van Hout, MC

Medicinal products detected as Novel Psychoactive Substances: the case of intravenous use of Tropicamide

http://researchonline.ljmu.ac.uk/8027/

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)


LJMU has developed LJMU Research Online for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

http://researchonline.ljmu.ac.uk/
Heroin Addiction and Related Clinical Problems

the official journal of

European Opiate Addiction Treatment Association

World Federation for the Treatment of Opioid Dependence
Addiction is a treatable disease

Millions of people worldwide are suffering from diseases of addiction

We at Indivior envision a day in which all patients around the world will have unrestricted access to quality treatments and services for the chronic relapsing conditions and co-morbidities of addiction.

Indivior Italia S.r.l.
Corso di Porta Romana, 68 - 20122, Milano, Italy
www.indivior.com
Editorial Board

Editor in Chief
Icro Maremmani
VP Dole Dual Disorder Unit, Santa Chiara University Hospital, University of Pisa, Italy, EU

Associate Editors
Thomas Clausen
SERAFA, Norwegian Centre for Addiction Research, University of Oslo, Norway
Pier Paolo Pani
Socio Health Local Area, Sardinia Region Health Protection Trust, Olbia, Italy, EU
Marta Torrens
University of Barcelona, Spain, EU

International Advisory Board
Hannu Alho
National Public Health Institute (KTL), University of Helsinki, Finland, EU
Marc Auriacombe
Victor Segalen University, Bordeaux, France, EU
Alexander Baldacchino
University of St Andrews Medical School, North Haugh, St Andrews, Scotland, United Kingdom, EU
James Bell
South London and Maudsley NHS Foundation Trust & Langston Centre, Sydney, Australia
Olof Blix
County Hospital Ryhov, Jönköping, Sweden, EU [Retired]
Barbara Broers
University Hospital of Geneva, Switzerland
Miguel Casas
Vall d’Hebron University Hospital, University of Barcelona, Spain, EU
Michael Farrell
National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia
Loretta Finnegan
National Institutes of Health, Bethesda, MD, USA [Retired]
Gabriele Fischer
Addiction Clinic, University of Vienna, Austria, EU
Carla Gambarana
Department of Molecular and Developmental Medicine, University of Siena, Italy
Gilberto Gerra
United Nations Office on Drugs and Crime (UNODC), Vienna
Gian Luigi Gessa
University of Cagliari, Italy, EU [Retired]
Leif Grönbladh
Institute of Addictive Diseases, University Hospital of Uppsala, Sweden, EU
Lars Gunne
University of Uppsala, Sweden, EU [Retired]
Herman Joseph
Stop Stigma Now; NAMARecovery, New York, NY, USA
Andrej Kastelic
Center for Treatment of Drug Addiction, University Hospital, Ljubljana, Slovenia, EU
Michael Krausz
St. Paul’s Hospital, University of British Columbia, Canada
Mary Jane Kreek
The Rockefeller University, New York, NY, USA
Evgeny Krupitsky
St. Petersburg Bekhterev Psychoneurological Research Institute, Saint Petersburg, Russia
Mercedes Lovrevecic
Institute of Public Health of the Republic of Slovenia, Ljubljana, Slovenia, EU
Joyce Lowinson
Albert Einstein College of Medicine, The Rockefeller University, New York, NY, USA, [Retired]
Angelo GI Maremmani
Department of Psychiatry, Northern-West Tuscany Region Local Health Unit, Versilian Zone, Viareggio, Italy, EU
Charles P. O’Brien
University of Pennsylvania, Philadelphia, PA, USA
Lubomir Okruhlica
Centre for Treatment of Drug Dependencies, Bratislava, Slovak Republic, EU
Matteo Pacini
Institute of Behavioural Sciences, Pisa, Italy, EU
Mark Parnino
American Association for the Treatment of Opioid Dependence, New York, NY, USA
Einat Peles
Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel
Giulio Perugi
Department of Clinical and Experimental Medicine, University of Pisa, Italy, EU
Jens Reimer
University of Hamburg, Germany and Psychiatry Health North, Bremen, Germany, EU
Marc Reisinger
European Opiate Addiction Treatment Association, Brussels, Belgium, EU
Lorenzo Somaini
Addiction Treatment Center, Cossato (Biella), Italy, EU
Marlene Stenbacka
Karolinska Institute, Stockholm, Sweden, EU
Ambros Uchtenhagen
Research Foundation on Public Health and Addiction, Zurich University, Switzerland
Helge Waal
Center for Addiction Research (SERAFA), University of Oslo, Norway, [Retired]
George Woody
University of Pennsylvania, Philadelphia, PA, USA
Editorial Coordinator

Marilena Guareschi  
Psychologist  
Association for the Application of Neuroscientific Knowledge to Social Aims, AU-CNS, Pietrasanta, Lucca, Italy, EU  
Coordinator Master in Addictologia, University of Pisa

Assistants

Silvia Bacciardi  
School of Psychiatry, and Master in Addictologia, University of Pisa, Italy, EU

Iacopo Belcari  
Psychologist and Master in Addictologia, University of Pisa, Italy, EU

Manuel Glaucu Carbone  
School of Psychiatry, University of Pisa, Italy, EU

Denise Gazzarrini  
Specialty in Psychiatry, and Master in Addictologia, University of Pisa, Italy, EU

Marco Maiello  
School of Psychiatry, University of Pisa, Italy, EU

Enrico Massimetti  
Specialty in Psychiatry and Master in Addictologia, University of Pisa, Italy, EU

Alessandro Pallucchini  
School of Psychiatry, and Master in Addictologia, University of Pisa

Fabio Rugani  
School of Psychiatry, University of Naples, Italy, EU  
Master in Addictologia, University of Pisa

Vincenza Spera  
School of Psychiatry, University of Pisa, Italy, EU

Publishers

Not for profit Agency
Via 20 Settembre, 83 - 55045 Pietrasanta, Lucca, Italy, EU  
Phone +39 0584 790073 - Fax +39 0584 72081 - E-mail: info@aucns.org  
Internet:http://www.aucns.org

Pacini Editore
Via A. Gherardesca - 56121 Ospedaletto, Pisa, Italy, EU  
Phone +39 050 313011 - Fax +39 050 3130300 - E-mail: info@pacinieditore.it  
Internet:http://www.pacinieditore.it

Cited in:
EMBASE Excerpta Medica Database  
SCOPUS  
EMCave  
Social Sciences Citation Index (SSCI) - Thomson Reuters

Open Access at:
http://www.heroinaddictionrelatedclinicalproblems.org
Addiction and self-reported associated sociodemographic factors in a small province of Iran
Zahra Sedaghat, Mohammad Fararouei, Gholamhosein Shahraki, Kambiz Karimzadeh Shirazi, and Roksana E. Haghighi

An evaluation of community pharmacist perception of the misuse and abuse of over-the-counter co-codamol in Cornwall and Devon, UK: A cross-sectional survey
Ravina Barrett, and Dalmar Costa

Switching between lyophilized and sub-lingual buprenorphine formulations in opioid-dependent patients: Observations on medication transfer during a safety and pharmacokinetic study
Kylie Reed, Alastair Knight, Shelagh Baillie, Karolina Bogdanowicz, James Bell, and John Strang

The SCL90-based psychopathological structure may be applied in Substance Use Disorder patients independently of the drug involved, even in heroin, alcohol and cocaine monodrug users
Manuel Glauco Carbone, Marco Maiello, Vincenza Spera, Corrado Manni, Alessandro Pallucchini, Angelo G. I. Maremmani, and Icro Maremmani

Comparing neurocognitive function in individuals receiving chronic methadone or buprenorphine for the treatment of opioid dependence: A systematic review.
Duncan Hill, Daniel Garner, and Alex Baldacchino

Medicinal products detected as novel psychoactive substances: The case of intravenous use of tropicamide.
Marie Claire Van Hout
Addiction and self-reported associated sociodemographic factors in a small province of Iran

Zahra Sedaghat¹, Mohammad Fararouei², Gholamhosein Shahraki³, Kambiz Karimzadeh Shirazi⁴, and Roksana E. Haghighi⁵

¹-Student Research Centre for Health Sciences, Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran
²-HIV/AIDS Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran.
³-Social Determinants of Health Research Centre, Yasuj University of Medical Sciences, Yasuj, Iran
⁴-Department of Public Health, Social Determinants of Health Research Centre, Yasuj University of Medical Sciences, Yasuj, Iran
⁵-Shiraz University of Medical Sciences, Shiraz, Iran

Summary

Background: Drug addiction is a chronic brain disorder caused by drug use. It is one of the most important social and health problems, as it is responsible for the serious deterioration of health, mental health and the socioeconomic status of individuals and the community. Aims: The aim of this study was to understand the views of drug users on the factors putatively involved in their initiation of substance use and in their propensity to make attempts to quit drug use in Yasuj, Iran. Methods: Using a self-administered questionnaire, 362 male addicted participants (selected through snowball sampling) provided us with the information required. Results: Among all participants, 83.6% reported that they were not aware of the health or social consequences of addiction. Also, 33.13% referred to their friends as being the main reason for their addiction and 69.46% declared that they had been introduced to drugs by a friend. Opium was reported to be the most prevalent (92.44%) substance at first drug administration, the most common route being via eating. The most common place for drug use was a friend’s home (29.52%). Among the participants, 82.34% were smokers who had started smoking when as young as 17.57±4.90 years of age. Family members were the main factor encouraging participants to attempt to quit (63.91%). Conclusion: Based on the information provided by the addicted participants, friendship is the most important initiating factor in addiction. Friends encouraged patients and provided them with drugs and a safe place to first administer them. On the other hand, family members and family relationships seem to help patients financially and emotionally to quit substance use. As a result, keeping or restoring family relationships may be helpful factors in predicting and treating addiction.

Key Words: Addiction; drug quitting; age of starting use of drug; self-reported

1. Introduction

Drug addiction is a chronic brain disorder caused by drug abuse [13]. Dependency on drugs is of great concern to social and health organizations because of the adverse effects of addiction, which include psychological and physiological disorders and socioeconomic impairment [14]. Along with the growing number of drug-injecting addicts, the prevalence of sexually and blood-transmitted infections is becoming an increasingly serious problem [9, 12]. It is estimated that 149 to 272 million economically active individuals (aged between 15 to 64 years) abuse drugs at least once in their lifetime. Moreover, about 11 to 21 million drug abusers administer drugs via injection, and run higher risks of blood transmitted diseases. In Iran, the prevalence of drug abuse is rising so sharply that addiction has become a national problem [12]. The types of illicit drugs that are used in each country are different, and the differences are of substantial importance. For example, the drugs most commonly used in Africa are heroin and co-
caine, in Europe heroin and cannabis, and in North and Central America cocaine [15]. In Asia, cannabis and opium are the drugs most widely used, including Iran, where the highest usage rate is that of opium derivatives [10]. To date, the number of addicts in Iran is estimated to be about 1.2 million (approximately 1.6% of the total population) [10], and opium derivatives are known to be the most commonly used illicit drugs [1, 4, 15]. It is estimated that every year about 1,100 tons of opium are used by 4 million drug abusers, 42% of them living in Iran. In particular, annual heroin use is estimated to be around 17 tons in Iran (about 5% of global use). With regard to the above facts, Iran is ranked first among countries with a high rate of opium use [10].

Among the many factors associated with addiction, age, sex and marriage status are the most important. The male to female ratio for addiction has been estimated at 9 to 1 [10], with 18.9% of addicts younger than 24 years of age [10]. The adverse effects of drug use on one hand, and situations in which no access to drug users is allowed on the other, make the provision of health and medical care to drug abusers a difficult task [12]. In addition, as is true of many other countries, in Iran the illicit use of drugs is punished severely. This makes addicted individuals even harder to reach when medical and social help should be delivered to patients. This leads to a limited or zero supply of reliable information about this vulnerable and hidden part of a community. Via the collection of data on the history of illicit drug use by filling in a self-administered questionnaire, male drug abusers in Yasuj (the capital of Kohgiluyeh and Boyer-Ahmad province) were selected and studied to understand their views on the factors putatively involved in the initiation to substance use and in their later propensity to make attempts to quit.

2. Methods

This descriptive study was conducted on 362 male addicts (aged 18 to 45 years of age) from March 2013 to December 2015 in Yasuj, the capital of Kohgiluyeh and Boyer-Ahmad province located in the southwestern part of Iran.

2.1. Sample

In Iran, addiction and carrying illicit drugs come with serious social and legal consequences, no formal access to drug abusers is available. As a result, no predefined population of illicit drug users exists, so that addicts are not easily accessible. However, there are many addicted individuals who are frequently arrested and registered by police, or else are admitted to rehabilitation camps or treatment centres. These registered individuals were not believed to be representative of the addicted community because of significant socioeconomic differences compared with the rest of the addicted community. As a result, the researchers decided not to conduct any type of probability sampling. Instead, they decided to recruit a more representative sample of the addicted urban population, and snowball sampling was the method chosen. In that regard, male addicted volunteers who had registered with police or with a rehabilitation or treatment centre were invited to assist in the sampling procedure after being trained by the research team. The assistants invited known male addicted individuals aged between 18 to 45 years to complete the questionnaire. The assistants delivered the questionnaire to the participants in a private place after a short interview to strengthen the confidence felt by participants in the confidentiality of the interview, and as to whether they were able to read and understand the questionnaire. An informed consent document was read and signed by the participants before the interview began.

2.2. Instruments

A self-administered questionnaire was drawn up by the research team and its validity was evaluated by an expert panel consisting of a psychologist, an epidemiologist and a public health nurse experienced in addiction therapy. A pilot study was also conducted on 30 addicted participants who completed the questionnaire twice (with a two-week interval). According to the results of a test-retest analysis, the questionnaire was reasonably reliable (Cronbach’s alpha=0.65). The questionnaire was designed to collect information on the participant's educational, social and behavioural characteristics as well as the history of their addiction and related knowledge and behaviours.

2.2.1. Study variables

The questionnaire consisted of four sections covering a wide range of areas, namely: A) Factors associated with the start of drug usage, that is, age at onset of drug use, main reason for using illicit drugs, who introduced you to illicit drugs, where the drug was administered for the first time, route of the first drug administration and type of the first drug to be administered; B) Current use of illicit drug(s), i.e., currently, with whom do you administer drugs, how
do you obtain drugs and what type(s) of drug do you use?; C) Knowledge and behaviour, i.e., being aware of the consequences of addiction (yes/no question), being aware of how HIV is transmitted (multiple choice question), the date of the last time you were tested for HIV, whether you use a shared syringe (yes/no question), have you been in a sexual relationship outside marriage (yes/no question), frequency of use of condom during sexual contact (whether it is: always, sometimes, never), aggressive behaviour (asking: always, sometimes, never), having a criminal record (yes/no question), smoking (yes/no question) and who encouraged you to start smoking; D) Quitting attempts, i.e., did you ever attempt to quit (yes/no question), way chosen for the first attempt to quit (multiple choice question), way chosen for second attempt to quit (multiple choice question), who encouraged patient to quit the first time and the reason for the first attempt to quit.

2.3. Data analysis

Descriptive methods were used to analyse data. All analyses were performed using SPSS (version 20, SPSS, Chicago, IL).

3. Results

Results are reported in table 1.

3.1. Addiction-related factors

Interestingly, 83.6% (CI%: 0.78, 0.87) of the participants reported that they were not aware of the health or social consequences of addiction. However, only 11.43% of the participants reported a history of shared syringe usage for drug injection. Among participants, 33.13% (CI: 44%, 57%) reported that their friends were the main cause of their addiction and 69.46% declared that they were introduced to drugs (for the first time) by a friend. Opium was the most common drug used on the first occasion and the most popular route of first drug use was eating (92.44%). Only 63.76% of the participants were buying their drug(s) from drug dealers. The rest obtained drugs from friends or relatives. The most common place to use drugs was a friend’s home (29.52%). Among the addicted participants, 82.34% were smokers who had started smoking when they were as young as 17.57±4.90 years of age. As reported by the smoker participants, 68.75% were encouraged to start smoking by a family member.

3.2. Risky behaviours

Having a sexual relationship outside marriage was reported by only 15.56% of the participants. Of the participants, 50.90% had taken no HIV test for longer than 3 years. Most addicts (95.51%) knew that blood transfusion, injection and having sexual relations are the common routes of HIV transmission, and only 4.49% were totally unaware of the main routes of HIV transmission. However, 56.29% of the participants reported that they did not use a condom during sexual intercourse. About 29.62% of the participants reported that they had been aggressive, and 52.87 % reported that they have a criminal record or have been arrested (at least) once by police.

Based on the participants’ reported information about quitting substance use, about 71.63% of the participants had attempted to quit at least once. Job lost or other social problems were indicated as the main reason for quitting (23.84%), and family members were the main encouraging factor for par-

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics of addicted participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors associated with start of drug usage</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Main reason for becoming addicted</td>
</tr>
<tr>
<td>To experience euphoria</td>
</tr>
<tr>
<td>A sense of curiosity</td>
</tr>
<tr>
<td>Unemployment</td>
</tr>
<tr>
<td>Being unaware of the consequences</td>
</tr>
<tr>
<td>Who introduced you to drugs?</td>
</tr>
<tr>
<td>Friends</td>
</tr>
<tr>
<td>It was a personal decision</td>
</tr>
<tr>
<td>Who encouraged you to start smoking?</td>
</tr>
</tbody>
</table>
participants to attempt quitting (63.91%).

4. Discussion

This is a descriptive study whose aim has been to examine self-reported data on factors associated with: first drug use, current drug use and attempts to quit. In addition, participants’ knowledge about the side-effects of addiction, HIV transmission, and social and sexual behaviours were measured. The results suggested that friends are the main reason for the onset of addiction in participants. It seems that peers play an important role in the personality and social behaviours of any individual [9]. Among all the types of drugs used, opium was the most common. This finding is in accordance with the studies conducted by Amiri and Javanbakht [1, 5]. In the present study, eating was the common route of first drug use among addicts. This finding is in accordance with the Christopher’s study [6]. Eating was the most commonly used route of opium administration among Iranian addicts. That finding could be due to the ease of eating opium, as no instruments are needed. When eating drugs (especially opium), there is also no smoke or smell at risk of being noticed by others when administering them, as would happen if it took place via smoking [2]. According to the results of the present study, addicts predominantly showed no awareness of the

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics of addicted participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors associated with start of drug usage</td>
</tr>
<tr>
<td>Friends</td>
</tr>
<tr>
<td>Family / Social problems</td>
</tr>
<tr>
<td>Where did you use drugs for the first time?</td>
</tr>
<tr>
<td>At home</td>
</tr>
<tr>
<td>At work</td>
</tr>
<tr>
<td>Parks or suburbs</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Friends’ home</td>
</tr>
<tr>
<td>Street</td>
</tr>
<tr>
<td>Route of first drug use</td>
</tr>
<tr>
<td>Inhalation</td>
</tr>
<tr>
<td>Eating</td>
</tr>
<tr>
<td>Injection</td>
</tr>
<tr>
<td>Drug used the first time</td>
</tr>
<tr>
<td>Opium</td>
</tr>
<tr>
<td>Marijuana</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Criminal history</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Current use of drugs</td>
</tr>
<tr>
<td>With whom do you use drugs?</td>
</tr>
<tr>
<td>I use them when I am alone</td>
</tr>
<tr>
<td>Friends</td>
</tr>
<tr>
<td>Family</td>
</tr>
<tr>
<td>Current use of drugs?</td>
</tr>
<tr>
<td>Opium</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Glass/Ampoule</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Knowledge</td>
</tr>
<tr>
<td>Were you aware of the consequences of addiction?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Use of a shared syringe</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Sexual relationship outside marriage</td>
</tr>
<tr>
<td>Often</td>
</tr>
<tr>
<td>Sometimes</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Use of condom during sexual contact</td>
</tr>
<tr>
<td>Often</td>
</tr>
</tbody>
</table>
health and social consequences of addiction. In the present study, most addicts knew that injection and sexual contacts are the common routes of HIV transmission. Most addicts, however, did not use a condom during sexual intercourse [11]. These findings are in accordance with the results of studies by Dariotis [3]. Accordingly, drug addicts and their spouses are at a higher risk of sexually transmitted diseases.

The results of the present study also suggest that among different methods of quitting substance use, the use of replacement drugs (e.g. methadone, bupropion, dextoam, phetamine and methamphetamine) was the most common among these participants. This is in concordance with a study conducted by Mehrjerdi [8], which suggested that usage of methamphetamine as a replacement for opium is very common especially among young addicts [8]. The results of the present study suggest that losing a job and other social problems are the main reasons prompting attempts to quit drug use. Viewed from another angle, family support and encouragement provide the main inspiration for patients to actually take that decision [7].

5. Conclusions

Based on the information provided by the addicted participants, friendship is the most impor-

### Table 1: Baseline characteristics of addicted participants

<table>
<thead>
<tr>
<th>Factors associated with start of drug usage</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sometimes</td>
<td>74</td>
<td>25.9</td>
</tr>
<tr>
<td>Never</td>
<td>161</td>
<td>56.3</td>
</tr>
<tr>
<td>Behaving aggressively with others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td>85</td>
<td>29.6</td>
</tr>
<tr>
<td>Sometimes</td>
<td>205</td>
<td>66.6</td>
</tr>
<tr>
<td>Never</td>
<td>97</td>
<td>33.3</td>
</tr>
<tr>
<td>HIV is transmitted via</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>28</td>
<td>11.4</td>
</tr>
<tr>
<td>Blood/Sexual contact</td>
<td>38</td>
<td>15.5</td>
</tr>
<tr>
<td>Injection</td>
<td>21</td>
<td>8.6</td>
</tr>
<tr>
<td>Injection/Blood</td>
<td>56</td>
<td>22.9</td>
</tr>
<tr>
<td>Injection/Sexual contact</td>
<td>61</td>
<td>24.9</td>
</tr>
<tr>
<td>Sexual contact</td>
<td>30</td>
<td>12.2</td>
</tr>
<tr>
<td>Other ways</td>
<td>11</td>
<td>4.5</td>
</tr>
<tr>
<td>Last time tested for HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year ago</td>
<td>40</td>
<td>24.0</td>
</tr>
<tr>
<td>1-3 years ago</td>
<td>42</td>
<td>25.2</td>
</tr>
<tr>
<td>&gt;3 years ago</td>
<td>85</td>
<td>50.9</td>
</tr>
<tr>
<td>Friends/Relatives</td>
<td>44</td>
<td>19.2</td>
</tr>
<tr>
<td>Drug seller</td>
<td>146</td>
<td>63.8</td>
</tr>
<tr>
<td>Quitting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever attempted to quit?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>80</td>
<td>28.4</td>
</tr>
<tr>
<td>Yes</td>
<td>202</td>
<td>71.6</td>
</tr>
<tr>
<td>Way of first attempting to quit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>50</td>
<td>30.1</td>
</tr>
<tr>
<td>Camp</td>
<td>40</td>
<td>24.1</td>
</tr>
<tr>
<td>Home</td>
<td>48</td>
<td>28.9</td>
</tr>
<tr>
<td>Quitting centres</td>
<td>28</td>
<td>16.9</td>
</tr>
<tr>
<td>Way of making second attempt to quit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>22</td>
<td>25.0</td>
</tr>
<tr>
<td>Community</td>
<td>27</td>
<td>30.7</td>
</tr>
<tr>
<td>Home</td>
<td>15</td>
<td>17.1</td>
</tr>
<tr>
<td>Who first encouraged you to quit drug use?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friends</td>
<td>15</td>
<td>11.3</td>
</tr>
<tr>
<td>Family</td>
<td>85</td>
<td>63.9</td>
</tr>
<tr>
<td>Myself</td>
<td>33</td>
<td>24.8</td>
</tr>
<tr>
<td>Reason for first quitting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losing job or other social problems</td>
<td>31</td>
<td>23.8</td>
</tr>
<tr>
<td>Friends</td>
<td>32</td>
<td>24.6</td>
</tr>
<tr>
<td>Family</td>
<td>9</td>
<td>6.9</td>
</tr>
<tr>
<td>Not reported</td>
<td>58</td>
<td>44.6</td>
</tr>
</tbody>
</table>
tant initiating factor in illicit drug use. It seems that friends encourage individuals to use illicit drugs for the first time by providing the substance itself and a safe place to administer it. On the other hand, family members and family relationships seem to support patients financially and emotionally in quitting substance use. However, it seems that the attempts to quit mostly ended up in relapse and failure. Independently of what the results of an attempt to quit are, a feeling of determination to quit addiction is a very important factor in achieving success in the quitting process. It follows that family supervision during adulthood and helping patients to rebuild family relationships may help them to prevent and to quit substance abuse, respectively. The results also suggested that most participants were unaware of the side-effects of addiction when they first started to use drugs. It may therefore be suggested that all individuals should be made aware of the consequences of addiction at an earlier stage (preferably while still at school).

References

1. Amiri M., Khosravi A., Chaman R. (2010): Drug Abuse Earlier stage (preferably while still at school). It may be made aware of the consequences of addiction at an earlier stage (preferably while still at school).


Acknowledgements

The authors would like to thank the deputy of research of Yasuj University of Medical Sciences for providing us with great supports in conducting the present research.

Role of the funding source

The present study was funded by the Yasuj University of Medical Sciences.

Contributors

Z.S., M.F., K.K., designed the study and wrote the protocol. Z.S., M.F., G.S., managed the literature searches and analyses. M.F., undertook the statistical analysis, and all the authors discussed the results. M.F., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.
Conflict of interest
Authors declared no conflict of interest.

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study does not require ethics committee approval because it was carried out according to a non-interventional protocol. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

Note
It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author accepted our service.

Received July 26, 2017 - Accepted December 27, 2017
An evaluation of community pharmacist perception of the misuse and abuse of over-the-counter co-codamol in Cornwall and Devon, UK: A cross-sectional survey

Ravina Barrett, and Dalmar Costa

University of Portsmouth, Portsmouth, UK

Summary

Background: Codeine containing preparations have the potential to cause harm and dependence. Recent UK regulatory changes to the pack-size and printed warnings have been instituted to reduce this potential. However, there is a reported increase in the misuse of codeine containing analgesics in countries where it is available over-the-counter. This is a challenge for pharmacies and pharmacists globally. Aim: To evaluate the perceptions of community pharmacists on the nature and management of Over-The-Counter (OTC) co-codamol (paracetamol and codeine combination preparations) misuse and abuse. Methods: A self-report, postal survey was developed and posted to 65 pharmacies in Cornwall and 85 pharmacies in Devon (n=150) in the UK. Qualitative and quantitative data was analysed using descriptive statistics, hypothesis testing and thematic analysis. Results: Most pharmacists perceived their patients and community as having some challenges with the misuse of co-codamol. Pharmacists think that co-codamol is not harmful if used as indicated. The behaviours pharmacist associated with misuse were frequent to purchase and misinformation provided by the patient during consultation. Counselling and referral are the main interventions utilised by pharmacist in such circumstances. Pharmacists who have received training on co-codamol abuse know where to refer customers. Conclusions: Community pharmacists face a difficult challenge when suspecting misuse. However, pharmacists believe co-codamol abuse can be reduced by increasing the public’s awareness of the addictive potential of co-codamol.

Key Words: Codeine; Misuse; Over the counter; Risk reduction; Community pharmacy

6. Introduction

The inappropriate use of OTC medications is referred to as misuse or abuse, due to their potential for addiction and dependency. Misuse and abuse can sometimes be misunderstood. For the purpose of this study, the definitions are adopted from EU commissioned report [18] concerning codeine use, misuse and dependence.

The definition of ‘misuse’ is: ‘The problematic consumption of codeine where risks and adverse consequences outweigh the benefits, and which includes use of codeine with or without prescription, outside of acceptable medical practice or guidelines, for recreational reasons, when self-medicating, with higher doses and for longer than advisable’ [3].

While the definition of ‘abuse’ is: ‘The use of drugs for nonmedical purposes is to experience their mind-altering effects, while “misuse” is applied to the use of a drug for legitimate medical purposes, but in an incorrect manner’ [1]. Both definitions imply recreational use. Although these definitions are limited to codeine abuse and misuse, we use these definition as they are relevant to co-codamol use.

In the UK, there are three categories of licenced medicines for human use: 1. General Sales List (GSL) medicines, which can be readily purchased from retailers, often containing a small quantity of analgesics and other preparations (not codeine-based). 2. Pharmacy (P) medicines, which can be purchased OTC from a registered pharmacy where a registered pharmacist oversees the sale (can be codeine-based). 3.
Prescription only medicines (POM), which must be supplied only against a valid prescription. Codeine preparations are sold OTC as P medicines or on a prescription. Some examples of other commonly abused medications include benzodiazepines, z-drugs and opioid painkillers.

The misuse and abuse of OTC medicines is a worldwide problem [4, 17]; the five key groups of abuse range from laxatives, cough products, sedative antihistamines, decongestants and codeine based analgesics [4, 9]. This is due to looser regulations, greater availability and self-medication [18, 16]. The misuse of codeine containing compound analgesics (normally in combination with ibuprofen or paracetamol) is increasing in countries where it can be purchased OTC [10]. Codeine containing analgesics are commonly associated with abuse and dependence due to the addictive and euphoric properties of codeine [18].

Associated with this euphoric effect is the consequence of overconsumption of the compounded analgesic such as paracetamol. The potential health risk as a direct consequence of paracetamol overdose is hepatotoxicity [8] related to the chronic use of such products [6, 5, 8]. Similarly, when codeine is combined with ibuprofen, overdose can result in nephrotoxicity and gastric irritation. These health harms are amplified with dose escalation, which is commonly observed with chronic codeine misuse [16], because patients build tolerance to that dose of codeine and need a greater amount of codeine to generate the same euphoric effect, while sustaining damage from paracetamol and ibuprofen overdose.

The initial use of such agents is often genuine and for appropriate indicated conditions. However, eventually it is taken for non-medical reasons and borders on dependency [8, 4, 15]. Some studies suggest that codeine dependence is subtly different to other opioid dependence. It requires different types of treatment, abusers have different mental health problems, and they have more similarities to the general population [11, 13]. Similarly, individuals mainly abusing codeine, labelled themselves as ‘social and economically active and different from illicit substance misusers’ [4]. Additionally, individuals have described their codeine abuse as the ‘blurring’ between therapeutic and problematic use, whereby they think they are using it to relieve pain, while in fact they are using it to prevent opioid withdrawal symptoms [12].

Aims: The primary aim was to investigate the perceptions of community pharmacists on the misuse and abuse of OTC co-codamol (research question: what do community pharmacists think about co-codamol misuse and abuse?)

The secondary aim was to understand how community pharmacists suspect and manage co-codamol misuse or abuse (research question: how do community pharmacists manage the phenomenon?)

7. Methods

The survey was developed from Carney et al’s [2] study. This study investigated views on regulatory changes, strategies used to identify misuse of codeine and how community pharmacists managed them.

To improve internal validity and reliability, the survey instrument was piloted, and cognitive testing (read aloud) was conducted on the final instrument. The feedback confirmed that the questions were interpreted properly. Accompanying the survey was a participant information sheet, that highlighted the purpose of the study and invited participation. Taking part in the study was voluntary and anonymous. A pre-paid, self-addressed envelope was included to facilitate survey responses. Implied consent was assumed if surveys were returned. The duration of data collection was approximately 3 months from 25/11/2016.

Community pharmacies in Cornwall (n=65) and Devon (n=85) were surveyed, a sample representing approximately 60% of pharmacies in both counties. Devon had previously run a codeine awareness campaign and Cornwall had not. Community pharmacies registered on NHS choices website were targeted. Registered and preregistration pharmacists were invited to complete the questionnaire. 32 completed surveys (out of 150) were returned (response rate 21%) from Devon (20) and Cornwall (12). 56% male and 44% females responded. 59% of respondents had eight years or more practice experience. 66% of these were full-time pharmacist.

Quantitative data were analysed using SPSS [7] software and qualitative data were analysed using NVivo [14] for thematic analysis.

7.1. Ethics statement

Prior to data collection, favourable ethical opinion was received from the School of Pharmacy and Biomedical Sciences Research Ethics Committee on (Reference number: 2016.17 – 005, Date submitted: 24-10-2016). This study is in line with declaration of Helsinki-ethical principles for medical research involving human subjects.
8. Results

88% of respondents reported knowing customers who regularly purchased co-codamol, with 44% purchasing co-codamol once or twice a week. 84% of respondents did not routinely recommend co-codamol for pain relief. Of these, 38% actively avoided recommending co-codamol for pain. 94% of all responders had offered alternatives to co-codamol during an OTC sale. 91% had denied prior sales of co-codamol to individual customers. 47% of respondents believe that OTC use of co-codamol is harmful. Of these, 41% believed it encouraged the risk of addictive behaviour, 28% believed there was a risk of paracetamol overdose, a similar percentage believe there was a risk of endorsing abuse, 22% believed there was a risk of liver damage with chronic high paracetamol intake. However, 72% of responders indicated that co-codamol should not be reclassified as a prescription only medicine (POM).

47% of respondents believed they served ‘lower-middle-class’ patients in their shop. 63% believed they knew where to refer customers for the treatment of co-codamol abuse. A Pearson chi-squared test statistic of 14.264 (p=0.002) rejects the null hypothesis that there is no association between perceived lower socio-economic status of patients and pharmacist’s knowledge of referral.

Thematic analysis of the challenges associated with OTC co-codamol sale identified the following themes: 1. Patients, 2. Abuse, 3. Pharmacies. Patients: patients repeatedly requesting co-codamol, failed to understand the impact of their abuse on their health. Abuse: respondents reported patient abuse towards them including aggressiveness, defensiveness and abusive language and actions. Pharmacies: some respondents would rather make a supply, even when they suspect abuse to secure revenues.

Thematic analysis of how patient’s health is safeguarded considering the above challenges revealed: 1. Use, 2. Patients, 3. Staff. Use: advice around safe use is given. Patients: patients are routinely questioned on their use of co-codamol. Staff: staff are locally made aware of frequent customers and the risk of abuse by individual patients.

66% of respondent had received no training on helping customers with co-codamol abuse. A Pearson chi-squared test statistic of 8.119 (p = 0.004) rejected the null hypothesis that there was no association between pharmacists that had received training and pharmacists who knew where to refer customers for treatment. All respondents that received training with co-codamol abuse know where to refer customers for abuse support. Hence, Devon’s public health campaign seems to have worked. 63% of all respondents would like to receive further training.

9. Discussion

Most of the responders were full-time pharmacists working in communities they perceived as upper-middle-class areas. The obstacles they face included low-level co-codamol abuse. The Pearson chi-squared test suggests that poorer communities that face challenges of co-codamol abuse/misuse are doubly disadvantaged because the community pharmacist lacks sufficient knowledge to be able to refer patients appropriately to address their addiction. Conversely, respondent working in upper-middle-class or middle-class backgrounds are more aware of appropriate referral pathways.

Pharmacist attempted to safeguard patients by asking questions and providing counselling for safe and appropriate use. They also shied away from recommending co-codamol and actively discourage its use. Many respondents had mixed opinions on the harm of OTC use of co-codamol. Most respondents concurred that OTC sale may risk ‘encouraging’ addictive behaviour.

Regardless of these harms, it must be stressed that respondent-pharmacists do not believe that co-codamol should be reclassified as prescription only, and many do not believe that the OTC use of co-codamol is harmful. These recommendations are in line with the recent studies that suggest raising public awareness and education is needed as the first step in combating this problem. This education should not just be for co-codamol, but include all OTC codeine containing products.

The main limitation of this study is the small sample size, where results are not generalisable. However, it provides a snapshot into current pharmacy practice. There was a high completion rate for most questions, however, responder bias is possible. Further in-depth study is warranted given the global status of the opioid epidemic.

10. Conclusions

Community pharmacists face a difficult challenge in gaining the right balance of safe co-codamol use. Community pharmacists in Devon and Cornwall believe that abuse can be reduced by raising public
awareness and training pharmacist to spot the early signs of abuse. The magnitude of this challenge remains small according to the respondent and pharmacists do not believe reclassification to POM is warranted.

Co-codamol abuse is a complex and difficult challenge, which can be reduced via policy or public health promotion. Pharmacist believed that mandatory counselling with co-codamol sale is essential. This could be achieved in several ways: having a designated ‘codeine’ staff, who is the single point of contact for codeine sales and is themselves additionally trained for issues around addiction. There could be barcode scanned prompts at point of sale for essential counselling with each sale. Further, local training and awareness of pharmacists and their support staff via e-learning courses could further raise awareness amongst pharmacy professionals, including local signposts for addiction support counselling services.

Patients are made aware of the risk of addiction on the packaging: in the UK, printed warning for safe use of three days as a maximum and pack sizes are restricted to a maximum of three-day supply. Further OTC opioid-analgesics awareness programs could be run by the government.

Safety as a quality can be linked to medication and their safe use. Safety, can also be linked to patient qualities and characteristics, where some patients have a greater propensity for safety versus addiction. It is this second group, which benefits most from these safer modalities exercised by pharmacy.

References

14. NVivo qualitative data analysis Software. QSR International Pty Ltd.; 2015.
Acknowledgements
Thank you to Dr Nicola Barnes for providing editorial guidance.

Role of the funding source
This study was funded by the University of Portsmouth.

Contributors
All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest
Authors declared no conflict of interest.

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

Note
It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author preferred not to use our service.
Switching between lyophilized and sub-lingual buprenorphine formulations in opioid-dependent patients: Observations on medication transfer during a safety and pharmacokinetic study

Kylie Reed 1,2, Alastair Knight 3, Shelagh Baillie 4, Karolina Bogdanowicz 1, James Bell 1,2, and John Strang 1,2

1-King’s College London, National Addiction Centre (Institute of Psychiatry, Psychology & Neuroscience), London, UK
2-Addictions Services, South London & Maudsley NHS Foundation Trust, London, UK
3-Evicom Ltd, Twickenham, UK
4-Martindale Pharmaceuticals Ltd, High Wycombe, Buckinghamshire, UK

Summary

Background: A new lyophilized, rapid-disintegrating buprenorphine tablet (“bup-lyo”) has been developed to potentially enhance adherence compared to conventional sublingual tablets (“bup-SL”) but with a higher bioavailability of buprenorphine. Aim: To examine the pharmacokinetics, efficacy and safety of switching between formulations. Methods: Within a randomized trial of opioid-dependent subjects, one arm received “bup-lyo”. After 2 weeks of treatment, all subjects switched back to standard sublingual “bup-SL” over 1-4 days in preparation for transfer back to their treating clinician. Observations were made of any change in clinical situation on transfer, or need for dose adjustment. Measurements included dose titration, treatment retention and within-subject comparisons of; pharmacokinetics (buprenorphine and norbuprenorphine), subjective scores of medication hold and dose adequacy, and safety assessments. Results: Subjects (N=23) were titrated to an effective and safe daily dose of “bup-lyo” (10.8 ± 4.85 mg) (N=22) and then returned to the same dose of “bup-SL” (N=21). There had been no significant difference in dose, medication hold and dose adequacy between formulations on optimized treatment. Bloods were provided by 5 “bup-lyo” subjects for pharmacokinetic analysis: despite within-subject similar dosing, buprenorphine Cmax and AUC0-3hr (mean ± SD) were significantly higher with “bup-lyo” than when switched to “bup-SL” (relative Cmax 185.8 ± 88.2%, AUC0-3hr 169.8 ± 62.0 %). However, for norbuprenorphine which is more associated with respiratory depression, the differences were not significant (relative Cmax 109.6 ± 42.2%, AUC0-3hr 105.0 ± 39.4 %). Adverse event incidence was slightly higher with “bup-lyo” but events were mild to moderate. Conclusion: Switching from “bup-lyo” to “bup-SL” did not require clinical adjustment of daily dose despite observed higher buprenorphine levels with “bup-lyo”. The bioavailability of the metabolite norbuprenorphine, which is a more potent respiratory depressant than buprenorphine, was comparable between formulations. This may explain the absence of clinical difference in vital signs or other adverse events observed on switching formulations.

Key Words: Buprenorphine; switching; lyophilized; pharmacokinetics

1. Introduction

Buprenorphine is a widely-approved replacement therapy of opioid addiction [7]. Evidence suggests it is a safer treatment than other opioids such as methadone although deaths, possibly associated with respiratory depression [1] due to buprenorphine overdose, are still reported in clinical and forensic practice.

Poor adherence and diversion of supplies are common obstacles to the success of opioid replacement therapy (ORT). Supervised dosing of standard sublingual buprenorphine [2] can take 5–10 min for tablets to dissolve and hence requires extended supervision which can be impractical, particularly in prisons and busy community pharmacies. The development of rapidly dissolving or rapid-dispersal formulations, such as combination buprenorphine/
naloxone film [11, 6] and rapid-dispersal tablets specifically designed for virtually instant disintegration [3, 12], may be beneficial in busy community pharmacies and custodial settings as it will enable wider prescribing of buprenorphine in these settings.

We [12] undertook a randomized, group comparison trial in opioid-dependent subjects comparing standard sublingual buprenorphine (“bup-SL”) [Subutex®, Indivior UK Ltd, Slough, UK] to a new lyophilized (rapid-disintegrating) buprenorphine (“bup-lyo”) [Espranor®, Martindale Pharmaceuticals Ltd, High Wycombe UK] and established complete disintegration by 3 min for more than 75% of “bup-lyo” administrations versus less than 25% of “bup-SL” administrations. Comparative safety and efficacy of these formulations was assessed against an observed suprabioavailability of “bup-lyo”. Further pharmacokinetic analysis of these data [13] included assessment of norbuprenorphine, the active metabolite of buprenorphine which has a greater potency for respiratory depression than buprenorphine and may be the main cause of the observed deaths on buprenorphine [5, 10]. This additional analysis provided evidence to suggest that the reason respiratory depression was not observed with suprabioavailable buprenorphine was because buprenorphine is only minimally directly depressing respiration and may indirectly be protective by competing for receptor occupancy with the active metabolite norbuprenorphine and its greater depressive effect on ventilation [8]. The purpose of this study was to examine further this hypothesis by comparing the two buprenorphine formulations amongst subjects in the randomized arm who received “bup-lyo” for 14 days and were then switched to “bup-SL”, utilising within-subject pharmacokinetic data for both buprenorphine and norbuprenorphine and examining dosage comparability through clinical outcome and safety assessments.

2. Methods

This supplementary report describes additional data from one arm of a randomized, open-label, group comparison trial in ORT subjects [12] which was approved by Brent Research Ethics Committee, UK with trial number UK/H/5385/01-02/DC. The study was subsequently, registered with EudraCT number: 2012-003560-49 and conducted according to the Declaration of Helsinki which required patients to sign informed consent to enter the documented screening process. As this was a small open-label study a separate data monitoring committee was not required by the ethics committee although safety was routinely monitored during the course of the trial by the Principal investigator (Prof John Strang) and one of two Medical safety advisors; Dr John St Clair Roberts and Dr Robert Miller who were otherwise not involved in the study. Subjects in this one arm of the trial were initially randomized to a new lyophilized (rapid-disintegrating) buprenorphine (“bup-lyo”). It was then necessary for all participating patients to be switched back to standard “bup-SL” during an extension period in preparation for transfer back to their treating clinician. Importantly, this part of the study included additional pharmacokinetic (PK) data from a sub-group of subjects consenting to blood sampling for PK analysis for up to 180 min post-dose “bup-lyo” and “bup-SL” treatment, in effect providing within-subject (crossover), PK comparison data. Through the research opportunity afforded by the clinical necessity to switch these patients from “bup-lyo” to standard “bup-SL”, along with supplementary analysis of this arm of the study we examine further the clinical practicalities of switching between these buprenorphine formulations. The following information was utilized; dosing comparability, subject retention, efficacy (subjective Likert scores (1=best, 4=worst) for adequacy of ‘hold’, withdrawals symptoms and intensity of craving) and safety data (adverse event reports and vital signs), together with new PK data.

The study design and methods undertaken within the group comparison arms of the trial have been described previously [12, 13]. In summary, consenting subjects already treated with or suitable for ORT, were screened for their suitability for the trial. Subjects were then randomized directly onto the assigned study medication, either to standard sublingual buprenorphine or to a new lyophilized (rapid-disintegrating) buprenorphine (“bup-lyo”). To enable a buprenorphine-free PK profile at the start of randomization, subjects received no buprenorphine or methadone replacement therapy for a minimum of one-day prior to randomization. Following randomization, subjects proceeded to a titration period of up to 7 days during which their dose of buprenorphine was increased in a step-wise manner from 1-2 mg daily based on post-dose safety data and efficacy data from Likert scores and validated opioid-withdrawal signs and symptom scales (Objective Opiate Withdrawal Scale [OOWS] and Subjective Opiate Withdrawal Scale [SOWS]), [4]. Thereafter, subjects proceeded to a maintenance period of 7 days during which they were assessed 24 hr post-dose at end of day 1 and 7 for safety and efficacy, and a sub-group also pro-
K. Reed et al.: Switching between lyophilized and sub-lingual buprenorphine formulations in opioid-dependent patients: Observations on medication transfer during a safety and pharmacokinetic study

provided blood samples for PK analysis after dosing. This was then the end of the group comparison study period. To ensure subjects returned safely back to a licensed formulation of buprenorphine (“bup-SL”) at an optimal dose, subjects then entered an extension period which included a switching period of up to 4 days where subjects were weaned-off “bup-lyo” onto “bup-SL” using daily safety and Likert score data to guide clinician judgement of buprenorphine dose. After this switching period subjects were maintained on the same dose of “bup-SL” for the rest of the extension period and reassessed on day 14 from start of switching for efficacy and safety, at which point the same sub-group provided an additional series of PK samples post-dose.

PK profiles of each subject within the PK subgroup at the end of the maintenance period on “bup-lyo” and at the end of the extension data on “bup-SL” (treatment for 14 days including optimal maintenance dosing for at least 7 days) were, where available, compared and Phoenix WinNonlin 6.3 (Certara USA Inc., Princeton, USA) software utilised to determine the Cmax, AUC0-3hr and Tmax parameters of buprenorphine and the metabolite, norbuprenorphine for each buprenorphine formulation. Since PK subjects were each on different doses of buprenorphine but on the same formulation dose within subjects, the % change of Cmax and AUC0-3hr on “bup-lyo” treatment compared to “bup-SL” treatment were determined for each subject and absolute values compared by paired t-test and summarized for all subjects as a mean % relative change. Corresponding Likert scores on “bup-lyo” and “bup-SL” were compared statistically using ANOVA. Safety data during the “bup-lyo” titration phase was assessed daily and included periods at sub-optimal dosing. To compare safety data at optimal dosing of both formulations only the adverse events (AEs) recorded during the maintenance phase (Day 2 and Day 7) on “bup-lyo” and the extension period after switching (Extension Day 4 or last day of switching and Extension Day 14) for “bup-SL” are reported. The incidence of all AEs, independent of dosing status, have been previously reported [12].

3. Results

The flow of and number of subjects recruited and randomized to the “bup-lyo” arm of a single-blind study and then switched to “bup-SL” are detailed in Figure 1. A total of 55 subjects were screened over a

---

**Figure 1. Study flow and subject numbers**

- 2 subjects were randomized but not treated (1 Lost to follow-up and 1 Withdrew consent).
- PK = Pharmacokinetic study population, DNA = Did Not Attend
two-week period. Thirty-eight were eligible for randomization (2:1) and excluded any ORT (buprenorphine/methadone) for a minimum of one day prior to randomization. Of these, 23 were randomized and commenced “bup-lyo” study treatment, including 8 who consented to PK blood sampling. These subjects formed the cohort for this additional analysis. The other 13 subjects were randomized to continued maintenance on “bup-SL” and their outcomes have been previously reported [12]. Of the 23 randomized and receiving “bup-lyo” medication, one subject withdrew consent during the titration period and one withdrew consent during the maintenance period. A total of 21 subjects completed the “bup-lyo” maintenance period. These subjects were then switched back to conventional “bup-SL” as part of an extension period of the trial. This included a ‘switching’ period of up to 4 days for dose adjustment, if required. One subject was lost to follow-up during ‘switching’, resulting in a total of 20 subjects who entered and completed the switch to “bup-SL” extension period of the trial. No subjects withdrew due to adverse events.

3.1. Demographics and medical history of the “switch to bup-SL” subjects

The demographics of the 23 subjects who were randomized, received “bup-lyo” and then expected to switch to “bup-SL” as part of the protocol, are described in detail in a previous publication [12]. In summary there were 20 males and 3 females with a mean ± SD age of 42.0 ± 8.0 years. The majority were Caucasian (65.2%). They reflect a typical population of opioid users with 22 of the 23 subjects including a history of opioid use >2 years, with a mean ± SD duration of opioid use of 16.6 ± 11.3 years. Mean ± SD age at first opioid use was 25.4 ± 8.7 years. Medical history for psychiatric disorders included; mild to moderate depression in 11 (6 ongoing), alcohol dependence in 2 (1 potentially ongoing as failed an initial screen test), and anxiety in 1 (ongoing). Medical history for infections included 7 with Hepatitis C (3 ongoing). At the start of screening, 15 of the randomized cohort were treated with buprenorphine, 6 with methadone and 2 had no treatment. No subjects had positive screens for amphetamine but 13 had positive screens for opioids at start of screening and were requested to stop use. Within the cohort being treated with “bup-SL” one subject stated they were a regular user of benzodiazepine therapy. The others stated they were non-regular users of benzodiazepine.

3.2. Dosing

The mean ± SD “bup-lyo” maintenance dose was 10.8 ± 4.85 mg (2-20 mg) and on switching back to “bup-SL” at the end of the extension 10.5 ± 4.98 mg (2-20 mg). These small dosing differences were not significantly different. Eighteen of 22 subjects (81.8%) were titrated to an optimal dose of “bup-lyo” within 3 days, the others within 7 days. On switching from “bup-lyo” to “bup-SL” all subjects were switched to the same dose of “bup-SL” as the dose of “bup-lyo” to which they had been titrated and on which they had been maintained for the second week of the study.

3.3. Pharmacokinetics

Eight subjects formed the PK sub-group which included PK sampling for buprenorphine and norbuprenorphine while on “bup-lyo” on Day 7 of the maintenance period. Five of these also had PK sampling while being treated with “bup-SL” at the end of the extension period. Three subjects did not have sampling performed at the end of extension (2 insufficient samples to establish PK profile due to cannula blockage, 1 withdrew (lost to follow-up)). The PK comparisons of the 5 paired PK assessments at the end of comparable durations of treatment, are detailed for each patient and summarised in Table 1.

Each subject had different doses of buprenorphine but within subject dosing for the buprenorphine formulations were the same. Significant increases in mean ± SD buprenorphine Cmax and AUC0-3hr were observed with “bup-lyo” relative (%) to “bup-SL” (Cmax 185.8 ± 88.2%, AUC0-3hr 169.8 ± 62.0 %) P<0.001, but the variation between subjects was great. Interestingly, for norbuprenorphine, a buprenorphine metabolite, the relative % mean ± SD PK parameter differences were not significantly different when comparing “bup-lyo” to “bup-SL” (Cmax relative 109.6 ± 42.2%, AUC0-3hr 105.0 ± 39.4 %). Tmax ranges for buprenorphine and norbuprenorphine were similar between formulations. A longer maximal Tmax range for norbuprenorphine (120 min) compared to buprenorphine (60 min) was observed as would be expected for this metabolite.

3.4. Subjective assessments - Medication hold and dose adequacy

Mean (SD) subjective scores for medication hold, intensity of withdrawal symptoms and intensity
Table 1. Comparative pharmacokinetics of buprenorphine and norbuprenorphine at the end of 14 days treatment with “bup-lyo” and “bup-SL”.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment</th>
<th>Visit</th>
<th>Dose (mg)</th>
<th>Buprenorphine</th>
<th>Norbuprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tmax (min)</td>
<td>Cmax (ng/mL)</td>
</tr>
<tr>
<td>1</td>
<td>“bup-lyo”</td>
<td>Maintenance D7</td>
<td>10</td>
<td>60</td>
<td>4.198</td>
</tr>
<tr>
<td></td>
<td>“bup-SL”</td>
<td>Extension End</td>
<td>10</td>
<td>60</td>
<td>3.272</td>
</tr>
<tr>
<td>2</td>
<td>“bup-lyo”</td>
<td>Maintenance D7</td>
<td>8</td>
<td>60</td>
<td>8.044</td>
</tr>
<tr>
<td></td>
<td>“bup-SL”</td>
<td>Extension End</td>
<td>8</td>
<td>60</td>
<td>2.554</td>
</tr>
<tr>
<td>3</td>
<td>“bup-lyo”</td>
<td>Maintenance D7</td>
<td>4</td>
<td>60</td>
<td>3.039</td>
</tr>
<tr>
<td></td>
<td>“bup-SL”</td>
<td>Extension End</td>
<td>4</td>
<td>60</td>
<td>1.281</td>
</tr>
<tr>
<td>4</td>
<td>“bup-lyo”</td>
<td>Maintenance D7</td>
<td>12</td>
<td>60</td>
<td>8.312</td>
</tr>
<tr>
<td></td>
<td>“bup-SL”</td>
<td>Extension End</td>
<td>12</td>
<td>60</td>
<td>5.681</td>
</tr>
<tr>
<td>5</td>
<td>“bup-lyo”</td>
<td>Maintenance D7</td>
<td>16</td>
<td>60</td>
<td>8.964</td>
</tr>
<tr>
<td></td>
<td>“bup-SL”</td>
<td>Extension End</td>
<td>16</td>
<td>60</td>
<td>8.729</td>
</tr>
</tbody>
</table>

Summary Statistics

<table>
<thead>
<tr>
<th></th>
<th>Tmax (min)</th>
<th>Tmax (min)</th>
<th>Cmax (%)</th>
<th>AUC 0-3hr (%)</th>
<th>Tmax (min)</th>
<th>Tmax (min)</th>
<th>Cmax (%)</th>
<th>AUC 0-3hr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“bup-lyo”</td>
<td>185.8</td>
<td>169.8</td>
<td>109.6</td>
<td>105.0</td>
<td>138.0</td>
<td>119.0</td>
<td>192.620</td>
<td>166.0</td>
</tr>
<tr>
<td>“bup-SL”</td>
<td>88.17</td>
<td>61.99</td>
<td>42.18</td>
<td>39.35</td>
<td>109.09</td>
<td>96.0</td>
<td>105.0</td>
<td>69.0</td>
</tr>
</tbody>
</table>

AUC0-3hr = area under the curve from 0 to 3 hours, Cmax = maximum concentration, PK = pharmacokinetic, Tmax = time to maximum concentration
Relative % Cmax and AUC0-3hr for subjects completing “bup-lyo” and “bup-SL”
**Figure 2a.** Likert categorical assessment scores for Adequacy of hold during buprenorphine formulation switching

**Figure 2b.** Likert categorical assessment scores for Withdrawal symptoms during buprenorphine formulation switching
K. Reed et al.: Switching between lyophilized and sub-lingual buprenorphine formulations in opioid-dependent patients: Observations on medication transfer during a safety and pharmacokinetic study

3.6. Adverse events

A summary of all AEs reported with each formulation during stable optimal dosing for at least a week are detailed in Table 2. There was a slightly larger number of AEs reported on “bup-lyo” than “bup-SL” which was also reflected in a larger proportion of subjects reporting AEs on “bup-lyo”. The most frequently reported TEAEs by system organ class were from clinical “Investigations” followed by “Musculoskeletal and connective disorders”. The proportion of subjects treated reporting these events was greater on “bup-lyo”. The most common AE was headache reported in 3 subjects (“bup-lyo” 2 subjects and “bup-SL” 1 subject), followed by athralgia, and ECG abnormalities reported each in 2 subjects (“bup-lyo” only). The majority of AEs were mild in both groups. No serious or severe adverse events were reported, and no subjects withdrew or discontinued from the study due to adverse events.

4. Discussion

Utilising within-subject, pharmacokinetic, comparative analysis this study supports the view from our

Figure 2c. Likert categorical assessment scores for Craving during buprenorphine formulation switching

of craving at the end of screening on “bup-SL”, on switching to “bup-lyo” during a titration period and a dose maintenance period, and on switching back to “bup-SL” during a switching period and an extension period are detailed in Figure 2a-c. All assessments were performed 24 hr post-dose. Following a stable dose of buprenorphine for 7 days none of the differences between buprenorphine formulation scores were statistically significant. The higher Likert scores observed during the initial days of the titration period reflected what would be expected for sub-optimal dosing.

3.5. Vital signs

Vital signs were assessed at each subject visit 24 hr post-dose and included respiratory rate. There were no significant differences between formulations in respiratory rate or blood pressure at the end of the maintenance period on “bup-lyo” and end of the extension period on “bup-SL”, despite the higher Cmax observed with “bup-lyo”.

3.6. Adverse events

A summary of all AEs reported with each formulation during stable optimal dosing for at least a week are detailed in Table 2. There was a slightly larger number of AEs reported on “bup-lyo” than “bup-SL” which was also reflected in a larger proportion of subjects reporting AEs on “bup-lyo”. The most frequently reported TEAEs by system organ class were from clinical “Investigations” followed by “Musculoskeletal and connective disorders”. The proportion of subjects treated reporting these events was greater on “bup-lyo”. The most common AE was headache reported in 3 subjects (“bup-lyo” 2 subjects and “bup-SL” 1 subject), followed by athralgia, and ECG abnormalities reported each in 2 subjects (“bup-lyo” only). The majority of AEs were mild in both groups. No serious or severe adverse events were reported, and no subjects withdrew or discontinued from the study due to adverse events.

4. Discussion

Utilising within-subject, pharmacokinetic, comparative analysis this study supports the view from our
### Table 2. Adverse events by buprenorphine treatment

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>&quot;bup-lyo&quot; N=22</th>
<th>(%)</th>
<th>&quot;bup-SL&quot; N=21</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>Overall</td>
<td>21</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one AE per subject</td>
<td>Overall</td>
<td>16 (72.7)</td>
<td>6 (28.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td>3 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoaesthesia oral</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toothache</td>
<td></td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>2 (9.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td>2 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza like illness</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel puncture site reaction</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthropod bite</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laceration</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle strain</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Overall</td>
<td>4 (18.2)</td>
<td>2 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood creatinine phosphokinase increased</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure diastolic decreased</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td></td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram abnormal</td>
<td></td>
<td>2 (9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective disorders</td>
<td>Overall</td>
<td>4 (18.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td>2 (9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular weakness</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Overall</td>
<td>2 (9.1)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>2 (9.1)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Overall</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin irritation</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Overall</td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td></td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>1 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
previous group comparison, dose-normalized analysis, that buprenorphine bioavailability with “bup-lyo” is higher than with “bup-SL” while norbuprenorphine bioavailability is similar [12, 13]. It can be postulated that a higher buprenorphine bioavailability with “bup-lyo” will require a lower dosing than conventional “bup-SL”: however, this study provides efficacy and safety evidence to suggest that the dosing of the two formulations are comparable across a dose range of 4-16 mg when adopting an initial dose-titration practice over a period of up to 7 days. No risk of any respiratory depression was observed when switching between “bup-lyo” at the same dose of “bup-SL” despite the higher bioavailability of buprenorphine. It has been proposed that norbuprenorphine, a buprenorphine metabolite with a known respiratory depressant potency up to 10 times that of buprenorphine in animal studies [9] is the likely mediator of any respiratory depression in buprenorphine tablet overdosing. This view is indirectly supported in this study by the lack of respiratory depression observed with “bup-lyo” at comparable dosing and the similarity of norbuprenorphine bioavailability between the formulations at the same dose. Adverse event incidence did appear to be slightly greater with “bup-lyo” than “bup-SL” at the same dose but all AEs observed were graded mild or moderate and none were classified as severe or serious.

Buprenorphine is comparable to methadone in suppressing opioid use but there is evidence to suggest it is slightly less effective in retaining patients as an ORT [7]. The use of a lyophilized formulation reduces the potential for concealment and subsequent diversion and abuse and thereby is expected to increase medication adherence and retention in treatment. Furthermore, it may make buprenorphine prescription more feasible in settings where time-consuming supervision proves an obstacle e.g. treatment in prison, or in a busy clinic. This study demonstrates that switching from conventional sub-lingual therapy is relatively simple and although a titration period of 7 days was utilized the vast majority of subjects were switched across to a comparable dose after 3 days, thus mitigating this risk.

Although the sample size is small and limits the strength of the observations made, it does highlight that clinical trials with a high frequency of hospital visits in opioid-dependent subjects are feasible and can produce meaningful qualitative outcome scores which are sensitive to changes in therapy dosing. This was highlighted by the recording of differences between Likert categorical assessments which were worse on initial titration day assessments with low starting doses compared to those at higher maintenance dosing.

5. Conclusions

In conclusion, this study suggests that opioid-dependent subjects can be switched between “bup-lyo” and conventional “bup-SL” therapy using similar dosing despite pharmacokinetic evidence suggesting comparative supra-bioavailability of buprenorphine. The bioavailability of the metabolite norbuprenorphine, which is a more potent respiratory depressant than buprenorphine, was comparable between formulations. This may explain the absence of clinical difference in vital signs or other adverse events observed on switching formulations.

References

Contributors

A.K., J.S., designed the study and wrote the protocol. K.R., A.K., S.B., K.B., J.B., J.S., managed the literature searches and analyses. K.R., A.K., S.B., K.B., J.B., J.S., undertook the statistical analysis, and all the authors discussed the results. K.R., A.K., S.B., J.S., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest

J.S. is a researcher and clinician and has worked with a range of types of treatment and rehabilitation service-providers. He has contributed to the work of various governmental and non-governmental organisations. He has also worked with pharmaceutical companies to seek to identify new or improved treatments (including, last 3 years, Martindale, Indivior, MundiPharma, Rusan/iGen, Braeburn/Camurus) from whom he and his employer (King’s College London) have received honoraria, travel costs, consultancy payments or trial medications. Funding provided by Martindale Pharma includes funding to the King’s Health Partners Clinical Trials Office for conduct of this study and also payment to J.S.’s university employer for consultancy input for his contribution to this work. Fuller detail of JS’s interests is given at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. J.B. has held consultancy agreements with Reckitt-Benckiser, Britannia Pharmaceuticals and Martindale Pharmaceuticals Ltd, and is PI on research grants funded by Reckitt-Benckiser and Martindale Pharmaceuticals Ltd. S.B. is Medical Director of Martindale Pharmaceuticals Ltd who have developed the study medication (“bup-lyo”) and A.K. is employed by Martindale Pharmaceuticals Ltd for specialist statistical advice on conduct and analyses of the study data. No other authors have a conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.
The SCL90-based psychopathological structure may be applied in Substance Use Disorder patients independently of the drug involved, even in heroin, alcohol and cocaine monodrug users

Manuel Glauco Carbone 1, Marco Maiello 1, Vincenza Spera 1, Corrado Manni 1, Alessandro Pallucchini 1, Angelo G. I. Maremmani 2,3,4, and Icro Maremmani 3,4,5

1. School of Psychiatry, University of Pisa, Italy
2. Department of Psychiatry, North-Western Tuscany Region NHS Local Health Unit, Versilian Zone, Viareggio, Italy, EU
3. Association for the Application of Neuroscience Knowledge to Social Aims (AU-CNS), Pietrasanta, Lucca, Italy, EU
4. G. De Lisi Institute of Behavioural Sciences, Pisa, Italy, EU
5. Vincent P. Dole Dual Disorders Unit, Department of Specialty Medicine, Psychiatric Unit 2, Santa Chiara University Hospital, University of Pisa, Italy, EU

Summary

Background. Using the SCL90 checklist, we previously showed that a cluster of five psychopathological symptoms could be found in Heroin Use Disorder patients. This aggregation demonstrated a high degree of stability, as it proved to be independent of addiction-related conditions such as treatment chosen, intoxication status, and presence of psychiatric problems. It was also applied, in patients with polysubstance use, independently of the drug involved (alcohol, cocaine or heroin). In this study, we have restricted the analysis to patients using only one substance of abuse by excluding patients with polysubstance use. Methods. 256 subjects with alcohol (AUD), heroin (HUD), or cocaine use disorder (CUD) and without a secondary substance of use were assigned to one of the five clusters (worthlessness-being trapped, somatic symptoms, sensitivity-psychoticism, panic anxiety, and violence-suicide). Differences between AUD, HUD and CUD patients in their psychopathological typology and its severity were analysed at univariate and multivariate level. Results. Despite some demographic distinctions, no differences were observed regarding psychopathological typology or its severity among AUD, HUD and CUD patients. Conclusions. This study further supports the independence of the proposed SCL90 five-dimensional structure of the various substances considered.

Key Words: Alcohol Use Disorder; Heroin Use Disorder; Cocaine Use Disorder; psychopathology specific to substance use disorder

Introduction

Psychiatric conditions of addictive diseases imply severe burdens. Psychopathological symptoms in Substance Use Disorder (SUD) patients are usually viewed as being assignable to the context of a personality trait or comorbidity, so precluding the presence of specific psychopathology that could only be related to the addiction process. The V.P. Dole Research Group at the University of Pisa, Italy, has studied the possible definition of a specific psychopathological dimension in SUD patients. In Heroin Use Disorder (HUD) subjects, using factor analysis on all the 90 items included in the SCL90 questionnaire, a 5-factor solution had been found. The first factor defined a depressive worthlessness and being trapped (W/BT) dimension. The second factor picked out a somatic symptoms (SS) dimension. The third identified a sensitivity-psychoticism (SP) dimension. The fourth isolated a panic anxiety (PA) aspect; and the fifth a ‘violence-suicide’ (V/S) dimension [14].

The W/BT dimension shows depressive, obsessive and psychotic features, and is characterized by feelings of being trapped, and uselessness. SUD sub-
jects report feelings of guilt and inferiority, interpersonal sensitivity, irritability, excessive worries, phobic anxiety and no sex drive. Obsessive-compulsive symptoms focus mainly on patients’ doubts about their capabilities, the decisions they must take and their actions. The SS domain is marked out by several anxious and somatic symptoms that are typical of opiate withdrawal. These patients report back pain, muscle aches, weakness and tiredness, heavy legs and arms, paraesthesia and loss of sensitivity somewhere in the body. Cold shivers and hot flushes are possible too, even aching stomach and nausea. Sleeping is difficult and, as a rule, even when sleep does come, it is then disrupted. The S/P factor features psychoticism and sensitivity. These subjects show suspiciousness, nuanced paranoid ideas, self-reference and persecution. They think people do not respect them because of their perspective. These behaviours can be considered as psychotic when patients feel sure that others influence, control, or read their thoughts. The PA factor comprises fear of going around alone, travelling by bus, train, and subway (agoraphobia), sensations of dizziness and episodes of critical anxiety and fear of feeling sick. Generalized fear is present, with the need to avoid activities or places to prevent acute anxiety. The fifth factor (V/S) includes aggressiveness directed against others as well as self-directed aggressiveness. Rage, anger, and impulsiveness are the critical components of this dimension. These patients have a habit of arguing with others and showing high energy levels, together with returning to ideas about death.

These psychopathological dimensions were closely linked with the behavioural covariate of craving in HUD patients [2, 5, 9-11] and were able to distinguish patients affected by addiction from those affected by psychiatric diseases such as major depressive disorder [7] and obesity [6]. The possibility of differentiating between HUD patients and Pathological Gamblers, using only the SS typology, suggests the applicability of these five dimensions even to a non-substance-related addictive disorder, bringing further support to the hypothesis that there is a psychopathology that is specific to addiction [8].

Our previous studies shed light on a specific aggregation of psychopathological symptoms in cases of SUD. We can say that these syndromes are stable regardless of demographic and clinical characteristics [12], kind of treatment chosen [19], active involvement in substance use [17], lifetime psychiatric problems [16] and the substance chosen [18].

As to the substance chosen, differences between HUD, AUD (alcohol use disorder) and CUD (cocaine use disorder) patients were analysed in terms of the frequency of the five clusters and their severity. The association between the secondary abuse of alcohol and cocaine and the five groups was also considered in a subsample of HUD patients. We confirmed a positive association of the SS dimension with the condition of HUD versus CUD and of the S/P and PA that successfully discriminated between patients as being AUD, HUD or CUD patients. In the subsample of HUD patients, no significant differences were observed. The available evidence given by our results, taken as a whole, seems to support the extension of the psychopathological structure previously found in opioid addicts to the population of AUD and CUD patients [18].

These results permit the delineation of a trait nature rather than a state nature in the perception of the structure of these five-factor psychopathological dimensions.

Aims: To further support the hypothesis that the SCL90-based five-dimensional structure may be applied independently of the drug involved, we decided to compare heroin, alcohol and cocaine monodrug user patients.

7. Methods

7.1. Design of the study

The Evaluation of the Therapeutic Community Treatments and Outcomes cohort study was conducted in 2008-2009, after recruiting a total of 2,533 patients who were admitted to a Therapeutic Community (TC) treatment for a substance use disorder in 8 Italian regions [15]. In the present analysis only baseline data were used, implementing a cross-sectional approach.

The study was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All subjects examined filled in an informed consent form to participate in this study. The local pertinent ethics committees approved both the consent form and the experimental procedures.

7.2. Sample

Inclusion criteria were: to be at least 18 years old, with a diagnosis of heroin, cocaine or alcohol dependence based on a clinical judgement, and information collected from the SCL90 questionnaire. Re-
flecting these criteria, the sample consisted of 2,314 subjects. Each participant was included in the sample once only. 256 patients, 207 (80.8%) males and 49 (19.2%) females, (mean age±SD = 39.40±9.4) were alcohol, cocaine or heroin monodrug. Out of 449 (19.4%) AUD patients, 114 (25.4) were alcohol monodrug users (mean age±SD = 44.05±8.9; 92, 81.4% males); out of 670 (28.9%) CUD patients 57 (8.50%) were cocaine monodrug users (mean age±SD = 435.73±9.0); in addition, out of 1,195 (51.6%) HUD patients, 85 (7.11%) were heroin monodrug users (mean age±SD = 35.71±7.6).

7.3. Instruments

7.3.1. Self-Report Symptom Inventory (SCL-90)

First developed by Derogatis and colleagues [3], the SCL90 consists of 90 items, each rated on a 5-point scale of severity. Among heroin-dependent patients, the 90 questions reflected the five primary symptom dimensions that are believed to underlie the vast majority of symptom behaviours observed in this kind of patient: Worthlessness-Being trapped, Somatic Symptoms, Sensitivity-Psychoticism, Panic Anxiety, Violence-Suicide [14].

In previous studies these five dimensions were empirically established and validated [12, 17, 19]. In the present study, SCL90 was administered to our sample of patients within 15 days, counting from the day of entry into TC.

7.3.2. Other instruments

Information on the sociodemographic and clinical characteristics of the patients included in the study was recorded through a questionnaire administered at the time of entering TC. The secondary substance of abuse (whether one or more) was self-reported by the patient.

7.4. Data analysis

SCL-90 factors were standardized into z-scores to compare scores. We assigned each subject to one of the five subgroups on the basis of the highest “z score” achieved. This procedure allows us to classify patients according to their foremost symptomatological cluster, so overcoming the problem of identifying a cut-off point for typifying patients. These subtypes are distinct [14].

The severity of the SCL90 5-dimensions was compared by identifying the monodrug used substance at univariate (T-Test) and, in cases of statistical significance, at multivariate (discriminant analysis) level. Discriminant analysis is used to statistically distinguish between two or more groups of cases. We used the stepwise procedure to select the best discriminating variables.

The numbers of patients belonging to each of the five subgroup clusters were then compared using the chi-square test, with Bonferroni’s correction, between alcohol, heroin or cocaine monodrug use patients. In cases of univariate statistical significance, a stepwise multinomial logistic regression analysis was then programmed with heroin, cocaine or alcohol as monodrug-dependent variable and the psychopathological subgroups as predictors, including sociodemographic and clinical variables as confounding factors (age, gender, marital status, detoxification status, living condition).

All analyses were performed using SPSS v. 4.0 (SPSS, Chicago, IL, USA). Statistical significance was set at the p= 0.05 level.

8. Results

8.1. Sociodemographic and addiction characteristics

In the overall sample (n=256), mean age was 39.40 ± 9.4 years. 207 (80.8%) of the subjects were male, 208 (81.2%) were single, 60 (23.5%) had a high educational level (with duration over 8 years), 183 (71.5%) of subjects were unemployed, and 67 (27.3%) lived alone. When looking at differences between alcohol, heroin and cocaine mono-user patients, mean age was 44.05±8.9 in alcohol mono-user, 35.61±7.6 in heroin mono-user, and 35.73±9.0 in cocaine mono-user patients. This difference was statistically significant (F = 30.38; p < 0.001), with heroin and Cocaine mono-users proving to be younger than alcohol mono-users. As regards marital status, the frequency of singles was 87.7% among patients with alcohol mono-dependence, 84.7% among those with heroin mono-dependence, and 63.2% among those with cocaine dependence (chi-square = 16.04; p < 0.001). Heroin and Cocaine mono-users were less frequently living alone (19.3% and 18.9%, respectively) than alcohol mono-users (37.6%). This difference was statistically significant (chi-square = 10.42; p = 0.005). Gender (chi-square = 2.83; p=0.243), educational level (chi-square = 4.00; p = 0.135), and being unemployed (chi-square = 1.97; p = 0.373) showed no statistically significant differences between the groups.
8.2. Psychopathological dimensions

Table 1 shows differences in psychopathological severity between alcohol, heroin and cocaine mono-user patients. The only statistically significant difference observed between the three groups was in the severity of the PA dimension. Panic anxiety symptoms were more severe in alcohol mono-user than in cocaine mono-user patients. Heroin mono-user patients were found to be in an intermediate position. No differences were observed, at univariate level, in regarding the other dimensions, or at multivariate level.

Table 2 shows differences in psychopathological typology between alcohol, heroin or cocaine mono-user patients. PA was the most frequent (around 29.0%) psychopathological typology in all three groups of patients. V/S was the least frequent psychopathological dimension in the alcohol mono-user (7.9%) and heroin mono-user (11.8%) groups. W-BT was the least frequent typology for the cocaine mono-user patients (8.8%). No statistically significant differences were observed between groups.

9. Discussion

Patients with alcohol, heroin and cocaine mono-dependence differ in some demographic characteristics investigated in the present study. Differences were observed in age, in the frequency of “single” marital status and the “living alone” condition. Alcohol mono-dependent patients were older and lived alone more often than heroin or cocaine mono-dependents. Cocaine mono-users were less frequently single than heroin or alcohol mono-users. Only marital status differed from what we have observed in polydrug users [18]. The differences found were consistent with the sociodemographic characteristics of the various populations of addicts reported in previous studies [4, 13, 21].

At univariate level, considering the severity of psychopathological symptoms of mono-dependent patients at treatment entry, PA symptoms showed the highest severity in alcohol monodrug and the lowest in cocaine monodrug users. It is not easy to explain the higher severity induced by alcohol mono-dependence than by cocaine mono-dependence in regarding PA symptoms. We have already observed this phenomenon in polydrug users typified according to the primary substance of use (alcohol, heroin or cocaine).
In this case too we can say that anxiety is a common symptom of cocaine intoxication, whereas in alcohol-dependent patients anxiety is expressed differently, as a component of withdrawal, even in mild forms of alcohol dependence. Moreover, we have also to keep in mind that anxiety related to alcohol withdrawal may last for months [1, 20]. Unlike what we observed in polydrug users [18], the differences observed at univariate level were not confirmed at multivariate level. In alcohol, heroin and cocaine monodrug users, therefore, psychopathological severity seems to be more homogeneous.

Looking at previous analyses carried out on samples of heroin-dependent patients only, no difference emerged in the use of alcohol or cocaine as the secondary substance of abuse, either in the severity or the frequency of the five psychopathological SCL90 dimensions [18]. Only polydrug use would, therefore, lead to differences in the severity of psychopathology related to SUDs. This last consideration is also supported by the fact that, in this study, no differences in psychopathological typology were observed in the monodrug users.

This lack of psychopathological differences (in severity and typology) may further be attributed to a psychic structure present in SUD patients that is common to the various forms of dependence, so that this structure is independent of the specific drug used. This result convinces us, so much so that addiction can now be defined as a unitary condition.

Limitations

The cross-sectional design does not allow us to be sure whether the previous presence and severity of symptoms included in our five-dimension psychopathology are a predictor of, or act as a predisposition to use, specific substances. Likewise, we cannot say whether, conversely, the use of, or a dependence on these substances may condition the development of the specific psychopathological picture. Other limitations on the validity of the SCL90 based psychopathological 5-dimension solution were commented on in our previous studies [14, 17-19]

10. Conclusions

Looking only at the population consisting of monodrug alcohol, heroin and cocaine users, no substantial differences in the severity and no differences in the typology of the psychic structure were demonstrated. These findings, together with those of previous studies that had shown the great stability of the five-factor structure observed in HUD patients, support its extension to the population of SUD patients, independently of the drug involved.

References

10. Marenmanni A. G. I., Rovai L., Bacciardi S., Massimetti E., Gazzarrini D., Pallucchini A., Rugani F., Pani P. P.,


**Acknowledgements**

None

**Role of the funding source**

Authors state that this study was financed with internal funds. No sponsor played a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

**Contributors**

A.G.I.M. and I.M., designed the study and wrote the protocol. M.G.C., M.M., V.S., C.M., A.P., managed the literature searches and analyses. I.M., undertook the statistical analysis, and all the authors discussed the results. A.G.I.M., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

**Conflict of interest**

Authors declared no conflict of interest. IM served as board member for D&A, Molteni, Indivior, Gilead, Merck, CT Sanremo.

**Ethics**

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

**Note**

It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author accepted our service.

*Received February 3, 2018 - Accepted May 14, 2018*
Comparing neurocognitive function in individuals receiving chronic methadone or buprenorphine for the treatment of opioid dependence: A systematic review.

Duncan Hill\textsuperscript{1,2}, Daniel Garner\textsuperscript{3}, and Alex Baldacchino\textsuperscript{3,4}

\textsuperscript{1}. Addictions Services, NHS Lanarkshire, Motherwell, Scotland, UK
\textsuperscript{2}. Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, UK
\textsuperscript{3}. School for Medicine, University of St Andrews, Fife, Scotland, UK
\textsuperscript{4}. NHS Fife, Queen Margaret Hospital, Whitefield Road, Dunfermline, Fife, Scotland, UK

Summary

\textbf{Introduction:} Agonist Opioid Treatments (AOT) have been, in comparison to healthy controls, associated with neurocognitive impairment in different domains. This review identifies differences in neurocognitive function as a result of treatment with either buprenorphine or methadone. \textbf{Method:} A qualitative and systematic literature review of published articles from 1946 to 29/2/2016 on neurocognitive function of patients prescribed buprenorphine or methadone and compared with healthy patients utilising the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. \textbf{Results:} The limited data demonstrate buprenorphine as presenting with fewer neurocognitive impairments, in cognitive impulsivity, cognitive flexibility and attention domains when compared with methadone. However both treatments modalities presented with more impairments in neurocognitive function domains, including short term memory, attention, cognitive flexibility, cognitive impulsivity, motor impulsivity and non planning impulsivity, when compared with healthy control groups. \textbf{Discussion:} The lack of published papers in comparing neurocognitive impairment between the treatment modalities limit interpretation of this systematic review. \textbf{Conclusion:} Further methodologically rigid and higher quality research into the neurocognitive effects of these treatment modalities in the opioid dependent populations, especially when in treatment, is urgently required.

\textit{Key Words:} Neurocognitive Impairment; buprenorphine; methadone; treatment; opioid dependence

11. Introduction

Treatment for opioid (and opiate) addiction using agonist opioid treatments (AOT) (i.e. methadone and buprenorphine) have been associated with neurocognitive impairment in comparison to healthy controls. For the purposes of this review we will use the term opioids to encompass both opiates and opioids. Opioids are widely used both legally in treatment, for their analgesic effects, and illicitly, for the psychotropic effects. The neurocognitive impairments associated with opioid use have already been documented \cite{4}

Opioids are known to alter receptor sensitivity and expression, demonstrating a tolerance effect, but also display psychological dependence by altering the brains behavioural circuits. The receptors affected by opioids, are located through the brain and spinal cord, including the thalamus, hypothalamus, hippocampus, amygdala and the cerebral cortex \cite{12}, which are important for neurocognitive function, but are also connected to the reward and reinforcement area in the brain, the nucleus accumbens.

Opioid use has been demonstrated in the brain to increase oxidative stress, which contributes to neurotoxicity leading to neurocognitive impairment \cite{7, 33}.

In the review by Büttner and Mall, they noted reduced neuronal density in majority of patients dying from heroin overdoses due to respiratory depression and associated brain hypoxia \cite{6}.

Consideration of other contributing factors other
than the direct opioid toxic effects on neurocognitive impairment needs to be considered. This can include bacterial and viral infection and other potential neuropathological insults [10]. These factors will not be reviewed in this systematic review.

To measure neurocognitive function in individuals the precise function being tested must be defined. Muriel Lezak, the author of the first book exploring neuropsychological assessment, wrote ‘Direct observation of the fully integrated functioning of living human brains will probably always be impossible’ [18]. Therefore, to assess neuropsychological function in the context of assessment, three domains (and subsequent sub-domains based on neurocognitive tests) need to be clearly defined to allow the objective observation of neurocognitive function in individuals:

- Intelligence
- Executive Function
- Memory and Learning

The use of an intelligence assessment allows an estimate the premorbid IQ of an individual. A vocabulary test is the primary assessment method use, e.g Shipley Institute of Living Scale (SILS) or Wechsler Adult Intelligence Scale – Revised & III [31, 38].

High level neurocognitive functions, known as Executive functions, allow for the control of behaviour to achieve a targeted outcome, this includes cognitive flexibility, cognitive planning, cognitive impulsivity, working memory and attention [5, 11, 36].

Memory and learning assesses an individual’s ability to recall and make new memories. The Atkinson-Shiffrin model of memory proposes three distinct ‘stores’ of memory: sensory memory (lasting a few milliseconds: providing a buffer for sensory information and allows us to address information when required), short-term memory (lasting 12-30 seconds without rehearsal: primarily auditory in nature, can store around seven chunks of information for a few seconds without rehearsal [22] duration of storage can be increased with the use of a phonological loop), and long term memory which can be indefinite (ability to store information for a lifetime [2] and can be further split into declarative memory requiring conscious though and procedural memory requiring no thought).

A recent meta analysis looking at the effects of chronic methadone use identified global impairments in neurocognitive function relative to healthy participants [5].

This article aims to determine if there are differences in the effects on the neurocognitive function of patients being treated with either buprenorphine or methadone.

12. Methods

12.1. Literature Search

A literature review identified articles relating to the neurocognitive effects of either buprenorphine

| Table 1: Inclusion and exclusion criteria for studies used in the review |
|-----------------------------|-----------------------------|
| **Inclusion**               | **Exclusion**               |
| Participants aged eighteen or over with chronic opioid dependence and currently engaged in an opioid maintenance programme | Cohorts with current uncontrolled poly-drug use (nicotine excluding). |
| Individuals needed to be compared to either healthy controls, abstinent individuals or another maintenance programme (methadone vs. buprenorphine) through the use of validated neuropsychological assessments. | Cohorts with a diagnosis of any Axis-1 psychiatric illness (excluding substance related disorders) as defined by DSM-IV/V (American Psychiatric Association 2000; American Psychiatric Association 2013). |
| Neuropsychological assessments needed to be identified and validated to allow for them to be classified into domains. If novel assessments were used a description of the cognitive functions assessed was used to classify by comparison to a defined assessment. | Cohorts with previous serious head injury. |
| Identified papers need to be of adequate quality matching the control/abstinent group to the maintained cohort, matching criteria should include: age, sex, years of education and years of heroin dependence | Articles with poor quality methodology, |
| Papers needed to report separate results for each cohort and test, papers which combined maintenance cohorts were excluded as it was not possible to extract the results required. | Cohorts including participants who were HIV serotype positive |
or methadone on patients receiving Agonist Opioid Treatment (AOT) for opioid dependence. The cohorts chosen where either direct comparison between individuals treated with methadone or buprenorphine or those compared against a healthy control group. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were employed and the inclusion and exclusion criteria used have been tabulated in Table 1.

An electronic based search using a number of databases and incorporating articles published from 1946 to 29/2/2016 were used. The databases used were Ovid MEDLINE (1946 to 29/2/2016); EMBASE (1974 to 29/2/2016); PUBMED (1964 to 29/2/2016); PsychINFO (1980 to 29/2/2016). There were no language constraints employed.

The articles were identified using the search headings in Table 2. The search terms ‘neuropsychological tests’ and ‘neurocognitive tests’ were then replaced with the sub-titles of neurocognitive domains e.g. Short Term Memory, Long Term Memory, Attention, Cognitive Flexibility, Cognitive Impulsivity, Motor Impulsivity and Non-Planning Impulsivity.

As this article is a literature review there was no requirement for ethical approval in relation to the study.

13. Results

13.1. Data analysis and study detail

The literature search provided very few articles published on the comparison of effects of treatment on the neurocognitive function of patients being treated with buprenorphine or methadone.

With the very limited number of published articles offering direct comparisons (3 articles identified) between buprenorphine and methadone, a wider but indirect comparison of the effects on neurocognitive function were used from articles comparing either of the two therapeutic intervention against a healthy patient control group. The results of these studies were used to comment on the potential for neurocognitive impairment from the treatment with ORT against a control group.

13.2. Assessment of study quality

The vast majority of selected articles for this review were assessed as fair in quality using the NIH Quality Framework for case-control studies (Table 3) (NIH 2014) with others ranging in quality from poor (2 articles) to good (1 article). All studies were observational case control studies.

13.3. Number of articles identified

The initial literature search identified 426 articles from literature and other sources. Once duplicates were removed the total number of relevant manuscripts was reduced to 179. Titles and abstracts of 31 articles included in the accepted abstracts were screened for eligibility with an additional six articles included in the full text screening (Figure 1: QUORUM). The full text of the remaining 36 articles was assessed using the inclusion and exclusion criteria on Table 1. This assessment excluded a further 20 articles which failed to meet the inclusion criteria in the full text with the remaining 16 articles included in this review.

13.4. Cohorts identified

The included articles described results from the direct comparison of 60 buprenorphine maintained individuals to 74 methadone maintained individuals from 3 published articles. When the search was extended to compare either methadone or buprenorphine maintained patients to a healthy control, there
Table 3: Characteristics of articles identified comparing methadone maintenance patients to healthy controls.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Quality</th>
<th>N</th>
<th>Mean Age (yrs)</th>
<th>Sex (nM/nF)</th>
<th>Education yrs</th>
<th>Mean IQ (sd)</th>
<th>Mean Opioid Use (yrs)</th>
<th>Methadone use (yrs)</th>
<th>Mean daily methadone dose (mg)</th>
<th>N</th>
<th>Mean Age (yrs)</th>
<th>Sex (nM/nF)</th>
<th>Education yrs</th>
<th>Mean IQ (sd)</th>
<th>Neuropsychological Tests Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darke et al. (2000)</td>
<td>Australia</td>
<td>Fair</td>
<td>30</td>
<td>35.8</td>
<td>18M/12F</td>
<td>11.2</td>
<td>91.5 (10.4)</td>
<td>5 (minimum)</td>
<td>5 (median)</td>
<td>78.6</td>
<td>30</td>
<td>35.2</td>
<td>18M/12F</td>
<td>11.7</td>
<td>92.6 (-11.1)</td>
<td>WAIS-III; WMSR (PAL-I &amp; II, VR-I &amp; II subtests); CVLT; RCFT; COWAT; WCST</td>
</tr>
<tr>
<td>Mintzer et al. (2002)</td>
<td>United States</td>
<td>Fair</td>
<td>18</td>
<td>37.6</td>
<td>7M/11F</td>
<td>11.8</td>
<td>87.4 (2.7)</td>
<td>15.3</td>
<td>3.78</td>
<td>67.2</td>
<td>21</td>
<td>34.9</td>
<td>10M/11F</td>
<td>12.1</td>
<td>94.0 (2.8)</td>
<td>DSST; TMT (A&amp;B); 2BT; GT; ST; SIlS (IQ)</td>
</tr>
<tr>
<td>Schindler et al. (2004)</td>
<td>Austria</td>
<td>Fair</td>
<td>15</td>
<td>25.8</td>
<td>9M/6F</td>
<td>Modal attainment Junior High School</td>
<td>n/a</td>
<td>4.28</td>
<td>1.55</td>
<td>45.7</td>
<td>Matched for age, sex and score in MAT (intelligence)</td>
<td>ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: n= Number of Participants; yrs = Years; nM/nF= Number Male/ Number Female; IQ = Intelligence quotient; sd= standard deviation; mg= milligrams; WAIS-III = Wechsler Adult Intelligence Scale; WMSR= Weschler Memory Scale-Revised; PAL-I&II= Paired Associate Learning; VR-I&II= Visual Reproduction; CVLT= California verbal learning test; RCFT; Rey Complex Figure Test; COWAT= Controlled oral word association test; WCST= Wisconsin Card Sorting Test; SILS= Shipley Institute of Living Scale; GT= Gambling Test; DSST= Digit Symbol Substitution Test; TMT= Trail Making Test; 2BT= Two Back Test; ST= Stroop Test; WAIS-R= Wechsler Adult Intelligence Scale - Revised; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; SODMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRL= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; 3DBCM= Three Dimensional Block Construction Model; StPW= Spot the Real World; CBT= Corsi Block Test; CRT= Choice Reaction Time; FTTF= Finger Tapping Test; TOVA= Test of Variables of Attention; STS= Stop Signal; PES= Post Error Slowing; NART= National Adult Reading Test; CGT= Cambridge Gambling Tasks; AGN= Affective Go/No Go; SOC= Stockings of Cambridge; AM= Austin Mare: n/a= not available; FDT= Five Digit Test; FAS= Fruits and Animals; IGT= Iowa Gambling Test; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1= Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15= Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15= Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment) KMSK= Kreek–McHugh–Schluger–Kellogg Scale.
Table 3: Characteristics of articles identified comparing methadone maintenance patients to healthy controls.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Quality</th>
<th>Sample Size</th>
<th>Gender</th>
<th>Age</th>
<th>IQ</th>
<th>Mini-M</th>
<th>Max-M</th>
<th>Educational Level</th>
<th>School Leaving</th>
<th>Cognitive Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotherham-Fuller et al. (2004)</td>
<td>United States</td>
<td>Fair</td>
<td>18</td>
<td>n/a</td>
<td>42.3</td>
<td>83.8</td>
<td>(9.7)</td>
<td>12.2</td>
<td>n/a</td>
<td>13.6</td>
<td>SILS (IQ); GT; WCST</td>
</tr>
<tr>
<td>Prosser et al. (2006)</td>
<td>United States</td>
<td>Fair</td>
<td>29</td>
<td>37.9</td>
<td>n/a</td>
<td>23M/6F</td>
<td>13</td>
<td>8.05</td>
<td>(2.19)</td>
<td>15.1</td>
<td>21M/8F</td>
</tr>
<tr>
<td>Pirastu et al. (2006)</td>
<td>Italy</td>
<td>Fair</td>
<td>30</td>
<td>35</td>
<td>n/a</td>
<td>29M/1F</td>
<td>8.37</td>
<td>85</td>
<td>15.5</td>
<td>8.3</td>
<td>66</td>
</tr>
<tr>
<td>Soyka et al. (2011)</td>
<td>Germany</td>
<td>Poor</td>
<td>24</td>
<td>32</td>
<td>n/a</td>
<td>16M/8F</td>
<td>n/a</td>
<td>11</td>
<td>n/a</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>Lin et al. (2012)</td>
<td>Taiwan</td>
<td>Fair</td>
<td>27</td>
<td>36.8</td>
<td>n/a</td>
<td>26M/1F</td>
<td>10.3</td>
<td>n/a</td>
<td>13.9</td>
<td>1.73</td>
<td>36</td>
</tr>
<tr>
<td>Liao et al. (2014)</td>
<td>Taiwan</td>
<td>Fair</td>
<td>65</td>
<td>40.2</td>
<td>n/a</td>
<td>65M/0F</td>
<td>8.6</td>
<td>n/a</td>
<td>14.3</td>
<td>0.5</td>
<td>45</td>
</tr>
<tr>
<td>Baldacchino et al. (2014)</td>
<td>United Kingdom</td>
<td>Good</td>
<td>29</td>
<td>27.3</td>
<td>n/a</td>
<td>29M/0F</td>
<td>10.6</td>
<td>109</td>
<td>(7.6)</td>
<td>8.8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Abbreviations: n= Number of Participants; yrs = Years; nM/nF= Number Male/ Number Female; IQ = Intelligence quotient; sd= standard deviation; mg= milligrams; WAIS-III = Wechsler Adult Intelligence Scale; WMRS = Wechsler Memory Scale-Revised; PAL-I&II= Paired Associate Learning; VR-I&II= Visual Reproduction; CVLT= California verbal learning test; RCF= Rey Complex Figure Test; COWAT= Controlled oral word association test; WCST= Wisconsin Card Sorting Test; SLS= Shipley Institute of Living Scale; GT= Gambling Test; DSST= Digit Symbol Substitution Test; TMT= Trail Making Test; 2BT= Two Back Test; ST= Stroop Test; WAIS-R= Wechsler Adult Intelligence Scale - Revised; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; 3DBC= Three Dimensional Block Construction Model; SpTW= Spot the Real World; CBT= Corsi Block Test; CRT= Choice Reaction Time; FTT= Finger Tapping Test; TOVA= Test of Variables of Attention; SS= Stop Signal; PES= Post Error Slowing; NART= National Adult Reading Test; CGT= Cambridge Gambling Task; AGN= Affective Go/No Go; SOC= Stockings of Cambridge; AM= Austin Maze; n/a= not available; FDT= Five Digit Test; FAS= Fruits and Animals; IGT= Iowa Gambling Test; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL= Test for Visual Structuring Ability, TT1s= Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT1s= Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment) KMSK= Kreek–McHugh–Schluger–Kellogg Scale.
Table 4: Characteristics of articles identified comparing buprenorphine maintenance patients to healthy controls.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Quality</th>
<th>n</th>
<th>Mean Age (yrs)</th>
<th>Sex (nM/nF)</th>
<th>Education</th>
<th>Mean IQ (sd)</th>
<th>Mean Opioid Use (yrs)</th>
<th>Buprenorphine Use (yrs)</th>
<th>Mean Daily Buprenorphine Dose (mg)</th>
<th>Mean Daily Opioid Use (yrs)</th>
<th>Matched for age, sex and score in MAT (intelligence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schindler et al. (2004)</td>
<td>Austria</td>
<td>Fair</td>
<td>15</td>
<td>25</td>
<td>5M / 10F</td>
<td>Modal attainment Junior High School</td>
<td>n/a</td>
<td>3.63</td>
<td>0.93</td>
<td>10</td>
<td>n/a</td>
<td>Matched for age, sex and score in MAT (intelligence)</td>
</tr>
<tr>
<td>Pirastu et al. (2006)</td>
<td>Italy</td>
<td>Fair</td>
<td>18</td>
<td>33</td>
<td>17M / 1F</td>
<td>8.72</td>
<td>89.3 (-3.45)</td>
<td>13.3</td>
<td>5.4</td>
<td>9</td>
<td>21</td>
<td>14M / 7F</td>
</tr>
<tr>
<td>Messinis et al. (2009)</td>
<td>Greece</td>
<td>Fair</td>
<td>18</td>
<td>36.5</td>
<td>15M / 3F</td>
<td>11</td>
<td>n/a</td>
<td>12.8</td>
<td>0.67</td>
<td>6.78</td>
<td>34</td>
<td>27M / 7F</td>
</tr>
<tr>
<td>Soyka et al. (2011)</td>
<td>Germany</td>
<td>Poor</td>
<td>22</td>
<td>34.2</td>
<td>11M / 11F</td>
<td>Modal attainment was general school leaving certificate (n=9) or “O” Level attainment (n=9)</td>
<td>n/a</td>
<td>11.6</td>
<td>0.19</td>
<td>10.4</td>
<td>25</td>
<td>114M / 11F</td>
</tr>
<tr>
<td>Shmygalev et al. (2011)</td>
<td>Germany</td>
<td>Fair</td>
<td>11</td>
<td>36.6</td>
<td>28M / 2F</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>5.5</td>
<td>7.7</td>
<td>90</td>
<td>84M / 6F</td>
</tr>
</tbody>
</table>

Abbreviations: n= Number of Participants; yrs= Years; nM/nF= Number Male/ Number Female; IQ= Intelligence Quotient; sd= Standard Deviation; mg= Milligrams; WAIS-III= Wechsler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Scoring Task; IGT= Iowa Gambling Task; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=1stest Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=1stest Measuring the Traffic-specific Perception Ability, Q1=Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT= Rey Auditory Verbal Learning Test; CTT= Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG= Vigilance Test; n/a= Not Available.
Table 5: Characteristics of articles identified comparing buprenorphine maintenance patients to methadone maintenance patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Quality</th>
<th>n</th>
<th>Mean Age (yrs)</th>
<th>Sex (nM/nF)</th>
<th>Education (yrs)</th>
<th>Mean IQ (sd)</th>
<th>Mean Opioid Use (yrs)</th>
<th>Buprenorphine use (yrs)</th>
<th>Mean daily buprenorphine dose (mg)</th>
<th>n</th>
<th>Mean Age (yrs)</th>
<th>Sex (nM/nF)</th>
<th>Education (yrs)</th>
<th>Mean IQ (sd)</th>
<th>Mean Opioid Use (yrs)</th>
<th>Methadone use (yrs)</th>
<th>Mean daily methadone dose (mg)</th>
<th>Neuropsychological Tests Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schindler et al. (2004)</td>
<td>Austria</td>
<td>Fair</td>
<td>15</td>
<td>25</td>
<td>5M / 10F</td>
<td>Modal attainment Junior High School</td>
<td>n/a</td>
<td>3.63</td>
<td>0.93</td>
<td>10</td>
<td>15</td>
<td>25.8</td>
<td>9M / 6F</td>
<td>Modal attainment Junior High School</td>
<td>n/a</td>
<td>4.28</td>
<td>1.55</td>
<td>45.7</td>
<td>ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)</td>
</tr>
<tr>
<td>Pirastu et al. (2006)</td>
<td>Italy</td>
<td>Fair</td>
<td>18</td>
<td>33</td>
<td>17M / 1F</td>
<td>8.72</td>
<td>89.3 (-3.45)</td>
<td>13.28</td>
<td>5.4</td>
<td>9</td>
<td>30</td>
<td>35</td>
<td>29M / 1F</td>
<td>8.37</td>
<td>85</td>
<td>15.53</td>
<td>8.3</td>
<td>66</td>
<td>WAIS-III (IQ); BVRT; WCST; IGT.</td>
</tr>
<tr>
<td>Beawert et al. (2007)</td>
<td>Austria</td>
<td>Fair</td>
<td>20</td>
<td>27</td>
<td>12M / 8F</td>
<td>n/a</td>
<td>n/a</td>
<td>5.8</td>
<td>1.43</td>
<td>13.4</td>
<td>20</td>
<td>27.9</td>
<td>7M / 13F</td>
<td>n/a</td>
<td>n/a</td>
<td>6.09</td>
<td>1.94</td>
<td>52.7</td>
<td>ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)</td>
</tr>
<tr>
<td>Soyka et al. (2011)</td>
<td>Germany</td>
<td>Poor</td>
<td>22</td>
<td>34.2</td>
<td>11M / 11F</td>
<td>Modal attainment was general school leaving certificate (n=9) or “O” Level attainment (n=9)</td>
<td>n/a</td>
<td>11.6</td>
<td>0.19</td>
<td>10.4</td>
<td>24</td>
<td>32</td>
<td>16M / 8F</td>
<td>Modal attainment was “O” levels (n=10)</td>
<td>n/a</td>
<td>11</td>
<td>0.4</td>
<td>56</td>
<td>ART-90 (PVT; TT15; Q1; RST3; DR2)</td>
</tr>
</tbody>
</table>

Abbreviations: n=Number of Participants; yrs=Years; nM/nF= Number Males/Number Females; IQ= Intelligence Quotient; sd= Standard Deviation; mg=Milligrams; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); WAIS-III= Wechsler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Sorting Test; IGT= Iowa Gambling Test; ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); n/a= Not Available.
were the neurocognitive assessments of 279 methadone maintained individuals from 10 published articles and 84 individuals maintained on buprenorphine compared to healthy controls from 5 published papers [34], although one article is included in each comparison in the table as it compared healthy controls against methadone and buprenorphine and in addition a direct comparison between methadone and buprenorphine groups.

The papers included are shown in table 6.

13.5. Neurocognitive impairments between groups

In the articles directly comparing patients on ORT treatment [1, 25, 34], all except one domain (cognitive impulsivity) showed no significant differences between cognitive functioning in methadone and buprenorphine treated individuals.

13.5.1. Cognitive impulsivity

Buprenorphine maintained individuals scored significantly better (p<0.05) on measures of cognitive impulsivity than methadone maintained individuals in all three selected studies [1, 25, 34]. This is also supported by all other selected studies measuring this
Table 6. Articles included, comparison groups and neurocognitive domain

<table>
<thead>
<tr>
<th>Article</th>
<th>Outcome Group and Number (n)</th>
<th>Control Group Type and Number (n)</th>
<th>Intelligence</th>
<th>Short Term Memory</th>
<th>Long Term Memory</th>
<th>Attention</th>
<th>Cognitive Flexibility</th>
<th>Cognitive Impulsivity</th>
<th>Motor Impulsivity</th>
<th>Non Planning Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone Maintenance Papers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darke et al. 2000</td>
<td>30</td>
<td>30</td>
<td>↓ - WAIS-III</td>
<td>↓ - WMSR, CVLT,</td>
<td>↓ - WSMR, CVLT</td>
<td>↓ - WAIS-III</td>
<td>↓ - COWAT, WCST</td>
<td>n/a</td>
<td>n/a</td>
<td>↓ - RCFT (Copy)</td>
</tr>
<tr>
<td>Mintzer et al. 2002</td>
<td>18</td>
<td>21</td>
<td>--- - SILO</td>
<td>--- - 2BT</td>
<td>n/a</td>
<td>↓ - DSST</td>
<td>↓ - TMT</td>
<td>↓ - GT</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Rotherham-Fuller et al. 2004</td>
<td>18</td>
<td>19</td>
<td>--- - SILO</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>--- - WCST</td>
<td>↓ - GT</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Schindler et al. 2004</td>
<td>15</td>
<td>Matched CON (See Demographic Table)</td>
<td>--- - MAT</td>
<td>n/a</td>
<td>n/a</td>
<td>↓ - DR2, Q1</td>
<td>□ - LL5, TT15</td>
<td>↓ - DR2</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Prosser et al. 2006</td>
<td>23</td>
<td>29</td>
<td>↓ - WAIS-III</td>
<td>↓ - BVRT</td>
<td>n/a</td>
<td>--- - ST</td>
<td>--- - COWAT</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Pirastu et al. 2006</td>
<td>30</td>
<td>21</td>
<td>↓ - WAIS-III</td>
<td>↓ - BVRT</td>
<td>n/a</td>
<td>n/a</td>
<td>↓ - WCST (errors)</td>
<td>↓ - GT</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Soyka et al. 2011</td>
<td>24</td>
<td>25</td>
<td>n/a</td>
<td>↓ - TT15</td>
<td>n/a</td>
<td>--- - PVT</td>
<td>↓ - TT15</td>
<td>↓ - DR2</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Lin et al. 2012</td>
<td>27</td>
<td>23</td>
<td>--- - WAIS-III</td>
<td>--- - BVRT, SOMT, WSLT, RRLET, SAVF</td>
<td>--- - RRLET, SAVF</td>
<td>--- - WAIS-R</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: n= Number of Participants; MMT= Methadone Maintenance Programme; CON= Healthy Control; ABST= Protracted Abstinence; BUP= Buprenorphine Maintenance; WAIS-III= Weschler Adult Intelligence Scale; SILO= Shipley Institute of Living Scale; MAT= Matrices Test; NART= National Adult Reading Test; WSMR= Weschler Memory Scale - Revised; RCF= Rey Complex Figure Test; 2BT= Two Back Test; BVRT= Benton Visual Retention Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; CVLT= California Verbal Learning Test; RAVLT= Rey Auditory Verbal Learning Test; RBANS= Repeatable Battery for the Assessment of Neurological Status; FAS= Fruits and Animals; DSST= Digit Symbol Substitution Test; ST= Stroop Test; CPT= Continuous Performance Test; WAIS-R Weschler Adult Intelligence Scale - Revised; SS= Stop Signal; PES= Post Error Sloping; FDT= Five Digit Test; Ruff= Ruff Selective Attention Test; CCT= Color Trails Test; COG= Attention Test; VIG= Vigilance Test; COWAT= Controlled Oral Word Association Test; WCST= Wisconsin Card Sorting Task; TMT= Trail Making Test; BNT= Boston Naming Test; VFT= Verbal Fluency Test; TAVT= Tachistoscopic Perception; GT= Gambling Test; CGT= Cambridge Gambling Test; FTT= Finger Tapping Test; AGN= Affective Go/No Go; DT= Determination Test; RCF= Rey Complex Figure Test; AM= Amtistin Maze; SOC= Stockings of Cambridge; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1= Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15= Test Measuring the Traffic-specific Perception Ability, DR= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test TT15= Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST= Reactive Stress Test, DR= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT= Rey Auditory Verbal Learning Test; CCT= Color Trails Test; Ruff= Ruff Selective Attention Test; COG= Attention Test; DT= Determination Test; TAVT= Tachistoscopic Perception; VIG= Vigilance Test; n/a= Not Available.
### Table 6. Articles included, comparison groups and neurocognitive domain

<table>
<thead>
<tr>
<th>Article Authors</th>
<th>Comparison Group (n)</th>
<th>Matched Comparison Group (See Demographic Table)</th>
<th>Comparison Papers</th>
<th>Neurocognitive Domain</th>
<th>Outcome Group vs. Control or Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liao et al. 2014</td>
<td>65</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Baldacchino et al. 2014</td>
<td>29</td>
<td>28 - NART</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Schindler et al. 2004</td>
<td>15</td>
<td>Matched CON (See Demographic Table)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Pirastu et al. 2006</td>
<td>18</td>
<td>21 - WAIS-III</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Messinis et al. 2009</td>
<td>18</td>
<td>34</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Soyka et al. 2011</td>
<td>22</td>
<td>25</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Shmygalev et al. 2011</td>
<td>11 (Per-protocol)</td>
<td>90</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Pirastu et al. 2006</td>
<td>18</td>
<td>30</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Baewert et al. 2007</td>
<td>20</td>
<td>20</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Key:**
- **Significantly Lower Score (p<0.05)**
- **Significantly Higher Score (p<0.05)**
- **No Significant Difference in score. (Outcome Group vs. Control or Comparison Group)**

**Abbreviations:**
- n= Number of Participants
- MMT= Methadone Maintenance Programme
- CON= Healthy Control
- ABST= Protracted Abstinence
- BUP= Buprenorphine Maintenance
- WAIS-III= Weschler Adult Intelligence Scale
- SLS= Shipley Institute of Living Scale
- MAT= Matrices Test
- NART= National Adult Reading Test
- WSMR= Weschler Memory Scale - Revised
- RCFT= Rey Complex Figure Test
- 2BT= Two Back Test
- BVRT= Benton Visual Retention Test
- SOMT= Six Object Memory Test
- WSLT= Word Sequence Learning Test
- RREL= Remote and Recent Life Event Test
- SAV= Semantic Association of Verbal Fluency
- CVLT= California Verbal Learning Test
- RAVLT= Rey Auditory Verbal Learning Test
- RBANS= Repeatable Battery for the Assessment of Neurological Status
- FAS= Fruits and Animals
- DSST= Digit Symbol Substitution Test
- T1= Stroop Test
- CPT= Continuous Performance Test
- WAIS-R Weschler Adult Intelligence Scale - Revised
- SS= Stop Signal
- PES= Post Error Slowing
- FDT= Five Digit Test
- Ruff= Ruff Selective Attention Test
- CTT= Color Trails Test
- COG= Attention Test
- VIG= Vigilance Test
- COWAT= Controlled Oral Word Association Test
- WCST= Wisconsin Card Sorting Task
- TMT= Trail Making Test
- VFT= Boston Naming Test
- VFT= Verbal Fluency Test
- TAVT= Tachistoscopic Perception
- GT= Gambling Test
- CTT= Cambridge Gambling Test
- FTT= Finger Tapping Test
- AGN= Attention
- No Go; Go
- DT= Determination Test
- RCFT= Rey Complex Figure Test
- AM= Austin Maze
- SOC= Stockings of Cambridge
- ART-2020= Act React Test System
- MMT= Matrices Test (non-verbal intelligence)
- Q1= Attention Under Monotonous Circumstances
- FAT= Test for Attention Flexibility
- LL5, TT15= Test for Visual Structuring Ability
- RST-3= Reactive Stress Test
- ART-90s= Act React Test (PVT= Peripheral Vision Test)
- TT15= Test Measuring the Traffic-specific Perception Ability
- DR1= Attention Under Monotonous Circumstances
- RST3= Reactive Stress Test
- DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment
- DR3= Decision and Reaction Behaviour in a Dynamic Driving Environment
- BMT= Boston Naming Test
- VFT= Verbal Fluency Test
- RAVLT= Rey Auditory Verbal Learning Test
- CTT= Color Trails Test
- Ruff= Ruff Selective Attention Test
- COG= Attention Test
- VIG= Vigilance Test
- n/a= Not Available.
cognitive domain and compared with healthy controls [3, 23, 25, 28, 30, 34]. There was however no significant difference found in cognitive impulsivity between buprenorphine maintained individuals and healthy controls [25, 30, 34].

13.5.2. Cognitive flexibility
In the three studies directly comparing methadone to buprenorphine treatment there were no significant differences in cognitive flexibility scores reported. However cognitive flexibility was more frequently reported as significantly impaired (p<0.05) in patients maintained on methadone, than those on buprenorphine when compared to healthy controls. Four of the ten selected studies [8, 23, 25, 34], showed impairment for methadone maintained individuals compared to healthy control. In comparison only one of five studies that reviewed cognitive flexibility in buprenorphine treated individuals identified impairment [34], with the other 4 papers finding no impairment in this domain in comparison to healthy controls.

13.5.3. Motor impulsivity
In the three papers conducting the direct comparison between methadone treatment and buprenorphine treatment, there were no reported differences in the motor impulsivity. However in the studies looking at comparison to healthy controls, both methadone and buprenorphine treated cohorts exhibited impairments in motor impulsivity when compared to healthy controls [32, 34].

13.5.4. Attention
One measure (DR2) in relation to the attention domain found buprenorphine individuals were less impaired than methadone in the papers comparing treatments against each other directly [1]. However the same paper found no significant difference on two other assessments of attention (Q1 & FAT). Soyka [34] also found no significant difference in attention test scores when comparing methadone to buprenorphine. Five articles that compared methadone to healthy controls identified a significant impairment in attention [8, 19, 23, 30, 34] with four buprenorphine comparison papers showed an impairment (p<0.05) in the attention domain [30, 21, 32, 34].

13.5.5. Short term memory
From the two direct comparison articles between methadone and buprenorphine cohorts that reported on Short Term Memory, there was no significant difference found [25, 34]. Short term memory was significantly impaired (p<0.05) relative to healthy controls in both methadone and buprenorphine cohorts. Four of the identified studies found a significant impairment (p<0.05) when methadone maintained individuals were compared to healthy controls [3, 8, 25, 27]. Three of the studies comparing buprenorphine to healthy controls showed significant impairment (p<0.05) in short term memory [21, 25, 34].

14. Discussion

14.1. Summary of findings
Buprenorphine maintained individuals demonstrate reduced impairment of cognitive impulsivity compared to those maintained on methadone. This was the most reliable conclusion drawn from the results as a significant difference was observed both in papers directly comparing methadone with buprenorphine and comparisons with control groups.

The attention domain shows that buprenorphine patients are less impaired than patients on methadone in the direct comparative studies. However, in the articles comparing methadone or buprenorphine to healthy controls, both treatments were shown to cause equal impairment. The differences between buprenorphine and methadone in relation to the attention domain could be due to the increased sedation experienced with a full opioid agonist in comparison to a partial agonist [29].

Cognitive flexibility was reported to be significantly less impaired (p<0.05) in buprenorphine maintained cohorts than methadone when compared to healthy controls. However this was not replicated in articles that directly compare the domain between methadone or buprenorphine maintained patients.

14.2. Significance
As the literature search demonstrated, using the strict criteria employed in this review, there is little evidence available currently to directly compare both buprenorphine and methadone maintenance therapies in relation to neurocognitive function. The articles that have been included highlights that there are differences between treatments and these may provide benefits for patients increasing the success of their treatment. However there is a lack of consistency in the tests employed in the research to date.

14.3. Strength and Limitations
The literature search found no Randomised Control Trials (RCTs) and all articles included are case-control studies. The lack of randomized blinded studies limits result reliability due to the possibility of increased bias [15]. Due to methodological difficulties, patients were not blinded to their interventional group with only two articles used a single blinded methodology [1, 30].

Articles were excluded if they included individuals affected by simultaneous illicit drug use or medication that might affecting neurocognitive function to minimise the effect of compounding factors. Most articles used different definitions of simultaneous drug use, showing differing application of exclusion criteria between papers. Some conducted urinalysis over a period of months and others allowed for positive urine test if the individual was not experiencing acute effects. The most commonly identified additional substance was benzodiazepines, which are known to have effects on neurocognitive function [8, 28, 34, 37]. These mitigate the acute effects of benzodiazepines on the result of the neurocognitive tests and question the cause of any reported neurocognitive impairments in these studies. This becomes more important when comparing buprenorphine due to the limited number of papers available covering this area. The less robust exclusion criteria used in Soyka’s [34] paper reduces the reliability of the results from this study. The results mirror those from the other three papers making this comparison [1, 25, 30], reducing the likelihood that benzodiazepine use caused these results. However it must be noted that benzodiazepine use is frequent amongst active heroin users, as well as those enrolled in maintenance opioid agonist replacement programmes. [16]. None of the studies considered the potential neurocognitive sequelae of chronic nicotine and/or cannabis use in this treatment seeking population.

The selected articles sample size lack consistency across the five studies investigating buprenorphine. They included 84 individuals, contrasting to 279 methadone maintained individuals across 10 selected studies. Potential root causes of this difference in articles identified are; (a) the limited period of time that buprenorphine preparations have been licensed for use in opioid dependence (mid-1990s for buprenorphine as opposed to methadone’s availability since the 1960s) and (b) methadone being the preferential use of methadone as a first line treatment to opioid dependence [39].

The published articles are using small numbers studying individuals attending diverse treatment systems. A large degree of heterogeneity existed between studies, e.g. mean opioid use ranged from six months to over fifteen years between methadone cohorts [25, 28]. Other demographics followed similar trends, e.g. mean buprenorphine dose ranged from 6.78mg [21] to 13.4mg [1]. There were significant differences reported between comparable populations within individual selected studies. There were discrepancies in age, gender and educational attainment between populations [3, 20, 25, 27]. Significant differences in the completed educational years could have a profound effect on the neurocognitive test scores reported by these groups in the intelligence domain. Matching controls based on an estimate of their pre-morbid intelligence (IQ) will reduce this bias.

The time between administration of the maintenance dose and conducting the neurocognitive assessments needs to be considered as variations in the time delay may have different impairments on neurocognitive function due to the acute sedative effects of the treatment modality used [5]. One paper analysed the difference in scores between peak levels (1.5 hours after administration) and trough levels (20 hours after administration) for both methadone and buprenorphine. The combined results showed that individuals at trough levels performed significantly worse on the RST3 assessment of motor impulsivity [1]. In this review, the majority of studies included did not specify the time between administration of the last dose and neuropsychological test which impacts on repeatability and result interpretation. The large variation in duration of action means that individuals maintained on different opioids may experience the onset of withdrawal symptoms, at different times which may affect the neurocognitive assessment. Thus, if the assessment is conducted at the same time post administration; the methadone maintained cohort may collectively experience withdrawal symptoms earlier than the buprenorphine maintained cohort in direct comparison studies. Some studies screened for opioid withdrawal at the time of testing ensuring participants were not in withdrawal [30, 37], whilst others conducted assessments well within the duration of action of treatments [3, 17].

Multiple different cognitive domains are described and used in the literature. For the purposes of this enquiry the domains set out by Baldacchino et al. [4] were used.

Until a standardised system of domains and assessment exists there will always be discrepancies and variations in the tests used and subsequent result classification, damaging the integrity of conclusions.
drawn from these studies

It is important to consider compounding factors affecting neurocognition, including head injury, alcohol use and overdose. Regression analysis was used by some papers to correct for variations of these factors. The rigorous inclusion criteria applied to papers is a strength of the review, and provides clear results comparing methadone/buprenorphine to a control or each other. This allowed a large array of data to be extracted from included papers. The majority of papers did not directly compare methadone to buprenorphine and further research into this area could address this factor.

Decreased neurocognitive test scores for both treatments were demonstrated in comparison to healthy controls. The comparison of each treatment option against healthy controls allows some inference to the effects of each treatment on the neurocognitive impairments experienced. The differences observed between the neurocognitive impairment and the prescribed treatment modality validates the need for further direct comparison research between the treatment options.

14.4. Clinical relevance

The relevance of this review can be demonstrated in the application to driving ability. It is illegal to drive whilst impaired under the influence of any drug. England and Wales have a blood concentration limit for methadone of 500mcg/L of blood [9]. Buprenorphine has no defined concentration limit. Therefore if supported by further research and one treatment is proven to provide improved scores this could influence treatment choice. Therefore this review helps to identify better the current knowledge base when making clinical decisions on choice of opioid used for ORT to improve road safety and treatment retention.

The effect on neurocognitive function could be extrapolated to other functions and abilities and assist in making treatment choices for patients which are better suited and many patients report to a “clear head” with buprenorphine as opposed to “clouding” with methadone [14, 29, 35]. This subjectively based reduced neurocognitive impairment would be of greater benefit to the patients recovery and treatment on the grounds of the limited evidence identified. E.g. decreased neurocognitive impairment would be preferential for patients who are currently employed or actively seeking employment, those with a carers’ role for either children or physically unwell individuals or those needing to be able to drive or operate heavy machinery. However for some patients a degree of cognitive impairment may be beneficial. E.g. states of increased boredom and “problematic thoughts that can increase the risk of relapse” [35]. This observation should be taken with extreme caution as this systematic review has highlighted the urgent need to conduct methodologically sound, unbiased and well powered studies to be able to identify better significant correlation between observed neurocognitive impairments and type of agonist opioid treatment used with clinical practice.

15. Conclusions

In conclusion, this systematic review of published literature into the neurocognitive function of individuals on methadone or buprenorphine maintenance treatment shows that there are fewer than expected reports of impaired neurocognitive function when patients are prescribed buprenorphine in comparison to methadone. There is a need for more rigorous and larger well matched longitudinal studies to reduce the variances caused due to opioid withdrawal influencing the result and to measure neurocognitive impairment of pharmacologically maintained individuals over time.

References


Acknowledgements

The authors would like to acknowledge the Medical School at the University of St Andrews for their support in preparing the article.

Role of the funding source

Financial support for the implementation of this review was provided by internal funds.

Contributors

The authors contributed equally to this review.

Conflict of interest

Authors declared no conflict of interest.
Medicinal products detected as novel psychoactive substances: The case of intravenous use of tropicamide.

Marie Claire Van Hout

Public Health Institute Liverpool John Moores University, Liverpool, United Kingdom

Summary

Use and abuse of novel psychoactive substances (NPS) remains a public health and law enforcement challenge across Europe and bordering countries. Increasingly NPS detected on the drug market include those with legitimate use as medicines or active pharmaceutical ingredients in medicines. This Short Communication wishes to draw attention to reports on the concerning upward trend of intravenous (IV) use of eyedrops containing tropicamide by problematic opiate users. Since 2013, trends of diversion by IV route are identified as a new phenomenon in Europe. Sales in Russia and Eastern Europe in particular have increased significantly in the past five years. Key indicators of suspected misuse include online interest particularly from Russia, Ukraine and other Eastern European countries, and pharmacovigilance and clinical alerts from Turkey, Italy, France, Georgia, Russia, Tajikistan, and Kazakhstan. Tropicamide is injected as secondary to the primary opiate addiction, and reportedly occurs as self-sufficient means to get high amongst opiate injectors when primary opiates such as heroin are not available, and as poly-substitute to further enhance the opiate effect and manage heroin (and to a lesser extent methadone) withdrawals. Anecdotally, injection of tropicamide is known as the ‘seven monther’ in relation to the length of time it takes to kill the user. The diversion of tropicamide is high risk, concentrated within problematic drug user networks, and conducted by individuals who may not be engaging with social and medical systems. Aside from dependence and physical/psychiatric harms, the risk pertaining to this injecting phenomenon as potential contribution toward virus transmission (HIV, Hepatitis C) within injecting networks are present. The Short Communication presents extant literature on the topic, and discusses implications for drug policy and service delivery.

Key Words: Novel Psychoactive Substance; Tropicamide; eyedrops
intravenous (IV) use of eyedrops containing tropicamide by problematic opiate users. Tropicamide is a mydriatic atropenic ophthalmic drug indicated for therapeutic or diagnostic procedures to dilate the pupils [12]. It is administered for very short-term exposure periods, at starting doses of one drop (150 μg of tropicamide) and not exceeding 3 ml of the solution. Effects at higher dosages include visual hallucinations, confused states, sedation and delirium [1, 9]. Since 2013, trends of diversion by IV route are identified as a new phenomenon in Europe. Sales in Russia and Eastern Europe in particular have increased significantly in the past five years [13-14, 19]. Key indicators of suspected misuse include online interest particularly from Russia, Ukraine and other Eastern European countries [3, 11], and pharmacovigilance and clinical alerts from Turkey [5], Italy [3, 15], France [11], Georgia [2], Russia [3, 19], Tajikistan [8, 10, 20], and Kazakhstan [13-14].

Tropicamide is injected as secondary to the primary opiate addiction, and reportedly occurs as self-sufficient means to get high amongst opiate injectors. Tropicamide is a mydriatic atropenic ophthalmic drug indicated for therapeutic or diagnostic procedures to dilate the pupils [12]. It is administered for very short-term exposure periods, at starting doses of one drop (150 μg of tropicamide) and not exceeding 3 ml of the solution. Effects at higher dosages include visual hallucinations, confused states, sedation and delirium [1, 9]. Since 2013, trends of diversion by IV route are identified as a new phenomenon in Europe. Sales in Russia and Eastern Europe in particular have increased significantly in the past five years [13-14, 19]. Key indicators of suspected misuse include online interest particularly from Russia, Ukraine and other Eastern European countries [3, 11], and pharmacovigilance and clinical alerts from Turkey [5], Italy [3, 15], France [11], Georgia [2], Russia [3, 19], Tajikistan [8, 10, 20], and Kazakhstan [13-14].

Tropicamide is injected as secondary to the primary opiate addiction, and reportedly occurs as self-sufficient means to get high amongst opiate injectors when primary opiates such as heroin are not available, and as poly-substitute to further enhance the opiate effect, and to manage heroin (and to a lesser extent methadone) withdrawals [2, 4, 5, 10, 15, 19, 20]. Additional factors supporting the rapid diffusion of this new injecting phenomenon within Russia and Eastern Europe are observed by Bersani and colleagues [4] in their mini-review and centre on rapid onset of effect, ease of availability and low cost, and visibility of user interest and experiences online. Prilutskaya and Kuliev [14] also speculate that tropicamide’s popularity is due to its readiness for injection, in contrast to other pharmacy sourced medicinal products such as codeine, ephedrine and desomorphine which require some level of home preparation prior to injecting (for example ‘Krokodil’, see [18]). Tropicamide eyedrops can easily be bought online and in pharmacies [4].

Acute intoxication characterised by hallucinations (‘open eye dreams’), dizziness, hyperthermia, tremors, convulsions, suicidal ideation, psychomotor agitation, tachycardia and psychosis, diagnosis of anticholinergic syndrome and adverse chronic health problems (severe weight loss, cognitive impairment, cardiovascular toxicity, renal or liver failure, post injection purulent soft tissue complications, viral transmission and both physical and psychological dependence) are reported [3-5, 11, 13-15]. Anecdotally, injection of tropicamide is known as the ‘seven monther’ in relation to the length of time it takes to kill the user [3]. In the past five years, fatalities in Russia have been reported in the media and on drug fora [3, 4, 16].

The diversion of tropicamide is high risk, concentrated within problematic drug user networks, and conducted by individuals who may not be engaging with social and medical systems [11]. Aside from dependence and physical/psychiatric harms, the risk pertaining to this injecting phenomenon as potential contribution toward virus transmission (HIV, Hepatitis C) within injecting networks are present. Given the fluctuations in opiate and diverted opioid availability in regions where tropicamide is used, this remains concerning, even though primary tropicamide abuse is not commonly reported, and it appears situated within poly substance use as ‘top up’ drug. Tropicamide’s craving’s specificity appears to get lost in addictive processes, with poly-substance abuse of tropicamide in opiate dependency going far beyond cross-tolerance mechanisms.

The rising reports in Russia and Eastern Europe, and more recently in France and Italy, of tropicamide abuse by known injecting networks of drug users therefore warrants a careful response, instigated by country and EU wide risk assessment. Gauging the public health risks within countries experiencing this injecting phenomenon is difficult, and yet are necessary to underpin further development and coverage of pharmaco and addicto-vigilance regulatory systems. National early warning systems are uniquely positioned to identify early and continued levels of abuse of this diverted medicinal product, particularly within existing problem drug user networks. Given the cross over between pharmacy and street supply of tropicamide, a multi-disciplinary approach to integrate regulation, enforcement, and surveillance of diversion and suspected abuse is imperative to monitor and respond to this type of medicinal diversion. Routine forensic detection, monitoring and surveillance of a broad reach of potential information sources both inside and outside countries experiencing this trend are therefore necessary. For countries experiencing this form of medicinal diversion, training of health, pharmacy and medical professionals in the detection of suspected abuse and appropriate clinical responses for those experiencing tropicamide related health problems and dependence are warranted [3, 5, 11, 14-15]. Research efforts can assist in the garnering of understanding tropicamide as relatively new drug situated within problem drug user populations, and can help support the development of targeted prevention and harm reduction initiatives. Within the wider EU domain, the regular surveillance of online drug...
fora and trend interest in tropicamide (and other pharmaceuticals with abuse liability) should continue.

References


Acknowledgements

None

Role of the funding source

Financial support for the implementation of this review was provided by internal funds.

Conflict of interest

Author declared no conflict of interest.

Ethics

Author confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

Note

It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers.

Received November 22, 2017 - Accepted March 2, 2018
Deal with the present, jump start the future