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Prospective pathways between heroin use and non-medical use of prescription opioids: Trajectories among young Swiss men

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Summary

Background. So far few studies have focused on the last steps of drug-use trajectories. Heroin has been described as a final stage, but the non-medical use of prescription opioids (NMUPOs) is often associated with heroin use. There is, however, no consensus yet about which one precedes the other. **Aims.** The objective of this study was to test which of these two substances was likely to be induced by the other using a prospective design. **Material and methods.** We used data from the Swiss Longitudinal Cohort Study on Substance Use Risk Factors (C-SURF) to assess exposure to heroin and NMUPO at two times points (N = 5,041). Cross-lagged panel models provided evidence regarding prospective pathways between heroin and NMUPOs. Power analyses provided evidence about significance and clinical relevance. **Results.** Results showed that heroin use predicted later NMUPO use ($\beta = 1.217$, $p < 0.001$) and that the reverse pathway was non-significant ($\beta = 0.240$, $p = .233$). Heroin use seems to be an important determinant, causing a 150% risk increase for NMUPO use at follow-up, whereas NMUPO use at baseline increases the risk of heroin use at follow-up by a mere non-significant 20%. **Conclusions**. Thus, heroin users were more likely to move to NMUPOs than non-heroin users, whereas NMUPO users were not likely to move to heroin use. The pathway of substance use seemed to include first heroin use, then NMUPO use.

Key Words: Drug use; longitudinal study; population-based sample.

1. Introduction

Involvement in drug use has to be a focus of attention because drug use is especially harmful and is responsible for a heavy burden of disease all over the world. The sequential stages of involvement in drug use is a commonly agreed model in modern Western societies [14, 19-21, 34], and heroin is often described as a final stage drug in the drug-use trajectory [1, 38, 39]. Heroin users are also known to be extensive users of non-medical use prescription drugs (i.e. the use of prescription drugs without a prescription or in ways not recommended by a doctor [3, 17, 22, 27]). Several studies investigating heroin users' non-medical use of prescription drugs have focused on non-medical use prescription opioids (NMUPOs), as these two kinds of substances may be used alternatively with similar effects. A conventional trajectory shows that NMUPOs act as substitutes for heroin; thus their use occurs a certain time after heroin initiation [8, 11, 16]. Some recent studies have, however, reported trajectories of misuse and dependence starting with NMUPOs and then moving on to heroin [7, 13, 24, 31, 32, 35]. Thus, causal pathways between heroin and NMUPO still

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call for clarification.

Moreover, several other methodological issues should be highlighted. First, previous studies focusing on the correlates of heroin use and NMUPOs mostly included all injectable-drug users (i.e. not focusing on heroin users alone) [24, 27] or heroin users engaged in methadone maintenance treatment [9, 26, 35], using syringe-exchange services [31] or convenience samples/respondents driven samples of heavy drug users [6, 10, 30]. Studies focusing on general pathways from population-based samples are still too few, and one can wonder about the common path for "occasional" or "experimental" heroin users who represent 90-95% of drug users [23]. Second, to our knowledge, all these studies took place in the United States. The likelihood of drug use depends on several factors, including contextual and cultural factors such as availability, opportunities or norms [5, 25]. For example, one common, well-studied prescription opioid in the United States is OxyContin®, which was reformulated in late 2010. The new formulation made OxyContin more difficult to manipulate for abuse than the older one [6, 15, 29], and some individuals who had previously abused OxyContin switched to heroin thereafter. This phenomenon may have induced an artifact impression of NMUPOs as a category of gateway drugs for heroin use, as described in recent US studies [7, 24, 31, 32]. Studies in other countries, especially in Europe, are too few in number. Lastly, most of these studies have a cross-sectional design. The questionnaires include questions about the first use of heroin and NMUPOs, but in a retrospective way. This procedure may be associated with increased bias, such as recall bias. Prospective studies are needed to study how drug users start to use drugs and the paths between one and another.

Thus, the aim of the present study has been to give some insight into stages of drug use involving heroin use and NMUPOs within a population-based sample of young Swiss men. Prospective pathways between heroin and NMUPOs were tested to identify which substance increased the likelihood of successive use of the other.

2. Materials and methods

2.1. Participants and procedures

We used data from the Cohort Study on Substance Use Risk Factors (C-SURF), a longitudinal study designed to assess substance use patterns in young Swiss men. Participants were enrolled in three of Switzerland's six army recruitment centres, covering 21 of the country's 26 cantons and located in (French-speaking) Lausanne, and in (German-speaking) Windisch and Mels. As army recruitment is compulsory in Switzerland, and there is no pre-selection for conscription, all young men around 20 years old were eligible for study inclusion. We carried out assessment outside the army environment and independently of eligibility for military service. Participants who gave their written consent to participate in recruitment centres were invited two weeks later by mail or email to fill in a pen-and-paper or an online questionnaire, according to the favourite way indicated by them in the written consent form. For follow-up, all the participants were similarly invited to fill in the questionnaire, by mail or email. We collected baseline data between September 2010 and March 2012, and follow-up data between January 2012 and April 2013. A total of 5,990 participants filled in the baseline questionnaire, and 5,223 (87.2%) filled in the follow-up questionnaire. Missing values were listwise deleted, and the final sample consisted of 5,041 participants (96.5% of the follow-up sample). Studer et al. [37] gave more information on sampling and non-response. Put briefly, non-respondents were most likely substance users, but the non-response bias was small. Lausanne University Medical School's Clinical Research Ethics Committee approved the study protocol (Protocol No. 15/07).

2.2. Measures

2.2.1.Heroin use.

We assessed heroin use by asking participants whether they had used heroin during the previous twelve months, both at baseline and then at follow-up. Answers were collected on a three-point scale ("never", "1-3 times", "4 times or more"), and recoded as 'used' or 'not used' because heavier use was very rare in the sample.

2.2.2.Non-medical use prescription opioids (NMUPOs).

We assessed the use of prescription opioids without a doctor's prescription or for reasons other than those indicated, during the previous twelve months, both at baseline and follow-up. The answers were collected on an eight-point scale ("never", "1 time/year", "2-3 times/year", "4-9 times/year", "1-2 times/month", "3-4 times/month", "2-3 times/week", "4 times or more/week") and recoded dichotomously as 'used' or 'not used', because heavy or even regular use was rare in the sample. The question dealt with

"strong painkillers": "e.g. based on Buprenorphine (Tamgesic®), Codeine (Benylin®), or opium-based products (Fentanyl, Hydrocodon, Jurnista®, Palladon®, Targin®, Oxycontin®, Vicodin®, Dilaudid®) or DXM (Bexin®) (not mere painkillers such as Aspirin or Paracetamol)." Thus, over-the-counter painkillers were excluded.

2.2.3. Use of other drugs.

We also assessed the use, over the previous 12 months, of other illicit drugs (i.e. cannabis, hallucinogens, salvia divinorum, speed, amphetamine, methamphetamine, crystal meth, poppers, solvents for sniffing, ecstasy, cocaine, ketamine, research chemicals, and spice) and of non-medical use of other prescription drugs: sleeping pills (e.g. Benzodiazepine (Dalmadorm®, Rohypnol®, Halcion®), Barbiturate, Chloralhydrate (Nervifene®), zopiclon, zolpidem (Imovane®, Stilnox®)), tranquilizers (e.g. Benzodiazepine (Valium®, Xanax®, Librax®, Temesta®, Normison®, Demetrin®, Dalmadorm®) or muscle-relaxing products), stimulants (e.g. Amphetaminsulphate (Aderall), Atomoxetine (Strattera®), Methylphenidate (Ritalin®)), antidepressants (Remeron®, Fluoxetine®, Citalopram®, Trimin®), and beta blockers (e.g. Propranolol (Inderal®), Atenolol (Atenil®, Tenormin®), Metoprolol (Lopresor®)). We computed four overall variables to cover the use of other drugs: 1) illicit drug use at baseline, 2) illicit drug use at follow-up, 3) non-medical use of prescription drugs at baseline, and 4) non-medical use of prescription drugs at follow-up. Each variable was coded dichotomously as 'used' if at least one drug of the class was used, or 'not used' otherwise.

Drug use was assessed using the standards of the European Monitoring Centre for Drugs and Drug Addiction (EMCDAD, see for example [10]).

2.3. Statistical analyses

We first calculated descriptive statistics to see the prevalence rate of heroin and NMUPO users within the sample. Then, we used cross-lagged panels models to test the predominant causal influence between heroin and NMUPO. The model included a) autoregression (i.e. regression between the same variable at baseline and follow-up), b) synchronous correlations (i.e. correlations between different variables at the same time point), c) causal paths with cross-lagged paths from heroin use to NMUPO, and d) reverse-causal paths with cross-lagged paths from NMUPO to heroin use. We used probit regressions with theta parameterization including a robust weighted least squares estimator (WLSMV). Due to low sample size, the model had to be tested by checking the following variables one by one: age, other illicit drug use, and non-medical use of other prescription drugs. To test whether the low sample size of heroin users led to a lack of power, we also performed power analyses. Simulation studies were carried out using non-parametric bootstrap in order to estimate achieved power for detecting significant relationships for various sample sizes. All statistical examinations were carried out using Mplus 7 [30] and R (2014).

3. Results

The mean age of the participants was 19.97 ± 1.22 years at baseline and 21.26 ± 1.23 years at follow-up. Around 15 months separated baseline data collection from follow-up data collection.

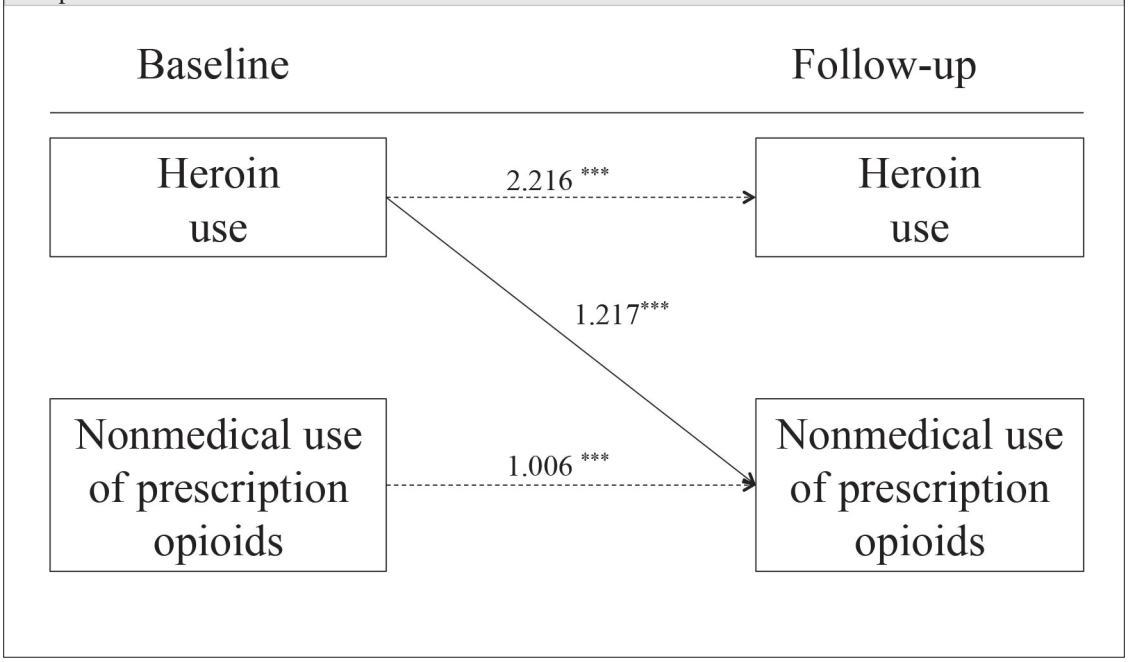
Descriptive statistics are shown in Table 1. A minority of the participants used heroin both at baseline (0.3%) and follow-up (0.8%). NMUPO had a higher prevalence rate, with 6.5% of users at baseline and 6.1% of users at follow-up.

Figure 1 presents the cross-lagged model testing the prospective pathways between heroin use and NMUPOs. Each drug at baseline significantly predicted the level of the same drug at follow-up: heroin use at baseline predicted heroin use at follow-up (β=2.216, $p<0.001$, 5.7-fold risk increase, power=100%), while NMUPO use at baseline predicted NMUPO use at follow-up (β=1.006, $p<0.001$, 2.1-fold risk increase, power=100%) Moreover, heroin use at baseline predicted NMUPO use at follow-up

Table 1. Prevalence rates of drug use

	Baseline, % (N)	Follow-up, % (N)
Heroin	0.3 (16)	0.8 (38)
Non-medical use of prescription opioids	6.65 (327)	6.1 (306)
Other illicit drugs	32.4 (1,631)	33.4 (1,685)
Non-medical use of other prescription drugs	10.4 (525)	9.5 (479)

Figure 1. Cross-lagged model examining the associations between heroin use and non-medical use of prescription opioids. (In the interests of clarity, this figure only presents significant cross-lagged paths. However, all the cross-lagged paths depicted in Figure 1 were included in the final model (within-time correlations between variables at both Time 1 and Time 2 and path from NMUPO to heroin use)).
*** p < .001.



(β=1.217, p<0.001, 2.5-fold increase, power=93%), but the reverse-causal path from NMUPO to heroin use was non-significant (β=0.240, p=0.233, 1.2-fold risk increase, power=26%, number of participants needed for a power=90%: 45,000). Adjustment by the previously mentioned covariates did not yield any significant change.

4. Discussion

This study aimed to give some insight into the stages of drug use involving use of heroin and NMUPOs within a large population-based sample of young Swiss men.

Heroin use was a problem in a minority of the sample, as less than 1% used heroin. On the other hand, NMUPO use was more frequent, as over 6% used opioids without a doctor's prescription. This result is in line with previous studies reporting opioids and painkillers as being the most common substances used after alcohol, tobacco, and cannabis [4, 12, 18, 28].

Prospective pathways showed that heroin users were more likely to start using an NMUPO, but not the reverse: NMUPO users were not significantly more prone to start using heroin. Indeed, cross-lagged panel models showed a causal path between heroin and NMUPO use, but not the reversed causal path. For this last path, the power analysis allowed the testing of whether there was a lack of significance due to low sample size. The results of the simulation study showed that our sample size yields a 26% power for detecting such an effect. If such a link exists, a sample size of 45,000 participants would be required to achieve a 90% power. It did not seem therefore, that the non-significant result was due to a lack of power. Moreover, even if there was a causal relationship between NMUPOs and later heroin use, this link remained marginal. Indeed, heroin use at baseline raised the risk of NMUPO use at follow-up by a nearly 2.5-fold factor, whereas NMUPO use at baseline was found to be of only marginal importance on heroin at follow-up (a 1.2-fold risk increase). Therefore, the clinical relevance of the relation between NMUPO use at baseline and heroin use at follow-up is questionable: NMUPO use at baseline increases the risk of heroin use at follow-up by a mere 20%, while in the reverse pathway, heroin use seems to be an important determinant, causing a 150% risk increase for NMUPO use at follow-up.

The main determinant of heroin use at follow-up appeared to be the use of heroin at baseline (470%). As a result, the main trajectory for heroin users was to continue to use heroin, and additionally to start using NMUPOs (150%), but not to have started initially with NMUPOs (20%). By contrast, there were opioid us-

ers whose initial use had been of an NMUPO (110%) and others who had started with heroin (150%).

These results supported the hypothesis of a pathway going from heroin to NMUPO use [8, 11, 16]. NMUPOs did not increase the likelihood of using heroin [24, 32, 35]. This result is an important one, as NMUPOs account for the most common non-medical use of prescription drugs, and their prevalence rate is second only to cannabis in the US [4, 12, 18, 28] and in Switzerland [2]. The Swiss drug scene is different from that in the US, where most of the studies focusing on paths between heroin and NMUPO were carried out. The main difference is found in the case of OxyContin use. This opioid is not especially popular among drug users in Switzerland, so the reformulation of OxyContin in late 2010 may not have induced a transition from NMUPO to heroin use, as was the case in the US, where the recreational use of OxyContin use was especially high [6, 15, 29]. Switzerland also differs from the US by offering many opportunities of substitution treatment for heroin users, who are not excluded from treatment centres if they happen to use heroin again, unlike the situation in the US. Other contextual factors are similar in these two countries. In the US, it is increasingly difficult to obtain prescription drugs, due to prescription drug monitoring programmes, whereas heroin has become cheaper and more accessible [36]. In Switzerland, opioids are not particularly easy to get, as drug users need a special prescription of narcotics to get opioids (except for codeine), but without there having been any recent change in prescription drug monitoring programmes. Heroin is also quite cheap in Switzerland. To sum up, these phenomena are more recent in the US, and may have contributed to the switch from NMUPO to heroin use. Further studies are needed in order to test whether these new contextual factors lead to trajectories involving first heroin, and then NMUPO use.

This study had several limitations. The major limitation was a reflection of the study's inherent strength: the sample was based on a population of young adults. De facto, the sample size of heroin users was small. Therefore, data from larger samples are now needed. Another shortcoming is that it was not feasible to include any women in the study. Further investigation is needed to see whether the prospective pathways highlighted in this study also fit women. A third limitation was that heroin use showed a quite late onset (22.1 years of age in the US, [33]), so it is possible that participants in the current study, who were 19.97 years of age on average at baseline, and 21.26 at follow-up, had not yet experienced heroin. Another shortcoming was that the study focused on substance use (i.e. use at least one time in the previous twelve months versus non-use). Studies in the US often deal with abuse and dependence. Therefore, further studies should include measures of frequency of use and misuse in order to identify users who will later develop problematic use. That procedure would allow testing whether the pathway identified for substance use also fits substance misuse and dependence. The 15-month follow-up was quite short in terms of the adequate assessment of such trajectories. Finally, we do not know whether NMUPOs were used by our participants to 'get high' or as self-medication; thus further research is now needed to investigate the reasons for use, and why users switched from heroin to an NMUPO.

5. Conclusion

In conclusion, this study yielded insights into the final stages of involvement in drug use in a population-based sample. Clinically relevant prospective pathways go from previous heroin use to continued heroin use and starting NMUPO use, whereas previous NMUPO use leads only to continuing with NMUPOs. The contexts in which drug users are embedded are especially important in acquiring an understanding of trajectories in drug course and paths from one drug to another. Contextual information should be included in studies focusing on sequential stages of involvement in drug use.

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Contributors

Dr Baggio drafted the initial manuscript, carried out the analyses, and approved the final manuscript as submitted. Dr Iglesias carried out the analyses, reviewed, revised, and approved the final manuscript as submitted. Dr Fournier carried out the analyses, performed the power analysis, reviewed and approved the final manuscript as submitted. Dr Studer participated in the data collection, made substantial contributions to the conception and design of the study, reviewed and approved the final manuscript as submitted. Mrs N'Goran and Dr Deline made substantial contributions to the conception and design of the study, reviewed and approved the final manuscript as submitted. Dr Mohler-Kuo participated in the conception and design of the study, coordinated and supervised data collection, reviewed and approved the final manuscript as submitted. Dr Gmel conceptualized and designed the study, coordinated and supervised data collection, reviewed, revised and approved the final manuscript as submitted. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

None

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