Chapter 1:
Panel Discussion: The Future of Sentencing and Treatment of Opiate Offenders: The Legislature's Perspective

Moderator:
Senator John Eklund
Chair, 131st General Assembly
Senate Criminal Justice Committee

Panelists:
Representative Jim Butler
Ohio House District 41

Senator Frank LaRose
Ohio Senate District 27

Senator Cecil Thomas
Ohio Senate District 9

Representative John Rogers
Ohio House District 60

Table of Contents

Various House and Senate Bill Links 1

Addiction—PowerPoint Presentation 3

Factors Affecting Repeated Cessations of Injecting Drug Use and Relapse During the Entire Injecting Career Among the Edinburgh Addiction Cohort 21

1. Introduction 26

2. Material and Methods 27

3. Results 32

4. Discussion 34

References 39
Figures 46
Table 1 51
Partial Recovery of Brain Dopamine Transporters in Methamphetamine (Meth) Abuser After Protracted Abstinence 55

Various House and Senate Bill Links

129th General Assembly	130th General Assembly	131st General Assembly	132nd General Assembly
H.B. 93	H.B. 399	H.B. 171	H.B. 4
	H.B. 465	H.C.R. 16	H.B. 49
	H.B. 367	H.B. 64	H.B. 73
	H.B. 394	H.B. 110	H.B. 117
	S.B. 276	H.B. 230	S.B. 1
	H.B. 314	S.B. 319	S.B. 42
	H.B. 341	H.B. 4	S.B. 66
	H.B. 366	S.B. 129	
	H.B. 170	H.B. 483	
	H.B. 59		
	H.B. 315		

Addiction

State Representative Robert Cole Sprague

83rd Ohio House District

Client Admissions for Opiate Abuse and Dependence

Ohio MACSIS Data - 2001

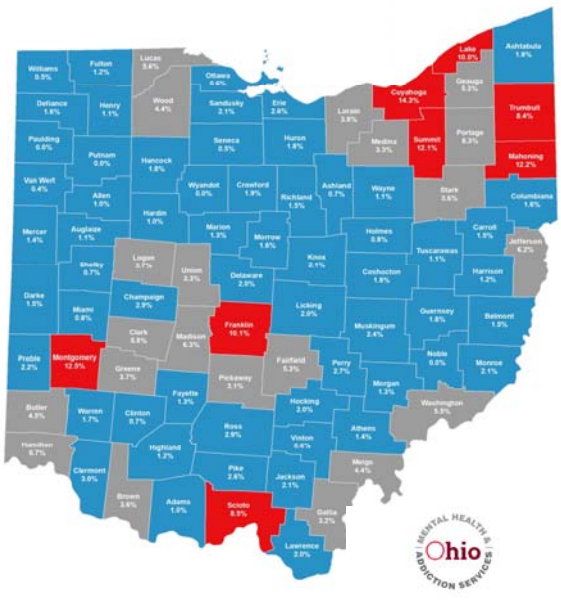
Legend

Opiate Addicts (%)

- 0.0% - 3.0%
- 3.1% - 6.7%
- 6.8% - 14.3%

Map Information:

This map represents the percentage of clients in treatment with an opiate-related diagnosis (heroin and prescription opioid). The highest concentrations of opiate admissions are in Cuyahoga (14.3%), Montgomery (12.5%), Mahoning (12.2%), Summit (12.1%) and Franklin (10.1%) counites. Noble, Paulding, Putnam and Wyandot did not have any opiate-related admissions.



Data Source:
Data from Multi Agency Community Information Systems (MACSIS)
Map produced April 2013

Client Admissions for Opiate Abuse and Dependence

Ohio MACSIS Data - 2003

Legend

Opiate Addicts (%)

- **0.0% - 3.0%**
- **3.1% - 6.7%**
- **6.8% - 16.3%**

Map Information:

This map represents the percentage of clients in treatment with an opiate-related diagnosis (heroin and prescription opioid). The highest concentrations for opiate admissions are in Cuyahoga (16.3%), Mahoning (15.8%) and Montgomery (14.9%) counties. Paulding, Putnam and Wyandot did not have any opiate-related admissions.

Data Source:
Data from Multi Agency Community Information Systems (MACSIS)
Map produced April 2013

Client Admissions for Opiate Abuse and Dependence

Ohio MACSIS Data - 2005

Legend

Opiate Addicts (%)

- **1.0% - 3.0%**
- **3.1% - 6.7%**
- **6.8% - 34.4%**

Map Information:

This map represents the percentage of clients in treatment with an opiate-related diagnosis (heroin and prescription opioid). The highest concentrations for opiate admissions are in Scioto (34.4%), Clark (21.1%) and Jackson (20.9%) counties. The counties with the lowest concentrations of an opiate-related diagnosis are Holmes (1.0%), Morgan (1.0%) and Henry (1.1%).

Data Source:
Data from Multi Agency Community Information Systems (MACSIS)
Map produced April 2013

Client Admissions for Opiate Abuse and Dependence

Ohio MACSIS Data - 2007

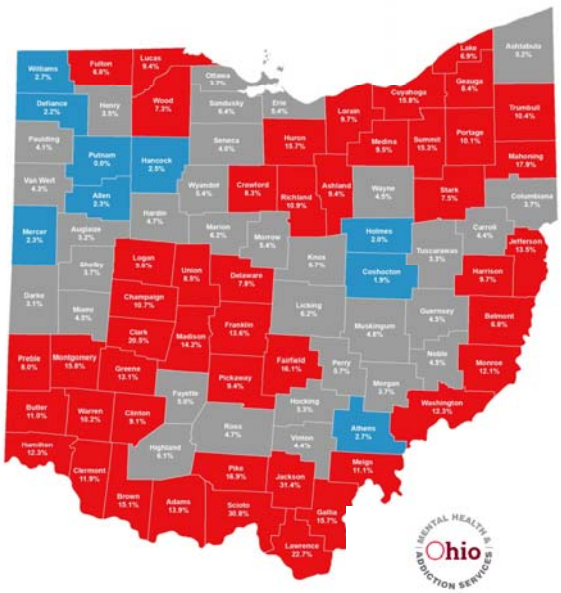
Legend

Opiate Addicts (%)

- **0.0% - 3.0%**
- **3.1% - 6.7%**
- **6.8% - 31.4%**

Map Information:

This map represents the percentage of clients in treatment with an opiate-related diagnosis (heroin and prescription opioid). The highest concentrations for opiate admissions are in Jackson (31.4%), Scioto (30.8%) and Lawrence (22.7%) counties. The counties with the lowest concentrations of an opiate-related diagnosis are Putnam (0.0%), Coshocton (1.9%) and Holmes (2.0%).



Data Source:
Data from Multi Agency Community Information Systems (MACSIS)
Map produced April 2013

Client Admissions for Opiate Abuse and Dependence

Ohio MACSIS Data - 2009

Legend

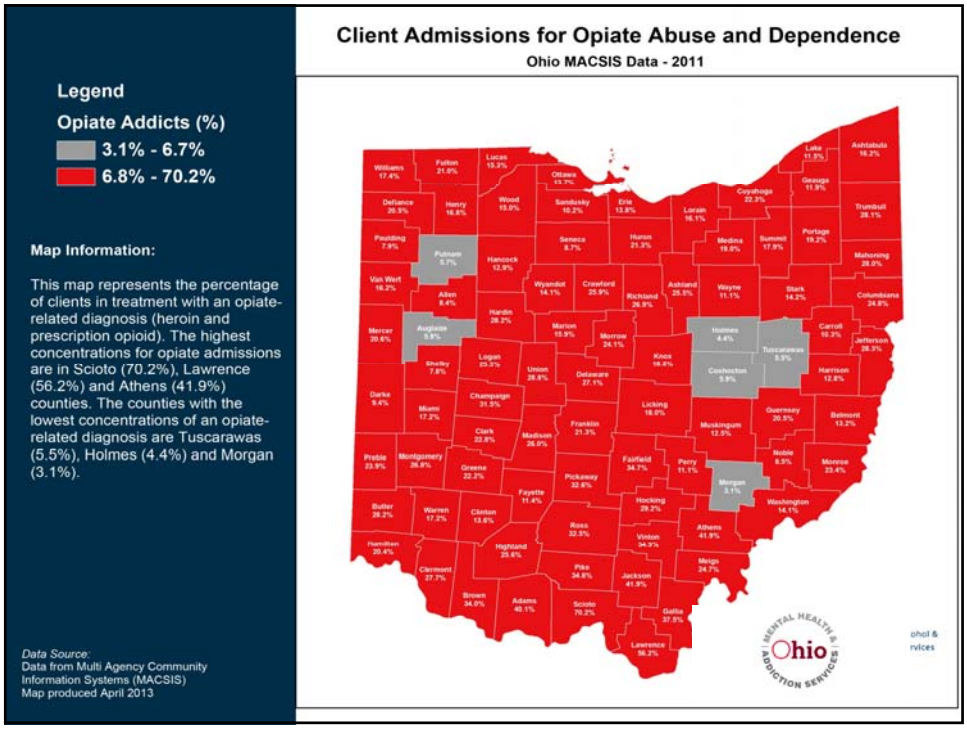
Opiate Addicts (%)

- **2.3% - 3.0%**
- **3.1% - 6.7%**
- **6.8% - 64.1%**

Map Information:

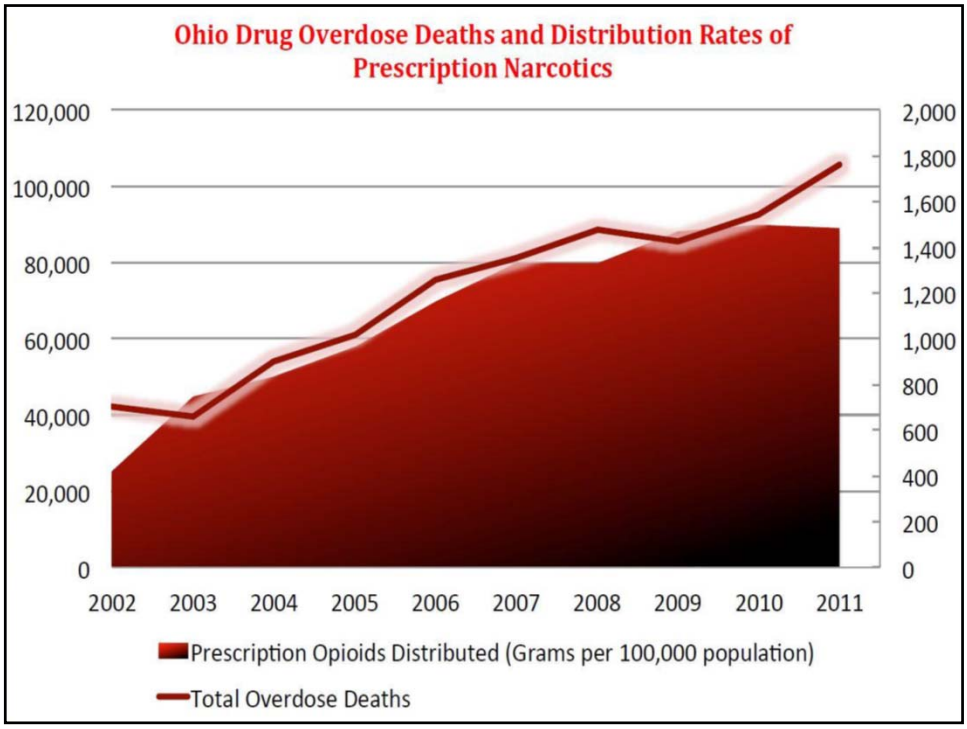
This map represents the percentage of clients in treatment with an opiate-related diagnosis (heroin and prescription opioid). The highest concentrations for opiate admissions are in Scioto (64.1%), Lawrence (49.5%) and Jackson (35.7%) counties. The counties with the lowest concentrations of an opiate-related diagnosis are Allen (2.3%), Coshocton (2.4%) and Carroll (3.5%).

Data Source:
Data from Multi Agency Community Information Systems (MACSIS)
Map produced April 2013



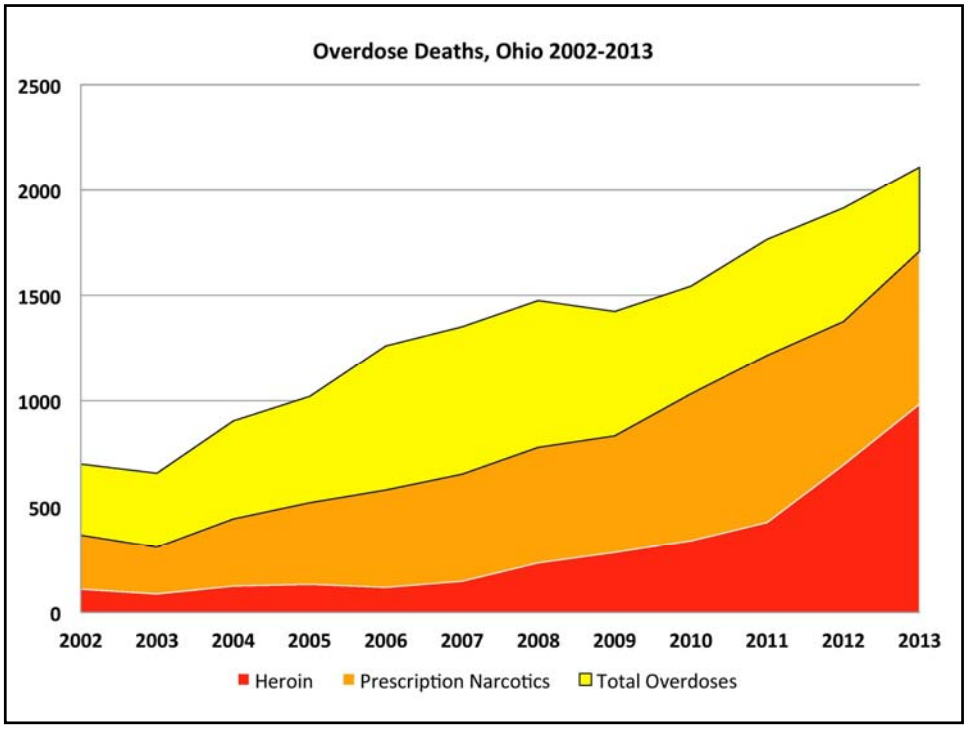
What has caused our current addiction epidemic?

- Pain as the Fifth Vital Sign
- Intractable Pain Act
- Introduction of new pain medications
- Marketing strategies
- Doctor shopping
- Diversion
- Pill mills
- Street value
- Increased prescribing
- Perception of prescription medication
- Patient satisfaction surveys



Unintentional Overdose Deaths

- In 2015, 3,050 Ohioans died from an unintentional drug overdose.
  - 20.5% increase from 2013 (2,531 deaths)
- 83rd Ohio House District (2010-2015 averages)
  - Hancock County: 11.6 deaths per 100,000 residents
  - Hardin County: 18.7 deaths per 100,000 residents
  - Logan County: 12.8 deaths per 100,000 residents



Legislative Approach

- Prevent more people from becoming addicted.
- Prevent diversion of prescription medication.
- Keep people alive.
- Improve Ohio's treatment system.

Recently Enacted or Effective Laws

Awareness Days

House Bill 399 and House Bill 465

(130th General Assembly)

- House Bill 399 designated the first Friday of May as "Prescription Drug Abuse Awareness and Education Day."
- House Bill 465 designated the first week of July as "Neonatal Abstinence Syndrome Awareness Week."

Addiction Education

House Bill 367

(130th General Assembly)

- Previously, Ohio law required health classes to cover topics such as nutrition, alcohol abuse, tobacco abuse, general drug abuse, and personal safety.
- As part of the health curriculum, the new law requires school districts to include information regarding prescription opioids and heroin.
  - Curriculum recommendations have been issued by the Governor's Cabinet Opiate Action Team.

Pregnant Women

House Bill 394 and Senate Bill 276

(130th General Assembly)

- Within these two bills, language was included that increased penalties for illegally providing controlled substances to pregnant women.
  - Specifically, for some substances, the new law implements felony charges for corrupting another with drugs and mandatory prison sentences.

Heroin Trafficking

House Bill 171

(131st General Assembly)

- This legislation reduced the amount of heroin required for first degree felony possession offenses, putting the figure in line with crack cocaine possession amounts.

Satisfaction Surveys

House Bill Concurrent Resolution 16

(131st General Assembly)

- Federally regulated patient satisfaction surveys are linked to hospital rating, reimbursement, and medical professional compensation. These surveys can add pressure on prescribers to prescribe pain medication.
- House Concurrent Resolution 16 urges the federal government to revise patient satisfaction surveys and removed questions related to pain.
- The federal government is in the process of removing pain-related questions.

Prescribing to Minors

House Bill 314

(130th General Assembly)

- Before prescribing an opioid to a minor, House Bill 314 requires prescribers to get consent from a parent or guardian.
  - The prescriber does not have to get consent:
    - during medical emergencies;
    - for surgeries;
    - when there is the possibility of a detriment to the minor's health or safety; and
    - if care is rendered in an institutional or residential setting.

Opioid Pill Mills

House Bill 93

(129th General Assembly)

- House Bill 93 was signed into law to stop unscrupulous prescribers, close the pill mills, and begin changing how chronic pain is treated.
  - Pain management clinics have to be licensed by the State Board of Pharmacy.
  - Laws were revised related to the treatment of chronic pain.
  - The Ohio Automatic Prescription Reporting System (OARRS) was improved by allowing:
    - data to be kept for a longer period of time in an aggregate manner;
    - the Board of Pharmacy to pursue a criminal case if the system is used improperly; and
    - regulatory boards of the prescribers to write rules for utilizing OARRS.

Buprenorphine Mills

House Bill 367 and House Bill 4

(130th and 131st General Assemblies)

- Due to loopholes in law, prescribers were using the disguise of addiction treatment, while improperly using buprenorphine, to exacerbate the addiction epidemic. Buprenorphine is a partial agonist used to treat opioid addiction, but it can be abused.

- In addition to addiction education language, House Bill 367, along with House Bill 4, contained language that provides greater oversight of buprenorphine providers. With similarities to legislation that was used to combat opioid pill mills, mechanisms were put into law to stop buprenorphine mills.

- The State Medical Board was required to adopt rules that integrates proper buprenorphine use and additional treatment services, when a patient is being treated for opioid addiction.

OARRS

House Bill 341

(130th General Assembly)

- The Ohio Automated Rx Reporting System (OARRS) is a tool, administered by the State Board of Pharmacy, used to monitor controlled substances for overutilization or doctor shopping.

- The recently enacted law requires all prescribers to utilize the Ohio Automated Rx Reporting System, at certain points in treatment, when prescribing an opioid or benzodiazepine.

Home Hospice Care

House Bill 366

(130th General Assembly)

- The law enacted through House Bill 366 is meant to ensure that there are less unused prescription medications being illegally diverted.
- Through this law, when they are no longer needed, home hospice programs must follow procedures to dispose of unused prescription opioids.

Naloxone

House Bill 170, House Bill 4, and House Bill 64

(130th and 131st General Assemblies)

- By detaching the opioid from receptors in the body, naloxone has the potential to reverse a drug overdose.
- House Bill 170 increased access to naloxone by authorizing prescribers to personally furnish or prescribe naloxone to a friend, family member, or other individual that can provide assistance to an individual who is at risk of experiencing an opioid-related overdose.
- House Bill 4 increased access to naloxone by allowing pharmacists and other individuals to furnish naloxone, while following a physician protocol, to individuals that are at risk for an overdose or can provide assistance to an individual who is at risk for an overdose.
- House Bill 64 provided funding for increasing access to the life-saving medication.

Good Samaritan

House Bill 110

(131st General Assembly)

- Typically, during a drug overdose, individuals are scared to call for help. The previous system resulted in an individual losing their life, no one being prosecuted, and no information being gathered to investigate traffickers and dealers.

- House Bill 110 was signed into law with language that is meant to urge individuals to call for help, in the event of a drug overdose. If individuals seek emergency assistance, the law provides immunity for minor drug possession offenses and connects individuals with the treatment system.

Information

House Bill 315 and House Bill 483 and Senate Bill 129

(130th and 131st General Assemblies)

- In order to change policies and provide resources in the most effective manner, laws have been enacted to track problems and treatment shortages throughout Ohio.

  - House Bill 315 requires hospitals to report the number of neonatal abstinence syndrome cases to the Ohio Department of Health.

  - Through House Bill 483 and Senate Bill 129, beginning in July of 2017, the Department of Mental Health and Addiction Services will maintain a statewide treatment services waiting list.

Funding, Prevention, and Treatment

House Bill 483 and Senate Bill 129

(130th and 131st General Assemblies)

- During the 130th General Assembly, language was signed into law to establish the full continuum of care in every behavioral health board service district throughout Ohio. The date for establishment was recently moved, because there are some boards still working to offer the complete continuum of care. In order to support this effort, $52.5 million was previously earmarked for various mental health and addiction initiatives. The money was targeted to be used for:
  - housing and crisis;
  - sober housing;
  - prevention;
  - residential State Supplement (R.S.S) funding for the mentally ill; and
  - funding for case managers in specialty drug dockets.

Drug Dockets

House Bill 59, House Bill 483, and House Bill 64

(130th and 131st General Assemblies)

- House Bill 64 supported the continuation of funding for the Supreme Court certified drug docket Addiction Treatment Pilot Program, which was started through House Bill 59. In addition, the bill expanded the program from five counties to fifteen counties and changed the name of the program to the Medication Assisted Treatment Drug Court Program.

- In addition to the Medication Assisted Treatment Drug Court Program, House Bill 483 and House Bill 64 included funding for case managers in Supreme Court certified drug dockets.

State Prisons

House Bill 64

(131st General Assembly)

- The bill required the Department of Rehabilitation and Correction to establish and operate a community-based substance use disorder treatment program for certain non-violent offenders.
- The Department of Rehabilitation and Correction was required to study the conversion of an existing facility to a substance abuse recovery prison.

Medicaid Managed Care

House Bill 64

(131st General Assembly)

- As behavioral health services are moved to Medicaid managed care, in order to ensure continued access to treatment, the Joint Medicaid Oversight Committee will monitor actions by the Department of Medicaid.
- In addition, the Joint Medicaid Oversight Committee is required to review and approve implementation prior to January 1, 2018.

Chemical Dependency Professionals Board

House Bill 230

(131st General Assembly)

- As part of the International Certification and Reciprocity Consortium, the Ohio Chemical Dependency Professionals Board sets standards and guidelines for the state's alcohol and drug counselors, prevention specialists, and clinical supervisors. These credentialing requirements are regularly updated every five to seven years.

- House Bill 230 updated definitions, broadening the number of professionals, and removed credentialing standards from the Ohio Revised Code, placing them in the Ohio Administrative Code. These change ensure the Ohio Chemical Dependency Professionals Board remains in compliance with international licensing trends and standards.

Opiate MBR

Senate Bill 319

(131st General Assembly)

- Once effective, this law:
  - requires prescribers of opioid analgesic drugs to obtain prior authorization and show medical necessity at certain points in the course of treating chronic pain;
  - removes the link between patient satisfaction surveys and reimbursement for prescribing or not prescribing opioids;
  - requires the registration of pharmacy technicians;
  - provides oversight of sole proprietors that handle dangerous drugs;
  - invalidates opioid prescriptions that have not been used in 30 days and puts a 90 day cap on the total day supply of opioids dispensed;

Opiate MBR (continued)
Senate Bill 319

- authorizes a 14 day pick-up window, from the prescriber's fill date, for opioid prescriptions;
- increases oversight of buprenorphine prescribers, through Board of Pharmacy licensing;
- further expands access to naloxone, by authorizing new facilities to have access to the life-saving medication (homeless shelters, halfway houses, schools, and treatment facilities);
- provides peace officers with civil protections, in the event that they attempt to save an individual's life with naloxone;
- revises the pharmacy benefit manager disclosure requirements, requiring aggregate reporting each quarter (does not apply to federally precluded plans);

Opiate MBR (continued)
Senate Bill 319

- requires pharmacy benefit managers to:
  - utilize the most recent pricing, when reimbursing pharmacies;
  - Provide available pricing updates, upon request;
- if a pharmacy appeals a drug price unsuccessfully, information regarding the wholesaler must be provided;
- improves access to treatment through revisions to the previously mentioned continuum of care and statewide waiting list;
- expands access to methadone treatment programs; and
- prohibits children services from taking action on a mother with an addiction, when a pregnant mother enrolls in a drug treatment program prior to the 20th week of pregnancy.

Future Policy Proposals

Factors affecting repeated cessations of injecting drug use and relapses during the entire injecting career among the Edinburgh Addiction Cohort

Article *in* Drug and alcohol dependence · March 2015

DOI: 10.1016/j.drugalcdep.2015.03.005

Accepted Manuscript

Title: Factors affecting repeated cessations of injecting drug use and relapses during the entire injecting career among the Edinburgh Addiction Cohort

Author: Yang Xia Shaun Seaman Matthew Hickman John Macleod Roy Robertson Lorraine Copeland Jim McKenzie Daniela De Angelis

PII: S0376-8716(15)00145-3
DOI: http://dx.doi.org/doi:10.1016/j.drugalcdep.2015.03.005
Reference: DAD 5509

To appear in: *Drug and Alcohol Dependence*

Received date: 3-8-2014
Revised date: 28-2-2015
Accepted date: 1-3-2015

Please cite this article as: Yang Xia, Shaun Seaman, Matthew Hickman, John Macleod, Roy Robertson, Lorraine Copeland, Jim McKenzie, Daniela De Angelis, Factors affecting repeated cessations of injecting drug use and relapses during the entire injecting career among the Edinburgh Addiction Cohort, *Drug and Alcohol Dependence* (2015), http://dx.doi.org/10.1016/j.drugalcdep.2015.03.005

Title:
Factors affecting repeated cessations of injecting drug use and relapses during the entire injecting career among the Edinburgh Addiction Cohort

Yang Xia[a], Shaun Seaman[a], Matthew Hickman[b], John Macleod[b], Roy Robertson[c,d], Lorraine Copeland[d], Jim McKenzie[d], Daniela De Angelis[a,e]

[a] MRC Biostatistics Unit, Institute of Public Health, Cambridge, CB2 0SR, UK

[b] School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK

[c] Department of Community Health Sciences, Edinburgh University

[d] Muirhouse Medical Group, 1 Muirhouse Avenue, Muirhouse, Edinburgh EH4 4PL, UK

[e] Health Protection Agency, Health Protection Services, London, UK

Corresponding author and postal address:
Yang Xia
2109 Landmark West Tower
22 Marsh Wall, London
E14 9AL
United Kingdom
Email and phone number:
yang.xia@mrc-bsu.cam.ac.uk
+44 7766 016006

Abstract

Background and Aims Injecting drug use is a chronic condition, with people who inject drugs (PWID) typically experiencing repeated cessations and relapses during their injection careers. We characterize patterns of ceasing and relapsing and the impact of opiate substitution treatment (OST) during the entire injecting careers of PWID in the Edinburgh Addiction Cohort (EAC).

Methods During 2005-2007, 432 surviving participants of the EAC were interviewed about their injecting histories. Adjusted associations between covariates and hazards of cessation and relapse were estimated using random-effects models.

Results OST was strongly associated with a higher hazard of cessation (HR = 1.71, $P < 0.001$), but there was no significant evidence of association with hazard of relapse (HR = 0.81, $P = 0.14$). Women and older PWID were less likely to relapse (HR = 0.73, $P = 0.02$ and HR = 0.55, $P < 0.001$, respectively). Hazards of both cessation and relapse decreased monotonically with time since last relapse/cessation (both $P < 0.001$). An individual's hazard of cessation increased with his/her number of previous cessations (HR = 3.58 for 10+ previous cessations, $P < 0.001$), but there was no evidence that an individual's hazard of relapse changed with number of previous relapses ($P = 0.37$). There was heterogeneity in the individual hazards of both cessation and relapse.

Conclusions OST was associated with reduced time to cessation, and there was some suggestion of increased time to relapse too. The likelihood of prolonged cessation is greater for women, increases with age, and decreases with time since last relapse.

Keywords Heroin addiction, opiate substitution treatment, random effects model, recurrent events, survival data, cessation, relapse

1 Introduction

Injecting drug use is an important public health problem in many countries (Mathers et al., 2010, 2008). People who inject drugs (PWID) have over ten times greater risk of premature mortality than the general population and may contribute over 10% of deaths among young people (Bargagli et al., 2006; Degenhardt et al., 2010a). PWID are at increased risk of HIV and Hepatitis C Virus infection in many countries (Alter and Moyer, 1998; De Angelis et al., 2009; Degenhardt et al., 2010b), and contribute substantially to the costs of crime and imprisonment (Godfrey and Eaton, 2002; Godfrey et al., 2004). Opiate substitution treatment is critical to reduction of drug related harm (Amato et al., 2005; van den Berg et al., 2007; Cornish et al., 2010; Degenhardt et al., 2010a; Gossop et al., 2005; Gowing et al., 2011; Turner et al., 2011) but its long-term effect on injecting cessation is uncertain.

PWID typically experience repeated periods of injecting and cessation, and has been characterized as a chronic health problem (McLellan et al., 2000; O'Brien, 2011; O'Brien and McLellan, 1996). An alternative perspective on the natural history of drug addiction has emphasized it as a problem starting in adolescence that people can 'mature out of' in adulthood (Harding et al., 1980; Maddux and Desmond, 1980, 1986; Winick, 1962, 1964), highlighting that some individuals will cease before becoming dependent or only after a short period of injecting (Biernacki, 1986; Robbins et al., 1975; Sweeting et al., 2009; Zinberg and Jacobson, 1976).

The duration of injecting, likelihood of long-term cessation and the factors that promote cessation and recovery are important both to policy on drug treatment and assessments of disease burden, but these quantities remain uncertain. In part this is because long-term follow-up and natural history studies of opiate and injecting drug use are rare. In this study we examine the pattern of ceasing and relapsing during the entire injecting career, and explore the association between opiate substitution

treatment and other covariates and risk of recovery and relapse.

2 Material and methods

2.1 Data source

The Edinburgh Addiction Cohort (EAC) is a prospective open cohort study of 794 opiate injectors recruited by Muirhouse Medical Group from 1980 to 2006 (Kimber et al., 2010; Macleod et al., 2010; Robertson et al., 1994; Skidmore et al., 1990). Information on opiate substitution treatment (OST) use (methadone, buprenorphine or dihyrocodeine) and age at onset was extracted from primary care case notes (Cornish et al., 2010; Robertson et al., 2006). In 2005–2007, the surviving participants were interviewed about their past patterns of injecting. A full account of this cohort is given elsewhere (Copeland et al., 2004; Macleod et al., 2010; Robertson et al., 1986; Robertson and Richardson, 2007). Case notes were available for 655 (83%) individuals (22 had no contact details, 30 not traced, 38 no response, 40 declined, 9 too ill). Of these, 223 had died before interview and 27 others had missing year of onset of injection. Here we focus on the 405 remaining individuals. For these 405 individuals, the mean (SD) number of years from recruitment to interview was 10.8 (7.2) and that from year of first injection to interview was 17.6 (9.0).

During the interviews, individuals filled out retrospective life grids indicating, for each calendar year since beginning to inject, whether they had injected in that year. For each year that an individual reported injecting, the individual was asked whether there was a period lasting at least three months in that year during which he/she did not inject (a 'non-injection period'). If there was such a period, the individual was asked to estimate the number of distinct such non-injection periods and the total number of days spent injecting in that year (Macleod et al., 2010). Periods of absti-

nence that lasted less than three months were not elicited. Interviews were anchored around memorable events (e.g. death of father, divorce) to aid recall (Macleod et al., 2010).

2.2 Cessation and relapse times

An injection career can be thought of as a sequence of recurrent events in which the injector switches repeatedly between injection and non-injection. We define a 'cessation' as the beginning of a non-injection period, and define a 'relapse' as the end of such a period. The data available from the interview questionnaires did not determine precisely when cessations and relapses occurred. So instead we used the following algorithm to impute these times. This algorithm aims to minimize the number of cessations and relapses, by assuming, whenever possible, that two periods of non-injecting reported in consecutive calendar years corresponded to a single continuous period of non-injecting spanning the new year. Figure 1 illustrates the algorithm.

For each individual, the algorithm begins by taking each calendar year in turn, in chronological order, and assigning non-injection periods in that year to the beginning, middle or end of the year. When there is only one non-injection period in the year, it is placed at the end of that year if the preceding year ended with an injecting period (Figure 1a), and at the beginning of the year otherwise (Figure 1b). When there are two non-injection periods, one is put at the beginning of the year and one at the end (Figure 1c). When there are three non-injection periods, they are put at the beginning, middle and end (Figure 1d). The exact beginning and end times of these non-injecting periods (i.e. times of cessation and relapse) are then imputed by partitioning the total number of days that the individual reported not injecting in that calendar year equally between the 1–3 non-injecting periods.

2.3 Statistical analysis

The Kaplan-Meier estimator was used to estimate the distribution of time from injection onset to first cessation and of the subsequent time to the next relapse.

Random-effects proportional-hazards models were used to investigate the dependence of the hazards of cessation and relapse on covariates, accounting for correlation between repeated times to event (cessation or relapse) within the same individual (Aalen et al., 2008). The time-constant covariates were sex, age at injection onset, and year of injection onset (before or after 1986); the time-varying covariates were current OST use, number of previous cessations/relapses, and current age. OST was a time-varying three-level categorical variable taking values 'currently prescribed OST', 'not currently prescribed OST' or 'unknown whether currently prescribed OST' (or 'on OST', 'off OST' and 'unknown OST' for short). Year of injection onset was dichotomized at 1986 because this is when HIV test became widely available, which may have altered injecting behavior. Data on all these covariates except OST use were obtained during the interview.

The model for relapse is as follows (that for cessation is analogous). Let $h_{ij}(t)$ denote the hazard of relapse for individual i at time t during his/her jth non-injection period (where time zero means beginning of that period). Let $\mathrm{OST}_{\mathrm{on},ij}(t)$ equal 1 if individual i is on OST at that time, and zero otherwise. Similarly, let $\mathrm{OST}_{\mathrm{na},ij}(t)$ equal 1 if the individual has unknown OST status at that time, and zero otherwise, and let $\boldsymbol{Z}_{ij}(t)$ denote the values of the remaining covariates (sex, current age, etc.) at that time. Then a basic random-effects proportional hazards model is given by

$$h_{ij}(t) = h_0(t) \exp[\beta_{\mathrm{on}} \mathrm{OST}_{\mathrm{on},ij}(t) + \beta_{\mathrm{na}} \mathrm{OST}_{\mathrm{na},ij}(t) + \boldsymbol{\beta}_Z \boldsymbol{Z}_{ij}(t) + u_i]$$

where $h_0(t)$ is the baseline hazard, and u_i is a random-effect specific to individual i. The random effects are assumed to be normally distributed with mean zero. A positive random effect u_i implies that individual i has a greater baseline hazard of

relapse than the average individual; negative u_i implies a lower than average hazard of relapse. Parameters β_{on} and β_{na} are the log hazard ratios of relapse when on OST and unknown OST, respectively, compared to when off OST; and $\boldsymbol{\beta}_Z$ are the log hazard ratios of the remaining covariates. Log hazard ratios greater than zero (or, equivalently, hazard ratios greater than one) imply a shorter expected time to relapse, and so shorter non-injection period; log hazard ratios less than zero (equivalently, hazard ratios less than one) imply a longer expected time to relapse, and so longer non-injection period.

The baseline hazard $h_0(t)$ for relapse was assumed to be piecewise-constant over four intervals: $\leq$ 2 months, $(2, 12]$ months, $(1, 2]$ years, and more than 2 years. For cessation, 5 intervals were used: $\leq$ 3 days, $(3, 7]$ days, $(1, 12]$ weeks, $(3, 12]$ months, and more than 1 year. These change points were chosen by examining plots of the cumulative hazards. This procedure was further aided by comparing nested models with increasing number of change points using likelihood ratio tests so that non-significant change points could be dropped.

A potential problem with this basic model is 'confounding by cluster' (Seaman et al., 2014). The basic model above assumes that the probability that individual i is on OST at any given time t ($OST_{\text{on},ij}(t) = 1$) is uncorrelated with his/her random effect u_i. In practice, however, it is possible that an individual with a high random effect for relapse (and so who tends to relapse quickly after cessation) may be more likely to be prescribed OST than another individual who has a lower random effect (and so who tends to relapse slower). This can cause difficulties with both interpretation and estimation of the OST effect parameters β_{on} and β_{na} (Seaman et al., 2014). To deal with this potential problem of confounding by cluster, we used the Poor Man's method of Neuhaus and Kalbfleisch (1998). This involves separating each of the OST effects β_{on} and β_{na} into a between-individual and a

within-individual effect, which is achieved by replacing the basic model above with

$$\begin{aligned} h_{ij}(t) &= h_0(t)\exp[\beta^B_{\text{on}}\overline{\text{OST}}_{\text{on},i} + \beta^W_{\text{on}}\{\text{OST}_{\text{on},ij}(t) - \overline{\text{OST}}_{\text{on},i}\} \\ &\quad +\beta^B_{\text{na}}\overline{\text{OST}}_{\text{na},i} + \beta^W_{\text{na}}\{\text{OST}_{\text{na},ij}(t) - \overline{\text{OST}}_{\text{na},i}\} + \boldsymbol{\beta}_Z\boldsymbol{Z}_{ij}(t) + u_i] \end{aligned}$$

where $\overline{\text{OST}}_{\text{on},i}$ and $\overline{\text{OST}}_{\text{na},i}$ denote the fractions of individual i's total follow-up spent on OST and with unknown OST, respectively. Parameter β^B_{on} describes the between-individual effect of being on OST, i.e. the log hazard ratio comparing *two different individuals*: the average individual who spends all his/her time on OST and the average individual who spends no time on OST. The parameter β^W_{on} describes the within-individual effect of being on OST, i.e. the log hazard ratio of *the same individual* at two different times: when on OST and when off OST. The between- and within-individual effects of having unknown OST, β^B_{na} and β^W_{na}, are analogous. Within-individual effects are of more interest than between-individual effects, because individuals who spend a lot of time on OST may differ in many unmeasured ways from individuals who spend little time on OST.

Finally, we carried out two sensitivity analyses. First, we fitted a Cox model with random effects, in order to avoid assuming a piecewise-constant form for $h_0(t)$. Second, we fitted a joint model for cessation and relapse, allowing the random effects for cessation and relapse to be correlated. This enabled us to check that such a correlation was not causing bias due to violation of our model's independent censoring assumption (Xia, 2013). The hazard ratio estimates and P values for OST and other covariates obtained from both these models were similar to those from the model described above, and so we do not report them here. The models with piecewise-constant hazard were fitted by maximum likelihood in STATA (StataCorp, 2009) and, for the joint model, in R using bespoke code (R Core Team, 2014); the Cox model with random effects was fitted using the coxme package in R (Therneau, 2012).

3 Results

Figure 2 (top) shows the distribution of the total number of transitions (either cessation or relapse) per individual during the follow-up period.The median (interquartile range, IQR) of the total number of transitions (either cessation or relapse) per individual during the follow-up period was 3 (1 – 4); the mean (SD) was 5 (9) and the maximum was 81. Eighteen (4%) individuals made no transitions, i.e. they injected throughout follow-up; 65 (16%) injected for less than one year with no further relapse; and 252 (65%) experienced at least one relapse. Figure 2 (bottom) shows the distribution of the total number of transitions per individual divided by his/her years of follow-up.

3.1 Kaplan-Meier curves

The Kaplan-Meier estimated probability that a first-time injector ceased within 12 months was 0.46 (95% CI: 0.41, 0.50) (Figure 3), and within 5 years was 0.72 (95% CI: 0.67, 0.76). The estimated median (IQR) time to first cessation was 1.5 (0.0 – 5.6) years. The estimated probability of subsequent relapse was 0.37 (95% CI: 0.32, 0.42) at 12 months and 0.59 (95% CI: 0.53, 0.63) at 5 years (Figure 4). The estimated median (IQR) time to subsequent relapse was 2.4 (0.5 – 23.8) years.

3.2 Regression models

Table 1 shows the estimated hazard ratios from the proportional hazards models with piecewise-constant baseline hazards. Opiate substitution treatment (OST) use was associated with higher hazard of cessation within an individual (HR = 1.71 for on OST, 95% CI: 1.40, 2.09, overall $P < 0.001$ from likelihood-ratio test on 2 degrees of freedom). The between-individual effect of OST provides evidence

of confounding (with hazard ratios in the opposite direction to within-individual effects), suggesting that those people who cease slower may also be those more likely to be prescribed OST. An individual's hazard of cessation increased with his/her number of previous cessations (overall $P < 0.001$): compared to the first injection period, the hazard was 1.19 times greater (95% CI: 0.97, 1.47) during the second and third periods, and was 3.58 times greater (95% CI: 2.42, 5.29) after the 10th period. People who inject drugs (PWID) who began injecting after 1986 had a higher hazard (HR = 1.37, 95% CI: 1.05, 1.80, $P = 0.02$). There was weak evidence that PWID who began injecting at an older age (≥ 20) had a higher hazard of cessation (HR = 1.32, 95%CI: 0.99, 1.76, $P = 0.06$). No evidence of the hazard differing by gender or current age has been found.

For hazard of relapse, there was some suggestion of a within-individual effect of OST (HR = 0.81 for on OST), but this was non-significant (overall $P = 0.14$). The between-individual effect of OST (HR = 1.67 for on OST, overall $P = 0.007$) was significant, which is probably again due to confounding: those PWID who relapse faster are also those who are more likely to be prescribed OST. Women had a lower hazard of relapse (HR = 0.73, 95% CI: 0.56, 0.94, $P = 0.02$). Current age was also significantly associated with hazard (overall $P = 0.001$), with the hazard after age 35 dropping to 55% of that at age < 20 (HR = 0.55, 95% CI: 0.41, 0.75). PWID who began injecting at an older age (≥ 20) had a higher hazard of relapse (HR = 1.40, 95% CI: 1.08, 1.83, $P = 0.01$). There was no evidence that an individual's hazard differed by calendar period of onset or changed as the number of his/her previous relapses increased.

The hazards of both cessation and relapse were monotonically decreasing with time since last relapse/cessation (overall $P < 0.001$ for both). The hazard of cessation during $(3, 7]$ days since last relapse was only 0.51 (95% CI: 0.40, 0.64) times the hazard during $[1, 3]$ days. Thereafter the hazard continued to decline, with the haz-

ard ratio reaching 0.03 after 1 year (95% CI: 0.03, 0.04) compared to that during $[1, 3]$ days. The hazard of relapse $(1, 2]$ years after most recent cessation was only 0.38 (95% CI: 0.30 and 0.50) times the hazard after ≤ 2 months; after 2 years this hazard ratio had decreased to 0.10 (95% CI: 0.08, 0.13).

We found evidence for significant heterogeneities in the hazards of cessation and relapse between individuals: variances of random effects were 0.90 (95% CI: 0.65, 1.24, $P < 0.001$) and 0.57 (95% CI: 0.33, 0.98, $P < 0.001$), respectively.

4 Discussion

We found evidence of a strong inverse association between being on opiate substitution treatment (OST) and the average duration of injection episodes. There was insufficient evidence, however, that OST exposure reduced the risk of relapse. Women had lower rates of relapse than men. Age was positively associated with lower rates of relapse but not with time to cessation. An individual's rate of cessation increased as he/she accumulated more previous cessations, but there was little evidence that his/her rate of relapse changed as he/she accumulated more previous relapses. The risk of cessation or relapse is not constant but decreases with time elapsed since the previous relapse or cessation, respectively. For example, the risk of relapse after more than three years of non-injecting was 10% of the risk at the start of a period of non-injecting. Thus, the likelihood that an individual experiences long-term cessation, though not explicitly modeled, increases with age, number of previous cessation events, and the duration of non-injecting. There was evidence of heterogeneity in the individual risks of both cessation and relapse.

4.1 Strengths and limitations

The Edinburgh Addiction Cohort (EAC) features a long period of follow-up (median 18.5 years). This has enabled us to examine long-term injecting patterns and to extend the analysis of patterns of injecting beyond first cessation and relapse.

However, our findings are subject to several limitations and potential biases. First, the cohort may under-represent people who inject drugs (PWID) for very short periods, because they may be less likely to experience health or other problems and therefore less likely to come to the attention of primary care. EAC participants were enrolled on the basis that they report injecting drug use or present with drug related problems in primary care; and though time from onset to recruitment was shorter for EAC than for many other cohorts (Macleod et al., 2010) there is likely to be some selection bias. For instance, approximately 16% of EAC report injecting periods of less than one year, which is slightly lower than the proportion estimated from other studies of between 20% and 50% (Sweeting et al., 2009), suggesting the potential for under-ascertainment.

Second, there is likely to be survivor bias, as information on transitions between injection and non-injection is available only for those who survived long enough to attend the inter- view. Unfortunately, the information from clinical notes on injecting patterns is not sufficiently complete to allow periods of injecting/non-injecting to be identified for the deceased cases (Macleod et al., 2012). The times to cessation and relapse and the impact of the covariates on these times, therefore, may differ for people who have not survived. Although the model presented in this paper does not include a long-term cessation state, we showed earlier that the effect of covariates on time to long-term cessation was not biased by excluding deceased cohort participants (Kimber et al., 2010).

Third, there also may be recall bias, since the data on these transitions were col-

lected retrospectively through a single questionnaire. We tried addressing the recall bias by including a categorical variable for decades (e.g. 1960s, 70s, 80s etc) in the regression model; the regression results were little affected and hence this decades variable was excluded in the model presented.

Fourth, cessation and relapse times were imputed from the interview data using the algorithm described in the Methods, because data on injecting periods was limited to the number of non-injecting periods in each calendar year. The algorithm minimizes the number of transitions, which may have caused the hazards of cessation and relapse to be underestimated. In addition, some of the cessations and relapses that we imputed as occurring when PWID were on OST may actually have occurred when they were off OST, and vice versa. This misclassification could cause bias in the estimated hazard ratios of OST. However, there are two reasons to believe that this will have little impact on our conclusions. Firstly, the data on OST use came from the case notes, rather than from interviews, and the method of imputing cessation/relapse times made no use of these OST data. Thus, any misclassification would be expected to dilute any true association between OST use and hazard of cessation or relapse, rather than to create an apparent association where none exists. Secondly, the main factor determining the estimated hazard ratios of OST are the total numbers of cessations/relapses occurring while on OST, off OST and unknown OST. 94% of both the imputed cessations and the imputed relapses took place in calendar years during which the PWID was entirely on OST, entirely off OST or had entirely unknown OST status. For these cessations and relapses, moving the imputed time to earlier or later in the year would not change whether they occurred when on, off or unknown OST, and so would not change the total numbers of cessations/relapses occurring while on OST, off OST and unknown OST.

Fifth, biases could have been introduced to the associations presented in Table 1 due to confounding by omitted time-dependent behavioral covariates, such as in-

carceration history. These data were poorly recorded in primary care notes and also unavailable through record linkage (Macleod et al., 2012).

4.2 Implications and other evidence

Out of the few longitudinal studies of injecting heroin use, most have tended to emphasize the persistence and high rates of relapse and high mortality rates associated with injecting heroin use (Galai et al., 2003; Goldstein and Herrera, 1995; Hser et al., 2001; Kimber et al., 2010; Rathod et al., 2005; Stimson and Oppenheimer, 1982; Termorshuizen et al., 2005a; Vaillant, 1973). Only a few studies have tried to characterize the injection career and explored factors that may influence injecting duration, notably the Amsterdam Cohort Study (ACS), the AIDS Link to Intravenous Experience (ALIVE) cohort in Baltimore and California Civil Addict Program (CAP) (Galai et al., 2003; Hser et al., 2007; Nosyk et al., 2013; Shah et al., 2006; Termorshuizen et al., 2005b; Vlahov et al., 1991). The ALIVE and ACS cohorts both have reported high rates of cessation and relapse during follow-up and that OST was associated with a faster time to cessation. For example, Shah et al. (2006) found that 86% of the non-injection/occasional use periods were followed by relapse within 5 years and estimated median time to cessation and relapse was 4 and 1 year respectively. Termorshuizen et al. (2005b) in an analysis of the ACS also found that OST was associated with longer injecting careers and did not appear to promote 'long-term cessation'. In addition, Nosyk et al. (2013) assessing the CAP show that long-term cessation or sustained abstinence often occurs after multiple periods of recovery and relapse, and that previous number of abstinent events and age are associated with duration of abstinence and time to next recovery event.

Galai et al. (2003) described several classes of injector based on persistence and number of relapses and found that group membership was associated with history of incarceration, age, and OST exposure. However, their classification of inject-

ing patterns could potentially bias the inferences, as length of follow-up may be a confounder for the relationship between the risk factors and injecting group membership. In addition, these previous analyses examine time to cessation after recruitment rather than from injecting onset which our analyses suggest may introduce bias since number of previous cessations and age are associated with time to cessation and hazard of relapse respectively.

It has been argued that a lack of association between injecting patterns and age or episode number is consistent with the thesis that addiction is a 'chronic relapsing problem' rather than a problem 'that people mature out of' (van den Berg et al., 2007; Langendam et al., 2000; McLellan et al., 2000; Termorshuizen et al., 2005b; Winick, 1962). We do find evidence of an association between cessation and relapse with age and episode number. However, very few of our cohort members remain 'untreated' and therefore can be considered as ceasing 'naturally' (if this is construed as without treatment) and so our findings also are consistent with a chronic relapsing disease.

References

Aalen, O.O., Borgan, Ø., Gjessing, H.K., 2008. Survival and Event History Analysis - A Process Point of View. Springer.

Alter, M., Moyer, L., 1998. The importance of preventing hepatitis C virus infection among injection drug users in the United States. J Acquir Immune Defic Syndr Hum Retrovirol 18, S6–10.

Amato, L., Davoli, M., Perucci, C., Ferri, M., Faggiano, F., Mattick, R., 2005. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical parctice and research. J Subst Abuse Treat 28, 321–329.

Bargagli, A., Hickman, M., Davoli, M., Perucci, C., Schifano, P., Buster, M., et al., 2006. Drug-related mortality and its impact on adult mortality in eight European countries. Eur J Public Health 16, 198–202.

van den Berg, C., van Brussel, G., Coutinho, R., M, P., 2007. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction 102, 1454–1462.

Biernacki, P., 1986. Pathways from Heroin Addiction: Recovery without treatment. Temple University Press, Philadelphia.

Copeland, L., Budd, J., Elton, R., 2004. Changing patterns in causes of death in a cohort of injecting drug users, 1980-2001. Arch Intern Med 164, 1214–1220.

Cornish, R., Macleod, J., Strang, J., Vickerman, P., Hickman, M., 2010. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ 341, c5475.

De Angelis, D., Sweeting, M., Ades, A., Hickman, M., Hope, V., Ramsay, M., 2009. An evidence synthesis approach to estimating hepatitis C prevalence in England and Wales. Stat Methods Med Res 18, 361–379.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., et al., 2010a. Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. Addiction 106, 32–51.

Degenhardt, L., Mathers, B., Vickerman, P., Rhodes, T., Latkin, C., Hickman, M., 2010b. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet 376, 285–301.

Galai, N., Safaeian, M., Vlahov, D., Bolotin, A., Celentano, D.D., ALIVE Study, 2003. Longitudinal patterns of drug injection behavior in the ALIVE Study cohort,1988-2000: description and determinants. Am J Epidemiol 158, 695–704.

Godfrey, C., Eaton, G., 2002. The economic and social costs of Class A drug use in England and Wales, 2000. Technical Report. Home Office Research, Development and Statistics Directorate.

Godfrey, C., Stewart, D., Gossop, M., 2004. Economic analysis of costs and consequences of the treatment of drug misuse: two year outcome data from the National Treatment Outcome Research Study (NTORS). Addiction 99, 697–707.

Goldstein, A., Herrera, J., 1995. Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. Drug Alcohol Depend 40, 139–150.

Gossop, M., Trakada, K., Stewart, D., Witton, J., 2005. Reductions in criminal convictions after addiction treatment: 5-year follow-up. Drug Alcohol Depend 79, 295–302.

Gowing, L., Farrell, M., Bornemann, R., Sullivan, L., Ali, R., 2011. Oral substitu-

tion treatment of injecting opioid users for prevention of HIV infection. Technical Report 8. Cochrane Database Syst Rev.

Harding, W., Zinberg, N., Stelmack, S., Barry, M., 1980. Formerly-addicted-now-controlled opiate users. Int J Addict 15, 47–60.

Hser, Y., Huang, D., Chou, C., Anglin, M., 2007. Trajectories of heroin addiction: growth mixture modeling results based on a 33-year follow-up study. Eval Rev 31, 548–563.

Hser, Y.I., Hoffman, V., Grella, C.E., Anglin, M.D., 2001. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry 58, 503–508.

Kimber, J., Copeland, L., Hickman, M., Macleod, J., McKenzie, J., De Angelis, D., Robertson, J.R., 2010. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ 341, c3172.

Langendam, M.W., Van Brussel, G.H.A., Coutinho, R.A., Van Ameijden, E.J.C., 2000. Methadone maintenance and cessation of injecting drug use: results from the Amsterdam Cohort Study. Addiction 95, 591–600.

Macleod, J., Copeland, L., Hickman, M., McKenzie, J., Kimber, J., De Angelis, D., Robertson, J.R., 2010. The Edinburgh Addiction Cohort: recruitment and follow-up of a primary care based sample of injection drug users and non drug-injecting controls. BMC Public Health 10, 1 – 13. URL: http://www.ncbi.nlm.nih.gov/pubmed/20187928.

Macleod, J., Hickman, M., Jones, H.E., Copeland, L., McKenzie, J.S., De Angelis, D., 2012. Early life influences on the risk of injecting drug use: case control study based on the Edinburgh Addiction Cohort. Addiction 108, 743–750.

Maddux, J., Desmond, D., 1980. New light on the maturing out hypothesis in opioid dependence. Bull Narc 32, 15–25.

Maddux, J., Desmond, D., 1986. Relapse and recovery in substance abuse careers. NIDA Res Monogr 72, 49–71.

Mathers, B., Degenhardt, L., Ali, H., Wiessing, L., Hickman, M., Mattick, R., et al., 2010. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet 375, 1014–1028.

Mathers, B., Degenhardt, L., Wiessing, L., Hickman, M., Strathdee, S., Wodak, A., et al., 2008. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet 372, 1733–1745.

McLellan, A., Lewis, D., O'Brien, C., Kleber, H., 2000. Drug dependence, a chronic medical illness: implications for treatment, insurance and outcomes evaluation. JAMA 284, 1689–1695.

Neuhaus, J.M., Kalbfleisch, J.D., 1998. Between- and within-cluster covariate effects in the analysis of clustered data. Biometrics 54, 638–645.

Nosyk, B., Anglin, M.D., Brecht, M.L., Lima, V.D., Hser, Y.I., 2013. Characterizing durations of heroin abstinence in the California Civil Addict Program: Results from a 33-year observational cohort study. American Journal of Epidemiology 177, 675–682.

O'Brien, C.P., 2011. Addiction and dependence in DSM-V. Addiction 106, 866–867.

O'Brien, C.P., McLellan, A.T., 1996. Myths about the treatment of addiction. Lancet 347, 237 – 240.

R Core Team, 2014. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria. URL: http://www.R-project.org/.

Rathod, N., Addenbrooke, W., Rosenbach, A., 2005. Heroin dependence in an English town: 33-year follow-up. Br J Psychiatry 187, 421–425.

Robbins, L., Helzer, J., DH, D., 1975. Narcotic use in southeast-Asia and afterward - interview study of 898 vietnam returnees. Arch Gen Psychiatry 32, 955–961.

Robertson, J., Bucknall, A., Welsby, P., Roberts, J., Inglis, J., Peutherer, J., Brettle, R., 1986. Epidemic of AIDS related virus (HTLV-III/LAV) infection among intravenous drug abusers. BMJ 292, 527–529.

Robertson, J.R., Raab, G.M., Bruce, M., McKenzie, J.S., Storkey, H.R., Salter, A., 2006. Addressing the efficacy of dihydrocodeine versus methadone as an alternative maintenance treatment for opiate dependence: A randomized controlled trial. Addiction 101, 1752–1759.

Robertson, J.R., Ronald, P.J., Raab, G.M., Ross, A.J., Parpia, T., 1994. Deaths, HIV infection, abstinence, and other outcomes in a cohort of injecting drug users followed up for 10 years. BMJ 309, 369–372.

Robertson, R., Richardson, A., 2007. Heroin injecting and the introduction of HIV/AIDS into a Scottish city. J R Soc Med 100, 491–494.

Seaman, S., Pavlou, M., Copas, A., 2014. Review of methods for handling confounding by cluster and informative cluster size in clustered data. Statistics in Medicine 33, 5371–5387.

Shah, N.G., Galai, N., Celentano, D.D., Vlahov, D., Strathdee, S.A., 2006. Longitudinal predictors of injection cessation and subsequent relapse among a cohort

of injection drug users in Baltimore, MD, 1988-2000. Drug Alcohol Depend 83, 147–156. doi:10.1016/j.drugalcdep.2005.11.007.

Skidmore, C.A., Robertson, J.R., Robertson, A.A., Elton, R.A., 1990. After the epidemic: follow up study of HIV seroprevalence and changing patterns of drug use. BMJ 300, 219–223.

StataCorp, 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.

Stimson, G., Oppenheimer, E., 1982. Heroin Addiction: Treatment and Control in Britain. Tavistock, London.

Sweeting, M., De Angelis, D., Ades, A., Hickman, M., 2009. Estimating the prevalence of ex-injecting drug use in the population. Stat Methods Med Res 18, 381–395.

Termorshuizen, F., Krol, A., Prins, M., van Ameijden, E.J.C., 2005a. Long-term outcome of chronic drug use: The Amsterdam Cohort Study among drug users. Am J Epidemiol 161, 271 – 279.

Termorshuizen, F., Krol, A., Prins, M., Geskus, R., van den Brink, W., van Ameijden, E.J.C., 2005b. Prediction of relapse to frequent heroin use and the role of methadone prescription: an analysis of the Amsterdam Cohort Study among drug users. Drug Alcohol Depend 79, 231–40.

Therneau, T., 2012. coxme: Mixed Effects Cox Models. URL: http://CRAN.R-project.org/package=coxme.

Turner, K., Hutchinson, S., Vickerman, P., Hope, V., Craine, N., Palmateer, N., et al, 2011. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction 106, 1978–1988.

Vaillant, G., 1973. A 20-year follow-up of New York nacotic addicts. Arch Gen Psychiatry 29, 237–241.

Vlahov, D., Anthony, J., Munoz, A., Margolick, J., Nelson, K., Celentano, D., et al, 1991. The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. NIDA Res Monogr 109, 75–100.

Winick, C., 1962. Maturing out of narcotic addiction. Bulletin of Narcotics 14, 1–7.

Winick, C., 1964. The life cycle of the narcotic addict and of addiction. Bull Narc 16, 1–11.

Xia, Y., 2013. Characterising patterns of injecting drug use. Ph.D. thesis. University of Cambridge. Cambridge, United Kingdom.

Zinberg, N., Jacobson, R., 1976. The natural history of chipping. Am J Psychiatry 133, 37–40.

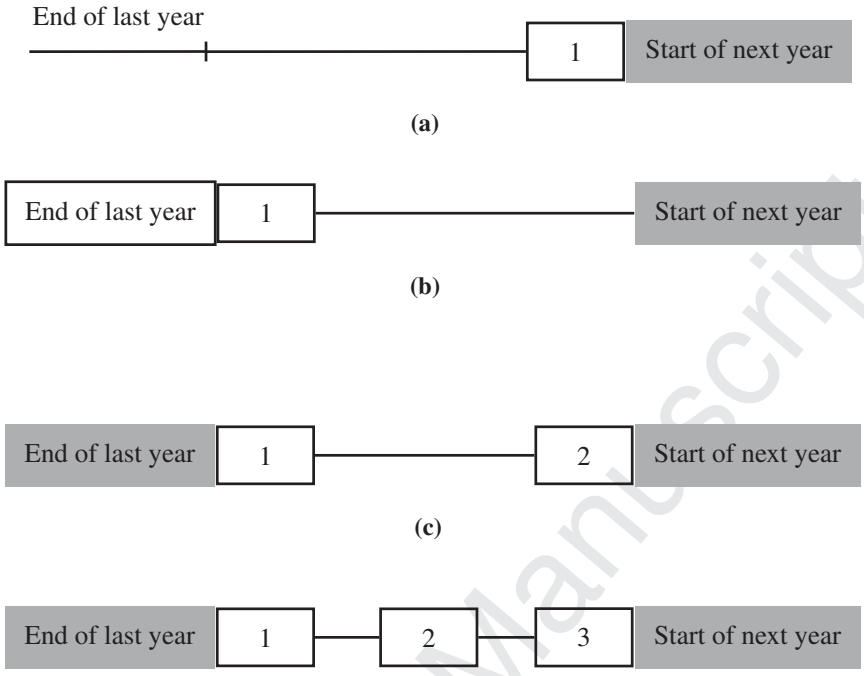
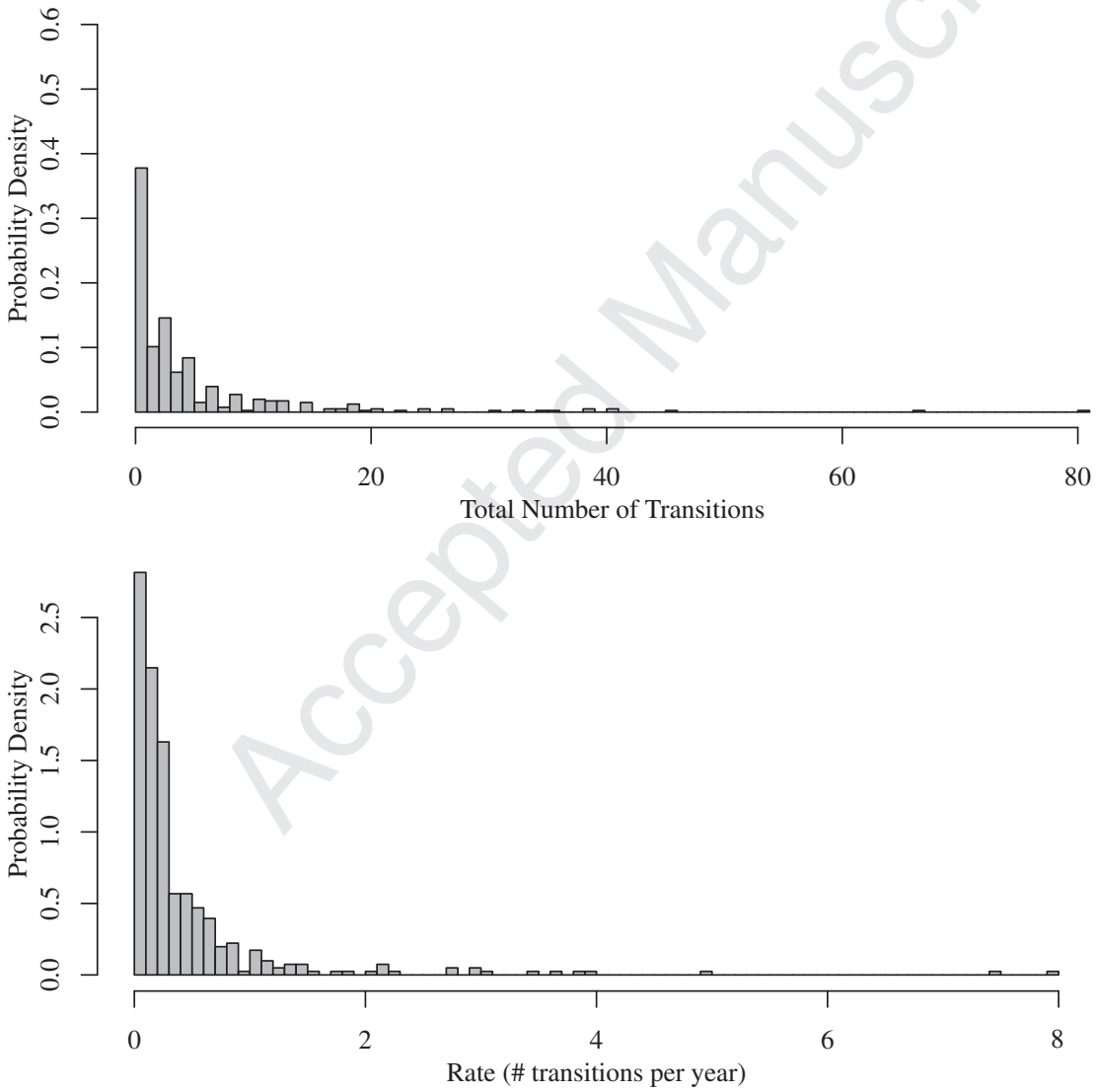
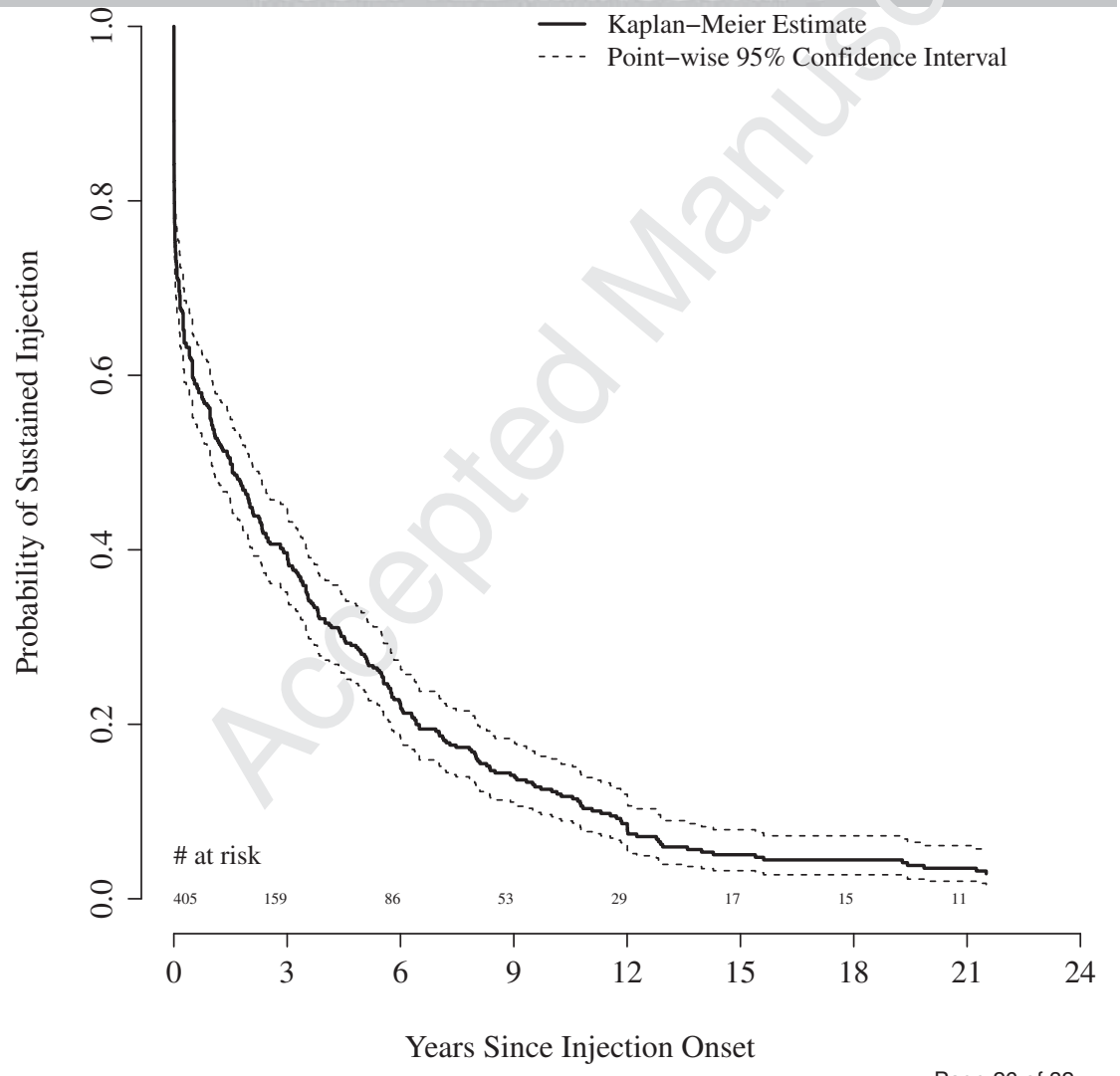


Figure 2



Figure



Figure

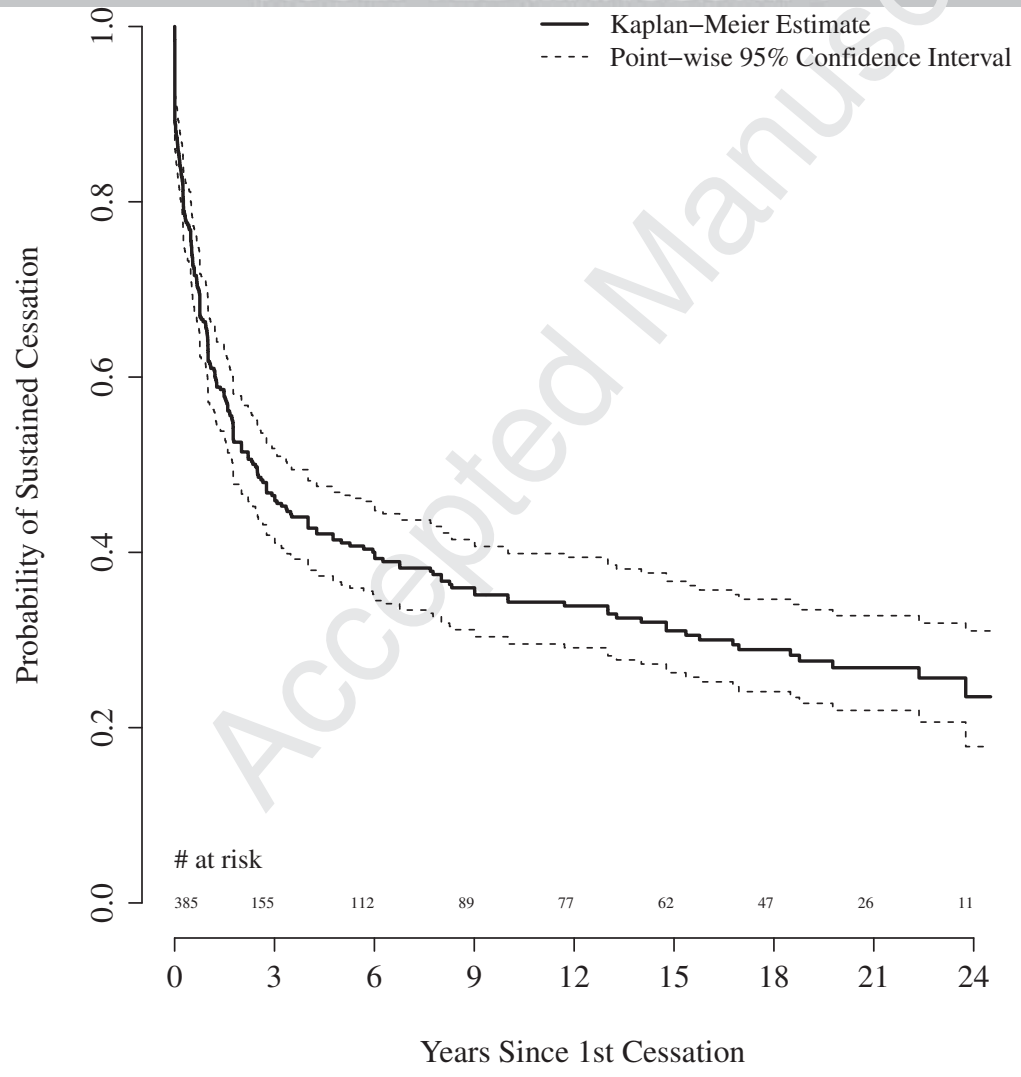


Figure 1: The Assignment of Non-injection Periods for the 405 PWID in the EAC, United Kingdom, 1980 – 2006.

Figure 1 (a): A single period of non-injection preceded by a period of injecting.

Figure 1 (b): A single period of non-injection preceded by a period of non-injection.

Figure 1 (c): Two non-injection periods within one year.

Figure 1 (d): Three non-injection periods within one year.

Figure 2: Histograms of the Total Number and Rate of Transitions for the 405 PWID in the EAC, United Kingdom, 1980-2006.

Figure 3: Kaplan-Meier Estimate of Time to First Cessation for the 405 PWID in the EAC, United Kingdom, 1980-2006.

Figure 4: Kaplan-Meier Estimate of Time to First Relapse for the 405 PWID in the EAC, United Kingdom, 1980-2006.

Table 1: Estimated Associations Between Covariates and Hazards of Cessation and Relapse Among the EAC, United Kingdom, 1980–2006.

	Cessation			Relapse		
	HR[a]	95% CI[a]	*P*-value	HR	95% CI	*P*-value
Sex						
Male (Ref)	1.00			1.00		
Female	1.05	0.81, 1.36	0.71	0.73	0.56, 0.94	0.02
Age at injection onset						
12–19 (Ref)	1.00			1.00		
20 +	1.32	0.99, 1.76	0.06	1.40	1.08, 1.83	0.01
Year of injection onset						
< 1986 (Ref)	1.00			1.00		
≥ 1986	1.37	1.05, 1.80	0.02	1.21	0.94, 1.58	0.14
Current age			0.62			0.001
<20	0.94	0.74, 1.18	0.59	1.06	0.78, 1.44	0.73
20 – 25 (Ref)	1.00			1.00		
26 – 30	0.96	0.79, 1.16	0.66	0.70	0.57, 0.87	0.001
31 – 35	1.10	0.87, 1.39	0.41	0.77	0.61, 0.98	0.04
35 +	1.15	0.85, 1.56	0.37	0.55	0.41, 0.75	<0.001
OST exposure						
Between-individual			<0.001			0.007
Not on OST (Ref)	1.00			1.00		
On OST	0.73	0.53, 1.02	0.07	1.67	1.16, 2.40	0.006
Unknown	0.35	0.21, 0.57	<0.001	1.95	1.18, 3.23	0.01
Within-individual			<0.001			0.14
Not on OST (Ref)	1.00			1.00		
On OST	1.71	1.40, 2.09	<0.001	0.81	0.65, 1.00	0.05
Unknown	1.11	0.81, 1.54	0.52	0.83	0.59, 1.18	0.30
No. of previous cessations/relapses			<0.001			0.37
0 (Ref)	1.00			1.00		
1 – 2	1.19	0.97, 1.47	0.09	1.27	1.00, 1.62	0.05
3 – 4	1.52	1.14, 2.03	0.005	1.36	0.96, 1.92	0.09
5 – 9	2.67	1.94, 3.69	<0.001	1.44	0.97, 2.14	0.07
≥ 10	3.58	2.42, 5.29	<0.001	1.54	0.96, 2.48	0.08
Baseline hazard for cessation			<0.001			
≤ 3 days (Ref)	1.00					
(3, 7] days	0.51	0.40, 0.64	<0.001			
(1, 12] weeks	0.09	0.08, 0.11	<0.001			
(3, 12] months	0.04	0.03, 0.05	<0.001			
> 1 year	0.03	0.03, 0.04	<0.001			
Baseline hazard for relapse						<0.001
≤ 2 months (Ref)				1.00		
(2, 12] months				0.87	0.74, 1.03	0.11
(1, 2] years				0.38	0.30, 0.50	<0.001
> 2 years				0.10	0.08, 0.13	<0.001
Variance of log-normal random effects	0.90	0.65, 1.24	<0.001	0.57	0.33, 0.98	<0.001

[a] CI, confidence interval; HR, hazard ratio

1. We examine the pattern of ceasing and relapsing during the entire injecting career.

2. OST reduces time to cessation but was not associated with lower risk of relapse.

3. Women and older PWID were less likely to relapse (had lower hazard of relapse).

4. With each relapse time to next cessation event is shortened.

5. We find evidence that PWID will mature out of injecting drug use aided by OST.

Role of funding source
The Edinburgh Addiction Study has been previously supported by the Scottish Home and Health Department and the Medical Research Council. The present follow up study is supported by the Chief Scientists Office for Scotland (grant nos. CZH/4/318 and CZH/4/40). The funders had no role in the design, execution, and writing up of the study.

Contributors

Yang Xia
- **analysis and interpretation of data**
- **drafting the article, revising the article critically for important intellectual content**
- **final approval of the version to be published**

Shaun Seaman
- **conception and design, analysis and interpretation of data**
- **revising the article critically for important intellectual content**
- **final approval of the version to be published**

Matthew Hickman
- **conception, design, and obtaining funding**
- **interpretation of data**
- **revising the article critically for important intellectual content**
- **final approval of the version to be published**

John Macleod
- **conception, design, and obtaining funding**
- **acquisition and interpretation of data**
- **reviewing the article critically for important intellectual content**
- **final approval of the version to be published**

Roy Robertson
- **conception, design, and obtaining funding**
- **acquisition and interpretation of data**
- **reviewing the article critically for important intellectual content**
- **final approval of the version to be published**

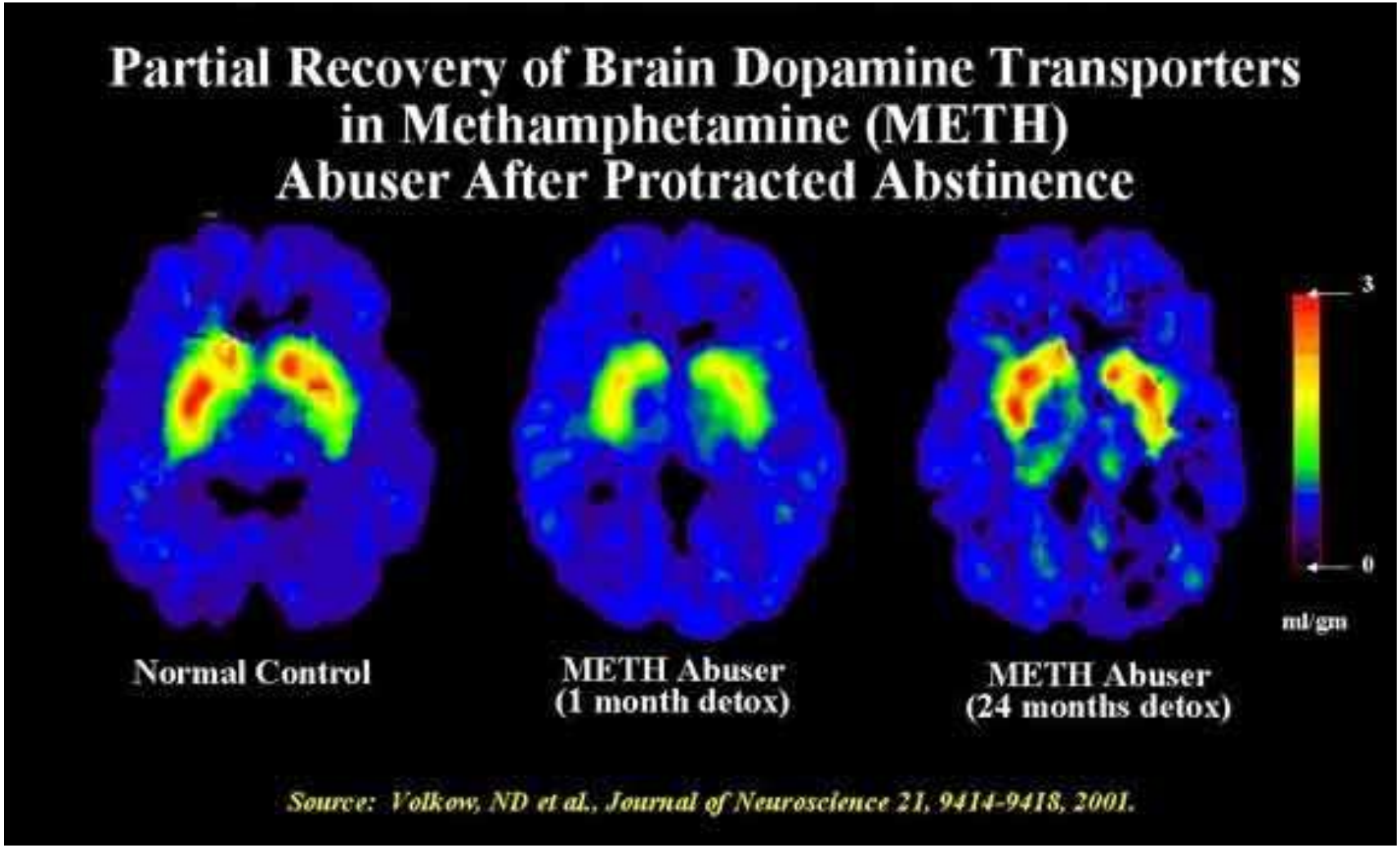
Lorraine Copeland
- **acquisition of data**
- **reviewing the article**
- **final approval of the version to be published**

James McKenzie
- **acquisition of data**
- **reviewing the article**
- **final approval of the version to be published**

Daniela De Angelis
- **conception and design, analysis and interpretation of data**
- **revising the article critically for important intellectual content**
- **final approval of the version to be published**

Conflict of interest
No conflict declared.

Acknowledgements
The work was undertaken with the support of The Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement (DECIPHer), a UKCRC Public Health Research: Centre of Excellence; and with support from NIHR School of Primary Care Research, NIHR School of Public Health Research, and NIHR Health Protection Research Unit in Evaluation of Interventions. The funders had no role in the design, execution, and writing up of the study.


Partial Recovery of Brain Dopamine Transporters
in Methamphetamine (METH)
Abuser After Protracted Abstinence
3
0
ml/gm
Normal Control
METH Abuser
(1 month detox)
METH Abuser
(24 months detox)
Source: Volkow, ND et al., Journal of Neuroscience 21, 9414-9418, 2001.