

215 Institution: University of Hertfordshire		
Unit of Assessment: 3 – Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Novel Psychoactive Substances: changing legislation, regulation, clinical practice and drug prevention strategies to protect public health.		
Period when the underpinning research was undertaken: 2010 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Fabrizio Schifano	Chair in Clinical Pharmacology and Therapeutics	2006 – present
Ornella Corazza	Reader in Substance Addictions and Behaviours	2009 – present
Jacqueline Stair	Senior Lecturer	2007 – present
John Corkery	Senior Lecturer	2011 – present
Amira Guirguis	Senior Lecturer	2013 – 2019
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact (indicative maximum 100 words)		
<p>Research at the University of Hertfordshire (UH) into rising misuse and severe ill-health effects of Novel Psychoactive Substances (NPS) has led to more effective legislation and regulation, and new measures to protect public health. The research contributed to UK law changes that reclassified two psychostimulants (4F-EPH and ethylphenidate) as Class B substances and two anticonvulsants (pregabalin and gabapentin) as Class C. It was key to recommendations by the UK Advisory Council on the Misuse of Drugs (ACMD) on misuse of Fentanyl and Gamma Hydroxybutyrate (GHB). UH studies informed reviews by the Home Office, Public Health England, NHS England and the United Nations Office on Drugs and Crime, and changed clinical and prescribing guidelines in the UK and Italy. The research led to the first Home Office license for a drug checking service, which informed a select committee inquiry into UK drugs policy and underpinned recommendations arising from an inquest into drug-related deaths at music festivals in Australia.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>The last decade has seen the rapid emergence of an increasingly diverse group of recreational psychotropic drugs marketed colloquially as 'legal highs', 'bath salts' or 'research chemicals'. These Novel Psychoactive Substances (NPS) pose a significant risk to public health; understanding of their chemical composition and toxicity is limited and the nature and severity of their adverse health effects are unpredictable and often unknown. The use of NPS can lead to acute anxiety, psychosis and addiction, and has been repeatedly linked to emergency hospitalisations and deaths.</p> <p>Multidisciplinary research by UH's Psychopharmacology, Drug Misuse and NPS Unit (led by Schifano) has investigated several issues associated with NPS: negative health consequences arising from their use; the epidemiology of NPS use and related mortality and 'near misses'; the abuse potential of prescription and over-the-counter NPS; identification and classification of illicit psychoactive substances. This body of work has made a leading contribution to the global knowledge base for this fast-evolving phenomenon, through over 200 peer-reviewed articles by members of the UH Unit since 2010. Studies under three EU programmes sought to provide health and law enforcement communities with evidence of the pharmacological properties and effects of NPS, how they are obtained and how to identify them. The UH-led, multi-centre Recreational Drugs European Network (ReDNeT) [G1] profiled emerging NPS and consumption patterns. The project led to a database of 650 NPS combinations, expanded upon the role of web-monitoring tools in mapping NPS diffusion and disseminated advice to EU health professionals, policymakers and crime agencies [3.1].</p> <p>The UH-led EU-MADNESS research programme [G2] identified the NPS that were causing the most harm. The data was used to develop educational resources for health professionals and policymakers, with Corkery leading the analysis of anonymised data on drug-related deaths for</p>		

correlations with misuse of NPS. The Unit were Co-Is on the 'Enhancing Police Skills concerning NPS' programme [G3], providing expertise in substance epidemiology and monitoring, chemical and mathematical modelling, and knowledge of the dark web to facilitate early recognition of NPS. Both programmes fed into the design of the Unit's novel web crawler software NPS.Finder®, which searches online discussion forums frequented by NPS users to identify the emergence of NPS and profile them. It has identified around 4,300 unique NPS, a figure four times higher than that reported by EU and UN agencies [3.2]. Under G3, the Unit developed a novel approach for the in-field identification and classification of NPS using Raman spectroscopy coupled with Principal Components Analysis (PCA). For the first time key structural features of potential 'unknown' NPS could be identified [3.3].

The Unit has investigated the misuse of prescription medications as recreational NPS. Studies highlighted concerns around the misuse of gabapentinoids (notably gabapentin and pregabalin), which are prescribed to treat epilepsy, neuropathic pain and anxiety [3.4, 3.5]. Researchers found that many gabapentinoid experimenters had a history of recreational polydrug misuse, who self-administer with very high dosages [3.4]. They found 6.6% and 4.8% of adverse drug reactions were associated with pregabalin and gabapentin respectively, with 27 and 86 fatalities [3.5]. A study with Sapienza University of Rome flagged the intravenous and potentially fatal misuse of tropicamide eye drops, which can lead to hyperthermia, convulsions and coma [3.6].

Fentanyl is a powerful opioid similar to morphine but 50-100 times more potent. A UH study [3.7], involving the analysis of fentanyl-related misuse over ten years, revealed a spike in adverse drug reactions between 2016 and 2018, especially when fentanyl was mixed with heroin. Large numbers of cases required prolonged hospitalisation or resulted in death, leading the team to conclude that fentanyl abuse should be considered a public health issue with significant implications for clinical practice. A separate study [3.8] of the misuse of GHB and gamma-butyrolactone (GBL), which had increased greatly since the 1990s, particularly among LGBT individuals in recreational settings (e.g. 'chemsex'), concluded that significant caution is needed when ingesting GHB/GHL, especially alongside alcohol, stimulants, benzodiazepines and ketamine. It found that risk of death is increased due to their CNS-depressant properties.

3. References to the research (indicative maximum of six references)

- 3.1** Corazza O, Assi S, Simonato P, Corkery J, Bersani FS, Demetrovics Z, Stair J, Fergus S, Pezzolesi C, Pasinetti M, Deluca P, Drummond C, Davey Z, Blaszkowski U, Moskalewicz J, Mervo B, Furia LD, Farre M, Flesland L, Pisarska A, Shapiro H, Siemann H, Skutle A, Sferrazza E, Torrens M, Sambola F, van der Kreeft P, Scherbaum N, Schifano F. Promoting innovation and excellence to face the rapid diffusion of novel psychoactive substances in the EU: the outcomes of the ReDNet project. *Hum Psychopharmacol*. 2013 Jul;28(4):317-23. <https://doi.org/f45czp>.
- 3.2** Schifano F, Napoletano F, Chiappini S, Guirguis A, Corkery JM, Bonaccorso S, Ricciardi A, Scherbaum N, Vento A. New/emerging psychoactive substances and associated psychopathological consequences. *Psychol Med*. 2021 Jan;51(1):30-42. <https://doi.org/fx5m>
- 3.3** Calvo-Castro, J., Guirguis, A., Zloh, E. G., Zloh, M., Kirton, S. B. and Stair, J. L. Detection of newly emerging Psychoactive Substances Using Raman Spectroscopy and Chemometrics. *RSC Advances*. 12 Sep 2018. 8, 31924. <https://doi.org/10.1039/C8RA05847D>.
- 3.4** Schifano, F. Misuse and Abuse of Pregabalin and Gabapentin: Cause for Concern? *CNS Drugs*. 2014 Jun;28(6):491-6. <https://doi.org/10.1007/s40263-014-0164-4>.
- 3.5** Chiappini, S, Schifano, F. A decade of gabapentinoid misuse: an analysis of the European Medicines Agency/EMA 'suspected adverse drug reactions' database. *CNS Drugs*, 2016; 30:647-54. <https://doi.org/10.1007/s40263-016-0359-y>.
- 3.6** Bersani, F.S., Corazza, O., Simonato, P., Mylokosta, A., Levari, E., Lovaste, R., Schifano, F., Drops of madness? Recreational misuse of tropicamide collyrium; early warning alerts from Russia and Italy, *General Hospital Psychiatry*, Vol 35, 5, pp 571-573, 2013. <https://doi.org/f2f3sj>.
- 3.7** Schifano F, Chiappini S, Corkery JM, Guirguis A. Assessing the 2004-2018 Fentanyl Misusing Issues Reported to an International Range of Adverse Reporting Systems. *Front Pharmacol*. 2019 10:46. <http://doi.org/10.3389/fphar.2019.00046>.

3.8 Corkery JM, Loi B, Claridge H, Goodair C, Schifano F. Deaths in the Lesbian, Gay, Bisexual and Transgender United Kingdom communities associated with GHB and precursors. *Current Drug Metabolism*, 2018. <http://doi.org/10.2174/1389200218666171108163817>.

Key underpinning grants

G1 European Commission, 2010-12. 'Recreational Drugs' European Network (ReDNet): An ICT prevention service addressing the use of novel compounds in vulnerable individuals. Total award: €833,333; amount to UH (coordinator): £195,258. **Winner of 2013 European Health Award.**

G2 European Commission, 2014-16. EU-MADNESS (EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS): integrated EU NPS monitoring & profiling to prevent health harms and update professionals. Total award: €635,215; amount to UH (coordinator): £226,378.

G3 European Commission, 2014-16; Project EPS/NPS – Enhancing Police Skills concerning NPS. Total award: €692,850; amount to UH: £193,105.

4. Details of the impact (indicative maximum 750 words)

UH research on NPS has: directly influenced action by the UK Government and public bodies to introduce new legislation, regulation and guidance to protect public health; changed NPS clinical and prescribing guidelines for health professionals; secured the first Home Office license for a drug checking service; and informed drug prevention strategies in the UK and overseas.

Impact on UK drug legislation, regulation and policymaking

UH research into NPS has been used by UK policymakers to identify the scale and nature of NPS use and its associated risks. Several papers published by the UH Unit were cited in the Home Office's *New Psychoactive Substances in England: A review of the evidence* (2014) [5.1]. The research has fed directly into the deliberations and recommendations of the ACMD on some of the most potentially harmful NPS on the market. Schifano was a full ACMD member until reaching his term limit in 2019; Corkery was a member of the ACMD's NPS Committee [5.2].

In 2015 the ACMD reviewed the harms associated with the misuse of pregabalin and gabapentin. ONS data had shown a sharp rise in deaths related to pregabalin (four in 2012 to 38 in 2014) and gabapentin (nine in 2013 to 26 in 2014). Studies led by Schifano had been raising safety concerns over the drugs; as an ACMD member, Schifano contributed his research insights, specifically 3.4 and 3.5, to the Review. The ACMD chair wrote to the Home Office Minister in January 2016, recommending the control of pregabalin and gabapentin as Class C substances. Paper 3.4 was cited in the recommendation [5.3]. This also referenced a review published by PHE and NHSE (2014) which in turn cited research by Schifano and Corazza as part of its evidence base [5.4]. Responding to the ACMD, the Government announced, in 2018, the reclassification of pregabalin and gabapentin as Class C controlled substances. Stronger controls were put in place to minimise the risk of stockpiling by patients.

Under [G2], in 2016 Corkery identified the first known death from '*complications of 4F-EPH*' (4-Fluoroethylphenidate). This molecule is an analogue of the medication Ritalin (methylphenidate). He also identified five deaths where ethylphenidate, an amphetamine-like psychostimulant, was implicated in the cause of death. As an ACMD NPS Committee member, Corkery published this data in the ACMD's report sent to the Home Office minister in March 2017 [5.5]. It recommended the control of 12 methylphenidate-related NPS, including 4F-EPH and ethylphenidate, as Class B substances. Only two months later, the molecules became Class B drugs following the passing of secondary legislation under the Misuse of Drugs Act 1971 and a Home Office circular was immediately sent to police forces and criminal justice bodies drawing their attention to the law change [5.5].

Fentanyl is a licensed medicine for anaesthesia and pain management; it is also classified as an illegal Class A substance in the UK. In 2017, the Home Secretary, responding to increasing

fentanyl-related deaths, commissioned the ACMD to review the number of known fentanyl analogues – and their known and likely risk factors. The ACMD's NPS Committee analysed the misuse potential of fentanyl compounds and associated harms. Key evidence was UH's 10-year assessment of fentanyl misuse in the UK, EU and US [3.7], which Corkery, as a committee member, fed directly into the review process [5.6]. The conclusions in the ACMD report, published in January 2020 and covered widely in the media, mirrored those in 3.7: *'fentanyl and fentanyl analogues present a significant risk to UK public health'* and *'current monitoring and surveillance systems should be adapted to help identify the true scale of this threat'*. It warned, as noted in 3.7, that a rise in the number of deaths in the UK was being driven by fentanyl being added to heroin. The Home Office said it would *'carefully consider'* the recommendations in its policy response.

In January 2020 the Home Secretary asked the ACMD to urgently review GHB, GBL and closely related compounds, responding to the use of GHB by the serial killer Stephen Port and suspected use of GHB by serial rapist Reynhard Sinaga. The ACMD published its report, widely covered in the media, in November 2020, recommending that GHB should become a Class B drug. Corkery's studies at UH, including 3.8, were cited 25 times as key evidence for the conclusions [5.7].

Impact on clinical and prescribing guidelines and practice

In July 2017 the Department of Health published *Drug misuse and dependence: UK guidelines for clinical management* for healthcare professionals. The chapter *Misuse of or dependence on gabapentinoids* used 3.4 as key evidence, warning that *'prescribers need to be aware of the risk that some patients may wish to accumulate supplies with a view to taking excessive doses for a psychoactive effect'*. It noted *'accumulating'* evidence of gabapentinoid misuse, particularly in those who misuse other drugs [5.8]. In 2018 the Royal College of Psychiatrists published *Our Invisible Addicts*, a report setting out the extent of substance-related health problems amongst older people. Citing 3.5, it highlighted the increase in adverse drug reactions associated with pregabalin and advised that *'vigilance is needed when co-prescribing pregabalin with opioid drugs'* [5.9]. Through a collaboration with the Royal Pharmaceutical Society (RPS), research under G2 and G3 formed the basis of a new section in the Society's 2018 edition of its *Medicines, Ethics and Practice* textbook, informing pharmacists about how NPS are controlled and associated harms. The textbook is accessed by all pharmacies in the UK and is part of both undergraduate pharmacy studies and pharmacy pre-registration national assessment. To accompany this, Guirguis co-authored an online NPS 'quick reference guide' that was made available in April 2018 to 27,000 RPS members, along with a factsheet for pharmacists available to both members and non-members [5.10].

Research into misuse of tropicamide [3.6] was carried out in response to an *'alarming'* rise in the non-prescription sale of tropicamide in pharmacies in Trentino, Italy [5.11]. The peer-reviewed paper and UH's follow-up review in *Human Psychopharmacology* in 2015 led to the Provincial Health Services Agency issuing an advisory notice to all physicians and pharmacists in Italy that tropicamide should not be sold without prescription. Product sales dropped as a result [5.11].

Impact on authorities' drug prevention strategies and the legal profession

Novel UH research into identifying emerging NPS via handheld spectroscopy [3.3, G3], in order to support police and staff in prisons and substance misuse units, resulted in the first drug checking service to be licensed by the UK Home Office. The drop-in service, a partnership between UH (PI: Guirguis) and charity Addaction, was run for the first time in Somerset in 2019; it allows people to have a sample of their drugs tested (using handheld spectroscopy) anonymously and to receive specialist advice. Covered widely in the media, an article in the *Guardian* [5.12] said the service *'marks a milestone for the harm reduction movement as well as a significant shift in government support for the approach'*. It quoted the drugs strategy lead at Avon and Somerset police as saying: *'We are confident that this approach will help those who are determined to take drugs keep safe from harm, inform them of the health dangers and*

remind them of the criminal consequences they could face [5.12]. In June 2019 the service was cited by a witness giving oral evidence on the benefits of drug testing to the Health and Social Care Select Committee inquiry into UK drugs policy. The Committee's report, published in October 2019, highlighted such testing as *'an effective early warning system ... about particular batches of drugs and the dangers they might pose, enabling public health messages to be put out to reduce wider harm'* [5.13].

The spectroscopy studies have helped coroners assess NPS-related fatalities. Guirgius acted as an Expert Witness for an inquest held in July 2019 in New South Wales, Australia into the deaths of six young people at music festivals. The coroners' report cited 3.3, discussed the Home Office-licensed checking service at length and referred to Guirgius's evidence 46 times [5.14]. The state premier and police had previously made their opposition to drug checking clear but the report made this key recommendation: *'That the Department of Premier and Cabinet permits and facilitates Pill Testing Australia, The Loop Australia, or another similarly qualified organisation to run front of house medically supervised pill testing/drug checking at music festivals in NSW'* [5.14].

Based on the Unit's combined research and collaboration with UN agencies under G2 and G3, the UN Office on Drugs and Crime (UNODC) asked Corazza to carry out the evidence analysis and prepare the first draft of Volume 21 of its Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) Update: *Understanding the global opioid crisis*. Published in English, Russian and Spanish, the UNODC emphasised its importance *'in enhancing international understanding of the threats posed by the non-medical use of opioids and identifying options for response'* [5.15].

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Home Office: New Psychoactive Substances in England: A review of the evidence, 2014. www.tinyurl.com/akrgpam8 (pp. 42, 43, 49, 50)

5.2 Letter from the Home Secretary confirming Schifano's position as a full ACMD member.

5.3 ACMD advice to the Home Office re the misuse of pregabalin and gabapentin, 2016. www.tinyurl.com/48pvmadyb (p. 2)

5.4 PHE/NHS: Advice for prescribers on the risk of the misuse of pregabalin and gabapentin, 2014. www.tinyurl.com/378zdlhp (p. 6)

5.5 ACMD report to the Home Office: Further advice on methylphenidate-related NPS. www.tinyurl.com/1m371sy2 (para 31); Home Office Circular 008/2017 on the control of 12 methylphenidate-related NPS: www.tinyurl.com/1rd306ht

5.6 ACMD report to the Home Secretary: Misuse of Fentanyl and Fentanyl Analogues, 2020. www.tinyurl.com/1t37rl0b (p. 58)

5.7 ACMD report to the Home Secretary: An assessment of the harms of GHB, GBL, and closely related compounds: www.tinyurl.com/3cryvo43 (Corkery's studies cited 25 times throughout).

5.8 Dept of Health: Drug misuse and dependence: UK guidelines on clinical management, 2017. www.tinyurl.com/49urgqghp (pp. 208, 254)

5.9 Royal College of Psychiatrists: Our Invisible Addicts, 2018. <https://bit.ly/3qNrYPX> (p. 159)

5.10 Royal Pharmaceutical Society: NPS reference guide and factsheet for pharmacists, 2018. www.tinyurl.com/bc9gfycs; www.tinyurl.com/4i53cq1z

5.11 Corroborating statement from Addiction Service, Provincial Health Services Agency, Italy.

5.12 'It's about saving lives': inside the UK's first licensed drug testing service, The Guardian 2019. www.tinyurl.com/3kxvz22c

5.13 Health and Social Care Committee inquiry into Drugs Policy (oral evidence and report), 2019. www.tinyurl.com/n3kpurnn (p. 14 and Q143)

5.14 State Coroners' Court of New South Wales inquest report, 2019.

[https://coroners.nsw.gov.au/coroners-court/download.html/documents/findings/2019/Music Festival Redacted findings in the inquest into deaths arising at music festivals .pdf](https://coroners.nsw.gov.au/coroners-court/download.html/documents/findings/2019/Music%20Festival%20Redacted%20findings%20in%20the%20inquest%20into%20deaths%20arising%20at%20music%20festivals.pdf) (46 citations throughout the report)

5.15 Corroborating statement from the Chief of the Laboratory and Scientific Section, UNODC.