correlated with time of escalation of both heroin and cocaine (Spearman correlations; not shown). We then examined this effect graphically, by plotting times of heroin and cocaine escalation, across tertiles for time of alcohol escalation (i.e., defined as "fast," "medium" and "slow" time of alcohol escalation) (Fig. 4). Tertiles were structured to the nearest whole year, while avoiding overlap (therefore, "n" values deviate slightly across the three categories). Unadjusted survival

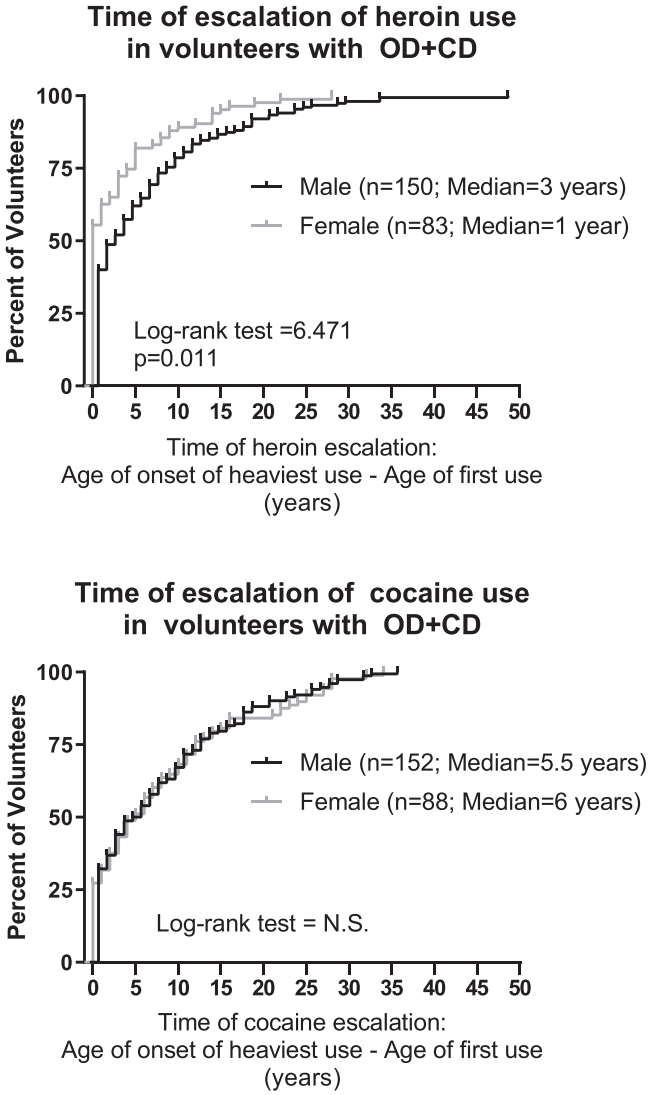


Fig. 3. Unadjusted survival curves for times of escalation of heroin and of cocaine use, in volunteers with OD + CD (males and females; upper and lower panels, respectively). Data were analyzed with Log-rank tests.

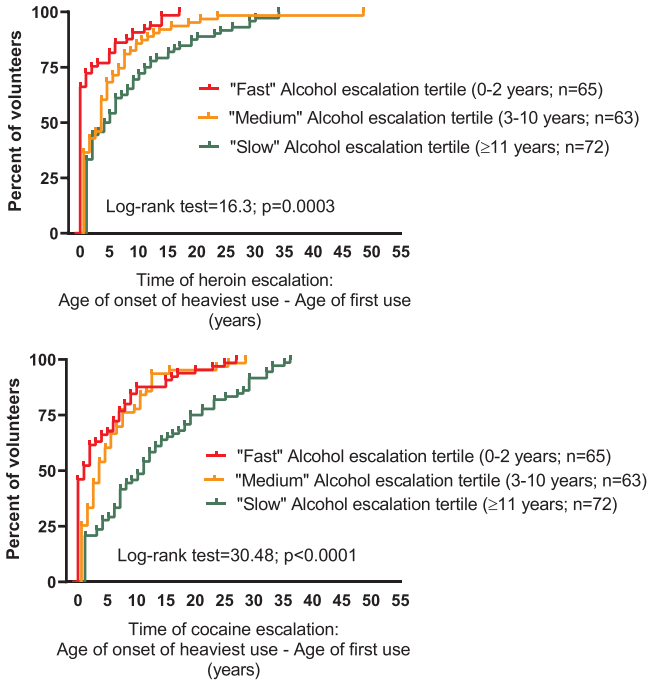


Fig. 4. Unadjusted survival curves for times of escalation of heroin and cocaine use (upper and lower panels, respectively), as a function of time of alcohol escalation, in volunteers with OD + CD. Volunteers were divided into tertiles for "fast," "medium" and "slow" times of alcohol escalation. Tertiles were built to the nearest whole year, avoiding overlap in values across the three escalation categories (therefore, "n" values deviate slightly across the tertiles). Data were analyzed with Log-rank tests.

analyses were significant, indicating that the volunteers in the "fast," "medium" and "slow" tertiles for time of alcohol escalation exhibited progressively longer times of heroin and cocaine escalation.

3.3.2. Multivariate adjusted Cox regressions, for time of heroin and cocaine escalation

Cox regression for time of heroin escalation as the outcome: Time of alcohol escalation was a significant predictor of time of heroin escalation ($p = 0.031$) (Table 3). That is, longer time of alcohol escalation was a predictor of longer time of heroin escalation. In this adjusted analysis, gender was not a significant predictor (adjusted $p = 0.061$; above the α level).

Cox regression for time of cocaine escalation as the outcome: Time of alcohol escalation was also a significant predictor of time of cocaine escalation ($p < 0.0001$) (Table 4). As above, a longer time of alcohol escalation was a predictor of longer time of cocaine escalation. Gender was not a significant predictor of time of cocaine escalation (adjusted $p = 0.466$).

4. Discussion

To our knowledge, this is one of the first studies to examine gender, trait impulsivity and dimensional measures of drug exposure and time of escalation in volunteers dually diagnosed with opioid and cocaine dependence. This dual diagnosis can be considered the most severe clinical presentation of a relatively common and highly morbid pattern of use of heroin and cocaine (Gladden et al., 2019).

4.1. Levels of exposure to drugs in volunteers with OD + CD

We found that median cannabis and alcohol KMSK scores were relatively high in these volunteers with OD + CD, with the majority having scores above the optimal "cutpoint" for DSM-IV cannabis or alcohol dependence diagnoses (Butelman et al., 2018b). These data are consistent with the known comorbidity of cannabis and alcohol use disorders with opioid or cocaine use disorders (Hayley et al., 2017; Olfson et al., 2018), and add new dimensional information of relevance to persons dually diagnosed with OD + CD.

4.2. Ages of first use and onset of heaviest use of drugs in volunteers with OD + CD

As expected, first use of both cannabis and alcohol occurred in adolescence, whereas first use of cocaine and heroin occurred in the transition from adolescence to emerging adulthood (Lynskey and Agrawal, 2018). However, the age of onset of heaviest use of cannabis (median age = 15) occurred earlier than for alcohol (median age = 19–20), and both of the aforementioned ages preceded those for heroin and cocaine, which occurred at ages 25-28. These data are consistent with prior reports (Butelman et al., 2018b; Rodriguez-Cintas et al., 2016), and add to our knowledge of early non-normative processes (i.e., heavy adolescent exposure to both cannabis and alcohol) that occur in persons who are later diagnosed with OD + CD.

4.3. Time of escalation of cannabis, alcohol, heroin and cocaine, in volunteers with OD + CD

We found some gender-specific profiles in the time of escalation across the four drugs studied here. In males, time of escalation of cannabis was more rapid than those of alcohol, heroin and cocaine (thus, median time of cannabis escalation was "0" years, whereas longer times were observed for the other drugs). In females, time of cannabis escalation was significantly faster than those of alcohol and cocaine, but not heroin. To our knowledge, these are the first comparative data on the times of escalation of these major drugs in volunteers dually diagnosed with OD + CD (Rodriguez-Cintas et al., 2016). We found that overall, cannabis escalation was relatively rapid in this clinical group and exhibited less variability than escalation of the other drugs. There is limited preclinical data available on escalation of intake of the main psychoactive component of cannabis (i.e., delta-9-THC) (Justinova et al., 2003). We found that the escalation of cannabis use occurred mostly in adolescence in these volunteers with OD + CD. However, it is unknown if the rapidity of cannabis escalation observed in humans with OD + CD is due to drug-specific or developmental factors (Chen et al., 2009; Wagner and Anthony, 2002).

Table 3
Adjusted Cox regression for time of heroin escalation, in volunteers with OD + CD.

Predictors		Hazard Ratios (95% CL)	p-value
Age at Ascertainment (years; time-varying covariate)		0.999 (0.981-1.018)	N.S.
Gender (Females as reference category)	**Males**	0.754 (0.561-1.013)	N.S.
Ethnicity (Caucasians as reference category)	**African American**	0.937 (0.641-1.368)	N.S.
	Hispanic	0.929 (0.626-1.377)	N.S.
	Other	1.208 (0.664-2.200)	N.S.
Time of alcohol escalation (years)		0.983 (0.968-0.998)	0.031

Table 4
Adjusted Cox regression for time of cocaine escalation, in volunteers with OD + CD.

Predictors		Hazard Ratios (95% CL)	p-value
Age at ascertainment (years; time varying covariate)		0.984 (0.965-1.004)	N.S.
Gender (Females as reference category)	**Males**	1.111 (0.838-1.472)	N.S.
Ethnicity (Caucasians as reference category)	**African American**	1.276 (0.885-1.842)	N.S.
	Hispanic	1.140 (0.769-1.692)	N.S.
	Other	1.176 (0.652-2.121)	N.S.
Time of alcohol escalation (years)		0.965 (0.950-0.981)	$p < 0.0001$

4.4. Predictors of time of heroin and cocaine escalation in volunteers with OD + CD

In two adjusted analyses, we found that longer time of alcohol escalation was associated with longer time of both heroin and cocaine escalation, in volunteers with OD + CD. To our knowledge, this is the first study to identify time of alcohol escalation as a predictor of heroin and cocaine escalation in such dually diagnosed persons. Preclinical studies show that escalation of alcohol intake can depend on several behavioral and neurobiological mechanisms (Kimbrough et al., 2017; Vendruscolo et al., 2012; Walker et al., 2012). Genetic, neurobiological, behavioral and environmental factors have also been implicated in escalation of alcohol use in humans (Huggett et al., 2018; Kapitau et al., 2019; Whelan et al., 2014). Based on the present findings, it would be of value to determine if there are shared underlying mechanisms in escalation of alcohol, mu-opioid agonists and cocaine use, in humans. By contrast, unadjusted analyses showed that time of cannabis escalation was not correlated with time of either heroin or cocaine escalation. However, it should be noted that time of escalation of cannabis was quite rapid overall and exhibited relatively small variability, compared to those of the other drugs (section 4.3).

In an unadjusted analysis, females were found to escalate heroin use faster than males. However, this finding was not preserved in the adjusted analysis, suggesting that this gender difference was not robust, in persons diagnosed with OD + CD. Some, but not all, studies have reported that females escalate heroin use, or enter treatment, more rapidly than males (Anglin et al., 1987; Hernandez-Avila et al., 2004; Hines et al., 2017; O'Keefe et al., 2016; Stoltman et al., 2015). Gender was not a significant predictor of the time of cocaine escalation, either in unadjusted or adjusted analyses. The magnitude of gender differences in escalation of cocaine also varies between studies (Haas and Peters, 2000; McCance-Katz et al., 1999; Wagner and Anthony, 2007). It is possible that some of these apparent differences are due to methodological variations between studies, including variations in severity of drug use. Overall, this is one of the first gender-based analyses of escalation, in persons dually diagnosed with opioid and cocaine dependence.

4.5. Limitations and design considerations

This observational study has several strengths, but also limitations. This type of design cannot exclude recall bias, and causality of predictors cannot be inferred. Age-related measures were obtained in whole years; therefore, we cannot exclude that measurements with greater precision (e.g., in months) could have uncovered further findings. Likewise, it is possible that other measures of trait impulsivity, as opposed to BIS-11 scores, could have been correlated with time of heroin or cocaine escalation.

Based on the SCID-I interview, other psychiatric diagnoses for these volunteers were also obtained, with depression being the most common lifetime comorbidity (Butelman et al., 2017). However, we do not have systematic data on the onset of depression compared to the age trajectory of drug use. Therefore, we could not enter depression comorbidity as predictor in the adjusted models, as it is known that such comorbidities could precede or follow the onset of specific substance use disorders (Maremmani et al., 2011). In a follow-up, we determined that in these volunteers with OD + CD, there was considerable comorbidity with a lifetime depression diagnosis overall (35.9% of volunteers), and this was greater in females than males (46.4% vs 29.2% respectively; chi-square test = 8.4, p = 0.003; not shown). Such psychiatric comorbidity has been examined in the trajectory of both opioid and cocaine use disorders (Marel et al., 2019; Martins and Gorelick, 2011).

This study used DSM-IV opioid and cocaine dependence diagnoses, as recruitment commenced prior to the adoption of the DSM-5 system. The analogous DSM-5 diagnoses (e.g., "moderate" and "severe" heroin or cocaine use disorders) are thought to be highly congruent with the respective DSM-IV dependence diagnoses (Hasin et al., 2013). Therefore, it is likely that these findings would hold if the relevant DSM-5 diagnoses were to be studied.

5. Conclusions

Using a simple dimensional instrument, we found that persons with a dual diagnosis of OD + CD (Hedegaard et al., 2018; Lorvick et al., 2018), tended to have a history of heavy adolescent exposure to both cannabis and alcohol. The age of onset of heaviest use of cannabis preceded that for alcohol. Furthermore, ages of onset of heaviest use of cannabis and alcohol both preceded those for heroin and cocaine. Intriguingly, gender was not robustly associated with times of heroin or cocaine escalation. We found for the first time that rapid alcohol escalation was a dimensional predictor of rapid escalation of both heroin and cocaine use. Overall, this study suggests that rapid adolescent escalation of alcohol use may be a potential vulnerability factor for rapid escalation of dual opioid and cocaine use. Future studies could thus examine this as a potential target for prevention and early intervention approaches, as well as mechanistic investigations.

Contributors

All authors designed the study. Statistical analyses and data preparation were completed by ERB and CYC. All authors were involved in article preparation. Funding sources had no involvement in the design, analysis or preparation of the article.

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Declaration of Competing Interest

No conflict declared.

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