UNIVERSITY of LIMERICK

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ADDRESSING THE HARMS RELATED TO YOUTH SUBSTANCE USE: TREATMENT OF INDIVIDUALS AND POPULATION FOCUSED LEGISLATIVE RESPONSES.

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Thesis submitted to Graduate Entry Medical School, University of Limerick in fulfilment of the requirements for the degree of Doctor of Philosophy.

March 2018

Abstract

Addressing the harms related to youth substance use: Treatment of individuals and population focused legislative responses.

Substance use, and substance use disorders (SUD), are major contributors to global burden of disease among youth. They constitute an important risk factor for other disorders, including mental disorders. This thesis seeks to examine methods to reduce the harm associated with youth substance use, looking at the impact of treatment on the individual adolescent with a SUD and at legislative measures operating at the population level. While treatment models for SUD have become more liberal and harm reduction orientated in recent decades, legislation remains conservative and prohibitionist. The archetypal harm reduction treatment is opiate substitution treatment (OST) used with heroin dependence. The evidence base for OST in adolescents is sparse. Outcome of OST was examined. It emerged that OST delivers early reductions in heroin use, which continue to improve significantly from month three to month twelve of treatment. Evidence of improved psychological wellbeing is also demonstrated by adolescents on OST. In order to explore the impact of conservative legislative measures on harm related to substance use, a quasi-experimental approach was undertaken to explore changes which occurred in Ireland before, during and after the arrival of a vast network of head shops selling new psychoactive substances (NPS). Evidence is presented indicating that the expansion of head shops coincided with increased NPS addiction episodes among both adolescents and young adults. There was also evidence of increased drug related psychiatric admissions. All of these harms began to diminish within months of the closure of the head shops. Overall, these findings lend support to the position of providing tolerant and responsive treatment which does not demand abstinence for the small subset of youth who develop a SUD, while simultaneously maintaining an intolerant and conservative approach to prevention of substance use at the wider population level.

Declaration

This is an article-based PhD thesis. It contains four research papers and one research letter which have all been published in peer reviewed scientific journals. It includes a fifth research paper which is accepted pending minor revisions by a peer reviewed scientific journal. Finally, it also contains a sixth research paper which is currently under review by a peer reviewed scientific journal. A separate chapter is devoted to each of these seven research outputs. The introductory chapters and the concluding chapter have not previously been published.

Permission to republish the research papers in this thesis has been obtained from each of the journal publishers.

Apart from the research letter, all six research papers involved collaboration with co-authors. I am the lead author of all papers. My contribution, and the contributions of co-authors, are specified in section 7 of each chapter presenting the individual research papers. Additional contributions by people who did not qualify for authorship are outlined in Appendix 1.

Acknowledgements

I owe a debt of gratitude to very many people. My supervisors have been patient, encouraging and wise throughout this journey. I am very grateful for the support received from Dr Khalifa Elmusharaf and Prof Michael Larvin, who have each provided vital input at key stages. I am particularly grateful to Prof Walter Cullen for his tireless work as supervisor, and for giving me the confidence to take on this task in the first place.

Many co-authors have assisted me with the completion of each of the research studies. Their input is acknowledged in each of the research chapters. While it may be unfair to single out just one co-author, Dr Catherine Darker played a particularly important role in two of the studies. Her unrelenting work and determination proved essential to the completion of those projects.

I am also indebted to a number of people for their assistance regarding statistical advice, only one of whom was a co-author. Firstly, Prof Alan Kelly of TCD provided a great deal of guidance and expertise at the outset of this process. I am also grateful to Dr Ailish Hannigan for her provision of prompt and clear advice on so many occasions over my years as a PhD student. I was also fortunate to obtain guidance from Dr Conor McDonald whose vast knowledge of maths served to reassure me on numerous occasions. While working in Brisbane I sought and obtained support, advice and guidance from Dr Jason Ferris regarding use of JoinPoint analysis. Jason was very generous with his time.

Many of my colleagues at the clinical services in which I work were involved in gathering the information upon which much of the treatment focused research relied. For these reasons, I am grateful to Ann Campbell, Triona Kearns, Philip James, Martin Meagher and Kevin Ducray. On this issue, Robbie Dolan from the Young Persons Program was particularly thorough, accommodating and endlessly helpful.

I would also like to acknowledge the assistance provided by Anne Marie Carew of the Health Research Board in response to my many queries about the National Drug Treatment Reporting System. Inspector Brian Roberts of the Garda National Drugs Unit was very generous with his time and demonstrated a great willingness to share information about the Garda analyses of head shops in Ireland.

Prof David Meagher was an inspiration at the outset of this journey and I probably would not have embarked upon it without his encouragement. Prof Colum Dunne was similarly supportive. Prof Joe Barry, Prof Tom O'Dowd and Dr Eamon Keenan have all acted as mentors to me over my years of involvement in research and for that grounding in research methods and writing, I am very grateful.

My managers have facilitated my pursuit of this PhD. They demonstrated flexibility in doing so. I am grateful for the support over the years from Ms Ann O'Shea and Mr David Tully in particular. Senior managers also facilitated the completion of the treatment-based studies

ensuring resources were available where needed and for that I am grateful to Sheila Heffernan, Hillary Coffey-Farrell & Seamus Noone of the National Drug Treatment Centre.

Closer to home, I must also acknowledge the massive input from family. My parents have played a crucial role in nurturing within me a love of learning. My siblings have all ensured that the bar is kept high. In completing a PhD, I am following in the footsteps of my father and Anne, albeit at a much later stage in life in my case. My wife, Mary has been a wonderful support throughout the years of work on the thesis and I simply wouldn't have been able to do it without her willingness to fill the gaps created by my frequent absences on the domestic front. This thesis is about youth. Watching Aaron, Lauren, Ben & Matthew grow and mature over the past 15 years has made me wonder about the world they are venturing into and provided part of the inspiration for the themes within this work.

Finally, I must acknowledge the young people who have accessed the clinical services in which I have worked over the years. Many of the questions addressed in the individual studies in this thesis have their origins in conversations with them.

Research publications arising from this thesis

Original research papers

Smyth BP, Kelly A, Cullen W, Darker C. Outcome for adolescents abusing alcohol and cannabis following outpatient treatment: how many 'reliably improve'? *Irish Medical Journal* 2015: 108; 137-139.
Journal ISSN: 0332-3102 (Print)
Journal Url: http://imj.ie/

Smyth BP, James P, Cullen W, Darker C. "So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban. *International Journal of Drugs Policy* 2015:26; 887–889. doi:10.1016/j.drugpo.2015.05.021
Journal ISSN: 0955-3959
Journal Url: https://www.journals.elsevier.com/international-journal-of-drug-policy/

Smyth, BP, Ducray K., & Cullen W. Changes in psychological well-being among heroin-dependent adolescents during psychologically supported opiate substitution treatment. *Early Intervention in Psychiatry*, 2016 Jan 23, doi:10.1111/eip.12318 [Epub ahead of print]
Journal ISSN: 1751-7893 (Electronic)
Journal Url: *http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1751-7893*

Smyth BP, Lyons S, Cullen W. Decline in new psychoactive substance use disorders following legislation targeting headshops: Evidence from national addiction treatment data. *Drug & Alcohol Review* 2017: 36; 609-617. doi:10.1111/dar.12527
Journal ISSN: 146-3362
Journal Url: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1465-3362

Smyth BP, Elmusharaf K, Cullen W. Opioid substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention over twelve months. *BMC Pediatrics* 2018: 18(1):151. doi: 10.1186/s12887-018-1137-4.
Journal Url: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-018-1137-4

Research letter

Smyth BP. New psychoactive substances in Ireland following the criminal justice (psychoactive substances) act—why all the pessimism? *Addiction* 2017: 112;1686-1686. doi:10.1111/add.13804
Journal ISSN: 1360-0443
Journal Url: http://onlinelibrary.wiley.com/doi/10.1111/add.v113.4/issuetoc

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List of Abbreviations

AA – Alcoholics Anonymous

ACRA – Adolescent Community Reinforcement Approach

ASSIST - Alcohol, Smoking and Substance Involvement Screening Test

AUDIT – Alcohol Use Disorders Identification Test

BT – Buprenorphine Treatment

BYI - Beck Youth Inventory

BZP – Benzylpiperazine

CBT – Cognitive Behavioural Therapy

CI - confidence interval

CRA - Community Reinforcement Approach

CSO – Central Statistics Office

CUD - Cannabis Use Disorder

DALYs - Disability adjusted life years

DARP - Drug Abuse Reporting Program

DoHC - Department of Health & Children

DRPA - Drug related psychiatric admissions

DSM – Diagnostic & Statistical Manual of the American Psychiatric Association

DUID – Driving under the influence of drugs

ED – Emergency department

EDDP – 5-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidine

ESPAD - European School Survey Project on Alcohol and Other Drugs

GBD Global Burden of Disease

GNDU - Garda National Drug Unit

HRB - Health Research Board

ICD – International Classification of Diseases

IQR – Interquartile range

JLO - Juvenile Liaison Officers

MAP - Maudsley Addiction Profile

M-CIDI - Munich Composite International Diagnostic Interview

MDFT - Multi-Dimensional Family Therapy

MI - motivational interviewing

MT - methadone treatment

MTF – Monitoring the Future survey

NA – Narcotics Anonymous

NACD – National Advisory Committee on Drugs

NACDA – National Advisory Committee on Drugs & Alcohol

NDTC - National Drug Treatment Centre

NDTRS - National Drug Treatment Reporting System

NIDA – National Institute of Drug Abuse

NPIRS - National Psychiatric In-Patient Reporting System

NPS - New psychoactive substance

NTA - National Treatment Agency in the UK

OST - Opioid (opiate) substitution treatment

PCM - Percentage change per month

SC - synthetic cannabinoids

SOCRATES - Stages of Change Readiness and Treatment Eagerness Scale

SPHE - Social Personal & Health Education

SUD - Substance Use Disorder

UDS - urine drugs screens

YPP - Young Persons' Programme

Chapter 1

Thesis Overview & Structure

1.1 Introduction

Substance use by young people is a cause of concern for societies and for health professionals across the world.(1) Approximately 10% of young people who use any specific substance will become dependent upon it, i.e. develop a substance use disorder (SUD).(2-4)

While dependence clearly causes harm, harms can also arise in young people who are not using a substance dependently. These other harms are frequently related to acute intoxication and can also include the adverse impact which substance use can exert upon mental health.(5, 6) There appears to be a complex and reciprocal relationship between substance use and mental health problems.(7, 8) Taken together, mental disorders and SUDs account for 45% of all years lost to disability globally among young people aged 10 to 24 years.(9)

The societal response to drug related harm is multifaceted.(6, 10, 11) Key components include the provision of treatment to individuals with substance use disorders and also broader population measures including legislation which prohibits use of most drugs.(5, 6, 11)

Treatment approaches have changed substantially in the past 40 years, moving away from abstinence based treatments and towards more liberal and tolerant harm reduction based treatments(12-16). Although this change is now generally accepted in most western countries for adults, there is some ongoing uncertainty about the appropriateness of harm reduction type treatments for adolescents.(11, 17, 18)

In the past decade, there has been increased discussion about legislative responses to drug use and there have been increasing calls for these to also move in a more tolerant direction.(10, 19) The ‘global drug prohibition regime’ of the past 50 years has been widely characterised as ineffective and possibly even harmful in itself.(20, 21)

In the past 15 years, Ireland has moved towards provision of harm reduction treatments to youth, perhaps moving further and faster down this route than many other countries, while simultaneously retaining the old 'prohibition-styled' approach to preventing drug use.(22)

1.2 Aims & Objectives

In this article-based PhD, I sought to gather evidence to build the case for and against this current position on drug related harm among youth in Ireland, which seems somewhat contradictory in simultaneously containing both quite liberal and quite conservative components.

More specifically, I sought to examine outcome for adolescents who receive harm reduction styled treatment for substance use disorders, and in particular examining the most controversial harm reduction treatment in the adolescent age range, this being opiate substitution treatment for heroin dependent adolescents.(17, 18) Secondly, I sought to examine the impact of prohibition styled legislation targeted at new psychoactive substances, examining three different types of harm. This strategy has been described by Donald Campbell as using a quasiexperimental approach to policy evaluation by using 'multiple measures of independent imperfection', and discussed more recently by Wayne Hall in the evaluation of alcohol policy.(23, 24)

1.3 Specific Research Outputs

In order to examine strategies which reduce harms related to youth substance use, at the level of the individual and across the populations, six studies were conducted. These were:-

1/ An examination of the treatment outcome for adolescents with alcohol and cannabis use disorders. This study describes the profile of Irish adolescents who attend addiction treatment, reports on rates of polysubstance use and examines motivation amongst this patient group. As harm reduction interventions have come to the fore, there has been a move away from abstinence as a sole acceptable outcome. This study utilises a somewhat novel approach to examine outcomes which fall short of abstinence, in seeking to determine

what proportion of patients with alcohol and cannabis use disorders achieve a 'reliably reduction' in their substance use.

2/ The archetypal harm reduction treatment is opiate substitution treatment (OST) for heroin dependence, which utilises agonist medications such as methadone and buprenorphine. In view of the great paucity of studies of OST in the adolescent age range, this study examines the reductions in heroin use during the first year of OST. Given the frequency of polydrug use, the study seeks to determine if OST also delivers reductions in use of other substances. Treatment retention, and its correlates, is also examined.

3/ Taking a broader view of OST and harms related to heroin use disorders, this third study examines the impact of OST upon psychological wellbeing of heroin dependent adolescents during treatment.

4/ Having explored the impact of treatment on individual adolescents with substance use disorders in the preceding studies, this fourth study seeks to determine if national legislative measures influence the pattern of adolescent substance use disorders. The study examines changes in use of new psychoactive substances (NPS) among adolescents attending the treatment service examined in the first study above, following a conservative and prohibition-styled legislative response to the arrival of head shops in Ireland.

5/ This study extends the theme of the previous study, by examining whether or not there is evidence of changes in the rate of addiction presentations related to NPS in young adults following the arrival and departure of the head shops. It uses evidence from the national drug treatment reporting system.

6/ Taking a broader view again of harms related to NPS and returning to the theme of mental health, this final study examines all drug related psychiatric admissions in Ireland during this head shop era. It seeks to determine if there was evidence of increased psychiatric presentations while the head shops were at their most active and whether this harm declined following their closure.

Table 1.1. Overview of research outputs from thesis

No.	Paper title	Journal	Paper Type	Status
1	Outcome for adolescents abusing alcohol and cannabis following outpatient treatment: how many 'reliably improve'?	*Irish Medical Journal*	Research paper	Published
2	Opioid substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention over twelve months	*BMC Paediatrics*	Research paper	Accepted for publication
3	Changes in psychological well-being among heroin-dependent adolescents during psychologically supported opiate substitution treatment.	*Early Intervention in Psychiatry*	Research paper	Published
4	"So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban.	*International Journal of Drug Policy*	Short report	Published
5	Decline in new psychoactive substance use disorders following legislation targeting headshops: evidence from national addiction treatment data.	*Drug & Alcohol Review*	Research paper	Published
6	Legislation targeting head shops selling new psychoactive substances and changes in drug related psychiatric admissions: A national database study	*BMC Psychiatry*	Research paper	Under review
7	New psychoactive substances in Ireland following the Criminal Justice (Psychoactive Substances) Act – why all the pessimism?	*Addiction*	Research Letter	Published

1.4 Thesis format – chapters

Following this brief overview, Chapter 2 will describe the background literature on substance use among youth and on the treatment and legislative strategies which are employed to reduce harms. Specifically, it will examine in more detail OST among adolescents and the international experience and evidence regarding legislative responses to the challenges posed by new psychoactive substances.

As each research paper had to be written as a 'stand alone' contribution to the scientific literature as a published article, some of the methodology sections are quite narrow in focus. In Chapter 3, I have sought to address this by discussing in more detail some of the methodological challenges encountered during the PhD process and provide more context to explain the rationale for use of the chosen methodologies.

Chapters 4 to 9 each contain individual research papers. Each chapter starts with a brief introduction which seeks to put that paper into context for the overall thesis. The final published version of two papers involved a shortened format (papers 1 and 4 from the list above). A more comprehensive and detailed version of each of these papers is included in the chapters, with content modified based upon the referees' comments regarding the submissions. There were limits on number of tables and figures for some journals which resulted in the use of on-line supplemental material linked to those papers. For ease of reading this thesis, that supplemental material has either been incorporated into the body of the chapter or added as an appendix to the chapter. The research letter published in *Addiction* forms the basis of Chapter 10, this summarising some of the key findings from the three studies examining temporal changes in NPS related harms.

To assist presentation of the published empiric research papers, a consistent formatting has been used across all chapters. Chapter Z is divided into the following sections:-

Z.1 = Introduction of context of this paper within overall thesis
Z.2 = Abstract
Z.3 = Introduction
Z.4 = Methods
Z.5 = Results
Z.6 = Discussion
Z.7 = Author Contributions.

For some studies, there was input and support provided by individuals, especially in the area of statistical methodology, who were not co-authors of the published research paper. The contribution of those individuals is described in Appendix 1.

Chapter 11 presents a synthesis of the key research findings from the individual studies and draws together the major themes and conclusions.

As journal specifications differ regarding referencing, the references in Chapters 4-10, which are taken from published papers, varies from one chapter to the next, consistent with the

required journal style. A bibliography is provided for references used in the remaining chapters (i.e. Chapters 1 to 3 and Chapter 11).

1.5 Terminology

1.5.1 "Youth"

This thesis is focused upon youth. There is no universally agreed definition of youth. While lamenting the challenges posed by adolescent behaviours, Shakespeare identified the years between 10 and 23 as constituting "youth" in *A Winter's Tale*. Modern neuroimaging studies have confirmed that brain development continues until the mid 20s.(6) Health reviews focused upon youth tend to use the years 10 to 24 years, especially those addressing mental health and substance use.(9, 25) Although substance use tends to commence during the teenage years, morbidity associated with drug use peaks between the ages of 20 and 34 years.(25, 26)

The treatment studies in this thesis are focused upon adolescents aged 18 years and under, this age cut-off being typical of adolescent addiction treatment services in Ireland and elsewhere. It is among this younger age group that treatment research is most sparse. The studies addressing the impact of policy upon harms related to substance use include a broader age span, which extends as far as 34 years.

1.5.2 Language used to describe drug use and associated problems

There are very many divisive issues in the sphere of drug policy. Language is certainly one of those issues. Many journals and professional bodies have strong policy statements on the appropriate use of language to describe the act of drug use, the people who use drugs and the problems which can arise from such use.(27, 28) Terms such as 'alcoholic' are now generally avoided. The word 'abuse' in the diagnostic term substance abuse is criticised by many as potentially stigmatising. Even the words 'dependence' and 'addiction' provoke some criticism.

In this thesis, many words and expressions are used to describe the act of drug use and the people who engage in that activity. While efforts have been made to reduce use of

potentially stigmatising language, some of the terminology used may still fall short of the ideal standard. For example, the term 'substance abuse' is used where studies quoting this DSM-IV diagnostic category are reported.

Apart from issues of stigma, the terms used to describe problems associated with drug use vary from the USA to Europe and have also changed over time. The biggest change in recent years has been the creation of a single diagnosis of substance use disorder in DSM V, this replacing the previous categorization of Substance Dependence and Substance Abuse.(29, 30) For the time being, ICD-10 retains two illness categories, these being Dependence Syndrome and Harmful Use. Some of these expressions are used interchangeably during the course of this thesis. Equivalent terms are outlined in table 1.2 below.

Table 1.2 Terms used to describe problematic substance use in this thesis

DSM IV	**DSM V**	**ICD 10**	**Other equivalent and colloquial terms**
Substance Dependence	Substance use disorder - severe	Dependence Syndrome	Addiction
Substance Abuse	Substance use disorder – Mild to moderate	Harmful Use	

Chapter 2

Background Literature

2.1 Overview of chapter

This chapter aims to put the overall thesis into context. It will briefly summarise potential harms which can arise for youth who use drugs. It will examine temporal trends in drug use internationally and nationally. It will characterise the potential progression to substance dependence, this dependence being a key focus of many of the studies in this thesis. It will examine some key approaches which societies employ to influence that potential journey. Specifically, it will introduce treatment responses to the subset of individual adolescents who progress to develop substance use disorders, and examine how the principles underpinning treatment have altered in recent decades to become more liberal and harm reduction orientated. In contrast, it will describe how legislative responses have remained largely unchanged and conservative, in spite of growing calls for their review. Finally, it will provide a detailed examination of the literature on (1) use of opiate substitution treatment (OST) in adolescents, and (2) impact of legislative responses upon new psychoactive substances (NPS) use and NPS related harms.

2.2 Potential harms which can arise from youth substance use

2.2.1 Range of Harms

It is not the *use* of substances in itself that is the primary concern for health professionals. It is the potential harms which may arise from their use.(5) These possible harms include:-

- Dependence, harmful use (or substance use disorders)(6)
- Problems related to acute intoxication(10)
    - Fatal overdose
    - Non-fatal accidental overdose
    - Medical event (e.g. seizure, cardiac arrhythmia)
    - Acute psychiatric disturbance (e.g. paranoia, acute anxiety, deliberate self harm, suicide)

    - Injury arising from impaired functioning (e.g. fall due to intoxication precipitated ataxia)
    - Risky behaviour (e.g. unplanned & unsafe sex, driving while intoxicated)
- Problems related to cumulative consumption over time
    - Carcinogenic effects (e.g. alcohol & oropharyngeal cancer, tobacco & lung cancer)
    - Potential neurotoxic effects (e.g. alcohol and dementia(31), cannabis and psychosis(32))
    - Coronary artery disease (e.g. tobacco, methamphetamine(33))
    - Deteriorating mental health – development of dual diagnosis.(8, 34)

In addition to these potential health risks and harms, there are also many negative social impacts which can arise secondary to substance use. These include issues such as intoxication fuelled anti-social behaviour and violence, acquisitive crime to fund substance use, negative impact on relationships and impaired academic performance.(5, 6) The fact that young people can end up with criminal charges arising from their drug use is increasingly recognised as a drug related harm for those individuals.(4, 10)

2.2.2 Quantifying the harms

The Global Burden of Disease (GBD) project has highlighted the vast extent of the morbidity related to substance use. GBD examines this in two ways. Firstly, it looks at the contribution made by substance *use* as a risk factor for other illnesses and disorders. Secondly, it measures disability arising from substance use *disorders* themselves. It has emerged that substance use constitutes the biggest single risk factor for morbidity globally, as measured in disability adjusted life years (DALYs), for 15 to 24 year-olds.(9) Neuropsychiatric disorders, which includes both mental and substance use disorders, account for 45% of all years lost to disability among 10-24 year-olds.(9) The contributions of various specific neuropsychiatric disorders to DALYs are provided in Figure 2.1.(26) It can be seen that drug use disorders emerge as a major contributor to disability in the late teens, being second only to depression as an issue during the 20s. Degenhardt et al examined the relative contribution of different specific substance use disorders to the overall morbidity caused by SUDs in another GBD study. In the 15 to 24 year old range, it emerges that opioid and cannabis use

disorders are the biggest specific contributors to DALYs, as shown in Figure 2.2.(35) The treatment studies in this thesis will focus upon heroin and cannabis use disorders.

Figure 2.1 Disability adjusted life years (DALYs) for each mental and substance use disorder in 2010, by age. (Reproduced with permission from Whiteford et al 2013:382;1575-86)(26)

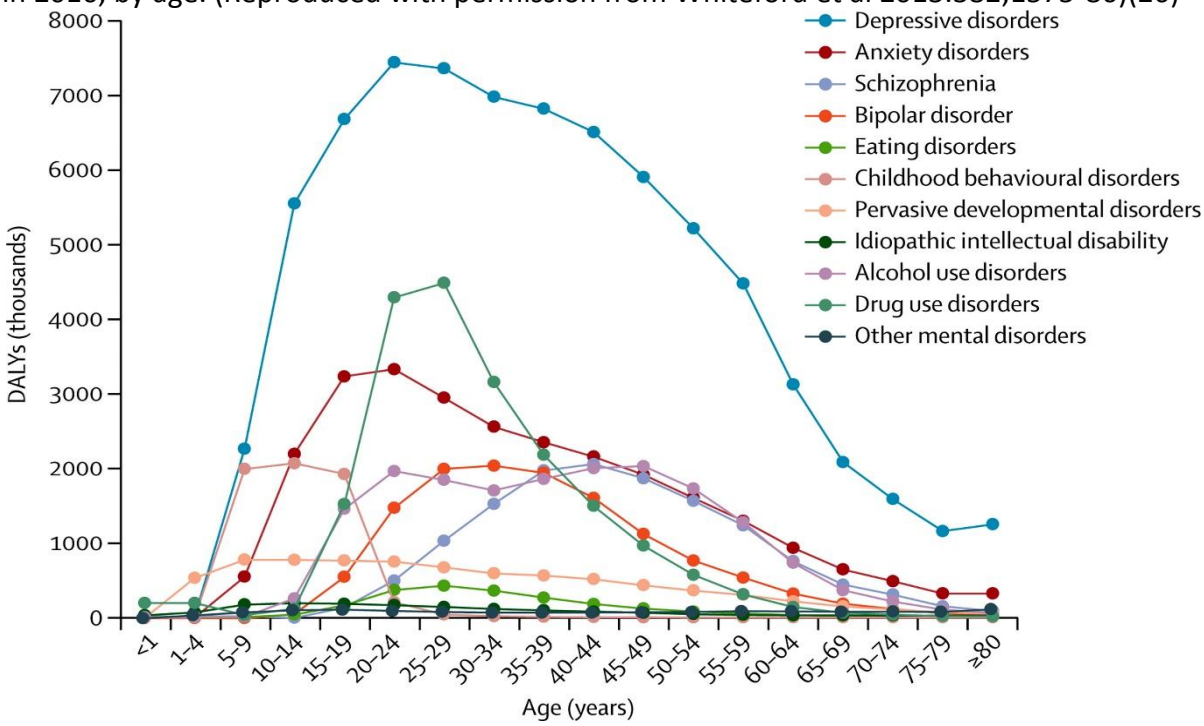
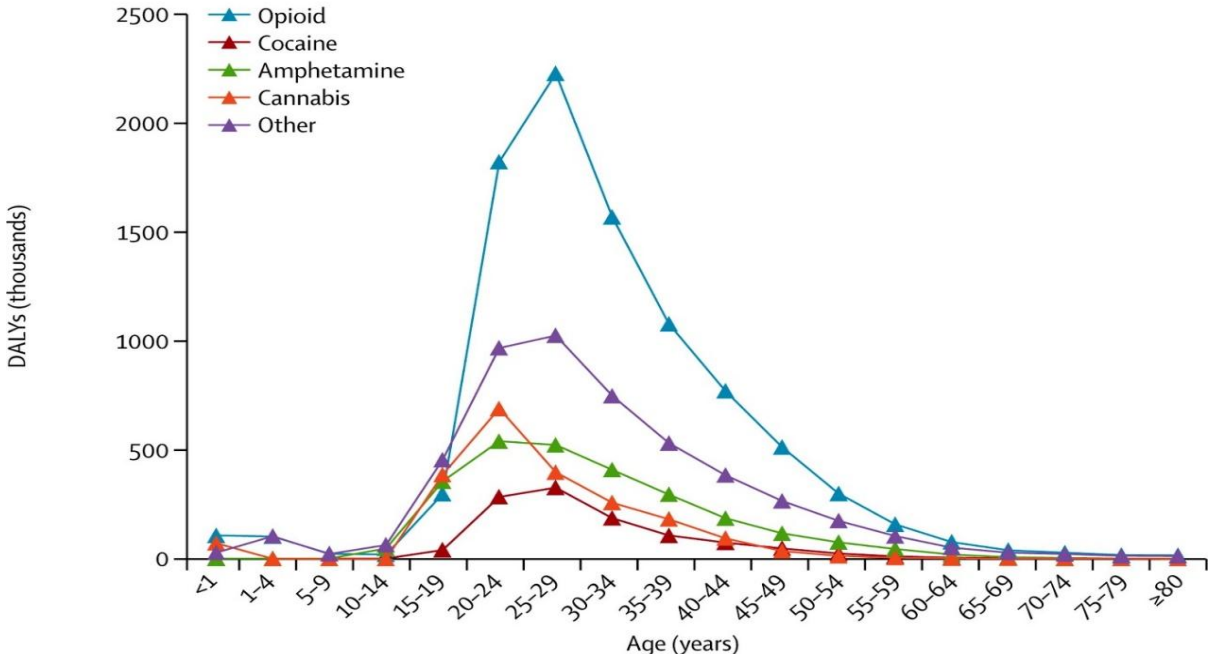


Figure 2.2 Disability adjusted life years (DALYs) attributable to each type of drug dependence by age in 2010. (Reproduced with permission from Degenhardt et al 2013:382;1564-74)(35)



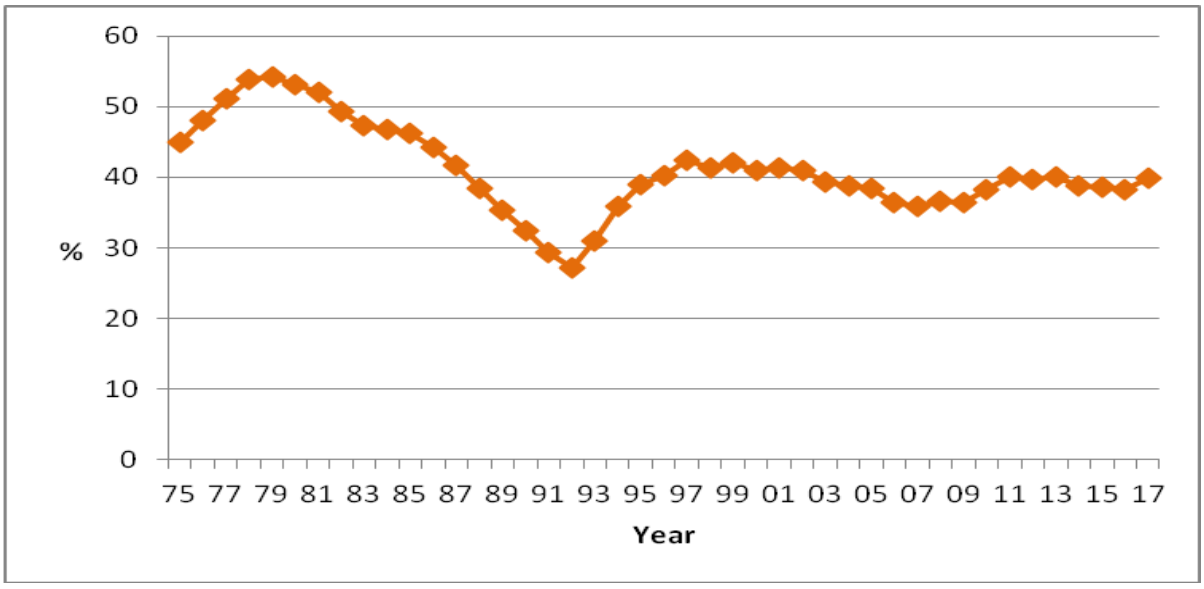
2.3 Patterns of substance use among Youth

Epidemiological data relevant to youth is considered in the sections below. Among youth, two age groups are considered separately, these being adolescents (aged under 18 years) and young adults (aged over 18 years).

2.3.1 Temporal and geographic variations among adolescents

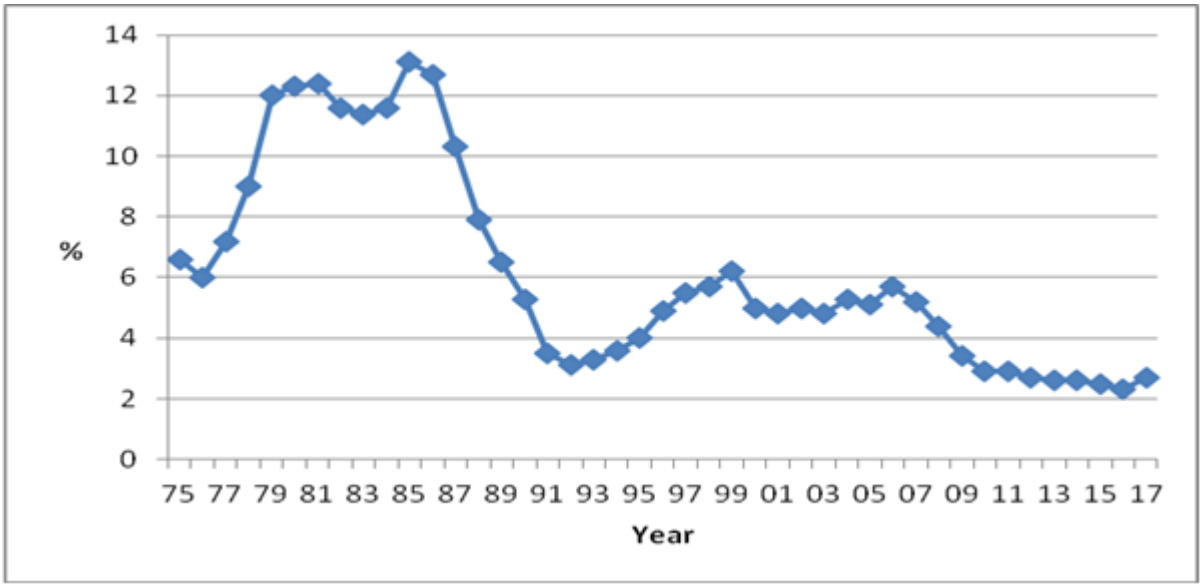
Patterns of substance use by adolescents vary greatly from one country to another and over time within individual countries. The USA has been monitoring this issue for a longer period than other countries. They have been measuring drug use by adolescents since 1975 in the annual Monitoring the Future (MTF) survey.(36, 37) Over the 40 years of this study, it was in 1979 that drug use hit its peak, with 54% of 12th grade (about 17 years of age) students reporting use of at least one illicit substance in the previous year (see Figure 2.3). This fell to 27% in 1992. By the late 1990s it had increased to 40% once again and it has been relatively stable (36% - 42%) at this level for the past 20 years.

Figure 2.3. Use of any illicit drug in the past year. 12th grade (circa 17 years old) students in USA. Monitoring the Future survey, 1975 to 2017



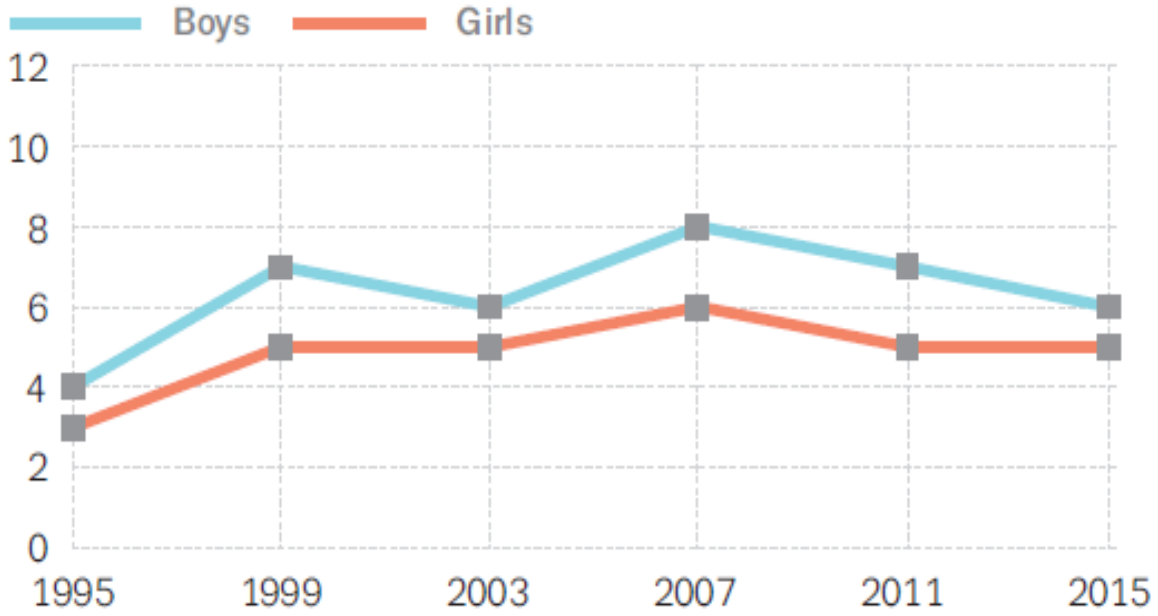
Cannabis has been the most commonly used illicit substance, it being used by the vast majority of students who reported use of any illicit substance. The temporal pattern of use of substances other than cannabis, such as cocaine, reveals greater fluctuations in use from peak to trough (13% in 1985 to 2% in 2016), as shown in Figure 2.4.

Figure 2.4. Use of Cocaine in the past year. 12th grade (age circa 17 years) students in USA. Monitoring the Future survey, 1975 to 2017



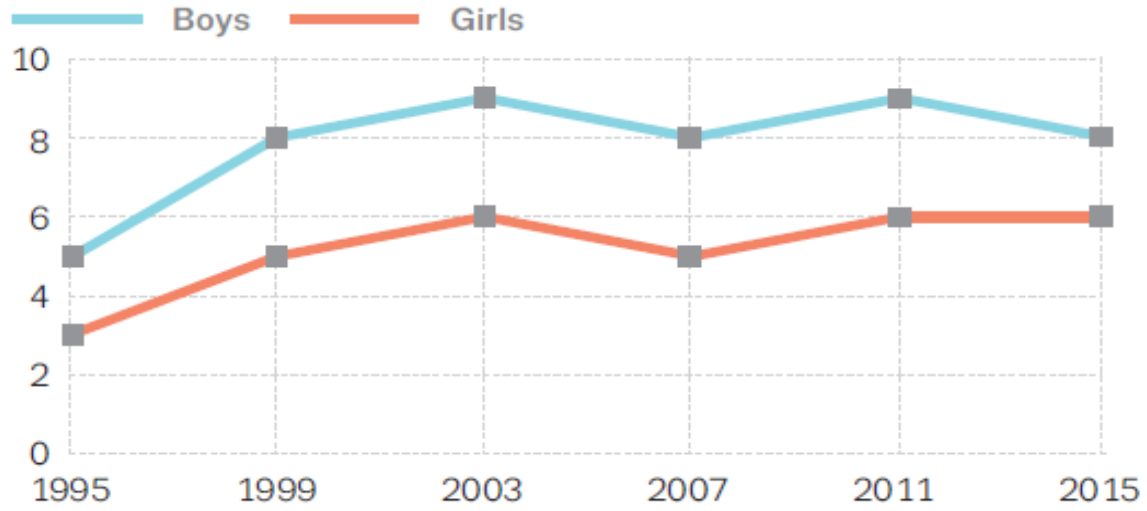
Across Europe, the European School Survey Project on Alcohol and Other Drugs (ESPAD) survey has been conducted in schools every four years since 1995, students being interviewed around the time of their 16th birthday.(1, 38, 39) Lifetime use of any illicit drug increased overall from 1995 to 2003, from 12% to 20%. Since then it has fallen slightly for boys from 23% to 20% in 2015. It has remained relatively stable for girls over the past 12 years at 15% to 17%. Like USA, cannabis is the most widely used illicit substance. Across the 20 year period, lifetime use of illicit drugs apart from cannabis was at its lowest in 1995, peaked in 2007 and has fallen marginally since then (see Figure 2.5)

Figure 2.5. ESPAD surveys of 16 year olds. Lifetime use of an illicit drug other than cannabis, by gender (%)



Past month cannabis use across Europe increased substantially from 1995 to 2003 (see Figure 2.6). It has remained quite stable since that time, being about 6% for girls and 8-9% for boys. While gender differences have tended to narrow over past decades, most international studies also demonstrate a higher prevalence of drug use among males.

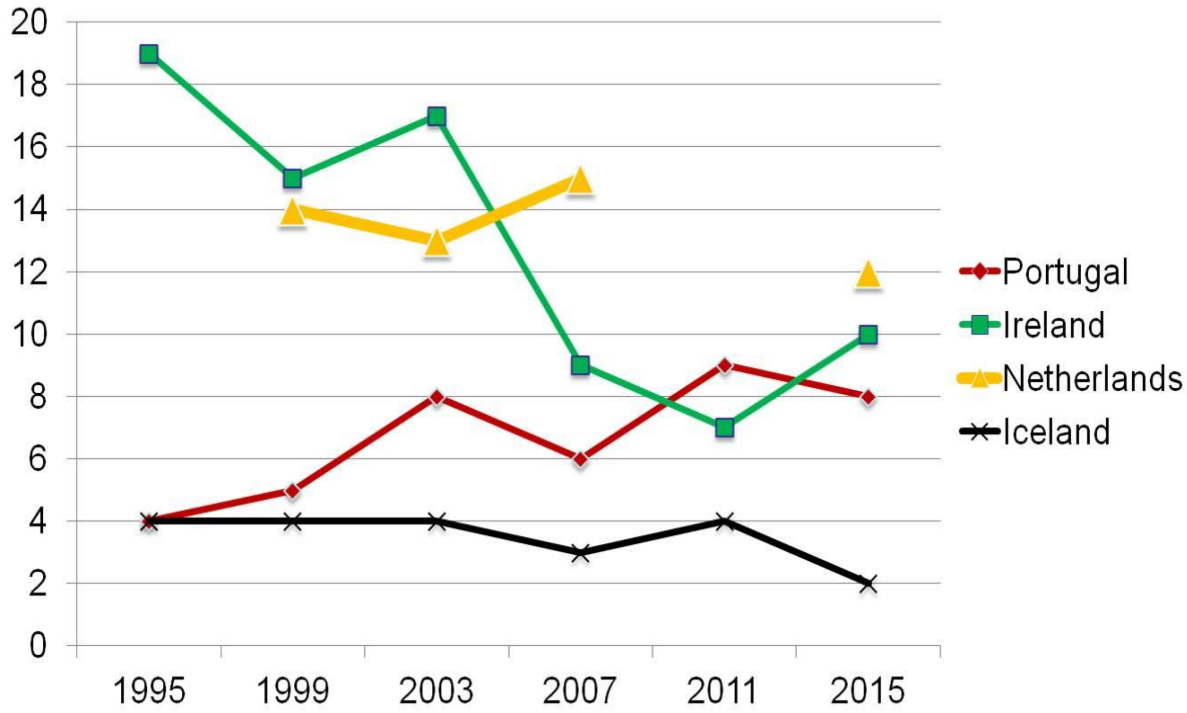
Figure 2.6. ESPAD surveys of 16 year olds. Cannabis use in the past 30 days, by gender (%)



This pattern of relative stability in use across Europe as a whole conceals substantial fluctuations within individual countries. Analysis by country also reveals movement in

opposite directions (see Figure 2.7).(39) In Ireland, past month cannabis use fell from 19% to 7% from 1995 to 2011, before then climbing again to 10% in 2015. In contrast, Portugal has demonstrated a pattern of increased use, albeit starting from a relatively low base. Iceland also started at a low base in 1995, avoided any increase over the following decades and then actually declined to just 2% in 2015.

Figure 2.7. ESPAD surveys of 16 year-olds. Past month cannabis use in four different countries (%)



Footnote to figure 2.7. Netherlands did not participate in ESPAD in 2011.

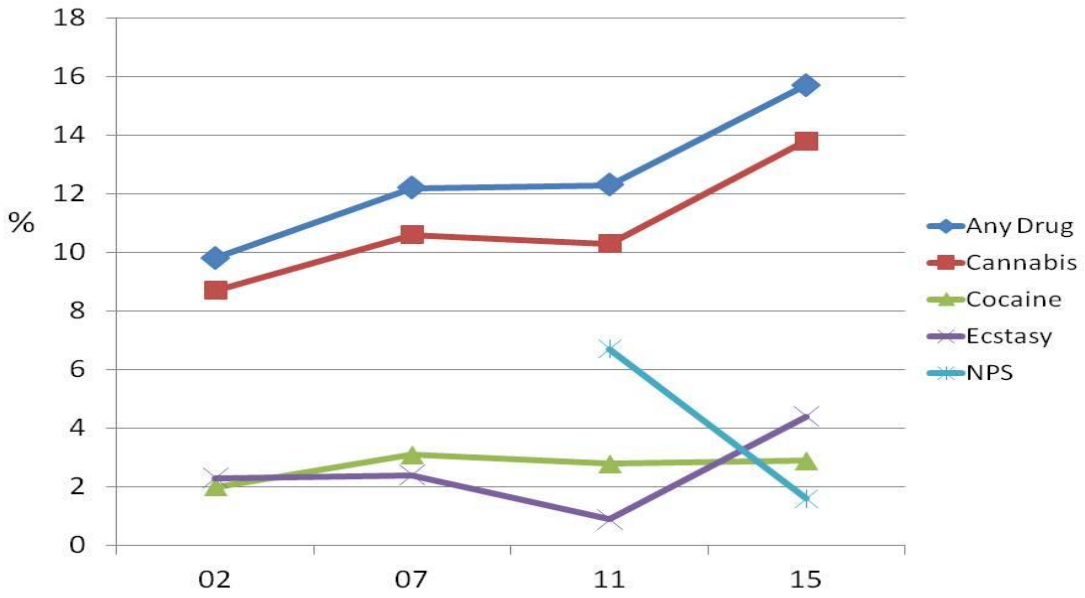
2.3.2 Temporal trends in substance use by young adults in Ireland.

Patterns of use among adolescents typically mirror changes in use among young adults within countries and over time. In Ireland, the National Advisory Committee on Drugs (NACD) has been conducting a survey of substance use in the general population every four years since 2002/3.(40, 41) Figure 2.8 shows the rate of past year use of a range of substances by young adults aged 15 to 34 years since that first survey. Over the twelve year period the proportion reporting use of at least one illicit drug has tended to increase, with

cannabis being a component of that substance use in 80-90% of cases, mirroring trends seen elsewhere.

In the 2010/11 survey, questions were asked for the first time about a class of drugs known as New Psychoactive Substances (NPS). NPS include a range of drugs such as synthetic cannabinoids, cathinones, piperazines and phenethylamines. They were designed to mimic the effects of traditional drugs such as cannabis, MDMA and cocaine. They were becoming an increasing source of national and international concern around 2009-2010 and consequently a question on their use was added to the survey in 2010/11. This revealed that NPS were the second most popular category of drug use, after cannabis, at that time. The 2015/16 survey indicates a substantial decline in NPS use.

Figure 2.8. Past year use of substances in Ireland by young adults, aged 15 to 34 years



2.4 Progression of substance use

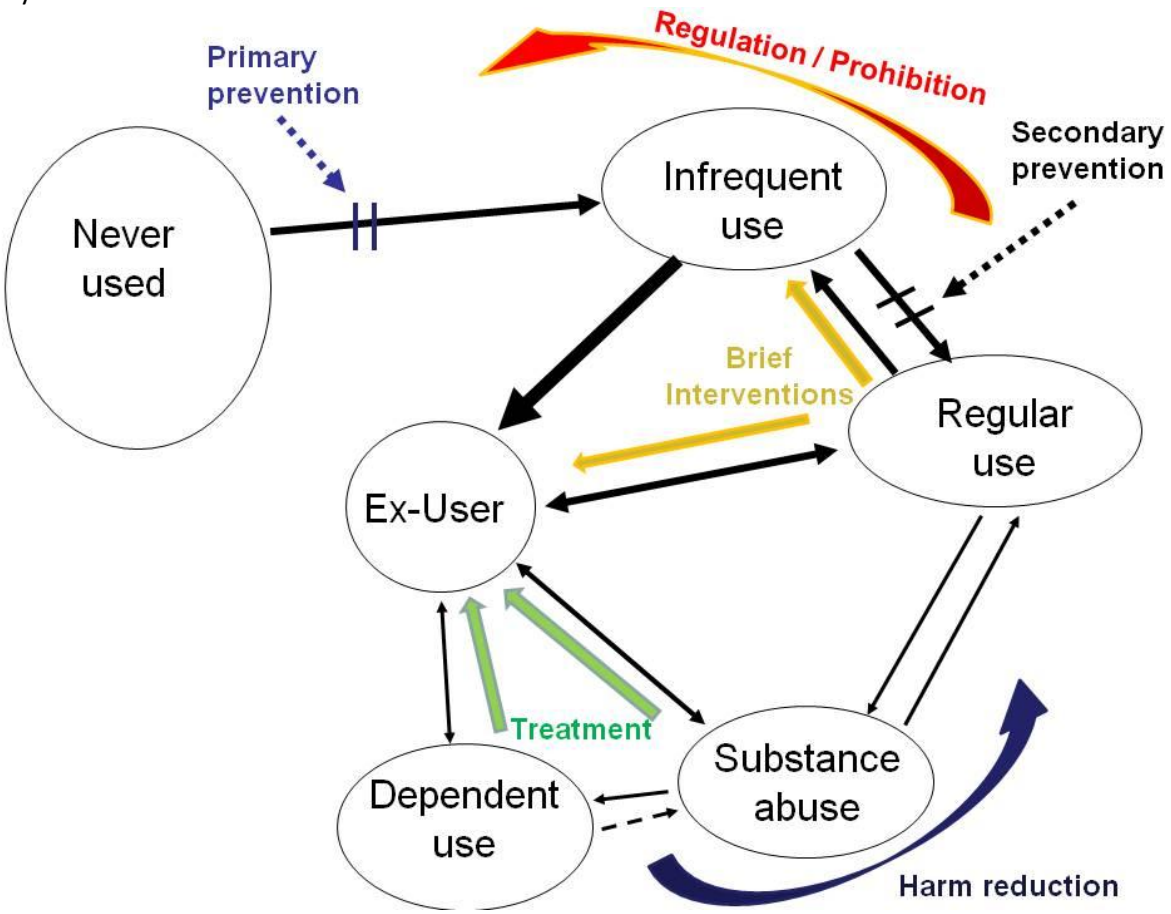
2.4.1 Journey into, through and out of substance use

Experimentation with substances typically commences in adolescence, and earlier age of onset tends to predict more rapid and more frequent progression to development of a substance use disorder.(25, 42) Most adults who develop substance dependence commenced their substance use as adolescents.(25, 43) However, many people who try a

substance do not persist with use, quickly becoming an ex-user.(42) Of those who do persist, some opt to use episodically and opportunistically.(44) This group of infrequent users face some risks associated with acute intoxication, as outlined in section 2.2. Other people may progress to more regular use, and increased frequency of use typically brings with it increased risk of harms.(45)

Across any given population, this potential progression of substance use can be presented diagrammatically as in Figure 2.9.(42) This presents the various categories of individuals according to their use profile. When followed up over time, some people move in a clock-wise direction towards patterns of increasing use, while others reduce, or potentially cease, their use.(42, 46)

Figure 2.9. Potential journey through stages of drug use and points of health service and public policy intervention



Individuals can make positive changes to their own substance use without any treatment or formal government intervention. For example, they may even move from a dependent pattern of use to abstinence, this being referred to as natural recovery.(46) This was highlighted in the study of Vietnam Veterans with histories of heroin dependence while at war who reverted to abstinence upon return to USA and also in follow up studies of adults with severe alcohol dependence.(47-50) Also it has been observed that some dependent users move back to regular but non-dependent use, and they may make this transition both with or without with assistance of a treatment intervention.(46, 51)

Others may revert from a pattern of regular use to abstinence or to very infrequent use.(46) In a survey of young adults aged 15-34 years in Ireland, it emerged that 74% of those who had used cannabis regularly in the past reported that they had ceased use at the time of interview.(52) The reasons for ceasing use were diverse but the five most frequently cited reasons were:- "Did not want to take anymore" (28%), "Health Concerns" (18.4%), "No longer part of social life" (16.1%), "Impact on Job/Friends/Family" (8.0%) and "Persuaded by friends / family" (7.6%).

A Canadian study of adults who had recovered from a cannabis use disorder (CUD) reported quite similar findings.(46) They found that the three main reasons given by people for addressing their CUD were self-incompatibility (i.e. level of use had become incompatible with lifestyle, values or goals), social incompatibility (i.e. incompatible with family, friends or society) and mental health concerns.

2.4.2 Societal and health service attempts to influence the substance use journey.

This diagram (Figure 2.9) also seeks to depict the points at which society or the health service strives to intervene in this potential journey towards escalating use. These interventions are delivered with the intention of reducing the harms associated with drug use.(10, 11)

Primary prevention aims to prevent any use of the substance.(53) Legislative bans, or prohibition, seek to achieve this goal by presenting a major obstacle to easy drug assess and providing a disincentive to use. This disincentive is of course the possibility of a criminal

conviction, a fine or some other punishment, possibly even imprisonment. A recent review concluded that there was evidence pointing towards the effectiveness of such interventions in reducing harm for adolescents.(11) The possible impact of a drug's legal status upon decision making by users will be discussed further in section 2.6.2.2.

Other primary prevention initiatives include universal school based education such as the Social Personal & Health Education (SPHE) program in Irish Secondary schools.(11) Secondary prevention seeks to curtail progression to more problematic substance use patterns where experimentation has already occurred. Such approaches are sometimes called indicated prevention, and may be targeted at specific high risk groups of youth.(53, 54)

In recent decades there has been an increased emphasis upon brief interventions with people who are engaging in substance use.(55, 56) Health professionals in many settings are encouraged to ask service users about substance use and to engage in a conversation about that use where it is reported.(57) The goal of these conversations is to nudge behaviour in a healthier direction, and to advise people of their treatment options if a treatment need has been identified. Such approaches have become an increasing component of health service delivery internationally. They have also been used in Ireland over the past 20 years in selective settings with specific patient groups.(58) Very recently, the *Making Every Contact Count* framework has been established in Ireland to generalise and increase the provision of brief interventions in all healthcare settings.(59)

Treatment interventions are typically confined to people with substance dependence or substance abuse. Prior to the 1980s, almost all treatment approaches had a sole goal of abstinence. In other words, the treatment goal was to support the patient in becoming an ex-user and remaining as an ex-user. Since the 1980's there has been a substantial increase in so called harm reduction treatment approaches.(60) These are not abstinence focused, and ongoing but reduced use both during and after treatment is seen as an acceptable outcome.(51, 60)

2.4.3 Characteristics of Irish youth based upon their substance use status

General population surveys, or surveys of specific age ranges within a population, can provide a snapshot of the population profile with regard to use of any particular drug. Surveys (such as Monitoring the Future [MTF] & ESPAD discussed earlier in section 2.3) typically report lifetime use, past year use and past month use.(37, 39) It is also possible to make estimates of the proportion of substance users who meet criteria for a diagnosis of substance abuse and for substance dependence using survey data from Ireland and elsewhere.

For the purposes of considering the situation in Ireland regarding substance use across the youth population in recent years, the following definitions are used to describe the characteristics of each distinct group in Figure 2.9. Every member of a population can be placed into one of these mutually exclusive categories for every individual substance (e.g. cigarettes, alcohol, LSD, heroin) at any given point in time.

"Never users" of substance X are those people who report never having used substance X at any point in their lives.

[Never users] = [Total population] - [Lifetime users]

"Ex-users" of substance X are people who report some lifetime use of X but no use in the past year.

[Ex-users] = [Lifetime users] – [Past year users]

"Infrequent users" of substance X are people who report some use of X in the past year but no use in the past month.

[Infrequent users] = [Past year users] – [Past month users]

"Dependent users" are estimated from the known or estimated fraction of past year users who meet criteria for dependence.

*[Dependent users] = [proportion of past year users who meet dependence criteria] * [Past year users]*

"Substance abusers" are estimated from the known or estimated fraction of past year users who meet criteria for Substance abuse, but not dependence.

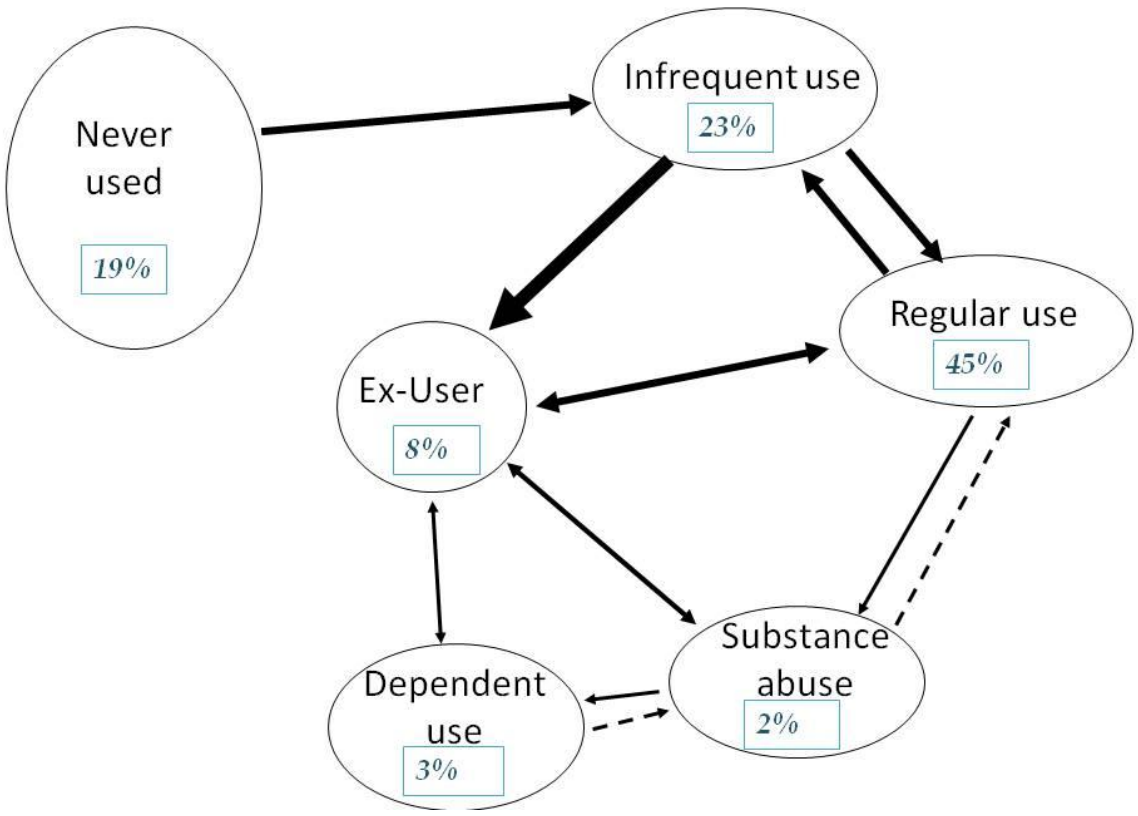
*[Substance abusers] = [proportion of past year users who meet substance abuse criteria] * [Past year users]*

In order to ensure the groups are mutually exclusive, then "Regular users" of substance X are those who have used in the past month, but do not meet criteria for a diagnosis of Dependence upon or abuse of substance X.

[Regular users] = [Past month users] – {[Dependent users] + [Substance abuse]}

Figures 2.10 to 2.13 present some Irish data making use of this approach to considering substance use across the population. Figure 2.10 outlines alcohol use from the ESPAD survey results of 2011, most Irish adolescents having consumed alcohol at least once by the time they reach 16 years.(38)

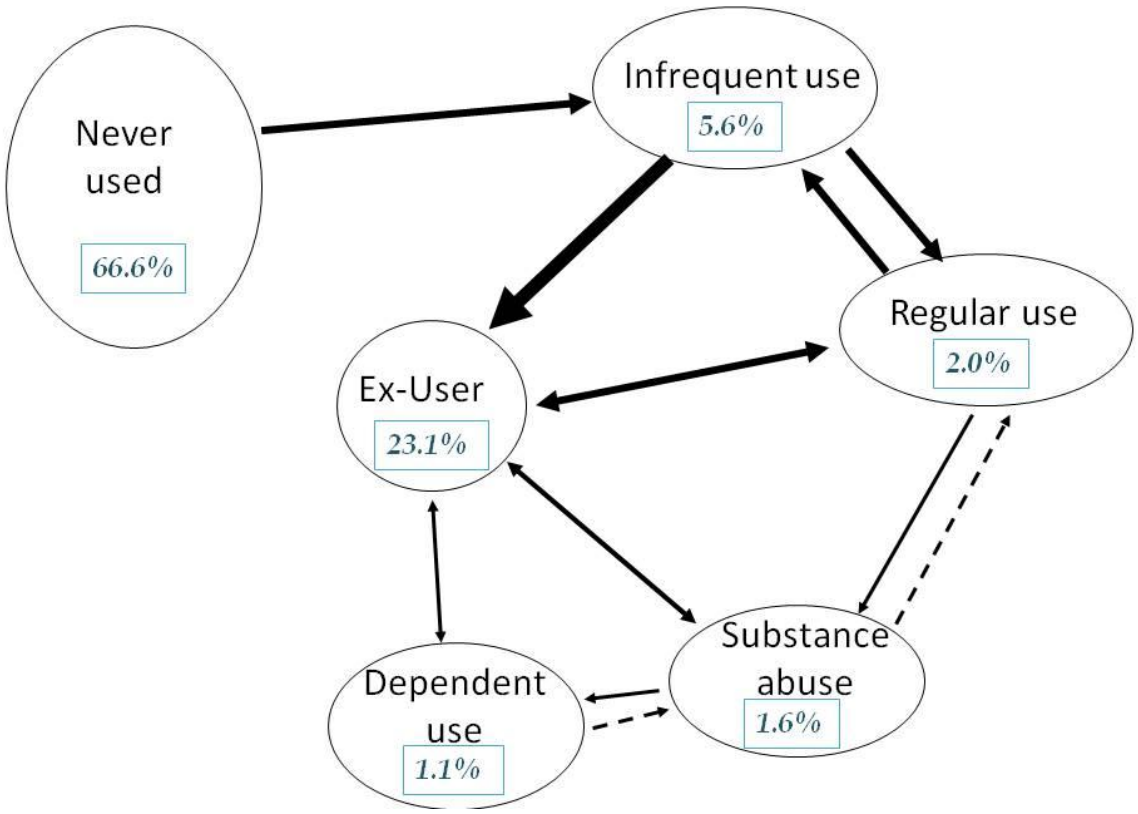
Figure 2.10. Profile of exposure to alcohol among 16-year-olds in Ireland in 2011



Footnote to Figure 2.10. ESPAD 2011, alcohol use in Ireland, Lifetime use = 81%, Past year use = 73%, Past month use = 50%.(38) The My World Survey included 786 4th Year students and was published in 2012.(61) The AUDIT was administered and this found that 3% had a score suggestive of dependence and 2% had a score suggestive of "hazardous drinking" which equates to abuse of alcohol. These are probably underestimates as the My World survey team used adult cut-offs when interpreting AUDIT score results, while the consensus is that cut-off scores need to be reduced for adolescents.

Cannabis is the most widely used illicit drug. Data on use is provided in the aforementioned NACDA General Population survey.(52) Figure 2.11 indicates the profile of cannabis use among people aged 15 to 34 years in 2010/11. The population estimates of dependence and abuse are derived from the Munich Composite International Diagnostic Interview (M-CIDI), a 19 item instrument reflecting the four cannabis abuse and seven cannabis dependence criteria, which used administered in that survey.

Figure 2.11 Profile of exposure to cannabis among young adults in Ireland in 2010/11, proportions

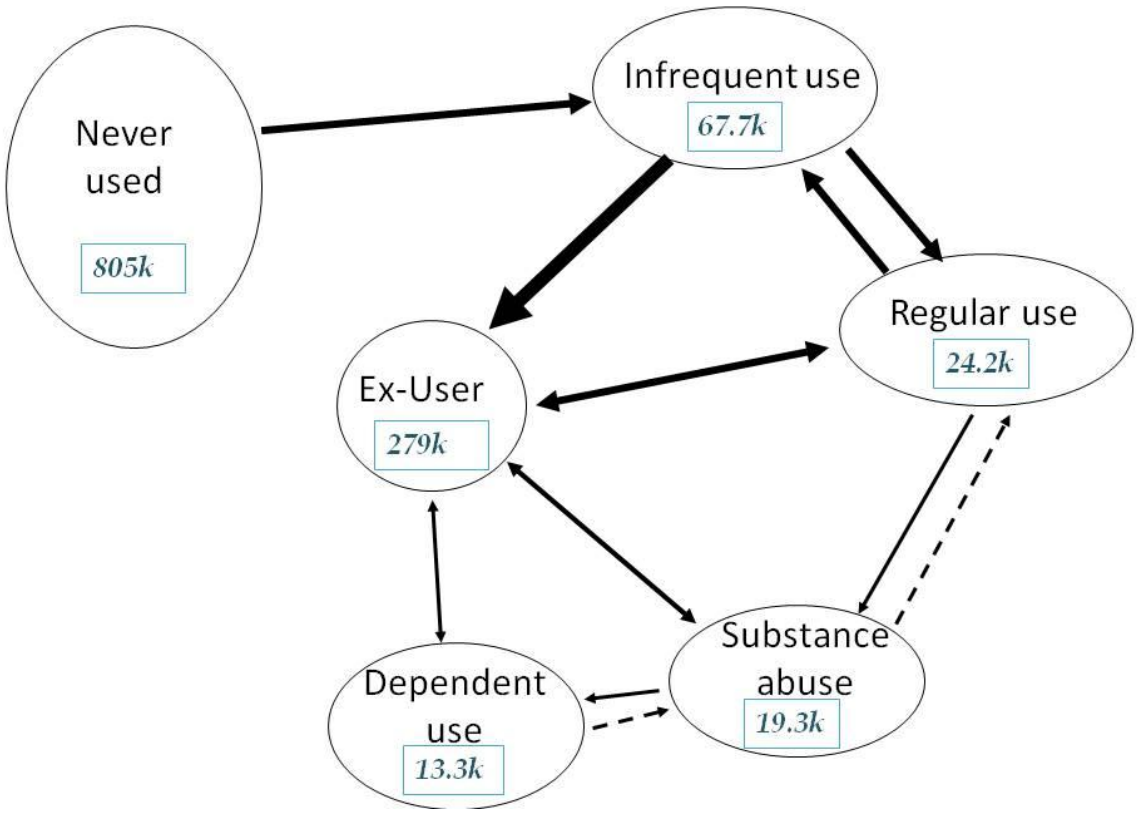


Footnote to figure 2.11. Data obtained from NACDA General Population survey 2010/11, cannabis use by 15-34yo.(61) Lifetime use = 33.4%, Past year use = 10.3%, Past month use = 4.7%, Cannabis Abuse 2.7% and cannabis dependence 1.1%. The proportions above assume that (a) all meeting these criteria for a current diagnosis had used in the past month and (b) all people meeting criteria for dependence also meet criteria for substance abuse.

According to the CSO website there were 1,208,633 people in Ireland aged 18 to 34 years in 2011. Figure 2.12 uses the prevalence estimates in Figure 2.11 to provide estimates of the number of people in each category in 2011. This indicates that 32,600 people aged 18-34 years met criteria for either cannabis abuse or cannabis dependence. People with such

diagnoses may choose to seek addiction treatment, especially those who are dependent.(46)

Figure 2.12 Profile of exposure to cannabis among young adults in Ireland in 2010/11, numbers (k=1000)



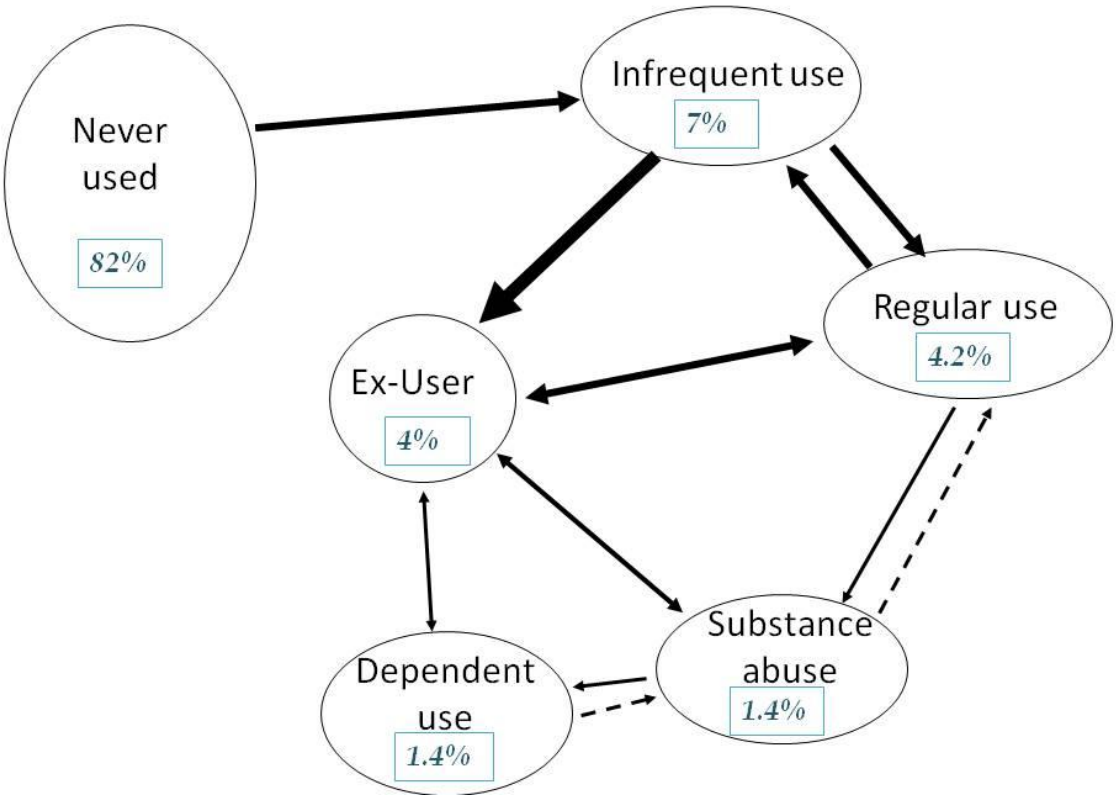
Footnote to figure 2.12. While the NACDA survey reports on people aged 15-34 years, the population estimates above relate to those aged 18-34 years only, and assumes that proportions are similar in this slightly smaller and slightly older group. The numbers above also assume that (a) all meeting these criteria for a current diagnosis had used in the past month and (b) all people meeting criteria for abuse also meet criteria for dependence.

The National Drug Treatment Reporting System (NDTRS) gathers data on all addiction treatment episodes in Ireland. A summary of this information can be accessed on line at www.drugsandalcohol.ie/tables/ . This dataset indicates that there were 1155 treatment episodes involving adults aged 18-34 years in 2011 where the primary substance problem related to cannabis use. There was a further 1994 treatment episodes where cannabis was a secondary problem (personal communication from Anne Marie Carew who works with the NDTRS in the Health Research Board [HRB] in Dec 2017). This yields a total of 3149 cannabis related treatment episodes in 2011 in this age range. This number equates to 9.7% of the

number of people with cannabis abuse / dependence noted above. An unknown number of people will have had more than one treatment episode during the year. It is certainly the case that the vast majority, over 90%, of young adults with cannabis abuse/dependence did not access treatment. The 'rule of thumb' for drug and alcohol use disorders states that about 10-12% of people will access treatment in any given year.(62) The data presented above for cannabis indicates that treatment attendance in Ireland is close to this international norm. This has relevance for this thesis, as many of the studies (Chapters 4 to 8) make use of data arising from that subset of youth who attend addiction treatment.

Figure 2.13 indicates the profile of cannabis use in 2011 among adolescents aged 16 years of age based upon the ESPAD survey.(38) In spite of their younger age relative to the young adults in Figure 2.11, the proportions in the categories of 'regular use', 'cannabis abuse' and 'dependence' are very similar. For the older group, the proportion of 'never users' is lower and the proportion of 'ex-users' is higher, these differences being a function of the increased opportunity for experimental use over increased years of life.

Figure 2.13. Profile of exposure to cannabis among 16-year-olds in Ireland in 2011, based upon ESPAD



Footnote to Figure 2.13. ESPAD 2011, cannabis use in Ireland, Lifetime use = 18%, Past year use = 14%, Past month use = 7%(62). (Data on dependence and abuse is not available for adolescents in Ireland. To estimate prevalence of abuse / dependence, we have used the 2010/11 General population survey which found that 20.1% of past year users aged 15-34yo met criteria for cannabis abuse and 9.8% of past year users met criteria for dependence.(52) The estimates above assume that (a) all meeting these criteria for a current diagnosis had used in the past month and (b) all people meeting criteria for abuse also meet criteria for dependence.

2.5 Drug Policy

2.5.1 Regulatory framework and treatment

Within this over-arching conceptual framework for considering substance use (Figure 2.9), there are dozens of areas worthy of more detailed exploration. This thesis will focus on two key areas. Firstly, there is the issue of treating young people who have reached the most harmful patterns of use, i.e. dependence and substance abuse. Secondly, the relationship between the wider regulatory / legislative context and the likelihood that young people develop dependence and serious mental health harms will be explored.

Ultimately, both treatment and legislation share the same goal of reducing the number of people who are dependent and the number experiencing serious harm, albeit operating at

different areas of the potential journey through substance use (see Figure 2.9).(11) The latter aspires to reduce the numbers who move in a clockwise direction and who progress to problematic and dependent use while the former seeks to divert people away from dependence once there.

2.5.2 Emergence of dissonance in drug policy

During the 1960s through to the early 1980s, there was a very clear and coherent message from Western societies, as articulated through drug policy, on issues pertaining to use of psychoactive substances. With the notable exceptions of alcohol and tobacco, the messages were consonant and uniformly very conservative. Firstly, the 'prevention' message to citizens was that you should not use drugs at all and you would be punished if you opted to do so. The foundation of this so called 'global drug prohibition regime' was the 1961 United Nations Single Convention on Narcotic Drugs (and amended by the 1972 Protocol).(10, 63) This international position was supplemented by national laws, such as the Misuse of Drugs Act in Ireland in 1977, which dictated that drug use was viewed as a criminal act and would bring with it a criminal sanction.

Citizens who opted to use drugs and who developed an addiction to illegal drugs were directed towards treatment programs which reflected the same style of intolerant message, this being that all drug use must completely cease.(64, 65) Abstinence was the only goal worthy of consideration for the person with an addiction and for the addiction treatment provider.

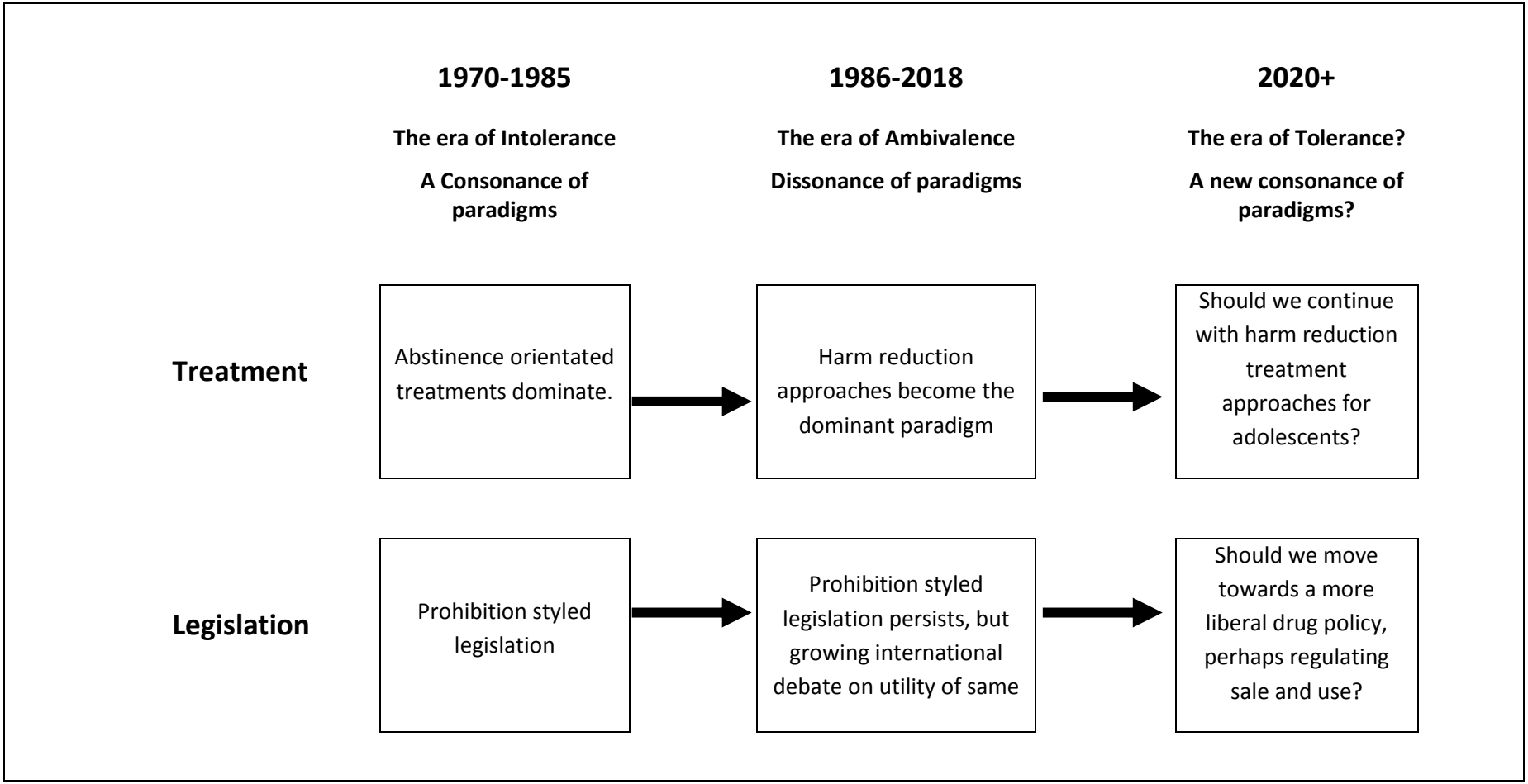
From the 1980s onwards, there has been a growing discrepancy between the treatment message and the prevention or prohibition message (see Figure 2.14). Treatment approaches built on harm reduction principles had begun to emerge in the 1970s.(15, 51) The archetypal harm reduction treatment was the provision of methadone, a long-acting opioid agonist, to people who were heroin dependent.(66) While such treatment approaches initially remained relatively marginalised and widely criticised within the wider world of addiction treatment, they gained a great deal of traction in the mid-1980s with the advent of HIV/AIDS.(65) Evidence mounted that delivery of methadone treatment to heroin dependent adults resulted in reduced heroin use, reduced unsafe injecting, reduced

mortality and reduced criminality.(14, 67) While such treatment remains somewhat divisive, it has certainly become a mainstream approach to treatment of heroin dependence in a wide number of western countries including US, UK, Australia, Ireland and the rest of Europe.(12) It is now also being used in quite different cultural contexts, such as China.(68) However, some countries remain steadfastly opposed to use of methadone or buprenorphine, such as Russia.(69) Many other countries globally remain very wary of OST, such as those in Latin America and Asia.(70) While it has been the mainstay of treatment in most western countries, it also continues to experience episodic criticism in those locations.(71, 72)

As mentioned earlier, research also began to emerge in the 1970s that some people with severe addiction problems could cease use themselves, or could even revert to non-problematic patterns of use, without treatment.(48) Treatments emerged which viewed 'controlled use' as a very acceptable treatment outcome. Their arrival provoked highly divisive debate.(15) Nevertheless, treatment approaches with goals other than abstinence have continued to gain a much more substantial foothold in the world of addiction treatment (e.g. motivational interviewing, Community Reinforcement Approach, CBT).(51, 60, 73)

In recent years the very concept of addiction or dependence has been challenged. In the latest revision of the diagnostic guidelines by the American Psychiatric Association, DSM V, major changes were made to substance related diagnoses.(30) It was determined that there was insufficient evidence of any clear aetiological or clinical difference between substance *abuse* and substance *dependence*. The terms were consequently abandoned. The expression 'Substance Use Disorder' is now used to capture the full spectrum of problems, which are simply ranked as mild, moderate or severe. This change constitutes a further challenge to the older abstinence based treatment models, such as the 12-step approach used in Narcotics Anonymous, Alcoholics Anonymous or those used in therapeutic communities.(74)

Figure 2.14. Substance use – divergence of treatment and legislative paradigms



2.5.3 Treatment in Ireland

In the midst of a huge increase in cases of heroin dependence in Dublin in the mid-1990s, a major policy shift occurred in Ireland, whereby the treatment of choice moved away from abstinence-based treatments. The standard first line treatment of heroin dependence had been the provision of a brief outpatient detox.(22) This then switched towards longer term maintenance treatment with methadone. The Methadone Protocol provided the template for treatment.(22) This new focus on harm reduction was further consolidated at the end of that decade by the first National Drugs Strategy 2000-2008. The four pillars of this strategy were Treatment, Prevention, Research and Supply Reduction. Although called a National Drugs Strategy, the vast bulk of the actions and resources within the Strategy were directed very clearly at heroin dependence and largely focused upon Dublin, where the heroin problem was most evident. The treatment arm prioritised expansion of methadone treatment programmes.

In 2006, the Department of Health & Children (DoHC) convened a working group to examine provision of addiction treatment services for adolescents under the age of 18 years with serious drug problems.(75) This group recommended a four tier model of treatment quite similar to that being developed in the UK.(76) The principle deficiency identified in the treatment service provision for adolescents at that time was the absence of a network of services operating at Tier three, these being outpatient specialist multidisciplinary adolescent addiction treatment services. While the working group was not prescriptive about the treatment approach, they did recommend treatments such as motivational interviewing and CBT, treatments which are not insistent upon abstinence as the sole acceptable goal.(11, 60) The Youth Drug & Alcohol (YoDA) service was developed as a result of pilot funding arising from this DoHC report. YoDA is the setting for two of the studies in this thesis (Chapters 4 & 7).

That DoHC report did note some ambivalence about harm reduction based treatments, especially the use of methadone.(75) The report states:-

> *"Different views have been expressed concerning harm reduction approaches as they apply to young people presenting with problem drug misuse. In particular, the role of methadone in the treatment of young persons gave rise to differing views. The Group felt that substitution treatment should only be prescribed to young*

persons within a specialist context and should be considered as only a short term solution."

The group and the report did not specify what constitutes "short term" however. The general view regarding use of substitution treatment among adults who are heroin dependent is that treatment should be long term. There is a consensus that imposing a predetermined time limit on treatment is associated with greater treatment drop out and greater harm for adult patients.(77, 78) The UK guidelines on use of psychopharmacology in adolescent addiction state:-

"Some [adolescents] will have severe dependence, a well established history of misuse and/or previous treatment and multiple difficulties including mental health problems, and will be at high risk of future overdose. These and other factors such as the age of the young person may indicate that they may be more suitable for maintenance."(79)

Many countries remain more wary than Ireland of the longer term use of medications such as methadone in the treatment of heroin dependent adolescents. In USA, clinics must obtain a special federal waiver to prescribe methadone to under 18s and even then they can only do so when the adolescent has had two failed treatment efforts to cease heroin use without medication.(17, 18) So although harm reduction based treatments have become the norm for adults, there is some ongoing ambivalence about their appropriateness in the treatment of addiction in adolescents, both nationally and internationally.

2.5.4 Drug related legislation in Ireland

While the treatment landscape is very different to a generation ago, the legislative approach to drug use has remained largely unchanged in most countries, including Ireland. Most fundamentally, drug use remains a criminal offence, as is possession, sale, supply and manufacture of drugs listed in the Misuse of Drugs Act. There is an apparent dissonance between a newer liberal and relatively tolerant approach to the treatment of *individuals with substance use disorders* and this older prohibition-styled punitive legislative framework to drug use in the *general population*. This dissonance is certainly still evident in Ireland as it is in most Western countries at this time. This has contributed in increased debate globally

about liberalising the legislative response to tackling drug use and related harms.(4, 10, 19, 80) The success of harm reduction based treatments and the failings of abstinence based treatment approaches have featured among the arguments for change. A small but growing number of countries have taken tentative steps down this path.(19)

2.5.5 Resolving the ambivalence – a new consonance with tolerant treatment and legislation?

The Netherlands initially decriminalised cannabis possession in the 1970s.(19) Some municipalities subsequently proceeded to tolerate small scale sale and distribution of cannabis via regulation of 'coffee shops'. There is some evidence though that alterations in the number of coffee shops correlated with changes in prevalence of cannabis use, increase in shop numbers being associated with increased use.(81) Although legal at the front door, the delivery of cannabis to the back door has remained illegal.(19, 81) Use of other drugs, such as cocaine and heroin, has remained a criminal offence.

Portugal opted to remove the automatic criminal sanction for people caught using any drug, from cannabis to heroin, in 2001. While criminal penalties may arise, the default consequence is a civil sanction which may include a mandatory referral to a so-called 'dissuasion commission'. Therefore, while Portugal decriminalised drug use, they did not depenalise use.(4)

A number of states in USA have recently decided to depenalise use and to also regulate sale and supply of cannabis, much in the same manner in which sale and supply of alcohol is regulated.(19) Canada appears to be on the cusp of making similar changes.(19) Uruguay has also opted to pursue a regulated cannabis market, albeit with many more controls in place compared to states such as Colorado in USA.(19)

New Zealand also passed legislation which acknowledged the possibility that psychoactive drugs could be manufactured, sold and used legally for commercial and leisure purposes. However, the important caveat in that apparently liberal legislation was the requirement placed upon the producer of the drug to first demonstrate the relative safety of their product. In reality, this requirement has resulted in the new law functioning as de facto prohibition.(82, 83)

In tandem with the increase in the number of countries which are experimenting with less conservative approaches to drug policy, a vast array of lobbying and advocacy groups and organizations have emerged to build support for liberalization of drugs policy. The term 'harm reduction' has moved outside the narrow treatment arena and into discussions on issues such as prevention and wider drug policy.(84) It is frequently cited as a reason for supporting more liberal policies, the argument being made that criminalising users is causing harm to them and to society, and is fuelling further criminal and antisocial activity.(85)

In 2016, the Johns Hopkins–Lancet Commission on Drug Policy and Health published a review of evidence on drug policy internationally.(4) Like many of the groups and organizations which advocate for liberalization of drugs policy, this commission was also funded by the Open Society Foundation. This concluded that current policy was failing society and stated that the world should "move gradually toward regulated drug markets." Commenting on the report, a Lancet editorial stated:-

> *"drug policies intended to protect people, but based on prohibition and criminalisation, have had detrimental effects on public health in multiple ways".(21)*

The view is espoused that moving away from the criminalization of drug use, and towards the regulation of use, will result in less net harm across society.(4, 80) Given the fact that the move away from conservative abstinence based treatment towards harm reduction treatments has been generally well received by clinicians and policy makers in the drugs field, it appears that very many experts in these fields are now favourably disposed to a more liberal policy on the legislative and regulatory fronts.(4, 86)

2.6 Two specific areas of ongoing controversy

2.6.1 Opiate Substitution treatment for adolescents with heroin dependence

As suggested earlier in this chapter, one area of controversy relates to use of longer-term opioid substitution medications such as methadone in the treatment of adolescents who are heroin dependent.(17, 18, 75) To explore this issue, the literature was reviewed to identify studies reporting outcome for opioid dependent adolescents who were provided with

opioid substitution treatment (OST) for three months or more. The outcomes of interest were (1) reductions in use of non-prescribed opioids, (2) retention in treatment and (3) changes in mental health or psychological well-being.

To conduct the electronic search, three biomedical electronic reference libraries, PubMed, Cochrane library and PsychINFO were searched using search terms that described opioid or heroin dependence and treatment. The search terms included a number of key words and combinations of key words (see table 2.1).

The searching was limited to articles published in English. The search was not limited to empirical research. A review of relevant clinical and professional material was also conducted. This included examination of professional documents, national reports on adolescent addiction treatment and relevant web based resources such as the National Treatment Agency in the UK and National Institute of Drug Abuse (NIDA) in USA. Articles and materials retrieved during the search were examined and included if appropriate. A manual search of the literature was also conducted. This included a reference search of the relevant articles identified through the electronic search.

Table 2.1 Literature search key words on use of OST for heroin dependent adolescents

Keywords	**Combination with keywords**
Heroin Dependence	Adolescent
Heroin Addiction	Teenager
Heroin Use Disorder	Youth
Heroin abuse	Substitution treatment
Opioid Dependence	Maintenance treatment
Opioid Addiction	Medication Assisted treatment
Opioid Use Disorder	Outcome
Adolescent	Treatment
Teenager	Depression
	Anxiety
	Anger
	Mental Health
	Retention
	Adherence

The resulting studies are summarised in Table 2.2 below. Most of the studies were conducted in USA. Sample sizes have tended to be very small relative to adult studies of OST. The two largest studies were conducted in the 1970s. While older studies focused upon

methadone as the treatment intervention, most studies in the past 15 years have examined treatment outcome with buprenorphine based treatments. Some of the included studies comprise primarily young adults, aged over 18 years, and fail to give specific outcome information on the few included adolescents aged under 18 years. Many of the studies provide information on treatment drop out. Few of the studies provide specific information on ongoing use of heroin or other drugs *during* treatment.

None of the studies provides information of changes in mental health symptoms during the course of OST. One study was identified which reported changes in mental health symptoms during the buprenorphine treatment of 18 adolescents.(87) However, this study examined changes in symptoms after a period of just four weeks and the treatment provided was a detoxification, rather than a longer term substitution treatment. They found significant improvements in internalizing symptoms. While the change in overall externalizing symptoms approached significance, there was no significant improvement in aggression and rule-breaking.

In addition to the table, there is a summary below of the key findings and some key methodological considerations for each of the studies.

Table 2.2. Summary of outcome studies examining opioid substitution treatment in adolescents

Author (Study)	Country	Year	Number <18 years (% of study sample)	Duration of treatment	Medication Utilised	Outcome Information Reported?		
						Treatment Retention	Changes in drug Use while on treatment	Changes in mental health
Millman, Khuri & Nyswander(88)	USA	1978	153 (100%)	One year	Methadone	Yes. 22% drop out, most in first few months.	Not reported	Not reported
Sells & Simpson (Drug Abuse Reporting Program [DARP])(89, 90)	USA	1979	127 (100%)	One year	Methadone	Yes. 63% drop out at 12/12 & 28% drop out at 4/12.	Yes. Reduced heroin use, but no specific information.	Not reported.
Crome (91)	UK	2000	48 (100%)	unclear	Methadone	Yes, but vague timeline. "80% retention"	Very vague. 37% had a "good outcome".	Not reported
Bell & Mutch(92)	Australia	2006	45 (100%)	One year	Methadone & Buprenorphine	Yes. 25% drop from Bup by day 5 and from Methadone by day 76.	Not reported	Not reported
Kellogg (93)	USA	2006	155 aged 15-23 years (??)	One year	Methadone	Yes. 48% retention at one year.	Yes, but ambiguous. Reduced heroin use reported.	Not reported
Subramaniam (NIDA Multisite Buprenorphine Treatment Trial)(94-96)	USA	2011	12 (16%)	12 weeks	Buprenorphine	Yes. 72% retention at 3 months from overall group, aged 15-21 yrs - no age specific data provided.	Yes. 77% opiate negative at week 10.	Not reported
Matson(97)	USA	2014	28 (27%)	One year	Buprenorphine	Yes. 25% drop out day two. 50% drop out by day 60	Not reported	Not reported
Mutlu (98)	Turkey	2016	112 (100%)	One year	Buprenorphine	Yes. 30% drop out within one month.	Yes. 10% abstinent at one year.	Not reported

A recent Cochrane review found that there are no clinical trials examining outcome of OST beyond three months in people aged under 18 years old.(99) There were only two clinical trials of less than three months and one of these, the NIDA Multisite Buprenorphine Treatment Trial is included in the summary above as it provides outcome information up to 12 weeks.(96) This NIDA study has generated many publications.(94-96)

There are a small number of 'open label' longer term studies. Two of the largest studies providing longer term outcome information on methadone treatment of heroin dependence in adolescents were conducted in United States in the 1970s. The DARP study reported outcome on 5400 young people under the age of 20 years who received a range of different treatments and presented with a variety of substance use disorders.(89) There were only 127 under 18s on methadone treatment (MT) in DARP. Among that subset, 63% dropped out within one year, with 28% dropping out within 120 days, these rates of unplanned exits being higher than those seen in the young adults on MT in DARP. It was reported that heroin use declined progressively over the year, although specific data is not provided. At follow-up, alcohol and cannabis problems had escalated from baseline levels. Millman, Khuri & Nyswander reported outcome from their MT program for 153 heroin-dependent adolescents in New York in the 1970s.(88) The methadone dose was limited to 20mgs, a dose which would be seen to be sub-therapeutic my modern standards.(100) The treatment goal was cessation of heroin use and detoxification from MT. Just 22% of people dropped out, most of whom did so during the first three months. No information is provided on cessation of heroin use among those who remained on MT.

More recently, Crome et al reported on the outcome of the first 48 patients with severe heroin dependence who were prescribed methadone at a youth treatment service in England.(91) It was reported that 80% were retained in treatment and that 37% had a "good" outcome but the criteria utilised to determine outcome were subjective and somewhat unclear.

An Australian study examined treatment adherence in a cohort of 45 teenagers on OST.(92) They found significantly better retention among those treated with methadone compared to buprenorphine, with 25% exiting MT by day 76 and 25% exiting buprenorphine treatment (BT) by day 5. No data were reported on rates of cessation of heroin use.

Matson et al reported outcome of a cohort of youth treated with buprenorphine/naloxone, among whom 28 were aged under 18 years.(97) This outpatient treatment program had a very high expectation that patients would cease heroin use and ongoing use during treatment could result in discharge. Only 50% of the under eighteen group remained in treatment for over 60 days. Among the overall group, retention was better in females, and in those who ceased heroin and cannabis use. Abstinence rates during treatment were not reported.

Mutlu et al reported the one year outcome of 112 heroin dependent adolescents who received outpatient buprenorphine/naloxone, following a two month inpatient admission for induction and stabilisation.(98) At 30 days, 70% were still in treatment and this dropped to 16% at one year. This study also examined the time to relapse to heroin use following inpatient admission and 63% had relapsed within 60 days, while only 10% remained abstinent for one year of outpatient BT. The mean buprenorphine dose was just 4mgs and this is low in comparison to advised maintenance doses.(101) It emerged that higher dose was associated with better retention and longer abstinence. Among the examined baseline characteristics, those who had a comorbid psychiatric disorder demonstrated better retention, but there were no predictors of abstinence.

The NIDA multisite buprenorphine/naloxone treatment trial mentioned earlier examined treatment of youth who were provided with an extended detoxification treatment and included 12 under eighteens(96). This clinical trial excluded patients with evidence of benzodiazepine or methadone use at baseline. Patients were provided BT for 9 weeks, followed by a 3 week dose taper. By week 10, 25% had dropped out of BT. Polydrug use was associated with increased risk of dropout.(95) At week eight, 23% of those retained on BT provided an opiate positive urine drug screen.(96) Abstinence from heroin at 12 weeks was associated with greater baseline medical and psychiatric problems, a history of recent injecting and evidence of early cessation of heroin use during BT.(94)

Kellogg et al reported one year outcome of a slightly older group of 15-23 year olds, with unknown proportion of under 18s.(93) They were treated with methadone, mean dose of 100mgs. Retention was 48% at twelve months, and half of the drop outs occurred in the first four months. Greater heroin and cocaine use during treatment was associated with drop out. Higher heroin use during treatment was associated with larger methadone doses.

Among the 48% who persisted with treatment for the full year, there was no evidence of heroin use in about half of the twelve individual months. There was a significant decline in heroin use over that year, but no significant changes in use of cocaine or benzodiazepines.

An overview of these studies, suggests 25% of patients drop out after about 2-3 months and 12 month retention on OST is 20-50%. Rates of retention appear better in MT than with BT. Although there is substantial heterogeneity in how studies define drop out, it seems more likely to occur in those with greater ongoing use of heroin and other drugs, especially cocaine. One of the explicit purposes of OST is to facilitate the patient to reduce, and ideally cease, their heroin use. Unfortunately, this current body of research does not make it clear what proportion of adolescents on OST cease heroin use during treatment. While providing no specific information on levels of use during treatment, the Kellogg et al and DARP studies suggest heroin abstinence does increase with longer treatment.(89, 93) As mentioned earlier, mental health outcomes on OST are not reported in any study. These gaps in the literature make it more difficult for adolescent patients, their parents, referrers, treatment providers to make informed decisions regarding this treatment. The limitations in information may also add to the reluctance of policy makers to support delivery of OST in this age range, especially longer term OST treatment.(17, 75)

This thesis seeks to address some of these gaps and uncertainties in the literature by addressing a number of questions:

- What proportion of adolescents on OST cease heroin use during treatment?
- Does abstinence from heroin simply plateau after three months or does it continue to improve for those who persist with treatment?
- Does the mental health of adolescents on OST improve, remain static or deteriorate?
- Are there patient or treatment characteristics which are associated with better adherence to OST and to better outcome during OST?

2.6.2 New Psychoactive Substances – a new test for old prohibition styled legislation

2.6.2.1 Arrival of New Psychoactive Substances in Ireland

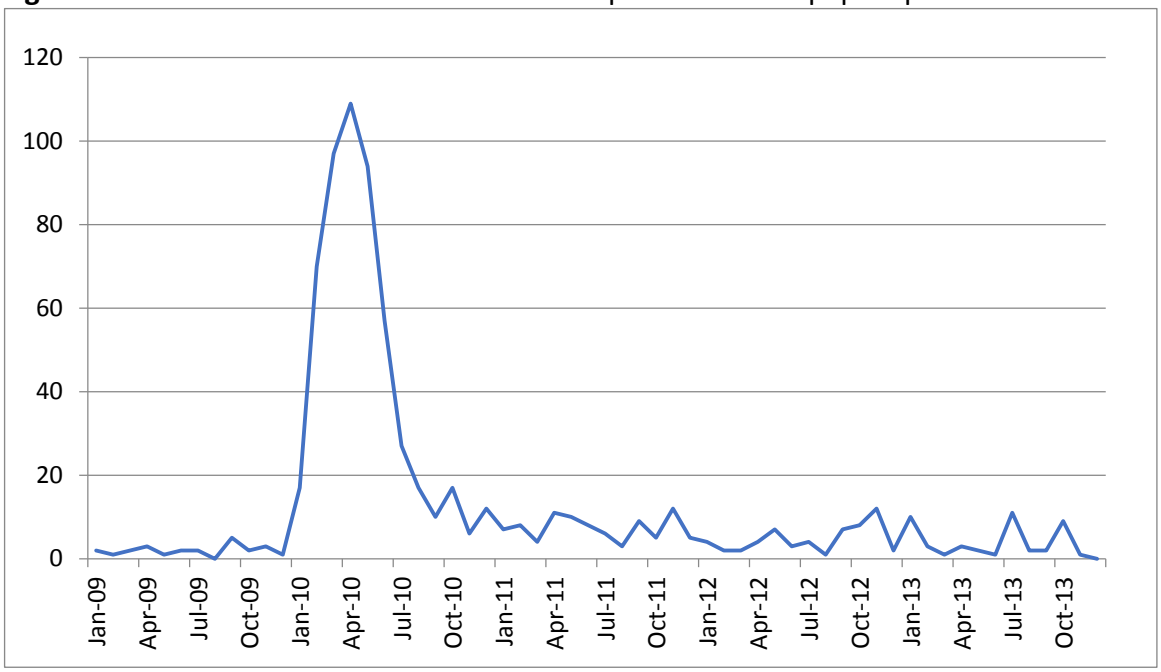
A second area of controversy relates to the legislation surrounding drug use. There is an emerging consensus that criminalising drug users and the drug market place is not just ineffective in reducing harm for society and for individuals, it is actually adding to harms.(4, 102) It is argued that international drug policy should move towards regulating sale and supply of drugs.(80, 102)

New psychoactive substances (NPS) arrived on the scene worldwide in dramatic fashion in the past decade.(103) These are drugs which are designed to mimic the effects of older 'traditional' illegal drugs such as cannabis, ecstasy, amphetamines and cocaine. They are generally synthetic. Due to the fact that they were not named in specific drugs legislation internationally, they began to be used and sold in a relatively open and commercial manner in many jurisdictions.(104) These new market places for drugs were completely unregulated.

For reasons that are unclear, use of NPS became particularly popular among youth in Ireland around 2010. A telephone survey of youth across Europe revealed that young people in Ireland reported the highest rate of lifetime use of NPS.(105) As indicated in Figure 2.8 earlier in this chapter, the NACD general population survey of drug use in 2010/11 reported that NPS as a group were second only to cannabis in popularity among young adults in Ireland.(40) Qualitative research conducted in Ireland indicated that most NPS users at this time had a history of use of other drugs, most notably cannabis, ecstasy and cocaine.(104) This growth in use of NPS in Ireland coincided with a large increase in the number of head shops selling NPS. There may have been a reciprocal relationship between numbers of head shops and use of NPS, demand driving the supply and supply possibly driving the demand.

There was widespread public concern regarding head shops. There were mass protests by communities across Ireland regarding their presence in their towns. There was intense debate within the media (See Figure 2.14 and 2.15) and among politicians regarding the appropriate response to this new challenge to Ireland's drug policy regime (see Figure 2.16).

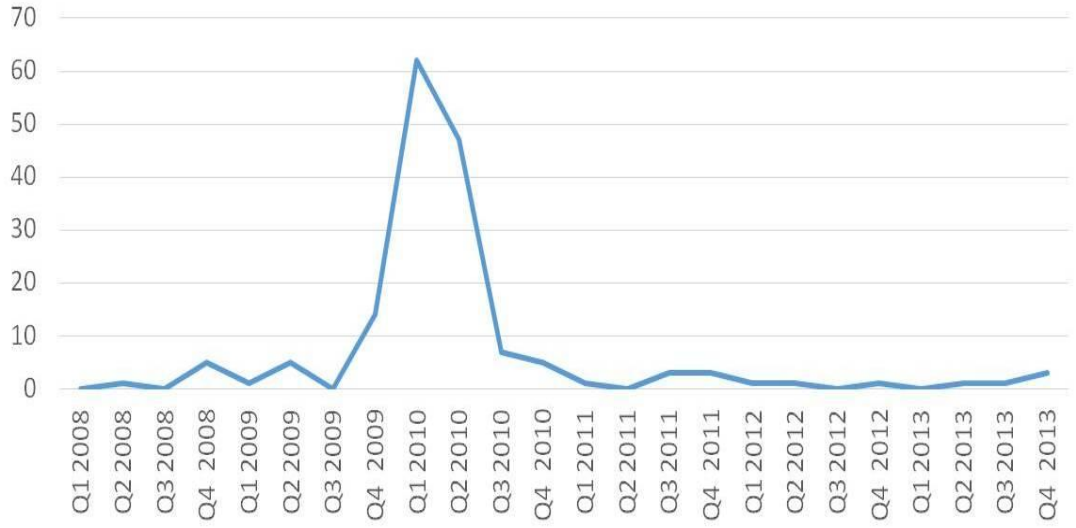
Figure 2.14. Number of mentions of “head shop” in Irish newspapers per month



Footnote to Figure 2.14. The graph depicts the number of mentions of the word/expression "headshop" or "headshops" or "head shop" or "head shops" in Irish Times newspaper, Irish Independent Newspaper and regional newspapers affiliated with the Independent Newspaper over the period Jan 2009 to December 2013. The data was obtained from Newspaper websites on 27th April 2016.

Figure 2.15. Head shops and NPS in the news: Newspaper headlines from 2010.

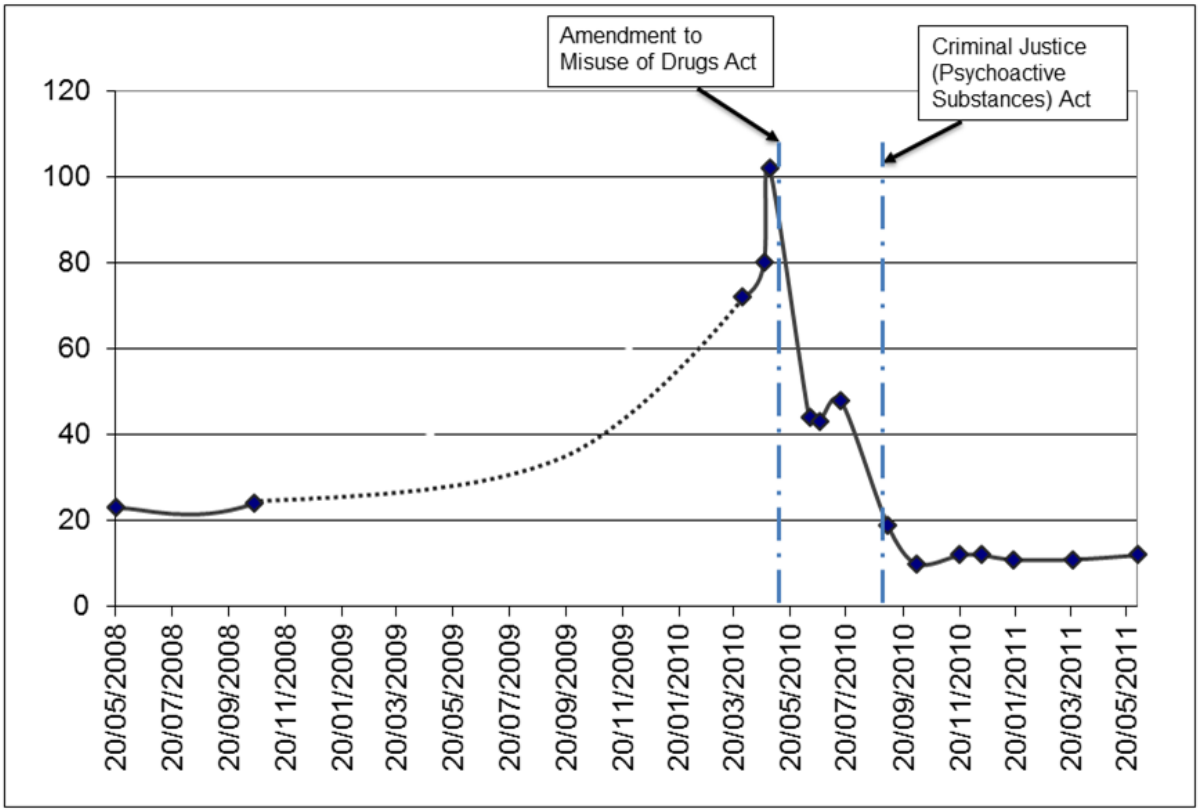
Figure 2.16. Number of mentions of the expression "head shop" in Dail Debates per quarter



Footnote to Figure 2.16. The graph depicts the number of mentions of "head shop" in Dail debates via a search of http://oireachtasdebates.oireachtas.ie/debates%20authoring/debateswebpack.nsf/fulltextsearch?readform . The figure presents the number of mentions per quarter from 1st quarter of 2008 to last quarter of 2013. Data was obtained from the Oireachtas website on 29th April 2016

There were about 20 head shops open across Ireland for a number of years prior to 2009. Figures 2.14 to 2.16 confirm that there was little or no political, public or media interest in these head shops in Ireland prior to very late in 2009. Up until then, they generally just sold drug related memorabilia such as t-shirts and some paraphernalia for drug use. There was occasional concern regarding their sale of a small number of psychoactive substances such as Pscylocibin found in 'magic mushrooms'. In 2008, the Garda National Drug Unit (GNDU) conducted an investigation of all head shops in Ireland as part of Operation Flourine (personal communication, GNDU). This was initiated due to concerns that they were selling natural plant products containing hallucinogenic substances such as Lysergamide, Pscylocibin & Mescaline. Concern increased once again in late 2009/early 2010 in tandem with the public protests, media coverage and political interest in NPS. Operation Kingfisher was commenced around this time and continued over the following 18 months (personal communication, GNDU). These Garda operations provide relatively detailed information on the number of headshops in Ireland over the period 2008 to 2011. This information is presented in Figure 2.16.

Figure 2.17. Number of head shops in Ireland, 2008 to 2011.



By May 2010, the number of head shops had increased to 102. Test purchasing of products obtained from headshops in 2010 confirmed a wide range of NPS were being sold commercially and legally.(106) There was a period of brief but intense debate as reflected in Figures 2.14 - 2.16. In the first instance, the Irish Government opted for the default strategy of simply adding over 100 NPS to the pre-existing Misuse of Drugs Act, thereby making it a criminal offence to use, possess, sell or distribute the specified NPS. This made these specific NPS illegal in exactly the same manner as 'traditional' drugs such as cannabis and cocaine.

About half of the entrepreneurs who had set up head shops in the preceding months then decided to immediately cease trading, their shops closing. The remaining shops simply opted to cease selling the recently banned NPS and commenced selling NPS which were not yet banned.(106) This provoked further debate during the summer of 2010. With minimal consultation and little warning (and in dramatic contrast to recently enacted similar legislation in the UK), the Irish Government opted to proceed with entirely novel and untested legislation. The Criminal Justice (Psychoactive Substances) Act was passed and enacted in late August 2010. This stated that 'a person who sells a psychoactive substance

knowing or being reckless as to whether that substance is being acquired or supplied for human consumption shall be guilty of an offence'.

In contrast to the Misuse of Drugs Act, this new legislation did not criminalise or prohibit use by individuals. Instead, it simply targeted the vendors. There was scepticism among legal experts and policy makers regarding this Act. There was a view that it would be difficult to prove in court and highly problematic to prosecute cases.(107, 108) However, it achieved its goal in that the remaining head shop owners opted not to test out its legal robustness and responded by either shutting their shops or by ceasing sale of NPS, reverting back to the type of business model which they had followed five years previously.(82) The GNDU continued to monitor their activities via Operation Kingfisher and compliance with legislation was observed to be good. There have been two successful prosecutions in the past seven years under the Criminal Justice (Psychoactive Substances) Act.(109)

Most predicted that the decision to persist with prohibitionist styled policies of the past would cause problems associated with NPS to continue unabated and possibly even to get worse as NPS users turned to drug dealers.(110-112) Indeed, surveys of drug users conducted at that time generally indicated that people intended to continue using NPS and declared an intention to move to the black market and to the internet to source NPS.(105)

There was general scorn among policy makers nationally and internationally for the approach adopted by the Irish Government. A national review of stakeholder views concluded that it constituted "a clear victory for traditional 'war on drugs' values".(107) There was a view that harms related to NPS had been exaggerated and action was driven by a media generated "moral panic" as opposed to evidence (see Figure 2.14 and 2.15). The connection between media coverage of the NPS issue and legislative action has also been examined in other countries. Those reviews have reached a similar view and have also highlighted the tight correlation between increased media reporting, often perceived to be sensationalist, and government action.(112, 113)

2.6.2.2 Motivations for use of NPS

Is it plausible that legal status of a drug, and change in same, influences use? In order to explore the factors which influenced the decision by drug users to use NPS specifically,

Barratt, Cakic & Lenton conducted a survey of users of synthetic cannabinoids (SC) in Australia.(114) The three most common reasons for choosing SC were curiosity (50%), legality (39%) and availability (23%). Another recent Australian study indicates that many high school students interpret legal sale as an indication of safety and report increased willingness to use NPS in that scenario.(115) A survey of patients admitted to a psychiatric hospital in Australia found that over half had used NPS and the most common reasons given for use were legality and availability.(116) In New Zealand, Sheridan & Butler interviewed BZP users.(117) They viewed their legal sale as an indication of their safety and reported advantages related to the legal status such as better availability and the desire to avoid going to drug dealers. In the year that the prohibition of BZP was imposed, two of the three main reasons given for stopping BZP use were because it was 'illegal' and 'didn't know where to get it now it's illegal', 43% reporting the former and 23% the latter (118).

An on line survey of drug users in Ireland was conducted in 2010 to explore use of NPS, most respondents having a history of use of drugs such as cannabis, ecstasy or cocaine.(104) The main sources of NPS were head shops (78%) and friends (66%). Sourcing NPS via the internet (16%) and from dealers (15%) was less common. Sixty-five per cent of respondents reported that there was a head shop within five kilometres of their home. Curiosity and availability were reportedly the main factors driving NPS use.(104)

The influence of legal status on decisions to use other drugs, such as cannabis has been demonstrated in students, who report its illegal status as a reason for avoiding use in a Canadian study.(119) The importance of legal status of drugs was also demonstrated in the aforementioned follow-up studies of Vietnam veterans returning to USA.(47) Although many had used heroin in Vietnam where they had easy access to cheap high quality heroin, few used upon their return. The reasons for avoiding use in USA included its illegal status and worries regarding criminal charges and family disapproval.(47, 120, 121) Most of those who had used heroin in Vietnam agreed that it should remain illegal in USA.(121)

These various studies provide some clues regarding the mechanisms via which prohibition styled legislation might influence both supply and demand for NPS. While legal, demand for NPS may increase as people confuse legality with safety. When made illegal, demand may fall as many people seem reluctant to migrate to drug dealers, some interpret illegality as implying greater health risk and some are put off simply by their illegal status. While legal

and sold commercially, supply and availability is obviously better than when made illegal, as high street shops compliment the always available black market. For regulated drugs such as alcohol, it is well established that increased access and availability lead to increased use and harms.(122)

2.6.2.3 Literature review of studies examining change in use or harms after legislation

Having identified this evidence that legal status of NPS may theoretically influence demand and supply, the international literature was explored. Research studies were sought which reported on some measure of NPS use or NPS related harm and provided data regarding same both before and after a legislative change. To conduct the electronic search, three biomedical electronic reference libraries, PubMed, Cochrane library and PsychINFO were searched using search terms that described NPS and legislation. The search terms included a number of key words and combinations of key words (see table 2.3).

The searching was limited to articles published in English. The search was not limited to empirical research. A review of relevant clinical and professional material was also conducted. This included examination of professional documents, national and international reports on NPS and conference abstracts. Articles and materials retrieved during the search were examined and included if appropriate. A manual search of the literature was also conducted. This involved a reference search of the relevant articles identified through the electronic search.

Table 2.3. Literature search key words on use of legislation to target NPS use and harms

Keywords	**Combination with keywords**
New psychoactive substances	Legislation
Novel psychoactive substances	Bans
Mephedrone	Prohibition
Synthetic cannabinoids	Prevention
Legal Highs	Harms
Cathinones	
Head shop drugs	

Studies reporting on the impact of NPS focused legislation were identified and their characteristics and key findings are summarised in Table 2.4.

Table 2.4. Summary of studies examining changes in NPS use and harms following legislative changes targeting NPS.

Author	Year	Country	NPS type	Study population or setting	Use or harm examined	Finding
Ledberg (123)	2010	Sweden	8 Specific NPS	Posts on web based discussion forums	Mention of specific drugs in posts.	For all eight substances the activity on the forum (measured as number of posts per day) showed a drastic decrease around the time of classification.
McNamara et al (124)	2010	Ireland	Mainly cathinones	Treatment attending Opiate dependent adults	Use based on urine drug toxicology screens	In the 10 weeks prior to scheduling of over 100 NPS in May 2010, over 30% of samples were positive for NPS. This remained over 30% for the month after the ban, then dropped to zero from months two to three post ban.
Wood, Green & Dargan (125)	2013	UK	Mephedrone	Emergency Department (ED)	Acute toxicity (poisoning)	Cases of mephedrone toxicity peaked just prior to legal ban and fell over following 6-12 months.
Stogner et al (126)	2012	USA	Salvia divinorum	Surveys of University students, pre and post a ban	Use	Past year use declined from 3% pre-ban to 0% post-ban.
National Poisons Information Service (127)	2012	UK	Mephedrone	Calls to Poison centres See Figure 6.4 on p37.	Concerns re Acute toxicity (poisoning)	Telephone enquires peaked in March 2010, month before ban. They fell by over 60% over the next three months, and remained at this lower level over following two years.
Wilkins & Sweetsur (118)	2013	New Zealand	Benzylpiperazine (BZP)	General population	Use	Decline in past year use from 15% to 3%. No evidence of switch to use of other, not yet illegal NPS, use of these also falling.
Sheridan et al, (128)	2013	New Zealand	BZP & other NPS	Online survey of young adults (18-30yo)	Use of BZP & other NPS	Use of BZP declined post ban. Use of still legal synthetic THC products also fell. Non-medical use of prescription drugs increased but use of stimulants was unchanged.
Loeffler & Craig (129)	2013	USA	Mephedrone	Calls to Poison centres	Acute toxicity (poisoning)	The number of calls per month fell by 89% over the 8 months after the legal ban.

Glue et al (130)	2015	New Zealand	Synthetic Cannabinoids (SC)	Patients presenting to an emergency psychiatric service	SC related psychiatric presentations	Comparing the three months before and after a legislative ban, there was a 52% reduction in patient presentations.
Kriikku et al (131)	2015	Finland	3, 4-methylenedioxypyrovalerone (MDPV)	People caught driving under the influence of drugs (DUID) 2009-12	Cases of DUID involving MDPV pre- and post ban.	Number of DUID cases involving MDPV declined by 51% post ban in June 2010.
Matsumoto et al (132)	2016	Japan	NPS	Psychiatric inpatients and outpatients	Drug related psychiatric disorders	NPS related presentations increased in the period after NPS focused legislation. Other drug related disorders also increased during this period.
Glue et al (133)	2016	New Zealand	Synthetic Cannabinoids (SC)	National Dataset of Patient presentations to general hospitals	Patient presentations to related to SC use	Steep declines in numbers of presentations occurred after each of three changes to legislation between 2011 and 2014.
Mathai et al (134)	2016	USA	Synthetic Cannabinoids (SC	ED presentations related to SC use	Referrals to hospital based addiction counsellor	SC presentations increased by about 100% following a local city ordinance targeting wide class of SC.
Cairns et al (135)	2017	Australia	Synthetic Cannabinoids (SC)	Calls to Poison centres	Acute SC toxicity (concerns re poisoning)	Federal bans of specific SC compounds had little impact. State-based legislation introduced in 2013 banning specific brand names of SC products was followed by a dramatic decrease in exposures, sustained for the two year follow-up period
Yeung et al (136)	2017	Scotland	Ethylphenidate	People who inject drugs	Injection related S. pyogenes &/or S. aureus infections	Rate of infection among PWID dropped from 4.9 to 2.0/week (i.e. 59% decline), following ban of Ethylphenidate

New Zealand was one of the first countries to encounter problems related to a NPS and to implement a response. Use of Benzylpiperazine (BZP) became popular among young people around 2005 and this substance was not covered by the country's existing legislation. Manufacturers promoted BZP tablets as legal and 'safe' alternatives to ecstasy and methamphetamine.(137) After a period of community and government tolerance of BZP use, there was further debate and BZP use was eventually prohibited in April 2008. This followed findings from a number of studies which indicated health risks. Past year prevalence of BZP among the general population fell from 15.3% in 2006 to 3.2% in 2009. (118)

Summarising the various studies in Table 2.4, it appears that problems related to individual substances generally declined following the prohibition of that substance. In those studies which monitored events on a monthly basis, the observed declines tended to commence rapidly. While few studies looked for evidence of movement towards other drugs, those which did found little or no evidence of this. All studies revealed evidence of some ongoing use or harms following bans, albeit at reduced rates. Wood, Measham & Dargan reported substantial ongoing use of mephedrone among young people attending dance clubs after the ban of that drug, although they failed to measure rates of use prior to the ban.(138) They found that use increased when they repeated the survey 12 months later. Therefore, it seems certain that prohibition styled legislation does not eliminate all use or all harms.

Many studies describe a pattern of multiple attempts by legislators to address these issues, with a series of new laws and regulations being introduced due to perceived deficiencies in the preceding legislative efforts.(133-135) The outcomes examined across the studies were quite diverse and included use in the general population, use by specific population subgroups, poisoning episodes and medical & psychiatric hospital attendances. It is striking that almost all of the studies reported some positive change, i.e. a reduction in harms and/or use. This may reflect a bias in submissions by researchers and/or a bias in journals towards reporting of positive rather than null findings.(139)

There were two studies which reported negative findings, one from Japan and one from Texas in USA.(132, 134) The Japanese study examined NPS related treatment episodes at psychiatric services before and after legislative measures which targeted synthetic

cannabinoid (SC) and cathinone derivatives, banning partial modifications to the chemical structure of already banned drugs.(139) The authors reported an increase in NPS related episodes at psychiatric services in spite of these supply reduction initiatives. Psychiatric attendances related to use of other banned drugs also increased over the same period, suggesting a general increase in drug related presentations at this time. This complicates interpretation of the findings. The study by Mathai et al examined referrals to an addiction counsellor from an emergency department and an inpatient psychiatric unit in Houston, Texas and examined the period Nov 2013 to Feb 2015.(139) There had been a number of legislative measures taken to target SC prior to Nov 2013 which included federal and state legislation. There was further federal and state legislation later in 2015. A city ordinance targeting SC during the study period was followed by increased SC related referrals. The authors describe the legislative process as "an arms race", with increasingly complex legislation being followed by diversification of SC subtypes being sold.

In terms of limitations of the presented studies, many simply report a change in rates of events pre- and post-legislation and did not subject these changes to any statistical analysis. Most of the studies focus on legislation which targeted a single drug or drug class and do not examine the possibility that problems related to another NPS may have increased as the problems related to the targeted NPS declined.

2.6.2.4 Rationale for studies focused upon Head shops and NPS in this thesis.

The events of 2009 and 2010 in Ireland provide the opportunity for a natural experiment. The arrival of a vast network of head shops selling NPS constituted a period of legal and commercialised sale of drugs, albeit entirely unregulated. It constituted a particularly liberal version of a legal drug market and is akin to the 'free market' approach to drug policy described by Rogeberg et al.(80) It was quite short-lived being dealt a blow in May 2010 via the additions to the Misuse of Drugs Act and ultimately terminated abruptly in late August 2010. Although quite brief in duration, these events provide the opportunity for 'a natural experiment' to examine some key questions of relevance not just for drug policy in Ireland, but also of international relevance.

1. Was there evidence of increased and significant harms related to NPS when access and availability increased via the expansion of the network of head shops?

2. If harms were evident during this period, did they persist once the head shops were closed, did they diminish or could the problems even have escalated?

Chapter 3

Methodological issues

3.1 Measuring addiction treatment outcome

3.1.1 What is meant by "outcome"?

Many years ago, a senior political figure was doing a brief tour of the building in which I worked. As they passed quickly through our adolescent addiction service, I was asked one question: "What are your outcomes?" As I fumbled through an incoherent response, they moved on to the next person. This encounter has always troubled me.

It is routine and common for people to ask about treatment outcomes in our health care system. Oncologists will quote the five year survival of the treatments they utilise. Infectious disease specialists will provide the response rate to their treatments. Even in mental health, psychiatrists and GPs will confidently state the response rate of depression to treatment with SSRI medications. Such information allows doctors, patients and health service managers and funders to make more informed decisions. While superficially attractive and clear, each of these apparently concrete measures conceals many uncertainties. Patients with cancer value quality of life as well as quantity of life. The clinical trials which provide much of the outcome data upon which we rely often exclude patients with comorbidities and those who demonstrate poor treatment adherence. Such patient attributes are very common in real world clinical settings. The definition of 'cure' used in clinical trials can seem quite arbitrary in many cases, perhaps being defined as a percentage decline in symptoms or symptoms falling below a cut-off point on a scale.

For many chronic conditions, doctors will be familiar with the rule of thirds which often appears to apply to treatments. About one third of people do very well, one third make a partial recovery and one third obtain no meaningful benefit.

When people outside the world of addiction treatment ask "what are your outcomes?", it seems likely that they mean "how many of your patients stop using drugs?" or attain abstinence. However, that apparently more straight-forward question contains many uncertainties. Does it mean stop using their *main* drug or *all* drugs? Does it mean ceasing alcohol use too? What about cigarette use? Over what time duration does "stop using"

apply? Does one month drug free count as abstinence? Does it mean life time abstinence?(140)

What about outcomes beyond drug use? There has been a growth in focus on recovery in both the addiction and mental health fields in recent years. This movement emphasises the importance of psychosocial functioning, participation in community and general well-being.(140) These treatment goals are viewed as at least as important as cessation of substance use. However, measurement of recovery is far from straight-forward and treatment providers seem to have very different perspectives to service users. (141)

With these challenges and issues in mind, I wished to identify methods of examining aspects of treatment outcome among the adolescent patients attending two different treatment settings in Dublin. A finite number of patients and finite research resources imposed substantial limitations on the components of 'outcome' which could be examined. Pragmatism had to take priority over idealism.

3.1.2 Outcome measures

The first study examined a group of patients who commenced treatment at the Youth Drug & Alcohol (YoDA) service. Although all patients had a substance use disorder, they were quite heterogeneous. Polysubstance use was the norm and there were a wide range of substance combinations reported. This reflects real world clinical practice in adolescent addiction services internationally.

There are two common methods for measuring drug use. Firstly, there is self-report and secondly there is biological screening with methodologies such as saliva or urine drug toxicology screenings. There are strengths and weaknesses with both methods. For biological screens, there may be concerns regarding the integrity of the screening process. For example, a urine sample may be tampered with by the patient or food may be consumed prior to provision of a saliva sample. The half-life for different substances varies greatly and the detection window will consequently be very different across a range of substances. Results of biological screens tend to be dichotomous, being simply positive or negative, and do not quantify level of use. The main concerns with self-report relates to under-reporting of use, which may be deliberate or accidental (forgetting).

Although urine screening is frequently conducted in YoDA it is not mandatory for patients and its frequency varies from patient to patient. Two self-report instruments were routinely used during assessment at YoDA. These were the Maudsley Addiction Profile (MAP) & the ASSIST. Both have been used with adolescent populations previously. Both seek to explore for use of a wide range of substances and they also provide quantification data on the level of recent use. Consequently, these self-report measures constituted the cornerstone of the assessment of outcome in the YoDA study (chapter 4).

In the study examining outcome of OST in adolescents (Chapter 5), we used urine drug screens as the main outcome measure. These had the advantage of being conducted routinely twice per week in the clinic. Routine clinical practice at this clinic at the time of this study involved provision of a urine sample which was supervised by a staff member of the same gender. This reduced the concerns regarding sample integrity outlined above. The frequency of testing also made it quite unlikely that drug use by patients would go undetected, even for drugs with a relatively short window of detection.

3.1.3 Control and comparison groups

Ideally in clinical outcome studies, a control or comparison group will be identified. If such groups had been included in the studies in this PhD, it would have allowed exploration of the question: "does the outcome of patients at this service differ from the outcome of those who received treatment X or no treatment?" The gold standard study would also include random assignment of patients and blinding of patients, treatment providers and outcome assessors.

A double blind RCT was quickly dismissed as a viable methodology in the treatment studies in this PhD. The reasons for this included:-

- Deemed unethical to provide no treatment to a control group
- No other comparison gold standard treatment available to the researcher.
- Minimal or no research funding to ensure blinding of a team of research assistants

Active consideration was given to including a comparison group of adolescents with untreated substance use disorder in the YoDA outcome study (chapter 4). I sought to identify adolescents with substance use disorders who were uninterested in treatment to

create a control group. I approached the paediatric emergency department at a nearby general hospital. I met with the consultant in paediatric emergency medicine. Agreement was obtained to recruit into the study adolescents who were admitted into hospital following a drug or alcohol related event. Ethical approval was obtained for this. We planned to interview adolescents with parental consent. One of the co-authors (CD) was available to interview adolescents the day after admission. Medical students also volunteered to conduct interviews out of hours, over weekends and during school holidays in the hope of recruiting increased numbers. Although hospital admission data and the estimates provided by the consultant in paediatric emergency medicine had indicated that sufficient numbers would be forthcoming, this did not materialise. Having invested many weeks in this process and recruiting less than five participants, we abandoned pursuit of this comparison group.

Simultaneously, with co-author CD, we approached An Garda Siochana and set up a meeting with the team of Juvenile Liaison Officers (JLO) in South West-Dublin. They indicated a willingness to recruit into the study young people who were referred to the JLO team who had a history of significant substance use. Unfortunately this also failed to yield reasonable numbers of participants. In practice, many of the JLOs were reluctant to discuss study participation with the young people they encountered, often on just one occasion. Many young people and their parents indicated to them that they were not interested in participating. Among the small number who reported interest to the JLO and agreed to be contacted by the interviewer (CD), they then refused to or failed to participate in a structured interview. Consequently, we also abandoned pursuit of that comparison group.

This then left us without any comparison group. We were therefore only able to conduct a within group comparison. Even for individuals with substance use disorders, their drug use tends to fluctuate over time. Given the nature of referral into addiction treatment, this tends to coincide with acute problems for the patient, or to occur at a time when their drug use is relatively increased. Consequently there are very real issues with regression to the mean. While this has been demonstrated primarily in adults, there is a tendency for the mean level of substance use across a group to reduce over time, even without treatment. For this reason, we sought to identify methodologies which would take this phenomenon into account. While primarily used in the realms of psychology, a small number of addiction outcome studies have utilised measurement of the ‘reliable change index’. We consequently

opted to use this approach. The method for same is described in the research paper (Chapter 4).

In the study examining changes in psychological wellbeing, we also had no capability to obtain a control group, primarily for ethical reasons. The study was hampered by declining number of potential participants as the incidence of heroin dependence among adolescents in Dublin continued to decline. Consequently, it became challenging to recruit even the target number of participants indicated by the power calculations for a simple pre- and post- comparison.

It seems likely that the relatively low incidence of heroin dependence in adolescents internationally explains the absence of any controlled clinical trials of OST in adolescents beyond a 12 week period, and the typically very small number of participants included in the few 'open label' studies published over the past 50 years (see Table 2.2 in previous chapter).(99, 142) The very limited existing scientific literature made it difficult to generate specific hypotheses for testing in the study of OST outcome. Consequently, the examination of baseline or treatment characteristics which might be associated with better outcome was deliberately exploratory. For this reason, simple associations, odds ratios, confidence intervals and p values are reported. For the same reason, a Bonferroni adjustment was not made.(143) If study sample sizes increase in future studies, those research teams can opt to examine the significant associations found in this and the few other studies in a priori or hypothesis driven manner.(144)

3.2 Exploration of Temporal trends

3.2.1 Determining the beginning and end of 'the head shop era'

In the NPS papers (Chapters 7-9), decisions had to be made regarding how best to explore for change over time. The key focus of the Thesis related to the arrival and departure of the head shops. This posed a number of challenges. It was difficult to determine both the start point and the end point of the head shop phenomenon, what I have called 'the head shop era'. Meetings were held with the Garda National Drug Unit. They provided useful information on the number of head shops at multiple time points and this has already been summarised in Chapter 2 (Figure 2.16). However, the exact timing of the increase in

numbers of head shops in 2009 remained unclear. It was also unclear when the pre-existing head shops began selling NPS.

Ideally in time series analysis there is a clear and absolute point of change when a policy is implemented. There were two pieces of legislation which appeared to act cumulatively to end widespread sale of NPS by head shops in Ireland. This staggered policy implementation complicated the estimation of the intervention point, something which is necessary for many of the standard or common time series modelling approaches.

The understanding of the time frame of the head shop phenomenon evolved over the course of the thesis in an iterative manner. An output of the study examining NPS use in adolescents attending addiction treatment at YoDA (Chapter 7) was greater clarity regarding the apparent beginning and end of the 'head shop era'. Although that study had hypothesised a priori that the key event was the Misuse of Drugs Act in May 2010, and which coincided with half of the head shops closing, it indicated that problematic use of NPS, especially the cathinone type drugs, remained very evident until the end of August 2010. This date coincided with the Criminal Justice (Psychoactive Substances) Act and the end of sale of NPS by head shops. Consequently, for the subsequent studies (Chapters 8 & 9), the timeframe of greatest interest for interrogation moved forward slightly to start in January 2010 and end in August 2010.

In addition to the challenge of estimating a beginning and end of the head shop era, further problems arise from that fact that this period was so brief, at only eight months. This short timeframe resulted in a finite and relatively small number of events occurring during the head shop era. This reduces power to identify significant changes.(144) Secondly, for time series analysis, one ideally wants a large number of time points from which to determine a trend or slope both before and after an intervention or policy change.

3.2.2 Time series analysis methods considered.

Specialist statistical advice was sought and obtained from an Associate Professor of Biomedical Statistics and from an engineer who held a mathematics PhD. Both had experience in use of time series analysis methodologies.

ARIMA modelling is generally viewed as the gold standard instrument for assessing change in a time series after a single policy implementation. It examines change at a specific and a priori determined time point. Secondly, it ideally requires data from at least 12 time periods (e.g. month or year) before and after the policy implementation under examination. Finally it ideally requires a minimum of about 100 events per unit of time (i.e. over a 100 events per month, or 100 events per year).(145) The circumstances of the head shop era in Ireland are therefore not ideal as none of these criteria were met for the harms and issues under examination.

Segmented regression time series analysis was also considered. This is capable of factoring in changes at more than one time point. However, the time points need to be defined in advance. Following implementation of a policy, change may occur immediately or gradually. An immediate change is called a 'step change' and a gradual change is a 'slope change'. It is possible that both may occur following real world policy changes. Segmented regression analysis permits exploration of both step changes and slope changes at each time point examined. The final equation which best fits the data may include both step and slopes changes. While the data requirements are not as onerous as in ARIMA, the limited number of data points and the relatively small number of events per data point reduce the power of this technology to detect significant changes.(145) Given the lack of certainty regarding both the beginning and end of the head shop era, a null finding with segmented regression would have been difficult to interpret. It may mean that the interventions had no impact upon the rate of harm or it could mean that we were looking for change at the wrong time location.

The chosen method of analysis was Joinpoint regression.(146) This is described in the relevant research papers (Chapters 8 & 9). Unlike the methods described above, it does not require the investigator to determine a priori a time point when a change may have occurred. It also has the ability to function where there are very few events per time point. Indeed it can be adapted to manage datasets where there are no events at some time points. One disadvantage that it has relative to segmented regression is that it only examines for presence of 'slope changes' in datasets. It does not examine for presence of step changes. Consequently, if a real world situation included a clinically significant step change, but no real slope change, Joinpoint analysis would likely produce a null finding.

Chapter 4

Outcome for adolescents abusing alcohol and cannabis following outpatient treatment: how many 'reliably improve'?

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Citation Reference:
Smyth BP, Kelly A, Cullen W, Darker C. Outcome for adolescents abusing alcohol and cannabis following outpatient treatment: how many 'reliably improve'? *Irish Medical Journal* 2015: 108; 137-139.
Journal ISSN: 0332-3102 (Print)
Journal Url: http://imj.ie/

4.1 Context within overall thesis

This chapter provides an overview of the client profile at YoDA, this being one of the two key clinical sites from which research participants were recruited in subsequent studies. Participants were recruited from this service into the study examining changes in psychological well being among patients on OST (Chapter 6) and into the study examining changes in NPS use in the adolescent age range (Chapter 7). This study characterises the polydrug use typical of treatment attending adolescents. It highlights the level of motivation which exists among adolescent treatment entrants and allows exploration of how this varies between illegal substances and the legal substance, alcohol. As mental health is a key focus of the overall thesis, being central to the studies in Chapter 6 and Chapter 9, this study also reports on mental health symptoms among treatment entrants. Most importantly, it provides an initial examination of changes in drug use following treatment, focusing on alcohol and cannabis. While examining abstinence, it also examines the more harm reduction orientated goal of 'reliable change'.

4.2 Abstract

Background: Alcohol and cannabis are the primary substances contributing to referrals of adolescents to substance abuse treatment services. Motivation to change substance use is typically poorer in adolescents than adults. Abstinence is only achieved by a minority of treatment attenders. It has been suggested that evaluations of treatment outcome should seek to measure the proportion of patients who achieve a reliable reduction in their substance use. *Method*: A three month follow-up was conducted in an outpatient adolescent treatment program which integrated motivational interviewing, CBT and family therapy. The primary outcome measure was days of substance use in the past month. The ASSIST was used to identify High Risk users of each substance. SOCRATES was used to measure motivation. *Results*: Among 108 adolescents assessed, we identified 42 (39%) and 77 (71%) with high risk use of alcohol and cannabis respectively. Among these high risk groups, 'problem recognition' was low or very low in 97% of drinkers and 83% of cannabis users. Follow-up interviews occurred with 87 (81%) participants. Although the high risk drinkers achieved a significant reduction in the median number of days drinking ($p=0.004$), only four (11%) were abstinent at follow up. A further five (14%) achieved a reliable reduction in days of drinking of seven or more per month. Among the high risk cannabis users, there was also a significant drop in the median days of use ($p<0.001$), although only six (11%) were abstinent at follow up. A further 20 (36%) achieved a reliable reduction in days of use of nine or more per month. *Conclusions*: Motivation among adolescents attending substance abuse treatment is poor, especially related to alcohol. Calculation of reliable change allows examination of outcomes which fall short of the elusive goal of abstinence.

4.3 Introduction

Irish teenagers demonstrate higher rates of use of both drugs and alcohol compared to most of their European counterparts, with 50% of 16 year olds having used alcohol in the past month and 18% report lifetime cannabis use.[1] Early initiation of alcohol use has been shown to be linked to later alcohol-related problems and substance use disorders. [2-3] Drug and alcohol abuse can have a negative impact on many domains of a young person's life, including their health, educational attainment and psychological well-being.[4]

While heroin emerged as a substantial problem among adolescents in the 1990s in Dublin, cannabis has become the dominant drug leading to referrals into adolescent addiction treatment services in the past 10 years.[5-6] Polysubstance use is however common for people entering addiction treatment, being evident in 68% of cases across all age ranges. [7] Adolescents accessing treatment for substance use disorders are heterogeneous, typically presenting with multiple and complex problems.[8] Motivation among adolescent treatment attenders tends to be poorer than among adults. [8-9] For example, only 20% of the adolescents in the large 'Cannabis Youth Treatment' study in USA perceived any need for help with problems associated with their drug or alcohol use.[8]

In large clinical trials examining the impact of treatment on adolescent cannabis use, therapeutic interventions tend to yield reductions of 25-38% in the mean number of days of cannabis use per month.[10-11] Heterogeneity in treatment interventions and in measured outcomes makes it difficult to provide succinct comment on treatment outcome for adolescents with alcohol use disorders.[12-13] Some interventions show no change, while others report up to 50% abstinence at three months.[13] Abstinence is rarely sustained in adolescents.[14] Consequently, harm reduction approaches have been advocated in adolescent treatment settings.[15]

It has been argued that evaluations of addiction treatments should seek to measure the proportion of patients who achieve reductions in substance use which are of clinical and statistical importance, but fall short of abstinence. To achieve this, Marsden et al propose more widespread use of statistical methods to measure the proportion of patients who achieve reliable change in their substance use.[16]

The primary aim of this study was to assess the three-month outcomes for patients presenting with high risk alcohol and high risk cannabis abuse following attendance at a specialist community treatment service for adolescents. We also sought to examine motivation in this patient group.

4.4 Methods

4.4.1 Participants

Adolescents who completed assessment at a specialist outpatient community drug and alcohol treatment facility for adolescents were eligible to participate. Patients were excluded from the study if living outside of Dublin, acutely intoxicated during assessment, poor literacy, living in a secure setting, judged to have no substance use disorder or were aged over 19 years or under 12 years.

4.4.2 Design

This study employed a before and after comparison of scores on related measures from baseline assessment (T1) to three months follow-up (T2). The primary outcome measure was the number of days consuming alcohol and/or cannabis in the previous month, as assessed by the Maudsley Addiction Profile.[17]

4.4.3 Setting & Intervention

The setting for this study is a specialist outpatient treatment service for young people experiencing problems related to their drug or alcohol use. It is located within an urban setting in Ireland. The service is provided by Ireland's Health Service Executive. Patients attending are not charged any fee for the treatment. There is an open referral system, with referrals being accepted from medical and other professionals, from parents and from young people themselves. The services provided include individual counselling (utilising motivational interviewing and cognitive behaviour therapy), family therapy and psychiatric assessment and treatment as needed. While abstinence is encouraged, there is no demand on patients to accept this treatment goal. Harm reduction goals were also accepted.

A bio-psycho-social clinical assessment typically occurs over two appointments. Involvement by parents, and other significant adults, in assessment and treatment is encouraged but is not mandatory. The treatment intervention is not manualised. Most treatment sessions involve one-to-one work with the young person, comprising weekly one-hour appointments. In parallel with this, family therapy is often offered, especially where there is evidence of poor communication or relationship problems between parents and teenager. While

treatment is tailored to the individual's needs, a basic treatment episode involves about six sessions in total, with family input into two or three of these. Therefore, for the purposes of this study, we viewed patients who left treatment in an unplanned manner prior to their sixth appointment as having had an 'inadequate dose of treatment'.

Consistent with practice in treatment approaches such as Adolescent Community Reinforcement Approach (ACRA) and Multi-Dimensional Family Therapy (MDFT), where adolescents are involved with other services in education, criminal justice or social work sectors, active efforts are made to work in a collaborative and interagency manner with those services.[18] This can involve meetings off-site with other agencies, typically including the adolescent and their family.

4.4.4 Procedure

Members of the clinical team within the treatment service conducted a baseline assessment of all patients entering the treatment service. We repeated an interview at a three-month follow up (T2) to assess any potential changes in drug and alcohol profile. This interview was conducted by a member of the clinical team or by one of the researchers (CD). Telephone interviews were conducted by a researcher (CD) at follow-up in instances where the young person was unavailable for face-to-face interview. Telephone interviews were briefer and focused upon the key outcome information regarding recent substance use.

All participants and parents gave their written informed consent to participate in the study and for all study materials to be passed to the research team. Ethical approval was obtained from the Research Ethics Committee of the National Drug Treatment Centre, Dublin.

4.4.5 Measures

The study instrument included:

(a) Maudsley Addiction Profile (MAP),[17] a brief, multi-dimensional instrument for assessing treatment outcomes for people with drug and/or alcohol problems which has been utilised

in many studies and has been found to be reliable and valid.[19] We used it to provide a measure of past month substance use.

(b) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) which provides life-time, as well as current, estimates of substance-related risk.[20] The ASSIST has been found to be a valid screening test for identifying psychoactive substance use in individuals who use a number of substances and have varying degrees of substance use. [21] It generates a separate score for each substance being used. It has been suggested that the ASSIST be modified slightly when used in adolescent cohorts, with removal of Question 7 and the application of lower, more age appropriate cut offs.[22] In our use of the ASSIST to identify 'high risk' users of each substance, we applied these modifications. For children aged 15-17yo, the high-risk cut offs for alcohol and cannabis are 18 and 12 respectively. The cut-off for amphetamines, inhalants and hallucinogens is 9. It is 7 for all other substances. For children aged under 15 years, the high risk cut-off is 6 for alcohol and inhalants. It is 2 for all other substance categories.

(c) Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES)[23] assesses an individuals motivation to change their substance use related behaviour. It examines alcohol and drugs separately, providing subscale scores including Problem Recognition and Taking Steps. SOCRATES has been found to be both reliable and valid. [24-25]

(d) Beck Youth Inventory (BYI)[26] assesses emotional and psychological impairment in adolescents. The BYI contains five subscales to measure self-concept, depression, anxiety, anger and disruptive behaviour. It has been shown to have good reliability and validity when tested.[27]

4.4.6 Analysis

The analyses were conducted within SPSS (version 19). To examine changes in days and quantity of use, we utilised the Related Sample Wilcoxin Signed Rank Test.

The phenomenon of ‘regression to the mean’ complicates assessment of behaviour change in simple pre / post study designs and thus when assessing treatment impact, it is useful to determine the proportion of patients who achieve a 'reliable change' in their baseline

substance use.[16] Hageman & Arrindell provide details of the computation involved in identifying individuals who have reliably improved, dis-improved and remained unchanged.[28] The calculations are contingent on estimating an appropriate standard error of the difference (score at time 2 minus score at time 1) from which the required 95% confidence interval for the difference is obtained. The standard error of the difference is derived from the standard deviation of the time 1 scores for all participants and the known reliability of the test instrument – see Hageman & Arrindell for details. [28]

We had limited power to detect factors associated with poorer outcome. We needed a sample of 58 patients to have 80% power to detect a dichotomous factor associated with good outcome with an odds ratio of 2.0, with p value set at 0.05.

4.5 Results

4.5.1 Characteristics of Baseline group

There were 143 consecutive patients assessed at the service during the recruitment period who were eligible to participate. Thirty-five of these did not enter the study. Of these, 16 adolescents refused to participate and we were unable to obtain consent from a person in parental authority in 14 cases. In five cases, the reason for non-participation was unclear.

There were 108 adolescents included in the study and their mean age was 16.4 years (Range 13 to 19 years). There were six (5%) participants aged under 15 years and 13 (12%) were aged 18 or 19 years. Other demographic details are presented in Table 4.1.

Table 4.1. Baseline demographic profile of 108 adolescents attending for specialist community based addiction treatment and route of exit from treatment.

	N (%)	Mean (Range)
Age (years)		16.4 (13-19)
Male	84 (78)	
Living with parents or family	99 (92)	
Ethnic background - white Irish	98 (91)	
Employment status		
In school or college	57 (53)	
Vocational training course	16 (15)	
Working	6 (6)	
Neither working nor in education	27 (25)	
Referral sources		
Family	39 (36)	
Social services	18 (17)	
Probation services	13 (12)	
Mental health services	11 (10)	
GP & other medical services	9 (8)	
Self	7 (7)	
School	6 (6)	
Other	4 (4)	
Previous treatment for an alcohol problem	9 (8)	
Previous treatment for a drug problem	16 (15)	
Route of exit from treatment		
Planned discharge	53 (49)	
Refusal to attend	6 (6)	
Repeated non-attendance	35 (32)	
Referred elsewhere	5 (5)	
Other reason (e.g. moved away, prison)	9 (8)	
Adequate Treatment Intervention*		
Adequate dose of treatment	82 (83)	
Inadequate dose of treatment	17 (17)	

* Patients were defined as having had an adequate dose of treatment if they attended at least six appointments or had a planned discharge prior to their 6th appointment. Nine cases could not be assigned due to missing data.

Table 4.2 presents information on the range of substances used and proportions of patients using these individual substances in a high risk manner. Among those reporting alcohol use in the past month, the median number of standard drinks per drinking day was 11 (Inter-Quartile range [IQR] 7 -15), which is 110 grams of alcohol. Excluding tobacco, 47 (44%) patients were identified as having 'high risk' use of a single substance, while 28 (26%) were demonstrating high risk use of two substances and 21 (19%) were using at least three substances in a high risk manner.

As outlined in Table 4.2, motivation to ‘Take Steps' and ‘Problem Recognition’ were low or very low among the majority of high risk users of each individual substance apart from high risk opioid users. Among those reporting high risk use of alcohol and high risk drug use, both ‘Problem Recognition’ and ‘Taking Steps' subscale scores were significantly higher regarding the drug problem compared to the alcohol problem (p=0.01 in each case).

Fifty-one per cent reported criminal activity in the month prior to treatment entry, with sale or distribution of drugs (30%) and shoplifting (22%) being most common. There was evidence of moderate to severe mental health problems in the areas of depression (33%), anxiety (32%), anger (29%), disruptive behaviour (52%) and self concept (47%) on the BYI subscales.

The median number of appointments attended by patients was seven (IQR 5-12). The median number of appointments attended by parents was three, and in 34% of cases parents did not attend any clinical appointments.

Table 4.2. Baseline substance use and motivation among 108 adolescents attending a specialist community based treatment service

	Ever Used (%)	Current Users - Any use in past Month (%)	Mean Days use in past month (SD)	Current Users with High Risk Use[a] (%)	Motivation among those with 'High Risk' Use[b]	
					Low or Very Low Problem Recognition (%)	Low or Very Low on 'Taking steps' (%)
Alcohol	104 (96)	95 (88)	7 (7)	42 (44)	35 (97)	29 (78)
Tobacco	100 (93)	90 (83)	27 (7)	80 (89)	NA	NA
Cannabis	98 (91)	87 (81)	20 (10)	77 (89)	57 (83)	43 (62)
Benzodiazepines	49 (45)	23 (21)	9 (8)	21 (91)	13 (68)	11 (61)
Cocaine	59 (55)	19 (18)	5 (6)	15 (79)	9 (75)	5 (38)
Amphetamine	56 (52)	13 (12)	3(5)	13 (100)	10 (83)	6 (50)
Opioids	9 (8)	7 (6)	24 (11)	7 (100)	2 (29)	2 (29)
Hallucinogens	20 (18)	4 (4)	1 (1)	0 (0)	NA	NA
Inhalants	21 (19)	3 (3)	1 (0)	2 (67)	2 (100)	0 (0)
Other substances	14 (13)	10 (9)	5 (9)	4 (40)	3 (75)	2 (50)

[a] Categorisation as a 'High Risk' user was determined by the ASSIST questionnaire.
[b] 13 participants did not complete the SOCRATES Questionnaire
NA = not applicable

4.5.2 Substance use outcomes

We conducted follow-up interviews with 87 (81%) participants. Follow-up interviews occurred over the telephone in 65% of cases. Those interviewed did not differ from those lost to follow-up by any socio-demographic, substance use, treatment adherence or motivation measure. The follow-up group did demonstrate greater baseline anxiety symptoms (p=0.04), but did not differ on other measures of psychological well-being.

4.5.2.1 Alcohol

Among those identified as High Risk drinkers, alcohol was their most problematic substance in just 52% of cases based upon ASSIST scores. Among these High Risk Drinkers, we had follow-up information in 35 (83%) cases. The median days of use reduced from 12 (IQR 6-15) at baseline to 7 (IQR 4-14) and this was statistically significant (p=0.004). The mean days dropped by 27%, from 11 days per month to 8 days. Among this group there was also a significant reduction in the number of standard drinks per month (p=0.007), reducing from a median of 120 (IQR 30-240) to 60 (IQR 24-105).

Calculation of the reliable change index for alcohol indicated that a change in days of use per month of seven or greater was reliable. Only four (11%) of the high risk drinkers were abstinent at follow-up, but a further five (14%) were reliably improved. One person had reliably deteriorated while 25 (71%) were unchanged. Nine of the high risk drinkers were drinking on seven days or less per month at baseline and therefore could not reliably improve even if they reduced their drinking to just one day per month.

There was no significant change in the drinking among those who reported baseline alcohol use in the Moderate Risk group.

4.5.2.2 Cannabis

Among those identified as high risk cannabis users, cannabis was the substance which had the highest ASSIST score in 79% of cases. Among this High Risk group, we had follow-up

information on 55 (71%) people. The median days of use reduced from 25 (IQR 15-30) at baseline to 15 (IQR 4-30) and this was statistically significant ($p<0.001$). The mean days dropped by 32%, from 22 days per month to 15 days.

Calculation of the reliable change index for cannabis indicated that a change in days of use per month of nine or greater was reliable. Six people (11%) were abstinent at follow-up and a further 20 (36%) had reliably improved. There were four (7%) patients who reliably deteriorated, while 25 (45%) were unchanged. Seven of the high risk group were using cannabis on nine days or less per month at baseline and therefore could not reliably improve even if they reduced their cannabis use to just one day per month.

We grouped together the 26 (47%) high risk cannabis users who either were abstinent or reliable improved to generate a "good outcome group" and the remaining patients were categorised as a "poorer outcome group". There was no statistically significant difference between the these groups in terms of gender, referral source, baseline mental health symptoms, baseline motivation, family involvement in treatment or dose of treatment.

There was no significant change in cannabis use among the 13 individuals who reported baseline use in the moderate risk category.

4.6 Discussion

4.6.1 Clinical Profile

Patients were typically male and lived with their parents. Despite their young age, almost one quarter were not in education, work or training. While referral sources were varied, parents, social services and probation were the largest source of referrals. Consistent with other Irish treatment settings, polysubstance use was the norm.[7] Co-existing problems with mental health and criminal behaviour were also regularly reported, in common with other treatment-attending cohorts internationally.[8] Motivation was very poor when compared to adult treatment-attending groups. [23] Motivation regarding alcohol problems was particularly poor. Although half the patients had a planned discharge following treatment completion,

about two in five left in an unplanned manner. Unfortunately poor treatment adherence is widespread in substance abusing adolescents.[29]

4.6.2 Alcohol

Daily drinking was very unusual even in the group with high risk drinking patterns, who typically reported drinking about three times per week at baseline. This is in contrast to adults entering alcohol treatment programs but in common with other adolescent treatment attending cohorts.[13,30] Half of those with a high risk drinking pattern had a coexisting and more problematic drug use problem. Where drug and alcohol problems co-occurred, patients were more motivated to address the drug problem. This highlights the complexity of motivation in real world clinical settings, where patients may be very motivated to make some changes while being unmotivated to address other issues. To complicate matters further, there is some evidence that drinking may increase in people who are seeking to reduce drug use.[31] Although high risk drinkers did reduce their days of drinking and total monthly alcohol consumption in this study, the magnitude of improvement was quite modest. While pharmacological agents to treat alcohol use disorders, such as disulfiram or Naltrexone, were not prescribed to this patient group, some have argued that they should be utilised more regularly in the adolescent age range.[13]

Only one in nine achieved abstinence, highlighting the elusive nature of this goal in these cohorts.[29] Our outcomes are probably poorer than those reported in studies internationally, although the vast majority of the outcome research has been conducted in USA.[12-13] The wider cultural approach and context of youth drinking is very different in USA, where the legal drinking age is 21 years compared to Ireland where people can buy alcohol at the age of 18 years. In recent decades in Ireland, the age of onset of drinking has moved progressively into earlier adolescence, while adult drinking has increased.[32] The majority of young Irish adults drink in a hazardous or harmful manner.[33] This 'wet' society may impact negatively on the ability of Irish adolescents to recognise their own unhealthy drinking and to change it when they do.

4.6.3 Cannabis

As expected, cannabis was the most frequently identified substance use problem in our patients. Although only one in nine of the high risk cannabis users were abstinent at follow-up, a further one third achieved substantial reductions in their cannabis use. Across the group of high risk cannabis users, the mean days used per month fell by 32%. While motivation to address cannabis problems was better than that to address alcohol, it was nevertheless low or very low in most cases.

The largest and most comprehensive evaluation of the treatment of adolescent cannabis use disorders was the Cannabis Youth Treatment (CYT) study conducted in USA.[8] Compared to the CYT study group, the adolescents in our study were older, less likely to be in education but had similar levels of criminal involvement. Our group reported more frequent alcohol and cannabis use at baseline. The treatment interventions used in CYT generally demonstrated higher rates of treatment adherence and treatment contact compared to our intervention. In the CYT study, almost one quarter of participants were "in recovery" at 3 month follow-up and mean days of cannabis use dropped 35% to 8 days per month. Compared to a recent Dutch study, our participants were similar in terms of age, gender and academic profile.[10] Our group had much higher alcohol use. The Dutch CBT group had similar dose of treatment but greater family input than our group. In their CBT intervention, the mean days use per month dropped 27% to 15 days per month.

Our study did not identify any patient or treatment adherence characteristics significantly associated with better treatment outcome, but it had very limited power to do so. Other studies have found that baseline mental health problems, lower motivation and low treatment adherence are associated with poorer outcome.[34] While we did not demonstrate improved outcome with greater family involvement in treatment, others have demonstrated such an effect.[35] Continuing care was not routinely offered to this patient group, but others have demonstrated that it is feasible and effective, whether by telephone or face-to-face.[36]

4.6.4 Limitations.

The treatment intervention was not manualised. This makes comparison with other studies and other treatment providers difficult. For ethical and practical reasons there was no control group in this study. Consequently, it is not possible to determine whether or not this treatment was better than no treatment. However, the use of the reliable change methodology compensates for this deficiency to some extent, by identifying the magnitude of change that is likely to be independent of the 'regression to the mean' phenomenon.[16] One of the weaknesses of the reliable change method is that it makes it impossible for participants with baseline use of less than the amount needed for a reliable change to achieve this outcome. Changes in substance use were reliant upon self report. However, studies have found that there is a high concordance between self-reported drug use and toxicology in young people.[37] Although the SOCRATES has been validated in adolescent patient groups, it did tend to cluster the vast majority of participants in this study into the low or very low categories.[25] Studies of cohorts such as this would benefit from an instrument which could better discriminate varying levels of motivation among participants.

4.6.5 Treatment Implications

In light of the frequency of polysubstance use among clinical populations in Ireland, services for adolescents with substance use disorders should be integrated, dealing with both alcohol and drugs together within the one service. As comorbid mental health problems are encountered with great frequency, adolescent services should have the capacity to assess and manage common mental health problems in this group.

As motivation tends to be quite low, especially for alcohol use disorders, services should assess it at the outset of treatment and target poor motivation where it does exist. Although the average reduction in substance use was modest and broadly in line with international studies, the proportion of patients who achieved abstinence was quite low. It is important that patients, parents, referrers and funders of adolescent drug and alcohol services have realistic expectations of treatment.

4.7 Author Contributions

BPS conceived the study questions. BPS lead on the examination of the background literature and CD also contributed substantially to this task. AK lead on the statistical analysis with input from CD & BPS. BPS & CD jointly identified the measures utilised in the study and designed the follow-up aspects of the study. CD took the lead in overseeing the follow-up interviews. AK, BPS, CD & WC were each involved in interpretation of the data. BPS lead on the drafting of the manuscript. CD, AK & WC also contributed to the drafting of the manuscript. BPS, AK, CD & WC each read and approved the final manuscript.

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Chapter 5

Opiate substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention.

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Citation reference:
Smyth BP, Elmusharaf K, Cullen W. Opioid substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention over twelve months. *BMC Pediatrics* 2018: *BMC Pediatrics* 2018: 18(1):151. doi: 10.1186/s12887-018-1137-4.
Journal Url: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-018-1137-4

5.1 Context of this chapter within overall Thesis

This study presents findings on changes in drug use among heroin dependent adolescents treated with OST. As one of the largest studies reporting twelve month outcome of this treatment group, it constitutes an important addition to the international literature. It provides further context for the study reported in Chapter 6, describing the treatment program and patient group attending the Young Person's Program (YPP), most patients in the Chapter 6 study being recruited from the YPP. Similar to the previous study in Chapter 4, it examines abstinence from the main drug of use at three months. Given that OST is typically a longer term treatment, it describes the patient group who persist with this treatment for a 12 month period and examines the achievement of heroin abstinence at that point. It seeks to identify patient and treatment characteristics which may be associated with heroin abstinence and with premature drop out from treatment in an exploratory analysis.

5.2 Abstract

Introduction and Aims: Few studies have examined opiate substitution treatment (OST) in adolescents, a controversial treatment internationally. We sought to measure changes in drug use among adolescents receiving OST and also to examine treatment attrition.

Design and Methods: We included all heroin dependent patients aged under 18.5 years commencing OST at one outpatient adolescent addiction service. Drug use was monitored by urine drugs screens (UDS). Change in the proportion of UDS negative for heroin was examined using the Wilcoxon signed rank test. Attrition was explored via a Cox Regression multivariate analysis.

Results: OST was commenced by 120 patients and 39 persisted until month 12. At month three, heroin abstinence was 21% (95% confidence interval [CI] = 9,36%) and it was 46% (95% CI=30,63%) at month 12. Heroin use declined significantly from baseline to month three ($p<0.001$) and from month three to month 12 ($p=0.01$). Use of other drugs did not change significantly. Unplanned exit occurred in 25% patients by 120 days. The independent predictors of attrition were having children, single parent family of origin, not being in a intimate relationship with another heroin user and evidence of baseline cocaine use.

Discussion and Conclusion: Adolescent patients who persist with OST achieve significant reductions in heroin use and these improve incrementally over the first year of treatment. While patient drop out remains a challenge, as it is in adults, it appears unreasonable to impose a time limit of less than one year of OST in this age range.

5.3 Introduction

There is global ongoing concern regarding opioid dependence. The prevalence of heroin dependence tends to fluctuate over time and is much more common in adults than adolescents.[1,2] In Dublin, heroin use first emerged as a concern among adolescents in the 1990s, in the midst of a dramatic increase in heroin dependence among adults.[2,3]

Opiate substitution treatment (OST) is now the main first line treatment intervention for heroin dependence among adults.[4] Among adolescents there is very little evidence to confirm its benefit and especially when used longer term.[1,5]

There are no clinical trials examining outcome of OST beyond three months in people aged under 18 years old.[5] There are a small number of 'open label' longer term studies. The largest study has involved just 153 patients and was conducted over 40 years ago.[6] The primary goal of OST is to assist the patient in reducing their heroin use but few studies provide any firm information on this issue. The DARP study did report a progressive decline in heroin use over the first year of methadone treatment (MT) but failed to provide any specific information on rates of heroin use during treatment.[7] More recently, the NIDA multisite buprenorphine/naloxone treatment (BT) trial examined treatment of youth over a three month period and included 12 under eighteens. At week eight, 77% of those retained on BT provided an opiate negative urine drug screen.[8] Abstinence from heroin at the end of the trial was associated with greater baseline medical and psychiatric problems, a history of recent injecting and evidence of early cessation of heroin use during BT.[9]

Treatment drop out has been examined by a few studies of OST in this age range. Studies of MT indicate that 25% of patients drop out within approximately four months.[6,7,10] Bell & Mutch found that the drop out from BT was significantly greater than from MT.[11] Other studies of BT in this age range also indicate frequent early drop out from treatment, with typically a quarter of patients exiting within 4 to 8 weeks.[12-14]

Given this paucity of outcome studies of OST in adolescent heroin dependence, we sought to address a number of questions which are of importance to clinicians and patients. What proportion of adolescents cease heroin use while on OST? Does abstinence increase incrementally or simply stabilise beyond three months on OST? What is the rate of drop out? Are there any baseline or treatment characteristics which are associated with either abstinence or drop out?

5.4 Method

5.4.1 Treatment context

5.4.1.1 Treatment Setting

The evolution of the heroin problem in Dublin commenced in the 1970s and is described in detail by O'Kelly & O'Kelly.[15] In 2000, due to the large number of heroin dependent adolescents presenting to treatment services in Dublin, and the growing recognition that their treatment needs differed to that of the adult population, the Young Persons' Programme (YPP) was developed at the National Drug Treatment Centre (NDTC) this programme provided a multi-disciplinary adolescent treatment service, working in a manner which was broadly consistent with the subsequently published UK guidelines on psychopharmacology in adolescent addiction treatment.[16] The team was led by a consultant child & adolescent psychiatrist and had input from nursing, clinical psychology, social work, project workers, counsellors and family therapy. The staff to patient ratio was over double that which existed in the adult MMT programs in NDTC. The YPP was based in central Dublin and provided treatment to opiate dependent teenagers from the greater Dublin area, which included the surrounding counties. Patients travelled up to 80 kilometres to attend the service.

National guidelines on the treatment of addiction in adolescents emphasise the need for multidisciplinary input into treatment.[17] Consequently, GPs or office based practitioners, rarely prescribe methadone to heroin dependent adolescents and they are not permitted to prescribe buprenorphine.

Patients were expected to be under the age of 18.5 years when they commenced attendance at the YPP. There was an expectation that patients progress from the service prior to their twentieth birthday. If there was a need for ongoing opiate substitution treatment, they were facilitated with a planned transfer to an adult addiction service. With declining incidence of adolescent heroin dependence in Dublin, these age limits were moved upwards in 2010.

5.4.1.2 Assessment

There was an open referral system to the YPP, with family and social workers the most common sources of referral. There was no waiting list. There were no exclusion criteria for opiate dependent patients, although patients who were deemed to need acute inpatient

treatment of a co-occurring medical or psychiatric disorder had their assessment postponed until this disorder was stabilised. Treatment was provided free of charge. Assessment occurred over a seven to ten day period, during which patients typically attended on three occasions to meet different members of the multi-disciplinary team. In addition to being assessed for heroin dependence using ICD-10 criteria, patients also provided three supervised urine samples as confirmatory evidence of regular heroin use. Assessment also sought to identify co-existing psychological, developmental, social and physical needs and where appropriate, provide or facilitate appropriate treatment.

People aged 16 years and above may consent to medical treatment on their own behalf in Ireland. However, we also sought parental agreement to treatment in these cases. Parental consent was required for patients under the age of 16 years.

The main pillars of treatment involved opiate agonist medication (methadone or buprenorphine), counselling (CBT, motivational interviewing or humanistic person centred therapy) and in some cases, family therapy. The psychosocial aspects of treatment are consistent with those outlined in James et al.[18] While patients were expected to attend counselling sessions on a weekly basis, failure to do so did not result in termination of treatment. In practice, it was our experience that approximately 50% of patients availed of individual counselling sessions per week. There were group activities during afternoons, which included art therapy and life-skills training. Attendance at groups was encouraged but not compulsory. Participation rates at groups were typically 40 to 60%.

5.4.1.3 Approach to Opiate Substitution Treatment

Initial methadone treatment typically commenced with a dose of 20mgs on day one, which was then increased by 10 mgs every three to four days, titrated against withdrawal symptoms, cravings, ongoing heroin use, while also monitoring for evidence of sedation. Stabilisation doses generally ranged between 40-70mgs. While this was lower than stabilisation doses typically recommended for adults, patients at lower doses had a personal preference for a relatively low dose and achieved stabilisation (i.e. absence of withdrawal

symptoms, control of cravings and heroin abstinence) on this dose. There was no pre-imposed upper limit on methadone dose.

Buprenorphine became available as a treatment option in 2005, initially as the sublingual mono buprenorphine tablets (Subutex®, Reckitt Benckiser Healthcare [UK] Ltd). In 2007, we switched to use of the buprenorphine-naloxone combined preparation Suboxone® (Reckitt Benckiser Healthcare [UK] Ltd). Induction typically involved provision of 2-4mgs buprenorphine during the morning of day 1, with a further 2-4mgs later that afternoon. Single daily doses of up to 8 to 12mgs were administered from day 2. Stabilisation doses were typically in the region of 6 to 12 mgs. Consistent with the recent guidelines on OST, buprenorphine was offered where patients had shorter heroin use histories and were striving towards detox on the short to medium term.[19,20,21] We found that about 40% of patients were unwilling to agree to buprenorphine treatment when it was recommended by the clinical team. In such cases, we then offered methadone.

If patients continued to use heroin or resumed use after a period of abstinence, an increase in dose of opiate substitution treatment was considered. They were also encouraged to participate in increased counselling sessions with a focus on functional analysis of drug use episodes and on relapse prevention skills.[22] Use of alcohol and other drugs is also addressed. Where the initial opiate agonist medication option was associated with a poor treatment response, the patient was offered the option of switching to the alternative.

Patients provided two supervised urine samples per week for on-site drug toxicology testing. These samples were screened for opiates, EDDP (a methadone metabolite), cocaine, benzodiazepines and alcohol. They were intermittently screened for amphetamines and cannabis. The provision of ‘take-away’ doses of medication was utilised as a contingent reinforcer of drug abstinence, as evidenced by urine toxicology. As patients established a period of opiate abstinence, they incrementally earned increased ‘take-away’ doses of medication. After two weeks of heroin abstinence, they received one ‘take-away’ dose, typically on a Saturday or Sunday. Once they attained a period of four weeks abstinence, they obtained a second ‘take-away’ dose. A subsequent lapse to heroin use resulted in an immediate loss of one of their ‘take-away’ doses. Ongoing heroin use resulted in loss of all ‘take-aways’. Use of cocaine or benzodiazepines could also result in reduced ‘take-aways’.

Patients were also provided with treatment of co-morbid medical or psychiatric problems. [23] They were actively supported in addressing co-existing housing, vocational and criminal justice related needs as part of their care plan. They were actively supported to re-engage with work, training or further education and, if they did so, they were provided with take-away doses of medication to facilitate their participation in same. Such patients typically attended the program just one or two days per week, receiving 'take-aways' for the remaining days.

We wished to avoid 'disciplinary discharges', and only considered this option where clients were seriously jeopardising the safety of other patients via drug dealing on the premises and acts of violence towards others. Where clients presented with high levels of aggression, transfer to the adult treatment service was considered.

The service was harm reduction oriented. Nevertheless, it held an aspiration, but not an insistence, that all patients progress towards complete abstinence via detoxification. Prior to detoxification, patients typically spend a number of months stabilising on OST, during which time they are expected to cease use of heroin and other drugs, while also addressing the co-existing psychological and social problems which might leave them vulnerable to relapse. Where detox, or dose tapering, occurred, it was generally conducted slowly on an outpatient basis over a period of about three months, negotiated with the individual patient. If the patient returned to heroin use during a detox, it was recommended that detox halt temporarily or else revert to a further period on a stabilisation dose. Where patients insisted on finishing a detox and leaving treatment despite evidence from urinalysis of ongoing heroin use, they were viewed as treatment drop outs. Patients had the option of referral to a residential specialist addiction treatment unit, under the care of the consultant child and adolescent psychiatrist, to commence and complete detox. In practice, about one third of the patients who complete detoxification utilise this latter option. Following detox, the YPP either provided ongoing psychological support or facilitated the patient in accessing same at an alternative, more locally accessible service. Where patients relapsed following detox, we strived to promptly re-engage them back into treatment. [24]

5.4.2 Patients

The inclusion criteria were:- heroin dependence, aged under 18.5 years and commenced treatment with opioid agonist medication. The cohort under study included patients who commenced treatment between May 2000 and June 2016. Patients with a primary diagnosis of dependence on prescription opioids were excluded.

5.4.3 Data Collection

The study was approved by the Research Ethics Committee of the NDTC. Baseline descriptive characteristics were obtained from the patients' initial structured assessment, this being adapted from the Maudsley Addiction Profile.[25] We recorded information on patient treatment participation at three, six and twelve months. If a patient was not attending the service on these dates, we noted the date of and reason for exit.

Those who were referred to and commenced on another opiate substitution treatment program were categorised as "transfers for ongoing treatment". Patients were categorised as exiting via "detox" if they completed the prescribed detox regime and showed urinalysis evidence of opiate abstinence at discharge from the treatment program. Patients who ended treatment because they were incarcerated were categorised as exiting due to "prison". Finally, patients who simply stopped attending, relocated without arranging alternative treatment or left treatment prematurely against medical advice were all categorised as being "drop outs". Patients were generally not deemed to have dropped out of their index treatment episode unless that had failed to attend for four weeks. If they were deemed a drop out, then the date of last attendance for medication was recorded as the date of discharge. Although many patients re-entered treatment after dropping out or following a relapse to heroin use after a successfully completed detox, only their first or index treatment episode was included for the purposes of this study.[24] If a patient switched from BT to MT or vice versa, but continued in treatment, this was not viewed as a treatment exit.

To examine changes in drug use, five periods during the first year of treatment contact were examined for each patient. The results of all urine drug screens (UDS) provided by each patient during each period was collated. The periods in question were (a) pre treatment assessment phase which was typically 7 to 10 days in duration and involved provision of 2-4 UDS, (b) induction phase which comprised the remaining days in that first month of patient contact after commencing OST, (c) third month of treatment, (d) sixth month of treatment and (e) twelfth month of treatment. During phases (b) to (e), patients were usually providing two UDS per week. For each patient, a dichotomous outcome variable to indicate abstinence/use was created for each of the phases they were being treated (a) to (e). They were deemed to be using heroin if any one UDS sample tested positive for opiates during that phase. If all UDS was opiate negative, they were deemed heroin abstinent. Similarly, a single positive for cocaine in a month resulted in that month being deemed one of cocaine use.

5.4.4 Statistics

In order to conduct an exploratory analysis, we used Pearson chi square test to examine association between categorical covariates and dichotomous outcome variables of interest, except in instances where a predicted cell value was less then 5, where Fisher's Exact test was utilised. Odds ratios and their 95% confidence intervals were calculated to indicate the direction and magnitude of associations. Continuous variables were converted into categorical variables, by choosing the median value as the point of split, apart from age where we used 18^{th} birthday as the cut-off.

When reporting the proportion of patients who were heroin abstinent, we also calculated the 95% confidence intervals of those rates using the exact confidence limits for binomial proportions. McNemar's paired proportions test with continuity correction was employed to determine whether OST was associated with changes in the binary category of drug use. We sought to confirm that heroin abstinence in month three was greater than baseline, and that abstinence at months six and twelve were greater than month three. We also examined changes in the proportion of samples which tested negative for heroin using the related

samples Wilcoxon signed rank test. For each period, we calculated this proportion by dividing the number of negative tests by the total number of UDS obtained. All of these analyses were confined to patients who persisted with OST.

To examine drop out and factors associated with same, the Kaplan-Meier test was conducted. The event of interest was unplanned exit from treatment via drop out or imprisonment. The time to treatment exit, in days, was recorded for each patient who left their index treatment episode during the first year, whether by unplanned exit or via planned exit (following detox completion or via transfer to another OST service). For patients who persisted with OST, the number of days entered was 365 days. The Log Rank was used to test for the equality of the survival distributions within each covariate. To facilitate interpretation of these differences, the estimated number of days to drop out by 25% is reported. In order to explore independent predictors of unplanned exit, we then conducted a multivariate analysis using Cox Regression. Covariates were selected for entry into the final equation using the forward and backward selection technique.

5.5 Results

There were 120 eligible patients who commenced OST. Their characteristics are provided in Table 5.1. Eight-eight per cent were using heroin daily at treatment entry. Thirty-nine patients persisted with treatment to month 12 and their profile is also outlined in Table 1. Twenty-nine (24%) left following detox completion and nine (8%) were transferred elsewhere for ongoing OST. There were 43 unplanned treatment exits, with 36 (30%) dropping out and 7 (6%) going to prison. There were no deaths during treatment.

Table 5.1. Characteristics of 120 adolescents commencing opiate substitution treatment, and subgroup who persisted in treatment until month 12.

	Total Group N (%)	Missing data	In treatment until month 12 N (%)	OR	95% CI OR	P value
Number in Treatment	120		39 (33)			
Socio-demographic characteristics						
Female	61 (51)		25 (41)	2.0	(0.9,4.4)	0.07
Aged under 18.0 years	104 (87)		35 (34)	1.5	(0.5,5.1)	0.49
Left school under 15 years	51 (46)	8	18 (35)	1.0	(0.5,2.3)	0.92
Not in employment, education or training	81 (70)	4	29 (36)	1.7	(0.7,4.1)	0.24
Two parent family support	59 (50)	1	27 (46)	3.8	(1.6,8.6)	0.001
Has a child	6 (5)		0 (0)	n/a		0.18 ^
Has been in care	38 (32)	2	10 (26)	0.7	(0.3,1.6)	0.35
Sibling Opiate Use	45 (39)	4	17 (38)	1.4	(0.6,3.0)	0.45
Parental Opiate Use	25 (22)	4	6 (24)	0.6	(0.2,1.5)	0.25
Partner uses heroin	47 (39)	1	18 (38)	1.5	(0.7,3.3)	0.30
Homeless or hostel in past month	34 (28)		11 (32)	0.9	(0.4,2.2)	0.89
Previous criminal convictions	46 (41)	8	14 (30)	0.9	(0.4,2.0)	0.80
Ever incarcerated	31 (27)	6	8 (26)	0.8	(0.3,1.9)	0.55
Psychiatric History						
Ever assessed by a psychiatrist	62 (53)	2	22 (36)	1.4	(0.6,2.9)	0.44
Inpatient psychiatric admission	10 (9)	4	6 (60)	3.2	(0.8,12)	0.09^
Past DSH	36 (31)	5	12 (33)	1.1	(0.5,2.5)	0.86
Substance Use						
Lifetime Drug Use						
Non-prescribed benzodiazepines	107 (90)	1	36 (34)	1.0	(0.3,3.6)	1.0^
Non-prescribed methadone	90 (78)	5	30 (33)	0.8	(0.3,1.9)	0.54
Cocaine use	76 (68)	8	30 (40)	2.7	(1.1,7.0)	0.04
Injected	53 (45)	2	17 (32)	1.0	(0.5,2.2)	0.99
Commenced heroin under 15 years of age	43 (36)	2	20 (47)	2.6	(1.2,5.7)	0.02
Regular heroin use for more than 12 mnts	73 (64)	6	26 (36)	1.2	(0.5,2.7)	0.67
Past Month Drug Use						
Non-prescribed benzodiazepines	71 (60)	1	26 (37)	1.4	(0.6,3.1)	0.40
Non-prescribed methadone	71 (60)	1	27 (38)	1.7	(0.7,3.7)	0.22
Cocaine	31 (26)	2	10 (32)	1.0	(0.4,2.3)	0.91
Cannabis	80 (73)	11	27 (34)	1.3	(0.5,3.4)	0.54
Amphetamine	9 (9)	19	4 (44)	1.9	(0.5,7.7)	0.45^
Alcohol	46 (45)	18	17 (37)	1.2	(0.5,2.8)	0.61
Injecting	35 (29)	1	13 (37)	1.5	(0.7,3.4)	0.34
Using > 3 ‘bags’ heroin per day	60 (53)	7	18 (30)	0.9	(0.4,2.0)	0.81
Pre-treatment UDS positives*						
Benzodiazepines	71 (59)		26 (37)	1.6	(0.7,3.6)	0.25
Methadone	67 (56)		20 (30)	0.8	(0.4,1.6)	0.49
Cocaine	13 (11)		3 (23)	0.6	(0.2,2.3)	0.54^
Cannabis	47 (47)	20	13 (28)	0.7	(0.3,1.6)	0.38
Early Treatment						
Suboxone Commenced	32 (27)		7 (22)	0.5	(0.2,1.3)	0.13
At least one heroin negative UDS during induction	50 (46)	12	14 (28)	0.6	(0.3,1.4)	0.28

^ P value calculated using Fishers Exact Test Statistic as estimated value in cell was less than 5

* UDS = Urine drug screen

Table 5.2 presents the results of urine drug screens from the subgroup of patients who persisted with OST for at least 12 months. This table indicates the proportion demonstrating abstinence from each drug at each time period examined. During the third month of treatment 8 (21% [95% confidence interval (CI) = 9,36%]) were abstinent from heroin. Six (15% [95%CI = 6,31%]) were abstinent from heroin, cocaine and benzodiazepines. At month 12, there were 18 (46% [95%CI=30,63%]) abstinent from heroin, of whom nine (23% [95%CI=11,39%]) were also abstinent from cocaine and benzodiazepines. Heroin abstinence increased significantly from baseline to three months, from baseline to twelve months and from third month to twelfth month. Rates of use of other substances did not change significantly from baseline. When looking beyond heroin abstinence to examine changes in the proportions of negative urine screens, it also emerged that there were significant reductions in heroin use between baseline and month 3 and from month 3 to month 12. However, there was no significant change in heroin use between months 3 and 6. When comparing the proportions of heroin negative urine screens between months 3 and 12, we found that eight (21%) patients deteriorated, six (15%) were unchanged and 25 (64%) improved.

Table 5.2. Evidence of drug use from urine drug screens (UDS), at baseline and during treatment, among 39 patients who persisted with treatment for 12 months.

	Month 1										Baseline vs Month 3	Baseline vs Month 12	Month 3 vs Month 6	Month 3 vs Month 12
	Pre-treatment baseline		Induction phase[#]		Month 3		Month 6		Month 12					
Median number of UDS conducted (range)	3 (2-4)		4 (0-7)		7 (2-10)		7 (1-9)		8 (1-11)					
											Related samples Wilcoxon signed rank test p value			
Median % of UDS heroin negative (interquartile range)	0 (0-0)		0 (0-33)		50 (0-89)		40 (0-100)		87 (33-100)		<0.001	<0.001	0.86	0.01
All UDS negative during period												p value from McNemar test		
Heroin	1	(3)	4	(11)	8	(21)	12	(31)	18	(46)	0.04	<0.001	0.34	0.04
Benzodiazepine	14	(36)	19	(53)	15	(38)	18	(46)	15	(38)	0.77	0.79		
Cannabis[^]	19/32	(59)	18/28	(64)	21/38	(55)	16/33	(48)	14/36	(39)	0.69	0.11		
Cocaine	36	(92)	36	(100)	32	(82)	31	(79)	33	(85)	0.22	0.45		
Heroin, benzos & cocaine	0	(0)	1	(3)	6	(15)	8	(21)	9	(23)			0.63	0.55

^ urine drug screens were randomly tested for cannabis, which caused information on use to be missing for some patients during each period.

[#] Three patients did not have any urine screens during induction.

There were very few pre-treatment characteristics significantly associated with heroin abstinence at month 12. Full results of this analysis are presented in Table 5.A1 in an appendix at the end of this paper. None of the patients who had a previous psychiatric admission were abstinent (p=0.02). Abstinence was not significantly associated with medication dose (p=0.88). All of the patients who were using cocaine during month 12 were also using heroin (p=0.02). Early reductions in heroin use, as evidenced by provision of at least one heroin negative sample during induction tended to be associated with reduced likelihood of heroin abstinence at month 12 (p=0.07). We repeated the analysis, with imputed positive heroin results for the 43 patients who had an unplanned discharge. This indicated that heroin abstinence was significantly associated with being in an intimate/sexual relationship with another heroin user (OR 3.4 [95%CI 1.1,10.0], p=0.02). No other baseline characteristic was significantly associated with abstinence in that analysis with imputed results.

Information on attrition during treatment is reported in Table 5.3. Overall, the estimated length of time to 25% leaving treatment in an unplanned manner was 120 (Standard Error 41) days. The table only presents results of the covariates where the Log Rank test indicated a p value of less than 0.2, although all covariates in Table 5.1 were explored. There was no significant difference between those commenced on Buprenorphine or methadone (log rank test 1.04, p=0.31). The Cox regression analysis indicated that patients who had no children, grew up in families with two parents, were in a intimate relationship with another heroin user and were abstinent from cocaine in pre-treatment drug screens demonstrated significantly lower rates of unplanned exit from treatment.

Of the 20 people commenced on buprenorphine who persisted with treatment for three months, six (30%) had switched to methadone at that point. Only one person (2%) had switched from methadone to buprenorphine by month three. Seven people who commenced buprenorphine remained in treatment for 12 months, by which time six has switched to methadone. Only two of the 32 commenced on methadone had switched to buprenorphine by month 12.

Table 5.3. Unplanned treatment exit among 120 heroin dependent adolescents during the first year on OST

	Univariate analysis[#]				Multivariate Cox Regression		
	Estimated 25% drop out Days	(SE)	Log rank statistic	P value	Odds ratio (OR)	(95% CI of OR)	P value
Overall	120	(41)					
Socio-demographic characteristics							
Sex							
Female	75	(9)					
Male	225	(55)	2.36	0.13			
Age							
Under 18 years	120	(45)					
Aged 18 years	62	(69)	0.14	0.70			
Early school leaver							
Left Education under age 15	75	(18)					
Left school after 15th birthday	197	(69)	1.83	0.18			
Family of origin							
Has two parents	270				1.0		
Single parent/other relative/adopted	75	(19)	8.56	0.003	3.5	(1.7,6.9)	0.001
Own children							
Has a child	72	(61)			5.3	(1.9,14.8)	0.001
No children	123	(40)	5.11	0.02	1.0		
History of being in social care							
Has been in care	75	(28)					
Never in social care	155	(41)	3.52	0.06			
Parental heroin use							
No heroin use by parents	186	(66)					
A parent has heroin problems	72	(52)	2.91	0.09			
Heroin use by partner							
Partner has used heroin	270	(89)			1.0		
No partner/No heroin use by partner	86	(19)	3.53	0.06	2.1	(1.1,4.3)	0.03
Accommodation in past month							
Homeless or hostel	69	(25)					
Stable accommodation	176	(54)	2.40	0.12			
Deliberate self harm (DSH)							
Has a history of DSH	75	(28)			1.8	(1.0,3.3)	0.07
No history of past DSH	176	(67)	2.21	0.14	1.0		
Pre-treatment Drug Use							
Lifetime Cocaine							
Use	103	(29)					
No use	176	(69)	2.99	0.08			
Past month non-prescribed methadone use							
Self reported Use	197	(29)					
No self reported use	73	(23)	3.42	0.07			
Cocaine							
Positive baseline urine drug screen	50	(15)			3.2	(1.4,7.4)	0.006
All baseline urine drug screens negative	176	(55)	3.97	<0.05	1.0		
Quantity of heroin use per day							
Using 3 ‘bags’ or more per day	69	(19)					
Using less than 3 ‘bags’ day	225	(40)	5.77	0.02			
Dose of OST at month three^							
On greater 50mgs methadone (or equivalent)	239	(24)					
On up to 50mgs methadone (or equivalent)	>365		2.90	0.09			

[#] Kaplan Meier Survival analysis. The model estimate of the number of days to unplanned discharge by 25% of patients with that characteristic is reported, for comparison.

^ includes the 72 people being prescribed OST after 90 days, with methadone equivalent dose for those on Suboxone being multiplied by 5 (i.e. if on 12mgs of Suboxone, assigned value of 60mgs in methadone equivalents)

5.6 Discussion

We found that half of the adolescents who persisted with OST demonstrated a sustained period of heroin abstinence throughout their twelfth month of treatment. Previous studies of OST in adolescent heroin dependence have largely ignored the issue of abstinence during treatment. In a slightly older cohort, Kellogg et al reported that patients who persisted with OST were heroin abstinent every other month on average, although urine drug screens were conducted inconsistently which increases the possibility that occasional use was not detected in that study.[10]

The rate of heroin abstinence in month twelve constituted a significant improvement compared to the third month of treatment. This is consistent with some other research in adolescents and also research on adult patients showing that longer treatment with OST builds incremental improvements in outcome.[7,10,26,27] In the NIDA clinical trial, Woody et al found a rapid return to heroin use once patients were tapered off their three months of buprenorphine treatment.[8]

Half of those who were heroin abstinent demonstrated some ongoing use of either cocaine or benzodiazepines. The rates of abstinence from drugs other than heroin did not increase significantly from pre-treatment levels. Studies of OST in adults suggest that they can achieve reductions in use of other drugs.[26,27] However, previous research on younger cohorts has also failed to demonstrate reductions in use of other drugs and the DARP study found some evidence of increased use of cannabis and alcohol at follow-up.[10,7]

In the exploratory analysis of baseline correlates of 12 month abstinence, there were few significant associations, mirroring the finding of others.[13] Those who had a previous psychiatric admission appeared less likely to be abstinent. Crome et al also reported better outcome in those without a psychiatric history.[28] However, Subramaniam et al found that greater baseline psychiatric problems was associated with better outcome in the NIDA clinical trial of buprenorphine.[9] Our previous research has indicated that there are improvements in mental health symptoms among the adolescents attending OST at this service.[23]

Our finding of increased abstinence, and better treatment retention, in those with a heroin using sexual partner was unexpected. The general view in addiction treatment is that increased social ties with other drug users brings poorer outcome.[29] In view of the large number of statistical tests conducted, and the decision not to alter the p value via a Bonferroni correction, this raises the possibility that the finding could constitute a type 1 statistical error. However, in a separate study examining outcome after inpatient detoxification of heroin dependent adults in Ireland, it also emerged that being in a relationship with another heroin user was associated with better outcome.[30] Although this finding is counter-intuitive it may warrant further exploration by other researchers.

We found that cocaine use during month 12 was associated with heroin use. The correlation between ongoing heroin use and cocaine use has been shown by others in both adolescents and adults.[10,31,32] We found no indication of a relationship between medication dose and heroin abstinence. There was no upper ceiling dose used in this service and our finding may indicate that dose was appropriately titrated against clinical need. There is research to indicate increased heroin use at lower doses in both adolescents and adults.[13,32] In contrast, Kellogg et al detected greater heroin use among those on higher methadone doses.[10]

The second main focus of this study was treatment retention. We found that 25% of patients had an unplanned treatment exit by 120 days. Retention rates were similar in DARP in the 1970s and in the more recent study by Kellogg et al.[7,10] Both of these studies examined methadone treatment. A number of studies report much higher rates of patient attrition and these have primarily examined buprenorphine treatment.[11-13] In contrast to Bell & Mutch, we found no significant difference between the two opioid agonist medications, although many patients did switch from buprenorphine to methadone during treatment.[11] One factor which complicates comparisons in retention rates across these studies relates to the variable criteria used to define ‘drop out’. In this study, patients who recommenced regular attendance after a period of up to four weeks non-attendance were viewed as still being in their index treatment episode. Other studies have viewed patients as having dropped out with much shorter periods of non-attendance.

We found that adolescents from families with two parents had better retention. Crome et al also found better outcome with increased family support.[28] Involvement of parents in both assessment and treatment was prioritised by the service. Efforts were made to include parents in the care plan. Family involvement in adolescent addiction treatment has been shown to improve outcomes. [33]

While cocaine use during treatment was associated with ongoing heroin use, cocaine use prior to treatment was associated with increases risk of drop out. This adverse association between cocaine use and poorer treatment adherence was also reported by Kellogg et al.[10] Adult studies have noted similar findings.[34,35]

The strengths of this study include the sample size which is quite large relative to other studies of OST in this age range. However, the sample size is still relatively small for statistical purposes and it is possible that some of the significant findings in the exploratory analyses constitute type 1 statistical errors. The treatment intervention was delivered at a single site making it easier for clinicians elsewhere to determine how applicable our findings may be to their own treatment setting. The monitoring of drug use by twice weekly supervised UDS constitutes a very thorough level of scrutiny and we can be reasonably confident that the patients whom we determined to be abstinent are truly abstinent. A limitation can arise from assessing change via urine screens. A patient could change from injecting heroin four times a day at treatment entry to smoking heroin just twice a week but urine screens would remain constantly positive in such a case indicating complete treatment failure in spite of the major harm reduction gains.

This study adds to the currently limited evidence for OST in adolescents who are heroin dependent. The positive outcomes appear broadly similar to those achieved in adults, among whom there is widespread acceptance of this treatment. There are concerns that it is underutilised internationally in adolescent populations for a range of reasons which include wariness by clinicians, political objections and many legislative obstacles.[1] Since DARP one of the lingering doubts about OST in adolescents relates to the limited success in achieving reductions in use of other drugs.[7] In spite of our efforts to address this use, we also found that levels of use of other substances remained stubbornly elevated. This does not negate the fact that the reductions in heroin use were substantial. Importantly,

abstinence increased significantly from month three to one year. It seems difficult to predict which patients are going to persist with this treatment and have better outcomes. However, use of cocaine, both prior to and during treatment, appears to be a negative prognostic factor. Overall, we echo the view of Woody et al that "clinicians should be in no hurry to stop an effective medication simply because the patient is young".[8]

5.7 Author Contributions

BPS conducted the analysis and lead on the drafting of the manuscript. KE & WC also contributed to the drafting of the manuscript. BPS, KE & WC were involved in interpretation of the data. BPS, KE & WC read and approved the final manuscript.

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Paper Appendix 5.1

Table 5.A1. Heroin abstinence during month 12 among 39 heroin dependent adolescents on opiate substitution treatment

	Total	**Heroin Abstinent during month 12**			
	N (%)	N (%)	OR	95% CI OR	P value
Number in Treatment	39 (100)	18 (46)			
Socio-demographic characteristics					
Female	25 (64)	13 (52)	2.0	(0.5,7.5)	0.33
Aged under 18.0 years	35 (90)	16 (46)	0.8	(0.1,6.7)	1.0^
Left school under 15 years	18 (47)	9 (50)	1.2	(0.3,4.4)	0.76
NEET	29 (76)	14 (48)	1.2	(0.3,5.2)	1.0^
Two parent family support	27 (71)	11 (40)	0.6	(0.1,2.4)	0.49
Has a child	0 (0)	N/a			
Has been in care	10 (27)	6 (60)	2.6	(0.6,11.3)	0.27^
Sibling Opiate Use	17 (45)	7 (41)	0.8	(0.2,2.8)	0.69
Parental Opiate Use	6 (16)	3 (50)	1.3	(0.2,7.4)	1.0^
Partner uses heroin	18 (47)	11 (61)	2.9	(0.8,10.9)	0.11
Homeless or hostel in past month	11 (28)	5 (46)	1.0	(0.2,3.9)	0.96
Previous criminal convictions	14 (38)	5 (36)	0.6	(0.2,2.4)	0.47
Ever incarcerated	8 (22)	2 (25)	0.4	(0.1,1.8)	0.24
Psychiatric History					
Ever seen a psychiatrist	22 (56)	9 (41)	0.6	(0.2,2.2)	0.46
Inpatient psychiatric admission	6 (15)	0 (0)			0.02^
Past DSH	12 (33)	4 (33)	0.4	(0.1,1.8)	0.24
Substance Use					
Lifetime Drug Use					
Non-prescribed benzodiazepines	36 (92)	17 (47)	1.8	(0.1,21.5)	1.0
Non-prescribed methadone	30 (77)	14 (47)	1.1	(0.3,5.1)	0.71
Cocaine	30 (83)	12 (40)	0.1	(0.01,1.3)	0.08
Injected	17 (44)	8 (47)	1.1	(0.3,3.8)	0.92
Commenced heroin under 15 years of age	20 (51)	10 (50)	1.4	(0.4,4.9)	0.62
Regular heroin use for more at least 12 months	26 (67)	11 (42)	0.6	(0.2,2.4)	0.50
Past Month Drug Use					
Non-prescribed benzodiazepines	26 (67)	12 (46)	1.0	(0.3,3.8)	1.0^
Non-prescribed methadone	27 (69)	13 (48)	1.3	(0.3,5.1)	0.71
Cocaine	10 (26)	4 (40)	0.8	(0.2,3.3)	1.0^
Cannabis	27 (80)	12 (44)	0.3	(0.1,1.9)	0.40^
Amphetamine	4 (13)	1 (25)	0.3	(0.03,3.1)	0.60^
Alcohol	17 (50)	6 (35)	0.4	(0.1,1.5)	0.17
Injecting	13 (33)	5 (38)	0.6	(0.2,2.4)	0.50
Using more than 3 ‘bags’ heroin per day	18 (51)	4 (44)	0.7	(0.2,2.7)	0.62
Pre-treatment urine drug screen (UDS)~ positives					
Benzodiazepines	26 (67)	14 (54)	2.6	(0.6,10.7)	0.17
Methadone	20 (51)	10 (50)	1.4	(0.4,4.9)	0.62
Cocaine	3 (8)	0 (0)			0.24
Cannabis	13 (41)	6 (46)	0.6	(0.2,2.6)	0.51
Treatment					
Suboxone Commenced	7 (18)	4 (57)	1.7	(0.3,8.9)	0.68
At least one opiate negative UDS during	14 (39)	4 (29)	0.3	(0.1,1.2)	0.07

induction					
Heroin abstinent throughout month 3	8 (21)	3 (38)	0.6	(0.1,3.2)	0.70
Heroin abstinent throughout month 6	12 (31)	8 (67)	3.4	(0.8,14.3)	0.09
Methadone dose at month 12 >50mgs [#]	20 (51)	9 (45)	0.9	(0.3,3.2)	0.88
UDS at month 12 indicate Benzodiazepine use	24 62)	9 (38)	0.4	(0.1,1.5)	0.17
UDS at month 12 indicate cocaine use	6 (15)	0 (0)			0.02^
UDS at month 12 indicate cannabis use	22 (58)	10 (46)	0.8	(0.2,3.0)	0.78

^ P value calculated using Fishers Exact Test Statistic as estimated value in cell was less than 5

[#] For those patients on buprenorphine, dose is multiplied by 5 to approximate to equivalent methadone dose

~ UDS = Urine drug screens, which were conducted twice weekly on average.

Chapter 6

Changes in psychological wellbeing among heroin dependent adolescents during psychologically supported opiate substitution treatment

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Citation reference:
Smyth BP, Ducray K, & Cullen W. Changes in psychological well-being among heroin-dependent adolescents during psychologically supported opiate substitution treatment. *Early Intervention in Psychiatry*, 2016 Jan 23, doi:10.1111/eip.12318 [Epub ahead of print]
Journal ISSN: 1751-7893 (Electronic)
Journal Url: *http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1751-7893*

6.1 Context of this chapter within overall Thesis

Having presented findings on changes in use of heroin and other drugs during OST in Chapter 5, this study examines another important outcome for this same patient group. Although mental health problems are known to be very prevalent among heroin dependent adolescents, previous international studies have failed to examine the impact of OST on such problems. This study sought to address that gap in the literature.

6.2 Abstract

Aim: Heroin dependent adolescents demonstrate high rates of comorbid psychological problems. Among heroin dependent adults, opiate substitution treatment (OST) programs appear to reduce mental health problems. We sought to examine the impact of OST on psychological wellbeing in adolescents, as this is unknown.

Methods: We conducted a prospective study examining psychological wellbeing in heroin dependent adolescents, aged 18 years or younger, engaged in outpatient psychologically supported OST. Patients were treated with either methadone or buprenorphine. This was complimented with individual key working and counselling (Motivational interviewing and CBT) and group work focusing on life skills. The Becks Youth Inventory was used to measure psychological well-being at treatment entry and repeated after four months of treatment.

Results: Among 55 consecutive treatment episodes, we examined the 32 episodes where the patient persisted with the OST program. Polysubstance use was the norm at treatment entry. At follow-up, the median doses of methadone and buprenorphine were 50mgs and 8mgs respectively. Only three patients were treated with antidepressant medication. There was significant improvement in the mean depression (65.0 to 57.9, p=0.001), anxiety (61.7 to 57.0, p=0.006) and anger (57.8 to 54.6, p=0.009) subscale scores. The self concept and disruptive behaviour subscale scores did not improve significantly.

Conclusion: In this relatively short-term follow up, psychosocially assisted OST appears to be associated with improved psychological wellbeing in heroin dependent adolescents, especially in the area of depressive and anxiety symptoms.

6.3 Introduction

Substance use disorders (SUDs) and mental health problems co-occur with great frequency, especially amongst adolescents.[1] 'Common factor' genesis, 'primary versus secondary causality', 'bidirectional' models and neurobiological alterations have been proposed to explain this comorbidity in adolescents.[2-4]

When contrasted with other drugs, opiate dependence is typically associated with poorer outcomes in all domains.[5] Heroin dependent adolescents experience greater baseline problems and psychological distress than adolescents with other SUDs, with depression being particularly evident.[6-7] Darke proposes that self medication of psychological problems plays a prominent role in the development and maintenance of heroin dependence.[5]

Albeit divisive, opiate substitution treatment (OST) has been thoroughly evaluated as a treatment modality.[8-9] There is considerable evidence in adults that OST has a significant effect in reducing all cause mortality, illicit opioid use, viral transmission, drug overdoses, criminality, other risk behaviours as well as increasing treatment retention.[9-11] Most studies with heroin dependent adults have shown that both psycho- social functioning and mental health improves following commencement of OST.[12-13] However, an examination of the impact of methadone maintenance treatment (MMT) in adults in Ireland failed to demonstrate any improvement in psychological wellbeing one year after treatment entry.[14]

When compared with adult-specific treatments, far less is known about the nature and extent of effective treatments for drug-abusing youth, [15] especially those with heroin use disorders.[16] Although there are a small number of studies suggesting the general efficacy of OST in adolescent populations,[17-18] further research on adolescent OST is considered an imperative.[19-20] While OST yields improvements in psychological wellbeing in adults, it cannot be assumed that it will do so in adolescents. There are examples in other areas of mental health where treatment effectiveness does not translate into adolescent populations.[21]

We are only aware of one study which has sought to systematically examine the impact of OST on psychological wellbeing in adolescents.[22] Moore et al looked at changes in mental health symptoms, using the Youth Self-Report (YSR) scale, over a 4-week period during a RCT comparing opioid detoxification treatments. [22] They found significant improvements in internalising symptoms overall, but there was no significant improvement in the anxiety or withdrawn YSR subscales. While the change in externalising symptoms approached significance, there was no significant improvement in aggression and rule-breaking.

Given the above context, this study seeks to address the knowledge gap on the impact of psycho- socially supported OST on measures of psychological wellbeing among heroin dependent adolescents. We hypothesised that psychological wellbeing would improve following exposure to this intervention.

6.4 Method

6.4.1 Study Design

We conducted a pragmatic prospective analysis of psychological well-being among heroin dependent adolescents during outpatient OST treatment in Dublin, using a pre- and post intervention methodology. We utilised the Beck Youth Inventories, 2nd edition [BYI-II] to assess psychological symptoms and impairment.[23] Baseline pre- treatment BYI-II scores obtained at intake (T0 scores) were compared with the first set of analogous of BYI- II scores obtained following commencement of treatment (T1 scores). These T1 scores were measured as a routine component of the first structured multi- disciplinary treatment plan review which occurred after four months of OST. This review was a collaborative treatment response appraisal process conducted with the patient, held approximately every four months throughout the course of treatment. The study was approved by the Research Ethics Committee of the National Drug Treatment Centre (NDTC).

6.4.2 Settings

6.4.2.1 HSE National Drug Treatment Centre -Young Persons Programme.

In 2000, due to the large number of heroin dependent adolescents presenting to treatment services in Dublin, and the growing recognition that their treatment needs differed to those of the adult population, [24] the Young Persons Program (YPP) was established at the NDTC, catering to the needs of young people aged 14 to 20 years. The team was led by a consultant child & adolescent psychiatrist and had input from a trainee psychiatrist, nursing, clinical psychology, social work, project workers, counsellors and family therapy. The staff to patient ratio was over double that which existed in the adult MMT programs in NDTC, with prompt and intensive treatment intervention being a core objective. [2] A decline in the incidence of adolescent heroin use disorders since 2000 resulted in a progressive fall in the numbers entering treatment over subsequent years.

The main pillars of treatment involved opiate substitution medication (methadone or buprenorphine), counselling (CBT, motivational interviewing or humanistic person centred therapy) and in some cases, family therapy. On each visit to the YPP, the patient met their

individual case manager. While patients were expected to attend counselling sessions on a weekly basis, failure to do so did not result in termination of treatment. There were group activities during afternoons, using art therapy and delivery of life-skills. Attendance at groups was encouraged but not compulsory. Participation rates at groups were typically 40 to 60%. Greater detail on the treatment model is provided in Smyth et al.[17]

6.4.2.2 Youth Drug and Alcohol Service (YoDA).

YoDA is an adolescent drug and alcohol treatment service of the HSE in South West Dublin. The multi-disciplinary team was developed with the aim of providing treatment for under-18's with a range of alcohol or other substance use disorders. There were a small number of patients availing of OST in that service and the approach to treatment was very similar to that in the YPP, both clinical services being led by the same consultant psychiatrist.

6.4.2.3 Features of treatment at YPP and YoDA

Whilst it was not possible to individually quantify the 'dose' of the psycho- social treatment received be each individual patient over the full period of treatment, all were offered a full spectrum of psycho- social supports including key working, CBT based interventions, social work resources, counselling and regular psychiatric reviews. Information on clinical contacts during the month before the follow-up assessment was recorded for each treatment episode included the study. Structured and psychologically informed treatment plans, encompassing a range of areas considered active ingredients of treatment,[25] were regularly reviewed during weekly multi- disciplinary team meetings, as well as by formal treatment plan reviews every four months.

The two OST options utilised at the YPP and YoDA were methadone (1mg/ml) and buprenorphine. The buprenorphine formulation used initially was the sublingual mono buprenorphine tablets (Subutex®, Reckitt Benckiser Healthcare [UK] Ltd). In 2007, we switched to use of the buprenorphine-naloxone combined preparation Suboxone® (Reckitt Benckiser Healthcare [UK] Ltd). Induction onto a stabilisation dose of methadone typically

takes two to three weeks. Buprenorphine dose induction is faster, taking two to five days in most cases. Daily attendance at the treatment service was required in the first few weeks of treatment. Patients could earn take-away doses of medication as they achieved stability in their drug use and general lifestyle. [17] Urine drug screens were conducted prior to treatment entry and then occurred twice weekly during the course of treatment.

6.4.3 Participants

All heroin dependent patients commencing OST at either treatment site between May 2006 and December 2013 were eligible for inclusion. It was in 2006 that we began to incorporate the BYI-II into both routine assessment and review. As this instrument is only valid for people aged 18 and under, we excluded the small number of patients who were aged 19 years. Only those patients who persisted with outpatient treatment until their first structured treatment plan review were included. Patients who embarked upon a brief detoxification based treatment were also excluded. No efforts were made to follow-up patients who had had a prior planned or unplanned exit from treatment. Individual patients who had more than one treatment episode during the study period were eligible for entry into the study a second time.

6.4.4 Measures

The outcome measure used was the BYI-II.[23] This is a self-report instrument of 100 items providing five scales to assess the adolescent's self-concept and experience of symptoms of depression, anxiety, anger and disruptive behaviour. Raw scores are converted into a T score indicating the level of problem severity and impairment for that psychological domain relative to an age and gender matched general population sample. Accordingly, T scores may be viewed either as a point on a severity continuum, or in a categorical manner. The categories are not diagnostic of psychiatric disorder. For the purposes of this study, a T-score on the self concept subscale of 44 or less was categorised as 'abnormal' and a T-score of 55 or higher on each of the other subscales was deemed 'abnormal'.

We examined drug use at baseline via the Maudsley Addiction profile and obtained other socio-demographic and clinical characteristics via a structured clinical interview. [26] We report the results of the urine drug screen obtained at the initial pre-treatment assessment and also at the time of completion of the follow-up BYI-II.

6.4.5 Statistical Analysis

When contrasting those who completed the follow-up BYI-II with those who did not, we utilised the Pearson Chi-square test or Fishers Exact test for categorical variables. We used the T-test or Mann-Whitney U test for quantitative variables, dependent upon normality of data distribution.

To test our hypothesis that psycho- socially assisted OST impacted positively on BYI-II measures of psychological wellbeing, we examined this from the complimentary perspectives of 1) changes in subscale T- scores and 2) changes in numbers of patients whose T- scores characterized them in a binary fashion as being in the 'normal' or 'abnormal' range.

Our previous use of the BYI and examination of other research papers using this instrument suggested that subscale scores were likely to be normally distributed. We therefore planned to conduct a paired sample t-test to examine change in subscale scores. We also computed the effect size (Cohen's d) as determined by a calculation of the standardised mean difference of the pre and post treatment groups, using their respective means and standard deviations. McNemar's paired proportions test with continuity correction was employed to determine whether OST was associated with changes in the binary category of subscale measures. We determined that for an effect size of 0.5, where alpha is 0.05 and power is 0.8, a sample size of 34 pairs was required in this study.

6.5. Results

6.5.1 Participants and treatment

In view of the declining numbers of patients presenting with heroin dependence we closed entry into this study in 2013, prior to reaching the optimal number of 34 participants. Figure 6.1 represents a flow diagram of the participants from assessment of eligibility to completion of the BYI-II follow- up. Among the 55 eligible episodes of OST where the baseline BYI was obtained, treatment non-adherence accounted for the vast majority of non-completion of the follow-up BYI-II. The socio-demographic and clinical characteristics of the 32 included treatment episodes are to be found in tables 6.1 and 6.2. These treatment episodes were undertaken by 29 individual patients, three patients completing a second treatment episode. Twenty-eight of the included treatment episodes occurred in the YPP and four in YoDA.

Figure 6.1. Overview of episodes of treated heroin dependence in adolescents – eligibility & participation

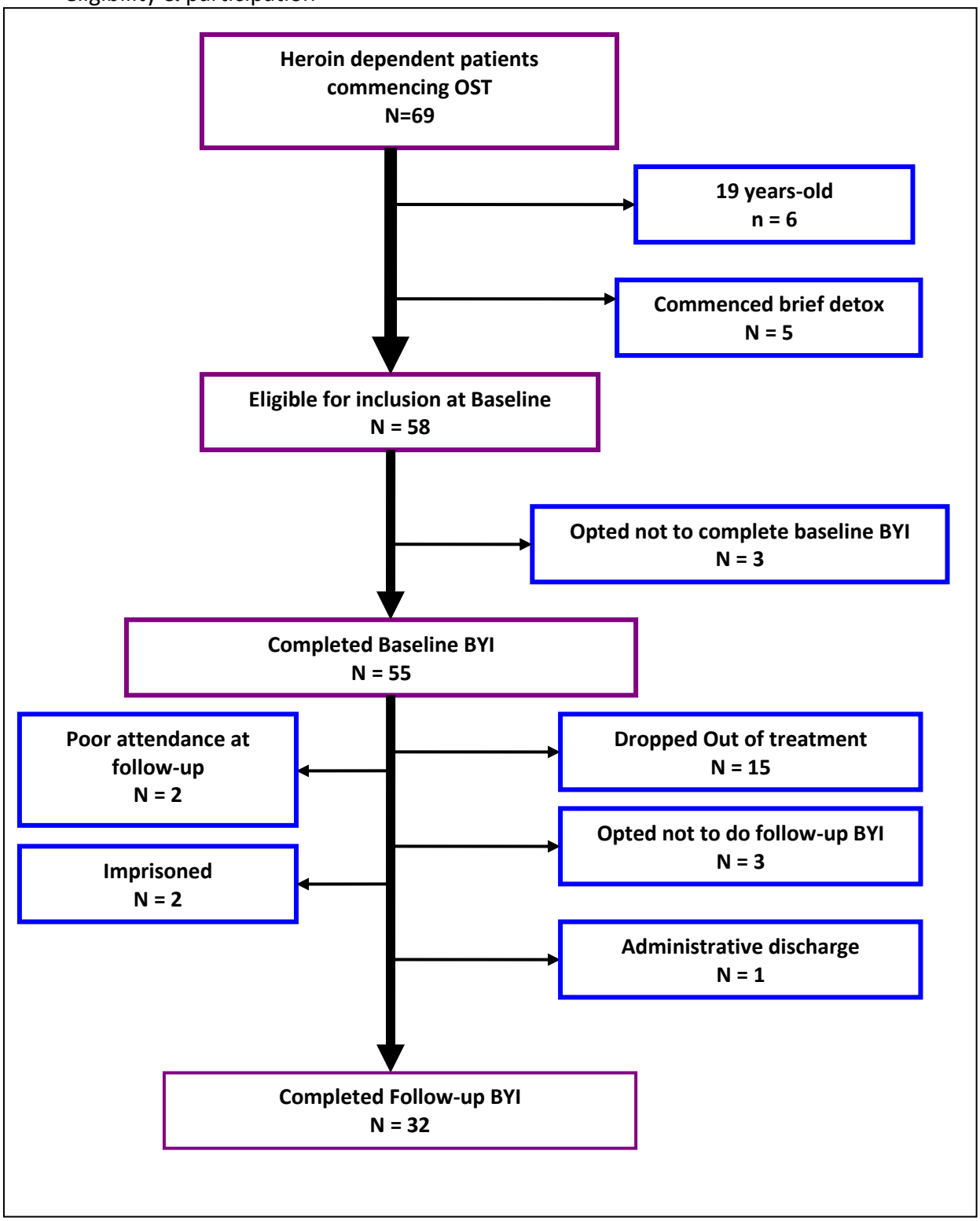

Table 6.1. Baseline characteristics of 55 episodes of OST for heroin dependence in teenagers, comparing those who completed a follow-up BYI with those who did not.

Characteristic	Total Eligible Group		Study Participants Completed follow-up BYI		Did not complete 2nd BYI	
	Number	(%)	Number	(%)	Number	(%)
Total group	55	(100)	32	(100)	23	(100)
Male gender	31	(56)	18	(56)	13	(56)
Accommodation						
Currently living with a parent	35	(64)	22	(69)	13	(56)
Currently Homeless	12	(22)	5	(16)	7	(30)
Ever Homeless	15	(27)	5	(16)	10	(43)
Education & Work						
Currently in School	7	(13)	5	(16)	2	(9)
Working	5	(9)	3	(9)	2	(9)
Family Characteristics						
Parental Support in Family Home						
Two parents	23	(42)	13	(41)	10	(43)
Lone Parent	27	(49)	17	(53)	10	(43)
No contact with parents	5	(9)	2	(6)	3	(13)
Family substance use problems						
Parental Alcohol problems [e]	28	(56)	16	(50)	12	(63)
Parental heroin problems [a]	18	(33)	8	(25)	10	(45)
Sibling heroin problems	13	(25)	7	(22)	6	(30)
History of being in care [c]	21	(40)	10	(32)	11	(52)
Relationships						
Has a current sexual partner	24	(44)	14	(44)	10	(43)
Current sexual partner uses heroin	19	(35)	13	(41)	6	(26)
Criminal Behaviour						
Past Convictions [d]	17	(33)	8	(26)	9	(43)
Past Incarceration [b]	14	(26)	5	(16)	9	(43)
Psychiatric History						
Past psychiatric contact for non-SUD reasons [a]	30	(56)	15	(47)	15	(68)
Ever prescribed psychotropic medications [c]	23	(44)	11	(34)	12	(60)
Past inpatient psychiatric treatment [a]	5	(9)	2	(6)	3	(14)
History of deliberate self harm [c]	24	(46)	13	(43)	11	(50)
Substance Use Characteristics						
Route of heroin Use						
Currently smoking ('chasing') only	46	(84)	25	(78)	21	(91)
Currently Injecting	9	(16)	7	(22)	2	(9)

Ever previously Injected [a]	20	(37)	13	(41)	7	(32)
Lifetime Substance use						
Benzodiazepines	47	(85)	27	(84)	20	(87)
Black Market Methadone	32	(58)	15	(47)	17	(74)
Cocaine [a]	34	(63)	20	(65)	14	(61)
Past Month Use of Substances other than heroin						
No secondary illicit drug use	4	(7)	3	(9)	1	(4)
Methadone [a]	27	(50)	12	(39)	15	(65)
Benzodiazepine	39	(71)	24	(75)	15	(65)
Alcohol [b]	26	(49)	16	(52)	10	(45)
Cannabis	35	(64)	23	(72)	12	(52)
Cocaine	20	(36)	9	(28)	11	(48)
Ecstasy/Amphetamines	4	(7)	2	(6)	2	(9)
Drugs detected in Baseline Urine Screen [b]						
Opiates	52	(98)	31	(97)	21	(100)
Methadone	23	(44)	7	(23)	16	(76)
Benzodiazepine	24	(55)	17	(53)	12	(57)
Cannabis [c]	28	(54)	16	(50)	12	(60)
Cocaine	7	(13)	0	(0)	7	(33)
Amphetamines	0	(0)	0	(0)	0	(0)
Opiate Only	7	(14)	6	(20)	1	(5)
Drugs detected in Urine Screen at follow-up BYI [f]						
Opiates			9	(28)		
Benzodiazepine			9	(28)		
Cocaine			1	(3)		
Abstinent for opiates, benzodiazepines & cocaine			18	(56)		

[a] Data missing in one case. [b] Data missing in two cases. [c] Data missing in three cases. [d] Data missing in four cases. [e] Data missing in five cases. [f] Cannabis and amphetamines are not routinely screened during the course of treatment.

Table 6.2. Characteristics of 55 episodes of OST for heroin dependence in teenagers, comparing those who completed a follow-up BYI with those who did not - quantitative variables.

Characteristic	**Total Eligible Group**		**Completed follow-up BYI**		**Did not do 2nd BYI**	
		(SD)/(IQR) [a]		(SD)/(IQR)		(SD)/(IQR)
Age (mean)	17.5	(0.7)	17.5	(0.8)	17.6	(0.6)
Age of school leaving (mean)	14.7	(1.8)	14.9	(1.7)	14.4	(1.9)
Age first illicit drug use (Mean)	12.6	(1.8)	12.8	(1.8)	12.3	(1.8)
Age first heroin use (mean)	15.1	(1.3)	15.0	(1.3)	15.3	(1.3)
Days of heroin use in past month (median)	30	(30-30)	30	(25-30)	30	(30-30)
Months of regular heroin use (median) [b]	12	(8-24)	12	(7-18)	18	(10-24)
Number 'bags' of heroin per day (median)	3	(2-4)	2.5	(2-3.5)	3.5	(2.5-5)
Baseline BYI Subscale T Scores						
Self Concept	36.6	(9.5)	36.4	(10.9)	36.9	(10.7)
Anxiety	61.7	(12.2)	61.7	(11.9)	61.8	(12.8)
Depression	65.2	(11.8)	65.0	(10.3)	65.6	(13.9)
Anger	59.5	(10.6)	57.8	(9.2)	61.7	(12.1)
Disruptive Behaviour	63.7	(10.9)	62.6	(9.6)	65.3	(12.5)

[a] IQR = Interquartile range
[b] Data missing in two cases

Those who did not complete the follow-up BYI were more likely to have experienced homelessness (p=0.02) and imprisonment (p=0.03). They were more likely to be misusing methadone (p<0.001), cocaine (p=0.001) and larger quantities of heroin (p=0.04) at baseline. There were no significant differences in baseline BYI subscale scores between those who persisted with OST and those who did not complete the follow-up assessment.

Among the included 32 treatment episodes, polysubstance use was the norm at treatment entry with benzodiazepines, cannabis, alcohol and methadone being the most commonly misused substances in addition to heroin. Their age ranged from 15 to 18 years. Almost half the participants had previous contact with psychiatric services for non-addiction reasons, one third had been prescribed psychotropic medication in the past and 43% had a history of deliberate self harm.

Buprenorphine was the predominant OST for 10 patients; 21 were treated principally with methadone, and one patient spent roughly equal periods on each of these medicines. At follow-up the median methadone dose was 50mgs (interquartile range [IQR] 40 - 60mgs) and the median buprenorphine dose was 8mgs (IQR 6 - 8mgs). Only three patients received prescribed antidepressants over the course of this study and other psychotropic medications were not prescribed. Table 6.3 outlines the number of formal clinical inputs availed of by patients during the included treatment episodes. At follow-up, a minority of patients were abusing other substances (see Table 6.1).

Table 6.3. Participation by patients in sessions with multidisciplinary team during month before follow-up

		Any Input		Number of clinical contacts [a]	
		N	(%)	Median	(IQR)
Psychologist or Counsellor					
	Brief Sessions [b]	22	(69%)	2	(0-2)
	Therapy Session	25	(78%)	3	(1-4)
	Any Session	27	(84%)	4	(3-6)
Project Worker					
	Brief Contact [b]	23	(72%)	1.5	(0-4)
	Review Meeting	21	(66%)	1	(0-4)
	Any Meeting	28	(88%)	4	(2-7)
Nursing Review		22	(69%)	1.5	(0-4)
Medical/Psychiatric Review		26	(81%)	2.5	(1-6)

[a] 13 (41%) had at least one meeting with the social worker. Six (19%) participated in family therapy.
[b] Brief sessions or contacts were 15-29 minutes. Therapy sessions and Review meetings were over 30 minutes

6.5.2 Changes in psychological well-being

Table 6.4 shows statistically significant improvement in the mean score on the anxiety, depression and anger subscales of the BYI over the course of OST, with effect sizes in the 0.4 to 0.6 range. While subscale scores for self-concept and disruptive behaviours each improved, these changes were not statistically significant. When examining changes in pathological category during treatment, we found significant improvement in the domains of depression and anxiety, with about one third of patients with a baseline abnormal score moving into the normal range at follow-up (see Table 6.5).

Table 6.4. Changes in psychological wellbeing among 32 episodes of OST for heroin dependence in teenagers.

	Baseline			Follow-Up			Effect	P value
	Median	Mean	(SD)	Median	Mean	(SD)	Size	
BYI Subscale scores								
Self Concept	35.5	36.4	(8.7)	37.5	37.5	(10.1)	0.12	0.43
Anxiety	62	61.7	(11.9)	57	57.0	(11.9)	0.39	0.006
Depression	65	65.0	(10.3)	59	57.9	(11.8)	0.64	0.001
Anger	58.5	57.8	(9.2)	54.5	54.6	(9.5)	0.35	0.009
Disruptive Behaviour	62	62.6	(9.6)	62	59.7	(10.5)	0.29	0.12

Table 6.5. Changes in pathological categories of psychological well-being during 32 episodes of OST for heroin dependence in teenagers.

BYI Subscale		Follow-up Normal (% changing)	Follow-up Abnormal (% changing)	P value [a]
Self Concept				
	Baseline Normal	3	4 (57)	
	Baseline Abnormal	3 (12)	22	1.0
Anxiety				
	Baseline Normal	6	0 (0)	
	Baseline Abnormal	9 (35)	17	0.007
Depression				
	Baseline Normal	3	0 (0)	
	Baseline Abnormal	8 (28)	21	0.01
Anger				
	Baseline Normal	10	2 (17)	
	Baseline Abnormal	6 (30)	14	0.33
Disruptive Behaviour				
	Baseline Normal	5	2 (29)	
	Baseline Abnormal	4 (19)	21	0.68

[a] McNemar's paired proportions test

The domain which demonstrated greatest change in mean score was depression. We opted to conduct an exploratory post-hoc analysis to examine the association between improvement in BYI Depression score and ongoing heroin use at follow-up. A linear regression analysis which included baseline BYI depression score in the model, supported the existence of such an association with greater improvement evident in those who were heroin abstinent (B=7.8 [95% confidence interval 0.8-14.8], p=0.03). The adjusted R^2 for the model was 0.25.

6.6 Discussion

Our findings were consistent with the hypothesis that psychosocially supported OST has a positive impact on psychological health in adolescents, especially in the domains of anxiety and depressive symptoms. This is consistent with findings in the scientific literature for OST in adults.[12-13] Our results also support and add to the very limited research which has been conducted in adolescent OST programs.[22] The study by Moore examined outcome during a brief four week detoxification treatment, as opposed to the four month period of substitution treatment examined in this study.[22]

Our participants appear comparable with other populations of treated heroin dependent adolescents internationally, with evidence of substantial social adversity, poor educational attainment, family problems, criminality and mental health difficulties.[19,27-29] OST was a key component of the treatment provided. The average doses of methadone and buprenorphine used in our patient group are slightly lower than the advised effective maintenance doses in adults.[30] Adolescents present with shorter histories of heroin use resulting in less tolerance to opioids than that seen in adults. Therefore, these lower doses seem appropriate. The substitution dose was determined in a collaborative manner, consistent with British guidelines, [31] involving doctor and patient and based upon assessment of issues such as ongoing heroin use, withdrawal symptoms and cravings.

Other research groups have noted that depression is particularly prevalent in adolescents with opioid use disorders.[29, 32] One third of our patients with elevated depression or anxiety scores normalised over the first few months of OST. Low mood is a common precursor to

episodes of heroin use among treated patients.[33] Therefore, there is a possible reciprocal relationship between reductions in internalising symptoms and reducing drug use.[15, 34] This possibility obtained some support from our finding of a greater reduction in depressive symptoms being evident in those who ceased heroin use.

Despite the fact that the majority of patients had abnormal depression scores at baseline, we utilised antidepressant medication in only 10% of cases. The two clinical services examined in this study have generally sought to minimise use of psychotropic medication. This clinical position is informed by both the widespread misuse of such medication among adolescents with SUD in Dublin,[35] the evidence base indicating reduced efficacy of antidepressant medication in adolescents in general [36] and the evidence indicating limited efficacy of such medication in depression in adults on OST.[37] It is possible that we were excessively conservative in prescribing of medication and that outcomes may have been enhanced by greater use of psychotropic medication.

Although anger problems escalated in a small number of cases, the mean subscale score on anger decreased significantly. While Moore et al did not find a significant improvement in aggression symptoms in their brief detoxification study,[22] treatment of general adolescent addiction has been shown to generate improvements in measures of hostility.[38]

While the mean self-concept scores increased, this did not approach the level of statistical significance. Self-concept and self-esteem appear less malleable than mood states such as anxiety and depression and it is therefore not surprising that we failed to demonstrate significant changes over the relatively short time-frame examined in this study.[39,40] Hser et al have demonstrated significant improvements in self esteem among adolescents one year after treatment of less complex SUDs.[38]

Limitations to this study include the small sample size and recruitment within a single city. As this service related research was borne out of a 'scientist- practitioner' attempt to measure the outcomes of routine clinical practice covering many years, it was not possible to fully measure many potential confounders such as treatment adherence, new major life events and all ongoing drug use. These limitations appear to be a ubiquitous feature of studies examining this population.[6,22,41] The multiple, complex and fluctuating needs of

these patients may contribute to the striking lack of outcome studies in this important clinical group.[20] There was no control group, so we cannot determine that the treatment program is better than no treatment. The detected improvement in symptoms could constitute a simple regression to the mean. The findings of the linear regression analysis are best viewed as tentative in view of the small sample and its post hoc origins.

Our findings suggest that psycho-socially supported OST is associated with an improvement in mental health among heroin dependent adolescents who persist with this treatment. This improvement is most evident in the areas of depressive and anxiety symptoms. Larger multi-centre studies will be required to identify active ingredients within this complex intervention.

6.7 Author Contributions

BPS conceived the study question and examined the background literature. BPS lead on the statistical analysis with input from KD. BPS, KD & WC were each involved in interpretation of the data. BPS lead on the drafting of the manuscript. KD & WC also contributed to the drafting of the manuscript. BPS, KD & WC read and approved the final manuscript.

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Chapter 7

"So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban.

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Citation reference:
Smyth BP, James P, Cullen W, Darker C. "So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban. *International Journal of Drugs Policy* 2015:26; 887–889.
doi:10.1016/j.drugpo.2015.05.021
Journal ISSN: 0955-3959
Journal Url: https://www.journals.elsevier.com/international-journal-of-drug-policy/

7.1 Context of this chapter within overall Thesis

This is the first chapter to report a study examining the legislative changes targeting headshops. It returns to YoDA, the treatment setting from which patients in the study of cannabis and alcohol treatment were recruited in Chapter 4. It examines changes in the patterns on NPS use prior to and after the closure of the head shops. It utilises the ASSIST questionnaire to examine NPS use, this being the key instrument used to measure drug use in Chapter 4. It seeks to identify the attributes of NPS users compared to the other adolescent treatment attenders. Given the concern that closure of the head shops required ongoing users of NPS to migrate to the black market, and this caused speculation that their

problems could become even greater, this study allowed comparison of pattern and problems associated with NPS use during both time periods.

7.2 Abstract

Background: Legislative changes targeting novel psychoactive substance (NPS) use were introduced in Ireland over the summer of 2010 and resulted in closure of 90% of headshops. We sought to examine use of NPS among adolescents attending addiction treatment both before and after this legislation.

Method: We included all adolescents entering assessment at one outpatient service comparing the six months immediately prior to the legislation in May 2010 to the same six-month period the following year. Clinicians identified problematic use of between one and four substances for each patient. Secondly, information was recorded on recent (past three months) use of NPS.

Results: There were 94 treatment episodes included, with mean age of 16.8 years. Problematic use of any NPS fell from 14 patients (34%) in the pre-legislation period to zero ($p<0.001$). There was also a significant decline in recent use of any NPS (82% vs 28%, $p<0.001$). Recent use of cocaine and amphetamines also declined, but problematic use of these drugs was unchanged.

Conclusion: Use of NPS among adolescents attending drug and alcohol treatment was substantially reduced six to twelve months after the introduction of legislation prohibiting sale of NPS and resultant closure of most headshops.

7.3 Introduction

Novel psychoactive substances (NPS) have become a source of international concern in recent years (UNODC, 2013; SAMSHA, 2012). While 'new' drugs come into use across societies every decade, such as the emergence of Ecstasy in the 1990s, the large number of new substances to gain a firm foothold in the drugs marketplace in recent years has been without precedent (UNODC, 2013; Munro & Wilkins, 2014). Like Ecstasy, many of these substances have been known for decades but it is only in recent years that their use has become widespread (Maxwell, 2014: UNODC, 2013; Munro & Wilkins, 2014).

While NPS are very heterogeneous, they can be broadly grouped by route of use. Firstly, there are the powdered stimulant drugs which typically are snorted, many of which are members of the cathinone family (Baumann, 2014). The most widely used member of this group is mephadrone (Kavanagh, 2014; Winstock, 2011). The next category of NPS are the synthetic cannabinoids which are smoked (SAMSHA, 2012; EMCDDA, 2009). Thirdly there are a range of tablets or pills with amphetamine and MDMA type effects, many of which are piperazines (Sheridan et al, 2007).

The marketplace for these drugs has also been novel and has posed many challenges for legislators across the world (Munro & Wilkins, 2014). As most of these NPS were not scheduled in relevant drugs legislation as being illegal, they have been sold commercially in a very open manner in many locations, and often being referred to as 'legal highs' (European Commission, 2011). In some countries the internet represents a major supply source for these drugs (Dargan et al, 2011; Deluca et al, 2012). In other countries, such as Ireland, specialist shops, known as 'headshops', opened up in towns and cities to cater for the increased demand for these substances (European Commission, 2011; Kelliher et al, 2011).

In a European survey of young adults in 2011, it emerged that the prevalence of lifetime use of these drugs was 5% across Europe, but peaked at 16% in Ireland (European Commission, 2011). Over the period from 2009 to 2010, there was a massive increase in the number of headshops in Ireland peaking at 102 premises in May 2010, which is about 1 shop per 45,000 people (Kelleher et al, 2011; Kavanagh & Power, 2014). There were increasing media reports of criminal, medical and mental health problems being associated with the

increased use of these NPS nationally and internationally (Kavanagh & Power, 2014). There were also reports in scientific papers about the harms associated with these drugs (El-Higaya, Ahmed & Hallahan, 2011; Winstock et al, 2011; Every-Palmer, 2010). There was intense public and political debate about how Ireland should respond to the challenge posed by the surge in use of NPS (Ryall & Butler, 2011).

Ultimately, the Irish government opted to proceed with a two-pronged legislative approach. Firstly, there was a legislative ban, adding over 100 substances to the Misuse of Drugs Act in May 2010 (Irish Statute Book, 2010a). This made possession, sale and supply of the named drugs a criminal offence. Then in August 2010, the Criminal Justice (Psychoactive Substances) Act was introduced (Irish Statute Book, 2010b). This Act was focused primarily at vendors of NPS. It states that 'a person who sells a psychoactive substance knowing or being reckless as to whether that substance is being acquired or supplied for human consumption shall be guilty of an offence'. These two acts resulted in a dramatic decline in the number of headshops, initially to 48 shops in June 2010, and then falling to 7 shops in 2011 (Kavanagh & Power, 2014).

Much of the international literature discussing NPS points to the potential futility of simply banning all of these drugs (Meacher, 2013). A review conducted in Ireland suggested that the ban had been excessive and driven by "a moral panic" (Ryall & Butler, 2011). It is argued that new drugs, which are not named in legislation, will quickly emerge to replace any banned substances (Hammersly, 2010; Dargan et al, 2011). There is evidence that this did indeed occur in Ireland over the summer of 2010 (Kavanagh & Power, 2014). It is also argued that a ban will simply move the drugs from their quasi-legal but unregulated status to enter the criminal drug supply networks (Winstock, Mitcheson & Marsden, 2010). For these reasons, there have been increasing calls to explore regulation of this marketplace (Hughes & Winstock 2012). New Zealand has taken significant steps in this direction with the enactment of the Psychoactive Substances Act 2013 in July 2013 (Munro & Wilkins, 2014).

In countries which have implemented a ban, there is some evidence for an impact on reducing NPS use. There was a reduction in attendances linked to mephadrone use at emergency departments in the UK following their legislative ban (Wood, Greene, Dargan,

2013). Stogner et al (2013) reported a decline in use by young adults of Salvia divinorum following a legislative ban in Florida. An examination of phone calls to poison centres also indicated a dramatic fall in calls related to cathinones following the legislative ban in the USA (Loeffler & Craig, 2013). In New Zealand, use of BZP in a general population sample declined substantially following a ban of that drug (Wilkins & Sweetsur, 2013). The UNODC (2013) has argued that the overall range of legislative bans of mephadrone have been effective in reducing use and associated harms.

Despite claims regarding the success of legislative bans, surveys of drug users report ongoing easy access to NPS and suggest that legislative bans had been ineffective at curtailing their use of these drugs (McElrath & O'Neill, 2011; Measham et al, 2011). A British study of club-goers indicated increased use of mephadrone in the year after the ban (Wood, Measham & Dargan, 2012). There have been no reports of the impact of the ban on populations attending addiction treatment or in adolescent populations.

We decided that the legislative changes made in Ireland in 2010 represented an opportunity to conduct a natural experiment, to examine the ban's impact on substance use among adolescents attending a specialist drug and alcohol treatment service. We hypothesised that (1) use of NPS would fall in this population after the legislative ban, (2) use of other substances would increase after the ban and (3) adolescents using NPS in the post-ban period would exhibit more problematic use of same. We also sought to identify patient characteristics associated with NPS use.

7.4 Method

7.4.1 Setting

The Youth Drug & Alcohol (YoDA) service is a specialist drug and alcohol treatment service for adolescents aged under 18 years, in mixed urban and suburban setting, serving a catchment area in south-west Dublin. Approximately 100 patients attend per annum. It is funded by the Health Service Executive and treatment is provided at no financial cost to the patient. Referrals are accepted from families, professionals and from young people

themselves. Following referral, adolescents are offered an assessment appointment, usually within one week of referral. Parents, or those in a caring role, are also invited to attend. The assessment seeks to gain an understanding of the adolescent's substance use, psychological wellbeing, social functioning and developmental trajectory. It involves clinical interview with the adolescent, their parents and completion of some structured clinical instruments. As motivation is frequently poor in adolescents attending substance use treatment services, clinical staff prioritise patient engagement and building of a therapeutic alliance over data gathering (Tims et al, 2002). Assessment typically takes two separate appointments about one week apart. The treatment approach is tailored to the individual patient's needs and utilises motivational interviewing, cognitive therapy and family therapy.

There were no changes to service delivery, referral criteria, staffing over the period 2009-2011. There were no new services which opened or closed within our catchment area which might have resulted in alteration to the patient profile attending YoDA.

Ethical approval was sought and obtained from the Research Ethics Committee of the National Drug Treatment Centre.

7.4.2 Measures

We utilised routinely gathered clinical information to examine the study hypotheses. All services which provide drug and alcohol treatment in Ireland are required to complete a form on all patients who complete assessment. This form is called the National Drug Treatment Report System (NDTRS) form (Bellerose, Carew & Lyons, 2011). In one section of this form, the clinician is required to enter the problem substance(s) which are currently causing difficulty for the patient. Between one and four substances, including alcohol but excluding tobacco, can be entered into the NDTRS form. The definition of "problem substance" is not operationalised.

As part of the assessment process in YoDA the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is utilised routinely. The ASSIST gathers information on life-time, as well as recent (i.e. past three month), use of substances. Additionally, it gathers information

on the problems associated with recent substance use. The ASSIST has been found to be a valid screening test for identifying psychoactive substance use in individuals who use a number of substances and have varying degrees of substance use (WHO ASSIST Working Group, 2002). It explores a range of substances during a structured clinician administered interview, and the interviewer is required to note use and non-use of each listed substance. For each substance ever used, questions are then asked about patterns of use and consequences relating to the three-month period prior to interview. This then generates a "risk score" for each substance ever used which ranges from 0 to 39. As the clinical team in YoDA noticed an increasing number of patients presenting with problematic use of NPS in early 2010, we opted to modify the ASSIST to include three additional drug categories, to reflect the range of NPS which were being used in Ireland. The three new categories were "Snortable Headshop drugs", "Smokable Headshop drugs", and "Headshop pills" (Kavanagh & Power, 2014). This amendment to the ASSIST was made on 14 Feb 2010.

7.4.3 Participants

We included consecutive patients who commenced assessment at YoDA during the time periods under examination in this study. Patients without a substance use disorder were excluded. Where an individual patient commenced assessment on more than one occasion, we included each separate episode of attendance.

7.4.4 Statistics

We consequently had two sources of information on use of NPS. Firstly, there was the NDTRS form which indicted current problematic use as identified by the clinician following the assessment. Secondly, we had the information from the ASSIST, albeit during a much shorter period of time in the pre-ban group (14 Feb 2010 to 10 May 2010). This provided self-reported use in the past three months and lifetime use for each category of NPS.

Assuming a baseline rate of problematic NPS use of 40% and a fall in use to 10%, we needed a sample of 38 people in each of the pre-ban and post-ban groups to have 80% power to detect such a change, with p value set at 0.05.

In order to assess levels of use prior to the legislative ban, we opted to include all adolescents entering the service during the six month period prior to the ban, anticipating that this would include about 50 treatment episodes and the routinely gathered clinical information would be complete in about 80% (40) of these cases. Consequently, the pre-ban period under examination was 11 Nov 2009 to 10 May 2010.

In order to assess use during the post-ban period we opted to include adolescents entering treatment during the same period, twelve months later, this being 11 Nov 2010 to 10 May 2011. By using the same time period, we ensured that seasonal impacts (such as school holidays, Christmas holidays and St Patrick's day) were similar in the pre-ban and post-ban periods under examination.

We decided a priori that the principal outcomes of interest were (1) use on any NPS and (2) problematic use of any NPS. We also planned to analyse secondary outcomes, examining changes in use of subcategories of NPS.

In order to examine for a significant difference between rates of use pre and post ban, we conducted a chi square test, or Fisher Exact test as appropriate. In order to control for possible confounding, we planned to conduct two separate logistic regression analyses to identify covariates associated with problematic use of any NPS (from the NDTRS responses) and with recent use of any NPS (from the ASSIST responses).

To examine variations in ASSIST risk scores before and after the ban we utilised the Mann Whittney U Test as scores are not normally distributed. Where a person reported use of more than one category of NPS, we utilised the category which generated the highest ASSIST score.

7.5 Results.

7.5.1 Participant characteristics and Univariate analysis.

There were 94 treatment episodes, by a total of 92 adolescents, included in the study, with 50 assessments during the six months immediately prior to the legislation in May 2010, and 44 assessments during the same six month period one year later. The characteristics of those adolescents are outlined in Table 7.1. Patients attending were generally white males living with their parents. The median age was 17 years (interquartile range [IQR] 15-17). Only 69% were engaged in education, training or employment. Parents were the main source of referral, followed by social workers, health professionals and the criminal justice system. There were significantly more females attending during the post-ban period. There were no other significant differences between the pre-ban and post-ban groups with regard to socio-demographic or referral characteristics.

There were seven treatment episodes regarding whom there was no information on use or non-use of NPS from either the NDTRS form or from the ASSIST. All had very brief contact with the service attending for just one or two appointments.

Table 7.1. Characteristics of 94 treatment episodes attending an adolescent substance use treatment program, before and after NPS legislation.

	Total		Pre-ban		Post-ban		p
	n	(%)	n	(%)	n	(%)	
Gender							
Male	78	(83)	46	(92)	32	(73)	
Female	16	(17)	4	(8)	12	(27)	0.01
Age - Mean (SD)	16.8	(1.2)	16.9	(1.2)	16.6	(1.2)	0.25
Living Situation[a]							
Parent(s)/Family	83	(89)	45	(92)	38	(86)	
Residential Care or Homeless	10	(11)	4	(8)	6	(14)	0.39
Work/Education[a]							
Student	47	(52)	23	(47)	24	(57)	
Vocational Training	12	(13)	8	(16)	4	(10)	
Working	4	(4)	4	(8)	0	(0)	
Not working or in education/training	28	(31)	14	(29)	14	(33)	0.18
Ethnicity[a]							
White Irish	83	(89)	45	(90)	38	(88)	
Traveller	5	(5)	3	(6)	2	(5)	
Other	5	(5)	2	(4)	3	(7)	0.80
Referral Source[a]							
Parents	41	(45)	23	(47)	18	(42)	
Social Work	19	(21)	7	(14)	12	(28)	
Crim Justice	11	(12)	8	(16)	3	(7)	
Other Health Professional	12	(13)	6	(12)	6	(14)	
Self	3	(3)	1	(2)	2	(5)	
School	6	(7)	4	(8)	2	(5)	0.44
Main Substance							
Alcohol	20	(21)	8	(16)	12	(27)	
Cannabis	60	(64)	33	(66)	27	(61)	
Sedatives[b]	7	(7)	3	(6)	4	(9)	
NPS	4	(4)	4	(8)	0	(0)	
Heroin	2	(2)	1	(2)	1	(2)	
Cocaine	1	(1)	1	(2)	0	(0)	0.29
Previous Treatment episode	14	(15)	7	(14)	7	(16)	0.80
NDTRS Form Completed	80	(85)	44	(88)	36	(82)	0.40
NPS Recorded on ASSIST [c]	48	(72)	17	(74)	31	(70)	0.77

NS - Not statistically significant

[a] Data missing in 1 to 3 cases.

[b] Benzodiazepines/Z Drug

[c] Specific questions on Novel Psychoactive Substances were added to ASSIST from 14/2/2010

Based upon NDTRS information, those attending prior to the ban were more likely to have problem alcohol use identified (Table 7.2). The Pre-ban assessments had a greater number of problem substances (Median =2, interquartile range [IQR] 1-3) compared to those assessed in the post ban period (Median =1, IQR1-2, p=0.005 [Mann Whitney U Test]). Adolescents attending in the pre-ban period were more likely to report recent use of amphetamines and cocaine.

Although rates of lifetime use of NPS were very similar in the post-ban period compared to the pre-ban period, adolescents attending after the ban demonstrated significantly lower rates of recent use and problematic use of any NPS, of Snortable NPS and of Smokable NPS.

Neither gender, referral source, educational status, recent or problematic use of alcohol, cannabis, cocaine nor amphetamines were significantly associated with problematic use of any NPS (based upon NDTRS Data). Those who reported recent (past 3 month) use of any NPS were more likely to also report recent cocaine use (83% vs 33%, p=0.003), recent use of amphetamine type drugs (82% vs 35%, p=0.007) and recent benzodiazepine use (69% vs 34%, p=0.03). There was no significant association between recent NPS use and age, referral source, education situation, recent or problematic use of alcohol or cannabis. Males tended to be more likely to report recent use of NPS (54% vs 14%, p=0.06[Fishers test]).

Table 7.2. Substance use among adolescents entering treatment before and after a legislative ban on Novel Psychoactive Substances (NPS)

	Total		Pre-ban		Post-ban		p value
	n	(%)	n	(%)	n	(%)	
Current problem substance use (n=80)							
Alcohol	49	(61)	32	(73)	17	(47)	0.02
Cannabis	70	(87)	40	(91)	30	(83)	0.33[a]
Sedatives [b]	14	(17)	7	(16)	7	(19)	0.68
Ecstasy	4	(5)	3	(7)	1	(3)	0.62[a]
Heroin	3	(4)	1	(2)	2	(6)	0.58[a]
Cocaine	15	(19)	10	(23)	5	(14)	0.31
Any NPS	14	(17)	14	(32)	0	(0)	<0.001
Snortable NPS	6	(7)	6	(14)	0	(0)	0.03[a]
Smokable NPS	7	(9)	7	(16)	0	(0)	0.01[a]
NPS oral pills	1	(1)	1	(2)	0	(0)	1.0[a]
Any use in past 3 months (n=48) [c]							
Alcohol	42	(91)	15	(94)	27	(90)	1.0[a]
Cannabis	43	(93)	15	(94)	28	(93)	1.0[a]
Sedatives [b]	16	(36)	8	(50)	8	(28)	0.13
Amphetamine	11	(24)	7	(44)	4	(14)	0.03[a]
Opioid	0	(0)	0	(0)	0	(0)	NA
Cocaine	12	(27)	9	(56)	3	(10)	0.002 [a]
Any NPS	22	(48)	14	(82)	8	(28)	<0.001
Snortable NPS	12	(26)	8	(50)	4	(13)	0.01[a]
Smokable NPS	15	(33)	10	(62)	5	(17)	0.002
NPS oral pills	5	(11)	3	(20)	2	(7)	0.31[a]
Lifetime Use (n=47)							
Any NPS	37	(79)	14	(82)	23	(77)	0.73[a]
Snortable NPS [d]	18	(41)	8	(50)	10	(36)	0.35
Smokable NPS [e]	31	(67)	11	(69)	20	(67)	0.89
NPS oral pills [d]	14	(32)	5	(33)	9	(31)	1.0[a]

[a] Fishers Test
[b] Benzodiazepines/Z Drug
[c] Data missing in 2 or 3 cases for each drug category
[d] Data missing in 3 cases
[e] Data missing in 1 case

Among those reporting recent use of any NPS, the NPS ASSIST risk score was significantly greater in the pre-ban period (n=19, median 16 [IQR 4-31] vs 2 [IQR 2-6], Mann Whitney U test, p=0.02).

Figure 7.1 presents changes in proportions of attendees presenting with problematic use of Snortable, Smokable and any NPS, from August 2009 to May 2011 inclusive. This includes 50 patients assessed and on whom NDTRS forms were completed between 11 May 2010 and 10 Nov 2010. This was during the intermediate period just after the Misuse of Drugs Act in May 2010 and during which the Criminal Justice (Psychoactive Substances) Act occurred. Patient presentations with problematic use of NPS peaked just after the initial legislative ban and then fell away rapidly. The fall in presentations linked to Smokable NPS occurred earlier than the fall in those associated with Snortable NPS.

Figure 7.2 depicts the changes in the proportion of patients who were reporting use of NPS substances in the three months prior to assessment and includes patients assessed from February 2010 to May 2011.

Figure 7.1. Change in Problematic Use of NPS before and after legislative ban among adolescents entering drug and alcohol treatment (n=152).

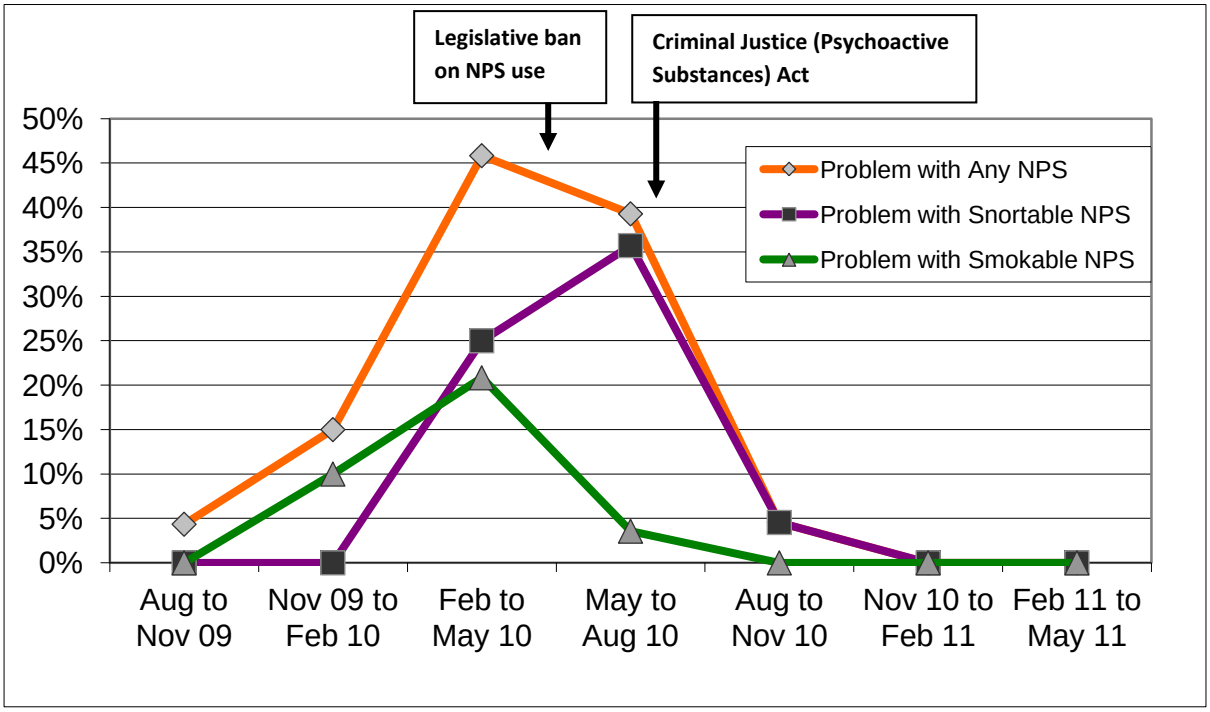
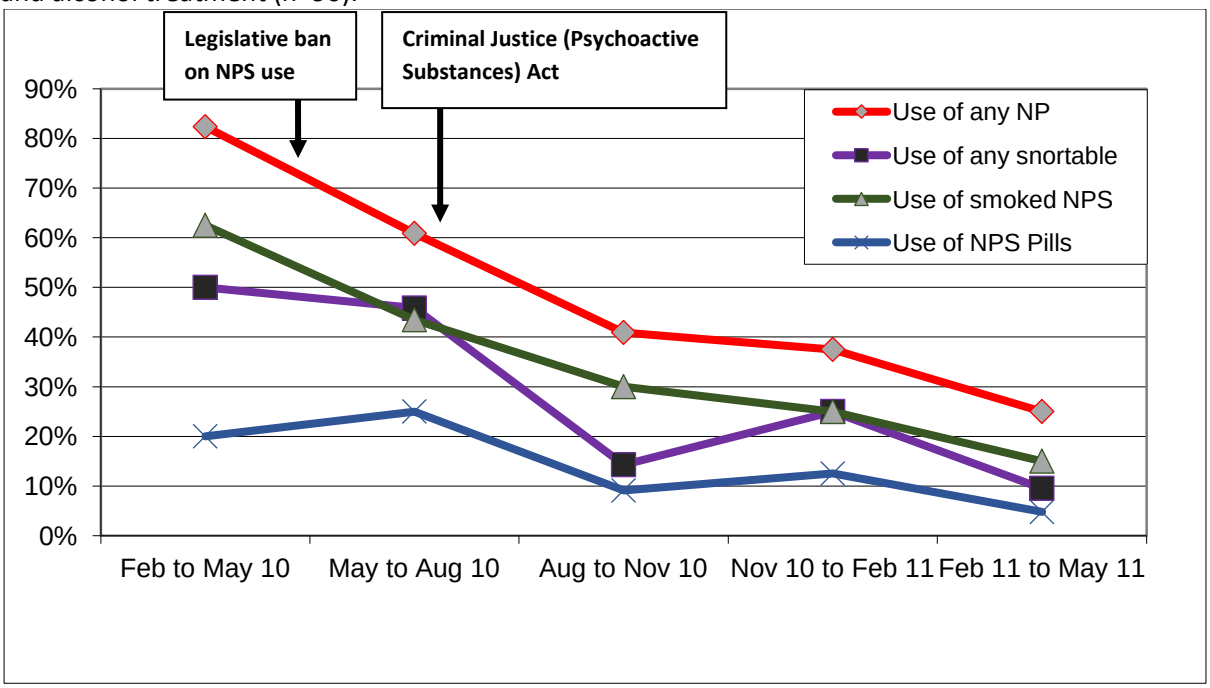


Figure 7.2 Change in use of NPS before and after legislative ban among adolescents entering drug and alcohol treatment (n=90).



7.5.2 Multivariate analysis

It was not possible to conduct a multivariate analysis of covariates associated with current problematic use of any NPS with the time-period (i.e. pre-ban vs post-ban) included in the equation, as there was no case identified as having current problematic use of any NPS in the post-ban period.

A multivariate analysis examining covariates associated with recent use (past 3 months) of any NPS was conducted to determine if the time period remained significantly associated with use. Following examination of the covariates associated with recent NPS use, a number of models were examined. The best fit involved a model which included time-period, gender and recent amphetamine use (Table 3). This confirmed that there was a significant reduction in use of any NPS in the post ban period (p=0.01). The 95% confidence intervals were very wide reflecting the small numbers involved. The model fit was very good, correctly predicting 82% of outcomes and the Nagelkerke R Square was 0.48.

Table 7.3. Logistic regression analysis of patient characteristics associated with use of any NPS (n=45)

	Odds Ratio [OR]	(95% CI OR)	p value
Period of attendance			
Nov 2009-May 2010	7.4	(1.5-37)	0.01
Nov 20010-May 2011	1.0		
Amphetamine use in past 3 months			
No use	1.0		
Some use	9.9	(1.0-98)	0.05
Gender			
Female	1.0		
Males	13.6	(0.6 - 334)	0.11

7.6 Discussion.

We found substantial reductions in use of NPS among treatment attending adolescents within a year after a legislative ban on their use, supply and sale. The detected reduction in use among these adolescents in this study does mirror reductions in use of specific categories of NPS in other populations following similar bans in other settings (Wood, Greene, Dargan, 2013; Stogner et al, 2013; Loeffler & Craig, 2013; Wilkins & Sweetsur, 2013). Reductions in use of cathinone and piperazine compounds have also been demonstrated in opiate dependent patients attending methadone maintenance treatment in Ireland during the year after the legislative ban (O'Byrne et al, 2013).

The legislation has certainly not eliminated use of these drugs. There was evidence of ongoing use of all categories of NPS six to twelve months after the law was changed. A recent European survey confirmed ongoing use of NPS among 15-25 year olds in Ireland, with 9% reporting some use of NPS in the past year (European Commission, 2014). We had speculated that young people who persisted with use of these drugs following their prohibition would exhibit more problematic patterns of use compared to those accessing them during the pre-ban period when they were readily available in headshops. We found no evidence to support this hypothesis. Indeed we found that the ASSIST scores present in users of NPS after the ban were significantly lower than those before the ban, indicating less frequent and less problematic use.

Why might a legislative ban have resulted in a reduction in the proportion of substance abusing teenagers who chose to use NPS and reduction in intensity of use among those who persisted with use? Our study cannot answer this question. Ninety-three per cent of the headshops closed in the year following the two new pieces of legislation. This appears to have had a massive impact of the nascent marketplace for these drugs in Ireland. Looking beyond NPS, we know that access and availability are key factors influencing patterns of use of other substances. Alcohol availability is a potent factor influencing alcohol use and harms (Babor et al, 2010). MacCoun & Reuter (2001) have argued that increased availability and commercialisation of cannabis in the Netherlands was associated with increased use of that drug among youth. While generally sceptical of the impact of supply-orientated policies,

Caulkins (2012) does acknowledge that such polices can be very efficient in certain types of drug markets. Therefore, our findings have face validity.

It seems unlikely that concerns regarding criminal sanction acted as an important deterrent for use of NPS in this group. They did demonstrate ongoing use of a broad range of similarly illegal drugs after the legislative ban. The consequences of an adolescent being caught by police in Ireland with drugs for personal use are relatively benign, typically resulting in no more than a caution. Criminal prosecution is very rarely proceeded with in this age range for this type of offence.

Simple drug policy measures can have unintended and adverse consequences (Greenfield & Paoli, 2012). We deliberately cast the net wide in terms of NPS in this study due to concerns that success at reducing use of a single drug such as mephadrone, might conceal increased use of other emerging and not yet illegal NPS (Dargan et al, 2011). We found a fall in rates of use of the broad group of NPS, as further new substances did indeed arrive into the drugs marketplace in Ireland following the legislation (Kavanagh & Power, 2014; O'Byrne et al, 2013).

We also examined the possibility that NPS may simply have temporarily displaced other more established illegal drugs such as cocaine, amphetamines and cannabis. Not only did we fail to find any evidence of increased use of these older drugs following the reduction in NPS use, we found that young people presenting for treatment in the post-ban period were less likely to be using cocaine and amphetamines. Polydrug use was more evident in the pre-ban period. While the reason for this is unclear it does not raise concerns regarding untoward effects of the legislation on patterns of use. Nevertheless, it is possible that the disruption which the legislation caused to patterns of drug use and to the drug marketplace may have generated other social or personal harms not examined in this study (Greenfield & Paoli, 2012).

Although, there were just two principal outcomes, we conducted multiple additional statistical tests to examine secondary outcomes and to explore factors associated with NPS use. Despite this, we opted to make no adjustments for the multiple tests undertaken because they can result in a higher type II error rate, reduced power, and increased

likelihood of missing important findings (Rothman, 1990). The key sources of information (i.e. the NDTRS form and the ASSIST) were unavailable in 15-30% of cases raising the possibility of selection bias. There was also scope for clinical subjectivity with regard to determinations of "problem substance use" in the NDTRS form as this term is not operationalised. The findings may not generalise to other settings with a more established pattern of NPS use or with a different network of supply of NPS. Specifically, legislative bans targeted primarily at headshops such as those which occurred in Ireland may have little or no impact where the internet acts as the major supplier.

Overall, the legislative measures undertaken in Ireland in response to escalating use of NPS coincided with reduced use of the broad category of NPS within this narrow but important group of high risk adolescents attending treatment services. While we watch with interest the outcome of attempts to regulate this marketplace, such as those in New Zealand, our findings do not provide a rationale for Ireland to alter its prohibitionist approach to NPS at this time.

7.7 Author Contributions

BPS conceived the study question and examined the background literature. BPS lead on the statistical analysis with input from CD. BPS, PJ, CD & WC were each involved in interpretation of the data. BPS lead on the drafting of the manuscript. CD, PJ & WC also contributed to the drafting of the manuscript. BPS, PJ, CD & WC read and approved the final manuscript.

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Chapter 8

Decline in new psychoactive substance use disorders following legislation targeting headshops: Evidence from national addiction treatment data

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Citation reference:
Smyth BP, Lyons S, Cullen W. Decline in new psychoactive substance use disorders following legislation targeting headshops: Evidence from national addiction treatment data. *Drug & Alcohol Review* 2017: 36; 609-617. doi:10.1111/dar.12527
Journal ISSN: 146-3362
Journal Url: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1465-3362

8.1 Context of this chapter within overall Thesis

Building upon the findings of the NPS study in chapter 8, this study seeks to determine if the changes observed in treatment attending adolescents at one treatment centre in Dublin generalise to young adults nationally. It characterises NPS users attending addiction treatment. It compares patterns of NPS use before and after the closure of the head shops. It uses JoinPoint trend analysis for the first time in the PhD. This permits exploration of the data on rates of NPS presentations over time to determine if that were any significant trend changes coinciding with either the arrival or departure of the head shops. It also examines for trend changes for presentations related to other drugs.

8.2 Abstract

Introduction and Aims: New psychoactive substances (NPS) have hedonic effects which may lead to dependence. Headshops selling NPS increased in number in Ireland from late 2009. Legislation was enacted in May and August of 2010 which caused their closure. It is unknown whether such events impact the rate of NPS use disorders.

*Designs and Methods***:** We conducted a population based study using the Irish national database of episodes of addiction treatment between 2009 and 2012. We examined trends in the rate of NPS related treatment episodes among young adults. Joinpoint trend analysis software was used to identify significant changes in trend.

Results: There were 31,284 episodes of addiction treatment commenced by adults aged 18 to 34 years, of which 756 (2.4%) were NPS related. In 2012, the 12-month moving average rate had fallen 48% from its peak in 2010, from 9.0/100,00 to 4.7/100,000. Joinpoint analysis indicated that the rate of NPS related episodes increased by 218% (95% CI 86 to 445, p=0.001) every four months until the first third of 2010. From that point, the rate declined by 9.8% (95% CI -14.1 to -5.4, p=0.001) per four-month period. There was no significant trend change in the rate of non-NPS related treatment episodes.

Discussion and Conclusions: Over the two years after the enactment of prohibition-styled legislation targeting NPS and headshops, the rate of NPS related addiction treatment episodes among young adults declined progressively and substantially. We found no coinciding trend change in the rate of episodes linked to other drug groups.

8.3 Introduction

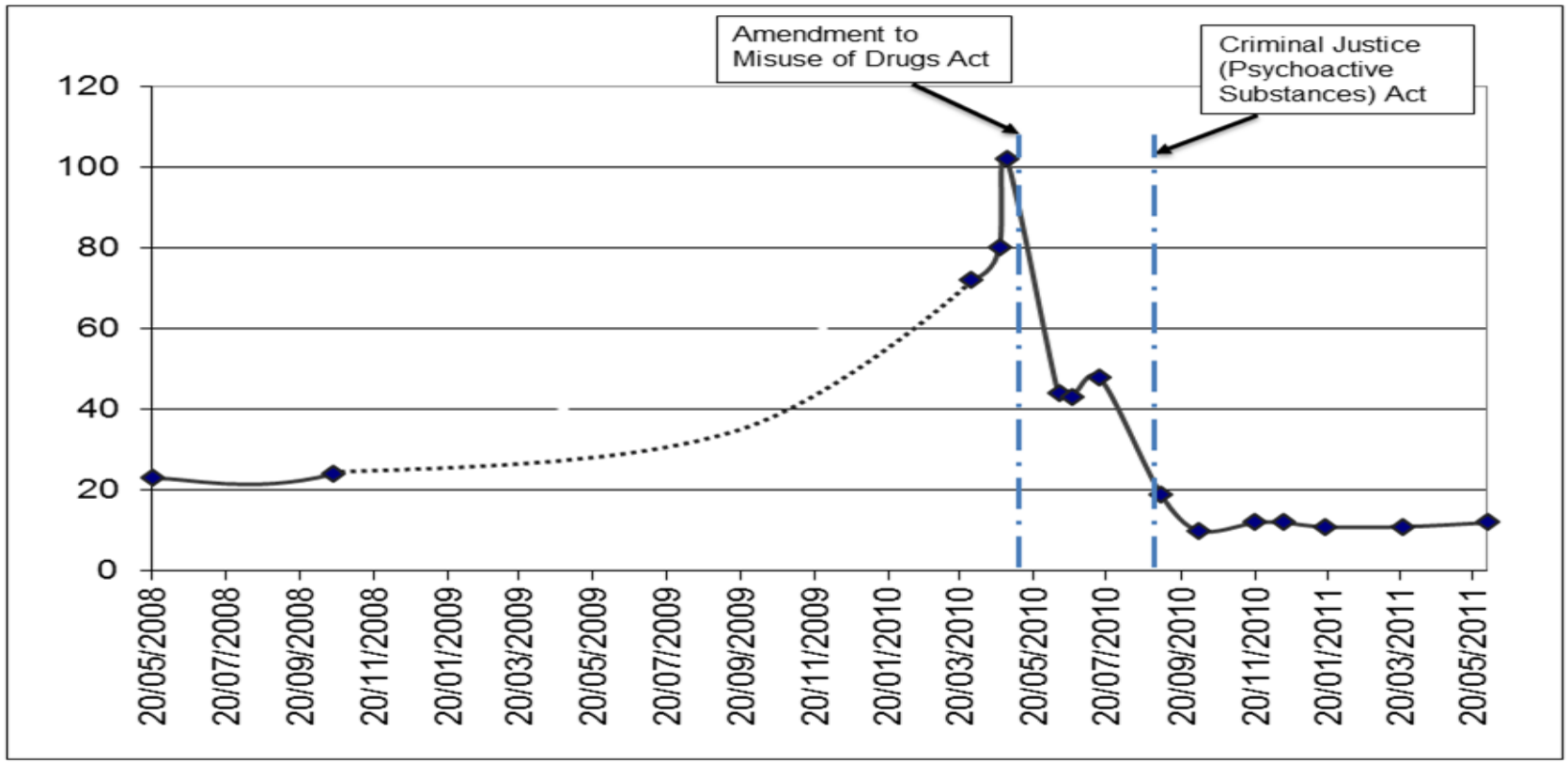
New psychoactive substances (NPS) have become a source of international concern in recent years.[1] These are new psychotropic drugs which are not controlled by previous 1961 or 1971 UN conventions “but which may pose a public health threat comparable to that posed to substances listed in those conventions”.[2] They include cathinones, synthetic cannabinoids and substances with amphetamine and MDMA type effects, many of which

are piperazines or phenethylamines.[3,4] NPS have many of the same hedonic effects as more established drug classes and therefore have potential to cause dependence.[3,5-6]

The marketplace for NPS has also been novel, posing challenges for legislators internationally.[2,7,8] While not scheduled as being illegal, NPS have been sold commercially in many jurisdictions.[9] In some countries the internet has constituted the major source of supply.[10,11] In countries such as Ireland, specialist shops, known as 'headshops', opened to meet demand for these drugs.[9,12] A European survey of young adults in 2011 found that the lifetime prevalence of NPS use was 5% overall, but highest in Ireland at 16%.[9] Over the period from late 2009 to 2010, there was a substantial increase in the number of headshops in Ireland peaking at 102 premises in May 2010, approximately one shop per 45,000 people (see Figure S1 in online supplement).[12,13] Their presence quickly prompted public protests and demands for urgent political action.[14]

In response, the Irish government opted to proceed with a two-pronged legislative approach. Firstly, there was a legislative ban, adding over 100 substances to the Misuse of Drugs Act in May 2010.[15] This made possession, sale and supply of the named drugs a criminal offence. Then in late August 2010, the Criminal Justice (Psychoactive Substances) Act was introduced.[16] This Act was focused primarily at vendors of NPS. It states that ‘a person who sells a psychoactive substance knowing or being reckless as to whether that substance is being acquired or supplied for human consumption shall be guilty of an offence’. These two Acts resulted in a dramatic decline in the number of headshops, initially to 48 shops in June 2010, and then falling to 10 shops by October 2010 (see Figure 8.1) .[13] Follow-up investigations by An Garda Síochána (Irish police) in late 2010 indicated that the remaining headshops were no longer selling NPS. Consequently, the eight-month period from January to August 2010 could be viewed as the Irish headshop era.

Figure 8.1 Number of headshops in Ireland, May 2008 to May 2011. (Copy of Figure 2.17 in Chapter 2)



Footnote to Figure 8.1 In mid-2008, An Garda Síochána (Irish police) were monitoring headshops due to concerns that some were selling Hawaiian Baby Woodrose seeds and Peyote cactus in contravention of the Misuse of Drugs Act, via Operation Flourine (See section 2.6.2.1 in Chapter 2). Monitoring of headshops then ceased on 17/10/2008. Due to concerns regarding widespread use of NPS, a second Garda operation commenced (Operation Kingfisher - See section 2.6.2.1 in Chapter 2) and a census of headshops was conducted on 30/03/2010, and intermittently over the following 14 months. From October 2008 to March 2010 (dotted line) the number of headshops was not measured, although Garda reports suggest that the number of headshops began to increase substantially in late 2009.

There is substantial contention internationally regarding the effectiveness of legislative bans. A review in Ireland suggested that the legislative response to NPS had been excessive and driven by "a moral panic".[14] There are international surveys of drug users which indicate ongoing easy access to and use of NPS following bans.[17,18] It has been argued that new drugs rapidly arrive to replace any specific banned substances.[10,19] There is evidence that this did indeed occur in Ireland over the summer of 2010, as drugs such as naphyrone and flourotropococaine went on sale in the remaining headshops.[13] This eventuality prompted the additional legislation in August. It is also possible that a ban just moves drugs from their quasi-legal status to enter criminal drug supply networks, with increased attendant risks or possibly diverts would-be NPS users towards other drugs.[20] There have been increasing calls to explore regulation of this marketplace.[21] New Zealand has taken initial steps in this direction with the enactment of the Psychoactive Substances Act in 2013.[2,7]

In countries which have proceeded down the more traditional route of prohibition and legislative bans, such as those adopted by Ireland, there is some evidence of an impact on reducing NPS use. There was a reduction in attendances linked to mephedrone at emergency departments following a legislative ban in Britain.[22] There was a decline in use of Salvia divinorum after a legislative ban in Florida.[23] There was a dramatic fall in phonecalls regarding cathinones to a poison centre in USA following legislation.[24] In New Zealand, use of benzylpiperazine (BZP) in the general population declined substantially following its prohibition.[25] A study examining NPS use among adolescents entering addiction treatment in Dublin found reduced use one year after the legislative changes.[26]

The emergence of headshops and the subsequent legislation provide an opportunity for a natural experiment.[8] We sought to examine whether the arrival and departure of the headshops coincided with changes in presentation of problem NPS use among adults attending addiction treatment services in Ireland.

8.4 METHOD

8.4.1 Setting

In Ireland, addiction treatment services are available across the country. There is a mixture of statutory, voluntary and private services. Most treatment is delivered on an outpatient basis. There are about 15,000 treatment episodes commenced annually, and almost half involve people entering treatment for the first time. Alcohol is the main problem drug in about half of episodes, while heroin and cannabis are the most common illegal drugs contributing to treatment episodes.[27] The proportion of primary heroin use disorders declined marginally 2007 to 2009, while treated cannabis use disorders increased over this period.[26] Most patients entering treatment for problem drug use present with problematic use of more than one drug.[27]

The general population survey of 2010-11 found that past year prevalence of cannabis use was 10% among 15-34 year olds, and this was unchanged since the preceding survey in 2006-07.[28] The past year prevalences of NPS, cocaine and amphetamines in this age range in 2010-11 were 7%, 3% and 1% respectively. Past year NPS use was only 1% among people aged over 34 years. Young males were three times more likely than young females to report past year NPS use.

Ireland underwent significant social changes over the period 2009-2012, entering a recession following a period of sustained economic growth. The youth unemployment rate increased dramatically from 19% in January 2009 to 27% in January 2010, and increased by a further 2-3% over the following two years.

8.4.2 Measures

We utilised routinely gathered epidemiological information from the National Drug Treatment Report System (NDTRS). Services which provide addiction treatment in Ireland are expected to return information on each new treatment episode to the NDTRS,[27] with 70% of services doing so. The therapist conducting the assessment writes the name of the main problem drug self-reported by the patient, and up to three additional problem drugs, onto the NDTRS form. The written text is then coded by staff at the NDTRS when entered into the database. Consequently, new drugs are captured once they begin presenting to treatment services. The definition of "problem drug" is not operationalised, although it is

generally understood to equate to dependence or harmful use as described in ICD-10. An episode of treatment, or case, was determined to be NPS-related if any NPS was identified as being a problem drug.

The NDTRS form also captures information on socio-demographic and past treatment. There is no unique patient identifier. Consequently, the unit of analysis reported in this study is treatment episode. However, incidence was calculated from cases who had never previously been treated for a drug problem, as these constituted unique individuals.

8.4.3 Population

We examined all episodes of treatment recorded in the NDTRS over the period 2009 to 2012. We excluded episodes where the patient was aged under 18 years as this group have previously been examined.[25] In light of the general population survey indicating much higher rates of use among young adults, we focused upon cases aged 18-34 years for the trend analysis.[28]

8.4.4 Statistics

We opted to examine treatment attendances per four-month block of time, or third of each year. In view of the time points for the legislative changes, there were four full months (January to April = 2010t1) in 2010 prior to the May legislation and a further four-month period (May to August = 2010t2) before the Psychoactive Substances Act at the end of August 2010. The NDTRS avoids reporting cell sizes of less than 5 people as patients may be identifiable. Analysis of treatment episodes in one or two month blocks would have resulted in frequent breach of this rule.

In order to contrast proportions, such as the characteristics of NPS-related treatment episodes and episodes unrelated to NPS, we utilised odds ratios. We also report estimates of the 95% confidence intervals of the odds ratio. These are estimates of the confidence intervals as the episodes are not completely independent. An unknown proportion of

episodes, which we estimate to be about 15-25%, involve re-attendance by individuals on more than one occasion during the four year period. We also used odds ratios to describe changes in the prominence of NPS (i.e. main problem substance versus a secondary problem) within NPS-related treatment episodes over the four year period.

We calculated the crude rate of all NPS-related treatment episodes among people aged 18-34 years. We also calculated the incidence of NPS-related treatment episodes in this age range using cases who entered addiction treatment for the first time. The population at risk was obtained from the population estimates provided by the Central Statistics Office. To smooth out the effect of seasonal variation in treatment attendance, the graphs also report 12 month moving averages, these being the average of the rates from the three preceding four-month blocks of time. As a comparator, we also measured the rate of addiction treatment episodes which were unrelated to NPS use.

Finally, we used the Joinpoint Regression Program, version 4.3.1.0 (National Cancer Institute, Bethesda, Maryland, USA, http://surveilance.cancer.gov/joinpoint) to further examine trends in the rate of attendances. Joinpoint regression is a log-linear model which uses Poisson regression, creating a Monte Carlo permutation test to identify points where the trend line changes significantly in magnitude or direction.[29] The location of the joinpoints is data driven. It starts by fitting a straight line (i.e. zero joinpoints) and tests whether the addition of one or more joinpoints yields a statistically significant improvement in fit. The percentage change per third of each year (PCT) is calculated for each line segment between joinpoints, along with 95% confidence intervals. The minimum number of observations from a joinpoint to either end of the data and the minimum number of observations between two joinpoints were set at three and four respectively (default settings). Consequently, with 12 observations, we could detect a maximum of two joinpoints per analysis. We used the Joinpoint software to explore for possible joinpoints in the trends of both NPS and non-NPS-related addiction treatment episodes, examining the rates of all episodes and of cases never previously treated. We further examined the non-NPS-related episodes by main problem drug to determine if there were any significant changes in trends of presentations linked to other drug classes (cannabis, cocaine, other stimulants [e.g. amphetamine, MDMA], sedatives and hypnotics [e.g. benzodiazepines, zopiclone], opioids and alcohol).

8.5 Results.

There were 58,251 treatment episodes, with some evidence of seasonal variation (35.5% of episodes occurred in the first third of the year versus 30.4% in the final third). Overall, 849 (1.46%) episodes involved problematic NPS use. Of these, a NPS was the main problem drug in 255 (30.0%) cases. In 2009, 36% (14/39) of the NPS related episodes involved a NPS as the main problem, and in 2010 this proportion was 39% (138/354). This proportion fell to 27% (75/278) in 2011 and then to 16% (28/178) in 2012. Compared to 2010, NPS-related treatment episodes in 2011 and 2012 were less likely to involve a NPS as the primary drug with odds ratios of 0.6 (95% CI 0.4 to 0.8) and 0.3 (95% CI 0.2 to 0.5) respectively.

The profiles of the NPS group and non-NPS group are provided in Table 8.1. Those episodes involving problem use of NPS were more likely to involve males and cases under 35 years of age. The median age of the NPS group was 25.0 years compared to 35.6 years in the non-NPS group. The route of NPS use was 62.4% intranasal, 18.8% smoked, 13.6% oral and 5.2% injected. Further information on the subgroups of NPS, and how these changed over time, is provided in Table 8.2.

Table 8.1. Socio-demographic characteristics of all adult treatment episodes involving an NPS as problem drug compared to those which were unrelated to any NPS, 2009 to 2012

	NPS (N = 849)		Non-NPS (N = 57402)		Odds ratio (OR)	95% CI of OR^
	N	%	N	%		
Gender						
Male	631	74.3%	39105	68.3%	1.3	(1.1-1.6)
Female	218	25.7%	18180	31.7%	1.0	
Age						
18 to 34 years	756	89.0%	30528	53.2%	7.2	(5.7-8.9)
35 years and older	93	11.0%	26874	46.8%	1.0	
Living with whom?						
Alone	124	14.6%	12007	20.9%	0.4	(0.3-0.5)
Parents/family	462	54.4%	19055	33.2%	1.0	
Friends	28	3.3%	1642	2.9%	0.7	(0.5-1.0)
With partner	94	11.0%	14529	25.3%	0.3	(0.2-0.3)
Alone with children	36	4.2%	3578	6.2%	0.4	(0.3-0.6)
Other/not known	105	12.4%	6591	11.5%	0.7	(0.5-0.8)
Accommodation						
Stable accommodation	721	84.9%	49691	86.6%	1.0	
Institution*	54	6.4%	1423	2.5%	2.6	(1.9-3.5)
Homeless	32	3.8%	3542	6.2%	0.6	(0.4-0.9)
Other unstable accommodation	27	3.2%	1884	3.3%	1.0	(0.7-1.5)
Not known	15	1.8%	862	1.5%	1.2	(0.7-2.0)
Employment						
In employment, education or training	236	27.8%	13133	22.9%	1.2	(1.0-1.4)
Not in employment, education or training	565	66.5%	37717	65.7%	1.0	
Retired/ unable to work/disability	33	3.9%	3945	6.9%	0.6	(0.4-0.8)
Other/not known	15	1.8%	2607	4.5%	0.4	(0.2-0.7)
Source of referral						
Self	266	31.3%	22796	39.7%	1.0	
Family/friends	127	15.0%	5780	10.1%	1.9	(1.5-2.3)
Other drug treatment centre	85	10.0%	5347	9.3%	1.4	(1.1-1.7)
Mental health professional	91	10.7%	3426	6.0%	2.3	(1.8-2.9)
Criminal justice system	83	9.8%	4385	7.6%	1.6	(1.3-2.1)
Other health care professional/facility	72	8.5%	9318	16.2%	0.7	(0.5-0.9)
Social services	73	8.6%	3373	5.9%	1.8	(1.4-2.4)
Other/not known	52	6.1%	2977	5.2%	1.5	(1.1-2.0)
Year of Treatment						
2009	39	4.6	13576	23.7	0.1	(0.1-0.2)
2010	354	41.7	14301	24.9	1.0	
2011	278	32.7	14966	26.1	0.7	(0.6-0.9)
2012	178	21.0	14559	25.4	0.5	(0.4-0.6)
Main Problem						
Alcohol	173	20.4%	31206	54.4%	1.0	
Any drug other than alcohol	676	79.6%	26196	45.6%	4.6	(3.9-5.5)

^ The 95% confidence intervals for odds ratios should be viewed as estimates, as reliable calculations of these confidence intervals requires episodes to be fully independent. We estimate that 15-25% of people re-attended addiction treatment during this four year period, so this rule of independence is breached.

* Institution includes prison, halfway house, residential centre

Table 8.2. Sub-type of NPS identified as problem substances by adults attending addiction treatment services, contrasting the period when headshops were selling NPS with the period after Headshops ceased their sale.

Category of NPS	Total		Jan 2009 to Aug 2010 (N = 320)		Sept 2010 to Dec 2012 (N = 554)		Odds ratio (OR)	95% CI of OR[a]
	N	%	N	%	N	%		
NPS Stimulant Powders[b]	530	61%	134	42%	396	71%	1.0	
NPS Cannabis-like substances[c]	114	13%	74	23%	40	7%	0.2	(0.1-0.3)
NPS Stimulant Party Pills[d]	31	4%	20	6%	11	2%	0.2	(0.1-0.4)
NPS Hallucinogenic Substances[e]	<5	0%	<5	1%	0	0%	NA	
Other Specified NPS	27	3%	15	5%	12	2%	0.3	(0.1-0.6)
Unspecified NPS	168	19%	73	23%	95	17%	0.4	(0.3-0.6)
NPS is the Primary drug Problem								
NPS Stimulant Powders	156	61%	49	40%	107	80%	1.0	
NPS Cannabis-like substances	45	18%	34	28%	11	8%	0.2	(0.1-0.3)
Other NPS	27	11%	19	16%	8	6%	0.2	(0.1-0.5)
Unspecified NPS	27	11%	20	16%	7	5%	0.2	(0.1-0.4)
NPS is the Secondary drug Problem								
NPS Stimulant Powders	374	60%	85	43%	289	69%	1.0	
NPS Cannabis-like substances	69	11%	40	20%	29	7%	0.2	(0.1-0.4)
Other NPS	35	6%	20	10%	15	4%	0.2	(0.1-0.5)
Unspecified NPS	141	23%	53	27%	88	21%	0.5	(0.3-0.8)
NPS Stimulant Powders								
Primary Substance Problem	156	29%	49	37%	107	27%	1.0	
Secondary Substance Problem	374	71%	85	63%	289	73%	1.6	(1.0-2.4)
NPS Cannabis-like substances								
Primary Substance Problem	45	39%	34	46%	11	28%	1.0	
Secondary Substance Problem	69	61%	40	54%	29	73%	2.2	(0.9-5.6)

Unspecified NPS								
Primary Substance Problem	27	16%	20	27%	7	7%	1.0	
Secondary Substance Problem	141	84%	53	73%	88	93%	4.7	(1.8-13.3)

[a] The 95% confidence intervals for odds ratios should be viewed as estimates, as reliable calculations of these confidence intervals requires episodes to be fully independent. We estimate that 15-25% of people re-attended addiction treatment during this four year period, so this rule of independence is breached.

[b] mephedrone, butylone, MDVP, flephedrone, methylone, “Snow”,”snowblow”, “bath salts”, “Bubble”. “Hurricane Charlie”, “Vanilla sky”, “Whack”, “Wildcat” or Unspecified NPS Stimulant powder.

[c] “smoke”, “spice”, “Bonsai”, “Pulse”, “King B”, Unspecified NPS Cannabis-like Substance.

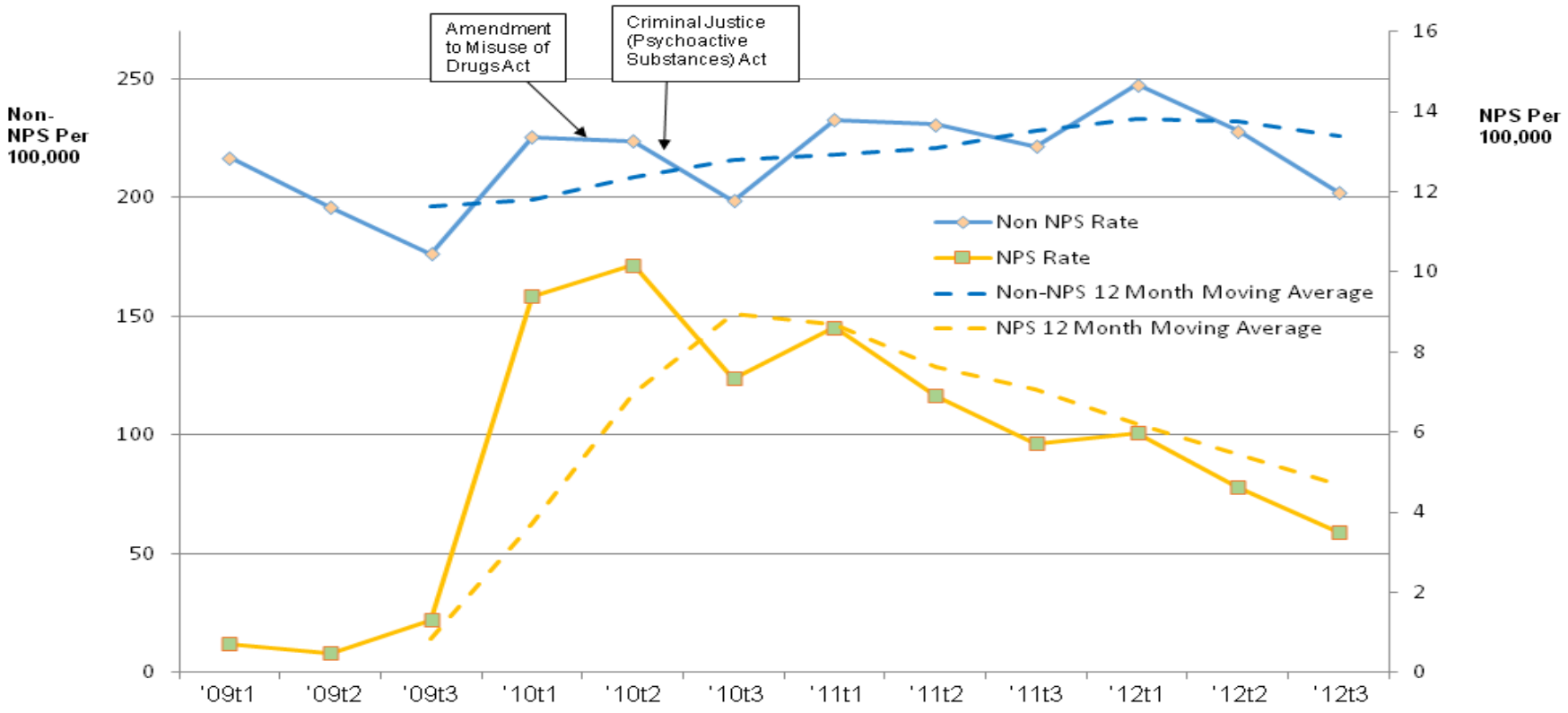
[d] “Rocket Fuel”, “Speed Freak”, “Exotic Super”, Unspecified NPS Stimulant Party

[e] Salvia, NPS Hallucinogenic Substances

There were 31,284 episodes of addiction treatment commenced by adults aged 18 to 34 years during this period, of which 756 (2.4%) were NPS-related. Figure 8.2 demonstrates the crude rates of NPS-related treatment episodes among these young adults. The rate rises rapidly, peaking in 2010t2 and then falls progressively after that point. During the headshop era from January to August 2010, 4.2% (n=236) of all addiction treatment episodes in this age range involved problematic NPS use. In 2012, the 12-month moving average rate had fallen 48% from its peak in 2010, from 9.0/100,000 to 4.7/100,000. In contrast, the rate of non-NPS-related treatment episodes was relatively stable.

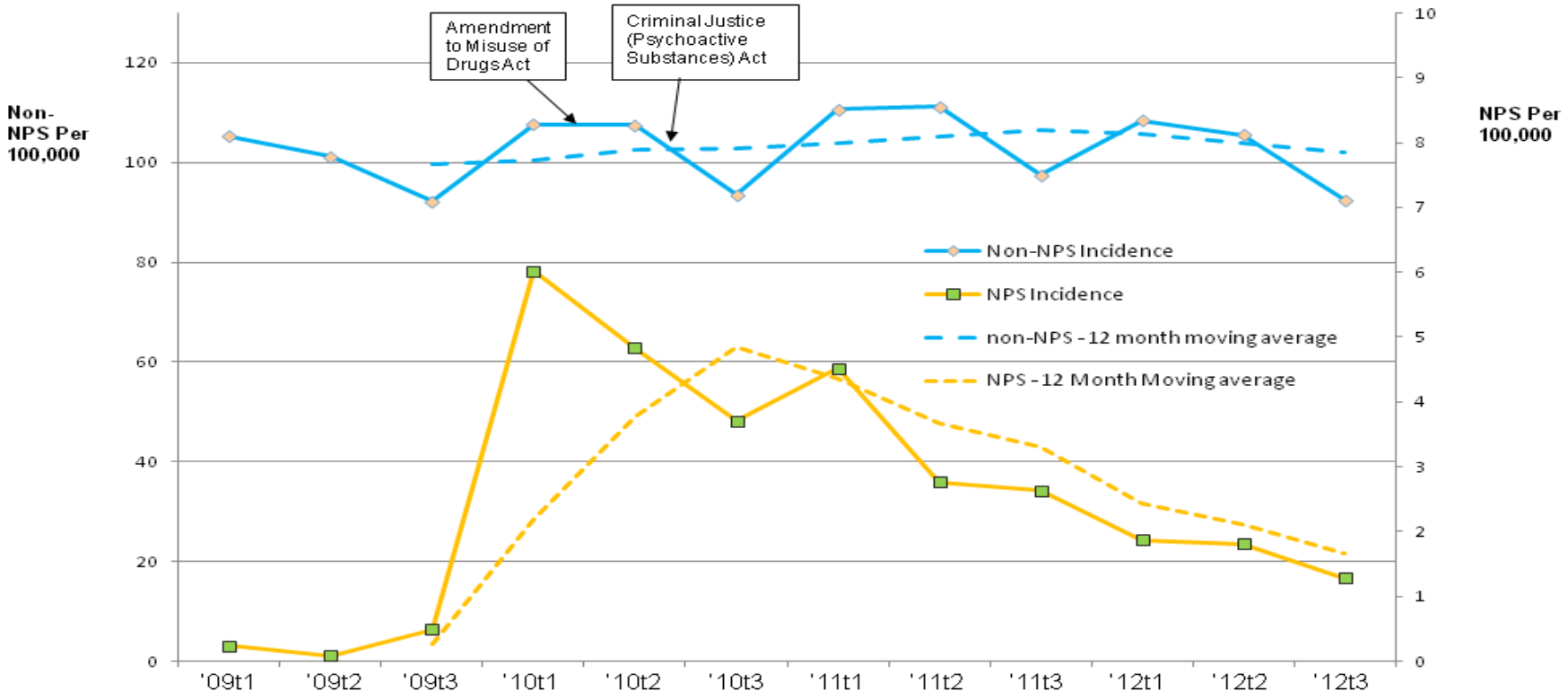
Figure 8.3 demonstrates the changes in incidence of NPS-related treatment episodes among 18-34 year-olds. These were cases who had never sought drug treatment previously. Incidence peaked in 2010t1 at 6.0 cases/100,000 and fell steadily after that point. By end of 2012, the 12-month moving average had fallen by 66% from its peak in 2010 of 4.9/100,000 to 1.7/100,000.

Figure 8.2 Rate of addiction treatment episodes among people aged 18-34 years-old, from 2009-2012, comparing episodes related to NPS to those related to all other substances



NPS related episodes	9	6	16	114	122	87	101	80	65	67	51	38

Figure 8.3 Incidence of new addiction treatment cases among people aged 18-34 years-old, from 2009-2012, comparing cases related to NPS to those related to all other substances



NPS Incident cases	*<5*	*<5*	*6*	*73*	*58*	*44*	*53*	*32*	*30*	*21*	*20*	*14*

Table 8.3 and Figure 8.4 to 8.9 provide the results of the joinpoint analyses. This indicates that the trend in the rate of total NPS-related episodes and in the incidence of new NPS cases changed in 2010t1. These rates were each rising substantially and significantly up to that period. Beyond that point, the rates declined progressively and significantly. No joinpoints were detected when the rates of non-NPS related episodes were examined, and the overall trend in rates across the period examined did not differ from zero.

The examination of all non-NPS related episodes by main problem drug indicted no significant change in trend (i.e. no joinpoint identified) for cannabis, cocaine, other stimulants, alcohol or opioids. There was a significant but steady decrease in the rate of cocaine-related episodes over the study period while the rates of cannabis and of sedatives and hypnotics related episodes increased steadily and significantly. Importantly, there was no change in these trends during these 4 years. There was a significant change in trend of presentations linked to sedatives and hypnotics among those who had never previously sought drug treatment. This occurred in 2012t1, when the trend of rising incidence reversed.

The examination of subcategories of NPS within NPS related treatment episodes (Table 8.2), indicates that NPS Stimulant Powders accounted for an increased proportion of NPS related cases after August 2010, while the proportion of NPS Cannabis-like substances declined. Among those presenting with problematic use of NPS Stimulant Powders, the proportion for whom this was a primary problem declined after August 2010.

Table 8.3. Trends in crude rates of addiction treatment episodes per third of a year, among people aged 18-34 years between 2009 and 2012.

	Period	PCT*	(95% CI PCT)	Joinpoint	(95% CI of Joinpoint)	Period	PCT	(95% CI PCT)
All Treatment Episodes								
NPS	2009t1 to 2010t1	218	(86 to 445)	2010t1	(2009t3 – 2010t2)	2010t1 to 2012t3	-9.8	(-14.1 to -5.4)
Non-NPS	2009t1 to 2012t3	1.1	(-0.5 to 2.8)					
Main Problem Drug among non-NPS episodes								
Cocaine	2009t1 to 2012t3	-3.5	(-6.2 to -0.7)					
Cannabis	2009t1 to 2012t3	5.1	(2.7 to 7.5)					
Other stimulants	2009t1 to 2012t3	-0.9	(-3.7 to 1.9)					
Sedatives & Hypnotics	2009t1 to 2012t3	12.5	(7.7 to 17.5)					
Alcohol	2009t1 to 2012t3	0.9	(-0.7 to 2.6)					
Opioids	2009t1 to 2012t3	-0.6	(-2.6 to 1.5)					
Incident Cases (never treated previously)								
NPS	2009t1 to 2010t1	310	(83-820)	2010t1	(2009t3 – 2010t2)	2010t1 to 2012t3	-15.7	(-21.1 to -6.1)
Non-NPS	2009t1 to 2012t3	0.0	(-1.4 to 1.4)					
Main Problem Drug among non-NPS episodes								
Cocaine	2009t1 to 2012t3	-4.8	(-7.1 to -2.4)					
Cannabis	2009t1 to 2012t3	4.1	(1.6 to 6.7)					
Other stimulants	2009t1 to 2012t3	-2.3	(-5.6 to 1.1)					
Sedatives & Hypnotics	2009t1 to 2012t1	16.4	(10.2 to 23.0)	2012t1	(2011t3 – 2012t1)	2012t1 to 2012t3	-20.8	(-52.2 to 31.3)
Alcohol	2009t1 to 2012t3	-0.5	(-2.1 to 1.0)					
Opioids	2009t1 to 2012t3	-2.4	(-4.7 to -0.2)					

* PCT = Estimated per cent change per third of a year from best fitting Joinpoint model

Figure 8.4 Joinpoint regression analysis of all **non-NPS related episodes** of addiction treatment
Rates per third of year and fitted joinpoint regression lines of trends for addiction treatment episodes among people aged 18-34years, from first third of 2009 (‘09t1) to final third of 2012 (‘12t3)

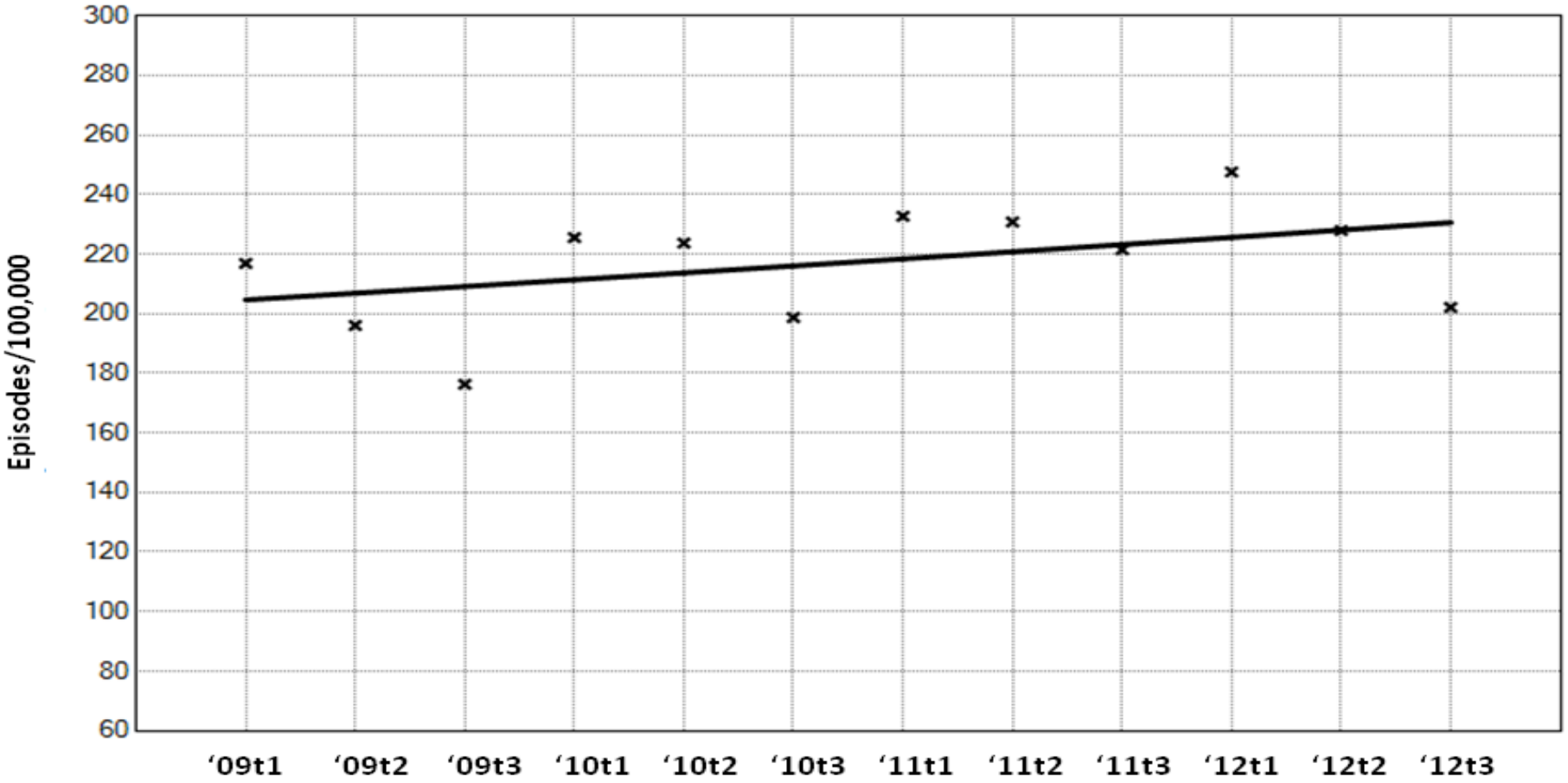


Figure 8.5 Joinpoint regression analysis of all new cases of addiction treatment **unrelated to NPS – Rate of incident cases**.
Rates per third of year and fitted joinpoint regression lines of trends for addiction treatment episodes among people aged 18-34years, from first third of 2009 (‘09t1) to final third of 2012 (‘12t3)

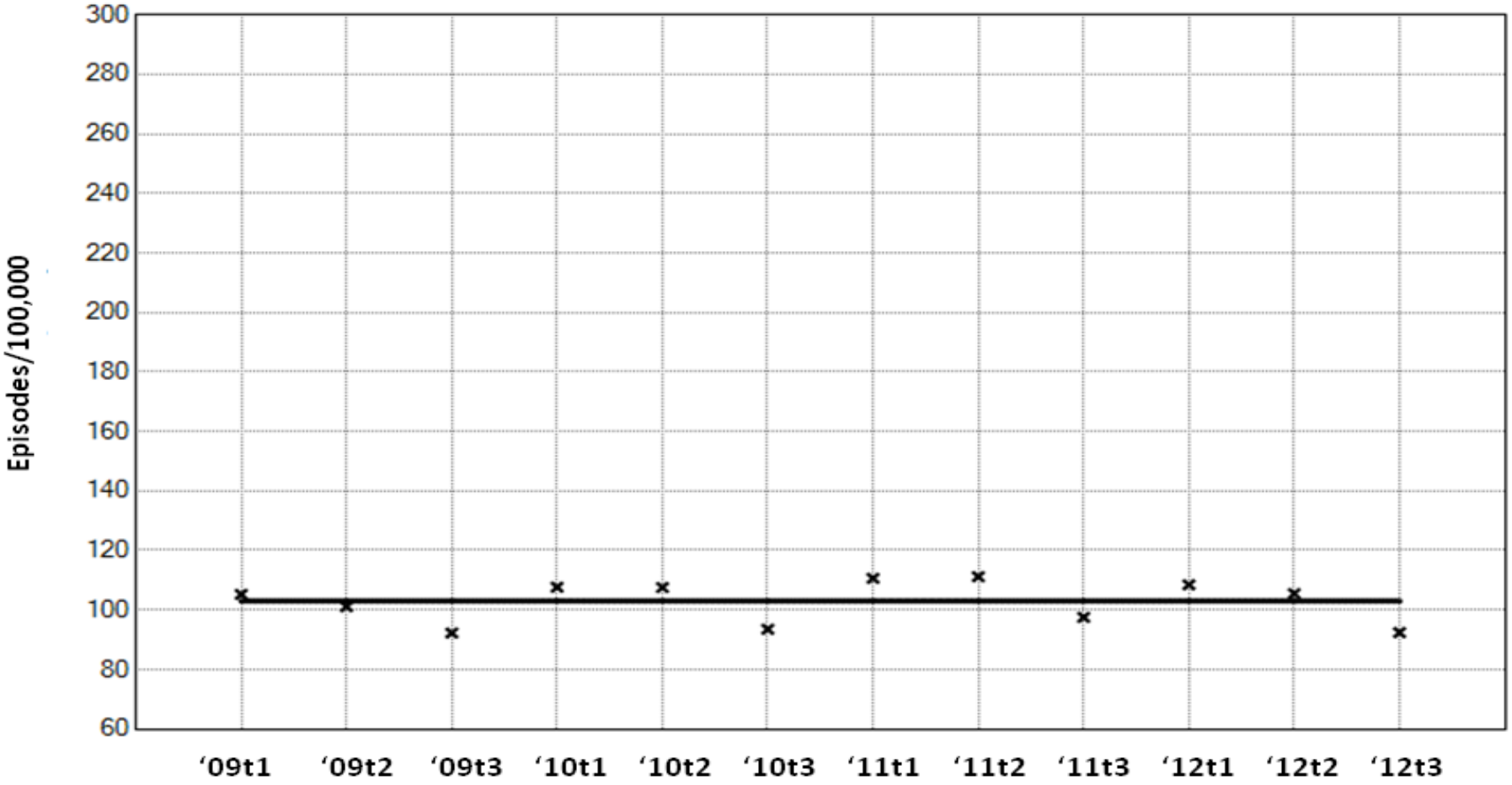


Figure 8.6 Joinpoint regression analysis of all **NPS related episodes** of addiction treatment
Rates per third of year and fitted joinpoint regression lines of trends for addiction treatment episodes among people aged 18-34years, from first third of 2009 (‘09t1) to final third of 2012 (‘12t3)

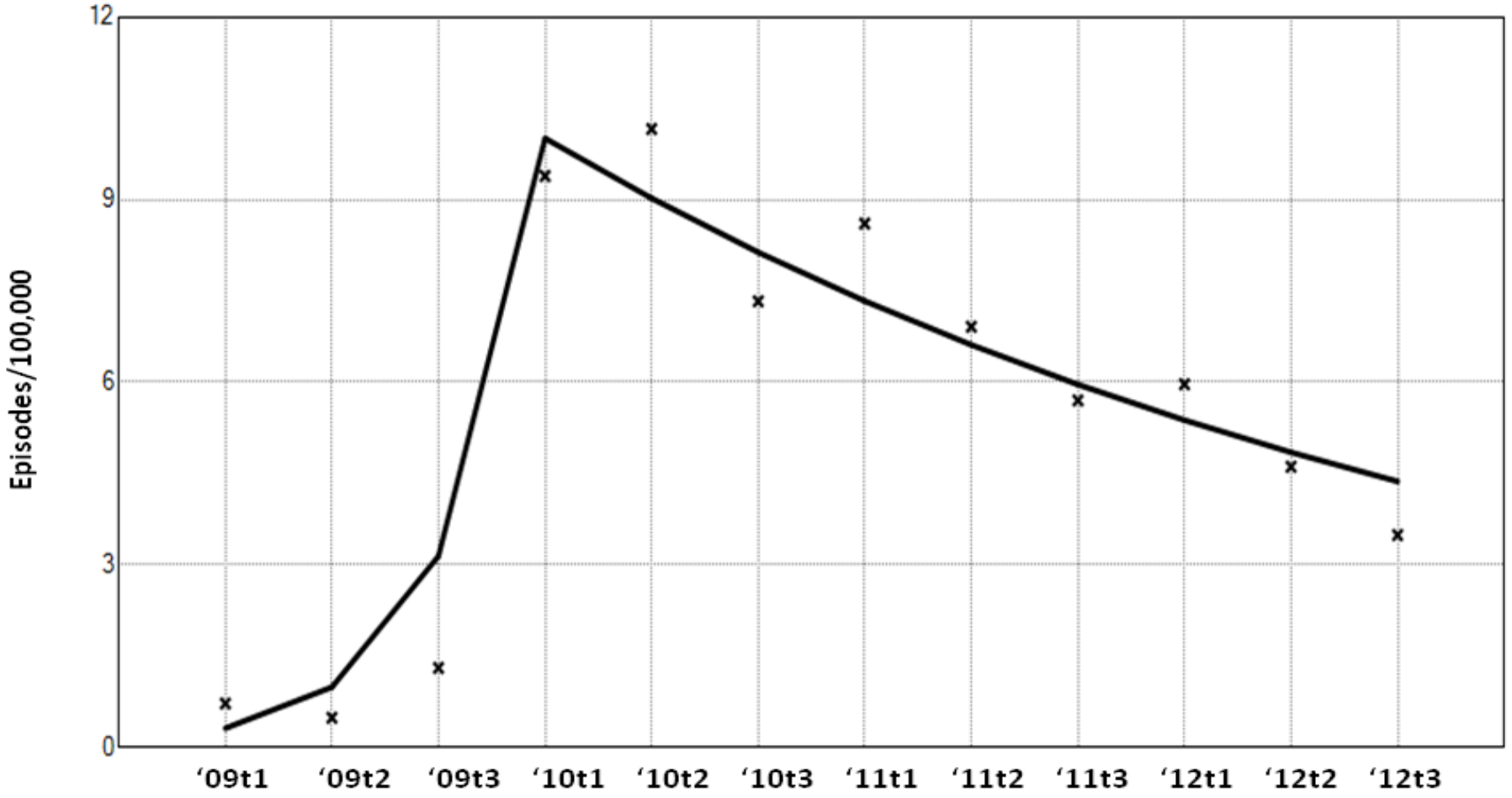


Figure 8.7 Joinpoint regression analysis of all new NPS related cases attending for a first ever episode of addiction treatment – **NPS incidence**. Rates per third of year and fitted joinpoint regression lines of trends for addiction treatment episodes among people aged 18-34years, from first third of 2009 (‘09t1) to final third of 2012 (‘12t3)

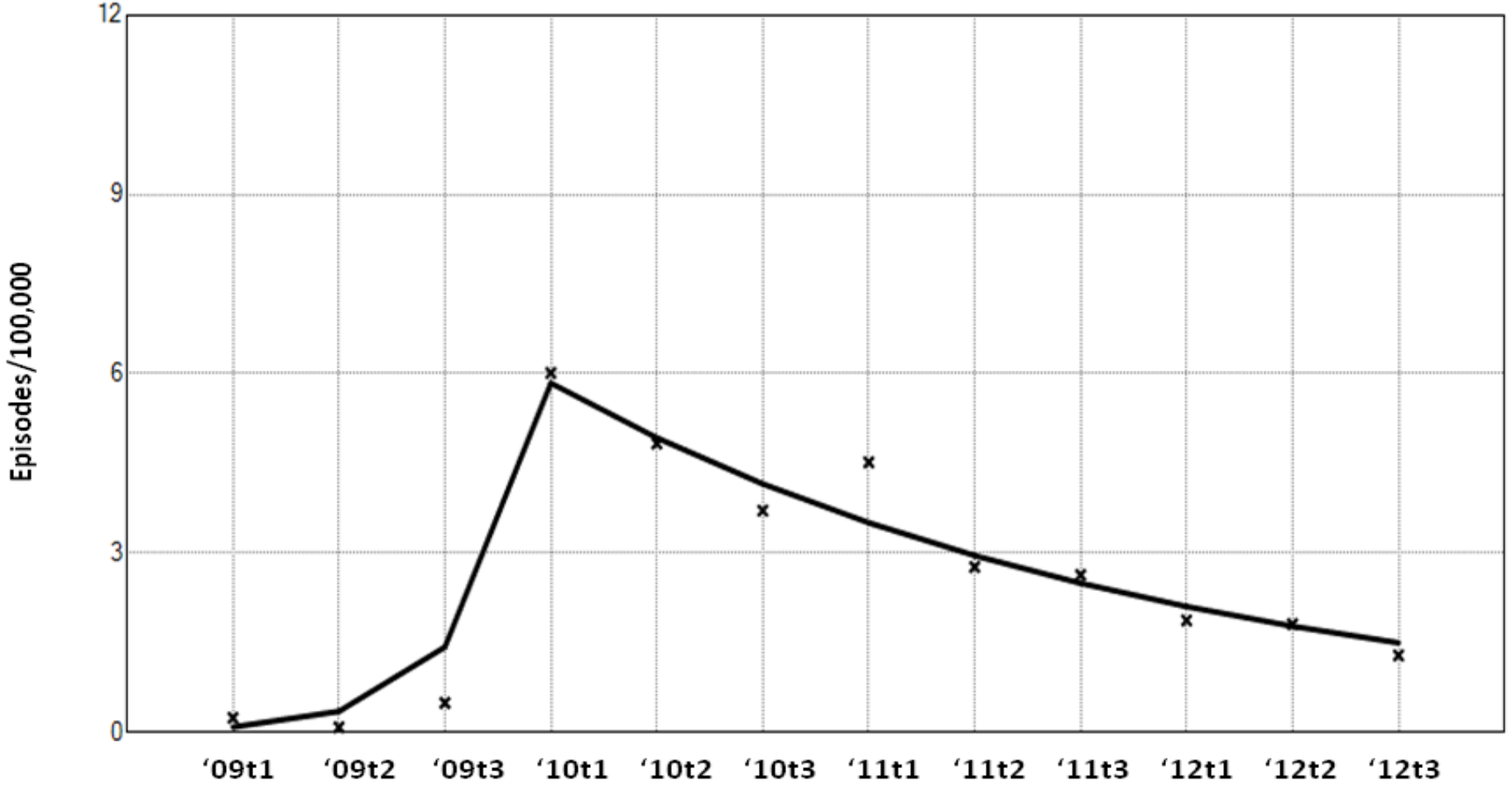


Figure 8.8 Joinpoint regression analysis of rate of presentations where **cannabis** was main drug among episodes unrelated to NPS.
Rates per third of year and fitted joinpoint regression lines of trends for addiction treatment episodes among people aged 18-34years, from first third of 2009 (‘09t1) to final third of 2012 (‘12t3)

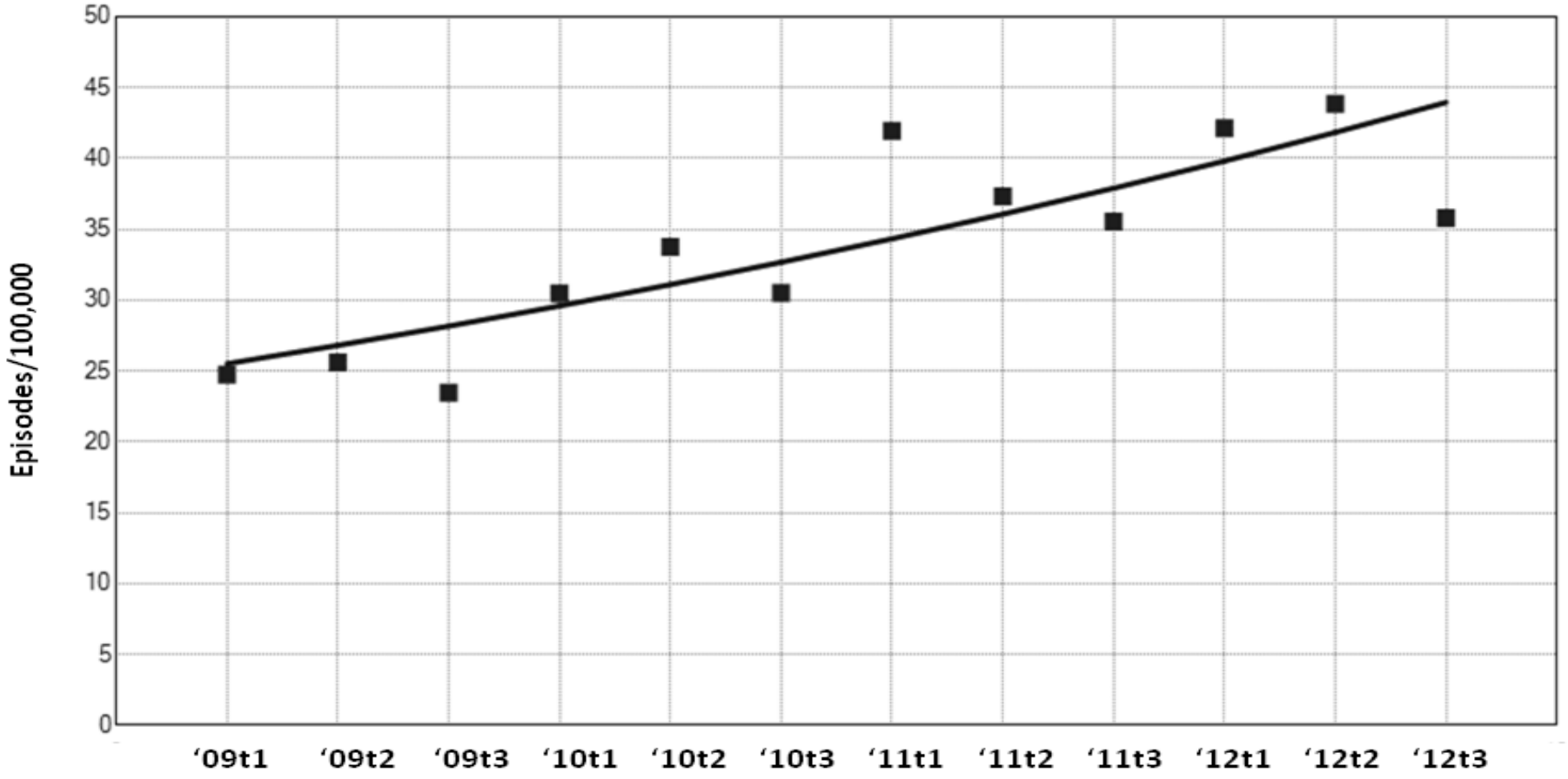
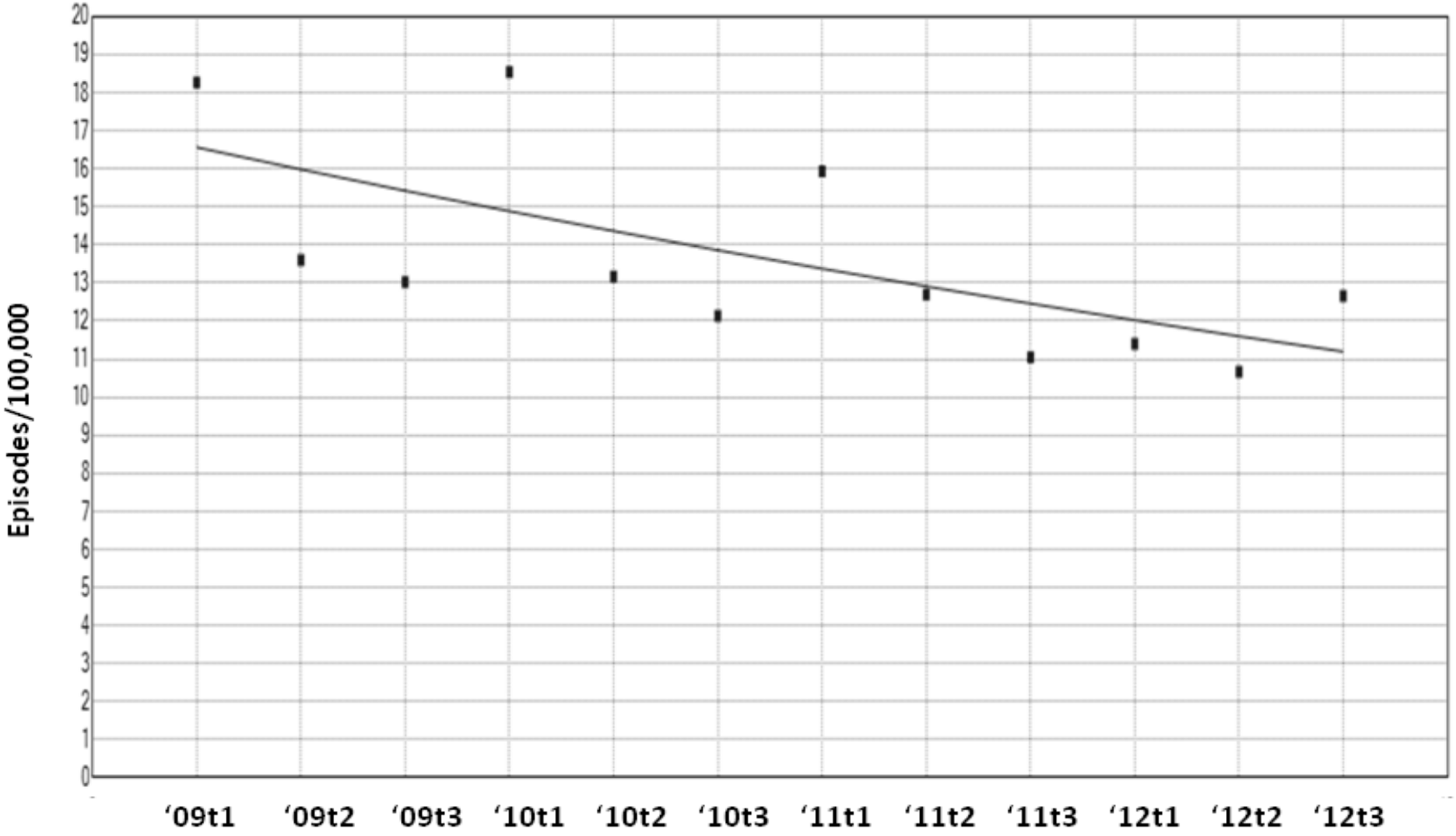


Figure 8.9 Joinpoint regression analysis of rate of presentations where **cocaine** was main drug among episodes unrelated to NPS.
Rates per third of year and fitted joinpoint regression lines of trends for addiction treatment episodes among people aged 18-34years, from first third of 2009 (‘09t1) to final third of 2012 (‘12t3)



8.6 Discussion

We found that NPS-related episodes of addiction treatment in Ireland increased from a very low base in 2009 to peak in early 2010, when headshops were also at their peak. During this headshop era, from January to August 2010, one in every 24 episodes of addiction treatment among young adults involved problematic NPS use. This adds to the evidence that NPS can indeed cause substance use disorders and do generate treatment demand. [30]. Although NPS were relatively new to the drugs marketplace in Ireland, they rapidly gained a substantial foothold among young people, being second only in popularity to cannabis.[28] If it was easy access via an extensive network of headshops which was contributing to the their popularity, it seems possible that the rate of treatment attending NPS related substance use disorders would have climbed higher in time.

The rate of attendance did not simply plateau following the headshop closures. It declined progressively by almost 50% over the two years after the termination of legal sale of NPS, and declined more acutely among young people who had never sought drug addiction treatment previously. The onset of the decline in NPS-related cases coincided with legislative changes which targeted NPS and which resulted in mass closure of headshops.

While a NPS was the main problem drug in 39% of NPS related attendances in 2010, this proportion fell to 16% in 2012. This indicates that problematic NPS use did continue to feature in treatment episodes following the headshop closures, but it was more likely to be a peripheral problem in those later cases. This mirrors the findings previously reported for adolescents attending addiction treatment.[26]

The examination of data on episodes of drug treatment which were unrelated to NPS indicates that the changes in trend of NPS episodes were not reflective of some general change in treatment seeking or treatment availability during the study period. We found no evidence of any adverse effect of the headshop closures on addiction treatment episodes linked to other specific substances. However, given the relatively

low rate of NPS related episodes compared to rates associated with other drugs, we think it unlikely that this analysis would have the ability to detect a substantial move of would-be NPS users to other drug categories.

Strengths of this study include the use of a national dataset involving a large number of treatment episodes and the ability to simultaneously explore for changes in non-NPS related treatment episodes. Limitations include the fact that there was no unique patient identifier, so an episode of treatment attendance is used as the unit of analysis and no adjustment could be made for possible multiple attendances by the same person. A separate analysis was conducted, however, for cases on their first treatment episode, these therefore being unique individuals. The patterns to emerge from that subset were similar to the full sample. Coverage of the NDTRS is over 70% of services but it is not possible to fully ascertain what effect or bias the exclusion of the data of the non-participating services may have had on the results. However there were no NPS-specific services in Ireland at the time and service participation did not alter over the study period. Treatment services have finite capacity. Consequently, if there had been any dramatic increase in demand for overall addiction treatment it would be unlikely to produce an immediate increase in treatment episodes of similar magnitude.

The previous Irish study of this issue involved a small sample, was specific to adolescents, confined to just one treatment site in one city and examined change over only a one year period.[26] That study found a very substantial fall in NPS-related cases following the headshop closures and found a decline in problem severity where NPS use did persist. This study indicates that these changes generalise to adults aged 18-34 years across the country and importantly, that they were sustained over a two year period at least. While the impact of legislation on the entire group of NPS has not been examined in other countries, there are many other examples of declines in use and harms following legislative bans of specific NPS.[22-25] For legal drugs such as alcohol and tobacco, it is generally accepted that curtailing availability is an effective strategy to reduce harm.[31,32] Recent Australian research indicates that many young

people interpret legal sale as an indication of safety and report increased willingness to use NPS in that scenario. [33]

Our findings are consistent with a hypothesis that the legislation and consequent closure of the headshops contributed to a reduction in NPS-related substance use disorders in Ireland. However, there are alternative possible explanations for the observations and the study design does not exclude the possibility that the observed change is simply a coincidence. It has been suggested that criminalization of drug use may cause people with dependence to be reluctant to access treatment.[34] Secondly, the substantial adverse publicity which NPS generated in Ireland during 2010 may have contributed to a peak in referrals, more vigilant screening for NPS use disorders among people accessing treatment and also to a preventative impact upon subsequent use in the general population. Patterns of drug use tend to fluctuate over time, whether legislative changes occur or not.[35] Escalating youth unemployment, which occurred over the period of this study, is an example of a contextual factor which can contribute to increases in drug problems.[36] Such societal changes complicate interpretation of our findings. If the decline in NPS-related presentations was indeed related to the closure of the headshops, this impact may not generalise to other countries where supply of NPS is primarily via the internet.

While the addition of many NPS to the Misuse of Drugs Act in May 2010 was associated with closure of many headshops, it was the Criminal Justice (Psychoactive Substances) Act which effectively ended the sale of NPS by headshops. This Act was innovative and controversial[8]. It sought to catch all current and future NPS, it aspired to end the 'cat and mouse game' being played out between legislators and the chemists designing NPS. Other countries in Europe have enacted similar legislation in recent years.[2,8] While legislation in New Zealand indicates a willingness in principal to regulate sale and supply of NPS, implementing this in practice has proven complex and the current regime appears to have resulted in de facto prohibition. [2,8] Whatever their legislative response, we hope that other countries will evaluate the impact of legislative changes on NPS related harms, as drawing general conclusions from the experience of individual countries has proving both divisive and problematic. [37]

The substantial and progressive decline in addiction treatment episodes linked to NPS in the two years after the enactment of legislation which targeted NPS and the headshops selling them is a very positive development from a public health perspective. While policy responses based on prohibition type principals appear to have fallen out of favour globally in the past decade, the experience of Ireland's response to NPS suggest that such polices remain a legitimate component of society's response to this complex and ever-changing challenge.

8.7 Author Contributions

BPS conceived the study question and examined the background literature. BPS lead on the statistical analysis with input from SL. BPS, SL & WC were each involved in interpretation of the data. BPS lead on the drafting of the manuscript. SL & WC also contributed to the drafting of the manuscript. BPS, SL & WC read and approved the final manuscript.

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Chapter 9

Legislation targeting head shops selling new psychoactive substances and changes in drug related psychiatric admissions: A national database study.

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9.1 Context of this chapter within overall Thesis

This final study builds upon the two previous studies in Chapters 7 & 8, to examine another aspect of potential NPS related harm. It returns to the harm examined in the OST study in chapter 6, this being mental health. Like the study in the previous chapter, this study makes use of a national database and focuses again on young adults. Given the evidence that NPS certainly have the potential to precipitate and exacerbate acute mental health problems, this study seeks to determine if there was any detected change in the trend of drug related psychiatric admissions in Ireland coinciding with the arrival and departure of head shops.

9.2 Abstract

Background: New psychoactive substance (NPS) use can cause or exacerbate acute psychiatric disorders. These may result in drug related psychiatric admissions (DRPA). In Ireland, there was a rapid expansion in the number of head shops selling NPS in early 2010. Young adults, especially young males, demonstrated high rates of NPS use. Government responded to public protests regarding the head shops by enacting legislation in May and August 2010 to end this trade. We sought to determine if changes in head shop activity coincided with changes in the rate of DRPA.

Methods: The national database on psychiatric admissions was examined. Eighteen to 34 year-olds admitted from 2008-2012 were included. There is no method of identifying NPS related DRPA specifically. The head shop era was taken as January to August 2010 inclusive. We compared the monthly rate of DRPA during this period to the same months in each of the other years. Joinpoint regression analysis was also utilised to examine for the presence of changes in trend of DRPA.

Results: There were 3670 DRPA over this 60-month period, 12% of all admissions. The median monthly rate/100,000 of DRPA was 6.1 in 2010 during the head shop era and this was significantly higher than the rates in 2008 (4.8, p=0.003), 2009 (5.0, p=0.005) and 2012 (5.0, p=0.003). The rate was 5.7 (p=0.065) in 2011. Joinpoint regression identified a significant downward trend change which occurred in July 2010 (95% CI Feb 2010 to April 2011). Young males aged 18 to 24 years showed evidence of greatest change in DRPA, a trend of rising admissions changing to one of declining admissions in May 2010 (95% CI Feb 2010 to October 2010). After May 2010, the model estimated a decline in DRPA of 1.4% per month (95% CI 0.7 to 3.7% decline) among those young males.

Conclusions: The expansion of a network of head shops selling NPS coincided with an increase in the overall rate of DRPA. The cessation of NPS sale by head shops coincided with a reversal in this upward trend. Causality cannot be determined. The changes in DRPA were most evident in very young men.

9.3 Introduction

New psychoactive substances (NPS) are a source of international concern, being associated with a range of addiction, medical and mental health problems.[1,2] The arrival of NPS, and the head shops selling them, has prompted substantial debate among policy makers.[3-6] Some countries have enacted novel legislative approaches in the hope of reducing NPS-related harms across the population.[1] Ireland passed the Criminal Justice (Psychoactive Substances) Act in August 2010 in response to widespread public protest at the vast number of head shops selling NPS which had

opened across the country in the preceding months.[7] This legislation successfully targeted the high-street businesses selling NPS. It provoked considerable criticism from experts in the fields of sociology and drugs policy.[3] Some predicted that prohibition styled legislative responses would increase harms.[8]

There is some data from Ireland indicating that addiction treatment episodes related to NPS use escalated very rapidly in the first months of 2010 and then declined in the two years after the closure of head shops.[9,10] NPS such as synthetic cannabinoids and cathinones appear to have a particular propensity to provoke or exacerbate psychiatric symptoms and this may result in hospitalization.[1,11-13] Lally et al conducted a survey of adults attending mental health services in Ireland when the head shops were at their peak level of activity and found that 24% of inpatients reported use of NPS in the past year, rates of use being highest in young males.[14]

If the expansion and subsequent abrupt closure of head shops was genuinely associated with changes in NPS use and related harms, it is possible that this may have manifested itself in changes to acute psychiatric presentations linked to NPS. If these events were sufficiently numerous, it seems possible that they may have had a detectible impact on the overall rate of drug related psychiatric admissions (DRPA). In this study, we sought to examine this possibility by exploring rates of DRPA in Ireland prior to, during and after the era of widespread head shop expansion.

9.4 Method

9.4.1 Setting & Context

In Ireland the usual route to mental health services is by referral from primary care or the emergency department and most patients are treated on an outpatient basis. There are about 20,000 psychiatric inpatient admissions per annum, with 90% of these being voluntary. The decision to admit is largely based upon clinical severity and this is determined by doctors trained in psychiatry. Around 2010, there was a significant increase in the number of psychiatric beds available for people aged under 18 years

and there have been determined efforts to avoid admitting children into adult psychiatric hospitals.

In recent decades Irish mental health services have altered their approach to addiction related presentations. In the latter part of the 20th century, alcohol dependence was a frequent reason for admission into psychiatric hospitals in Ireland, accounting for about 20% of all admissions.[15] At that time, a person could be involuntarily detained and treated in a psychiatric hospital for the treatment of addiction. In 2006, Ireland's mental health policy document, 'A Vision for Change', stated that "the major responsibility for care of people with addiction lies outside the mental health system". That same year, a revised Mental Health Act was implemented and this removed addiction as a reason for involuntary admission (i.e. 'sectioning' a patient). The rate of alcohol related psychiatric admissions declined by two-thirds from 1990 to 2006.[16,17]

Ireland underwent significant social changes over the period 2008-2012, the economy entering into a recession after a decade of sustained growth. Youth unemployment increased rapidly and a pattern of immigration quickly turned into a period of emigration. The youth unemployment rate increased dramatically from 10% in January 2008 to 27% in January 2010, and then peaked at 31% in January 2012, before falling back slightly to 28% in January 2013.

The Irish general population survey of 2010-11 found that past year prevalence of cannabis use was 10% among 15-34 year olds, and this was unchanged since the 2006-07 survey. [18] The past year prevalence of NPS, cocaine and amphetamines in this age range were 7%, 3% and 1% respectively. Past year NPS use was only 1% in people aged over 34 years. Young males were three times more likely than young females to have used NPS in the past year.

9.4.2 Head shops

Over the period from 2009 to 2010, there was a substantial increase in the number of head shops in Ireland peaking at 102 premises in May 2010, which is about one shop per 45,000 people.[7,10,19] This constituted a five-fold increase in the number of

head shops in existence in 2008. In response to public protests surrounding these new businesses which began selling a wide range of NPS in late 2009, the Irish government opted to proceed with a two-pronged legislative approach. Firstly, there was a legislative ban, adding over 100 substances to the pre-existing Misuse of Drugs Act in May 2010.[20] This made possession, sale and supply of the named drugs a criminal offence. While this Act coincided with closure of many head shops, it seems likely that it contributed to the prompt arrival of non-banned substances such as naphyrone and flourotropococaine which were then implicated in further DRPA.[7,21] This phenomenon of head shops simply switching from a banned drug to a drug not yet banned has been seen in many countries.[22]

In the hope of ending this game of 'cat and mouse', the controversial Criminal Justice (Psychoactive Substances) Act was enacted in late August 2010.[23] This Act was focused primarily at vendors of NPS. It states that 'a person who sells a psychoactive substance knowing or being reckless as to whether that substance is being acquired or supplied for human consumption shall be guilty of an offence'.

These two Acts resulted in a dramatic decline in the number of head shops, initially to 48 shops in June 2010, and then falling to 10 shops by October 2010.[10] Undercover investigations by the Irish police force indicated that those few shops which remained open after September 2010 were no longer selling NPS. Based upon the changes in the known number of head shops and the evidence that NPS related addiction treatment episodes escalated greatly at the start of 2010, we view the months from January 2010 to August 2010 as the 'head shop era' in Ireland.[9,10]

9.4.3 Measures

Basic clinical information on all admissions is completed by the treating team following a psychiatric admission. At discharge the clinical team determine the primary diagnosis, and any additional diagnoses, which led to the admission. Diagnosis is determined using ICD-10 criteria. These data, along with demographic information, are sent to Ireland's Health Research Board (HRB) for entry into the National

Psychiatric In-Patient Reporting System (NPIRS) database. For the purposes of this study, hospitalisations were defined as being a drug-related psychiatric admission (DRPA) if either the primary or any secondary discharge diagnosis was in the F11 to F19 ICD-10 diagnostic categories.

Every psychiatric inpatient unit in the Republic Of Ireland participates in NPIRS. There were no changes to NPIRS during the study period. An audit of the NPIRS database took place in 2012. This audit returned an accuracy rate for the data of 97.8% (2.2% discrepancy rate) with the majority of fields exceeding a 99% accuracy rate. All fields were within acceptable levels of completeness. Both the accuracy and completeness rate were within the benchmark set for the audit of 95% (5% discrepancy rate).

9.4.4 Participants. Inclusion and exclusion criteria

We examined all psychiatric admissions of people aged between 18 years and 34 years inclusive in the Republic of Ireland over the five years from 2008 to 2012. We excluded people under the age of 18 years in view of the policy changes regarding psychiatric admissions among this age range over the period in question. We opted to focus upon adults under 35 years of age as it was this age range which demonstrated the highest rates of NPS use in both general population and mental health service user studies.[14,18] Therefore, if the arrival and departure of the head shops resulted in changes in psychiatric events linked to NPS use, it was in this age range that change should be most evident. There is no unique patient identifier in Ireland. Therefore, the unit of analysis was episode of admission, not individual patient. Ethical approval was provided by the research ethics committee of the National Drug Treatment Centre. For data protection reasons, cell values of less than 5 episodes are not reported.

9.4.5 Statistics

In order to contrast proportions, such as the characteristics of DRPA and admissions unrelated to drug use, we utilised the chi square test. We also reported odds ratios

and estimates of the 95% confidence intervals of the odds ratio to indicate the direction and magnitude of differences. These are estimates of the confidence intervals as the episodes are not completely independent. An unknown proportion of episodes involve re-admission of some individuals on more than one occasion during the five year period.

We calculated the crude rate of admissions per month among people aged 18-34 years. Rates are reported per 100,000. The population at risk was obtained from the population estimates provided by the Central Statistics Office. In view of the age and gender differences in NPS use in the general population samples and in NPS related addiction treatment episodes, we examined the rates by gender and age group (18-24 years and 25-34 years).[10,18]

In order to contrast DRPA during the head shop era with the period before and after the head shops, we focused upon the months January to August inclusive in each year to ensure seasonal factors would not confound the results. We used the Mann Whitney U test to compare the monthly rates of DRPA during this period of 2010 against those of the other four years.

Finally, we used the Joinpoint Regression Program, version 4.3.1.0 (National Cancer Institute, Bethesda, Maryland, USA, http://surveilance.cancer.gov/joinpoint) to further examine trends in the rate of admissions. Joinpoint regression is a log-linear model which uses Poisson regression, creating a Monte Carlo permutation test to identify points where the trend line changes significantly in magnitude or direction.[24] Although initially developed for use in examining changes in cancer trends, it has been widely used to examine trends in rates of other disorders, including psychiatric conditions.[25,26] The location of the joinpoints is data driven. Analysis starts by fitting a straight line (i.e. zero joinpoints) and tests whether the addition of one or more joinpoints yields a statistically significant improvement in fit. The estimated percentage change per month (PCM) is calculated for each best fitting line segment between joinpoints, along with 95% confidence intervals of the PCM. The minimum number of observations from a joinpoint to either end of the data and the

minimum number of observations between two joinpoints were set at three and four respectively (these being the default settings).

9.5 Results.

9.5.1 Characteristics of DRPA

There were 30647 psychiatric admissions of young adults over the course of this study, and 12.0% of these were DRPA. The characteristics of these admissions are outlined in Table 9.1, along with a comparison between DRPA and the non-drug related admissions. Admission for drug related reasons was associated with male gender, younger age, unstable accommodation, being single or divorced and less skilled work. DRPA were more likely to be voluntary, a first admission and in a public hospital. In 2010, 13.6% of all admissions were DRPA and this was a significantly greater proportion than that observed in any other individual year.

Table 9.1 Characteristics of 30647 admissions to psychiatric hospitals from 2008-2012 by people aged 18-34 years, by drug related admission.

	Total		Drug Related		Non-Drug Related		OR[a]	95% CI	p
	N	(%)	N	(%)	N	(%)		OR	value
Total	30647	(100)	3670	(12.0)	26977	(88.0)			
Gender									
Male	17152	(56.0)	2799	(76.3)	14353	(53.2)	2.8	(2.6-3.1)	<0.001
Female	13495	(44.0)	871	(23.7)	12624	(46.8)	1.0		
Age									
Under 25years	10568	(34.5)	1546	(42.1)	9022	(33.4)	1.4	(1.3-1.5)	<0.001
25-34 years	20079	(65.5)	2124	(57.9)	17955	(66.6)	1.0		
Accommodation									
No Fixed Abode	453	(1.5)	121	(3.3)	332	(1.2)	2.7	(2.2-3.4)	<0.001
Has accommodation	30194	(98.5)	3549	(96.7)	26645	(98.8)	1.0		
Marital Status									
Married	2425	(7.9)	137	(3.7)	2288	(8.5)	1.0		
Single	26177	(85.4)	3320	(90.5)	22857	(84.7)	2.4	(2.0-2.9)	<0.001
Widowed	36	(0.1)	<5	(0.1)	34	(0.1)	1.0		0.98
Divorced	117	(0.4)	12	(0.3)	105	(0.4)	1.9	(1.0-3.7)	0.04
Unspecified	1892	(6.2)	199	(5.4)	1693	(6.3)			
Socio-Economic Group									
Professional,							1.0		
Employer	3212	(10.5)	171	(4.7)	3041	(11.3)			
Agricultural sector	321	(1.0)	11	(0.3)	310	(1.1)	0.6	(0.3-1.2)	0.14
Non-Manual	4481	(14.6)	358	(9.8)	4123	(15.3)	1.5	(1.3-1.9)	<0.001
Skilled/semi-skilled	4080	(13.3)	573	(15.6)	3507	(13.0)	2.9	(2.4-3.5)	<0.001
unskilled	1934	(6.3)	284	(7.7)	1650	(6.1)	3.1	(2.5-3.7)	<0.001
unspecified	16619	(54.2)	2273	(61.9)	14346	(53.2)			
Voluntary Admission									
Voluntary	27731	(90.5)	3400	(92.6)	24331	(90.2)	1.0		
Involuntary							0.7	(0.6-0.8)	<0.001
('sectioned')	2916	(9.5)	270	(7.4)	2646	(9.8)			
Previous admission									
First Admission	11681	(38.1)	1533	(41.8)	10148	(37.6)	1.2	(1.1-1.3)	<0.001
Readmission	18966	(61.9)	2137	(58.2)	16829	(62.4)	1.0		
Hospital Type									
Public hospitals	25726	(83.9)	3256	(88.7)	22470	(83.3)	1.6	(1.4-1.8)	<0.001
Private hospitals	4921	(16.1)	414	(11.3)	4507	(16.7)	1.0		
Admission Year									
2008	6,524	(21.3)	669	(18.2)	5,855	(21.7)	0.7	(0.6-0.8)	<0.001
2009	6268	(20.5)	713	(19.4)	5555	(20.6)	0.8	(0.7-0.9)	<0.001
2010	6316	(20.6)	857	(23.4)	5459	(20.2)	1.0		
2011	5927	(19.3)	729	(19.9)	5198	(19.3)	0.9	(0.8-1.0)	0.04
2012	5612	(18.3)	702	(19.1)	4910	(18.2)	0.9	(0.8-1.0)	0.04

[a] OR = Odds ratio

Table 9.2 outlines the drugs involved in the DRPA. The most common drug category was F19 which indicates multiple drugs or drugs other than the typical substance groups. The most frequently encountered specific drug category contributing to DRPA was cannabinoids (F12). While the exact type of psychiatric disorder was unspecified in 44.4% of cases, the most common types specified were acute intoxication, psychotic disorder and dependence.

Table 9.2 Characteristics of 3670 drug related psychiatric admissions among 18-34yo, 2008-12

	Number	(%)
Type of Drug Related Admission		
1^{o} Diagnosis is F11-19	2875	(78.3)
2^{o} diagnosis, but not 1^{o} diagnosis, is F11-19	795	(21.7)
Specific Primary Drug related diagnosis		
F11 - Opioids	227	(7.9)
F12 - Cannabinoids	368	(12.8)
F13 - Sedatives	72	(2.5)
F14 - Cocaine	46	(1.6)
F15 - Other stimulants	30	(1.0)
F16 - Hallucinogens	19	(0.7)
F17 - Tobacco	<5	(0.0)
F18 - Volatile Substances	6	(0.2)
F19 - Multiple drug use or Other drugs	2106	(73.3)
Primary Drug related disorder type		
F1x - clinical condition not specified	1277	(44.4)
F1x.0 - Acute intoxication	444	(15.4)
F1x.1 - harmful use	209	(7.3)
F1x.2 - Dependence	402	(14.0)
F1x.3 - Withdrawal state	36	(1.3)
F1x.4 - Withdrawal state with delirium	10	(0.3)
F1x.5 - Psychotic Disorder	443	(15.4)
F1x.6 - Amnesic syndrome	8	(0.3)
F1x.7 - Residual psychotic disorder	9	(0.3)
F1x.8 - Other mental disorder	28	(1.0)
F1x.9 - unspecified mental disorder	9	(0.3)
Non-drug related primary diagnosis for admissions with drug related secondary diagnosis		
F10 : Alcohol related disorders	210	(26.4)
F20-29 : Schizophrenia, schizotypal, delusional disorders	184	(23.1)
F30-39 : Mood (affective) disorder	219	(27.5)
F40-49 : Neurotic, stress-related & somatoform disorders	55	(6.9)
F60-69 : Disorders of adult personality and behaviour	113	(14.2)
F00-09, 50-59, 70-99 : Other disorders	14	(1.8)

9.5.2 Comparison between the head shop era and other years

Table 9.3 contrasts the crude monthly rates of DRPA over the eight month head shop era with the same months in the other four individual years. It indicates that the rates of admission in 2010 were significantly higher than in 2008, 2009 and 2012. The actual crude rates of DRPA per 100,000 during this eight month period for each of the years from 2008 to 2012 are 38.2, 40.1, 48.4, 44.2 and 41.9 respectively. The increase from 2008 to 2010 was 27% and the decrease from 2010 to 2012 was 13%.

Table 9.3. Rates of drug related psychiatric admissions per month among 18-34 year olds, comparing the head shop era of January to August 2010 with the same period in other years.

Year	Monthly rate/100,000		Comparison with 2010
	Median	(IQR)	p value
2008	4.8	(3.9 to 5.7)	0.003
2009	5.0	(4.4 to 5.6)	0.005
2010	6.1	(5.6 to 6.6)	N/A
2011	5.7	(4.9 to 6.0)	0.065
2012	5.0	(4.9 to 5.8)	0.003

9.5.3 Joinpoint trend analysis

Table 9.4 and Figures 9.1 to 9.3 present the results of the Joinpoint trend analysis. This analysis found no evidence of a trend change in the rate of all psychiatric admissions in this age range and the overall trend was not significantly different from zero (Figure 9.1, p=0.25). For DRPA, the best fitting joinpoint model indicated a trend change in July 2010 (Figure 2). Over the 30 months prior to this, the rate of DRPA was increasing significantly by 1.0% per month (p=0.002). Then in July 2010, this trend of increasing DRPA turned downwards. The downward slope after July 2010 was not significantly different from zero (p=0.14). Analysis of the female subgroups and the older male subgroup revealed no significant trend changes (i.e. zero joinpoints). Analysis of the young adult males revealed two trend changes, the first occurring in January 2010 when there was a substantial increase in the rate of DRPA (Figure 9.3). This was then followed four months later by a downward turn in the rate in May 2010 until the end of the study period. This decline of 1.4% per month after May 2010 was significantly different from zero (p<0.001).

Table 9.4. Trends in crude rates of psychiatric admissions per month among people aged 18-34 years between 2008 and 2012.

	Period	PCM[a]	(95% CI PCM)[b]	First Joinpoint	(95% CI of Joinpoint)	Period 2	PCM	(95% CI PCM)	Second Joinpoint	(95% CI of Joinpoint)	Period 3	PCM	(95% CI PCM)
All admissions	Jan 08 to Dec 12	-0.1	(-0.2, 0.0)										
DRPA[c]	Jan 08 to Jul 10	1.0	(0.4, 1.6)	Jul 10	(Feb 10, Apr 11)	Jul 10 to Dec 12	-0.5	(-1.1, 0.2)					
DRPA													
18-24 yo Males	Jan 08 to Jan 10	0.8	(-0.5, 2.1)	Jan 10	(Nov 08, Apr 10)	Jan 10 to May 10	12.8	(-15.6, 50.8)	May 10	(Feb 10, Oct 10)	May 10 to Dec 12	-1.4	(-0.7, -3.7)
18-24 yo Females	Jan 08 to Dec 12	0.4	(-0.3, 1.0)										
25-34 yo Males	Jan 08 to Dec 12	0.0	(-0.3, 0.3)										
25-34 yo Females	Jan 08 to Dec 12	0.3	(-0.3, 0.8)										

[a] PCM = Estimated per cent change per month for this segment from the best fitting Joinpoint model

[b] CI = confidence interval

[c] DRPA = Drug related psychiatric admission

Figure 9.1. Monthly rate of psychiatric admissions for all diagnoses among 18 to 34 year olds, and trend line from the joinpoint analysis indicating the best fitting model.

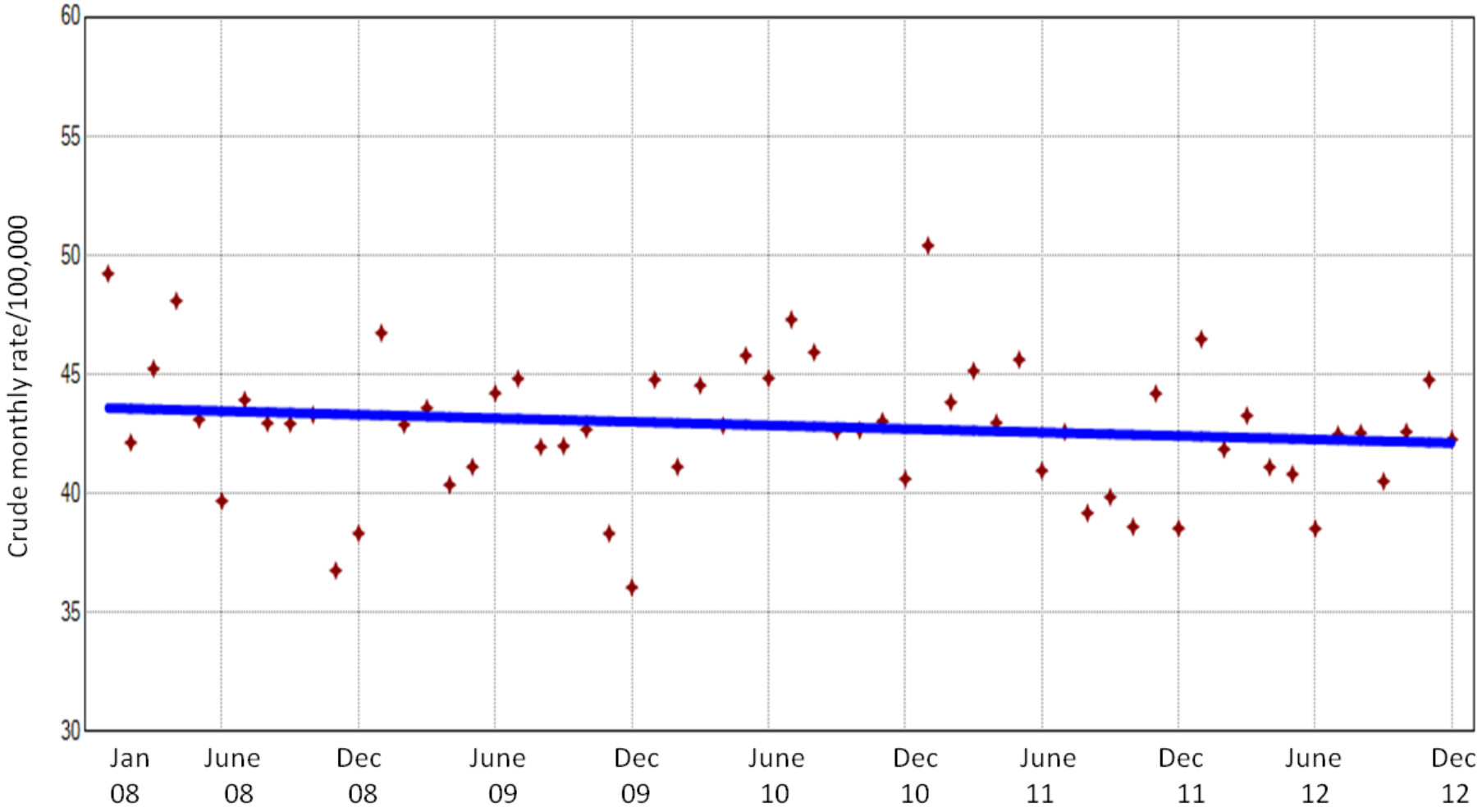


Figure 9.2. Monthly rate of DRPA among 18 to 34 year olds, and trend line from the joinpoint analysis indicating the best fitting model.

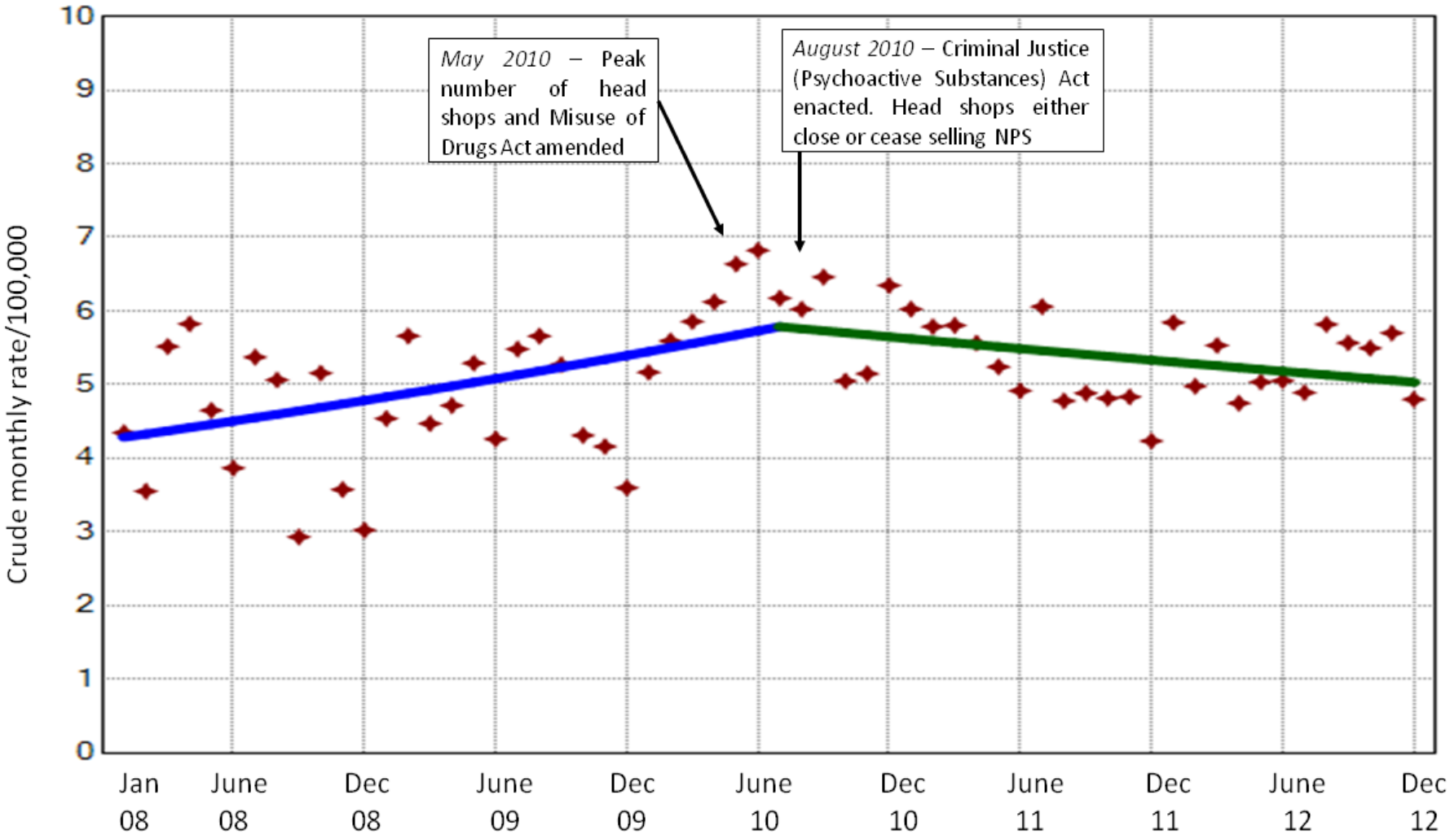
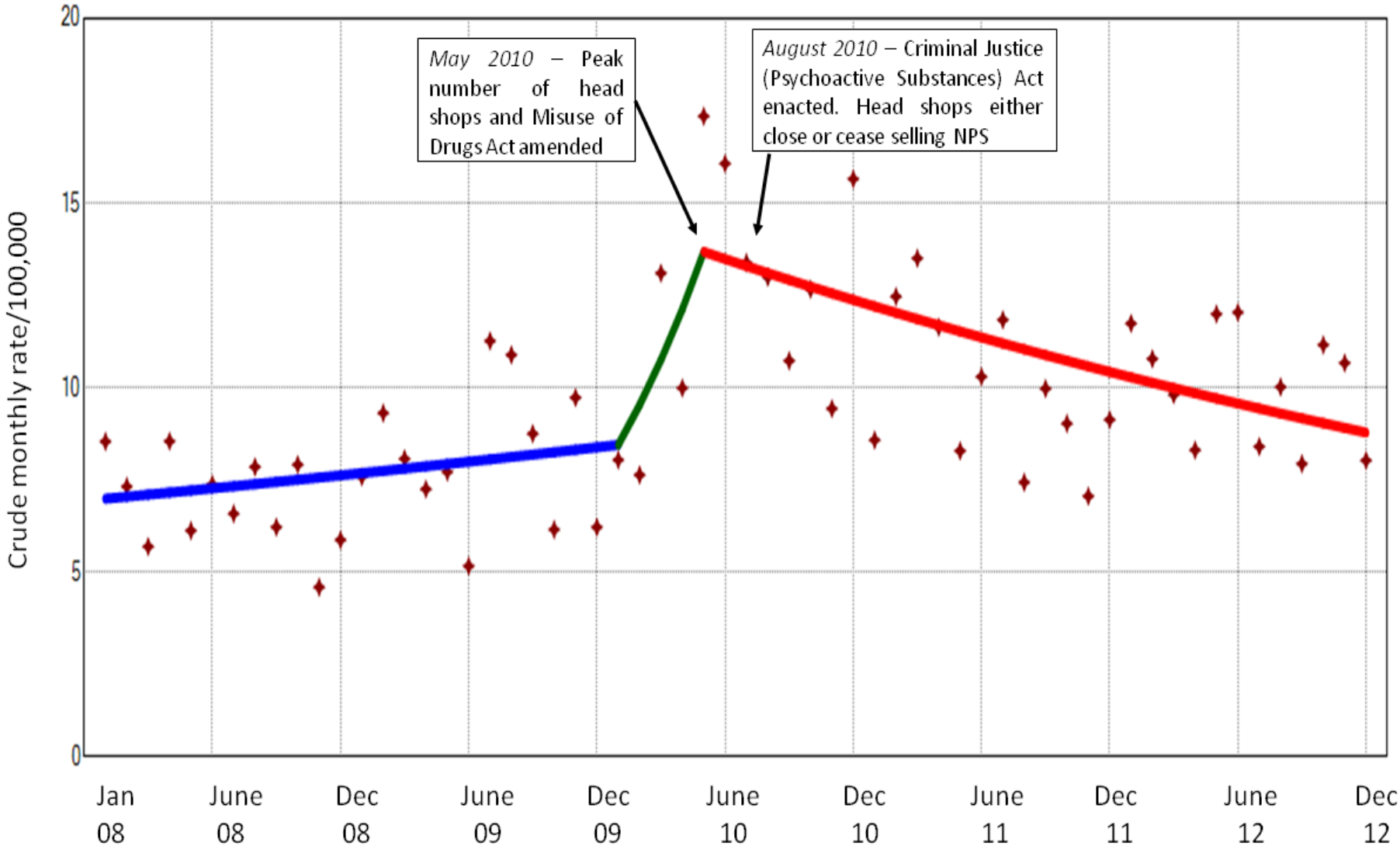


Figure 9.3. Monthly rate of DRPA among 18 to 24 year old males, and trend line from the joinpoint analysis indicating the best fitting model.



9.6 Discussion.

9.6.1 Changes in DRPA

We found that the rate of DRPA was significantly higher in 2010 during the head shop era than it was over the same months in the years before the major head shop expansion and also significantly higher than in 2012. The joinpoint trend analysis indicates that the pattern of escalating DRPA reversed and the best estimate of the turning point is July 2010, two months after the initial legislation beginning the head shop closures. These changes cannot be explained by alterations in the rate of overall psychiatric admissions among young adults in Ireland over the period 2008 to 2012 as these were static.

The most enthusiastic users of NPS in Ireland in 2010 were young males, who reported a rate of past year NPS use of 9.7%. This was approaching that of cannabis and vastly exceeded that of other 'traditional' drugs such as cocaine or ecstasy.[18] The study of Irish mental health service users also found the highest rates of NPS use among young males.[14] It was this subgroup of the population which also showed the most change in DRPA over this study period. The onset of the head shop era in January 2010 coincided with a dramatic increase in the rate of such admissions. The trend then reversed early in the summer of 2010, the best fitting joinpoint being May 2010, which coincides with the month in which the head shops began closing following the changes to the Misuse of Drugs Act. These changes in DRPA closely mirror the observed changes in NPS related addiction treatment episodes in Ireland which peaked in the first third of 2010 and then fell progressively by 48% over the following two years.[10] NPS related addiction treatment episodes also declined in adolescents.[9] The general population survey of 2014-15 also confirms that NPS use among young males reduced greatly, with past year use falling by four-fifths to 1.9%.[27,28] These changes along with those reported in this study are all pointing in the one direction.

9.6.2 Critics of prohibition styled policy towards NPS

In a review of stakeholders' views in Ireland following the Government action on NPS, it was concluded that the legislative changes were driven by a "moral panic" and constituted "a clear victory for traditional 'war on drugs' values".[3] Our finding of increased DRPA, along with the previous findings confirming high rates of NPS use by Irish psychiatric inpatients and increased NPS related addiction episodes, adds support to the view that Government action was preceded by evidence of real harms. This suggests that the early criticisms were probably excessive and premature.

The frequent role of NPS in psychiatric admissions has been described both in Ireland and elsewhere in the intervening years.[13,21] The study by Lally et al of mental health service users coincided with the peak in head shop activity. One third of the patients reporting NPS use denied use of illegal drugs.[14] Most of those who did report past use of illegal drugs indicated that NPS use was now supplemented on top of that use which continued unchanged. Both findings suggest that the arrival of NPS was adding to the overall burden of drug use and not simply displacing use of traditional drugs.

The UK has recently proceeded with its own version of the Psychoactive Substances Act, along with some other European countries.[1,6] In contrast to the UK, the equivalent Irish legislation was enacted with little or no warning and minimal consultation. In common with the Irish Act, the UK legislation has been greeted with criticisms from drug policy experts.[5,6]

Included among the criticisms, there were predictions that closure of the head shops would result simply in an immediate and effective migration of the NPS market to drug dealers and to the internet, with possible increased attendant risks.[8] Although there was clearly some movement of supply towards the black market, the evidence from this or other Irish studies does not support the pessimistic view that problems would persist unchanged or possibly deteriorate.[9,10,28] Following the head shop closures, the increasing rate of DRPA abruptly halted and began to decline. The simple comparison of the overall monthly rates indicates that they were significantly lower in 2012 compared to 2010, reverting back towards the rates seen in 2008 when the few existing head shops were not selling NPS. In the demographic group with the highest

rate of DRPA, young males, this decline was sustained and significant based upon the joinpoint analysis.

9.6.3 Impact of legislative bans elsewhere

In other countries which have proceeded down the route of legislative bans, there is a growing body of evidence for an impact on reducing NPS use and related harms. Of greatest specific relevance to our study, it was found in New Zealand that emergency psychiatric presentations linked to use of synthetic cannabinoids declined by 42% following legislation and there was also a sustained decline in general hospital admissions related to these drugs.[29,30] Also in New Zealand, use of BZP in a general population sample declined substantially following a ban of that drug.[31] In Scotland, a temporary class drug order on ethylphenidate was effective in reducing infections among people who inject drugs.[32] There was a reduction in attendances linked to mephedrone at emergency departments in the UK following the ban of that drug.[33] Stogner et al reported a decline in use by young adults of Salvia divinorum following a legislative ban in Florida.[34] Our findings appear to be the first which suggest a more general impact across a broad health related measure, as opposed to the drug specific changes highlighted here.

9.6.4 Impact on services

In spite of the policy changes on management of addiction issues by Irish mental health services in the years immediately preceding this study, DRPA continued to account for one in every eight admissions in this age range. This was the primary diagnosis in 78% of such admissions. Therefore changes to DRPA are not simply of academic interest. They impact substantially on the workload of adult mental health services.[13] DRPA were more likely to involve younger males, mirroring the higher prevalence of drug use in that demographic.[18] The analysis sheds very little light on the type of drugs involved in these admissions, most being coded as F19, indicating polydrug use or use of an individual substance which fell outside the specific

substance categories noted in ICD-10. Polydrug use is common among youth drug users in particular.[9, 35]

We know from data on addiction treatment episodes, mental health services and from drug user surveys that the most widely used NPS during this period in Ireland were synthetic cannabinoids and cathinone type substances.[9,10,14,19] Depending on the knowledge of both patient and doctor, a presentation linked to NPS could have been coded as F12, F15, F16 or F19. Consequently it was not possible to explore changes in NPS related psychiatric admissions specifically. Future iterations of the ICD diagnostic system may need to consider increasing the number of substances specified with a unique code to permit easier examination of trends relating to individual drugs or drug classes.

There is some evidence to indicate that NPS have a greater propensity to cause adverse psychiatric symptoms when compared to the more established drugs which they mimic such as cannabis or amphetamines,[11,12,28] Common mental health symptoms in people who use NPS include anxiety, paranoia and occasionally, psychosis.[2,14,21,28]

9.6.5 Strengths and limitations

Our inability to examine NPS related psychiatric admissions specifically could be viewed as a weakness of this study. However, from a public health perspective, the impact of the arrival and departure of the head shops on all DRPA is of most interest in any case. Simple drug policy measures can have unintended and adverse consequences.[36] In theory, increased NPS use may have diverted young people away from more psychotogenic substances. Similarly, reductions in NPS use due to curtailed access following head shop closures could theoretically cause users to return to other traditional but more dangerous substances. Consequently, we view the examination of the entire group of DRPA to be a feature which adds to the importance of these findings.

Overall, this study reveals a strong temporal relationship between the timing of the expansion and extinction of the sale of NPS by head shops with increases and then decreases in DRPA. This does not confirm causality. It is possible that some other unmeasured factor contributed to changes in DRPA. If the trends in DRPA are indeed related to NPS, there are factors other than legislation and head shop availability that may have lead to a decline in use. Patterns of drug use tend to wax and wane over time.[37] There was widespread media coverage of adverse effects of NPS use and health service education campaigns on this topic.[3] These may also have lead to reduced use and harms. It is also possible that the media attention around NPS at this time caused psychiatrists to be more likely to attribute psychiatric symptoms to drug use during this period. Although both pieces of legislation in Ireland occurred with minimal advance warning, it is possible that they caused short term changes in retailer or purchaser behaviour resulting in acute increases in sales and related harms. Ideally in epidemiological studies, one hopes that they occur over a period of social stability. This was not the case in Ireland which entered a major recession during these years. Rising youth unemployment may certainly have contributed to increased DRPA.[37] However, it cannot explain the downward turn in DRPA seen after 2010, as youth unemployment remained above those 2010 levels over the next two years.

Use of a national database with complete coverage of all psychiatric inpatient units constitutes a strength of this study. The absence of a unique patient identifier in Ireland represents a weakness. An unknown number of admissions comprised readmissions by the same individual during the five year study period. Data is not systematically gathered on outpatient attendances at mental health services in Ireland. Consequently, this study is confined to the small minority of patients with drug related psychiatric disorders who were admitted. This fact reduced our power to detect significant changes in such disorders.

9.6.6 Conclusions

Our findings indicate that the situation regarding DRPA in Ireland was on a trajectory of deterioration prior to Government action on head shops. While accepting the

important caveat that correlation does not prove causation, we found that this trend came to an abrupt halt around the time which the head shops ceased sale of NPS. The rate of admissions declined over the following two years as opposed to simply stabilising. Taken together with the other evidence on reduced NPS use in the general population, reduced NPS addiction treatment episodes, our findings on DRPA lend weight to the view that the steps taken in Ireland to address NPS were associated with a positive public health impact.

9.7 Authors contributions

BPS conceived the study question. BPS conducted the analysis and took the lead on the drafting of the manuscript. BPS, AD, KE, MC, SC and WC contributed to interpretation of results. BPS, AD, KE, MC, SC and WC read and approved the final manuscript.

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Chapter 10

New psychoactive substances in Ireland following the Criminal Justice (Psychoactive Substances) Act – why all the pessimism?

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Citation Reference:
Smyth BP. New psychoactive substances in Ireland following the criminal justice (psychoactive substances) act—why all the pessimism? *Addiction* 2017: 112;1686-1686. doi:10.1111/add.13804
Journal ISSN: 1360-0443
Journal Url: http://onlinelibrary.wiley.com/doi/10.1111/add.v113.4/issuetoc

10.1 Context of this chapter within the overall Thesis.

This brief chapter brings together the key findings of the preceding three chapters which examined different aspects of harms related to NPS. The letter was prompted by a review paper by Reuter & Pardo, published in the highly regarded journal *Addiction*, and entitled "Can NPS be regulated effectively? An assessment of the British Psychoactive Substances Bill". When reporting on the international evidence, this review stated:-

> *Governments around the world have attempted various solutions to the NPS problem, with depressing results.*

Although it acknowledged that Ireland was the “pioneer” of the type of “blanket prohibition” being contemplated by Britain, it reported that there was no systematic evaluation of its impact in Ireland. I felt that the NPS related studies included in this thesis could address that reported gap in the literature and challenge the view that the results of government action were “depressing”.

10.2 Research letter

The recent review paper on new psychoactive substances (NPS) by Reuter & Pardo (2017), and the subsequent commentaries, outline the multiple and complex policy challenges posed by this phenomenon [1]. They critique the Psychoactive Substances Bill , recently enacted in the UK. They are sceptical that it will have any real impact on demand, use and harms. They note that Ireland was the first country to proceed with this type of legislation, enacting the Criminal Justice (Psychoactive Substances) Act in late August 2010. This Act was focused primarily at vendors of NPS. It states that ‘a person who sells a psychoactive substance knowing or being reckless as to whether that substance is being acquired or supplied for human consumption shall be guilty of an offence’. The vast majority of the head shops in Ireland closed within weeks of its arrival, and the remaining head shops ceased sale of NPS. The number of head shops in Ireland had already dropped from their peak of May 2010, following the addition of over 100 NPS to the pre-existing Misuse of Drugs Act in that month.

What is the evidence from Ireland on NPS use and harms following those developments? Firstly, there is now good evidence of a decline in population use of NPS. The National Drug Prevalence Survey occurs every 4 years. By good fortune, it

occurred in 2010/11, so questions on past year use overlapped with that period of time when head shops were active and widespread [2]. Past year use of NPS among 15-24year olds was 9.7% and among 25-34 year olds, it was 4.6%. The survey was repeated in 2014/15 and the corresponding prevalence rates were 1.9% and 1.3%, indicating a very dramatic decline [3].

There is also evidence of declines in NPS-related substance use disorders presenting to addiction treatment services. A small study at one clinic for adolescents in Dublin found that one in three presentations involved problematic use of NPS in early 2010 while the head shops were open [4]. There were no cases of problematic NPS use during the same period one year later. The proportion of clients reporting any NPS use in the preceding 3 month period dropped from 82% to 28%.

Among young adults, aged 18 to 34 years, attending addiction treatment in Ireland, there was also a substantial change in NPS-related presentations over this period [5]. They rose very steeply from early 2009 to the first third of 2010. The closure of the head shops coincided with the onset of a significant and steady decline in NPS related addiction treatment episodes over the following two years. The 12 month moving average rate of NPS related presentations fell by 48% from 2010 to 2012.

The expansion of the network of head shops selling NPS coincided with an increase in the overall rate of drug related psychiatric admissions (DRPA) in Ireland. The cessation of NPS sale by head shops coincided with a reversal in this upward trend. The changes in DRPA were most evident in young men aged 18-24 years, these being the demographic with the highest prevalence of NPS use based upon the population

surveys mentioned above. After May 2010, the model estimated a progressive decline in DRPA of 1.4% per month among those young males over the following 30 months.

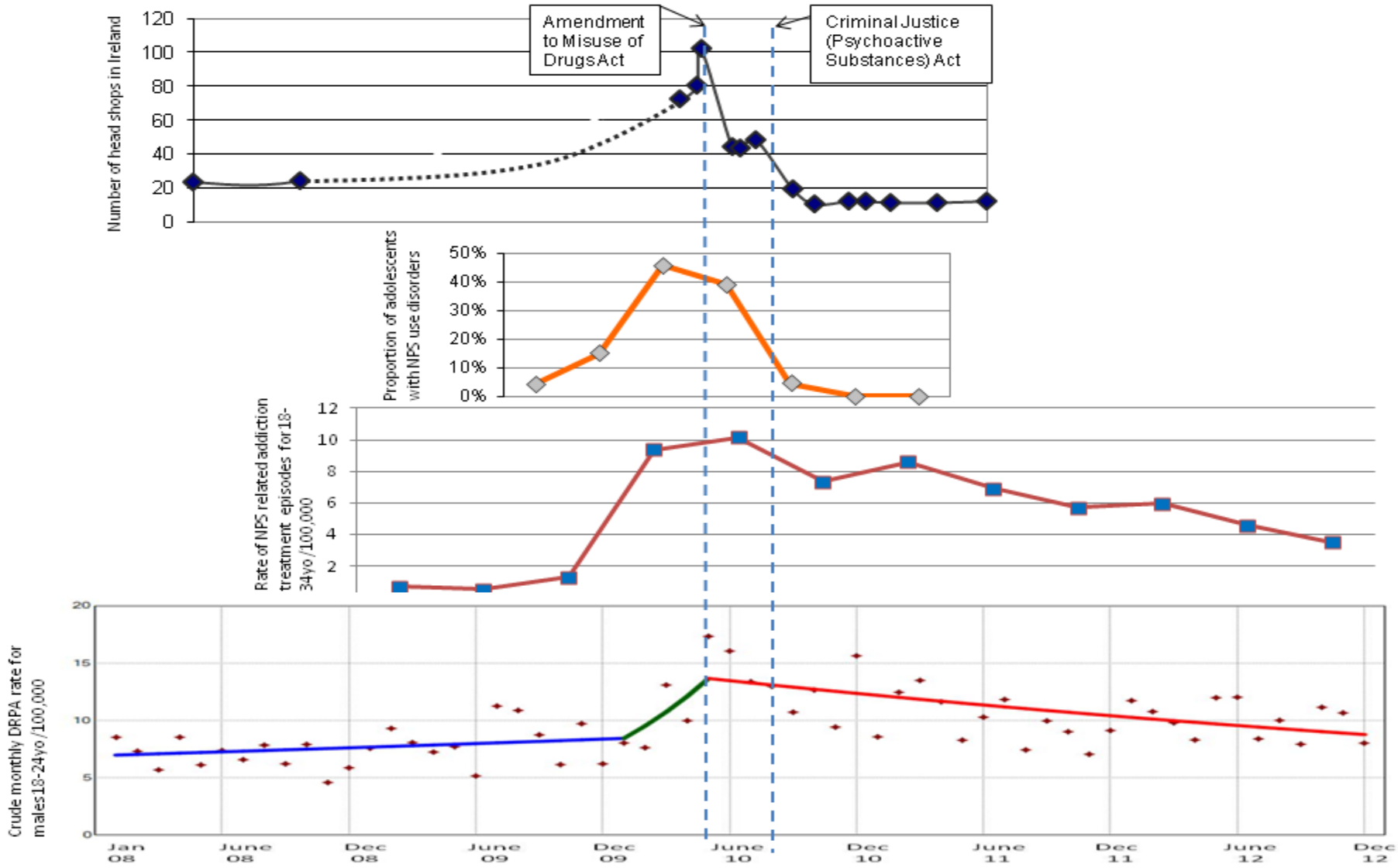
Figure 10.1 seeks to collate of the findings regarding these actual and potential NPS related harms, and gives an indication of how they relate to the number of head shops and the specific legislative actions.

Unfortunately, most of the international discussion about the experience of Ireland following the NPS inspired legislation has suggested that it was largely ineffective. The reality appears to be very different. Any suggestion that the NPS landscape was unchanged in Ireland following the closure of head shops seems entirely contradicted by the data above. Obviously causality cannot be attributed, but the pessimism seems misplaced. Ongoing monitoring will be required to see if the observed reductions during these first 2-3 years persist into the future. It would also be premature to read too much into the experiences of a single country. However, informed debate will hopefully be assisted by dissemination of accurate information.

10.3 Author contributions

BPS was the sole author of this letter.

Figure 10.1. Measures of potential NPS related harms over time



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Chapter 11

Discussion & Conclusions

11.1 Objectives

This thesis sought to examine strategies which strive to tackle a range of harms that can arise for youth who use psychoactive substances. It explored the impact of treatment on *individuals* with substance use disorders, seeking to determine if there were reductions in substance use and improvements in mental health. Secondly, it sought to identify evidence which might point towards a positive public health impact across the wider youth *population* arising from prohibition styled legislative actions. To do this, data on episodes of addiction treatment and psychiatric hospitalizations among youth were interrogated.

11.2 Key findings from each chapter.

11.2.1 *Study 1: Outcome for adolescents abusing alcohol and cannabis following outpatient treatment*

This study is the first study to report outcome of an outpatient adolescent addiction treatment service in Ireland. It confirms that abstinence at three months is indeed elusive. It emerged that only 11% of those with a cannabis use disorder and 11% of those with an alcohol use disorder were abstinent for the full month of follow-up. This is at the lower end of the range reported in international studies.(3, 147-152) This relatively low rate of abstinence could be used to build a case for a move back towards more explicitly abstinence focused treatments.

However, another key finding of this study was the very poor motivation evident among adolescents with substance use disorders. Problem recognition was determined to be low or very low in the majority (68-97%) of adolescents with risky use of all substances apart from the small number of heroin users. Other studies have highlighted poor motivation among adolescents in particular.(153, 154) It is likely to

prove challenging to persuade such a group of poorly motivated adolescents to embrace a goal of abstinence.(3) Demanding that they do so, could result in a substantial increase in unplanned treatment exits and could thereby result in increased use and increased harms.(155)

Many of the National Institute of Drug Abuse (NIDA) recommended and evidence based treatment approaches in adolescent addiction, including ACRA, CBT and Motivational enhancement therapy, avoid any demand for abstinence.(156)

The study examined the proportion of adolescents who achieved a reliable reduction in their alcohol and cannabis use.(157, 158) Although this methodology has been used to explore treatment outcome in adults, there are very few studies which have used this approach in adolescent addiction.(159) It emerged that 36% of the high risk cannabis users achieved a reliable reduction in use, although only 14% of the high risk drinkers did so.

We also found that high risk drinkers were significantly less motivated than high risk users of illegal drugs. It seems possible that this poorer motivation among drinkers may have contributed to their poorer outcomes.(160, 161) Given the wider focus of this thesis on legislation it is interesting to note that motivation to change use of the legal drug was less than that to change use of the illegal drug.

By measuring the size of change, this study can be useful is estimating change for use in power calculations if clinical trials are conducted with similar patient groups in similar settings in the future.

11.2.2 Study 2: Opioid substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention over twelve months

This study found that 21% of patients were abstinent from heroin in their third month of treatment. This rate of abstinence is almost double that achieved for cannabis or alcohol in the previous study. Importantly, the proportion of patients who demonstrated abstinence from heroin increased substantially and significantly after

12 months of treatment. This finding of clinically and statistically significant improvement in outcome over time poses a challenge to the view articulated in the report on adolescent addiction treatment by the Department of Health & Children which advised that OST "should only be considered as a short term solution".(75)

It is not really possible to accurately compare the rates of abstinence achieved in this study with those of other studies of OST in adolescents as most other studies fail to report on use *during* treatment and those which do used different methodology involving very infrequent drug testing.(93)

The study failed to find evidence of a significant reduction in use of other drugs. However, there was no evidence of an increase either, this being suggested as a possibility in the DARP study.(89)

11.2.3 Study 3: Changes in psychological well-being among heroin-dependent adolescents during psychologically supported opiate substitution treatment.

This is the first ever study to report upon changes in mental health symptoms among heroin dependent adolescents in receipt of OST over a three-month period. We found evidence of significant improvement in the domains of depression, anxiety and anger. This is an encouraging finding. While it mirrors the findings from adult studies of OST,(67, 162) it is noteworthy that the only Irish study to examine this issue among adults failed to find a significant improvement in mental health during OST.(163)

Although only conducted as a post hoc analysis, it was interesting to note that the improvement is depressive symptoms was significantly greater in those who ceased heroin use at follow-up. This again highlights the inter-relationship between drug use and mental health, although it doesn't point towards a direction of causality.(164)

11.2.4 Study 4: Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban.

This study confirmed that NPS can indeed cause substance use disorders in adolescents and that these increased rapidly during the period of head shop expansion, being an issue for 34% of adolescents attending the service in the months prior to the initial legislative action. There was a significant decline in NPS substance use disorders and in self-reported NPS use one year later, at which point all of the head shops had either closed or ceased selling NPS. However, there was still some NPS use which confirms that there was some migration of use into the black market.(165) In the few cases where use persisted in the black market era, this was associated with significantly less problems than occurred among users during the head shop era.

11.2.5 Study 5: Decline in new psychoactive substance use disorders following legislation targeting headshops: evidence from national addiction treatment data.

Building on the findings of the previous study, this study confirmed that NPS use disorders were also evident in the young adult age range across Ireland using a national dataset. NPS related presentation increased very rapidly during the period of head shop expansion, peaked in the first four months of 2010 and then the trend changed significantly. The rate of NPS presentations fell progressively over the following two years, albeit not as dramatically as that observed among the adolescents in study 4. Where cases involving a NPS use disorder did present after the closure of the head shops, it was less likely to be the primary disorder. This mirrors the finding in the study of adolescents (study 4) which found reduced harm associated with NPS use in the post head shop era. As such it challenges the dire predictions of the opponents to the legislative bans.(102, 166-168)

11.2.6 Study 6: Legislation targeting head shops selling new psychoactive substances and changes in drug related psychiatric admissions: A national database study

The presence and variety of mental health difficulties among adolescents with substance use disorders was highlighted in studies 1 and 3, these findings mirroring those seen across the world.(7, 164, 169, 170)

Having found evidence of changes in NPS related addiction episodes coinciding with the expansion and contraction of the head shop network, this study was ambitious in examining for changes in a much broader public health impact. It utilised a national database of all drug related psychiatric admissions (DRPA) among young adults. It emerged that there was a trend change in DRPA and the best estimate for the timing of this change was July 2010. When we looked at young males, the group known to be the heaviest users on NPS in Irish general populations surveys, it emerged that the best fitting join point model had two trend changes.(40) There was an increase in DRPA in January 2010 and the upward trend turned downwards in May 2010.

While this study could confirm that the changes in DRPA *coincided* with changes in NPS availability through head shops, it could not confirm that NPS *caused* or even contributed to the observed change. However, a study by Lally et al of patients attending adult mental health services during the head shop era in Ireland did confirm that NPS use featured very prominently amongst the drug use by patients at that time.(171) Research from elsewhere has also highlighted the contribution of NPS to mental health difficulties among inpatients.(116, 130, 172) One of these studies in the UK found that NPS use was reported by 22% of psychiatric admissions, especially in those of young males.(155) The NPS use was deemed to have contributed to the admission in most cases.

11.3 Methodological issues which emerged

Statistical analysis was hampered by small sample sizes in the treatment studies and small number of events per unit of time in the NPS trend studies.(144) The small samples were due to the finite number of heroin dependent adolescents in Dublin, and the rate of entry into studies declined progressively as the incidence of adolescent heroin dependence dropped progressively. Although two of the NPS trend studies made use of national datasets, trend changes would have been easier to detect if the population was 50 million, such as in the UK, instead of just 5 million in Ireland. In order to ensure adequate number of event per time period, we had to widen the unit of time to four months in study 5 as opposed to just one month.(145) This

consequently reduces the ability to specify the exact point at which a trend changed. The timing of the trend changes in the Joinpoint analysis constitute estimates in all cases, and the 95% confidence intervals are quite wide, this again being a function of the relatively small number of events per unit of time.

Joinpoint appears to be a very interesting and useful tool for exploring trend changes in time series type data.(146) It probably has utility for examining trend changes in a range of national databases across health and other sectors, not just NDTRS & NPIRS.(173-175)

All studies received ethical approval from research ethics committees. (Appendix 2 collates the information on ethics approval for all of the studies.) The study which posed the most ethical challenges was the treatment study examining outcome of alcohol and cannabis use disorders. These challenges arose primarily due to the follow-up components of that study design. It is necessary to obtain consent to follow people up after their treatment. Complications with consent are typical of research focusing on adolescents.(176) Although there is legislation to indicate that people aged 16 and over can consent to medical treatment on their own behalf in Ireland, this has not been confirmed by case law. In view of this uncertainty, we only accepted adolescents into that study where we obtained consent from both the adolescent and a parent (or legal guardian). This then posed a limitation on our ability to recruit into the study adolescents who are in voluntary care of social services, and had minimal ongoing parental contact.

11.4 Interconnections between the studies

Polysubstance use was evident across the studies examining both treatment outcome and NPS related harms. Many researchers having identified this as a particular challenge among younger drug users.(177) There was some evidence of variation in treatment outcome across substances. Others have noted that reductions in use of the main drug can be associated with increases in use of other substances.(178, 179) Previous researchers have noted that treatment outcomes for substances such as

cannabis and alcohol tends to be poorer that that for other substances.(3) We found that motivation to address alcohol problems was poorer that that to address illegal drugs and that meaningful reductions in alcohol use appear harder to achieve than reductions in cannabis use. While not designed as a head to head comparison, the heroin dependent adolescents were at least as likely to be abstinent from that drug after three months (21%) as the adolescents with alcohol (11%) or cannabis (11%) use disorders treated in the YoDA service. Within the treated heroin dependent group, reductions in use of other substances were not evident.

The studies in this thesis highlight the many and varied intersections between mental health and substance use. We added to the substantial literature which indicates that very many youth who access addiction treatment have histories of mental health difficulties and/or evidence of current mental health problems.(7, 8, 142, 170, 180) We found evidence that addiction treatment delivers improvements in psychological wellbeing, with the first ever study to examine impact of OST on mental health in adolescents. Finally, we found evidence that polices which are focused on reducing easy access to drugs may have an impact upon levels of drug related psychiatric disorders in the community. Others have demonstrated that policy measures targeting alcohol and drugs can have an impact upon mental health outcomes, suicide in particular.(181, 182)

Although the legislative changes targeting head shops and NPS were quite generic, both studies examining changes in NPS use among people attending addiction treatment generate information which pointed towards a lesser or delayed impact on cathinone type NPS relative to that observed upon the synthetic cannabinoids. It is unclear why this might have occurred but it suggests that cathinone type NPS were less impacted by the closure of the head shops, if it was indeed the closure of the head shops which explains the overall changes.

11.5 Overall weaknesses and strengths of the studies.

Five of the six studies focused upon people who attend for addiction treatment. As described in section 2.4.3, about 10% who use a drug will become dependent upon it and only 10% of those will seek treatment in any given year.(2, 6, 44, 62, 183) Consequently, treatment attenders constitute only the tip of the iceberg in terms of drug use across the population.(3, 156) They are nevertheless a very important subgroup and likely to include the individuals at greatest risk of harm.(121)

Section 2.3 highlighted the fact that patterns of substance use do change over time. While society strives to influence those changes, they often occur with minimal explanation.(37) The trend changes detected in these studies may constitute this type of random fluctuation. However, the facts that we were able to examine time periods shorter than one year and that the location of change across studies appeared to coincide quite closely with changes in head shop activity, add weight to the argument that they may be causally related.

In the two studies which examined addiction treatment outcome (Studies 1 & 2), there was minimal success in identifying either patient or treatment characteristics associated with better outcome, even with the exploratory analysis and decision not to adjust for multiple statistical testing.(143) This may be in part down to the limitations of sample size discussed above in section 11.3. However, many other studies have struggled to identify patient characteristics associated with better outcome.(98, 184)

The two studies of OST were confined to analysing data obtained during treatment. Ideally it would have been useful to interview people who had left treatment regarding their drug use and mental health. However, consent was not obtained to follow people up in that manner.

11.6 Implications for practice and policy

Polysubstance use must be assessed and efforts made to address it. In doing so, it will be important to be mindful of possibility of quite variable motivation by the individual to address use of separate substances.(177, 185, 186)

Mental health competencies seem essential for staff working in services providing treatment to adolescents with substance use disorders.(7, 8) The ongoing separation of addiction treatment services from mental health services in Ireland would appear to warrant review.(187) If it is to persist, there is a need for excellent inter agency collaboration between youth addiction treatment services and youth mental health services.(188, 189)

National polices focused upon improvements in mental health should include measures which address substance use, in view of the evidence suggesting an impact of the latter upon the former.(181)

While adolescents, parents, policy makers, politicians and treatment providers may all have a preference for the duration of OST to be as short as possible, enforcing a time limit on OST for heroin dependent adolescents appears unreasonable.(79, 96)

Given the evidence from these studies that expansion of the network of head shops coincided with increased NPS use disorders and increased DRPA, and their departure saw these trends reverse, it would appear reasonable that Ireland maintain its intolerant attitude towards sale of NPS by head shops. This position is also largely supported by the findings from the literature review in section 2.6.2.3, and a very recently published review of this literature by Meader, Mdege & McCambridge.(190) The Criminal Justice (Psychoactive Substances) Act was novel and has faced some legitimate scrutiny.(82, 83, 107) However, it has withstood the test of the courtroom, with a couple of successful prosecutions and more importantly there has been no return to widespread availability of NPS in head shops.(109) The legislation has also received the ultimate form of flattery in that it has been imitated in a number of other jurisdictions.(83)

While it probably should not need to be said, it seems clear that no policy can completely eliminate all substance use and every related harm.(10, 20) Complete cessation of use and all harms across the entire population has certainly not been a goal of drugs policy in Ireland in recent decades.(22, 191, 192) The UNODC declared a goal of “a drug free world” as recently as the 1990s and argued that legislative bans could assist in delivering that state of perfection.(10, 193) Declaring unachievable

targets brings into disrepute the effective measures employed to reduce use and associated harms once those impossible goals are not delivered upon.(10, 20, 24)

11.7 Implications for future research.

Cannabis policy is hotly debated currently, both in Ireland and internationally.(19, 194-199) While only a tentative finding, the variability in motivation and possibility of poorer outcome for alcohol use disorders warrants further exploration. If this relates to its legal status and widespread availability and use of alcohol across society, then this raises the possibility of adverse and untoward consequences for society if cannabis use is normalised and policy is liberalized.(119) The literature on NPS suggests that their legal status influenced decision making regarding their use.(117) As society moves towards a more benign view of cannabis and there is increasing discourse of that drug as a possible medicine and candidate for regulated sale, like alcohol, it seems likely that people will view use as increasingly normal and less risky. Such views regarding drugs tend to be associated with increased use.(6, 36, 200, 201) Cannabis use is on an upward trajectory in Ireland in recent years among both adolescents and young adults (see Figures 2.7 & 2.8).(39, 41) Study 5 produced an incidental finding that the rate of treated cannabis use disorders (CUD) among youth in Ireland rose significantly during the period 2009 to 2012. It will be important to monitor changing rates of use, changing incidence of CUD and the potential impact on treatment outcome for that subset of users who develop a CUD.(196, 202-204)

Studies 4 & 5 both found evidence that cathinone type drugs seemed to persist more effectively after the closure of the head shops, relative to other NPS subclasses. There is certainly some ongoing concern regarding use of these drugs by specific populations of drug users, especially people who inject drugs.(205, 206) There may be opportunities to interrogate the NDTRS dataset to better characterise those who have persisted with cathinone use in the post-head shop era. A better understanding of that patient group may permit development of a targeted response to reduce harm.

The NACD general population surveys may also provide opportunities to characterise NPS users. Given the fact that the 2010/11 survey overlapped with the head shop era, there may be an opportunity to determine if there have been changes to the profile of NPS user during the commercialised sale of NPS via head shops versus the NPS user in the 2014/15 survey.(40, 41)

Finally there are other potential measures of independent imperfection which could be interrogated to see if there is further evidence of increased harms while the head shops expanded and reduction in harms after the shops were closed.(23) Specifically, the Hospital In-Patient Enquiry (HIPE) system could be examined to see if there were trend changes in drug related medical admissions over this period. It may be possible to utilise data from An Garda Siochana (e.g. the Police Using Leading Systems Effectively database) to determine if drug related incidents of public disorder changed.

11.8 Is harm reduction treatment appropriate for youth with SUDs?

The archetypical harm reduction treatment is OST. It remains controversial among adults in spite of the fact that it has more evidence that almost any other treatment in addiction.(5, 12, 14, 22, 68, 207, 208) However, the evidence for OST in adolescents has been weak and this has added to the caution in its utilization in this age range.(17, 96, 99) Heroin dependence generally commences in early adulthood not adolescence, and consequently cases are relatively rare.(209) There appears to be a circular problem with lack of evidence driving clinician wariness and clinician wariness making it more difficult to generate evidence.(18)

The studies of OST in this thesis point towards respectable and incremental reductions in heroin use and towards improvements in mental health among the adolescents who persist with this treatment. Consequently, the thesis adds weight to the argument in favour of this harm reducing treatment.(18, 79, 92)

A previous examination of a residential abstinence based treatment in Ireland demonstrated that that vast majority of patients relapsed to heroin use within months of discharge, with younger patients being particularly likely to relapse.(184, 210)

Previous studies on OST in adolescents in Dublin also highlighted frequent relapse after detoxification.(211) Relapse following detoxification is particularly hazardous as it brings with it an increased risk of fatal accidental overdose.(212)

It seems appropriate that both treatments, OST and abstinence based, be available to patients and to clinicians.(207) It would appear unreasonable to demand that patients pursue either path. If the addiction treatment guidelines for adolescents are being reviewed by the Department of Health & Children, the findings of this thesis suggest the removal of the recommendation that OST "be viewed as only a short term solution".(75)

11.9 Is prohibition an acceptable strategy for reduction of population based harm among youth?

As mentioned in Chapter 1, Donald Campbell suggested a quasi-experimental approach to policy evaluation by using 'multiple measures of independent imperfection'.(23) In this thesis, three imperfect but independent measures were examined. All point towards emerging and escalating harm while the head shops were openly selling NPS and expanding across Ireland. All point towards a reversal of this trend around the time when the head shops closed. While no single study provides proof, taken together they do appear to constitute an important body of evidence that the legislative measures may well have had a substantial positive impact in Ireland. This view is further bolstered by the evidence which emerged from the latest iteration of the NACDA general population survey which happen to be repeated during the course of this PhD. It found that past year use of NPS among 15-24year olds was 1.9% in 2014/15, having been 9.7% in 2010/11.(41) Finally it is also consistent with quite a substantial body of research indicating reduced NPS use and/or harms following legislative restrictions in other jurisdictions.(130, 133, 135, 213, 214) These were summarised in section 2.6.2.3.

While this thesis only examined this one aspect of the prohibition styled legislation in Ireland, it does lend support to this approach and does not build a case for moving away from this approach within Ireland.

While there have been many reviews of drug policy in recent years which have examined novel, and generally liberal, approaches to policy, there is one country which has been largely ignored by these reviews.(4, 80, 82) In the 1990s, teenagers in Iceland demonstrated very concerning levels of drunkenness, higher than almost any other country in Europe.(39) Drug use was lower than the EU average at that time. Nevertheless, they implemented a comprehensive and multifaceted sweep of measures focused primarily on alcohol use. These included an increase in the legal drinking age to 20 years and legal restrictions on the ability of children to be out at night unaccompanied. Alcohol taxes are very high, advertising and sponsorship are banned and off-sales alcohol can only be purchased in state owned off licenses.(122) In sum, these were very conservative measures. They have delivered remarkable results with teenage drunkenness now being one of the lowest in Europe and rates of past month cannabis use falling also (See Figure 2.7 in Chapter 2).(215-217)

A recent international review of evidence based measures to reduce harms associated with adolescent substance use concluded that enforcement of laws was effective.(11) While New Zealand was hailed as the standard bearer for those countries seeking to contemplate a more liberal approach to drug use via its Psychoactive Substances Act, a recent review of this initiative has highlighted its many pitfalls.(218) It has proved largely unworkable and has highlighted the need for substantial ongoing law enforcement and extensive regulatory structures and resources.

11.10 Can harm reduction and prohibition co-exist?

Returning to the quandary presented in Figure 2.14, can liberal treatment approaches such as harm reduction interventions like OST appropriately co-exist with conservative and ‘out of fashion’ approaches to prevention such as prohibition?

It may well be the case that this apparent paradox in superficially contradictory policies is far from unique. Without delving into another topic in any great detail, efforts to tackle injury from road traffic collisions involves the exact same apparent contradictions. The WHO's "World report on road traffic injury prevention" advises a number of actions. (219)These include "Setting and securing compliance with key road safety rules" (i.e. legal requirements to adhere to low risk driving, assertive monitoring of driver behaviour and administration of punishments to those who fail to do so). The report simultaneously recommends "Delivering post-crash care". This involves prompt arrival of trained medical personnel to the crash site and high quality care in the emergency department, irrespective of the possible contribution of driver behaviour to their own injuries. In other words, treatment of individuals who experience harm should be responsive, high quality and non-judgemental. At the same time, the wider population of drivers should be assertively monitored. Those who drive in a high risk manner should be identified and punished, and potentially lose the right to drive altogether if they repeatedly drive in an unsafe manner.

The Drugs & Public Policy Group have stated:-

> *The drug policy debate is dominated in many countries by false dichotomies which can mislead policy maker about the range of legitimate options and their expected impact. Law enforcement and health services approaches each contribute to the other's mission.(5)*

The studies presented here suggest that current treatment approaches deliver meaningful reductions in harm for individuals with substance dependence. At the same time, prohibition styled legislative responses appear to deliver reductions in harm at the population level. The weight of evidence in this thesis indicates that, just like the efforts to reduce morbidity caused by road traffic collisions, the policy approach to reducing harm related to drug use across society should simultaneously include a liberal approach to treatment for those few individuals who experience significant harm (i.e. develop addiction) and a conservative and intolerant approach to drug use at the broader population level.

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Appendix 1. **Additional information on contributions to research papers.**

In section 7 of each of the chapters reporting a research paper, (i.e. Chapters 4 to 9 inclusive), there is a section on Author Contributions. This describes the input provided by the co-authors.

In addition to that support into the various studies, there was also important input by a number of individuals into some of these research papers. This occurred particularly in the area of statistical methodology. These contributions are described below.

Outcome for adolescents abusing alcohol and cannabis following outpatient treatment: how many 'reliably improve'? (Chapter 4)

Professor Joe Barry provided advice on the research questions and on the study methodology. He provided guidance on strategies to ensure better recruitment and retention of research participants.

Opiate substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention (Chapter 5)

Professor Alan Kelly and Dr Ailish Hannigan provided advice on statistical methodology for this study. Dr Conor McDonald also assisted with the statistical analysis.

Changes in psychological wellbeing among heroin dependent adolescents during psychologically supported opiate substitution treatment (Chapter 6)

Dr Ailish Hannigan was consulted regarding statistical methodology for this study.

"So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban (Chapter 7)

Dr Ailish Hannigan was advised on the statistical methodology for this study.

Decline in new psychoactive substance use disorders following legislation targeting headshops: Evidence from national addiction treatment data (Chapter 8)

Advice and guidance on statistical methods for this study was obtained from Dr Ailish Hannigan, Dr Conor McDonald and Dr Jason Ferris.

Legislation targeting head shops selling new psychoactive substances and changes in drug related psychiatric admissions: A national database study (Chapter 9)

Advice and guidance on statistical methods for this study was obtained from Dr Jason Ferris. In addition to this, Dr Ailish Hannigan and Dr Conor McDonald both assisted with the statistical analysis.

Appendix 2. **Information on the approval obtained from Research Ethics Committee (REC) for each of the studies in the thesis.**

No.	Study title	Research Ethics Committee(s) which provided approval	Contact Information for REC	
1	Outcome for adolescents abusing alcohol and cannabis following outpatient treatment: how many 'reliably improve'?	1/ National Drug Treatment Centre Board Research Ethics Committee 2/ St James Hospital & AMNCH Research Ethics Committee	Mr Seamus Noone Vice-Chairman NDTC REC 30/31 Pearse St Dublin 2 Phone: 01-6488600 Daniel Lynch Secretary SJH/AMNCH REC AMNCH Tallaght Dublin 24 Phone: 01-4142000	
2	Opioid substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention over twelve months	National Drug Treatment Centre Board Research Ethics Committee	Mr Seamus Noone Vice-Chairman NDTC REC 30/31 Pearse St Dublin 2 Phone: 01-6488600	

3	Changes in psychological well-being among heroin-dependent adolescents during psychologically supported opiate substitution treatment.	National Drug Treatment Centre Board Research Ethics Committee	Mr Seamus Noone Vice-Chairman NDTC REC 30/31 Pearse St Dublin 2 Phone: 01-6488600	
4	"So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban.	National Drug Treatment Centre Board Research Ethics Committee	Mr Seamus Noone Vice-Chairman NDTC REC 30/31 Pearse St Dublin 2 Phone: 01-6488600	
5	Decline in new psychoactive substance use disorders following legislation targeting headshops: evidence from national addiction treatment data.	National Drug Treatment Centre Board Research Ethics Committee	Mr Seamus Noone Vice-Chairman NDTC REC 30/31 Pearse St Dublin 2 Phone: 01-6488600	
6	Legislation targeting head shops selling new psychoactive substances and changes in drug related psychiatric admissions: A national database study	National Drug Treatment Centre Board Research Ethics Committee	Mr Seamus Noone Vice-Chairman NDTC REC 30/31 Pearse St Dublin 2 Phone: 01-6488600	