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Exploring Age of Onset as a Causal Link between Major Depression and Nonmedical Use of Prescription Medications

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Abstract

Background—Nonmedical use of prescription medications (NUPM) has been associated with major depression (MDD), but the specific processes by which they might interact and influence one another are understudied. This investigation attempted to clarify the relationship between MDD and NUPM by examining whether age of MDD onset influenced current and past NUPM and by examining whether age of NUPM onset influenced lifetime or past year MDD.

Methods—These goals were met though use of data from the 2005–2007 National Survey on Drug Use and Health. Analyses utilized design-based logistic regression, and current age and order of MDD onset and NUPM initiation were examined in interactions with age of MDD or NUPM onset.

Results—For each year MDD onset was delayed, odds of lifetime, past year, past 30-day NUPM and substance dependence from NUPM were decreased by 2.3%, 2.6%, 1.9% and 2.3%, respectively. Earlier NUPM onset increased odds of past year (3.8%) and lifetime MDD (4.3%) in young adults, and lifetime MDD (2.5%) in the 26–34 age group. Current age also interacted with age of MDD onset, with effects on NUPM pronounced in the 65 and older cohort. Order of MDD/NUPM onset generally did not interact with age of MDD onset, but it did interact with age of NUPM onset; the effects of NUPM onset on past year MDD were only significant in those with NUPM first.

Conclusions—These results highlight the need for further investigations of the interactions between depression and NUPM, particularly to evaluate potential causal relationships.

Keywords

Nonmedical prescription use; Major Depression; Age of Onset; Etiology

1. Introduction

While the use of many addictive substances has declined since the early 1990s, nonmedical use of prescription medication (NUPM) rates appeared to increase in the past 20 years

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(Compton and Volkow, 2006b; Substance Abuse and Mental Health Services Administration [SAMHSA], 2010b). NUPM is often defined as the intentional use of an addictive medication, outside of treatment for a legitimate medical condition under a physician's supervision (Compton and Volkow, 2006a) and it focuses on four classes of medication: opioids, tranquilizers (typically benzodiazepines), stimulants and sedatives.

Currently, NUPM rates follow only those of alcohol, tobacco and marijuana across age groups (SAMHSA, 2010b). Past year initiates of NUPM in 2009 roughly equaled the number of new initiates of marijuana, cocaine and hallucinogens combined (SAMHSA, 2010b), and data indicates that as NUPM has grown, so have rates of NUPM-related treatment utilization, emergency department visits and overdose deaths (Manchikanti and Singh, 2008; SAMHSA, 2010a; SAMHSA, 2009). These data underscore two points: one, NUPM is likely to be a significant public health concern in the coming decades; and two, there is a need to understand NUPM-related processes to maximize interventions aimed at reducing its scope.

While NUPM is understudied (Barrett et al., 2008; Boyd and McCabe, 2008), research indicates that NUPM is associated with psychopathology (e.g., Huang et al., 2006). Given that the medication classes noted above either have primary indications for the treatment of psychiatric symptoms (e.g., tranquilizers treat insomnia) or ameliorate symptoms as a secondary effect, the link between NUPM and psychopathology appears to warrant further study. Major depression (MDD) appears to be a particularly salient correlate of NUPM (Culberson and Ziska, 2008; Goodwin and Hasin, 2002; Wu et al., 2008a), as it is associated with substance use disorder (SUD) symptoms from NUPM in adolescents (Schepis and Krishnan-Sarin, 2008; Wu et al., 2008b), increased odds of NUPM-related SUD in adults (Huang et al., 2006) and a more severe profile of problematic nonmedical opioid use (Wu et al., 2011). Higher levels of depressive symptoms are linked to non-oral administration and more frequent stimulant nonmedical use (Teter et al., 2010). Finally, higher levels of depressive symptoms are seen in a subgroup of nonmedical users that may be at higher risk for other psychopathology and more frequent NUPM (Hall et al., 2010).

Despite these links, few investigations have looked at potential mechanisms by which depressive symptoms and NUPM interact. These interactions are likely to be captured by one of three causal models. In one, NUPM could be initiated to treat symptoms of depression, or to self-medicate (e.g., Khantzian, 1985). To illustrate, medications in the classes noted above produce some degree of euphoria or pleasure, which could combat sadness and anhedonia; furthermore, stimulants would directly combat many depressive symptoms, while sedatives and tranquilizers could help ameliorate insomnia. Opioids may be nonmedically used to treat somatic symptoms that often occur in MDD. Conversely, NUPM could precipitate depressive symptom development through neurobiological alterations (e.g., Brady and Sinha, 2005). Finally, NUPM and depressive symptoms could also be related through a higher-order third factor that separately causes each (e.g., shared genetic and environmental vulnerabilities; Kendler et al., 2003; McGue and Iacono, 2005).

The strong cross-sectional links between MDD and NUPM would indicate that it is important to evaluate these potential causal relationships. Nonetheless, only one published investigation has done so, using cross-sectional data from wave 1 of the National Epidemiological Study on Alcoholism and Related Conditions (NESARC) to examine nonmedical opioid use (Martins et al., 2009). This work found support for both causal models and the higher-order third factor model noted above, with MDD preceding NUPM indicators in some cases, and NUPM preceding MDD in others.

Thus, the aim of this work was to clarify relationships between MDD and NUPM by examining the role of age of MDD onset on current NUPM and the role of age of NUPM initiation on MDD. Earlier age of MDD onset has been linked to a greater likelihood of poor outcomes in adulthood (Klein et al., 1999; van Noorden et al., 2011; Zisook et al., 2007), and it has been posited to be a distinct, more severe form of the disorder (Kaufman et al., 2001). Earlier NUPM onset appears to increase the risk for SUD from NUPM in adults (McCabe et al., 2007). Age of onset of one has not been evaluated as an influence on the other (e.g., age of MDD onset on current NUPM or vice versa). Given the links between MDD and NUPM, age of onset may be an important factor in the course of both MDD and NUPM. Furthermore, the medications typically used nonmedically can have vastly different properties and interact differently with MDD; thus, a final aim of this work is to evaluate the potential relationships noted above separately by medication class.

For age of MDD onset, our hypotheses were as follows: 1) earlier age of MDD onset would significantly increase the odds of lifetime, past year and past 30-day NUPM and of substance dependence or abuse from NUPM; 2) these effects would vary by current age, as NUPM estimates vary significantly by current age (SAMHSA, 2010b); and 3) the effect of age of MDD onset would be stronger in those who had MDD onset prior to NUPM initiation. For age of NUPM onset, our hypotheses were that: 1) earlier age of NUPM onset would significantly increase the odds of past year and current MDD; 2) these effects would vary by age, given the age differences in NUPM referenced above; and 3) the effect of age of NUPM onset would be stronger in those who had NUPM initiation prior to MDD onset.

2. Methods

The aims of this work will be met through the use of the 2005–2007 versions of the National Survey on Drug Use and Health (NSDUH), a yearly in-home survey of the civilian, non-institutionalized US population conducted by SAMHSA. These versions of the NSUDH were selected to give a large sample while preserving a consistent format for the survey; versions prior to 2005 and after 2007 included a different psychopathology assessment, raising concerns about the consistency of MDD prevalence estimates (SAMHSA, 2010b).

2.1 NSDUH Design

The NSDUH creates a sample that is representative of the US at the time of the survey. Households were selected for screening, and an in-person screening to identify individuals aged 12 and older was conducted. Following identification of eligible households, full interviews were conducted on a random sample of one or more household members, selected to meet the specifications for that sampling area. The NSUDH combined both computer-assisted interviewing and audio computer-assisted self-interviewing (ACASI) methods. During the ACASI portion of the survey, the participant wore headphones to hear all questions and the field interviewer remained out of view of the computer screen; these procedures were employed to preserve respondent privacy and maximize honest responding. All NUPM and psychopathology measures were asked in the ACASI format.

The 2005–2007 NSDUH versions included automatic skip-outs and questions serving as consistency checks based on previous answers; both were meant to increase full responding and data consistency. In cases where NUPM data remained inconsistent or missing, statistical imputation was used to reduce missing data; imputation rates ranged from 0.27% (sedative use recency) to 0.93% (opioid recency). MDD-related data were not imputed.

2.2 Participants

The NSDUH is designed to oversample adolescents, young adults, African-Americans and Hispanics, using an independent, multistage area probability sample for all states and the District of Columbia. Beginning in 2002, yearly population estimates have been created by the Population Estimates Branch of the US Census Bureau to create population-based weights. For the 2005–2007, the unweighted sample size was 166,617. Of that, 32.8% were young adults aged 18–25 (n= 54,725) and 32.8% were adolescents aged 12–17 (n= 54,719). Females composed 52% of the sample (n= 86,641), with Caucasian (n= 106,777; 64.1%), Hispanic/Latino (n= 25,550; 15.3%) and African-American individuals (n= 20,897; 12.5%) comprising the three largest ethnic groups.

2.3 Measures

The primary measures are lifetime, past year and past month NUPM, substance dependence or abuse from NUPM, age of NUPM onset, age of MDD onset and past year and lifetime MDD. Current age is used as a between-subject factor in analyses for hypothesis 2; otherwise, it is included as a control variable. Other control variables were race/ethnicity, marital status, educational attainment and population density in area of residence.

Current age was a six-level variable. Groups were aged 12–17, 18–25, 26–34, 35–49, 50–64 and 65-plus.

Lifetime NUPM is defined as medication use when “the drug was not prescribed for you, or you took the drug only for the experience or feeling it caused.” Thus, lifetime NUPM could include one-time nonmedical use, though the NSDUH definition excludes accidental misuse. To aid recall, participants are shown medication cards with pictures of all queried medications.

Recency of NUPM is queried in participants endorsing lifetime NUPM. Dichotomous summary variables were created for both past-30 day and past year NUPM.

NUPM-related SUD is assessed in participants who endorsed past year NUPM through questions for each class of medication nonmedically used based on the DSM-IV criteria (American Psychiatric Association, 2001; SAMHSA, 2006). Dichotomous summary variables were created for both current dependence and abuse.

Age of NUPM initiation is queried in lifetime nonmedical users. Participants enter a number for their age of initiation, which is revised using imputation to create a summary variable coding age of initiation or never use status for each class of medication nonmedically used.

Lifetime and past year major depression were estimated using questions from the National Comorbidity Study-Replication, based on the DSM-IV (American Psychiatric Association, 2001; SAMHSA, 2006). Participants begin with an assessment of lifetime MDD, and if present, are assessed for past year MDD. Data indicate that this assessment has good reliability and validity (Ventura et al., 1998; Zanarini and Frankenburg, 2001), with kappa values in the good range (k= .59) for lifetime MDD and fair range (k= .40) for past year MDD (Kessler et al., 2003). MDD is coded as present even when it is caused by bereavement, a general medical condition or substance use. Also, the MDD assessment uses ACASI self-interview methods, while the psychometric data are from assessments using trained interviewers; ACASI methodology may adversely impact the reliability and validity of the assessment.

Age of MDD Onset: Participants with lifetime MDD are asked the age at which they experienced their first episode of MDD (not first symptom). Participants enter their age of

onset, which is revised to create a summary variable coding age of onset or never MDD status.

2.4 Analyses

All analyses were performed in SUDAAN, version 10.1 (Research Triangle Park, NC) because of its ability to account for the complex design of the NSUDH. Data were sorted by the appropriate design variables to account for the 50% overlap between successive years in estimates of variance and standard error. Adjusted person-level weights (weight/3) were applied to create population-based estimates, accounting for the 3 years of data used.

For all hypotheses, design-based logistic regression was utilized. The first set of analyses examined age of MDD onset and the outcome variable was one of the three NUPM recency variables, substance dependence or abuse from NUPM. The second analyses examined age of NUPM initiation, with outcomes of lifetime or past year MDD. The sociodemographic control variables listed above were included in all analyses.

For all hypotheses, age of MDD onset (set 1) or age of NUPM initiation (set 2) was the independent variable. For the second hypothesis in each set, current age was included as a between-subject factor and in an interaction term with age of MDD onset (set 1) or age of NUPM initiation (set 2). Finally, analyses for hypothesis three used a variable capturing order of MDD onset and NUPM initiation. Individuals who experienced MDD first were compared to those who initiated NUPM first, through inclusion of this term as a between-subject factor and in an interaction term with age of MDD onset (set 1) or age of NUPM initiation (set 2). Given that data in hypothesis three was from individuals who endorsed both lifetime NUPM and MDD, lifetime NUPM or MDD were excluded as outcomes.

3. Results

3.1 Age of MDD Onset: Hypothesis 1

Across the sample, age of MDD onset was a significant correlate of all NUPM outcomes except for NUPM-related substance abuse. For each year MDD onset was delayed, the odds of lifetime NUPM were decreased by 2.3% (Adjusted Odds Ratio [AOR]=.98, 95% Confidence Interval [CI]=.97–.98), the odds of past year NUPM were decreased by 2.6% (AOR=.97, 95%CI=.97–.98) and the odds of past 30-day NUPM were decreased by 1.9% (AOR=.98, 95%CI=.97–.99). Finally, odds of NUPM-related dependence were decreased by 2.3% for each year MDD onset was delayed (AOR=.98, 95%CI=.96–.99). These results are captured in Table 1.

All four medication classes evidenced a significant relationship between age of MDD onset and both lifetime and past year NUPM, with later age of MDD onset decreasing odds of lifetime NMPU by 0.9% (sedatives) to 2.7% (opioids) and odds of past year NMPU by 2.4% (opioids) to 3.5% (tranquilizers). In addition, 30-day opioid (1.6% decrease per year MDD is delayed) and tranquilizer use (2.9% decrease) displayed a relationship with age of MDD onset. Finally, opioid dependence was 1.8% less likely and tranquilizer and stimulant abuse were 7.6% and 6.5% less likely for every year that MDD was delayed. These results are summarized in Table 2.

3.2 Age of MDD Onset and Current Age Cohort: Hypothesis 2

Analyses of the entire sample indicated significant interactions between age of MDD onset and current age (12–17, 18–25, 26-4, 35–49, 50–64 and 65 and older) for past year NUPM (p=.0172; [Wald] χ^2=13.76), past 30-day NUPM (p<.0001; χ^2=33.56) and substance abuse diagnosis from NUPM (interaction p=.0392; Wald χ^2=11.70). Analysis of slopes indicated

that the age interactions were driven primarily by the 65 and older cohort (past year: p=.0002, χ^2=14.16; past 30-day: p<.0001, χ^2=31.45; substance abuse, p<.0001, χ^2=39.25). No other age groups had significant slopes. Analyses by age group supported this, with no significant relationships between age of MDD onset and NUPM in adolescents, and only one in young adults (lifetime NUPM: p=.008; χ^2=7.04; AOR=.98, 95%CI=.965–.995).

By medication class, every medication displayed a cohort effect for NUPM-related abuse (opioids: p=.028, χ^2=10.84; tranquilizers: p=.0003, χ^2=20.95; stimulants: p< .0001, χ^2=117.41; sedatives: p<.0001, χ^2=98.4), with both the 50–64 and 65 and older cohorts showing significant slopes in every case (all ps<.05). Interactions were seen for NUPM-related dependence for every medication except sedatives (opioids: p=.046, χ^2=9.71; tranquilizers: p<.0001, χ^2=24.79; stimulants: p<.0001, χ^2=42.62). For the tranquilizers and stimulants, the 65 and older cohort seemed to drive the interaction (tranquilizers: p<.0001, χ^2=54.17; stimulants: p<.0001, χ^2=49.77), while the only significant slope for the opioids was for the 26–34 cohort (p=.008, χ^2=6.95). Finally, 30-day opioids (p=.0006, χ^2=21.53) and tranquilizer (p<.0001, χ^2=36.22) nonmedical use had significant age cohort interactions with age of MDD onset, again driven by the 65 and older cohort (opioids: p<.0001, χ^2=20.34; tranquilizers: p<.0001, χ^2=48.43).

3.3 Age of MDD Onset, Ordering of MDD Onset and NUPM Initiation: Hypothesis 3

Among both the entire NSUDH sample (p=.0073; χ^2=7.19) and the cohort of adults aged 26 and older (p=.0353; χ^2=4.43), a significant interaction was found between age of MDD onset and the order of MDD/NUPM onset variable for past year NUPM. Only those with MDD onset first evidenced a significant relationship between age of MDD onset and past year NUPM (whole sample p=.0232, χ^2=5.15; 26+ cohort p=.0365, χ^2=4.37). Analyses by medication class did not produce significant results.

Outcomes in adolescents were unaffected by inclusion of the ordering variable, but young adults evidenced an effect for NUPM-related substance dependence (p=.0080; χ^2=7.04). Only the slope for MDD first individuals was significant (p=.0162; Wald χ^2=5.78).

3.4 Age of NUPM Initiation: Hypothesis 1

Across the sample, age of NUPM initiation was not significantly related to lifetime or past year MDD. These results are captured in Table 3. For opioids, with every year opioid nonmedical use was delayed, there was a 2.1% decrease in odds of both lifetime (p=.005; χ^2=7.94; AOR=.98, 95%CI=.98–.99) and past year MDD (p=.013; χ^2=6.13; AOR=.98, 95%CI=.98–.99). No other significant results were seen by medication class.

3.5 Age of NUPM Initiation and Current Age Cohort: Hypothesis 2

Age cohort interacted with age of NUPM initiation for lifetime MDD (p=.042; χ^2=11.50). Both young adults (p=.001; χ^2=10.78) and the 26–34 age group (p=.025; χ^2=5.04) evidenced significant slopes for the relationship between lifetime MDD and age of NUPM onset. No interaction was observed for past year MDD (p=.178; χ^2=7.64). Analyses by age group supported these findings. In young adults, odds of lifetime MDD were decreased by 3.8% (p<.0001; χ^2=16.66; AOR=.96, 95%CI=.95–.98) and odds of past year MDD were decreased by 4.3% for each year that NUPM initiation was delayed (p=.0001; χ^2=14.69; AOR=.96, 95%CI=.94–.98). In the 26–34 age group, odds of lifetime MDD were decreased by 2.5% for each year that NUPM onset was delayed (p=.013; χ^2=6.15; AOR=.97, 95%CI=.95–.99). No significant effects were seen by medication class.

3.6 Age of NUPM Initiation and Ordering of MDD and NUPM Onset: Hypothesis 3

A significant interaction was found between age of NUPM initiation and the MDD/NUPM ordering variable for past year MDD (p=.0067; χ^2=7.34). Analysis of simple slopes revealed age of NUPM onset influenced odds of past year MDD in those individuals who initiated NUPM prior to MDD onset (p=.0071; χ^2=7.26) but not in those with MDD first (p=.417; χ2=.658). These effects may have been driven primarily by opioid nonmedical use, as only age of opioid initiation interacted with order of MDD/NUPM for past year MDD (p=.0003; χ^2=13.16).

4. Discussion

These results indicate that earlier age of MDD onset increases odds of lifetime, past year, past 30-day NUPM and NUPM-related substance dependence. In all cases, the odds were between 2.6 and 1.9% higher for each year that MDD onset is earlier. These effects appeared generally across medication classes, though opioids and tranquilizers demonstrated more consistent effects. Current age also influenced the relationship between age of MDD onset and NUPM, as relationships strongest in the 65 and older cohort. Age of NUPM initiation only evidenced a relationship with lifetime and past year MDD in young adults, with a 3.8% and 4.3% increase in odds for each year NUPM initiation is earlier, respectively. Those in the 26–34 age group also had increased odds (2.5%) of lifetime MDD with earlier NUPM initiation. Examination by medication class indicated the opioids largely drove these findings, but analyses by medication class also revealed that odds of substance abuse from nonmedical tranquilizer and stimulant use were increased by early onset MDD. Unlike age of MDD onset, where ordering of MDD/NUPM onset was non-significant, the effects of age of NUPM initiation on MDD were present only in those who initiated NUPM first. This also appeared to be largely due to opioid nonmedical use.

The relationship between age of MDD onset and NUPM is consistent with previous reports (e.g., Huang et al., 2006). The lack of a consistently stronger relationship in MDD first individuals, however, may argue against a direct influence for age of MDD on NUPM. Conversely, the effect of age of NUPM initiation was significant in those, across ages, who initiated NUPM first. This seems to provide stronger evidence for a precipitation model, where NUPM leads to MDD, than for a self-medication model.

That said, neither a third factor nor self-medication model can be ruled out. Examining the results by medication class would seem to indicate, if self-medication was operating, that treatment of somatic symptoms might be the strongest motivator for NUPM, as the opioids had the strongest and most consistent effects. Self-medication of accompanying anxiety and of insomnia, via the tranquilizers, could also be at work. Given that the NSDUH assessment captures only age of initial MDD *diagnosis*, not symptoms, self-medication cannot be ruled out, as individuals may have initiated NUPM to treat initial depressive symptoms, with NUPM still preceding full diagnosis. Furthermore, cross-sectional data cannot establish causality; further research using longitudinal data is required for this.

Another notable finding is that current age moderates the effects of age of NUPM initiation or MDD onset. While retrospective bias may have influenced this result, controlling for current age should have limited this confound. The simplest explanation is that a cohort effect is at work. Martins et al. (2010) found that both opioid nonmedical use and use disorder rates increased over the 10-year period from 1991–1992 to 2001–2002 and that the effects were more pronounced in younger adults. Greater availability and a willingness to divert medications (McCabe and Boyd, 2005; Schepis and Krishnan-Sarin, 2009) may mean that young adults can more readily self-medicate depressive symptoms.

Conversely, NUPM may be restricted in the 65 and older cohort to those with the greatest levels of other psychosocial problems. Early MDD may mark a unique and more deleterious form of MDD (Kaufman et al., 2001), so those in the 65 and older cohort with earlier MDD onset may necessarily be at greatest risk for NUPM because of their more severe depressive profile. An alternative explanation may be that age of MDD onset is a delayed risk factor, requiring a significant time to exert effects. This may explain the non-significant results in adolescents and young adults, where the time since age of MDD onset is compressed.

Clinically, these results highlight the importance of screening younger individuals for age of NUPM onset and older individuals for age of MDD onset. While adolescents who initiated NUPM early were not at increased odds of MDD, their briefer time since initiation may be the primary cause of that non-significant finding. As the relationship may become significant through the transition to young adulthood, it is wise to screen adolescents for age of NUPM initiation. Furthermore, screening the 65 and older cohort for age of MDD onset appears important in highlighting those at higher risk for NUPM. These results also point to the need for primary prevention to limit the early onset of both NUPM and MDD. Such programs are warranted to not only limit the risk for each, but also to limit the risk that early onset predisposes individuals to the later experience of the other phenomenon.

Some limitations should be noted. First, some retrospective bias is likely, as the primary variables may assess events in the past. We controlled for this by including current age as a between-subject factor in analyses, but bias may remain. Second, the NSDUH does not exclude cases of MDD due to substance use, bereavement or a general medical condition. The NESARC indicates that 0.09% of participants were classified with substance-induced MDD (Grant et al., 2004); the NSUDH does not allow for such exclusion, and these results must be interpreted in light of this limitation. Third, roughly one-quarter of those approached did not participate in the full NSDUH survey, allowing for some self-selection bias. Finally, while the use of ACASI methods was likely to have maximized honest reporting, the self-report data allow for participant misreporting. In particular, this may be important for a clinical diagnosis like MDD. The use of ACASI self-report methods, rather than a clinical interview, is likely to result in some incorrect categorization as to MDD diagnosis (e.g., Myers and Weissman, 1980).

In summary, this work indicates that earlier onset of MDD increases the odds of lifetime, past year and past 30-day NUPM and substance dependence from NUPM, particularly in those aged 65 and older. Earlier initiation of NUPM also increased odds of lifetime and past year MDD in young adults and lifetime MDD in the 26–34 cohort. Finally, earlier NUPM initiation increased odds of past year MDD only in individuals who initiated NUPM prior to MDD onset. The evidence of a direct influence of earlier NUPM on current MDD seems to support the precipitation model more than the self-medication model; this needs evaluation in a longitudinal sample to establish causality, however. Further exploration of the longitudinal relationships between MDD and NUPM and individual medication class effects (e.g., early MDD onset increasing odds for opioid dependence) are needed to establish the course of the comorbid condition and potential causal relationships between these variables.

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TABLE 1

Influence of Age of MDD Onset on NUPM Outcome Variables (N = 24,238)

	Lifetime NUPM	Past Year NUPM	Past 30-Day NUPM	NUPM Dependence	NUPM Abuse
Sample Size	8,849	4,186	1,729	653	256
% (95%CI)	36.02 (34.96–37.09)	12.55 (11.93–13.20)	5.38 (4.96–5.85)	1.85 (1.63–2.10)	0.62 (0.50–0.77)
Overall Equation	$\chi^2 = 577.70$, $p < .0001$	$\chi^2 = 3353.19$, $p < .0001$	$\chi^2 = 3988.24$, $p < .0001$	$\chi^2 = 3460.60$, $p < .0001$	$\chi^2 = 1073.64$, $p < .0001$
Age Group	$\chi^2 = 1.26$, $p = .26$	$\chi^2 = 37.20$, $p < .0001$	$\chi^2 = 10.26$, $p = .001$	$\chi^2 = 4.62$, $p = .03$	$\chi^2 = 0.0002$, $p = .99$
Ethnicity	$\chi^2 = 60.95$, $p < .0001$	$\chi^2 = 23.27$, $p < .0001$	$\chi^2 = 7.36$, $p = .06$	$\chi^2 = 5.95$, $p = .11$	$\chi^2 = 13.41$, $p = .003$
Gender	$\chi^2 = 16.00$, $p < .0001$	$\chi^2 = 5.12$, $p = .02$	$\chi^2 = 8.20$, $p = .004$	$\chi^2 = 2.98$, $p = .08$	$\chi^2 = 1.27$, $p = .26$
Marital Status	$\chi^2 = 59.14$, $p < .0001$	$\chi^2 = 73.75$, $p < .0001$	$\chi^2 = 31.41$, $p < .0001$	$\chi^2 = 31.03$, $p < .0001$	$\chi^2 = 15.54$, $p = .001$
Education	$\chi^2 = 0.96$, $p = .62$	$\chi^2 = 9.65$, $p = .008$	$\chi^2 = 15.97$, $p = .0003$	$\chi^2 = 13.66$, $p = .001$	$\chi^2 = 5.10$, $p = .08$
Urbanicity	$\chi^2 = 4.66$, $p = .10$	$\chi^2 = 2.01$, $p = .37$	$\chi^2 = 0.26$, $p = .88$	$\chi^2 = 1.10$, $p = .56$	$\chi^2 = 4.06$, $p = .13$
MDD Onset Age	$\chi^2 = 91.34$, $p < .0001$	$\chi^2 = 56.82$, $p < .0001$	$\chi^2 = 13.22$, $p = .0003$	$\chi^2 = 6.95$, $p = .01$	$\chi^2 = 1.84$, $p = .17$
OR, 95% CI	0.98 (0.97–0.98)	0.97 (0.97–0.98)	0.98 (0.97–0.99)	0.98 (0.96–0.99)	0.98 (0.94–1.01)

Notes: χ^2 is the Wald χ^2 for the variable; AOR = Odds Ratio; 95% CI = the 95% confidence interval (of prevalence or odds ratio)

Listed Ns are unweighted; percentages endorsing NUPM indicators are weighted

TABLE 2

Influence of Age of MDD Onset on NUPM Outcome Variables by Medication Class (N = 24,238)

	Lifetime NUPM	Past Year NUPM	Past 30-Day NUPM	NUPM Dependence	NUPM Abuse
Opioids	24.70% (23.80–25.63)	9.57% (9.03–10.14)	3.83% (3.47–4.23)	1.51% (1.30–1.74)	0.47% (0.36–0.61)
Statistics	**χ^2 = 103.67, p < .0001**	**χ^2 = 36.92, p < .0001**	**χ^2 = 6.62, p = .01**	**χ^2 = 3.96, p = .046**	χ^2 = 0.35, p = .55
OR, 95% CI	**0.97 (0.96–0.98)**	**0.98 (0.97–0.98)**	**0.98 (0.97–0.99)**	**0.98 (0.96–0.99)**	0.99 (0.95–1.03)
Tranquilizers	18.00% (17.14–18.84)	4.76% (4.39–5.17)	1.70% (1.48–1.97)	0.34% (0.23–0.49)	0.22% (0.16–0.29)
Statistics	**χ^2 = 57.12, p < .0001**	**χ^2 = 33.04, p < .0001**	**χ^2 = 8.96, p = .003**	χ^2 = 0.79, p = .37	**χ^2 = 28.31, p < .0001**
OR, 95% CI	**0.98 (0.97–0.98)**	**0.96 (0.95–0.98)**	**0.97 (0.95–0.99)**	0.98 (0.92–1.03)	**0.92 (0.90–0.95)**
Stimulants	15.89% (15.09–16.73)	2.82% (2.53–3.14)	1.07% (0.90–1.28)	0.44% (0.32–0.59)	0.13% (0.09–0.20)
Statistics	**χ^2 = 25.76, p < .0001**	**χ^2 = 9.05, p = .003**	χ^2 = 2.05, p = .15	χ^2 = 0.01, p = .91	**χ^2 = 9.95, p = .002**
OR, 95% CI	**0.98 (0.98–0.99)**	**0.98 (0.97–0.99)**	0.98 (0.96–1.01)	1.00 (0.97–1.04)	**0.94 (0.90–0.97)**
Sedatives	7.55% (6.94–8.20)	0.80% (0.66–0.96)	0.28% (0.21–0.39)	0.10% (0.07–0.16)	0.03% (0.02–0.06)
Statistics	**χ^2 = 4.42, p = .036**	**χ^2 = 5.36, p = .02**	χ^2 = 1.52, p = .22	χ^2 = 1.01, p = .31	χ^2 = 0.52, p = .47
OR, 95% CI	**0.99 (0.98–0.99)**	**0.97 (0.95–0.99)**	0.97 (0.93–1.02)	0.98 (0.96–1.01)	0.97 (0.89–1.06)

Notes: χ^2 is the Wald χ^2 for the variable; AOR = Odds Ratio; 95% CI = the 95% confidence interval

Bolded entries are significant at a *p*-value of .05 or less.

Listed Ns are unweighted; percentages endorsing NUPM indicators are weighted, with 95% confidence intervals in parentheses

TABLE 3

Influence of Age of NUPM Onset on MDD Outcome Variables (N = 35,155)

	Lifetime MDD	**Past Year MDD**
Sample Size	9,032	5,533
% (95%CI)	25.03 (25.26–25.18)	14.16 (13.56–14.77)
Overall Equation	$\chi^2 = 3820.74$, $p < .0001$	$\chi^2 = 6255.32$, $p < .0001$
Age Group	$\chi^2 = 27.82$, $p = .002$	$\chi^2 = 14.08$, $p = .002$
Ethnicity	$\chi^2 = 22.95$, $p = .082$	$\chi^2 = 6.70$, $p = .082$
Gender	$\chi^2 = 255.56$, $p < .0001$	$\chi^2 = 150.25$, $p < .0001$
Marital Status	$\chi^2 = 121.44$, $p < .0001$	$\chi^2 = 106.60$, $p < .0001$
Education	$\chi^2 = 9.51$, $p = .009$	$\chi^2 = 18.74$, $p = .0001$
Urbanicity	$\chi^2 = 5.66$, $p = .059$	$\chi^2 = 8.38$, $p = .015$
NUPM Onset Age	$\chi^2 = 1.78$, $p = .182$	$\chi^2 = .068$, $p = .794$
OR, 95% CI	1.00 (0.990–1.01)	1.00 (0.990–1.01)

Notes: χ^2 is the Wald χ^2 for the variable; AOR = Odds Ratio; 95% CI = the 95% confidence interval

Listed Ns are unweighted; percentages endorsing MDD indicators are weighted