‘Ecstasy’ and the Use of Sleep Medications in a General Community Sample: A Four Year Follow-up

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Declaration of interest The PATH study was supported by an NHMRC Program Grant 179805 and NHMRC Project Grant 157125. The sponsors had no role in the design, conduct or reporting of the research. None of the authors have connections (direct or indirect) with the tobacco, alcohol, pharmaceutical or gaming industries or any body substantially funded by one of these organisations.

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Ecstasy and Sleep Medications

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Keywords:

Longitudinal; cohort; ecstasy, 3,4-Methylenedioxymethamphetamine (MDMA), meth/amphetamine, general community sample

Word count

Text: 3361 (max 3500)
Abstract: 248 (max 250)

Abstract

Aims: Animal models show that a single dose of MDMA ('ecstasy') can result in long-term disruption of sleep. We evaluated the relationship between ecstasy consumption and the use of sleep medications in humans after controlling for key factors.

Design The Personality and Total Health Through Life project uses a longitudinal cohort with follow-up every four years. This study reports data from waves two and three.

Setting: Participants were recruited from the electoral roll in the Australian Capital Territory and Queanbeyan, New South Wales, Australia.

Participants: Participants were aged 20-24 years at wave one (1999-2000).

Measures: The study collected self-reported data on ecstasy, meth/amphetamine, cannabis, alcohol, tobacco and use of sleeping medications (pharmaceutical or other substances). Depression was categorised with the Brief Patient Health Questionnaire (BPHQ). Other psychosocial measures included lifetime traumas. We used generalised estimating equations to model outcomes.

Results: Ecstasy data were available from 2128 people at wave two and 1977 at wave three: sleeping medication use was reported by 227 (10.7%) respondents at wave two and 239 (12.1%) at wave three. Increased odds ratios (OR) for sleeping medication use was found for those with depression (OR=1.88, (95% confidence interval (CI) 1.39, 2.53), women (OR=1.44, 95% CI 1.13, 1.84), and increased by 19% for each lifetime trauma. Ecstasy use was not a significant predictor, but ≥monthly *versus* never meth/amphetamine use increased the odds (OR=3.03, 95% CI 1.30, 7.03).

Conclusion: Use of ecstasy appears to be associated with the use of sleeping medications but this association can be accounted for by other factors.

Introduction

'Ecstasy' (3,4-methylenedioxymethamhetamine, MDMA) is widely used, with an estimated 10.5 to 25.8 million users globally (1). In Australia, the highest prevalence is among those aged 20-29 years where nearly 10% report using ecstasy in the last year (2). This consumption raises potential health concerns as the use of ecstasy appears to have long-lasting impacts on serotonin function (3). Data from animal studies, including among non-human primates, have indicated neurotoxic effects of MDMA on the serotonin 5-HT system at doses equivalent to those used by recreational ecstasy users (4-5). Potential serotonergic neurotoxicity has been implicated in depressed mood (6-8). However, pre-existing mental health disorders in stimulant users (9), environmental and genetic risk factors plus other demographic factors (e.g. unemployment, lower education) may also account for this association (10-11).

Sleep disruption may account for, or in part account for, the increased levels of depressive symptomology often observed in ecstasy users. Sleep disruption is a prevalent symptom of mood disorder (12) and included in many measures of depression and emotional distress (13-15). It is also a potential consequence of ecstasy use due to the pharmaceutical properties of the drug (16-17) or lifestyle factors associated with its use (18). Data from animal studies has shown that even a single exposure of 15mg/kg MDMA in rats can produce increased wakefulness and motor activity evident to 28 days (19) with some impacts on sleep function still evident at 180 days in rats (20). In a sample of social drug users, clinically important levels of sleep disturbance have been observed among ecstasy users after controlling for poly-drug use (21). However, findings regarding the persistent impacts of ecstasy use on sleep patterns in humans are inconsistent, and indicate that sleep differences between users and non-users may be pre-existing or due to other drug use (22).

Few ecologically valid studies of the relationship between ecstasy use and sleep disturbance have been conducted to investigate whether or not the data from the laboratory translates to external settings. Moreover, interpretation of these findings is complicated by (a) the exact constitution of 'ecstasy' consumed outside the laboratory, which may contain a range of other psychoactive substances in addition to MDMA, and (b), the co-use of alcohol and other drugs that also impact on sleep. The acute use of meth/amphetamine is expected to increase wakefulness and reduce the total amount of sleep, followed by a rebound period of extended sleep, and then a period of sleep disruption (23-24). Both cannabis and alcohol may initially appear to have sleep-inducing properties. However, tolerance develops to the sleep-inducing effect of cannabis (22) and alcohol increases the fragmentation of sleep, with alcohol withdrawal associated with considerable sleep disruption (24). A recent study by Ogeil and colleagues considered this issue by controlling for poly-drug use (21), but did not examine the potentially important, differential impacts of different categories of drugs.

The aim of this study was to use prospective data from a representative, adult community cohort to examine the relationship between the ecstasy consumption and sleep problems, operationalised as the use of sleeping medications (pharmaceutical or other substances). To address the aforementioned limitations of former ecological studies these analyses will control for key factors, in particular, cannabis, meth/amphetamine hazardous/harmful use of alcohol and mood problems. Sleep disturbance is also associated with trauma and is one of the diagnostic features of post-traumatic stress disorder (12) so a measure of lifetime traumatic events was included too. Thus, the study will make a unique contribution in identifying whether or not the posited link between recreational use of ecstasy and depression is likely to be due to increased sleep problems.

Method

Sample

The "Personality and Total Health Through Life Project" (PATH) is a cohort study that assesses adult lifespan changes in wellbeing, mental health, personality and cognitive function. At recruitment, the cohorts were aged 20-24, 40-44 and 60-64 years with follow-up conducted every four years. The recruitment process has previously been described in detail and the sample is largely representative of the 2001 Australian Census data for the Canberra (Australian Capital Territory) and Queanbeyan (New South Wales) area of Australia (25-26). The current paper focuses on the youngest cohort due to the low lifetime prevalence of ecstasy use in the other groups. At baseline (wave one), conducted in 1999-2000, 2404 people were recruited; at wave two (2003-2004) there were 2139 (89%) re-interviews, 190 refusals, seven people had died and 68 could not be contacted. At wave three, conducted in 2007-2008, there were 1978 (82.3%) interviews, 272 refusals, 7 deaths and 51 could not be contacted and 96 had withdrawn at an earlier wave (see online Appendix A for STROBE diagram and check list). Ecstasy data were only collected at waves two and three. At both follow-ups, original participants were contacted via telephone calls, visits to their last known address, e-mail contact, use of secondary contacts, electronic telephone database and the electoral roll. For those who had moved out of the area in-person interviews were arranged if possible, but overseas participants were asked to complete a postal/email survey. The original sample size was determined by factors including estimated prevalence of the principal disorders of interest and anticipated transition rates through the course of the study. All participants in the original study who met criteria for inclusion in the current study (i.e. answered the questions on the use of ecstasy at wave two) were included in analyses.

Measures

Sleep problems were defined as self-reported, current use of any sleeping medications (*In the last month have you taken or used any pills or medications (including herbal remedies) to help you sleep).* This approach has been used in previous epidemiological studies (27). Ever use of ecstasy was assessed with *Have you ever tried any of the following Ecstasy (pills, eccy, XTC, MDMA)*. Those who endorsed this item were then asked if they had used ecstasy in the last 12 months (yes/no) and their frequency of use in this period *(options: every day, once a week, about once a month, every few months, once or twice a year, less often, don't currently use)*. The use of *amphetamines for non-medical purposes (speed, go-ee, whiz, rev, crystal, meth, crystal meth, ice, shabu, batu, uppers, ox-blood, liquid speed)* was assessed with the same pattern of questions and frequency of use options. However, an error in the skip programming at wave three resulted in those who reported no ecstasy use in the last 12 months not being asked for frequency data on their meth/amphetamine use: these people were included in the analysis as 'frequency unknown'. Thus, at wave three there were 258 people (13% of the sample or 43% of those who had used meth/amphetamine) who reported meth/amphetamine use but not the frequency of use. Alcohol use was assessed with the Alcohol Use Disorders Identification Test (AUDIT) with those scoring 8 or greater classified as hazardous users (28). At wave three, question 3 of the AUDIT was modified to reflect the Australian Guidelines in place at the time (29): women were asked about consuming five or more standard drinks and men about consuming seven or more. Cannabis use was assessed using items from an existing survey and a two item screening test (30-31). Based on these questions participants were classified as either "never users", "not current users" (last used more than 12 months prior to interview or reported "don't currently use") or "infrequent users" (used in the last 12 months, once or twice per year to every 1-4 months"), "≥monthly" (used in the last 12 months, once per month to "once a week or more"). Ecstasy use was classified into the same categories, as was meth/amphetamine except as noted above, at wave

three data on frequency was not collected for some cases. Smoking tobacco was classified as "current", "former", "never" smokers. The presence of major or other depression was derived from the standard algorithm for the nine-item Brief Patient Health Questionnaire (BPHQ) (15) (e.g. "major depression": question 1a or b and five or more of items a-h are "more than half the days" or item i endorsed: "other depression" as per major depression except endorsing two to four items.) Response options refer to feelings over the last two-weeks and are: *not at all, several days, more than half the days, nearly every day*. The BPHQ gives a 'provisional' diagnosis: to make a formal diagnosis other causes must be ruled out such as bereavement, a history of manic episodes, physical illness, medications and drug use. Lifetime trauma was assessed with ten items adapted from the National Survey of Mental Health and Wellbeing and including combat experience, life threatening accident, natural disaster, rape, sexual molestation, serious assault, torture (32). Lifetime trauma was the sum of events prior to wave two, plus events between waves two and three.

Analysis

At baseline, socio-demographic and substance use variables were compared between groups (those who have never *versus* ever used ecstasy at wave two) using chi square analysis for differences in proportions, and *t*-tests for continuous measures. The respective descriptive statistics were numbers with percentages and means with standard deviations (SD). For the longitudinal analysis, generalised estimating equation (GEE) models were used (SPSS 20.0.0). This approach overcomes many of the limitations of traditional repeated measures methods, in that it uses all available data without requiring substitution or estimation of missing values, whilst still accounting for non-independence of data from the same individuals. This avoids the exclusion of cases with non-complete data and does not assume homogeneity of correlations over waves of measurement (33). Akaike's information criterion was used to select the covariance structure (lower values showing better fit). The analyses

used binominal distributions with logit link, an unstructured correlation matrix and hybrid (Fisher plus Newton-Raphson) estimation. The model included substance use variables, lifetime trauma and socio-demographic variables that showed significant differences between users and non-users of ecstasy at wave two. The structure was specified with subject number as the repeated measure and wave the within subject variable. Cases with missing dependent variable or covariate data are excluded by GEE. The interaction of ecstasy and time was examined to explore whether differences in ecstasy use across waves was associated with differences in sleep. This interaction was not significant and is thus not reported in the results. Finally, logistic regression, with simultaneous entry of measures, was used to predict wave three sleeping medications from wave two data.

Table 1 here

Results

Of the 2139 participants at wave two, 2128 (99.5%) provided data on ecstasy use of whom 227 (10.7%) reported use of sleep medications. Of the 1978 participants at wave three, 1977 (99.9%) provided ecstasy data (658, 33% ever used: 1319, 67% never used), of whom 239 (12.1%) used sleep medications. At both waves, of those who had ever used ecstasy, a greater proportion were male, only had high school education, were employed, had never been married, had higher trauma scores and a greater proportion used sleep medications. They also had a greater proportion reporting current tobacco, cannabis and meth/amphetamine use and were classified as hazardous alcohol consumers (Table 1). Participants could record multiple types of sleeping medications or aids, with the most frequently reported at both waves being benzodiazepines (or other hypnotics), herbal remedies, and antihistamines (Table 2). Notably, a greater percentage of ecstasy users reported the use of benzodiazepines at both waves, compared to non-ecstasy users. Finally, there were significant correlations between all types of substances used, in particular ecstasy and meth/amphetamine (Spearman's rho wave two .708: wave three .693) (online Appendix B).

Table 2 here

Table 3 shows the GEE model on the left hand side. The odds of using sleep medications was increased for females (odds ratio (OR) = 1.44 95% confidence interval (CI) 1.13, 1.84) and for those who were classified as having depression (OR = 1.88 95% CI 1.39, 2.53). Each major trauma increased the odds of sleeping medication use by 19% (95% CI 1.12, 1.26). The association between ≥monthly ecstasy (*versus* never) (OR = 1.10) and sleep medication was not significant. Those who used meth/amphetamine ≥monthly *versus* never had increased odds of sleep medication use (OR = 3.03, 95% CI 1.30, 7.03). In addition, ≥monthly cannabis use (*versus* never) (OR = 1.78 95% CI 1.05, 3.01) was associated with an increased odds of using sleeping medications. Logistic regression of wave two data on wave three sleeping medication showed that none of the substance use variables were significant predictors, but that gender (OR = 1.37), depression (OR = 1.65) and trauma (OR = 1.17) remained significant predictors (Table 3 right hand side).

Table 3 here

Two sensitivity analyses were conducted. The first restricted sleep medications to 'pharmacist only' or prescription medications, defined as benzodiazepines (or other hypnotics), antihistamines, and analgesics combined with antihistamines. This analysis was conducted to determine whether the above findings were biased by the inclusion of non-specific or less effective products. There were 85 (4.0%) people using these at wave two and 115 (5.8%) at wave three. In replicating the earlier analytic plan, ecstasy use was still not significantly related to the use of sleep medication. Meth/amphetamine produced similar results to those of the main analysis (>monthly OR = 4.18), with gender (female OR = 1.63) and depression (OR = 1.94) significantly increasing the odds of using sleep medications, while each additional trauma increased the odds by 24%. The second sensitivity analysis

excluded participants with missing data on the frequency of meth/amphetamine use at wave three (Table 4, right hand half). The results were similar to those in the main analysis.

Table 4 here

Discussion

Data from animal studies have shown that the use of MDMA ('ecstasy') disrupts sleep patterns over an extended period (19). However, findings from human ecstasy users are equivocal with studies finding increases and decreases in sleep (16, 34). Furthermore, data from naturalistic settings have typically recruited purposefully sampled groups or convenience samples and even where poly-drug use has been accounted for in analyses, the effects of different drug classes are not examined separately (21). This study makes an important contribution through its employment of a general population sample to assess the relationship between the use of ecstasy and sleep problems, indexed as the use of sleeping medications (pharmaceutical or other substances) while controlling for other key factors. Univariate statistics showed that ecstasy users reported greater rates of sleep medication use. However, multivariate models found no increased odds of sleep medication use for ecstasy users compared to non-users, when their use of other drugs was accounted for. Use of meth/amphetamine or cannabis were associated with a greater likelihood of sleeping medication use in these models. These findings were largely replicated in a sensitivity analysis restricted to prescription or pharmacist only sleeping medications.

Poly-drug use is prevalent amongst ecstasy consumers (10-11, 35) and is one of the limiting factors in translating data from animal models involving MDMA to human ecstasy users. In the present study, people who used meth/amphetamine monthly or more had three times the odds of using any sleeping medication and four times the odds of using a prescription or pharmacist only medication. Amphetamine-induced sleep disorder with insomnia in the acute

phase and hypersomnia during withdrawal is well characterised (12). However, after a few days of hypersomnia, insomnia is likely, continuing at least until 20 days (23). Given this disruption, the use of sleeping medications is unsurprising following the use of meth/amphetamine in either the immediate aftermath or to cope with persistent insomnia.

The absence of a significant relationship between ecstasy and sleeping medication use once other drug use was accounted for indicates that the higher rates of sleeping medication reported amongst ecstasy users in our community sample is attributable to the greater use of methamphetamines and/or cannabis also observed amongst this group. It is worth noting, however, that this is a statistical finding and does not rule out the possibility that (some) ecstasy users do take sleeping medications to address the effects of this drug. However, the use of other drugs that are more strongly associated with sleep medication use amongst this group means that it not possible to definitively identify which drug may lead to medication consumption. Further, the absence of a multivariate association between ecstasy use and sleep medication use is an important finding and contribution to the literature as it demonstrates the importance of measuring and controlling for poly-drug use. Inability to do so may lead to erroneous conclusions about sleeping problems amongst ecstasy users.

The use of sleeping medications was also associated with: being female, being categorised with depression and life-time traumatic events. Reasons for the higher prevalence of sleeping problems among women (36) is not clearly understood, but both lifespan and menstrual fluctuations in hormones levels have been implicated (37). The relationship between sleep disturbance, traumatic events and mental health problems is complex, with insomnia associated with the risk of developing depression (38); pre-existing sleep disturbance being a risk factor for the development of mental health problems following traumatic events (39)

and traumatic events disrupting sleep (40). Thus, the triumvirate of non-substance use risk factors reported in the current study are consistent with the literature.

The consumption of sleeping medications was used as a proxy for sleep disturbance in this study. The BPHQ (which was included as a covariate in our models) contains two items pertaining to sleep ('Trouble falling or staying asleep, or sleeping too much' and 'Feeling tired or having little energy'). Thus, it is possible that the inclusion of the BPHQ as a measure of depression may mask some of the relationship between meth/amphetamine use, or indeed ecstasy use, and sleeping medications. A sensitivity analysis (results not shown) removing the BPHQ from the model marginally increased the odds ratio for meth/amphetamine but not for ecstasy, reinforcing the interpretation that the extent of sleep disruption for ecstasy users in this group was not severe.

There are a number of limitations associated with this study. First, sleep disruption was not directly assessed either with self-report measures or polysonography. However, even self-reported sleep data is not without criticisms (41). Second, the temporal relationship between drug use and sleep medication cannot be guaranteed. The use of sleeping medications in the PATH study had a reference period of the last month and substance use data was collected for the last year. Thus, whilst it is likely that the latter was consumed first, the length of time between drug use and sleep medication use may vary. That is, it was monthly or more frequent use or that was associated with the use of sleeping medications, but it is unknown if this was during the acute phase or during a later period when sleep disruptions may persist. Third, the purity and presents of adulterants in the ecstasy is unknown. Street 'ecstasy' may contain little or no MDMA and instead maybe a mixture of meth/amphetamine, ketamine and other substances (42). Over the period 2003-2008, the purity of Australian drug seizures for

this class of drugs remained relatively stable, although the proportion of ecstasy users in the ACT reporting 'high' purity declined (43-44). Thus, these findings may not generalise to settings with different purity formulations of ecstasy. Four, the missing frequency data on 258 meth/amphetamine users at wave three represent 43% of those using this substance. If all these cases were ≥monthly users, the magnitude of the OR would be reduced but still significant: if they were all infrequent users, this category would still not be significant (analysis not shown). Nevertheless, these shortcoming should not negate the importance of data collected from a representative community cohort in contrast to the previous overreliance on snowballing and purposive recruitment (18).

Conclusion

Animal models show long-term disruption of sleep following exposure to MDMA. The present study is one of few to examine this relationship in a representative general community sample, and the first to account for concurrent use of other drugs associated with sleeping problems that are commonly consumed by ecstasy users. We found that ecstasy use was not associated with the use of sleeping medications when other drug use was accounted for. There was, however, a strong relationship between the use of meth/amphetamine and sleep medication. Future studies must measure and account for this association to avoid misinterpretation of the univariate link between ecstasy use and poor sleep.

Acknowledgements

We thank Kaarin Anstey, Anthony Jorm, Bryan Rodgers, Trish Jacomb, Karen Maxwell and the PATH interviewing team for their contribution to the PATH Through Life Project.

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Table 1: Participant characteristics, sub-divided by ecstasy use status at wave two and wave three

Variable		Ecstasy: never used (n = 1459: 69%)	Ecstasy: ever used (n = 669: 21%)	Statistic	Ecstasy: never used (n = 1319: 67%)	Ecstasy: ever used (n = 658: 23%)	Statistic
			Wave 2			**Wave 3**	
Gender	female n (%)	823 (56)	297 (44)	χ^2 26.6 (1)	743 (56)	314 (48)	χ^2 13.1 (1)
	male n (%)	636(44)	372 (56)	*p*<.001	576 (44)	344(52)	*p*<.001
Education	high school n (%)	257 (18)	151 (23)	χ^2 7.4 (2)	156 (12)	116 (18)	χ^2 14.4 (2)
	post school n (%)	541 (37)	239 (36)	*p*=.025	496 (38)	248 (38)	*p*=.001
	tertiary n (%)	659 (45)	279 (42)		646 (50)	281 (44)	
Employment	full or part time n (%)	1259 (86)	587 (88)	χ^2 8.6 (2)	2438 (88)	1179 (89)	χ^2 13.1 (2)
	want more work/unemployed n (%)	68 (5)	43 (6)	*p*=.012	94 (3)	71 (5)	*p*=.001
	not in the labour force n (%)	132 (9)	39 (6)		246 (9)	77 (6)	
Ever married/de facto	yes n (%)	521 (36)	101 (15)	χ^2 94.6 (1) *p*<.001	762 (58)	241 (37)	χ^2 78.8 (1) *p*<.001
BPHQ	major or other n (%)	148 (10)	92 (14)	χ^2 6.0 (1) *p*=.015	127 (10)	58 (9)	χ^2 0.4 (1) *p*=.555
Lifetime trauma	mean (SD)	1.2 (1.4)	1.5 (1.6)	*t* 4.2 (2089) *p*<.001	1.8 (1.8)	2.0 (1.9)	*t* 2.7 (1870) *p*=.007
Sleep medications	yes n (%)	131 (9)	96 (14)	χ^2 13.8 (1) *p*<.001	141 (11)	98 (15)	χ^2 7.3 (1) *p*=.007
Hazardous alcohol [a]	yes n (%)	279 (19)	324 (49)	χ^2 193.7 (1) *p*<.001	194 (15)	284 (44)	χ^2 197.0 (1) *p*<.001
Tobacco	never n (%)	979 (67)	245 (37)	χ^2 192.5 (2)	900 (68)	261 (40)	χ^2 157.6 (2)
	former n (%)	198 (14)	121 (18)		228 (17)	175 (27)	

	current n (%)	281 (19)	302 (45)	p<.001	191 (15)	222 (34)	p<.001
Cannabis	never n (%)	507 (35)	7 (1)	χ^2 640.0 (3)	438 (33)	9 (1)	χ^2 419.7 (3)
	not current user n (%)	815 (56)	303 (46)	p<.001	809 (62)	442 (67)	p<.001
	infrequent user n (%)	101 (7)	184 (27)		33 (3)	123 (19)	
	≥monthly user n (%)	31 (2)	173 (26)		33 (3)	82 (13)	
Meth/amphetamine	never n (%)	1338 (94)	201 (30)	χ^2 982.6 (3)	1202 (91)	174 (27)	χ^2 1007.5 (3)
	not current user n (%)	80 (6)	256 (38)	p<.001	114 (9)	127 (19)	p<.001
	infrequent user n (%)	11 (<1)	169 (25)		2 (<1)	85 (13)	
	≥monthly user n (%)	0 (0)	42 (6)		1 (<1)	13 (2)	
	unknown frequency n (%)	-	-		0 (0)	258 (39)	
Ecstasy	never n (%)	1459 (100)	-	Not assessed	1319 (100)	-	Not assessed
	not current user n (%)	-	353 (53)		-	477 (73)	
	infrequent user n (%)	-	247 (37)		-	163 (25)	
	≥monthly user n (%)	-	69 (10)		-	18 (3)	

[a] AUDIT score ≥8 = hazardous: BPHQ = Brief Patient Health Questionnaire classified with major or other depression.
Not current user = not in the last 12 months: Infrequent user = in the last 12 months but less than monthly use

Missing data wave two: gender 0: education 2: employment 0: married 2: BPHQ 13: lifetime trauma 37: sleep medications 1: alcohol 12: tobacco 2: cannabis 7: Meth/amphetamine 1

Missing data wave three: gender 0: education 34: employment 0: married 1: BPHQ 10: lifetime trauma 105: sleep medications 1: alcohol 39: tobacco 0: cannabis 8: Meth/amphetamine 1

Table 2 Sleeping aids reported at wave two (n = 227) and at wave three (n = 239): multiple substances could be recorded

Categories		Ecstasy: never used n=131 **Wave 2**	Ecstasy: ever used n=96 **Wave 2**	Ecstasy: never used n=141 **Wave 3**	Ecstasy: ever used n=98 **Wave 3**
Antidepressants	n (%)	5 (3)	0 (0)	5 (3)	0 (0)
Antihistamines	n (%)	17 (10)	12 (9)	30 (17)	7 (6)
Antihistamines + Analgesics	n (%)	7 (4)	1 (1)	4 (3)	7 (6)
Benzodiazepines or other hypnotics [a]	n (%)	28 (17)	38 (28)	30 (17)	31 (27)
Cannabis &/or alcohol	n (%)	0 (0)	5 (4)	2 (1)	2 (2)
"Cold & 'flu" medication	n (%)	4 (2)	4 (3)	5 (3)	0 (0)
Magnesium &/or calcium supplement	n (%)	2 (1)	3 (2)	4 (2)	4 (3)
Melatonin	n (%)	1 (1)	1 (1)	1 (1)	3 (3)
Other analgesics	n (%)	22 (13)	6 (5)	13 (7)	9 (8)
Other herbal	n (%)	34 (21)	30 (23)	34 (19)	17 (15)
Valerian	n (%)	32 (20)	24 (18)	32 (18)	15 (13)
Other	n (%)	12 (7)	9 (7)	6 (3)	7 (6)
Total substances	n	**164**	**133**	**175**	**116**

Generic & trademark brands named in each category
Antihistamines: Dozile, Doxylamine Succinate, Phenergan, Polaramine, Restavit,
Antihistamine + Analgesic: Dolased, Mersyndol

Benzodiazepines: Alodorm, Mogadon, Normison, Serpax, Temazepam, Temaze, Temtabs, Valium, Xanax
Other analgesics: Ibuprofen, Naproxen, Nurophen, Paracetamol, Panadine Forte, Panadol, Tylenol
Other herbal includes: Camomile tea, Chinese herbal medicine, lavender, ‘tranquil night’ tablets
[a] “Stilnox or Imovane”

Table 3: Predictors of sleeping medication use at waves two and three (left hand side, generalised estimating equation GEE model: n=2082) and predictors of wave three sleeping medications from wave two data (right hand side, logistic regression: n=1852)

Variable	**(reference group)**	**GEE**			**Logistic Regression**		
		***p* value**	**B**	**95 % CI**	***p* value**	**B**	**95 % CI**
Gender	(male)	**.004**	**1.44**	1.13-1.84	**.041**	**1.37**	1.01, 1.86
Education	Tertiary	.468	1.13	0.82-1.55	.841	0.96	0.53, 1.17
	Post-school (≤high school certificate)	.876	0.98	0.72-1.33	.231	0.78	0.65, 1.43
Employment	Not in labour force	.737	0.93	0.62-1.40	.671	0.88	0.49, 1.58
	P-T want more work/unemployed (full-time/part-time)	.134	1.40	0.90-2.19	.227	1.43	0.80, 2.57
Ever married /de facto	(yes)	.158	1.19	0.94-1.51	.166	1.28	0.90, 1.80
Depression	(no)	**<.001**	**1.88**	1.39-2.53	**.015**	**1.65**	1.10, 2.47
Lifetime trauma	(none)	**<.001**	**1.19**	1.12-1.26	**.002**	**1.17**	1.06, 1.28
Hazardous alcohol	(no)	.132	1.22	0.94-1.58	.652	1.08	0.77, 1.53
Tobacco	Current	.172	1.24	0.91-1.69	.370	1.19	0.81, 1.75
	Former (never)	.742	0.95	0.68-1.31	.163	1.34	0.89, 2.03
Cannabis	≥monthly	**.031**	**1.78**	1.05-3.01	.598	1.20	0.61, 2.36
	infrequent	.868	1.04	0.64-1.70	.984	0.99	0.55, 1.79
	not current (never)	.077	1.36	0.97-1.91	.547	1.14	0.74, 1.75
Ecstasy	≥monthly	.834	1.10	0.47-2.54	.250	1.80	0.66, 4.90
	infrequent	.556	1.16	0.71-1.90	.095	1.64	0.92, 2.94
	not current (never)	.681	0.93	0.65-1.32	.093	1.46	0.94, 2.27
Meth/amphetamine	≥monthly	**.010**	**3.03**	1.30-7.03		0.82	0.24, 2.79
	infrequent	.465	1.23	0.71-2.15		0.96	0.50, 1.82
	frequency unknown	**.026**	**1.70**	1.07-2.71		--	--
	not current (never)	.640	1.09	0.75-1.59		0.85	0.53, 1.35

PT = part-time: Goodness of fit quasi likelihood criterion: 2583.65

Table 4 Sensitivity analyses a) for use of prescription or pharmacist only sleeping medications (left half of table n=2082) and b) excluding those with unknown frequency of meth/amphetamine use at wave three (right half n=2079).

Variable	**(reference group)**	***p* value**	**B**	**95 % CI**	***p* value**	**B**	**95 % CI**
		Prescription / pharmacist only			***Excluding 258 unknown frequency cases***		
Gender	(male)	**.006**	**1.63**	1.05-2.32	**.002**	**1.50**	1.15-1.89
Depression	(no)	**.001**	**1.94**	1.31-2.87	**<.001**	**1.77**	1.32-2.46
Lifetime trauma	(no)	**<.001**	**1.24**	1.15-1.34	**<.001**	**1.27**	1.34-2.33
Meth/amphetamine	≥monthly	**.020**	**4.18**	1.25-13.99	**.010**	**3.08**	1.31-7.27
	infrequent	.993	1.00	0.41-2.48	.524	1.20	0.68-2.13
	frequency unknown	.177	1.60	0.81-3.18	--	--	--
	not current (never)	.906	0.97	0.55-1.70	.662	1.09	0.74-1.60

Model (a) included all the variables from table 3. Goodness of fit quasi likelihood criterion: 1447.24:
Model (b) included all the variables from table 3. Goodness of fit quasi likelihood criterion: 2388.20

Appendix A

STROBE Diagram

20s cohort

Wave 1 mail out		**Percentages of 12411**
Letters sent	12411	100
Out of age range	5058	40.7
Moved out of area	1061	8.5
Not found	2190	17.6

Wave 1 eligible 1999-2000		**Percentages of 4105**
Eligible contacts	4105	100
Refused	1701	41.4
Interviewed wave 1	2404	58.6

↓

Wave 2 2003-4		**Percentages of 2404**
Not found	68	2.8
Dead	7	0.3
Refused	190	7.9
Interviewed	2139	89.0
Reported ecstasy status	2138	88.9

↓

Wave 3 2007-8		**Percentages of 2404**
Withdrew at earlier wave	96	4.0
Not found	51	2.1
Dead	7	0.3
Refused	272	11.3
Interviews	1978	82.3
Reported ecstasy status	1977	82.2

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓
Methods			
Study design	4	Present key elements of study design early in the paper	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ n/a
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓
Bias	9	Describe any efforts to address potential sources of bias	✓
Study size	10	Explain how the study size was arrived at	✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers **potentially eligible,** examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓
		(b) Give reasons for non-participation at each stage	✓
		(c) Consider use of a flow diagram	✓
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓
		(b) Indicate number of participants with missing data for each variable of interest	✓
		(c) Summarise follow-up time (eg, average and total amount)	✓
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓
		(*b*) Report category boundaries when continuous variables were categorized	✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential	✓

		bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix B (online supplement)

Spearman's correlation coefficients between each category of substances reported. Below the diagonal are results from wave two: above the diagonal from wave three

	Alcohol	**Tobacco**	**Cannabis**	**Ecstasy**	**Meth/amphetamine**	**Sleep medications**
Alcohol		.267	.303	.350	.297	.075 *p*=.001
Tobacco	.209		.435	.291	.367	.071 *p*=.002
Cannabis	.336	.441		.476	.464	.068 *p*=.003
Ecstasy	.333	.300	.555		.693	.062 *p*=.006
Meth/amphetamine	.313	.370	.552	.708		.078 *p*=.001
Sleep medications	.065 *p*=.003	.123	.111	.092	.118	

All p values <.001 except as marked

Categories: alcohol (Hazardous use yes/no), tobacco (current, former, never), cannabis (≥ monthly, infrequent, former, never), ecstasy (≥ monthly, infrequent, former, never), meth/amphetamine (wave two: ≥ monthly, infrequent, former, never) (wave three:frequency unknown, ≥ monthly, infrequent, former, never)