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Female-male differences in prescription pain reliever dependence levels: Evidence on newly incident adolescent and young adult users in the United States, 2002–2014

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ABSTRACT

Background: A comprehensive epidemiology of dependence on prescription opioid pain relievers requires evidence about age-specific female-male differences, possibly manifest during adolescent and early adult years. In this study, we identified newly incident extra-medical users of prescription pain relievers (EMPPR), all observed with onsets before the 22nd birthday. We then quantified female-male differences in clinical features or manifestations of opioid dependence (OD), devised a measurement-equivalent OD dimension, and estimated age-specific female-male differences in OD levels.

Method: The population under study included 12-to-21-year-old non-institutionalized civilian community residents of United States sampled for recent nation-scale surveys. Confidential computer-assisted self-interviews identified newly incident EMPPR users (n = 10,188). Analysis-weighted estimation procedures yielded cumulative incidence proportions for each OD feature, evaluated measurement non-equivalence across subgroups, and estimated female-male differences age-by-age.

Results: (1) Tolerance and salience ('spending a lot of time') are most common OD features. (2) Measurement non-equivalence (bias) was found across sex- and onset-age groups. (3) With biasing features removed, we can see elevated OD levels for female new initiates, age-by-age. Subsidiary analyses suggested possibly accelerated progression toward higher OD levels when extra-medical PPR use starts before age 18.

Conclusions: Dimensional approaches to OD and other drug use disorders have gained popularity but can be fragile when differential measurement biases are left uncontrolled. This study's bias-corrected dimensional view of female-male differences shows elevated OD levels among newly incident female EMPPR users relative to new male initiates. Future studies can check for accelerated progression to higher OD levels when EM use starts before age 18 years.

1. Introduction

This study's point of departure is the international consensus description of an opioid dependence syndrome (OD) occurring after extra-medical use of prescription pain relievers (i.e., without appropriate medical supervision), as substantiated in past and proposed versions of the International Classification of Diseases (ICD). Historical origins of this syndrome include 'morphinismus ('morphinism')' and 'morbid craving for morphia' described as a general medical syndrome by Levinstein (1878), with the more contemporary case definitions of the past four decades influenced by an Edwards-Gross dimensional view of 'alcohol dependence syndrome' (Edwards, 1986; Edwards and Gross, 1976).

Within the contemporary ICD, the OD construct is not too distant from the DSM-IV OD construct in the American Psychiatric Association Diagnostic and Statistical Manual, Fourth Edition, DSM-IV (American Psychiatric Association, 2000). OD vestiges can be seen in the DSM Fifth Edition's construct of 'opioid use disorders' (OUD; DSM-5). DSM-5 also is noteworthy in its specification of an OUD severity evaluation in terms of a simple unweighted counting up of clinical features that indicate fulfillment of diagnostic criteria (American Psychiatric Association, 2013).

A comprehensive or systematic review is not appropriate for this empirical research report, but any potted history of female-male variations in OD epidemiology before the 21st century will include several observations. First, depending upon opioids under study, there

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generally was a traditional male excess among reported OD cases (e.g., opium compounds, morphine) (Shand et al., 2011; Warner et al., 1995).

Second, a shift in female-male ratios in the US may have occurred late in the 19th century. During those years, unscrupulous 19th century patent medicine vendors were allowed to market non-prescription opioid-containing products without disclosing opioid contents. Women might have been more likely to use these products and then to be maintained by physicians allowed to prescribe opioids under a liberal regime (Calkins, 1871; Levinstein, 1878; Terry and Pellens, 1928).

Third, respected authorities such as O'Donnell (1969) considered his unit's studies of patients admitted to US federal hospitals and wondered about biases against women being recognized and admitted to these facilities. He also entertained a possibility that women (but not men) might be more conforming in response to opioid-restrictive US laws.

Fourth, by 1975, other respected authorities such as DeFleur (2006) had analyzed the same biases and had concluded that official statistics in the US were of little value when studying female-male variations. It is noteworthy that this sentiment was not expressed in the United Kingdom, where Home Office registry statistics disclosed that roughly one-third of opioid treatment cases were female. Perhaps reflective of DeFleur's sentiment, Clausen (1957) had declined to discuss female-male variations in his overview of social and psychological processes leading toward OD in the US.

Fifth, important OD studies of that era focused exclusively on males and generally included no females in their samples (Ball and Chambers, 1970; Chein et al., 1964; Clayton and Voss, 1981; O'Donnell et al., 1976; Robins et al., 1974; Vaillant, 1966). O'Donnell et al. (1976) justified exclusion of women from an early nationwide epidemiological survey as follows: "…. the number of drug users would be limited and might be too small to permit the derivation of stable estimates."

Sixth, during the 1960s and 1970s, in the US, United Kingdom, Sweden, and elsewhere, official treatment statistics and registry data showed an increased proportion of female cases among all OD admissions, perhaps as a manifestation of increased outpatient OD treatment options and outreach programs (e.g., see Bejerot, 1972; Rootman, 1972). In addition, during that era, a female preponderance was discovered in US nation-wide community surveys of recently active psychotherapeutic drug use. Nevertheless, at that time, the use of prescription and over-the-counter medicines with the adjective 'psychotherapeutic' was defined to encompass relief of 'psychic distress.' The use of opioid prescription pain relievers was declared to be outside the boundaries of 'psychotherapeutic' use as defined by those researchers (Parry et al., 1973).

Seventh, once the sample designs for US community surveys of local areas and of national scope were re-specified to include women as well as men, general impressions about female-male ratios of OD cases began to shift. Examples of recent surveys with relatively balanced female-ratios of both prevalent and newly incident occurrence of OD include Parker et al. (2018) and Vsevolozhskaya and Anthony (2015). Notwithstanding these US estimates, a recent global burden of disease report suggested a higher OD prevalence among males in most regions of the world, including in East Asia (Degenhardt et al., 2014).

Against this background of epidemiological evidence on a general male excess in population-level statistics on the occurrence of opioid dependence, we identified several reports on the possibility that females might progress toward opioid dependence and treatment entries with a more prominent and accelerated course once use of prescription pain relievers begins outside the boundaries of appropriate medically supervised use (i.e., 'extra-medical' use as defined by Parker and Anthony, 2015; Hernandez-Avila et al., 2004; Katz et al., 2013; Kerridge et al., 2015).

Given that female-male variations are crucially important elements in any comprehensive review of opioid dependence epidemiology, we wondered whether a mixed pattern of epidemiological survey evidence about female-male variations might be traced to measurement errors or biases. After all, the traditional categorical approaches to diagnosis of OD and OUD (including DSM-5 specifications) require a counting up of OD/OUD manifestations and give an equal weight to each manifestation so as to create a severity gradient across 'mild' versus 'moderate' versus 'severe' values. Despite cost-efficiency and utility of this clinical diagnostic approach with equivalent weights given to each OD/OUD manifestation, this equal weighting approach might create measurement-related biases or distortions if the intent is to make comparisons of mean levels of opioid dependence across population subgroups, including contrasts of females who have just started to use PPR extra-medically versus male counterparts.

This mixed pattern of evidence about female-male variations and the recently published studies prompted the current investigation of female-male variations in mean levels of opioid dependence processes as observed soon after onset of extra-medical use of prescription pain relievers. Whereas prior US epidemiological studies have produced estimates for the categorical diagnostic OD and OUD categories, in this research project, we shifted from the categorical approach to an increasingly popular dimensional approach (Becker and Hu, 2008; Degenhardt et al., 2014; Kerridge et al., 2015; Martins et al., 2017; McCabe et al., 2013; Parker and Anthony, 2015; Vsevolozhskaya and Anthony, 2015; Wu et al., 2011).

As we reviewed the published literature in preparation for this research project, we were surprised to find the mixed epidemiological results and a puzzling gap in published estimates on whether males or females in the US might be similar or different in terms of vulnerability or susceptibility to transition from an initial extra-medical use of an opioid prescription pain reliever and to become a newly incident case of opioid dependence or opioid use disorder. For the most part, the published evidence is based on prevalence proportions– i.e., estimated prevalence of being a recently active OD/OUD case. For example, studying recently active cases of opioid use disorders as defined in the Fourth Edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV; American Psychiatric Association, 1994), John et al. found a preponderance of females among OUD cases seen in US emergency medicine departments (John and Wu, 2019). In one of the few published articles on the incidence and risk of becoming an OD or OUD case, Vsevolozhskaya and Anthony (2015) noted that there might be a female excess in the probability of transitioning quickly and becoming a case of DSM-IV opioid dependence soon after the onset of extra-medical use of prescription pain relievers (EMPPR); however, small numbers of newly incident cases precluded resolution of this issue.

Nevertheless, virtually all of the other US epidemiological studies of female-male differences in OD/OUD prevalence proportions and incidence rates have suggested either no female-male variations or a modest male excess in steps leading from initial EMPPR use toward formation of OD/OUD syndromes. For example, Becker et al. (2008) reported a modest male preponderance among recently active cases of DSM-IV opioid use disorders. Martins et al. (2017) found a larger proportion of males among initiates but mentioned no female-male variation in prevalence proportions for DSM-IV opioid dependence or other OUD. Virtually all of the other published articles on this epidemiological topic provide evidence of little or no female-male imbalances in vulnerability or susceptibility to progress from initial EMPPR use onward toward an opioid dependence syndrome or other OUD or do not comment on female-male variations (e.g., see Degenhardt et al., 2014; Kerridge et al., 2015; Parker and Anthony, 2015; Wu et al., 2011).

Concerned that there might have been a neglect of potential female-male variations in vulnerability or susceptibility differences in what happens after the first extra-medical use of a prescription pain reliever, we were prompted to wonder about measurement issues. Again, to repeat what already has been stated, the recent diagnostic formulations utilize a simple counting up of observed criteria of opioid use disorders. For diagnosis, each manifestation is given what is essentially an equal weight.

2. Materials and methods

2.1. Study population and sample

The population under study encompassed non-institutionalized civilian residents aged 12 to 21 years living in all 50 States and the District of Columbia of the United States (US), as sampled for National Surveys on Drug Use and Health (NSDUH), with field operations conducted from 2002 through 2014. Due to changes in NSDUH assessments in 2015, we could not combine 2015–2017 NSDUH data with the 2002–2014 data. Please see Supplementary Information 1 for more details.

Each NSDUH multi-stage probability sampling plan is designed to yield a nationally representative sample with oversampling of 12-to-17-year-olds (irrespective of school attendance). Sampling frames include non-household group quarters such as homeless shelters and college dormitories. NSDUH participant recruitment is via child assent and parental or adult consent, based upon protocols approved by cognizant human subjects protection committees. More than 30,000 12-to-21-year-old participants are included in each year's NSDUH sample (United States, 2014).

2.2. Assessment and measures

NSDUH confidential audio computer-assisted self-interviews (ACASI) assess histories of extra-medical PPR use, with questions for newly incident users about the month and year when the first extra-medical PPR use occurred. The ACASI approach was designed to promote reliability, accuracy, and truthfulness of participant reports about potentially sensitive behaviors and characteristics. Focus on newly incident users means long-term memory errors and reporting artefacts are constrained. PPRs in this study include the following drugs that require a doctor's prescription (as provided to the participants by NSDUH assessment): Darvocet, Darvon, Tylenol with codeine, Percocet, Percodan, Tylox, Vicodin®, Lortab, Lorcet, Codeine, Demerol, Dilaudid, Fioricet, Fiorinal, Hydrocodone, Methadone, Morphine, Oxycontin, Phenaphen, Propoxyphene, SK65, Stadol, Talacen, Talwin, Talwin-NX, Tramadol, and Ultram. All these PPRs contain opioids.

The key outcome variables measured in this study are seven preselected problems and experiences listed as clinical features of DSM-IV OD: 'tolerance', 'withdrawal', 'salience' (i.e., spending a lot of time getting, using, or getting over the effect of PPRs), 'difficulty cutting down', 'using more than intended', 'using despite physical or psychological problems', and 'giving up important activities for PPR use' (American Psychiatric Association, 1994). Supplementary Table S1 lists NSDUH questions for assessment of each clinical feature.

Sex (female-male) and age at first extra-medical PPR use are from the self-report self-interview. When skipped, NSDUH drew upon dwelling unit roster information to create variables for sex and age. Gender self-identification was not covered in NSDUH 2002–2014.

Newly incident PPR users are those who used PPR extra-medically for the first time during the 12 months prior to the assessment (Parker and Anthony, 2015, 2018). In aggregate, 10,448 12-to-21-year-old new extra-medical PPR users were identified, among whom 260 (2.5%) individuals had missing values on all seven clinical features of DSM-IV prescription OD. Therefore, the analytic sample consisted of 10,188 newly incident extra-medical PPR users pooled from 2002 to 2014.

2.3. Analysis

In the initial description steps, we produced analysis-weighted estimates of the occurrence of individual clinical features for female versus male new users in each of five age-of-onset strata. We then studied female-male variation in these estimates via generalized linear models with the logit link function.

Our first analytical steps consisted of multivariate modeling of dimensionally conceptualized OD levels that include measurement equivalence testing. Here, each of the inter-correlated seven clinical features is specified as a manifest indicator variable for a dimensional latent OD construct (Gelhorn et al., 2008; Jöreskog, 1971; Martin et al., 2006). We first assessed goodness of fit for a one-dimension OD latent construct for each of the 10 age-sex strata via inspection of the following fit indices: root mean square of approximation (RMSEA) (Steiger, 1990), comparative fit index (CFI) (Bentler, 1990), and Tucker-Lewis index (TLI) (Tucker and Lewis, 1973). Typically, an RMSEA < 0.05 and CFI/TLI > 0.95 serve as indications of reasonable model fit (Hu and Bentler, 1999; Muthén and Asparouhov, 2014) with all factor loadings (λ) greater than 0.40 (Ford et al., 1986).

Next, an adjusted chi-square test was used to compare two nested models: the full equivalence model (i.e., intercepts and slopes constrained to be equal across all subgroups; the scalar model) vs. full variance model (i.e., intercepts and slopes freely estimated for each subgroup; the configural model) (Kim and Yoon, 2011; Stark et al., 2006). If the adjusted chi-square test indicates measurement non-equivalence (i.e., $p < 0.05$), inspection of intercepts and λ slope estimates was conducted to investigate any clinical feature variable that might be functioning differentially across subgroups (Stark et al., 2006). Differential item functioning refers to differential probabilities in item responses across subgroups of individuals at the same level of PPR dependence. An example of differential item functioning involves girls asserting their experience of a remarkable opioid response (e.g., withdrawal) at a lower dependence level compared to boys. More detailed discussion of differential item functioning has been discussed in previous publications (e.g., Kim and Yoon, 2011; Stark et al., 2006). After dropping clinical feature indicator variables for which there is evidence suggesting differential functioning, we re-checked these measurement equivalence issues to achieve a calibrated result. After calibration, we conducted a multiple-group analysis to estimate female-male differences in the level of OD for each of the five age-of-onset groups using weighted least squares mean and variance adjusted estimators for estimation (WLSMV; Asparouhov and Muthén, 2010). This approach has been used to study female-male difference in the level of alcohol dependence in one of our previous publications, where more details about this analytical approach is provided (Cheng and Anthony, 2018a,b).

For this study's estimates, unless stated to the contrary, NSDUH-constructed analysis-weights account for differential selection probabilities and post-stratification adjustments to US Census distributions. Taylor series linearization variances account for interdependent observations due to complex sample design features.

3. Results

Table 1 shows the estimated occurrence of each clinical feature of OD for 10 age-of-onset- and sex-strata of newly incident extra-medical PPR users. In all subgroups, 'tolerance' and 'salience' are the two most common clinical features observed within 12 months after first extra-medical use (Table 1). Fig. 1 shows female-male ratios of the seven clinical features of OD among newly incident PPR users by age-of-onset groups. Point estimates show a dominant pattern of higher occurrence among females for all clinical features in all age-of-onset groups except for 20-21-year olds (i.e., a majority of point estimates lie to the right of each panel), for which there are null female-male ratios (i.e., 95% CIs cross the axis at 1). Greater estimates can be seen for PPR withdrawal among females (vs. males) across all age groups except for 20-21-year olds. In contrast, some of the female-male odds ratios show variation across age strata (e.g., the OR for using 'more than intended').

Fit indices for the CFA one-dimension OD model indicate good fit for the study population as a whole and for all subgroups based on criteria described in Section 2.3. Under an assumption of measurement equivalence for a one-dimension model with all seven clinical features between males and females (chi-square = 1.5, df = 5, p = 0.915

Table 1
Estimated sex-specific and onset-age-specific occurrence of individual DSM-IV clinical features of prescription pain reliever (PPR) dependence among 12-to-21-year-old newly incident extra-medical users. Data from the United States National Surveys on Drug Use and Health, 2002–2014 (Unweighted n = 10,188).

	Panel A. Females									
Age at first extra-medical PPR use	12-13 (n = 560)		14-15 (n = 1564)		16-17 (n = 1584)		18-19 (n = 1033)		20-21 (n = 716)	
	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]
DSM-IV opioid dependence	10 (713)	63	9 (7, 11)	148	7 (5, 9)	108	5 (3, 7)	38	3 (2, 4)	23
Clinical feature	**% (se)[a]**	**n[a]**	**% (se)[a]**	**n[a]**	**% (se)[a]**	**n[a]**	**% (se)[a]**	**n[a]**	**% (se)[a]**	**n[a]**
Salience[b]	17.9 (2.2)	104	16.8 (1.2)	274	14.1 (1.1)	230	9.5 (1.3)	90	6.8 (1.2)	54
Use more than intended	1.1 (0.4)	10	3.0 (0.6)	44	3.3 (0.6)	46	1.9 (0.6)	20	1.7 (0.6)	10
Tolerance	22.0 (2.6)	119	20.9 (1.3)	327	16.1 (1.2)	252	12.3 (1.4)	119	8.6 (1.3)	67
Withdrawal	14.6 (2.2)	80	9.3 (0.9)	159	8.4 (1.0)	117	5.1 (1.0)	44	3.3 (0.8)	25
Continue despite problems	5.6 (1.0)	43	8.0 (0.9)	118	5.5 (0.8)	75	3.0 (0.8)	25	1.8 (0.6)	16
Give up activities	10.8 (1.6)	64	7.2 (0.9)	105	4.9 (0.7)	78	3.1 (0.7)	26	1.8 (0.6)	17
Difficulty cutting down	1.9 (0.6)	16	3.2 (0.6)	51	2.7 (0.5)	40	2.1 (0.6)	20	1.2 (0.5)	10
	Panel B. Males									
Age at first extra-medical PPR use	12-13 (n = 294)		14-15 (n = 1123)		16-17 (n = 1702)		18-19 (n = 1000)		20-21 (n = 612)	
	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]	% (95% CI)[a]	n[a]
DSM-IV opioid dependence	4 (2, 7)	17	5 (4, 7)	65	4 (3, 6)	65	2 (1, 4)	23	3 (2, 5)	22
Clinical feature	**% (se)[a]**	**n[a]**	**% (se) [a]**	**n[a]**	**% (se)[a]**	**n[a]**	**% (se)[a]**	**n[a]**	**% (se)[a]**	**n[a]**
Salience[b]	12.4 (2.4)	39	12.3 (1.2)	137	10.6 (1.1)	170	6.6 (0.9)	74	6.4 (1.3)	44
Use more than intended	2.6 (1.3)	7	2.4 (0.6)	26	1.5 (0.5)	24	1.0 (0.3)	11	1.8 (0.8)	8
Tolerance	15.4 (2.5)	54	15.9 (1.4)	181	15.2 (1.3)	248	9.3 (1.0)	101	8.7 (1.5)	52
Withdrawal	5.6 (1.7)	21	6.6 (0.8)	89	4.6 (0.8)	73	1.6 (0.4)	23	3.3 (0.9)	24
Continue despite problems	2.4 (1.0)	9	2.9 (0.6)	38	2.6 (0.5)	47	1.5 (0.6)	10	1.1 (0.5)	8
Give up activities	5.6 (1.8)	16	5.5 (0.9)	61	2.9 (0.5)	52	2.3 (0.6)	19	1.0 (0.5)	7
Difficulty cutting down	2.3 (1.2)	5	2.4 (0.7)	25	1.9 (0.5)	26	1.2 (0.4)	9	1.5 (0.6)	10

[a] %, weighted proportion and standard error; n, unweighted number of cases.
[b] Salience refers to either spending a lot of time getting or using PPR or spending a lot of time getting over the effects of PPR.

comparing the configural and scalar model), we studied 12-21-year olds as an aggregate. This analysis shows a higher level of OD among female newly incident extra-medical PPR users within the first 12 months of extra-medical PPR use compared to male new users (β = 0.28; 95% CI = 0.17, 0.39).

Next, we studied female-male differences for each age-of-onset group. In a formal comparison of configural versus scalar modeling (all seven DSM-IV PPR clinical features), the adjusted chi-square test favors the configural model over the scalar model (chi-square = 87.2, df = 45, $p < 0.001$). Studying each intercept and λ estimate across subgroups, we observed considerable variation across subgroups in estimated intercepts and slopes for 'withdrawal' and 'continued use despite physical or psychological problems' (intercept and slope estimates from the configural model are shown in Supplementary Table S2).With these two items dropped, CFA modeling demonstrated a good fit for all subgroups, and measurement equivalence is supported (chi-square = 34.3, df = 27, p = 0.158). The resulting five-item full equivalence model for the OD dimension among newly incident extra-medical PPR users has reasonable fit indices (RMSEA = 0.026, 90% CI = 0.019, 0.033; CFI = 0.984; TLI = 0.982).

Subsequent multiple-group analysis with restriction to the five clinical features disclosed higher levels of OD among female newly incident extra-medical PPR users between 14 and 17 years of age— i.e., a higher opioid dependence level for females (14-15-year olds: β = 0.26, 95% CI = 0.02, 0.50; 16-17-year olds: β = 0.23, 95% CI = 0.03, 0.42). That is, the mean level of opioid dependence is an estimated 0.23 standard deviations higher among 16-17-year-old females compared to 16-17-year-old males. The largest point estimate for female-male difference is found in 12-13-year olds, but the confidence interval touched the null value (β = 0.38, 95% CI = > -0.01, 0.77). For young-adult extra-medical PPR users, the female-male difference estimates are not statistically robust but point estimates are similar to 14-17-year olds (Fig. 2).

For interested readers, we offer a supplementary figure to present sex-specific variations in OD levels across age-of-onset subgroups, as observed within 12 months after the first extra-medical PPR use (Supplementary Fig. S1). OD levels show similar patterns among males and females with elevated dependence levels in 14-17-year olds.

Because the focal points for the evidence presented in Figs. 1 and 2 are age-of-onset-specific sex differences and sex-specific age-of-onset differences, the reference group shifts from one comparison to the next. Readers interested in estimates that hold constant the comparison group will find them in Supplementary Fig. S2. In brief, 14-to-17-year-old female newly incident extra-medical PPR users have the highest level of OD; 20-to-21-year-old males have the lowest level of OD (i.e., comparison group in Supplementary Fig. S2).

Supplementary material also shows results from our post-estimation exploratory analysis steps. In multiple-group analysis with all seven clinical features (no items dropped), the pattern of estimated female-male difference is congruent with the pattern shown in Fig. 1 for our five-item model (Supplementary Fig. S3), notwithstanding the apparent measurement non-equivalence problem in the seven-item approach.

4. Discussion

The most interesting finding of this study is the higher level of OD among females (vs. males) soon after the first extra-medical PPR use across all age-of-onset groups among adolescents and young adults 12–21 years of age, once measurement equivalence calibrations are made. Our confidence in this higher level among females is greater for the five-item assessment of OD levels, which showed measurement equivalence properties. Nonetheless, a similar female-male difference pattern was seen with OD level assessed via all seven items, even when troublesome items (e.g., withdrawal) are not dropped. That is, whereas

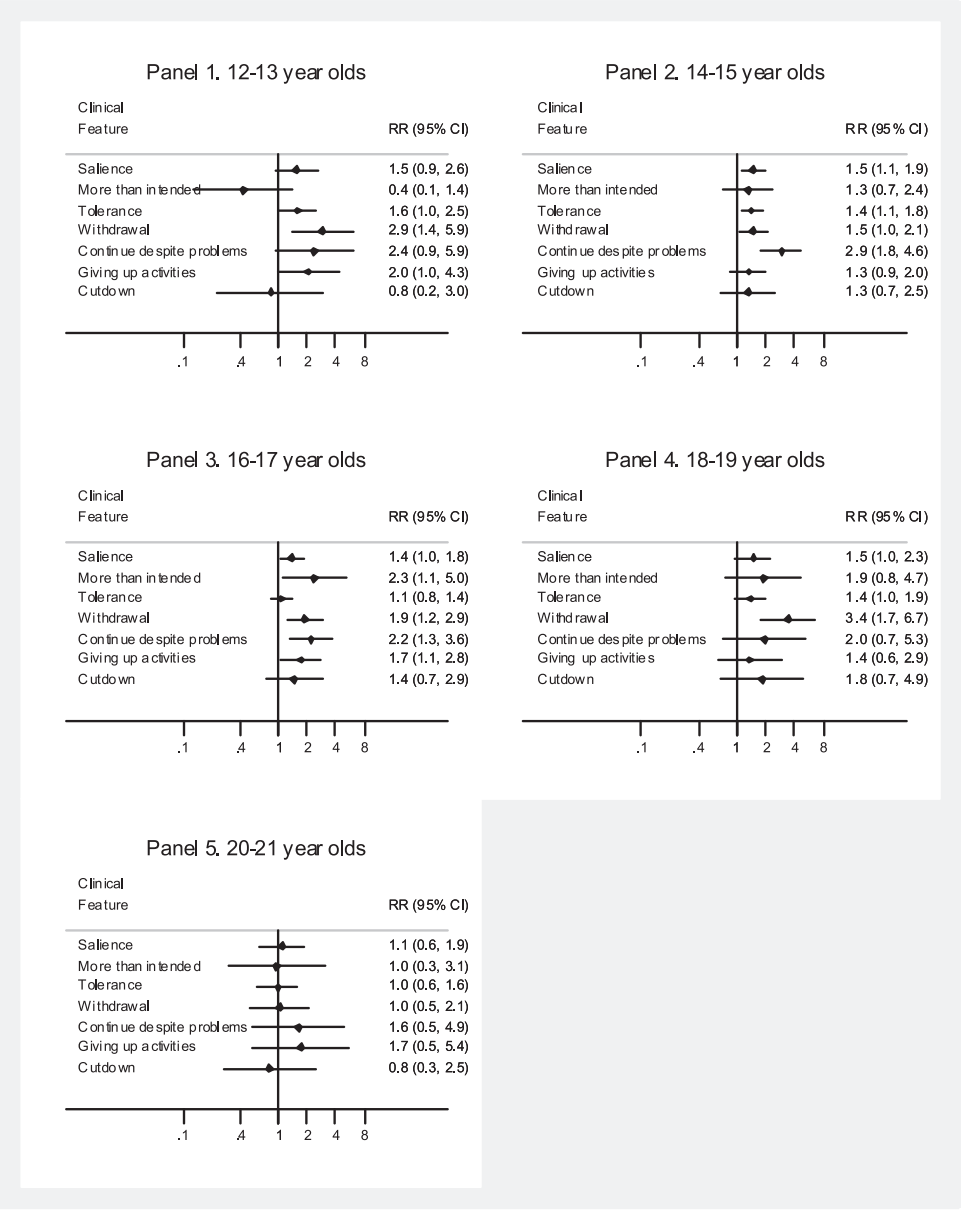

Fig. 1. Estimated female-male ratios of features of prescription pain reliever dependence in five age-of-onset groups among newly incident extra-medical users (reference group = males at the same age of first use). Data from the United States National Surveys on Drug Use and Health, 2002–2014 (Unweighted n = 10,188). Note: Salience refers to either spending a lot of time getting or using PPR or spending a lot of time getting over the effects of PPR.

there is considerable variation in 'withdrawal' and 'continued use despite problems' parameter estimates across subgroups, the manifestation of measurement non-equivalence is not large enough to disrupt the general pattern of the female-male difference estimates.

Before detailed discussion of these results, several of the more important study limitations merit attention. First, with respect to the population under study, the focus on young people in the US during the interval from 2002 through 2014 leaves open the possibility that the study findings do not generalize for other years of US experience (e.g., more recent years) or for youthful populations of other countries. Re-study of these relationships with new study populations will provide evidence about reproducibility and generalizability. We must note that methodological changes in NSDUH assessments in 2015 made it impossible to include the most recent NSDUH data in this study, and the NSDUH instructions argue against pooling of data across the pre-2015 and post-2015 years. Before too long it should become possible to revisit this study protocol and apply it to the NSDUH data gathered in 2015-2018. At present, it is not yet possible to complete this investigation due to small numbers in the age-sex cells of OD cross-classification tables.

Our study population included newly incident users who used PPR extra-medically for the first time during the 12 months prior to the assessment. The actual duration since first extra-medical PPR use might vary from 0 month to 12 months. Therefore, newly incident PPR users might differ in the duration of exposure, and in theory, there might be female-male or age variations in this duration. Nonetheless, a parsimonious assumption is one of no variation. Plus, NSDUH administration is irrespective of sex or age of onset of extra-medical PPR. This assumption can be checked once extramural researchers are granted access to the month-by-month NSDUH datasets, but this access is disabled at present.

In addition, the NSDUH does not collect data to assess assumptions about what is akin to left-truncation and left-censoring errors in follow-up studies. These assumptions involve (1) who is left out of the samples by virtue of their drug use and (2) who is not fully assessed about whether OD developed between onset of use and date of assessment.

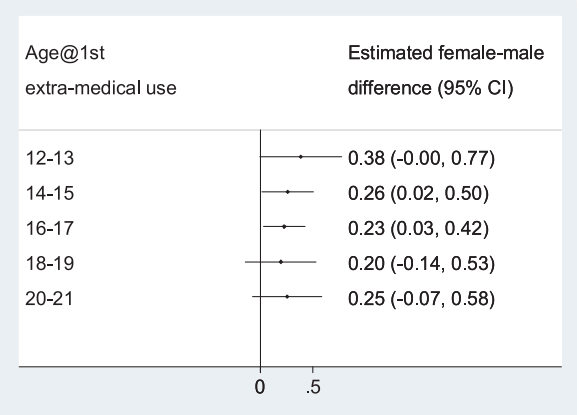

Fig. 2. Estimated female-male differences in the level of prescription pain reliever dependence as measured by five clinical features across age groups among 12-to-21-year-old newly incident extra-medical users (reference group = males at the same age of first use). Data from the United States National Surveys on Drug Use and Health, 2002–2014 (Unweighted n = 10,188).

Whereas overdose is fairly rare in the new user population, especially among adolescents (Centers for Disease Control and Prevention (CDC), 2013), there is some evidence that males are more likely to overdose (Paulozzi et al., 2011). If so, male OD users might be left out of NSDUH samples differentially. Similarly, new extra-medical PPR users with high levels of dependence may be less likely to be included in NSDUH sampling frames and might not participate in surveys, even if included. Longitudinal studies might help to clarify the degree to which this issue affects the observed female-male differences in research of this type, but the baseline samples of most longitudinal studies also involve this particular methods challenge.

Another issue involves our focus on extra-medical PPR use in this study, due to NSDUH failure to ask about month of onset of use when it is appropriate and medically supervised as such. One might imagine that the first medical use of PPR occurred before the 12 months window prior to the assessment, with OD developing soon thereafter, and with the month of first extra-medical PPR use occurring after onset of OD. If that is the case, and if there is a female-male imbalance in these processes, we will need to re-visit this study's estimates by excluding medically supervised and appropriate PPR users. This can be done with NSDUH data from 2015 onward but is not yet possible with the NSDUH released to extra-mural scientists.

Lastly, the NSDUH sampling scheme does not include institutionalized individuals. As a result, adolescents and young adults admitted to institutional inpatient treatment units, in juvenile detention centers, or other institutions were not assessed. Here we have an unanswered question because we are unable to find any comparison of drug use estimates from field surveys that have sampling frames with and without residents of institutional facilities. The result is an open question for future research on 12-to-21-year-olds.

Counter-balancing strengths of this investigation include large samples of US civilian populations designed to be nationally representative. Compared to prospective studies, this study is relatively free of sample attrition that is usually present as a missing data mechanism in longitudinal research on OD. The calibration for measurement equivalence helps constrain potentially substantial assessment issues across sex and age-of-onset groups. The origins of the differential item functioning might be of substantive importance (e.g., female-male differences in the actual 'side effect' phenotypes). If the issues can be traced to differential (a) interpretation of certain words, or (b) understanding of the concept of OD, then a methods solution is indicated (e.g., drop the questions with potential differential functioning).

Finally, we should mention that in this study we specified OD as a dimensional variable in a fashion that might help improve generalizability to other study population contexts. Accordingly, our approach involved deliberate omission of NSDUH standardized items on 'troubled use' and social maladaptation secondary to extra-medical PPR use (e.g., getting into trouble with the family). Responses to these omitted items can be heavily norm- and context-dependent, particularly when study populations are drawn from culturally diverse jurisdictions with varying norms and social contexts regarding extra-medical drug use. By omitting items on 'troubled use' and social maladaptation secondary to drug use, we intend to constrain both conceptual and measurement difficulties in drug dependence research (Anthony, 2010; Edwards, 1986; Martin et al., 2014).

Even with limitations of the type just described, in this study of newly incident male and female users, we have found that the female new users had higher levels of OD with or without calibration for measurement equivalence. This interesting result is in contrast to a large body of evidence about a male excess in drug use behaviors and dependence, based primarily on studies of 'prevalent users' and rarely on studies of newly incident users (Kuhn, 2015; Storr et al., 2010; Wells et al., 2011).

With respect to opioid use disorders specifically, there actually is mixed evidence on sex differences in the US adult population. For example, in some studies, adult male extra-medical PPR users have been found to be at a higher risk of developing PPR use disorders (including socially maladaptive PPR use and OD) prospectively (Katz et al., 2013) and cross-sectionally (Han et al., 2017). This observation is suported by preclinical evidence on more male opioid tolerance and withdrawal in rodents versus females (e.g., Bodnar and Kest, 2010; Cicero et al., 2002). In contrast, some other human studies have documented higher levels of opiate abuse-related physical problems (Greenfield et al., 2003) and craving (Back et al., 2011) among females compared to males, whereas other studies found no sex differences in the severity of OD (Wu et al., 2011) and in persistence of extra-medical PPR use (Dowling et al., 2006; Parker and Anthony, 2018).

Nonetheless, for some forms of drug dependence, higher levels among females have been documented. For example, some early evidence suggested a more compressed course of alcohol dependence among females compared to males in clinical populations (Schuckit et al., 1998). Studying alcohol involvement, and with a more refined specification of age groups, we found shifting female-male differences across age groups. An observed higher level in alcohol dependence is observed among females during the years of early adolescence; a lower level for female drinkers is observed later in adolescence and early adulthood (Cheng et al., 2016b; Cheng and Anthony, 2018a). Something similar has been documented for cannabis use disorders in US nationally representative data of adults (Khan et al., 2013). Chen and Jacobson (2012) found higher levels of alcohol and cannbis use during early adolescence, but it was males who had higher levels during late adolescence and young adulthood (Chen and Jacobson, 2012).

Here, in the present study on opioids, we found a dissimilar pattern. No shift of these types is observed. In addition, there are consistently higher OD levels among females across age strata. It is possible that the observed higher level of alcohol dependence among early-adolescent females (vs. early-adolescent males) is determined by the same influences that shape OD levels. If so, a question for future research is how it happens that there are age- or development-related female-male shifts for alcohol but not for opioids.

Potential mechanisms for the larger female OD levels include an observation of greater sensitivity to pain in females (Fillingim et al., 2009), interactions between estradiol and reinforcing effects of PPRs (Lynch et al., 2002; Roth et al., 2004), as well as socio-environmental factors such as access to prescription opioids, peer affiliation, and peer-to-peer sharing of opioids (Mars et al., 2014; Shand et al., 2011; Vaughn et al., 2016).

Future studies are needed to look into explanations and mechanisms that might account for what this study identifies as observed higher

levels of OD among females. Information about socio-environmental variables as well as more individual-level biomedical variables should be collected in such studies. The emergence of dependence syndromes and related addictive states involves a complex interplay of processes, some observable as individual differences, and some of them involving interpersonal and social contexts (Chartoff and McHugh, 2016; Wise and Koob, 2014).

Our discovery that 'withdrawal' and 'continued use despite physical or psychological problems' are problematic OD items merits some discussion. We cannot claim that these items should be dropped from OD assessments. We appreciate that these manifestations, as experienced by users, can be central to our understanding and case definitions for any OD syndrome and might be especially important in the clinical setting. Nonetheless, if the goal is a comparison of mean OD levels, and a dimensional conceptualization is specified to study subgroup variations in OD, this research alerts investigators to potential measurement non-equivalence. If future research can confirm this kind of measurement issue with 'withdrawal' and 'continued use despite problems' items, reasons for measurement non-equivalence should be probed using a mixed methods approach. For example, questions can be asked about acute withdrawal versus withdrawal as a result of neuro-adaptation and questions about particular physical or psychological problems experienced.

The results from this study may offer useful information for the design and implementation of effective intervention strategies. According to our findings, females may develop OD syndrome more rapidly than males during adolescence and young adulthood, the period when most PPR users start using PPR (Meier et al., 2012; Parker and Anthony, 2015). The concept of "prevescalation" refers to the prevention of escalation of drug use and the development of problematic use (Dishion and Andrews, 1995; Piper et al., 2017; Villanti et al., 2018). This concept is pertinent in PPR research and public health program planning for newly incident PPR users as they move along OD dimensions and accumulate dependence-related problems.

Here, we see that across all sex- and age-groups under study, 'tolerance' and 'salience' are the two most common clinical features. When physicians, parents, peers, and teachers become aware that adolescents and young adults have started using PPR extra-medically and have been increasing their PPR consumption or spending more time engaging in PPR-related activities, a few targeted questions might be especially useful. For example, during this interval, it is time to investigate salience and tolerance and to consider brief interventions with a capacity to prevent an escalation toward the fully-formed OD syndrome as well as secondary PPR-dependence-related consequences.

Of course, males and females can vary in PPR access and routes of administration. Specifically, males seem to be more likely to access PPR from friends at school, and females were more likely to access from parents; males seem more likely to snort PPR compared to females (Osborne et al., 2018). The observed variation in the level of OD across sex and age-of-onset groups for OD levels may signify a need to modify the nature or intensity of interventions in relation to sex and age (Brady et al., 1993; Kuhn, 2015; Schulte et al., 2009).

In summary, the standard DSM-5 approach of grading severity by adding up opioid-related diagnostic criteria represents somewhat of a step forward beyond strictly categorical diagnostic approaches. Nevertheless, this study offers a novel discovery about specific manifestations of OD that might create a bias when the goal is to investigate females who have just started to take opioids extra-medically and to compare them with male peers. Namely, the standard DSM-5 approach of adding up criteria might require modification. Whereas adding-up represents a relatively easy-to-achieve 'best practice' in medical workup of opioid-involved patients, it can be a sub-optimal approach when the scientific aim is to compare females and males using the same meter stick for measurements of the subgroups.

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Contributors

HGC and JCA designed the study. HGC and MAP reviewed the literature. HGC conducted data analysis. HGC wrote the first draft. MAP and JCA substantially revised the manuscript. Each author has contributed significantly to the work and agrees to the submission.

Declaration of Competing Interest

None. Other COI: Ongoing fiduciary and contractual obligations of the corresponding author create COI for investigators employed by the following academic units (Mental Health at JHU; School of Public Health at Columbia University; Epidemiology at University of West Virginia; Biostatistics at University of Kentucky). This COI narrows selection of reviewers employed by these academic units. Past COI: HC worked with a Purdue Pharma collaborator in research on re-formulation of Oxycontin but has no on-going relationship with that firm.

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Appendix A. Supplementary data

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