
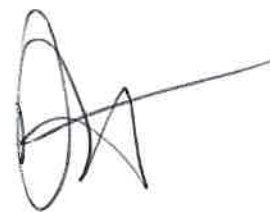


This is Exhibit^A..... referred to in the
affidavit of Professor David Nutt
sworn before me, this 29th
day of April 20²⁴

A COMMISSIONER, ETC

Sworn remotely by Professor David Nutt in the city of Bristol, England,
with commissioner Joanna Shaw in the city of Toronto, Ontario.

JOANNA KATHLEEN SHAW,
a Commissioner, etc., Province of Ontario,
for LEWIN & SAGARA LLP,
BARRISTERS AND SOLICITORS.
Expires October 16, 2026.



CURRICULUM VITAE**NAME:** David John NUTT**DATE OF BIRTH:** 16 April 1951**NATIONALITY:** British**MARITAL STATUS:** Married Four children<https://www.imperial.ac.uk/people/d.nutt>**PRESENT POSITION:**

The Edmond J Safra Chair in Neuropsychopharmacology
 Head Centre for Psychedelic Research
 Division of Psychiatry
 Dept of Medicine
 Imperial College London
 Hammersmith Hospital
 Du Cane Rd
 London
 W12 0NN
 d.nutt@imperial.ac.uk
 Mobile +447590250428

Overview

David is currently the Edmund J Safra Professor of Neuropsychopharmacology and Head of the Centre for Psychedelic Research in the Division of Psychiatry, Dept of Medicine, Hammersmith Hospital, Imperial College London.

After 11+ entry to Bristol Grammar he won an Open Scholarship to Downing College Cambridge, then completed his clinical training at Guy's Hospital London. After a period in neurology to MRCP he moved to Oxford to a research position in psychiatry at the MRC Clinical Pharmacology Unit where he obtained his DM. On completing his psychiatric training in Oxford, he continued there as a lecturer and then later as a Wellcome Senior Fellow in psychiatry. He then spent two years as Chief of the Section of Clinical Science in the National Institute of Alcohol Abuse and Alcoholism in NIH, Bethesda, USA. He returned to England in 1988 to set up the Psychopharmacology Unit in Bristol University, an interdisciplinary research grouping spanning the departments of Psychiatry and Pharmacology before moving to Imperial College London in December 2008 where he leads a similar group with a particular focus on brain imaging especially PET and fMRI in the study of psychedelic medicines. In 2018 he co-founded the first academic psychedelic research centre in the world.

He is founder and scientific chair of the charity DrugScience. He has been President of major national and international organisations: the British Neuroscience Association, the British Association for Psychopharmacology, the European Brain Council and the European College of Neuropsychopharmacology. In recognition of his research success he has been made a Fellow of the Royal Colleges of Physicians, of Psychiatrists, of the Academy of Medical Sciences and the British Pharmacological Society. He edited the Journal of Psychopharmacology for over twenty-five years and now edits the journal Drugscience policy and law. For 20 years he was a psychiatry drugs advisor to the British National Formulary. He has published over 500 original research papers, a similar number of reviews and books chapters, eight government reports on drugs, nearly 40 books including five for the general public, and one, Drugs without the hot air, won the Transmission book prize in 2014.

He has held significant government positions as member and Chair of the Advisory Committee on the Misuse of Drugs (ACMD – 1998-2009, member of the HEFCE/NHS Senior Lecturer Selection Panel and



member of the MRC Neuroscience Board. Other previous national contributions include serving as the medical expert on the Independent Inquiry into the Misuse of Drugs Act (2000 Runciman report), and membership of the Committee on Safety of Medicines, the Committee on NHS drugs and the Ministry of Defence Science Advisory Board. He was the clinical scientific lead on the 2004/5 UK Government Foresight initiative "Brain science, addiction and drugs" that provided a 25-year vision for this area of science and public policy.

He broadcasts widely to the general public both on radio and television. Highlights include being a subject for The Life Scientific on BBC radio 4, several BBC Horizon programs and the Channel 4 documentaries Ecstasy-live and Cannabis live and the BBC documentary "The psychedelic drug trial". His research has been featured as a play "All you need is LSD". Additionally is much in demand for public affairs programs on therapeutic as well as illicit drugs, their harms and their classification. His also lecturers widely to the public as well as to the scientific and medical communities at the Cheltenham the How The Light Gets In science festivals and at Glastonbury and other music festivals. In 2010 The Times Eureka science magazine voted him one of the 100 most important figures in British Science, and the only psychiatrist in the list and in 2013 he was awarded the John Maddox Prize from Nature/Sense about Science for standing up for science in the face of hostility and intimidation.

Career Overview

SCHOOL: Bristol Grammar School

UNIVERSITY:

1969 - 1972 Downing College, Cambridge - Open Scholarship

1972 - 1975 Guy's Hospital, London

QUALIFICATIONS:

1972	BA (Cantab)
1975	MB BChir (Cantab)
1977	MRCP (London)
1981	MA, MB, BChir (Oxon) (by Incorporation).
1982	DM (Oxon)
1983	MRCPSych (UK)
1994	FRCPSych (UK)
2002	FMedSci
2002	FRCP
2016	Doctor of Laws honoris causa (Bath university)

GENERAL MEDICAL COUNCIL REGISTRATION 2251774

POSITIONS HELD

1969	Technician, Dr A Rogers, Physiology Dept, Bristol University
1975	House Physician, Guy's Hospital
1976	House Surgeon, Royal Sussex County Hospital, Brighton
1976	Senior House Officer, Dermatology, Guy's Hospital
1977	Senior House Officer, Neurology, St. Mary's Hospital, Paddington
1978	Senior House Officer, Psychiatry, Guy's Hospital
1978-1982	Clinical Scientist in the MRC Unit of Clinical Pharmacology, Radcliffe Infirmary, Oxford (Professor D G Grahame-Smith).
1982-1983	Registrar in Psychiatry on the Oxford Rotational Training Scheme.

1983-1985	Lecturer in Psychiatry, University of Oxford, attached to the Psychopharmacology Research Unit, Littlemore Hospital, Oxford.
1985-1986	Wellcome Senior Fellow in Clinical Science; University Department of Psychiatry, Warneford Hospital, Oxford. Honorary Consultant Psychiatrist.
1986-1988	Fogarty Visiting Scientist NIH and Chief of the Section of Clinical Science, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland.
1988-date	Director, Psychopharmacology Unit, University of Bristol; Senior Research Fellow in Pharmacology and in Mental Health; Honorary Consultant Psychiatrist, United Bristol Healthcare Trust.
1994	Professor of Psychopharmacology, University of Bristol
1996-1997	Head, Division of Psychiatry, University of Bristol
1997-2003	Head of Department of Clinical Medicine
2000-2003	Dean of Clinical Medicine and Dentistry
2003- 2008	Head of the Department of Community Based Medicine
2008- 2016	Edmond J Safra Chair of Neuropsychopharmacology Imperial College London

AWARDS & PRIZES

1969-1975	Saunders Open Scholarship
1969-1975	Christchurch & Bushmills Scholarships
1971	Badminton "Blue"
1972	JCR President Downing College
1972-1975	Clinical Prizes: First Clinical Prize Guys Hospital: Gillespie Prize in Psychiatry Gilbert Prize in Rheumatology Dermatology Prize Beany Prize in Pathology
1972-1975	University "Purple" and Captain of Badminton, London University
1975	Mental Health Trust Essay Competition: "The Significance of Life Changes in the Development of Illness"
1984	Royal College of Psychiatrists Research Prize, Proxime Accessit: "The experimental pharmacology of anxiety: New concepts of benzodiazepine receptor function"
2009	Daily Telegraph Briton of the year – top 25
2009	2 nd (to Banksy) as Bristolian of the year
2010	69 th place in The Times list of 100 most influential figures in UK science
2013	Winner the John Maddox prize for Standing up for Science
2014	The Transmission prize for science communication

COLLEGE APPOINTMENT

1983-1988	Research Fellow in Medical Sciences, Corpus Christi College, Oxford
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LEARNED SOCIETIES by examination or election

Royal College of Physicians
 Royal College of Psychiatrists
 British Association for Psychopharmacology – Past President - 2000-2002 (BAP)
 European College of Neuro-Psychopharmacology (ECNP) – President 2007-2010
 Collegium Internationale Neuro-Psychopharmacologicum (CINP)
 British Pharmacological Society (BPS)

Editor: Journal of Psychopharmacology since 1989
 Drug Science, Policy and Law since 2013

UNIVERSITY AWARDS

Visiting Professor University of Maastricht	2004-date
Visiting Professor Imperial College University of London	2006 -2011
Visiting Professor University of Otago, New Zealand	2004-2008
Raine visiting professor, University of Western Australia	2006
Visiting Professor The Open University	2014

ROYAL COLLEGE OF PSYCHIATRY

Basic Sciences Exam Committee (Part II)	1990-date
Psychopharmacology Sub-Committee	1994-1997
Steering group of Biological Psychiatry Special Interest Group	1996- 2000

MRC

Subcommittee for site visit - Institute of Psychiatry	1991
Neuroscience Approach to Mental Health steering group	1992-1993
Addiction Field Review working party	1992-94
Neuroscience Project Grant Committee	1993-1997
Alcohol Treatment Research Working Group	1994
Suicide and Parasuicide Review Panel	1994
Neuroscience Advisory Board	1998-2005
Neuroscience and Mental Health Board	2006 -2009
Lead (with Robbins Cambridge) MRC ICCAM research cluster in Addiction	2009-2012
Addiction Initiative Stakeholder group	2009-2012

ESRC

UK Psychology Benchmarking Review Steering Group Member	2010
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REF – Neuroscience Psychiatry and Psychology panel member 2013-2014

President British Neuroscience Association 2011-2013

GOVERNMENT RESPONSIBILITIES**Home office**

Advisory Council on the Misuse of Drugs	1996-2008
Chair: Advisory Council on the Misuse of Drugs	2008 -2009
Chair of Technical Committee, ACMD	2000-2008
Cross departmental research group	2008
Home Office Scientific Advisory Committee	2008

Science and technology/ DTI/OSI

Parliamentary Office of Science and Technology 'Soft' Drugs Steering Committee	1995-1999
Scientific Lead DTI Foresight Program "Brain Science Addiction and Drugs"	2003-2005

Dept of health

Advisory Committee on NHS Drugs	1995-2000
British National Formulary (BNF) Adviser	2000-date
Committee on Safety of Medicines	2000-2005
NICE reviewer for depression, panic and social anxiety disorders and the Z-drug hypnotics	1999-date

Ministry of Defence

Consultant	1990 - 2004
Member Defence Sciences Advisory Council - DSAC	2005- 2007

Parliamentary evidence

To House of Lords committee on cannabis	2000
Home Affairs committee on drugs	2004
Evidence to All part drugs interest group	2005
Evidence to the Select Committee on Science and Technology; Scientific Advice, Risk and Evidence:	2006
Cocaine and related drugs	2009
Home affairs Select Committee review of the drug laws	2012

MISCELLANEOUS:

Police Foundation	1997-2000
UBHT - Medicines Advisory committee	1993-2000
UBHT - Medical Research committee	1993-1997
District psychiatric training committee	1993-2000
External Examiner, University of Birmingham	1994-1997
British Pharmacological Society, Clinical Pharmacology Section Expert	1996-date
British Association of Psychopharmacology - President	2000-2001
Trustee of the Sir Robert Mond Memorial Trust	1998-2004
BBSRC Functional Imaging Course Board Member	1999-2001

INTERNATIONAL POSITIONS

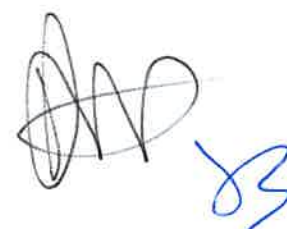
Faculty Member, European Certificate in Anxiety Disorder	1993-1995
Director of the European Certificate of Affective disorders course	1995-date
CINP International Scientific Program Committee member	1996-1998
ECNP Council Member	1998-2017
ECNP President	2007 - 2010
World Psychiatric Association, Co-Chair Section on Biological Psychiatry	1999-2001
Member of the EC Working Party on PET and SPECT ligands	1992
Council member European Brain Council	2007 -2011
Vice President European Brain Council	2011-2013
President - European Brain Council	2013 - 2017
Adviser Grand Challenges in Mental Health	2010
Advisor to Swedish government review on drug alcohol and tobacco research	2011-2012
EU scientific committee for Month of the Brain 2013	2012-2013

Charitable work

Founder and current Chair DrugScience.org.uk (formerly ISCD)	2010 - on
Founder/Chair London Joint Working Group on Drug Abuse and Hepatitis C	2009 - 2014

Refereeing for grants and fellowships: MRC, BBSRC, ESRC, Wellcome Trust, The Netherlands MRC, NIHR, INSERM, German-Israel research fund, NIH

Research and consulting for pharma companies: I have received research grants from a number of companies [Investigator initiated grants] including MSD, SKB, Organon, Wyeth, BMS, Lundbeck. In addition my group has acted as a study site for a number of clinical trials of new treatments in anxiety, depression, sleep and addiction, with me as a named investigator, sometimes as national PI. I also have acted as a consultant/advisory board member to many companies including AZ, Actelion,



Bionomics, GSK (SKB), Hythiam, Johnson & Johnson, Lundbeck, MSD, Nalparm, Neurogen, Organon, Opiant, Orexigen, Pfizer, Schering-Plough, Wyeth, Yamanuchi.

SUPERVISION OF RESEARCH STUDENTS:

	Date completed
1. S Taylor DPhil (Oxon, with Dr Little)	1984
2. C Gleiter PhD (Tubigen)	1989
3. T Wolinski PhD (New York University)	1989
4. A McDermott PhD (London, CASE with Dr Wilkin)	1991
5. P Glue MD (Bristol)	1992
6. C Watson PhD (Nottingham, CASE with Dr Bennett)	1992
7. N French PhD (Strathclyde, CASE with Dr Pratt)	1993
8. S Jordan PhD (Aston, CASE with Dr Hanley)	1993
9. A Hudson PhD (Bristol)	1994
10. A Weinstein PhD (Bristol)	1994
11. L Lione PhD (CASE, with SmithKline Beecham)	1997
12. N Coupland MD (Bristol)	1998
13. A Malizia (MD)	1998
14. S Wilson PhD (Bristol)	1999
15. M Lilies PhD (Bristol)	1999
16. H Crofts PhD (with Dr Sue Wilson)	1999
17. C Parker PhD {with Dr Alan Hudson}	1999
18. C Bryce PhD (with Prof Smith, Psychology)	1999
19. E Robinson PhD {with Dr Alan Hudson}	1999
20. D Finn PhD (Bristol) {with Dr Alan Hudson}	2000
21. J Potokar MD (Bristol)	2000
22. R Price PhD (Bristol) {with Dr Alan Hudson}	2002
23. T Wright PhD (with Prof Smith, Psychology)	2002
24. C Bell MD (Bristol)	2003
25. N Muggleton PhD [with Dr Sue Wilson]	2003
26. M Edwards PhD {with Dr Alan Hudson}	2003
27. T Mazarkis PhD [with Dr Sue Wilson]	2004
28. S Argyropoulos MD (Bristol)	2004
29. J Melichar MD (Bristol)	2004
30. R Hayward [with Dr Lingford – Hughes]	2004
31. D Slattery PhD [with Dr Alan Hudson]	2003
32. G Jackson PhD [with Dr Alan Hudson]	2004
33. A Kimura PhD [with Dr Alan Hudson]	2004
34. L Paterson PhD [with Dr Alan Hudson]	2004
35. N Anderson PhD [with Dr Alan Hudson]	2005
36. J Man PhD [with Dr Alan Hudson]	2006
37. M Daghish MD [with Dr Lingford-Hughes]	2009
38. H Abou Gazaleh PhD [with Dr Alan Hudson]	2008
39. J Hicks MD [with Dr Sue Wilson]	2009
40. A Papadopolous PhD [with Prof Hans Ruel]	2010
41. R Carhart-Harris PhD [with Dr Sue Wilson]	2009
42. T Williams MD [with Anne Dr Anne Lingford-Hughes]	2010
43. J Myers [with Anne Dr Anne Lingford-Hughes]	2012
44. D Quelch [with Dr Christine Parker]	2014
45. M Nazanin PhD [with Dr Magdalena Sastre]	2016
46. K Mendel PhD [with Dr Robin Carhart-Harris]	2016
47. A Santos Ribeiro [with Dr J McGonigle]	2016
48. C Timmerman-Slater [with Dr Carhart-Harris]	2019

Drugscience Cannabis report for 38th Expert Committee meeting 2016
[p://www.drugscience.org.uk/assets/WHOCannabisreport.pdf](http://www.drugscience.org.uk/assets/WHOCannabisreport.pdf)

Rolles S et al (2017) A framework for a regulated market for cannabis in the UK: Recommendations from an expert panel
https://d3n8a8pro7vhm.cloudfront.net/libdems/pages/10794/attachments/original/1457398164/A_framework_for_a_regulated_market_for_cannabis_in_the_UK.pdf?1457398164

Parliamentary evidence

- To House of Lords committee on cannabis – 2000
- Home affairs committee on drugs – 2004
- Evidence to All part drugs interest group 2005
- Rawlins M and Nutt DJ Advisory Council on the Misuse of Drugs: Evidence to the Select Committee on Science and Technology March 2006
- To Home Affairs Select Committee on the Drug laws June 2012

Books

1. Sarter M., Nutt DJ., Lister, RG. (1994) Inverse agonists. John Wiley and Sons 1-304; i-x
2. Nutt, DJ & Mendelson, WB. (1995) Hypnotics and Anxiolytics. Baillière's Clinical Psychiatry. Ed. Byres, C. Baillière's Tindall Ltd, London 1-509; i-ix
3. Nutt, DJ., Bell CJ., Potokar J. (1997) Depression, Anxiety and mixed Conditions. Martin Dunitz Publishers, London 1-72
4. Nutt, DJ., Ballenger, JC., Lépine, JP. (1998) Panic disorder: clinical diagnosis and treatment. Martin Dunitz Publishers, London 1-237, i-ix
5. Nutt, DJ., Argyropoulos, S., Forshall, S. (1998) Generalized anxiety disorder: diagnosis, treatment and its relationship to other anxiety disorders. Martin Dunitz Publishers, London, pp: 1-97
6. Shiloh, R., Nutt, DJ., Weizman, A. (1999) Atlas of Psychiatric Pharmacotherapy. Martin Dunitz Publishers, London 1-235, i-ix. ISBN 1-85317-630-3
7. Briley, M & Nutt, DJ. (2000) Milestones in Drug Therapy: Anxiolytics. Birkhäuser Verlag, Basel, Switzerland 1-181, i-ix. ISBN3-7643-6032-1
8. Nutt, DJ., Davidson, J., Zohar, J. (2000) Post traumatic stress disorder: diagnosis, management and treatment. Martin Dunitz Publishers, London 1-260, ISBN 1-85317-926-4
- second edition. 2008
9. Nutt, DJ., Hood, SE., Argyropoulos, SV (2000) Clinician's manual on anxiety disorder and comorbid depression. Science Press, London 1-56. ISBN 1-85873-397-9
10. Griez, E.J.L., Faravelli, C., Nutt, DJ., Zohar, J. (2001) Anxiety disorders: an introduction to clinical management and research. John Wiley & Sons Ltd, Sussex 1-380, i-xxii. ISBN 0-471-97873-6
11. Nutt, DJ., Bell, C., Masterson, C., Short, C. (2001) Mood and anxiety disorders in children and adolescents. Martin Dunitz Limited, London 1-110, i-viii. ISBN 1-85317-924-8
12. Nutt DJ, Feeney A, Argyropoulos S. (2002) Anxiety disorders comorbid with depression: panic disorder and agoraphobia. Martin Dunitz Limited, London 1-111. ISBN 1-84184-049-1
13. Nutt DJ, Rickels K, Davidson J. (2002) Generalised Anxiety Disorder: Symptomatology, Pathogenesis and Management. Martin Dunitz Limited, London. i-xii, 1-204. ISBN 1-84184-131-5
14. Nutt, DJ & Ballenger, JC. (2003) Anxiety disorders. Blackwell Science Limited, Oxford. I-xii, 1-542. ISBN 0-632-05938-9.
15. Kennedy SH, Lam RW, Nutt DJ, Thase ME. (2004) Treating depression effectively: applying clinical guidelines. Martin Dunitz Limited, London. 1-154. ISBN 1-84184-328-8
16. Doble A, Martin IL, Nutt DJ. (2004) Calming the brain: benzodiazepines and related drugs from laboratory to clinic. Martin Dunitz Limited, London. i-vi, 1-185. ISBN 1-84184-05201.

17. Nutt DJ, Robbins TW, Stimson, GV Ince M and Jackson. A (2006) Drugs and the Future: Brain Science, Addiction and Society. Elsevier. ISBN 0-12-370624-6
18. Shiloh, R., Weizman, A Nutt, DJ. (2007) Atlas of Psychiatric Pharmacotherapy. Martin Dunitz Publishers, London 1-235, i-ix. ISBN 1-85317-630-3. 2006
19. Monti JM, Pandi-Perumal SR, Jacobs B, Nutt DJ (2007) Serotonin and sleep; molecular functional and clinical aspects Birkhauser-Verlag Boston
20. Kennedy SH, Lam RW, Nutt DJ, Thase ME - 2nd edition (2007) Treating depression effectively: applying clinical guidelines. Martin Dunitz Limited, London. 1-154. ISBN 1-84184-328-8
21. Nutt, DJ, Stein M, Zohar, J. Post traumatic stress disorder: diagnosis, management and treatment. 2nd edition second edition in preparation for 2008 Taylor Francis
22. Blanchard RJ, Blanchard DC, Greibel G, and Nutt DJ (2008) Handbook of Fear and Anxiety. New York: Elsevier, 2008. 517 pp. ISBN 978-0-444-53065-3
23. Latt N, Conigrave KM, Marshall J, Nutt DJ, Saunders JB (2008) Addiction: Oxford Specialist Handbook. Oxford UK. 2ND EDITION 2017
24. Wilson SJ and Nutt DJ (2008) Sleep Disorders; Oxford Psychiatry Library - reprinted 2013
- 25 Robbins TR, Everitt B, Nutt DJ (2008) The Neurobiology of Addiction – New Vistas. Philosophical Transcriptions of the Royal Society
26. Pariante CM, Ness R, Nutt DJ, Wolpert L (2009) Treating depression: a translational approach
27. Robbins TR, Everitt B, Nutt DJ (2010) The Neurobiology of Addiction – New Vistas OUP
28. Nutt DJ; Drugs: without the hot air (2012) UIT press ISBN 13: 9781906860165 2nd edition 2018
29. Nutt DJ and Nestor L (2013) Drug Addiction OUP 2nd edition 2018
30. Drug and alcohol policy in Europe – the ALICE RAP report. OUP
31. Neuroscience based Nomenclature – ECNP/ACNP/ publication
32. Wilson SJ and Nutt DJ (2018) Sleep Disorders; Oxford Psychiatry Library 2nd edition
33. Nutt DJ and Nestor L (2018) Drug Addiction 2ND edition OUP
- 34 DRINK ? (2020) Hodder
- 35 Nutt Uncut (autobiography) 2020 – Waterside press
- 36 Cannabis – seeing throu the smoke (2021) Hodder
- 37 Brain and mind without the hot air (2021) Waterside press
- 38 Nutt DJ and Castle D (2022) Psychedelic as Psychiatric Medicines Oxford University Press
- 39 Nutt DJ Psychedelics (2023) Hodder

Grants

Wellcome Trust (with Dr H Little)	1983-1984	£15K
Masons Trust	1984	£4K
Nuffield Foundation	1985	£6K
Wellcome Trust Snr Clinical Fellowship	1985-1989	£140K
Nuffield Foundation	1985	£5K
Reckitt & Colman	1988-1992	£28000K
MRC CASE awards x 2	1989-1992	£50K
National Institute of Mental Health, USA	1992	£22K
National Institute of Alcohol Abuse, USA	1992-1994	£100K
Upjohn-Duphar	1992-1993	£40K
SmithKline Beecham	1992-1993	£30K
MRC project grant (with Prof A Smith)	1993	£29K
MRC CASE award	1993-1996	£30K
UCB Pharma	1993-1996	£450K
Roche (with Prof A Smith)	1993-1995	£180K
Burden trust	1993	£5K
Pfizer	1993-1994	£40K
Wellcome Trust	1994	£53K

Wellcome training fellowship (Dr Malizia)	1994-1996	£143K
SW Region (with Dr Evans & Prof Morgan)	1994-1995	£29K
Wellcome Trust	1994-1996	£58K
MRC project grant (with Prof Lewis)	1994-1995	£45K
MRC project grant (with Dr Myles, Prof Lewis)	1994-1995	£40K
NHS research initiative (with Dr Myles)	1995-1997	£60K
MOD	1994-1997	£65K
MRC project grant (with Dr Myles)	1994-1995	£37K
Lilly	1995-1996	£88K
Proctor and Gamble (with Prof Smith)	1995-1997	£233K
BBSRC CASE (with Knoll Pharmaceuticals)	1995-1998	£45K
MRC ROPA (with Prof Lewis)	1995-1998	£129K
Wellcome Trust	1995-1997	£170K
NHS Executive S&W	1995-1996	£40K
Interneuron Pharmaceuticals	1996-1997	£50K
Wyeth Laboratories	1995-1997	£50K
NHS Executive S&W	1995-1997	£60K
MRC project grant	1996-1997	£41K
MOD	1996	£12K
Wellcome Trust	1996-1998	£140K
Servier, France	1996-1997	£95K
Wellcome Trust	1996-1998	£85K
Merck Pharmaceuticals	1997-1998	£47K
MRC ROPA	1997-1999	£92K
MRC project grant	1997-2000	£243K
MRC Programme grant: neurotransmitters in addiction	1997-2002	£1,059K
Organon Pharmaceuticals	1997-1 998	£50K
DERA CBDE grant	1998-1999	£10K
Pharmacia & Upjohn	1998	£40K
BBSRC CASE (with Knoll Pharmaceuticals)	1998-2001	£45K
DERA CBDE grant	1998-2001	£50K
Noise on Health (with Prof Smith)	1998-2001	£120K
NIMH	1999-2001	£103K
Institute de Recherche Piere Fabre,	2001 -2002	£73K
Wellcome Trust Imidazoline receptors	2000-2003	£204K
Bial Foundation	2001-2003	£20K
Wellcome Trust and SHRIFT – Capital funds Neurosciencebuilding –P.I. Lightman	2004	£8500K
DTI Brain Science and Addiction (Foresight)	2005-2006	£46K
AWP PET imaging	2003-2004	£19K
AWP Brain Dopamine release and opiate addiction	2004	£20K
Wellcome Trust career award Dr Lowry	2002-2007	£480K
MSD – Caffeine-induced insomnia	2003-2005	£57K
BBSRC Caffeine, genes and performance (P.I. P Rogers)	2004-2007	£340K
Wellcome Trust overseas award –Estonia. SSRI effect on CCK	2004-2007	£65K
AWP Insomnia Trazodone Study	2004-2006	£23K
AWP research grants	2005-2007	£123K
MRC program Neurotransmitters in opiate and alcohol addiction	2006-2011	£1200K
GlaxoSmithKline – GAD CO2 Study	2006	£119K
BBSRC Cognitive approaches to Animal Welfare (P.I.Mendl)	2006 -2011	£3000K
Organon MRI Effects of Acute Hydrocortisone	2006-2007	£55K
MERCK – P1Vital	2007	£50K
Organon contract	2007	£68K



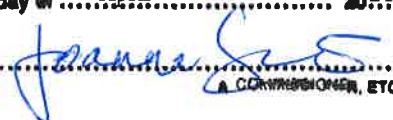
David Telling trust	2007	£9K
Servier Research & Development	2007	£40K
MRC Genetic predictors antidepressant response (P.I. Glyn Lewis)	2005 -2008	£670K
Johnson and Johnson/P1Vital	2006-2008	£288K
MRC biomarkers – a2 receptors	2008-2010	£1020K
Astra Zeneca anxiety and CO2 contract	2008	£106K
Beckley foundation: MRI Imaging cannabis	2008-2009	£30k
Wolfson foundation – a 3T MRI facility	2008 - 2009	£1500K
Special Trustees – sleep studies	2008-2010	£84K
MRC experimental medicine	2008-2010	£240K
CFS gene expression	2006-2008	£65K
Neuroendocrinology Charitable Trust	2007-2009	£54K
MRC: Mood disorders at 17 in the ALSPAC cohort (P.I. Glyn Lewis)	2008-2010	£670K
MRC Addiction in ALSPAC at 17yrs (P.I. John McCleod)	2008-1010	£450K
Wellcome trust ALSPAC at 17. (P.I. Glyn Lewis)	2008-2010	£360K
ECNP fellowship award Dr Maron Estonia	2009	£40K
MRC : dopamine receptors in alcohol dependence (PI Anne Lingford-Hughes)	2010-2011	£250K
MRC: ICCAM New Drugs for Addiction	2010-2013	£1800K
ESF 7th framework program – part of ALICERAP: addiction program	2010-2015	£120k
MRC: Neurotransmitters in addiction	2011-2016	£1600K
MRC Psilocybin treatment of depression	2012-2014	£600k
MRC Saracantanib in the psilocybin model of psychosis (With AZ)	2013-2015	£ 400k
MRC Gut hormones as possible treatments for addiction	2014-2017	£1900k
MRC DPFS with GSK imidazoline receptor PET tracers	2015-2018	£650 k
Centre for Psychedelic Research	2018- date	£3,500k
Wellcome Trust New tools for psychopharmacology research	2018-2024	£1400k
NIHR UK Psilocybin for opioid addiction	2024-2027	£1760k

Publications

Over 500 original research papers

Over 500 reviews, book chapters and other outputs

See <https://www.imperial.ac.uk/people/d.nutt/publications.html>

This is Exhibit B referred to in the
affidavit of Professor David Nutt
sworn before me, this 29th
day of April 20²⁴

..... A. COMMISSIONER, ETC

Sworn remotely by Professor David Nutt in the city of Bristol, England,
with commissioner Joanna Shaw in the city of Toronto, Ontario.

JOANNA KATHLEEN SHAW,
a Commissioner, etc., Province of Ontario,
for LEWIN & SAGARA LLP,
BARRISTERS AND SOLICITORS.
Expires October 16, 2026.



Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression

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Abstract

Objective: To identify patients' perceptions of the value of psilocybin as a treatment for depression. **Method:** Twenty patients enrolled in an open-label trial of psilocybin for treatment-resistant depression participated in a semistructured interview at 6-month follow-up. Thematic analysis was used to identify patients' experiences of the treatment and how it compared with previous treatments. **Results:** Two main change processes were identified in relation to the treatment. The first concerned change from disconnection (from self, others, and world) to connection, and the second concerned change from avoidance (of emotion) to acceptance. A third theme concerned comparison between psilocybin and conventional treatments. Patients reported that medications and some short-term talking therapies tended to reinforce their sense of disconnection and avoidance, whereas treatment with psilocybin encouraged connection and acceptance. **Conclusions:** These results suggest

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that psilocybin treatment for depression may work via paradigmatically novel means, antithetical to antidepressant medications, and some short-term talking therapies.

Keywords

psilocybin, psychedelic therapy, depression, treatment-resistant depression

We are like islands in the sea, separate on the surface but connected in the deep

—William James

Over the past 10 years, there has been a growing interest in psychedelic substances as treatments in psychiatry (Griffiths & Grob, 2010; Moreno, Wiegand, Taitano, & Delgado, 2006). Recent clinical trials have found promising safety, tolerability, and efficacy (Nichols, 2016). Treatment models typically involve one or two dosing sessions with a psychedelic substance as part of a brief psychotherapy. The impressive results of these modern trials are beginning to excite the attention of the scientific and medical establishment and motivate careful thinking about the value of this approach and how it may complement and/or challenge conventional treatment models. These developments come after a 50-year hiatus in human psychedelic research and represent an intriguing new zeitgeist in modern psychiatry.

Modern investigations into the therapeutic potential of psychedelics started in the mid-1990s with basic human psychology (Strassman & Qualls, 1994) and neuroimaging research (Vollenweider et al., 1997) before transitioning back into psychiatry in the 2000s (Moreno et al., 2006). Since 2006, there have been nine separate studies conducted by eight independent research teams on the clinical utility of psychedelics (Bogenschutz et al., 2015; Carhart-Harris, Bolstridge, et al., 2016; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Johnson, Garcia-Romeu, & Griffiths, 2016; Moreno et al., 2006; Osorio Fde et al., 2015; Ross et al., 2016). Much of this work has focused on conventional clinical outcomes, however, and there has been relatively little discussion of underlying psychological mechanisms. The motivation of the present qualitative analysis was to address this lacuna in order to better determine and communicate the psychological mechanisms involved in this promising and distinctive treatment modality.

Qualitative studies are useful for clarifying and defining the complex composite of components that make up novel therapeutic approaches (Braun & Clarke, 2013). Such work may inform future research and guide the



development of psychedelic-based treatments in clinical practice. Qualitative studies are an important adjunct to quantitative data (Hill, Chui, & Baumann, 2013; Lewin, Glenton, & Oxman, 2009; Midgley, Ansaldo, & Target, 2014). Information about patient experience can supplement information obtained from neuroimaging and psychometric measures, for example, to provide fuller, richer accounts of treatment mechanisms. Qualitative research is also a useful way of providing extra information on long-term progress; for example, subjective accounts of the nature and duration of change may shed light on how therapeutic benefits may be maximized, for example, through complementary treatments or behaviors, or repeat dosing after a particular period.

Two recent clinical trials involving psychedelic-based treatments have included qualitative analyses of patient experiences as reported at 6- or 12-month follow-up (Belser et al., 2017; Gasser, Kirchner, & Passie, 2015). Both trials focused on psychedelic treatment of anxiety related to life-threatening illnesses and both qualitative analyses of patient-reported experiences found themes relating to similar concepts, although they were described and organized in different ways. The present study is, to our knowledge, the first qualitative analysis of the effects of psychedelic treatment on patients with depression in a modern controlled trial.

The current qualitative study involved interviewing patients from the first clinical trial of psilocybin for Treatment-Resistant Depression (TRD; Carhart-Harris, Bolstridge, et al., 2016) using a phenomenological approach. In the clinical trial, 20 patients who met clinical criteria for TRD (i.e., failure of at least two different medications within the current depressive episode) were seen for six appointments: one screening session, one preparation session, a low-dose (10 mg) psilocybin session, a high-dose psilocybin session (25 mg), and two follow-up sessions at 1 day and 1 week after the high-dose session. Each patient was allocated two experienced clinicians (either psychiatrists or clinical psychologists) as the therapeutic “guides” who were introduced to the patient at screening and thereafter attended all visits.

Screening sessions explored patient history and presenting problems and the preparation session involved discussion of possible drug effects and sought to build trust and rapport. During the two dosing sessions, patients reclined on a bed, wearing eyeshades, and listened to a specific music playlist. (Note. A separate paper will address patients’ perceptions of the music.) Patients were encouraged to follow the natural lead of the music and to adopt an introspective focus. Guides provided support by “checking-in” with the patient every 30 to 60 minutes, which involved enquiring how they were feeling. Gentle reassurance was provided if distress or discomfort was apparent and patients were encouraged to “surrender” or “let go” to the drug effects without resistance. Posttreatment sessions provided time for the patient to

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describe their experience, and focused on helping them draw together a narrative of what they had experienced, and what it might mean for them going forward. The traditional psychological/psychotherapeutic approach used in this trial and similar previous trials (e.g., Griffiths et al., 2016; Ross et al., 2016) is often somewhat of a composite of approaches, tailored (it is assumed) to the idiosyncratic nature of the psychedelic experience (Grof, 1980; Richards, 2015). The practice of “guiding” in the current study required clinical skills emphasized in humanistic psychology: empathy, unconditional positive regard, and genuineness (Rogers, 1951).

A report on clinical outcomes in the first 12 subjects (Carhart-Harris, Bolstridge, et al., 2016) has been published and an update with the data from the full 20 is currently in preparation. In brief, before versus after treatment effect sizes (Cohen’s d) were exceptionally large (e.g., >2) at 1, 2, 3, and 5 weeks posttreatment follow-up but dropped to levels associated with more conventional treatments at 3 and 6 months (i.e., Cohen’s $d = 1.5-1.6$, respectively). Fifteen of the 20 patients showed some degree of reduction in depressive symptoms at 6 months follow-up, with 7 continuing to meet criteria for clinical response (50% reduction in depressive symptoms) and 6 meeting criteria for remission (Carhart-Harris, Bolstridge, et al., 2016; Carhart-Harris, 2017). Formal reports on the clinical and neuroimaging data are currently in preparation. It should be noted that subjective drug effects were barely detectable (both doses) for three of the patients. Two of these reported no drug effects at all and no discernable changes in their depression (P10, P20) whereas the remaining patient reported some perceptual distortions during the high dose but no clinical benefits (P13).

In the current study, patients were interviewed about their experiences 6 months after the high-dose session. Core research questions were the following:

- What were the patients’ experiences of the dosing sessions?
- How did they feel in the weeks and months afterward?
- What (if any) were the major processes of change?
- What did the patients see as the main benefits and harms of the treatment?

Method

Current Study: Patients

Twenty patients with TRD enrolled in a clinical trial of psilocybin for TRD conducted at Imperial College London. All 20 in the clinical trial took part in the qualitative follow-up interview.

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Six women and 13 men (15 White, 3 Black, 1 Asian, and 1 Hispanic) aged between 30 and 64 years. Key entry criteria were the following: TRD, defined by a score of 17+ on the Hamilton Depression Scale, and to have tried at least two different antidepressant medications without response. Key exclusion criteria were the following: no personal or immediate familiar member with a current or previously diagnosed psychotic disorder (see Carhart-Harris, Bolstridge, et al., 2016, for further details). Five patients had previously tried a psychedelic drug; in four of five cases, this had occurred in recreational contexts in early adulthood. All but one had undergone at least one trial of cognitive behavioral therapy (CBT).

Procedures: Qualitative Interviews

Six months after their dose, patients were invited to be included in an optional follow-up interview. Nineteen patients gave their informed consent to take part and were interviewed in person or over Skype using a semistructured interview, which consisted of a series of questions tracking patient experience, for example, *What was your experience of depression before the study? What treatments have you tried? What happened during dosing? How did you feel in the weeks and months afterward? How does it compare to other treatments?* (see the appendix for complete interview schedule). Prompts were used to encourage elaboration, if this was lacking. Interviews lasted about an hour and were recorded and transcribed by the first author. The first author acted as a guide for three patients. For transparency, references to these three patients have been marked with an asterisk.

Analysis

Thematic analysis (Braun & Clarke, 2013) was used to identify central themes for each patient. Data were analyzed sequentially by the first author, using a process of constant comparison (Corbin & Strauss, 2008), which is an iterative method of content analysis where each emerging category is searched for in the entire data set. In accordance with good qualitative research practice guidelines (e.g., Stiles, 1999), the other authors read transcripts to verify that the final themes were a fair representation of the data set. Respondent validity checks (Torrance, 2011) were carried out.

Results

The thematic analysis generated three superordinate or “master” themes (see Table 1). The first two reflect the most commonly reported change processes.



Table 1. Themes.

Theme	Number of endorsing patients
A. Change Process 1: Disconnection to Connection	17
A.1. Disconnection	20
A.1.1. "Trapped in my mind"	18
A.1.2. Disconnected from senses	8
A.1.3. Disconnected from self	20
A.1.4. Disconnected from others	19
A.1.5. Disconnected from the world	19
A.2. Connection	17
A.2.1. Mind "rebooted"/"opened up"/"switched on"	14
A.2.2. Connected to senses	10
A.2.3. Connected to self	16
A.2.4. Connected to others	16
A.2.5. Connected to the world	16
A.2.6. Connected to a spiritual principle	9
B. Change Process 2—Avoidance of Emotion to Acceptance	16
B.1. Avoidance of emotion	16
B.1.1. Rumination shuts down emotional repertoire	11
B.1.2. "Numb"—Unable to feel emotions	11
B.1.3. Attempt to avoid painful emotions	13
B.1.4. Attempt to avoid traumatic childhood memories	10
B.2. Acceptance of emotion	16
B.2.1. Intensity of feeling during the dose	16
B.2.2. Surrender to emotion	13
B.2.3. Trauma memories from childhood confronted	8
B.2.4. Memories of love accessed	12
B.2.5. Embodiment of emotion	10
B.2.6. Emotional repertoire expanded long-term	15
C. Psychedelic Therapy Compared With Traditional Therapy	20
C.1. Traditional treatments reinforce disconnection and avoidance	16
C.1.1. Talking therapy—Difficult to access substantial treatment	15
C.1.2. Some therapists unable/unwilling to address traumatic experiences	11
C.1.3. Structured treatments can prevent rapport and trust developing	11
C.1.4. Therapy can feel like it is exacerbating depression	8
C.1.5. Antidepressants—avoidance of underlying issues	18
C.1.6. Antidepressants—debilitating side effects	12
C.2. Psychedelic treatment reinforces connection and acceptance	17
C.2.1. Given the time and space to talk about the hard things (insufficient integration)	(4)
C.2.2. Focus on preparing for turbulence (inadequate preparation for withdrawal from antidepressants)	8 (2)

(continued)

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Table 1. (continued)

Theme	Number of endorsing patients
C.2.3. Music enables surrender to painful emotions (study playlist seen as restrictive/too “dark”)	14 (3)
C.2.4. Connection to guides (difficulties with guides)	17 (2)
C.2.5. Connection to “inner therapist”	6
C.2.6. Connection to others who have experienced psychedelics	12
C.2.7. Psychedelic treatment considered preferable to other treatments	20
C.2.8. Sense of well-being/meaning retained after symptoms return	14
C.2.9. Further psilocybin treatment obtained elsewhere	3

First, patients described depression as a state of disconnection (from self, others, and the world around them) that was (often profoundly) rectified by psychedelic treatment. Second, patients reported histories of avoiding painful thoughts, feelings, and memories and found that psychedelic treatment helped them confront, process, and accept these things. The third theme reflected their views of previous treatments (i.e., talking therapy and antidepressant medication) as compared with the psilocybin treatment they received in the trial. They described previous treatments as mirroring their sense of disconnection and tendency to avoid painful emotions, while the psychedelic treatment program worked in the opposite direction, to promote reconnection and acceptance.

Note. In what follows, we refer to “the dose” or “dosing session,” without differentiating between whether this was the high- or low-dose session. This is because patients did not often differentiate between these sessions. When probed about this, patients would typically report that they were referring to their high-dose session or that they could not quite remember which particular session they were referring to (because it had been 6 months).

A. Change Process I: Disconnection to Connection

A.1. Depression is Disconnection

A.1.1. *Trapped in the prison of the mind.* Patients spoke about their experience of depression as being “trapped in their minds.” Three referred to living in a “mental prison” (P8, P2, P16). P11 described a sense of being “enclosed in the most narrow confined space imaginable, it was like a sack over my head,” an image similar to P14’s description of a metal cage “locking him in”

from the shoulders up. Metaphors used to describe depression were aggressive and violent; patients reported feeling persecuted and besieged, retreating into ever smaller and darker corners of their mind. One patient reported his thoughts “attacking [him] from morning til night” (P4).

Other patients used metaphors of their minds feeling like computers that have been “switched off” (P11), “short circuited” (P2), or “shut down” (P16): “it felt like when a computer gets locked and you can’t do anything about it” (P1).

All patients described a process they referred to as “rumination,” whereby their thoughts would get “stuck” on a single track. For some, this “gridlock” (P15) of automatic single-tracked negative thoughts happened almost constantly:

I had this washing machine in my head going round and round, I didn’t even need to be there, it was an automatic process. (P2)

A. 1.2. *Disconnected from the senses.* Most patients described that their senses were shut down. The most commonly reported deterioration in sensing was a lack of response to music they used to enjoy. Patients variously described reductions in appetite, sense of touch, and visual perception:

Depression had worn down all sensation, and I had no sexual response. (P15)

I would look at orchids and intellectually understand that there was beauty, but not experience it. (P3)

One patient described living in a world that was “flat” and “gray” (*P14).

A. 1.3. *Disconnected from self.* One patient directly described feeling disconnected from their “self” (P7), and many others described that the things they used to enjoy had retreated far from their minds. Patients reported that their rumination “took up hours and hours of time” (P19), “robs you of confidence in yourself” (*P14), and “traps you, because you’re simply struggling to get by rather than thinking about things that you could do to improve your life” (*P18).

Patients described becoming a much diminished form of who they once were or who they might become (were they not depressed).

A. 1.4. *Disconnection from others.* A sense of disconnection from others was particularly distressing for all patients. For most, the response to the first interview question: “Can you describe your depression?” was contextualized in the social sphere; human contact was what they missed most.



I had less and less in common with my peers, I felt so alone. (P9)

I felt isolated. I was never part of any groups and I didn't really have any close friends. I couldn't relate to my peers. I was almost agoraphobic. I craved emotional company. (P11)

For some, the process of disconnection from others had gone so far that they no longer felt able to be touched:

I always put up resistance to being held, I used to be tactile before I was depressed, but then I didn't like being hugged, even by my mum. (P8)

A. 1.5. Disconnection from the world. In the broadest terms, patients reported feeling unable to engage with their environment. Many reported spending unusually long hours in bed:

I couldn't leave my bed for a year. (P15)

If I had a day off, like on the weekend, I wasn't happy to wake up. (P7)

A. 2. Psilocybin Treatment as Bringing Connection

A. 2.1. Mind is opened up/"rebooted"/the lights switching on. Regardless of the quality and valence of the drug experience, nearly all of the patients who showed a clinically significant response to the treatment described its most salient effect as a sudden dramatic change in the quality of their consciousness. Whereas depression had felt like a mental prison, they reported feeling a sense of mental freedom after the treatment. This feeling of expanded mental "space" was often exhilarating during the dose, and seemed to last for weeks to months after the treatment.

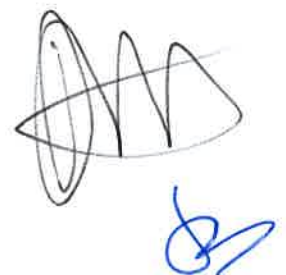
[During the dose] It was like a holiday away from the prison of my brain, I was a ball of energy bouncing around the planet, I felt free, carefree, re-energised. (P8)

[After the dose] It was like this great shroud had been lifted. (P1)

You're not immersed in thought patterns, the concrete coat had come off. (P4)

I felt spatial, not depressed. (P6)

A feeling of space and openness. (P17)



And where depression had been likened to a computer that had been locked and shut down, patients reported feeling “rebooted” or “reset” after the treatment:

The reset switch had been pressed so everything could run properly, thoughts could run more freely, all these networks could work again. It unlocked certain parts which were restricted before. (P1)

I felt my brain was rebooted, I had the mental agility to overcome problems. (P8)

It was like when you defrag the hard drive on your computer, I experienced blocks going into place, things being rearranged in my mind, I visualized as it was all put into order, a beautiful experience with these gold blocks going into black drawers that would illuminate and I thought: ‘My brain is bring defragged, how brilliant is that! (P11)

Many described the sense of mental clarity, sometimes likened to a light going on or a fog evaporating:

It flicked on a switch, clarity from the inside out. (P12)

It was like the light switch being turned on in a dark house. (*P16)

I had a clear mind, it lifted the fog of depression. I could see my life, like a light in the tunnel. (P7)

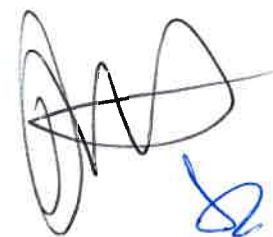
I was lucid and alert, the depression had evaporated. It puts your head above the fog. (*P14)

My mind felt sharper and clearer and less foggy. (P17)

The experience of mental spaciousness and clarity reminded one patient of a state he had reached during a long meditation retreat. Going back to this clear and open state made him realize that the heavy concrete mind-set that he felt trapped in during depression was not the “truth” and could be escaped from (P19).

Patients reported ruminating less for many weeks afterwards: “not stuck on thoughts—more in the moment now” (P15). Six months on, some reported ruminating much less:

It was a change of state, to be stuck in that place of rumination and to be able to move out. It reconfigures you somehow. (P2)



My mind works differently [now]. I ruminate much less, and my thoughts feel ordered, contextualized. Rumination was like thoughts out of context, out of time; now my thoughts feel like they make sense, with context and logical flow. (P11)

However, one patient for whom the treatment was effective overall mentioned that rumination was not improved:

If I start those [ruminative] thoughts, I get stuck, I think it was the same even when I came out of the dose. (P15)

A. 2.2. Connection to the senses. The dosing experiences, for the 17 patients who experienced a normal (i.e., “intense”) level of subjective drug effects, were rich in sensory phenomena. Four described seeing colored shapes toward the start of the dose; otherwise sensory experiences were unique to different patients but tended to be described as awe-inspiring and “four dimensional,” as if the senses were hyperalert.

Interestingly, patients described improvements in sensory capacities following dosing. Two patients whose depression affected their sensitivity to touch, reported dramatic improvements during the dose. P6 reported a hypersensitivity to textures that meant “everything felt like sandpaper,” but during the dose “all that went out the window [and] everything felt like it did when I was a kid, the blanket felt brilliant.” P15 had the opposite problem however; he was previously so undersensitive that he reported feeling no sensations in his body, and his experiences during the dose were “pure sensory, tactile, sexual bliss.” This connection to senses was long-lasting for P6 but not P15. However, both described the connection to sensation, even if short-lived, as a very significant and meaningful experience. Another participant found his sensation to be so heightened in the dose that he described it as a “mental orgasm, a state of pure bliss and ecstasy that went on for hours and hours” (*P18).

Some other sensory experiences during the session(s) were claimed to have led to a long-term improvement in sensing. Many patients described being able to enjoy listening to music again afterwards, and sight was sharpened. Some also specifically referred to an appreciation of the aesthetics of the natural world:

[After the dose] When I went outside, everything was very bright and colourful and it felt different. I noticed things I didn't notice usually, the leaves on the trees and the birds, small details. (P7)

A veil dropped from my eyes, things were suddenly clear, glowing, bright. I looked at plants and felt their beauty. I can still look at my orchids and experience that: that is the one thing that has really lasted. (P3)



Things look different even now. I would look over at the park and it would be so green, a type of green I'd never experienced before. Being among the trees was incredible, like experiencing them for the first time, so vibrant, so alive. (P12)

A. 2.3. Connection to self. One of the strongest themes was the connection to self, which happened in a number of different ways and at different times (e.g., during and after the treatment). Examples include the following: a boost of self-worth; restarting previous hobbies and reconnecting to “who they had been” before the depression developed; fresh perspectives; and engaging in new activities that reflected new values.

A. 2.3.1. Self-worth. Nearly half of the sample had realizations of being a “good person” (P3) and feelings of self-worth and self-compassion:

I realized how nurturing and protective I am. (P11)

I had an encounter with a being, with a strong feeling that that was myself, telling me it's alright, I don't need to be sorry for all the things I've done. I had an experience of tenderness towards myself. During that experience, there was a feeling of true compassion I had never felt before. (*P16)

Some felt more “confident, more resilient” (P5), “able to take on anything” (P1), and efficient: “My center of gravity is stronger, I'm gliding through life, getting things done, [being more] effective” (P2).

One patient was able to write and deliver a eulogy at a funeral, something he would not have considered previously, “I was willing to expose myself more” (P19).

A. 2.3.2. Reconnecting to past activities. All patients for whom the treatment was effective reported engaging in past activities like teaching classes (P2), and taking up old hobbies such as writing music (P1). One participant described flying on a plane again after avoiding this for a long time (P11), and another who had not seen his extended family for more than a decade was able to drive a long distance to visit them (*P16).

Four patients described themselves as “depression-free” for a while, in which time they reconnected to who they had been before depression had diminished their lives. Elsewhere, accounts of psychedelic experience have referred to a ‘rebirth’ process (Grof, 1980) and although none of the patients in the current study used that analogy, many of them described “connecting back to myself again” (P7).

At it's most basic, I feel like I used to before the depression. (P1)



A. 2.3.3. *Discovering new values/perspectives.* A sense of connecting to a new version of themselves was a very strong theme. Most patients reported having gained a fresh perspective on their lives.

I was thinking about relationships I had with other people and thinking I could see them clearly almost as if for the first time. I had fresh insight into things. It was almost as if suddenly the scales dropped from my eyes, I could see things as they really are. (*P18)

Sometimes these lessons were viewed as having come from an “outer teacher”:

This teacher student relationship came about, so although I knew it was going on in my head, it was as if there was somebody there giving me prompts, think about this or that, it could weave its way and drop you straight into an image. Direct revelations [occurred]. (*P14)

In two cases, patients reported experiencing apparently spontaneous “lessons” about eating plants instead of animals, and many had lessons that they were loved and perfect and did not need to feel lonely.

These voices were ancient, she was so eloquent. She kept calling me “my darling”: “Life is to be lived my darling.” She talked to me in such a loving way, all these things to say about my life. (P12)

As a result of these lessons, there were some major lifestyle changes; nearly half of the sample reported improvements to diet, exercise, and cutting down on drinking alcohol. One described the improvement to his diet that happened after the dose as “life-changing,” although he was not sure how these changes came about as he did not receive direct “lessons” about diet:

Before, I had stomach problems, food sensitivities. [During the dosing session] I had stomach pains, it (psilocybin) was going where it needed to go. After [the dosing session], I changed my mindset and then my diet, and my sensitivities have gone. I know what I need to eat now, my understanding of how food affects me is a new thing. (P6)

Another patient described how after the dose he instinctively stopped doing things that had caused him problems before, without receiving direct “lessons.” These changes seemed to materialize without conscious awareness, they were *felt* rather than thought about:

I lost a lot of weight just purely because I didn’t want to eat badly and that went on for some months. I couldn’t eat what I knew wasn’t good for me. And I



couldn't watch pornography after the second dose. I started feeling it was sullyng and not wholesome. I just didn't want to do that. (P19)

A. 2.3.4. *New activities.* A whole range of new activities were started after the treatment, ranging from going out more, getting new jobs, learning to drive, building a new kitchen, rock climbing, volunteering with refugees, attending acting classes, comedy classes, dance classes, and traveling.

Many described changing social circles to allow for the changes within themselves:

Friends that have been giving me a hard time, I've let go of, I've just backed away. I've made good new friends, that share my values. (P2)

I refuse to compromise any more, this enlightenment has made me a bit more focused on the blue sky; [to] go and swim in it, [to] do what you want to do; let her do that, let him do that, I'll do what I want to do! (P11)

A. 2.4. *Connection to others*

A. 2.4.1. *Connection to those who had abused and wronged them.* Some patients felt that they gained understanding about the circumstances of abuse that they reported having suffered in childhood. One participant, felt a sense of compassion toward his mother, who he said had inflicted unbearable suffering on him:

When I was being toilet trained my mother lost it with me and drowned me in my own human waste and throughout my life, I tend to replay that. [In the dosing session], I realised that my mother was out on an ledge, we were two people out on an ledge, she too was completely unconnected, disconnected. I felt some compassion for her . . . a different perspective, that it wasn't an all powerful world and universe against me, my mother too was out on a ledge. (P19)

A. 2.4.2. *Close family and friends.* Patients described strengthening bonds with loved ones (friends, children, parents, colleagues, and spouses) after the dose:

[My wife and I] went for dinner for the first time in 6 years: we were like a couple of teenagers. (*P16)

For many, there was a general sense of ease and well-being when socializing with friends in situations that might have previously caused anxiety and discomfort:

Now there's a greater sense of "we're all in the same boat"; less unease. (P19)

A. 2.4.3. *Strangers*. This sense of connection to people often extended to strangers such as shop assistants, people on trains and in the street:

I went past a bike shop and went in off the street and said “can I hang out and help out?” I went there for 6 months and helped renovate his shop. (P9)

I was talking to strangers. I had these full long conversations with everybody I came into contact with. (P1)

I would look at people on the street and think “how interesting we are”—I felt connected to them all. (P3)

A. 2.4.4. *All humanity*. Many patients described how the sense of connection seemed to spread wider, a “deep connection to everyone” (P4).

This connection, its just a lovely feeling . . . this sense of connectedness, we are all interconnected, it’s like a miracle! (P1)

A. 2.5. *Connection to the world*. Four patients described having powerful insights about the European refugee crisis during the dose, which was unexpected and uncharacteristic for them (P9, P12, P15, P4), and some others reported becoming more concerned about global issues in the months after their treatment:

I got a wider perspective, I stepped back. It helped me appreciate that the world is a big place that there’s a lot more going on than just the minor things that were going on in my head. (P17)

Some patients thought more about climate change, and many felt more connected to nature:

I felt like sunshine twinkling through leaves, I *was* nature. (P8)

Before I enjoyed nature, now I feel part of it. Before I was looking at it as a thing, like TV or a painting. You’re part of it, there’s no separation or distinction, you *are* it. (P1)

When describing their depression, the patients had not spontaneously referred to feeling disconnected from nature. It seems rather they had not realized that they were missing it/disconnected from it until reminded of its value during and after their experience with psilocybin.



A. 2.6. Connection to a spiritual principle. Some patients who did not previously identify themselves as spiritual reported having spiritual-like experiences under the psilocybin: “connecting to all other souls” (P15), “I wonder if this is how the pope feels!” (P4). One patient, who had described his depression as “psychological and spiritual lethargy,” reported becoming more “wholesome” and less “sullyng” in his habits after the dose (P19). He began to partake in “movement meditation” and silent retreats.

Two patients had experiences of feeling the presence of God:

Not God in some dogmatic way, a God-like archetype within your psyche, that is real and within you. I know this exists, I directly experienced it. I was suddenly taken in a rapture and I was floating in midair, with my eyes wide open and my mouth open, completely in a state of awe and ecstasy. It’s a very powerful message to take away. (*P18)

Then I felt the presence of God: I have always thought that he was a man because of the way I was raised, reading the bible, but it felt like a female energy. (P7)

Another patient described a female “ancient being” who, although not referred to as “God,” was omnipotent and unconditionally loving (P12).

Some saw religious imagery and/or iconography during the dose, such as temples (P4 and P2) and Hindu gods (P2, P3). At one point during the peak of the experience, P3 identified with a deity: “I was Shiva, dancing.”

For some patients, although a spiritual principle was not directly referred to, they described “love” as a powerful supernatural force (P11, P3, P8).

For some patients, the overall sense of expanding connection, was said to be so intensely felt during the dosing session that they struggled to put it into words. Their attempts at description 6 months later were often beautiful and poetic, and spoken passionately:

[During the dose] I was everybody, unity, one life with 6 billion faces, I was the one asking for love and giving love, I was swimming in the sea, and the sea was me. (P3)

Echoes of these unitive experiences often lasted for weeks or months:

Like google earth, I had zoomed out. [For weeks afterwards], I was absolutely connected to myself, to every living thing, to the universe. (P4)

B. Change Process 2: Avoidance to Acceptance

Patients described another change that took place. Most patients described depression as a state of being cut off from their emotions in one way or another, and the treatment helped them surrender feelings long suppressed.



B.1. Depression as Avoidance of Emotion

B. 1.1. Rumination narrows emotional repertoire. For some, before the dose, fixed negative thinking patterns left little space for processing emotions, as if their emotional repertoire had become constricted due to constant rumination. One patient referred to this as the “emotional erosion of rumination” (P15). Attempts to think their way out of their problems were said to have left them feeling stuck in their heads and unable to feel; described as a detached, numb state: “you miss so many things because you can’t feel them” (P7).

B. 1.2. Emotions avoided or repressed. For many, when stressful or painful things happened, emotions were avoided, distanced, suppressed, or disguised.

After a while of having overwhelming negative emotions it wears you down and you end up feeling nothing in the end. Dad [became seriously ill], I was so detached I wasn’t able to be with him. I was so numb; I wasn’t feeling emotions, I wasn’t really there. (P15)

Some of the male patients described how social norms around masculinity had restricted their emotional repertoires. One described how in adult life he “had always found it difficult to be emotional, found it uncomfortable to be around other people if they were emotional” and saw “emotions as weakness.” As a child, his parents had told him that “boys don’t cry,” and as he matured he had learned to “put his feelings in a box because you can’t be upset, you’re a man” (P17).

Some patients avoided emotions not so much because of cultural expectations, but more because they felt they did not have the inner resources to “face” or “accept” all the negative feelings that had been building up since childhood. The image of putting feelings into a box came up again.

A lot happened when I was younger, more than I could deal with. I put it all in a box. I used to sidestep things emotionally, push things away, but that doesn’t get rid of what you’ve avoided, what you’ve sidestepped is still there. (P4)

Patients had developed a range of strategies for keeping painful emotions at bay, including avoidance of talking about emotions:

If I was speaking about something traumatic that was happening, I would speak about it in the 3rd person, very detached. (P7)

And the use of food or substances to try and manage/suppress painful feelings:

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My whole life I've self-medicated to try to make emotions more bearable, sometimes with food, cigarettes, painkillers. I felt anger but it was not expressed. I might be in touch with resentment but not anger, because there is a fear of being overwhelmed by anger. (P5)

I would drink to alleviate the symptoms of depression, but the depression would return very severely if I drank a lot of alcohol. (P19)

In an attempt to manage their emotional state, many had tried to disguise particular emotions for other emotions. Patients reported covering up anger with sadness, or covering up sadness with anger. And this culminated in attempts to control particular emotions that they felt they could not express, leaving them either in constant battle with the negative thoughts (P14 and P10) or living inauthentically, "acting a role" (P1).

B. 1.3. Avoid trauma memories. Patients were particularly focused on battling with trauma memories. Most could pinpoint particular events in childhood which they felt played a causal role in the development of depression, and they had usually tried to avoid talking about these memories, because the emotions they could trigger were so powerful: overwhelming fear, shame, guilt, disgust.

Upsetting incidents and experiences would start flashing in my mind and I would desperately try to negate them by reading one of my favorite books, anything to distract from it. (P11)

It was more than just avoiding or denying [memories of abuse], it was "if I don't remember it, it never happened." (P16)

B. 2. Psilocybin Treatment Bringing Acceptance of Emotions. Some of the dosing sessions involved experiences of surrendering to trauma memories.

Letting go of resistance and facing pain was hard for people, but after these intense "cathartic" experiences, patients described a feeling of openness to experiencing emotions that was often long-lasting.

B. 2.1. Intensity of feeling during the dose. During the dosing sessions themselves, patients described feeling intense emotions: joy, fear, terror, "tragedy, humour and love" (P14). Strong feelings of compassion, love, and bliss were frequently described. For one patient (P15) who described himself as having felt "numb" to emotion and sensation for a number of years prior to the study, the high-dose session was experienced as "overwhelming bliss." The intensity was so strong that he became uncommunicative for approximately 2 hours:

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The blissful feeling got more intense, really overwhelming, the glow grew until I was just that feeling, I had become bliss. (P15)

More commonly, emotional experience was labile, with highs and lows, and periods of turbulence and calm: one patient described his experience as a “rollercoaster” (P1).

Incredibly funny and tears of joy, then crying because of the poignancy of the music. (P5)

The intensity of feeling was described as frightening at times:

The beauty and the sadness, I was terrified by the depth of emotions. (P7)

The hardest thing is to give in to what you’re experiencing, it’s as if you’re in a car heading for the edge of the cliff, and you have to try not to turn the steering wheel. (*P14)

B. 2.2. Surrendering to emotions during the dose. People described that during the dosing session, unlike in their daily lives, they just could not avoid or hide from negative emotion: It was too overwhelming. And they found that when they finally surrendered after years of trying to avoid or fight these feelings, the feelings would swell and then diminish:

There was a lot of sadness, really really deep sadness: the loss the grief, it was love and sadness together, and letting go, I could feel the grief and then let it go because holding onto it was hurting me, holding me back. It was a process of unblocking. (P2)

Excursions into grief, loneliness and rage, abandonment. Once I went into the anger it went ‘pouf’ and evaporated. I got the lesson that you need to go into the scary basement, once you get into it, there is no scary basement to go into [anymore]. (P3)

There was this huge terrifying creature with a rifle, and instead of running away, I looked at it, and it wasn’t as scary as it had seemed. [My] fear subsided, it suddenly seemed ridiculous, I started laughing. If I had avoided it, it would have got more terrifying. (P4)

Two patients who showed less marked improvements in symptoms posttreatment described not really being able to “let go” (P9 and P5), implying that “letting-go” may be a key factor in lasting responses.

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B. 2.3. Trauma memories from childhood confronted during the dose. It seemed that some of the most powerful experiences during dosing days were moments when past traumas were apparently revisited. Some reported seeing their abusers abusing them, or reliving traumas in infancy. Sometimes these memories came back in fragments—like sensory puzzle pieces that did not make sense until afterward:

I had lots of waves of different feelings [which made it hard to] describe what they were and how they related to my life, but after the experience, it felt like they were a puzzle, [and] when I started thinking about what it meant, it made sense, it was about that time in my life. (P7)

It was different, separate fragments of that experience that all came together, colours, sounds, smells, and afterwards when I was talking, I started to see how they were all connected, all aspects of that experience when I was younger, it became clear that was where the problems I've had all stemmed from. (*P16)

Some commented that the “memories” they revisited were not the ones they expected; some were anticipating a focus on recent challenges, problems in their adult life, and yet they were “taken back” to childhood.

Two patients described “going back to a memory I didn't realise was there” (P17). One reported seeing, from the perspective of himself as an infant, a pillow held over his face by a caregiver, and felt a deep fear of annihilation. Although this experience brought up many painful questions, the patient later felt that this putative “memory” helped him understand some things about himself (*P14).

Another reported:

[I] became myself at age 7, after my [grandparent] had died. I totally was back there, so vivid, so real, I had the emotions that I would have felt at the time: fearful, why did this happen, the naivety, the shock and confusion. I was getting overly upset and my parents were saying “boys don't cry.”

This helped him realize how his unhealthy emotional habits as an adult developed.

I saw that it's not [a] weakness to be emotional, that's an unhealthy attitude. (P17)

B. 2.4. Memories of love revisited during the drug experience. Drug experiences were often interspersed with memories of love as well as trauma, which provided much-needed relief and sustenance. Some examples of this



include revisiting being safe in the womb, playing as children, happy times as teenagers, being in places where they had felt secure, like playing with perfumes at a great Aunt's dressing table, being with loved ones before they died, performing heroic acts, and times when they felt proud of themselves. In all these experiences, patients reported feeling as if they really were there, rather than just recalling something.

About an apparent reliving of being at a great Aunt's house, one patient said: "I saw things about that house that I'd completely forgotten, I was right back there after all these years" (P12).

B. 2.5. Embodiment of emotions during the dose. Many patients had quite physical responses during the dosing session. The most common bodily reaction was powerful bouts of sobbing, which were displayed by 10 of the patients. Some said they had not cried for many years, either because they could not access and express grief, or because it felt too exposing to show such vulnerability. One described how he had learned through years of abuse in childhood to "hang on to my tears" as a way of defending himself. Whatever the reason, tears had been suppressed, and sobbing during the experience was described as a welcome, physical "purging" or "purification":

I had lost my ability to grieve and cry. [During the dosing session] I cried and that was a cathartic experience for me, a very welcoming sweet experience. (P19)

It was a relief, physical, I felt lighter afterwards. (P17)

I was weeping, tears were flowing out of me, it wasn't a painful crying, it was like turning on the taps, like a washing, a washing out. (*P18)

For many, the experience of surrendering to emotion was described as an embodied experience: "I didn't understand the emotions, it opened a box in my chest I didn't know was there" (P17).

Some also reported specific physical sensations, and they interpreted these as emotions that had manifested as somatic symptoms because they had not been expressed.

I felt an ulcer where I was holding onto grief. (P2)

During the dose, these physical sensations sometimes resolved. Some patients thought this happened because they had an opportunity to freely express and process emotions that had been suppressed.



The dose helped me realise why I felt the pain in my chest, I saw it visually and felt it emotionally, then I felt so much lighter, like something had been released. It was an emotional purging, the weight and anxiety and depression had been lifted. (P11)

There was an implication, because of the challenge of this, I had gone through something. I had been shaking and then after, I accepted it, it was like my body just relaxed. (P16)

My migraines stopped for a few months, I think I had them because I worried so much. (P7)

B. 2.6. After the dosing session: emotional repertoire expanded, more open to emotions. One of the most prevalent themes regarding posttreatment change was a long-lasting openness to emotional experience. Patients reported that this openness lasted even after the symptoms of depression came back.

I took away from the experience that I used to get angry about having anxiety, now I think I can have the anxiety, I can just feel it and it will go, I don't have to have the fear or run away. (P2)

I saw negative patterns in my life where if something bad happens, I used to just put it [to the back of my mind]. Afterwards, I allowed myself to experience everything - even if it is sadness. Now I know how to deal with my feelings rather than repress them. (P7)

I have felt a sense of acceptance; more acceptance of agony, boredom, loneliness, and also appreciation of the wonderful times. [A] willingness to try to accept the negative times. (P5)

Some patients reported that their partners had noticed that they were more able to connect emotionally:

My relationship with my girlfriend has improved, now I'm more able to open up and chat, more able to express myself. (P17)

Alongside this "openness," some other personality changes were reported: For example, being less impulsive, having fewer arguments with other people, and responding to difficult situations with a new sense of calm, patience, and responsibility:

It helped me take responsibility for my emotions. I feel like before [the treatment] I would hide, now I'm not hiding. . . . I am responsible for how I



react when the same thing happens again. Knowing that it's not my fault helped me respond differently. The way people respond to me now is very different to a year ago. (P8)

This process of going from avoidance to acceptance of emotion was described metaphorically by *P18:

Depression is like when you have a dead leg and the psilocybin made the bloodflow start to come back.

C. Comparison of Psychedelic Treatment to Previous Treatments

The patients in this trial were by definition “resistant to treatment,” so it was not surprising that they did not have very positive views of talking therapy and antidepressant medication they had tried. However, there was a certain consistency in the nature of the criticisms.

Only three patients had positive experiences of talking therapy: two cases of psychodynamic psychotherapy and one case of CBT. The effects of this CBT were described by the recipient as “not long-lasting, it only helped while I was seeing the therapist” (*P14). Only psychodynamic therapy was described as having provided long-lasting benefits, and both cases were privately funded. Interestingly, one of these patients described that during Jungian analysis he had a dream that was very similar to his experience of psilocybin.

In analysis, I had a dream where I saw a guitar playing itself . . . you're in the presence of the Divine, in wholeness connecting, it left me with a warm feeling inside which lasted for several days, a feeling of wellbeing and warmth inside me. I went through a good phase after that. (*P18)

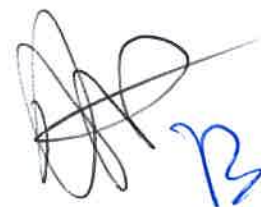
C.1. Traditional Treatments for Depression Reinforce Disconnection and Avoidance

C. 1.1. Talking therapy: Difficult to access substantial treatment. Many patients described having difficulty accessing talking therapy. They were often prescribed antidepressants, but struggled to access psychotherapy:

It was “here's some tablets now go away.” (P1)

Patients reported that sometimes therapy was promised but not delivered and sometimes it was withheld for no clear reason:

I have been trying to get talking therapy since January 2014, still nothing. I'm making a complaint as a last resort to get some help. (P15)

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It was that NHS thing of offering talking therapy but it never actually happens. (P10)

They told me to speak to MIND. I made an appointment with this girl of about 25, she said "Hi I'm an assessor, we can offer 12 weeks of CBT, I'm going to ask you some questions, it will last 45 minutes." After 5 minutes she stopped and said "I don't think our services will be able to help you." She didn't say why. (P9)

Services were seen as incompetent, with poor communication between different teams, and to patients:

The mental health team was quite dismissive—I wasn't a strong enough case, go away, we only deal with proper patients. (P1)

This department don't talk to that department, the waiting lists are so long, they don't call when they say they will. (P4)

For some who did access talking therapy, it was very short term:

I got nothing out of it. I had 4 or 5 different people for a few sessions each. (P12)

I tried so many talking therapies, nothing made a difference, they are all so short you never get anywhere, just as you settle in you have to stop. (P6)

Many found themselves bouncing from one short-term intervention to the next, and felt strongly about the damaging effect of having to tell their story over and over again to different people.

I'm sick to the back teeth of telling people again and again the backstory. All the talking therapies, each time you go for an 8 or 6 week course of that stuff, you spend the first few weeks going over the stuff, they ask all the questions again then its session 4, and then, you think who's learning something here, 'cos I'm not. You are! (P13)

The problem, the pattern is NHS offering a certain period of time, I have a whole history of short-term stuff and endings. It just becomes a sense of being a failure. Most therapists aren't trained enough in how to not to make you feel like that, it left me with a feeling of somehow I've failed. Short-term therapy is awful, you leave the most difficult things right to the end, then that awful feeling on a last session. (P5)



C. 1.2. Some therapists are unwilling/unable to address traumatic experiences. Some patients talked about how it takes a while to build up therapeutic rapport that you can only get so far in a short series of 1-hour sessions. The short-term nature of therapy meant that some patients never had a chance to reveal information about their past that they felt was important or difficult to tell.

It was not necessarily treatment brevity that prevented patients from receiving appropriate support to explore their trauma histories. Anecdotes about poor clinical practice were described with alarming frequency.

Two patients who had bravely disclosed childhood abuse described feeling desolate after a health professional responded inappropriately (P16, P4). "I got up the courage to tell him, I'd never told anyone. And he just looked at his shoes" (*P16).

Sometimes, patients felt that therapists were unable to contain and explore their distress, and thus exacerbated it:

[In private long-term CBT] The counselor kept saying don't talk about your abuse yet, wait 'til later. It was just delaying tactics to prolong the therapy to get more money, it made me feel awful. (P4)

There was a young chap, sat there stroking his beard, [who] just said "I can tell you, in my experience, it will get better." You can't tell people that! There are people for whom it hasn't got better! You can't tell me, with your miniscule experience, *that*, in *that* tone! (P5)

It should be noted that for some patients, therapy had taken place many years previously: Therefore, current clinical practice standards may not have been in place. Also, attentional biases that are a common feature of depression could have increased the saliency of memories of the more negative aspects of therapy.

C. 1.3. Structured treatments can prevent a therapeutic relationship developing. Most of the talking therapies described were CBT and they were mainly reported to have been unhelpful, as the patients felt that they were rigid and prescriptive:

The lady there was "It's my way or the highway, you've got to listen, you've got to do this, you've got to do that." (P1)

Overall, it seemed to be the directive nature of therapies received that was the most frustrating and upsetting for patients:

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I once lost my temper in a group therapy session, this woman saying “you’ve got to own your illness”. What does that mean? “You’ve got to!” That’s not the kind of help I need. Another clinical psychologist, lecturing me, “you’ve got to face up to the fact that . . .” (P11)

Goal setting was discussed by many as an example of directive therapy seeming condescending:

Going, talking, setting goals. I was like, if I can’t accomplish this on my own, putting it on paper and them saying go do it, I mean you’re telling me to go do something I already know I need to do. They try and motivate you but it doesn’t work if the motivation is coming from your therapist, it has to come from inside. (P12)

I found CBT really simplistic, condescending, “oh you’re feeling a little bit sad, buy yourself some flowers to cheer yourself up.” (P10)

Goal setting exercises, if delivered in an unhelpful way, could also exacerbate a sense of guilt and low self-esteem.

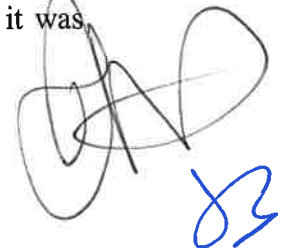
Maybe there are therapies out there that would work better than the ones I’ve had, but I’ve had quite a few. They all seemed to be trying to fit a person into a preconceived set of patterns: “try to do this,” “make this your goal, and we’ll measure it.” But just having these goals set for you is more pressure and when you don’t meet those goals, you feel even worse because you’re letting them down, and you already feel let down yourself! (P1)

C. 1.4. Therapy seen as exacerbating depression. As above, goals-based talking therapies were said by some to have exacerbated their depression. For three patients, community mental health team services were described as so disappointing that ongoing struggles to receive adequate care worsened their stress levels their and sense of despair (P9, P15, P4).

I went to see the local mental health team, these people are frauds, so useless. They get their money and they do not give a shit. (P9)

In one case, a course of psychodynamic therapy was described as exacerbating depression, despite a competent therapist and good rapport: weekly analysis of problems did not lead to any relief or change:

I felt like I was being squeezed in a vice by the therapy, it was incredibly painful, that’s why I stopped, I just couldn’t cope, it was too much, it was making my depression worse. (*P18)

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C. 1.5. *Antidepressants: Avoidance of the underlying issues.* Most of the patients described how antidepressants were the first line of treatment suggested by the general practitioner, and for some, the only treatment available. All patients had tried a range of antidepressant medication. Some reported temporary benefits: medications were described as dampening some symptoms of depression and anxiety. During crises, this emotional blunting could be very valuable: “the citalopram kept me afloat” (P4). However, even for the few patients who reported being helped by antidepressants, taking tablets to suppress pain was seen as avoidance of the real issues that were driving their depression:

It did help. It cut the bottom off the peaks and troughs which helped me cope. It didn't solve anything, but it helped me manage in the day to day. Some people might argue that's all you'd want but it wasn't really dealing with the issue underlying the problem. (P4)

Medications just suppress, it never feels like it's making a change. (P5)

It's like taking a painkiller for a toothache, you don't get to the source of the problem. (P1)

And one patient pointed out how taking antidepressants, while significant life problems went unaddressed, made him feel even worse about himself:

I remember occasions when I met my ex. I felt so bad after, I felt at my most desperate because I thought “well I'm on these antidepressants now and I still feel this bad so what do I do?” (P4)

Generally, antidepressants were seen as a short term rather than long-term solution.

C. 1.6. *Antidepressants as debilitating.* The other problem reported by those patients who considered antidepressants to have had some benefits was that they were only effective while taking them. This encouraged dependency:

I get depressed, I go on the pills, they eventually work partially, then I try to come off them. I'm ok for 6 months, then it comes back, that's been the pattern. (*P18)

Many patients described negative reactions to antidepressants. Three referred to antidepressants as making them feel like a “zombie” (P9, P1, P6).

It stopped all thoughts, I was a zombie, I felt a bit like a machine. (P1)



For some, the side effects were debilitating, weight gain, excessive sedation and sleep, and suicidal ideation were all reported.

I tried it must be 15 [different medications] over the years, many caused weight gain, which I've never gotten off, and all of them made me sleep all the time. (P12)

I was sedated, I didn't care about anything. (P8)

It was absurd, antidepressants were pretty much forced on me and they made me feel awful and suicidal. (P11)

Many patients reported that coming off medications led to severe withdrawal symptoms:

When I went off them, I felt I had electric shocks going off in my brain. (P8)

It's horrible to come off, and if I forget to take one pill I can't sleep, and I have to change the bedsheets, It's one of the worst things I ever experienced. (P20)

They were a horror to come off, I would not go back on them unless things were seriously bad. (P14)

At the time of the 6-month follow-up, some of the patients had indeed gone back on to these medications to manage the return of symptoms of depression. They typically said that this was because antidepressants were the only option available.

C.2. Psychedelic Treatment Enhances Connection and Acceptance of Emotion

C. 2.1. Given the time and space to talk about the hard things. Many patients referred to the length of preparation, dosing, and integration sessions as being a refreshing change. Rather than standard hour sessions with a therapist, they were seen for sessions ranging from 90 minutes (prep sessions) to 8 hours (dosing sessions). This allowed them to settle in to the sessions, knowing that they had as much time as they needed to bring up issues that were hard to talk about.

All the treatments I'd had previously were very dismissive, rushed, and when I went there (the study) it felt like I was being given the time to express how I felt. (P1)

Two patients mentioned talking to their guides about things they had never been able to say to a therapist before:



The guides were so sweet. I talked about stuff I don't usually say to people.
(P10)

Patients reported that the preparation helped them feel safe to cry during the dosing session. However, although prep and dosing sessions were felt to be sufficient, three patients would have like more therapy sessions afterwards. Two who did not have strong support from family or friends described feeling vulnerable and alienated afterward:

There should be more sessions with the therapist afterwards. I needed support to incorporate it into my life, maybe just for a few weeks. I couldn't go to a therapist that doesn't know about the research, I might feel stupid telling them "I had a drug and had some insights." (P7)

One patient (P14) whose session included what seemed to him to be a re-experiencing of a repressed memory of an attempted suffocation in infancy said that he would have benefitted from additional "integration" sessions with an expert. Despite integration work at one week posttreatment, he reported still feeling unsure about what his experience meant.

Ok it could be just symbolic, but it was cruel. It feels like there is something there that wasn't there before, and I'm still finding it hard to come to terms with. But it explained why I've felt the way I've felt as an adult and that is something talking therapy has never done. (*P14)

C. 2.2. Preparation sessions: Anticipating turbulence. Patients described how they had been prepared for difficult experiences, and given reassurance that this would not harm them, and could lead to good treatment outcomes. They described how this enabled them to look their demons in the eye. This was seen as crucial, as otherwise they might have thought they were having a "bad trip" and panicked, rather than being able to engage with whatever arose for them.

However, although patients had been told about the possibility of psychological turbulence during dosing, some of them had a very difficult time withdrawing from their antidepressants in the lead up to the study, which they felt inadequately prepared for.

This focus on the challenging aspects of psychedelic treatment during the preparation sessions, and accessing information on the web about challenging trips meant that seven people reported high anxiety going into the dose. This did not seem to affect outcome or treatment effectiveness. Some who expected to have a difficult time found their drug experiences to be very pleasant and vice versa.

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Before the high dose, I was quite scared. I had read a lot of things about “ego death.” I almost accepted I was going to die in a way, it was that scary. I felt I was being brave, I had no idea about what was going to happen to me, if I would come out in one piece, where it would take me, how terrifying it would be. I’d read some terrifying experiences, and you are just jumping off. But in fact it was gentle, powerful and benign. (*P18)

The patient who was perhaps the most skeptical about the treatment found it to be very effective and found his worldview very much changed:

To be honest, I didn’t think it was going to work because I didn’t have a good response to medications in the past, therapy had kind of disappointed me. (P4)

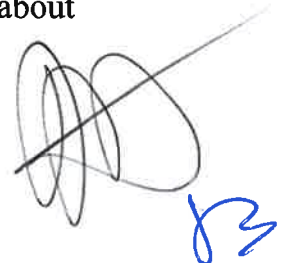
Many people described how the hospital setting made them feel that no matter what happened they would be safe. However, two patients did not like the setting. For P9, it was too clinical and cold, and he said he would have preferred a holistic treatment center with a more artistic and informal feel. For P5, the hospital setting felt uncomfortable and lonely in the postdose state.

That feeling at 5 p.m., alone in a hospital with a hospital dinner, someone watching TV which I don’t want on, it’s all a bit of a downer. (P5)

C. 2.3. The music enables surrender to and acceptance of painful emotions. Most patients considered the music playlist an integral part of the treatment and commented on how their experience was guided by the music. Sometimes, the particular genre of a track could trigger specific images, for example, a tribal drum beat could lead to visions of Bedouins in the desert. Most commonly, the music seemed to facilitate change process two (avoidance of emotion to acceptance) very powerfully. The emotional tone of the music could lead to a surge of the same emotion, which could lead to memories of childhood when that emotion had been present. Music also seemed to provoke emotions that had been long repressed. Many people referred to some of the darker pieces of music as directing the inner journey toward places of pain and despair:

There was this point in the music, Gorecki, it was as though suddenly everything went quiet and there was just this bell, like a church bell ringing, chiming, and suddenly the atmosphere got very spooky. (*P18)

The darkness of some of the pieces of music was sometimes felt to be unbearable and a few patients reflected that they would have wanted to remove the Gorecki track if they were to do the study again (this piece of music is about

A handwritten scribble consisting of several overlapping loops and lines, with a blue signature or initials 'JB' written below it.

a young Jewish woman being prepared for death; it evokes deep sorrow). This brings up an important question about how directive sessions should be. Most patients were happy to accept all elements of the session, but a few wanted freedom to change the music, and one wanted much more freedom generally:

They wanted me to stay lying down, to keep the blindfold on and headphones in with music they chose. I hoped for having my eyes open, seeing things around me, talking. I wanted to do things under the effect of the drug, they were not keen on that. They wanted me to listen to their music, but it was quite sickening and nauseating . . . —but they wouldn't change the music so that was annoying. (P15)

C. 2.4. Connection to guides. Patients described good rapport with their guides and felt well looked after. After the dose, many reported feeling bonded to their guides, saying they had been through something substantial together. Rapport helped build trust that they were in safe hands and gave them a sense of an equal relationship rather than a traditional “doctor vs. patient” dyad.

Patients valued the integration sessions after dosing, which helped them weave a story of what happened. Guides were able to support the patients in this process. Overall, support from skilled guides was seen as a key part of the intervention. Some patients commented that although they wanted further psychedelic treatment, they would not take psilocybin in any context other than a research trial because they would not expose themselves to such vulnerable states of mind without experienced clinicians supporting them.

There were two reports of negative interactions with guides. The first was P15 who wanted more freedom (see above). And one other who seemed to have had problematic transference:

I felt that Dr. A, I dunno, honestly there was a part of me, I didn't feel he was sincere or caring. . . . I think I told Dr. A this, a part of me imprinted onto him. I had this horrible stepfather growing up, I imprinted that on to him. (P9)

Both patients still reported positive treatment outcomes, although P15 did not come back the next day for the scan. His experience of the dose was very intense, and although he described it as “sexual bliss,” it was quite overwhelming for him.

C. 2.5. Connection to inner therapist. Many referred to a new capacity for psychological self-reflection. This was very strong after the dose but was often still present after 6 months:



It's almost as if when you take the capsules It's like taking onboard your own psychotherapist. (*P14)

Interestingly, guides were rarely referred to in much detail as patients recounted their experiences; during interviews, they recalled more vividly the things they had realized for themselves during the dosing session than the things their guides had said to them.

Whereas patients had often found their previous therapists condescending, proffering advice that felt irrelevant or inaccessible, or trying to motivate them from the "outside," the psilocybin helped people access an "inner voice," which they said felt immensely powerful and highly motivating. Some said that the "inner voice" had now faded, but the memory of empowered self-reflection and capacity for change brought them hope that they might access such states again.

C. 2.6. Connections to others who have experienced psychedelics. Some patients commented how the 6-month follow-up interview (on which the present analysis is based) helped them reconnect to how they had felt during their dosing days, and thought that follow-up talk sessions with others involved in the study months or even years afterwards could help maximize the benefits.

The memory of the experience of unity has become something I can only intellectually appreciate, but as we are talking about it, I can actually connect with it emotionally, I've been able to revisit that experience which is interesting because I wouldn't have expected that. All of the emotion [cries]: in an emotional sense, it's like being back there for a moment or two. (P3)

C. 2.7. Psychedelic treatment considered preferable to other treatments. For those whose symptoms of depression had returned, or for whom it had not worked, the radically different nature of this treatment approach was still seen as refreshing and offering hope. All 20 patients said that they would like to experience the psychedelic treatment at Imperial again, and some suggested that in order to maintain benefits, they would probably require at least one "booster dose" (i.e., a repeat dosing session). Two said they would have wanted a booster dose after 1 month but on average, 3 months was seen as the ideal time for this. Three patients felt that they did not yet require a top-up, although they did not rule it out for the future.

All patients for whom the treatment was effective said that they considered psilocybin to be a more promising model than other treatments they had tried. The three patients who identified as "depression free" at the follow-up were unequivocal in their enthusiasm:

A handwritten signature in black ink, consisting of a large, stylized 'A' or 'O' shape with a horizontal line through it, followed by the number '82' in blue ink.

No comparison. It works, whereas the other stuff doesn't. (P1)

There is no comparison. There is the Nissan Micra and the Range Rover. (P2)

My previous treatments, talking therapy and meds, were next to useless, utterly useless. My experience of psilocybin has been very positive. I believe there is an unknown physiological and neurochemical change in me, I am absolutely convinced of that. (P11)

A further four patients were formally in remission although some symptoms of depression had returned, and 10 patients who described psilocybin as reducing symptoms of depression for a number of weeks or months were depressed again at the time of the follow-up interview. These patients, although disappointed by the return of symptoms, did maintain that the psilocybin treatment had been a positive experience for them and still considered it the most effective treatment they had tried to date.

C. 2.8. Sense of well-being/meaning retained after symptoms return. Focusing on patients' experiences of depression returning, for many, this process was gradual, for example, after a few months, they noticed old behaviors returning:

I felt a reluctance to go and see people, the feelings and behaviours just came back, subtle at first and then slowly built back up. (*P16)

The way I was able to communicate and write (after dose): it's gone again. (*P18)

For some, depression came back and then went again:

I was really good for 6 weeks, 2 months, and then the depression started to come back, I recognised the symptoms and so I started taking meds but it still got me quite bad. But now fortunately, I'm back on the sunny side of the street again. (P19)

For one patient, P14 who experienced the apparent re-living of a suffocation, the depression seemed to dissipate for a few months and was then replaced by anger:

I'm still off the meds. . . . So the depression is not there, I'm not back in the void. I felt really good for a few months but now it has been replaced by anger and irritability. (P14)

Handwritten signature and initials in blue ink, consisting of a large, stylized 'W' and the number '83' below it.

One patient who had felt extremely low without reprieve or change for the past 5 years described that after the dose, he was shifting in and out of remission. He also described how his perception of treatment effectiveness would alter in line with these shifts:

It's a feeling that I'm not depressed and I don't have this depression and problems, I feel free of them, and then I think "hang on, have I ever been depressed?" and then I think maybe this trial helped me feel that way. But when it comes back, and at the moment, I'm depressed again. It feels like it's always been there, it never left and will always be there. (P15)

For many of the patients, depression symptoms had returned, but not back to baseline, and alongside the depression they also felt an improved a sense of well-being, meaning, purpose, and hope.

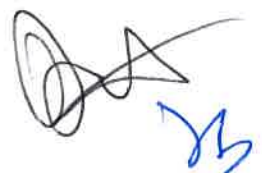
Now nothing is the same as it was before, things have gone downhill but not back, they've not gone back to what they were like; things are different, I am not the same, and that's hard to explain. My mood has dropped and my depression has come back and it's not very pleasant, but I feel this hope. A faith that nature will provide the treatments we need, it's all there, it grows in the ground. (*P16)

I noticed when I started to feel nervous around other people again, it was gradual, that connection and lack of worry and anxiety about interacting with others gradually faded away and the replays started happening again, but there was no moment where I lost sight of everything or went back to my default pattern, It's been gradual. And while I was in a much better place in the 3-4 months after the trial, I can't forget what I've experienced. While things may be 90% back to my old self, (well except I believe my real self is what I experienced there and in the months after)—yeah, I've still got the residue of that experience, so it still helps to an extent. (P4)

C. 2.9. Further psilocybin treatment obtained elsewhere. Some patients experiencing relapse reported wishing to seek psychedelic therapy elsewhere, something the trial team felt we could not condone, even if the therapy was legal (e.g., in another country). In at least three cases, this course of action had been enacted (at 4, 5, and 8 months posttreatment). Two patients reported having benefited, while another reported a less positive response, including feelings of guilt. It was not clear what dose had been taken, although all patients reported taking psilocybe mushrooms and feeling some acute subjective effects.

Discussion

A qualitative, thematic analysis performed on 6-month follow-up interview data in a recently completed clinical trial of psilocybin for TRD generated



two major themes relating to how the treatment had been effective. Specifically, patients described the treatment as having driven a change from disconnection to connection, and from emotional avoidance to acceptance. Additionally, patients described previous treatments as being reinforcing of disconnection and avoidance, and so the psilocybin treatment was seen as a welcome and valuable alternative.

As will be detailed in a forthcoming formal study report (Carhart-Harris, 2017) average treatment effects were exceptionally large for the first 5 weeks and then dropped to levels associated with more conventional treatments at 3 and 6 months. Most patients still reported feeling some discernable benefits after 6 months, however, and all reported preferring psilocybin to conventional treatments they had previously tried and expressed an interest in further psilocybin therapy. None reported classic craving behavior in relation to psilocybin, consistent with evidence that psilocybin carries no recognizable addiction potential (Bogenschutz et al., 2015). There were also no reports of enduring psychoses, persisting “hallucinations,” or phenomena consistent with hallucinogen persisting perceptual disorder.

Regarding the first change process, whereas the experience of depression was described as a sense of the world getting smaller until patients felt like they lived inside their minds, the psilocybin treatment was described as providing an experience of *expansion*: the mind “rebooted,” they were able to connect to their senses, others, and the outside world again. Such a rebooting process was often described as a “normalization” back to how they had been before the depression, rather than a hypomanic-like response.

Alongside this expansion outward, an “inner” expansion also seemed to have taken place: During dosing sessions, patients were able to accept rather than avoid painful feelings and memories, and reported a range of intense emotions. For many, a sense of openness to emotion persisted for months afterward, including long-term improvements in willingness to accept difficult memories and painful feelings, and also the capacity to feel compassion, love, and appreciation. This is consistent with previous findings of sustained increases in trait Openness in healthy volunteers after high dose psilocybin sessions (MacLean, Johnson, & Griffiths, 2011). The notion of an expanded “emotional repertoire” seems consistent with the length and descriptiveness of patients’ accounts of their experiences. The 17 who reported feeling significant drug effects during the dosing sessions gave far richer accounts of both their depression and psychedelic treatment than the three patients who did not have appreciable drug experiences.

Mechanistically, the above described “expansion” resonates with insights gleaned from recent neuroimaging and pharmacological studies of psychedelics. Psychedelics are known to stimulate serotonin receptors in the brain (the 2A subtype) that mediate flexible thinking (Boulougouris, Glennon, &



Robbins, 2008; Carhart-Harris, Kaelen, et al., 2016; Kuypers et al., 2016). Moreover, acute brain imaging has suggested that the brain enters a hyperplastic state under psychedelics that may facilitate learning and change (Carhart-Harris et al., 2012; Carhart-Harris, Kaelen, et al., 2016; Carhart-Harris, Muthukumaraswamy, et al., 2016). Such a process can be likened to annealing in metallurgy, where a metal is heated in order to make it malleable. In this case, the metal is analogous to the mind and brain and the heat is the excitatory action of the psychedelic. In line with this analogy, future research is required to investigate how crucial psychological priming and environmental factors are in determining the short- and long-term effects of psychedelics. From the reports provided here, one suspects that drug \times environment interactions are essential determiners of the quality of responses.

The processes of connection and acceptance have parallels to ideas from depth psychology: for example, Jungian notions of the collective unconscious, symbolism, archetypes and the shadow, and Freudian themes of the unconscious, dreamwork, abreaction, and catharsis. Maslow's notions of self-actualization, and the assimilation of problematic experiences model (Stiles et al., 1990) are also relevant.

Initiatives to systematically examine the relative merits of different therapeutic approaches and environmental components (e.g., music) are currently being considered, and this work should ideally lead to a standardization of the therapeutic approach for psychedelic therapy. This process should help address present ambiguities about what psychedelic "psychotherapy" actually entails (see Fadiman, 2011; Goldsmith, 2011; Grof, 1980; Masters & Houston, 1966; Meckel Fisher, 2015, Richards, 2015; Stolaroff, 2004, for a variety of approaches) and what components are essential (or not) for maximizing positive therapeutic outcomes.

Acceptance and commitment therapy (ACT) is an approach that may be particularly complementary to the specific character of the psychedelic experience. ACT aims to improve "psychological flexibility" via six key processes, all of which resonate with the themes generated by patients in this study, that is, willingness to experience painful emotions, "defragging" rigid thought patterns, exploration/observation of experience, contact with the present moment, focusing on values, and committing to actions in the service of those values. There is a growing evidence base to suggest that ACT has long-term benefits for patients with depression (Forman, Herbert, Moitra, Yeomans, & Geller, 2007; Forman, Shaw, Goetter, Herbert, & Park, 2012). What ACT and depth psychology have in common is the focus on exploration, acceptance, and integration of painful experience and difficult emotions, rather than attempting to change those emotional states. Future research may be carried out to assess the possibility of using ACT in conjunction with



psychedelics. Group therapy may also be complementary to psychedelics, as it aims to facilitate reconnection (Yalom & Leszcz, 2005).

Patients in this study reported feeling disenchanting with traditional treatments for depression. Antidepressants and poorly delivered short-term talking therapies were seen as repeating and reinforcing the disconnection and emotional avoidance that they knew was a fundamental feature of their depression. For some, these treatments are seen as promoting a view of psychological pain as something that should be systematically suppressed, rather than explored as a symptom of an underlying problem that needs to be accessed and processed. Granted CBT and antidepressants have solid evidence bases of safety and efficacy (Pilling, Anderson, Goldberg, Meader, & Taylor, 2009); however, the patients in the current study appeared to value the opportunity the present treatment afforded them to access their emotional pain. This was described as cathartic for many, bringing tears of relief, and reports of feeling lighter and more open afterwards.

The novelty and potential antithetical nature of psychedelic therapy in relation to conventional talking and pharmacological therapies could be seen as a major positive, since it suggests that patients and clinicians may be granted a broader palette of treatment options in the future, affording them an opportunity to select a treatment that best suits the specific needs and/or desires of a given patient. Also, rather than viewing psychedelic treatment as competitive with conventional treatments, future studies may wish to examine the possibility of using psychedelic therapy as a possible catalyst of and/or supplement to these conventional treatments. For example, a psychedelic experience could be introduced at a strategic point within a standard 12-week course of CBT, with the intention of improving insight and motivation. A similar design was piloted in a recent psilocybin for tobacco addiction trial, with considerable success (Johnson et al., 2016).

Focusing on limitations of psychedelic treatment, an alternative explanation for the replicable benefits reported by patients here is that the level of care and attention from the research team was exceptional, especially in relation to previous treatments they had received. This level of care will likely have enhanced transference relationships and the (perhaps implicit) desire of the patients to get well for their therapists. Expectation is known to play a role in determining treatment outcomes (Greenberg, Constantino, & Bruce, 2006; Visla, Constantino, Newkirk, Ogrodniczuk, & Söchting, 2016; Wampold, 2015; Wampold et al., 2005) and it is likely that many of the patients in this trial had positive expectations and/or experienced a positive modulation of their expectations in response to their intense drug experience(s) and the positive attention they received from their therapists. The researchers' implicit positive regard toward the treatment may also have



biased outcomes and patients may have easily gleaned the study demand characteristics and felt an implicit desire to confirm them. All these factors can and will be better controlled and tested in future studies assessing the efficacy of psychedelic therapy.

Regarding other biases, it is likely that there was a (self)-selection bias, that is, that patients sought out this trial because they were “believers” wanting to demonstrate that it could and would be effective for them. Moreover, since all of the patients had treatment-resistant depression, it is not surprising they held negative views about their previous unsuccessful treatments and were thus inclined to see a novel, unconventional intervention such as psilocybin, in a positive light. This probably does not account for how marked and enduring the positive outcomes were for many of the patients and how specific and consistent their criticisms were about past failed treatments. Nevertheless, the issue of selection bias must be better addressed in future trials, for example, by recruiting more patients through external referral mechanisms rather than self-referral, and measuring expectations at baseline and calculating their explanatory power.

The present article focuses on positive outcomes. However, this positive “bias” is a product of the data. The two positive change themes were the dominant themes expressed by the patients (see Table 1). Enquiries were made about negative outcomes of the treatment but comparatively little was offered in this respect. Previous qualitative analyses of patient-reported experiences of psychedelic treatment have found similarly positive regard for these interventions (Gasser et al., 2015; Belser et al., 2017). In the current study, a very small number of patients criticized some aspect of the way the therapists delivered the treatment (i.e., one did not warm to a specific guide and three wanted more therapeutic support posttreatment) but there was nothing substantial relating to the intervention itself. There were no serious adverse events reported during the dosing sessions or their aftermath.

Regarding specific cases, Patient 14 reported an apparent “reliving” of a childhood trauma. The therapy team felt it unwise to offer a judgment on whether this was a real memory or fantasy, however, and instead chose to treat it as psychologically interesting and worthy of discussion regardless of its veridicality. This ambiguity was initially uncomfortable for the patient, however, who hoped for an “expert answer” about whether what he had “seen” was true. This desire for closure subsided in time, however, as the patient talked through the incident with the study team. Another patient (P15) had a particularly intense high-dose session, becoming uncommunicative for a prolonged period (i.e., 2-3 hours) during the peak drug effects. The patient’s vital signs remained normal throughout, however, barely



whenever you like. If you feel upset at any point we can stop. Do you have any questions before we start?"

1. Think back to yourself before you heard about the study—Can you briefly describe what your experience of depression was like?
2. How did you hear about the study and what made you decide to take part?
3. What was it like for you coming to Imperial for the first few meetings—the screening, and then the prep session? What were they like for you?
4. What happened during the session when you were given the first dose—the low dose?
Probe: Both positive and negative experiences.
Probe: Interactions with guides—how did it feel [also ask about afterward]
5. The second dose—the high dose—what happened?
Probe: Both positive and negative experiences.
Probe: Interactions with guides
6. How did you feel in the first week after the high dose? What about the next few weeks? Did you notice any changes in yourself?
Probe: Both positive and negative experiences
7. What about later on? How have you felt over the past 6 (or however many) months after the session?
Probe: both positive and negative experiences
8. Has the psilocybin had any effect, positive or negative, on your depression? Thinking about yourself now, do you think there are any other changes from the way you were before the dosing?
9. How do you understand what happened to you? What do you think the psilocybin did? (on the dosing day and since)
10. Anything else you would like to add about your experience?

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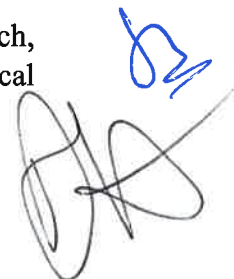
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treatment relapse, their comments during the 6-month interviews suggested major persistent changes in their perspectives and behaviors. This suggests that improved measures, more sensitive to changes in psychological well-being for example, should be considered to help capture and communicate real-world changes that are not adequately picked up by standard rating scales. It could be said that patients were not just losing symptoms of depression but were, in many cases, gaining happiness, which has been defined as “pleasure, engagement, and meaning” (Seligman, Parks, & Steen, 2004). Happiness, or psychological well-being, may be a valuable construct in this context. For example, it seemed that months after the psilocybin, patients were still able to benefit from the renewed *meaning* in their lives. To take one particular example from a patient whose depression had returned at the time of interview, she reported still feeling connected to what she described as her “inner teacher,” remained vegetarian (since the dosing session), and said that the trees continued to look greener:

[The treatment] flicks on a switch. It opens a door. I can appreciate life [now] and because of that I can go on living. You feel it on the inside—it’s from the inside out. I’m looking at life and it doesn’t feel bad. There will always be suffering. If you only focus on that then you don’t get to see the beauty around you. (P12)

In conclusion, via thematic analysis applied to structured interviews performed 6 months after psilocybin for treatment-resistant depression in 20 patients, we identified two major themes relating to how the treatment had been beneficial: (a) a change from disconnection (from the self, others, and the outside world) to connection and (b) a change from avoidance of difficult emotions and memories to acceptance. Provocatively, patients reported that previous treatments functioned to reinforce defensive strategies of disconnection/retreat and avoidance, whereas treatment with psilocybin promoted a confrontation and subsequent reconnection that was lasting in many cases. The approach taken here complements more formal, quantitative analyses of the utility of psilocybin (Carhart-Harris, Bolstridge, et al., 2016; Carhart-Harris, 2017; Gasser et al., 2014; Griffiths et al., 2016; Ross et al., 2016) and should help inform and enrich understanding of this novel treatment and its mechanisms of action, helping generate new hypotheses that can be tested in subsequent research.

Appendix

Semi-Structured Interview

“This interview will cover your experience of trying psilocybin as a treatment for depression. It will last about an hour. You are welcome to take breaks



deviating from predrug baseline, and subsequent interviews revealed that this period had mostly been extremely “blissful” for the patient. For the therapy team, this putative mutism was concerning for a period; however, hindsight has taught us to simply sit out such situations (unless vital signs suggest otherwise), waiting for the idiosyncratic symptoms to subside. The positive physiological safety profile of psilocybin can offer reassurance in this regard.

There is a need for further qualitative research within studies assessing psychedelics for other indications, such as addiction (Bogenschutz & Johnson, 2016) and obsessive compulsive disorder (Moreno et al., 2006). Subthemes identified in the current study closely matched themes identified in previous qualitative analyses of psychedelic treatment studies, for example, “deschematizing and viewing experiences in another perspective,” “facilitated access to emotions and catharsis,” and “no negative aspects of the treatment” (Gasser et al., 2015); “relational embeddedness,” “emotional range,” and “desire to repeat the psilocybin experience” (Belser et al., 2017).

It is notable that psychedelic treatment has been found to help a wide range of conditions, such as posttraumatic stress disorder, addictions, obsessive-compulsive disorder, depression, smoking cessation, and end-of-life anxiety (Griffiths et al., 2016; Ross et al., 2016). It may be that psychedelics have an impact on certain fundamental processes that underlie many psychiatric conditions. Perhaps the diagnosed disorders represent different manifest expressions of consistent latent problems, such as repression of emotional pain and/or ego-dystonic psychological material (Freud, 1995), and/or a lack of meaning (Frankl, 1961) and/or disconnection from others (Bowlby, 1978). Thus, psychedelic research may help further our knowledge of core, root features of mental ill-being. Over the past 20 years, there has been an ever-increasing push in psychiatry to start promoting consideration of disease *spectrums* rather than distinct entities, and perhaps psychedelics could play a role in informing and improving the way we think about, and treat, mental illness, and wellness. It is inevitable that such a paradigmatic shift will meet resistance as it treads on the toes of convention, but its “success” may ultimately prove irresistible, if its foundations are strong.

Within the current medical model of mental illness, treatments are designed to mollify symptoms. However, in the present study, the benefit of treatment was not restricted to a reduction in symptomatology. When rumination started again after a few months, several patients still reported feeling better than before the treatment, claiming that there was greater meaning in their lives. For some, although scores on standard depression rating scales indicated



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Author Biographies

Rosalind Watts completed her clinical psychology doctoral training in London, and after 6 years of practicing psychotherapy, she joined the Imperial College Psilocybin for Depression Study as a therapist “guide.” She believes that psychedelic treatments can have an important role in changing the way we conceptualize and treat mental health difficulties. Her research includes qualitative analysis of the therapeutic impact of psilocybin and LSD, which has informed her interest in “connection to self, others, and world” as a mechanism of change. She is currently working alongside Dr. Robin Carhart-Harris planning the upcoming Imperial psilocybin for depression trial.


Camilla Day, BA, MBChB, MRPsych, studied psychology and physiology at Oxford University and fast-track medicine at Warwick Medical School. She is currently General Adult Psychiatry Registrar working full-time in South East London for South London and Maudsley NHS Trust. She is also honorary research associate working in the Psychedelic Research Group of the Centre of Neuropsychopharmacology in the Brain Sciences Division of Imperial College London Faculty of Medicine.

Jacob Krzanowski is training in psychiatry at the South London and Maudsley NHS Foundation Trust and is an honorary clinical research fellow with Imperial College London.

David Nutt is a psychiatrist at Imperial College London. He trained at Cambridge, Guys Hospital, Oxford University, and NIH. His research focuses on the use of positron emission tomography and functional magnetic resonance imaging to understand how drugs work in the brain and the mechanism underpinning psychiatric disorders particularly addiction and anxiety disorders.

Robin Carhart-Harris Rosalind Watts completed her clinical psychology doctoral training at University College London and practiced psychotherapy for six years before joining the Imperial Psychedelic Research Group as a therapist ‘guide’ and researcher. Her research includes qualitative analysis of the therapeutic effects of psilocybin and LSD. Current projects include designing clinical aspects of the upcoming psilocybin trial at Imperial, and consultancy work developing training models for therapists.



This is Exhibit^C..... referred to in the
affidavit of Professor David Nutt
sworn before me, this²⁹th
day of April 20²⁴

A COMMISSIONER, ETC

Sworn remotely by Professor David Nutt in the city of Bristol, England,
with commissioner Joanna Shaw in the city of Toronto, Ontario.

JOANNA KATHLEEN SHAW,
a Commissioner, etc., Province of Ontario,
for LEWIN & SAGARA LLP,
BARRISTERS AND SOLICITORS.
Expires October 16, 2026.





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Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later

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Abstract

Psilocybin has been used for centuries for religious purposes; however little is known scientifically about its long-term effects. We previously reported the effects of a double-blind study evaluating the psychological effects of a high psilocybin dose. This report presents the 14-month follow-up and examines the relationship of the follow-up results to data obtained at screening and on drug session days. Participants were 36 hallucinogen-naïve adults reporting regular participation in religious/spiritual activities. Oral psilocybin (30 mg/70kg) was administered on one of two or three sessions, with methylphenidate (40 mg/70kg) administered on the other session(s). During sessions, volunteers were encouraged to close their eyes and direct their attention inward. At the 14-month follow-up, 58% and 67%, respectively, of volunteers rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives; 64% indicated the experience increased well-being or life satisfaction; 58% met criteria for having had a “complete” mystical experience. Correlation and regression analyses indicated a central role of the mystical experience assessed on the session day in the high ratings of personal meaning and spiritual significance at follow-up. Of the measures of personality, affect, quality of life, and spirituality assessed across the study, only a scale measuring mystical experience showed a difference from screening. When administered under supportive conditions, psilocybin occasioned experiences similar to spontaneously-occurring mystical experiences that, at 14-month follow-up, were considered by volunteers to be among the most personally meaningful and spiritually significant of their lives.

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Keywords

psilocybin; hallucinogen; mystical experience; spiritual; religion; humans; entheogen; psychedelic

Introduction

Although many have anecdotally claimed that psilocybin, the principal psychoactive component of various hallucinogenic mushroom species, can facilitate experiences providing sustained, positively-valued impact, little is known scientifically about such effects. Psilocybin has been used as a sacrament for centuries, possibly millennia, in structured religious ceremonies (Wasson 1980; Stamets 1996; Metzner 2004). Like other classical hallucinogens (*α*-lysergic acid diethylamide [LSD], mescaline, *N,N*-dimethyltryptamine [DMT]), the effects of psilocybin are primarily mediated at 5-HT_{2A} receptor sites (Nichols 2004), and the acute subjective effects include robust changes in perception, cognition, affect, volition, and somaesthesia (Isbell 1959; Wolbach et al., 1962; Rosenberg et al., 1964).

The degree to which responses to psilocybin are influenced by nonpharmacological variables was not understood by early researchers (e.g., Isbell 1959; Malitz et al., 1960; Rinkel et al., 1960; Hollister 1961). By providing more preparation and interpersonal support during drug action, subsequent research described more positively valued experiences and fewer adverse effects (e.g., panic and paranoia) (Chwelos et al., 1959; Leary et al., 1963; Metzner et al., 1965; Pahnke 1969). In response to the hallucinogen abuse of the 1960s, human hallucinogen research largely ceased and has only recently resumed. Notably, Vollenweider and colleagues in Switzerland and Gouzoulis-Mayfrank and colleagues in Germany have studied the neurocognitive, perceptual, and psychosis-mimicking effects of psilocybin (e.g., Vollenweider et al., 1998; Gouzoulis-Mayfrank et al., 1999; Hasler et al., 2004; Carter et al., 2005, 2007).

Recently, we used rigorous double-blind methods to evaluate the acute (7 hour) and longer-term (2 months) psychological effects of a high dose of psilocybin (30 mg/70 kg) relative to an active comparison compound (40 mg/70 kg methylphenidate) in 36 hallucinogen-naïve volunteers (Griffiths et al., 2006). In contrast to the aforementioned recent psilocybin studies, the study optimized the potential for positively-valued experiences by providing 8 hours of preparation and by instructing volunteers to focus explicitly on the phenomenology of the drug experience rather than perform tasks. The results showed psilocybin to occasion experiences with substantial personal meaning and spiritual significance when evaluated 2 months after psilocybin. We have subsequently conducted a follow-up study evaluating effects at 14 months after their last drug session. Volunteers completed questionnaires that assessed personality, affect, quality of life, spiritual experience, and persisting changes in attitude and behavior attributed to the blinded psilocybin session. This report analyzes these 14-month follow-up results and the contribution of baseline characteristics and immediate drug effects to long-term persisting effects.

Methods

Participants

Participants were recruited through flyers announcing a study of states of consciousness brought about by a naturally occurring psychoactive substance used sacramentally in some cultures. The 36 study participants were medically and psychiatrically healthy and without histories of hallucinogen use. Sixteen participants were males (incorrectly reported as 14 in the previous publication [Griffiths et al., 2006]). Participants had an average age of 46 years



(range 24 to 64); 97% were college graduates; and 56% had post-graduate degrees. All were employed full- or part-time. Fifty-three percent indicated affiliation with a religious or spiritual community, such as a church, synagogue, or meditation group. All volunteers indicated at least intermittent participation in religious or spiritual activities such as religious services, prayer, meditation, or study groups. Volunteers did not receive monetary compensation for participation. Additional information about participant recruitment and demographics has been described previously (Griffiths et al., 2006).

Study design

The study compared the effects of orally administered psilocybin (30 mg/70 kg) and methylphenidate hydrochloride (40 mg/70 kg) using a double-blind design that involved two or three 8-hour drug sessions conducted at 2 month intervals. Thirty-six volunteers were randomly assigned to receive either two sessions (n=30) or three sessions (n=6). The volunteers who received two sessions were then randomly assigned to receive psilocybin or methylphenidate on the first session (15 per group), with the alternative drug administered on the second session. The third group (n=6) received methylphenidate on the first two sessions and unblinded psilocybin on the third session. The purpose of having the possibility of a third session was to help control for expectancy effects (Griffiths et al., 2006).

Preparation and drug session procedures

Participants and monitors were informed that participants would have either two or three sessions, that in at least one session they would receive a moderate or high dose of psilocybin, and that an inactive placebo, a low dose of psilocybin, or various other drugs could be administered in the other session(s). Participants and monitors were unblinded to drug conditions after all participants had completed the 14-month follow-up. The primary monitor met with each volunteer on four occasions before the first session to develop rapport and trust.

The 8-hr drug sessions were conducted in a living-room-like environment. During the session, two monitors were present with a single participant. Participants were encouraged to focus their attention inward by lying down on the couch and wearing an eye mask and headphones through which a program of classical music was played. Additional details of instructions to volunteers, volunteer-monitor meetings before and after sessions, and outcome measures have been described previously (Griffiths et al., 2006).

Measures of personality, affect, quality of life, and spirituality assessed at screening, 2 months after each session, and at the 14-month follow-up

The following instruments were assessed: NEO Personality Inventory (NEO PI-R)(Costa and McCrae 1992); Positive and Negative Affect Scale - Expanded Form (PANAS-X) for how one feels generally (Watson and Clark 1994); Quality of Life Inventory raw score (Frisch, 1994); Measure of Actualization Potential (Leclerc et al., 1999); Mysticism Scale (described below); Spiritual Transcendence Scale (Piedmont 1999, 2007a); Faith Maturity Scale - 12 item version (Benson et al., 1993); Functional Assessment of Chronic Illness Therapy - Non-Illness - Spiritual Well-Being Scale (FACIT-Sp-NI-12) (Peterman et al., 2002).

Measures assessed throughout the session

At 0.5 to 6 hr after capsule administration, monitors rated several dimensions of participant behavior and mood including a rating of the overall drug effect on a 5-point scale from 0=none to 4=extreme. Data were the mean of the two monitors peak scores (i.e. the maximum value from 0.5 to 6 hr after capsule administration for each monitor).

Measures assessed 7 hours after drug administration

When the major drug effects had subsided, the participant completed two questionnaires assessing subjective drug effects: Hallucinogen Rating Scale (HRS)(Strassman et al., 1994); and APZ (assessing altered states of consciousness)(Dittrich 1998).

Participants also completed two questionnaires assessing mystical experience. The Mysticism Scale (9-point version) has been extensively studied, demonstrates cross-cultural generalizability, and is well-regarded in the psychology of religion (Hood et al., 2001; Spilka et al., 2003). When administered 7 hours after drug administration, participants were instructed to complete the questionnaire with reference to their experiences since they received the capsules that morning. For the lifetime version of the questionnaire, participants were instructed to answer with reference to their total life experiences.

As part of the States of Consciousness Questionnaire, volunteers completed the Pahnke-Richards Mystical Experience Questionnaire (Griffiths et al., 2006), which assesses seven domains of mystical experiences: internal unity (pure awareness; a merging with ultimate reality); external unity (unity of all things; all things are alive; all is one); transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words); sense of sacredness (awe); noetic quality (claim of intuitive knowledge of ultimate reality); and deeply-felt positive mood (joy, peace, love). Ratings were made on a 6-point scale relative to the participant's overall life experience. Data on each scale were expressed as a proportion of the maximum possible score. A mean total score was calculated as the mean of the following six domains: unity (either internal or external, whichever was greater), transcendence of time and space; ineffability, sense of sacredness, noetic quality, and positive mood. Based on prior research (Pahnke 1969, Griffiths et al., 2006), criteria for designating a volunteer as having had a "complete" mystical experience were that scores on each of the six domains were ≥ 0.6 .

Measures assessed two-months post-session

For this assessment participants completed the previously described standardized measures and the Persisting Effects Questionnaire, a measure of changes in attitudes, mood, and social and other behavior (Griffiths et al., 2006). The questionnaire also included three questions: I. How personally meaningful was the experience? (1=no more than routine, everyday experiences; 2=similar to meaningful experiences that occur on average once or more a week; 3=similar to meaningful experiences that occur on average once a month; 4=similar to meaningful experiences that occur on average once a year; 5=similar to meaningful experiences that occur on average once every 5 years; 6=among the 10 most meaningful experiences of my life; 7=among the 5 most meaningful experiences of my life; 8=the single most meaningful experience of my life); II. Indicate the degree to which the experience was spiritually significant to you? (1=not at all; 2=slightly; 3=moderately; 4=very much; 5=among the 5 most spiritually significant experiences of my life; 6=the single most spiritually significant experience of my life); III. Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction? (+3=Increased very much to -3=Decreased very much). This questionnaire was developed after the initiation of the study and was completed by 29 of the 36 participants (approximately the same percent within all three groups).

14-month follow-up

This assessment was conducted 14 months after the last session, which was 16 months after the psilocybin session in volunteers who received psilocybin in session 1, and 14 months after psilocybin in volunteers who received psilocybin in sessions 2 or 3. For this assessment, all 36 participants completed the Retrospective Questionnaire as well as the

previously described standardized measures. At this same time volunteers participated in an open-ended clinical interview reflecting on study experiences and current life situation.

For purposes of completing the Retrospective Questionnaire, volunteers were first asked to identify on which session they experienced the “most pronounced changes in your ordinary mental processes.” All but one volunteer identified the psilocybin session. That volunteer, who reported having unusual experiences during both sessions, was asked to complete the questionnaire with regard to the psilocybin session. The remaining volunteers completed the questionnaire in reference to the identified session.

Forty-three items on this questionnaire comprised the previously described Pahnke-Richards Mystical Experience Questionnaire, which was completed looking back on the session and rating the degree to which various phenomena were experienced during the session. The rationale for reassessing these ratings at the 14-month follow-up was that the ratings were made relative to the participant’s overall life experience, which could have changed over the intervening follow-up period. Eighty-nine items comprised the previously described Persisting Effects Questionnaire. For these items, volunteers were asked to rate any current persisting effects that they attribute to the experience. Within the Retrospective Questionnaire, volunteers were also asked to provide written descriptions of what was most memorable and what was most spiritually significant about the experience.

Statistical Analysis

Inspection of the data indicated that the results from the 30 subjects who received each drug once were similar to results from the 6 subjects who received methylphenidate twice followed by psilocybin once. Therefore, data from all 36 subjects are analyzed below. Data from the first methylphenidate session were used for the 6 who received it twice.

To characterize the study sample on measures of personality, affect, quality of life, and spirituality relative to the general population, individual subject data at screening were converted to T-scores using norms for: the five factors of the NEO PI-R (Costa and McCrae 1992); the Positive and Negative Affect factors of the PANAS-X (Watson and Clark 1994); raw score on the Quality of Life Inventory (Frisch, 1994); the overall mean on the Measure of Actualization Potential (Leclerc et al., 1999); total score on the Mysticism Scale-Lifetime (Hood and Williamson 2000; Hood 2007); and total score of the Spiritual Transcendence Scale (Piedmont 2007b). T-scores below 45 or above 55 were considered low or high, respectively, on that dimension.

Repeated measures analysis of variance (ANOVA) was conducted to examine changes in the measures of personality, affect, quality of life, and spirituality that were assessed at screening, 2 months after the psilocybin session, and 14 months after the last session (N=36). Bonferroni-corrected t-tests were used to assess differences among the three time points. ANOVA with Bonferroni-corrected t-tests were also conducted with the Persisting Effects Questionnaire data (n=29) assessed at 2 months post-methylphenidate and post-psilocybin, and again retrospectively for psilocybin at the 14-month follow-up, and with the Pahnke-Richards Mystical Experience Questionnaire data (N=36) assessed seven hours post-methylphenidate and post-psilocybin, and again retrospectively for psilocybin at the 14-month follow-up.

To examine differences in the proportion of subjects endorsing specific answers on the Persisting Effects Questionnaire, z-tests of proportions compared data at 2 months post-methylphenidate, 2 months post-psilocybin, and again retrospectively for psilocybin at the 14-month follow-up. For ratings of personally meaningful and spiritually significant, endorsement was defined as rating either “among the top 5” or “the single most.” For ratings



of increased well-being or life satisfaction, endorsement was defined as rating “increased moderately” or “increased very much.” For ratings of positive behavioral change, endorsement was defined as rating “moderate”, “strong”, or “extreme.”

Pearson’s correlations were calculated to examine the relationships between: 1. volunteer’s ratings of personal meaning and spiritual significance at the 14-month follow-up, and 2. the following screening measures: scores on the five factor subscales of the NEO Personality Inventory, total scores on the Mysticism Scale, Spiritual Transcendence Scale, Faith Maturity Scale, and FACIT-Sp-NI, and mean overall score on the Measure of Actualization Potential questionnaire.

Pearson’s correlations were calculated between: 1. volunteer’s ratings of personal meaning and spiritual significance at the 14-month follow-up, and 2. data obtained on the psilocybin session day. The psilocybin session data used for these calculations were: peak monitor ratings of six dimensions of participant’s behavior during sessions (overall drug effect, anxiety or fearfulness, distance from ordinary reality, tearing/crying, joy/intense happiness, and peace/harmony); the six subscales of the HRS; the three subscales of the APZ questionnaire; total scores on the post-session Mysticism Scale; and mean score on the post-session Pahnke-Richards Mystical Experience Questionnaire. The follow-up data used for these calculations were the volunteer ratings of personal meaning and spiritual significance attributed to the psilocybin session experience.

Significant correlations between the total scores on the Mysticism Scale and follow-up measures of personal meaning or spiritual significance were further examined using a multiple regression model to control for any confounding by intensity of drug effect. Three separate measures of drug effect intensity were examined: peak monitor ratings of overall drug effect; subject-rated intensity as measured by the Intensity subscale of the HRS; and subject-rated intensity from the single item rating “Intensity” in the HRS. In separate analyses for each intensity measure, the intensity measure was entered into the regression first and the post-session Mysticism Scale score was entered second to assess its effect on the follow-up measures independently of intensity.

For statistical tests, $p < .05$ was considered significant except for correlations (for which a more conservative $p < .01$ was used) and for the Bonferroni-corrected t-tests.

Results

Measures of personality, affect, quality of life, and spirituality assessed at screening, 2 months after the psilocybin session, and at the 14-month follow-up

The measures of personality, affect, quality of life, and spirituality assessed at screening indicated that the volunteers were generally well-adjusted, outgoing, open, and high in spirituality. More specifically, relative to adult norms, the mean T-score for the group of volunteers on the NEO PI-R were low on Neuroticism (T-score 41.8) and high on Extroversion, Openness, and Agreeableness (55.3, 65.7, and 55.7, respectively); low on Negative Affect on the PANAS-X (44.4); and high on the Measure of Actualization Potential (59.2), Mysticism Scale-Lifetime (55.6), and Spiritual Transcendence Scale (63.1).

Of the eight questionnaires assessed, only the Mysticism Scale-Lifetime showed significant changes across the study. For the Mysticism Scale-Lifetime, the total score (Figure 1) and the scores on each of the three factors (Interpretation, Introvertive Mysticism, and Extrovertive Mysticism) were significantly greater than screening at both the 2-month and 14-month assessments.



Pahnke-Richards Mystical Experience Questionnaire assessed immediately after sessions and at the 14-month follow-up

The psilocybin session experience, when rated immediately post-session and when rated retrospectively at the 14-month follow-up, produced significant elevations compared to the methylphenidate experience in each of seven domains of mystical experience and the mean total score on the Pahnke-Richards Mystical Experience Questionnaire (Table 1). The 14-month retrospective rating for psilocybin did not differ significantly from the immediate post-session rating. Based on a priori criteria, 22 of the 36 volunteers had a “complete” mystical experience based on immediate post-session ratings; at follow-up, 21 volunteers continued to fulfill these criteria.

Measures of persisting effects assessed 2 months after drug sessions and at the 14-month follow-up

Compared to methylphenidate, the psilocybin session experience produced significant increases in ratings of positive attitudes, mood, social effects, and behavior when rated retrospectively at both 2 months and at the 14-month follow-up (Table 2). The ratings at the 14-month follow-up did not differ significantly from those at 2 months. The ratings of negative changes on these same dimensions were very low and not significantly different across conditions.

Table 2 also shows that the psilocybin session was associated with significant increases in ratings of the personal meaning of the experience, the spiritual significance of the experience, and well-being or life satisfaction due to the experience. No volunteer rated the experience as having decreased his or her sense of well-being or life satisfaction at either 2 months or the 14-month follow-up. Figure 2 shows ratings from these three questions plus a question on positive behavior change expressed as the percentage of the participants endorsing specific answers. Even at the 14-month follow-up, 58% of 36 volunteers rated the experience on the psilocybin session as among the five most personally meaningful experiences of their lives and 67% rated it among the five most spiritually significant experiences of their lives, with 11% and 17%, respectively, indicating that it was the single most meaningful experience, and the single most spiritually significant experience. Furthermore, 64% of the 36 volunteers indicated that the psilocybin session experience increased their sense of well-being or life satisfaction either moderately or very much; and 61% rated that the experience was associated with moderate to extreme positive behavior change.

Relationships between screening data and the 14-month follow-up data on volunteer ratings of personal meaning and spiritual significance

Because attribution at follow-up of sustained high personal meaning and spiritual significance to the psilocybin session experience was so striking, correlations were used to examine the relationships between data obtained at screening and the 14-month follow-up data on volunteer’s ratings of personal meaning and spiritual significance. Ratings of personal meaning at follow-up were significantly correlated (Pearson’s r , d.f. 34, 2-tailed $p < .01$) with negative affect on the PANAS-X ($r = -.51$), raw score on the Quality of Life Inventory ($r = +.47$), total score on the Faith Maturity Scale ($r = +.41$), and mean score of the Measure of Actualization Potential questionnaire ($r = +.44$). There were no significant correlations between any of the outcome measures and the subscales of the NEO Personality Inventory (Neuroticism, Extroversion, Openness, Agreeableness and Conscientiousness) or the total scores on the Mysticism Scale, Spiritual Transcendence Scale, or FACIT-Sp-NI.

Relationships between psilocybin session data and the 14-month follow-up data on volunteer ratings of personal meaning and spiritual significance

To further understand the sustained ratings of high personal meaning and spiritual significance, correlations were used to examine the relationships between data obtained on the psilocybin session day and the 14-month follow-up data of volunteer's ratings of personal meaning and spiritual significance. Rating of the experience as personally meaningful correlated significantly (Pearson's r , $d.f.=34$, 2-tailed $p<.01$) with the Hallucinogen Rating Scale subscales Somaesthesia, Affect, Perception and Cognition ($r=.35$, $.49$, $.42$, and $.46$, respectively), the APZ questionnaire subscales OSE-oceanic boundlessness ($r=.55$) and VUS-visual restructuralization ($r=.54$), total score on Mysticism Scale ($r=.65$), and total score on Pahnke-Richards Mystical Experience Questionnaire ($r=.65$). Rating of spiritual significance showed a significant correlation with the APZ questionnaire subscales OSE ($r=.56$) and VUS ($r=.48$), total score on Mysticism Scale ($r=.77$), and total score on Pahnke-Richards Mystical Experience Questionnaire ($r=.66$). Ratings of personally meaningful and spiritual significance did not significantly correlate with peak monitor ratings during the session of overall drug effect, anxiety or fearfulness, distance from ordinary reality, tearing/crying, joy/intense happiness, or peace/harmony. Figure 3 illustrates the robust correlation between the score on the Mysticism Scale (completed 7 hours after psilocybin administration and with reference to the experience during the session) and ratings of the spiritual significance of the experience at the 14-month follow-up. For contrast, the figure also shows the relative lack of relationship between the subject-rated Intensity (of drug effect) HRS scale completed 7 hours after psilocybin administration and ratings of the spiritual significance of the experience at the 14-month follow-up.

To further examine the contribution of mystical experience (as measured immediately post-session by the Mysticism Scale) to these follow-up measures, regression analysis controlling for intensity of drug effects was undertaken. Three separate measures of intensity of drug effect were used: peak monitor ratings of overall drug effect; subject-rated intensity as reflected in the Intensity subscale of the HRS questionnaire; and subject-rated intensity as assessed by the single item rating "Intensity" in the HRS questionnaire. For both the rating of personally meaningful and the rating of spiritual significance, the measures of intensity contributed only small non-significant effects. The resulting r values for scores on Mysticism Scale remained highly significant ($p<.0001$): personally meaningful ($.65$, $.61$, and $.61$ controlling for the three measures of intensity, respectively); spiritually significant ($.77$, $.78$, and $.74$ controlling for the three measures of intensity, respectively).

Verbatim comments at the 14-month follow-up about the nature of the psilocybin-occasioned spiritual experience

Although the patterns of responses on the various subscales of questionnaires provide an empirical representation of the nature of the psilocybin session experiences, unstructured comments from volunteers are helpful to further understand the sustained high ratings of spiritual significance at the 14-month follow-up. Table 3 presents verbatim written comments about the nature of the spiritual experience for all 24 volunteers who rated the experience at the 14-month follow-up as being among the top five spiritual experiences of their lives. Although not easily summarized, several themes from these unstructured comments include a sense of the unity of all things, a separate "self" ceasing to exist, and merging and/or an encounter with ultimate reality (or God).

Open-ended clinical interview at the 14-month follow-up

An open-ended clinical interview at the 14-month follow-up provided a clinical context conducive to the spontaneous reporting of study-associated adverse events. There were no reports of persisting perceptual phenomena sometimes attributed to hallucinogen use or of

recreational abuse of hallucinogens. Overall, all participants appeared to continue to be well-adjusted, high-functioning, and productive members of society.

Comment

The most striking finding from this 14-month follow-up evaluation of the effects of psilocybin and methylphenidate administered to hallucinogen-naïve volunteers is that a large proportion of volunteers rate their “psilocybin experience”¹ as among the most personally meaningful and spiritually significant of their lives. Fifty-eight percent and 67% of volunteers, respectively, rated the experience as being among the five most personally meaningful experiences of their lives, and the five most spiritually significant experiences of their lives; 11% and 17%, respectively, indicated that it was the single most meaningful experience, and the single most spiritually significant experience. Furthermore, 64% of the volunteers also indicated that the psilocybin experience increased their sense of well-being or life satisfaction moderately or very much, and no volunteer rated the experience as having decreased well-being or life satisfaction. The magnitude of these effects was undiminished from similar ratings completed 2 months after the psilocybin session and were substantially and significantly greater than ratings completed 2 months after the methylphenidate session. Compared to methylphenidate, attributions to the psilocybin experience also included positive changes in attitudes, mood, altruism, and other behavior. Although the generalizability of the findings is limited by the study population (hallucinogen-naïve, well-educated, spiritually-active, middle-aged adults), it is remarkable that an 8-hour laboratory-based intervention could have such large and sustained personally and spiritually significant effects in such a large proportion of volunteers. The findings of sustained reports of positive effects after psilocybin are consistent with a 25-year follow-up study (Doblin 1991) of seven theological seminary students who received psilocybin in the context of a religious service (the Good Friday Experiment: Pahnke 1963,1967).

One mechanism underlying these effects appears to be that psilocybin occasioned an experience having features similar to spontaneously-occurring classical mystical or religious experiences. Of the eight questionnaires measuring personality, affect, quality of life, and spirituality assessed before the study and at follow-up, only the Mysticism Scale-Lifetime showed significant differences (Figure 1). This extensively studied, empirically-derived scale is based on the dimensions of mystical experience originally described by William James in 1902 in his classic book *The Varieties of Religious Experience* (James 1902) and further elaborated by Stace in 1960 (Stace 1960). Because the version of the scale shown in Figure 1 assesses mystical experience over the entire life-time, it is not possible to attribute the increases observed at both the 2-month and 14-month assessment to the psilocybin experience per se. However, the original study (Griffiths et al., 2006) showed that the version of this questionnaire that assessed experience at the end of the session was significantly increased after psilocybin compared to methylphenidate, suggesting that the increases at 2 and 14 months were probably due to the psilocybin experience. Eight dimensions of the mystical experience were also assessed by the Pahnke-Richards Mystical Experience Questionnaire, which documented robust increases on all dimensions after psilocybin (Table 1). Based on a priori criteria, almost 60% of the volunteers at the 14-month follow-up continued to fulfill the criteria for having had a “complete” mystical experience during the psilocybin session. Correlation and regression analyses provided further evidence suggesting a central role of this mystical-type experience in the sustained high ratings of personal meaning and spiritual significance at follow-up, with *r* values from

¹Use of the phrase “psilocybin experience” is not intended to imply that a single type of psilocybin experience exists. Qualitative features of the “psilocybin experience” may vary widely. The experience is best understood as formed of many factors, including psychological state (i.e., set) and environment (i.e., setting), in addition to the drug.

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regression analyses ranging from .74 to .78 for the analyses between Mysticism Scale scores immediately after psilocybin sessions and the follow-up ratings of the spiritual significance of the experience. Finally, unstructured written comments in a retrospective questionnaire completed at follow-up asked what was most memorable and spiritually significant about the experience. Responses were suggestive of a sense of the unity (e.g., the unity of all things and merging and/or an encounter with ultimate reality), which is a core aspect of mystical experiences as described by James and Stace, and as assessed by the Mysticism Scale. Thus, the domain(s) of experience assessed by the Mysticism Scale appear to be closely related to later attributions of spiritual significance and personal meaning.

Notably, none of the assessments of personality, affect, quality of life, or spirituality conducted at screening were predictive of (i.e., correlated with) ratings of spiritual significance at follow-up, and only a few of these measures significantly correlated with ratings of personal meaning. Given the large number of correlations conducted and the seeming inconsistency across different types of measures that presumably assess similar domains (e.g., openness as a personality trait was assessed by both the NEO and by the Measurement of Actualization Potential; spirituality as assessed by four separate measures), there do not appear to be any strong predictors of these sustained effects of psilocybin. Future research should explore the replicability of the observed negative correlation of ratings of personal meaning with negative affect and positive correlation with quality of life. Finally, it should be noted that, by design, the volunteer group of this study was relatively homogeneous, with screening measures showing low neuroticism and negative affect and high extroversion, openness, agreeableness, and spirituality. It is possible that predictive relationships with such screening measures might emerge in a group showing more variability on such measures.

A limit to the generality of the study is that all of the participants reported at least intermittent participation in religious or spiritual activities before the study. It is plausible that such interests increased the likelihood that the psilocybin experience would be interpreted as having substantial spiritual significance and personal meaning. A systematic replication of the study comparing groups having different levels of spiritual/religious dispositions or interests could be informative.

Although the 14-month follow-up provided no evidence of adverse effects of the psilocybin exposure, it is important not to underestimate the potential risks of hallucinogen exposure. These risks include: 1. panic or fear reactions resulting in dangerous behavior during the time of drug action; 2. precipitation or exacerbation of enduring psychiatric conditions; 3. long-lasting perceptual disturbances; and 4. development of a pattern of abuse or dependence on hallucinogens (Abraham et al., 1996; Halpern and Pope 1999; Johnson et al., in press). In the original report of this study (Griffiths et al., 2006), we reported that 11 of the 36 volunteers experienced a period of significant fear during the psilocybin session, with 6 having transient ideas of reference/paranoia. These effects did not persist beyond the session. Given the extensive screening, preparation, and supportive monitoring in the study protocol, this rate of difficult experience is notable and underscores the possible risk of under-supervised use escalating to panic or dangerous behavior. Elsewhere, we provide a detailed discussion of the risks of human hallucinogen administration and safety guidelines for minimizing these risks in the context of human research (Johnson et al., in press).

The high personal meaning and spiritual significance ascribed to the psilocybin-occasioned mystical-type experience prompts consideration of whether such effects could be used to facilitate treatment of some psychiatric and behavioral disorders. Descriptive research suggests that naturally occurring instances of dramatic positive behavioral change are sometimes associated with spontaneously occurring, transformative psychological



experiences, frequently of a mystical-type variety (Miller and C' de Baca, 2001; C' de Baca and Wilbourne, 2004; Forchimes, 2004). Consistent with this, observations in early studies with classical hallucinogens that examined treatment of drug and alcohol dependence (Chwelos et al., 1959; Kurland et al., 1971; Savage and McCabe, 1973) and psychological distress associated with advanced cancer (Pahnke et al., 1969; Richards et al., 1977) suggested that the occurrence of a mystical-type (i.e., transcendent or peak) experience played a key role in positive therapeutic outcome. Unfortunately, many of the early studies of therapeutic use of hallucinogens used sub-optimal procedures for supporting the experience and/or lacked modern methodological controls now expected of rigorous clinical trials (see Mangini, 1998). The present demonstration that mystical experiences having sustained meaning can be occasioned in a high proportion of volunteers suggests that there may be value to re-initiating therapeutic trials with classical hallucinogens.

When administered under supportive conditions, psilocybin occasioned experiences similar to spontaneously-occurring mystical experiences that, over a year later, were considered by volunteers to be among the most personally meaningful and spiritually significant experiences of their lives and to have produced positive changes in attitudes, mood, altruism, behavior, and life satisfaction. In addition to possible therapeutic applications, the ability to prospectively produce mystical-type experiences should permit rigorous scientific investigations about their causes and consequences, and may provide novel information about the biological bases of moral and religious behavior.

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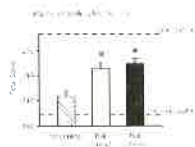


Figure 1. Total score on lifetime version of the Mysticism Scale at screening, 2 months following psilocybin, and at the 14-month follow-up. Bars are mean scores with brackets showing 1 S.E.M. (N=36). Asterisks show significant differences from the screening assessment. For comparison, lower dashed line shows mean score for college students (Hood et al., 2001; Hood, 2007); upper dashed line show maximum possible score.

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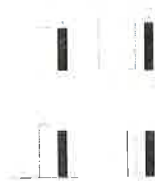


Figure 2. Percentage of volunteers endorsing specific answers on the Persisting Effects Questionnaire completed 2 months following the methylphenidate (Methp) and psilocybin (Psil) sessions ($n=29$), and again retrospectively for psilocybin at the 14-month follow-up ($N=36$). For ratings of personally meaningful and spiritually significant (top two panels), the data are the percentage rating “among the top 5” or “the single most.” For ratings of increased well-being or life satisfaction, the data are the percentage rating “increased moderately” or “increased very much.” For ratings of positive behavioral change, the data are the percentage rating “moderate”, “strong”, or “extreme.” Asterisks show significant differences ($p<.05$, z-test of proportions, $n=29$ at each assessment) from the methylphenidate 2-month assessment; there were no significant differences between the psilocybin 2-month condition and the psilocybin 14-month follow-up assessment. For the methylphenidate results, the data presented are from the first methylphenidate session for the 5 subjects who received methylphenidate on two sessions and who completed this questionnaire.



Figure 3. Ratings of the spiritual significance of the psilocybin session experience at the 14-month follow-up as a function of subject ratings complete 7 hours after psilocybin administration on the Mysticism Scale (upper panel) and the Intensity subscale of the Hallucinogen Rating Scale (HRS). Data points represent individual subject data (N=36); slope and correlation coefficients are shown.

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Table 1

Volunteer Ratings on the Pahnke-Richards Mystical Experience Questionnaire section of the State of Consciousness Questionnaire completed at the end of methylphenidate and psilocybin sessions, and again retrospectively for psilocybin at the 14-month follow-up ^a

Scale Description	Methylphenidate (post-session) ^b (N=36)	Psilocybin (post-session) (N=36)	Psilocybin (14 months) (N=36)
Internal unity	0.26 (0.04)	0.73 (0.05)*	0.71 (0.05)*
External unity	0.22 (0.04)	0.64 (0.05)*	0.67 (0.05)*
Sacredness	0.38 (0.04)	0.80 (0.04)*	0.78 (0.04)*
Intuitive knowledge	0.32 (0.05)	0.74 (0.05)*	0.73 (0.04)*
Transcendence of time and space	0.27 (0.04)	0.75 (0.04)*	0.75 (0.04)*
Deeply felt positive mood	0.39 (0.04)	0.75 (0.04)*	0.70 (0.05)*
Ineffability and paradoxicality	0.33 (0.04)	0.80 (0.04)*	0.78 (0.05)*
Mean total score	0.33 (0.04)	0.76 (0.04)*	0.75 (0.04)*

^a Data are mean scores with 1 S.E.M. shown in parentheses; data are expressed as a proportion of the maximum possible score

^b For the 6 subjects who received methylphenidate on two sessions, the data are from the first session

* Indicates significant difference from the post-methylphenidate condition ($p < .05$); there were no significant differences between the psilocybin post-session condition and the psilocybin 14-month follow-up

Table 2

Volunteer ratings on the Persisting Effects Questionnaire completed 2 months following the methylphenidate and psilocybin sessions, and again retrospectively for psilocybin at the 14-month follow-up^{a,b}

Scale or Question Description	Methylphenidate (2 months) (n=29) ^c	Psilocybin (2 months) (n=29)	Psilocybin (14 months) (n=29)	Psilocybin (14 months) (N=36) ^d
Positive attitudes about life and/or self	23.4 (4.0)	53.1 (4.6)*	53.5 (5.4)*	53.6 (4.7)
Negative attitudes about life and/or self	0.3 (0.1)	0.6 (0.3)	0.5 (0.3)	0.7 (0.3)
Positive mood changes	16.6 (3.1)	37.4 (4.7)*	36.0 (5.5)*	37.9 (4.8)
Negative mood changes	0.5 (0.4)	1.4 (0.6)	1.6 (0.9)	1.7 (0.8)
Altruistic/positive social effects	19.0 (4.1)	44.5 (5.3)*	45.5 (6.3)*	46.3 (5.4)
Antisocial/negative social effects	0.3 (0.2)	0.7 (0.4)	0.7 (0.4)	0.6 (0.4)
Positive behavior changes	29.7 (6.1)	56.6 (5.0)*	58.3 (5.4)*	58.1 (4.9)
Negative behavior changes	1.4 (1.0)	0 (0)	0.7 (0.7)	0.6 (0.6)
How personally meaningful was the experience?	3.6 (0.3)	6.4 (0.2)*	6.3 (0.3)*	6.1 (0.2)
How spiritually significant was the experience?	2.7 (0.2)	4.8 (0.2)*	4.5 (0.3)*	4.5 (0.2)
Did the experience change your sense of well-being or or life satisfaction?	+0.9 (0.2)	+1.9 (0.2)*	+1.9 (0.2)*	+1.8 (0.2)

^aData are mean ratings with 1 S.E.M. shown in parentheses

^bData on attitudes, mood, social, and behavior changes are expressed as percentage of maximum possible score; data for the three questions are raw scores

^cFor the 5 subjects who received methylphenidate on two sessions and who completed this questionnaire, the data are from the first session


^dData for the full group of 36 was not available for the 2-month assessments but is presented here for comparison

* Indicates significant difference from methylphenidate 2-month assessment ($p < .0001$); there were no significant differences between the psilocybin 2-month condition and the psilocybin 14-month follow-up ($n=29$)

Table 3

Verbatim written comments about the nature of the spiritual experience for all 24 volunteers who rated the experience at the 14-month follow-up as being among the top five (including the single most) spiritual experiences of their lives. These comments were excerpted from the Retrospective Questionnaire that asked open-ended questions about what was most memorable and what was most spiritually significant about the experience.

Volunteer	Verbatim Comments
02	The understanding that in the eyes of God - all people...were all equally important and equally loved by God. I have had other transcendent experiences, however, this one was important because it reminded and comforted me that God is truly and unconditionally loving and present.
03	Freedom from every conceivable thing including time, space, relationships, self, etc... It was as if the embodied "me" experienced ultimate transcendence - even of myself.
04	A non-self self held/suspended in an almost tactile field of light.
05	That in every horrible experience or frightening experience, if you stay with it, enter into it, you will find God. That the horror is in reality only an illusion and God lies beneath it all. It has become a guiding principal in my life.
07	The utter joy and freedom of letting go - without anxiety - without direction - beyond ego self
08	Collapse of ordinary space and time sense. Realization of unity of existence and relativity of ordinary consciousness... I have had glimpses of this before -- but this was profound and sustained.
09	The 'knowing' was so powerful and yet personal. Experiencing the Beloved and falling in love.
13	The sense that all is One, that I experienced the essence of the Universe and the knowing that God asks nothing of us except to receive love.
17	I became like a point of awareness able to travel inside myself, others, and the outside world. No reference to time or space... The feeling of joy and sadness at the same time - paradoxical.
21	The experience of death, which initially was very uncomfortable, followed by absolute peace and being in the presence of God. It was so awesome to be with God that words can't describe the experience.
23	To cease to "BE," as I understand it, was not frightening. It was safe and much greater than I have words for or understanding of. Whatever is larger than the state of being is what was holding me.
27	"Surrender" is intensely powerful. To "let go" and become enveloped in the beauty of - in this case - music - was enormously spiritual.
28	The feeling of no boundaries - where I didn't know where I ended and my surroundings began. Somehow I was able to comprehend what oneness is.
29	The profound grief I experienced as if all of the pain and sadness of the world were passing through me cell by cell tearing apart my being.
32	The breath of God/wind/and my breath are all the same... I really enjoy the deep knowings or truths and laughing about them with "God."
36	It opened my third eye - I could see many spiritual beliefs that I hold/held and linked them - a more cohesive and comprehensive spiritual landscape became apparent to me.
37	The experience expanded my conscious awareness permanently. It allows me to let go of negative ideas faster. I accept "what is" easier.
39	[I experienced] a reality that was clear, beautiful, bright and joyful... In short, this experience opened me up (gave me a tangible vision) of what I think is attainable every day.
40	I felt as if tons of information about "what is" was being downloaded quickly into my knowing/understanding.
43	The part that continues to stick out for me was "knowing" and "seeing" and "experiencing" with every sense and fiber of my being that all things are connected.
45	When I confronted my shadow and yelled "What do you want?" and it disappeared in a puff of smoke.
46	The complete and utter loss of self... The sense of unity was awesome... I now truly do believe in God as an ultimate reality.
47	My conversation with God (golden streams of light) assuring me that everything on this plane is perfect; but I do not have the physical body/mind to fully understand.
50	I remember feeling a profound sense of loss of [my family]... I remember after I resolved my fears, the shift then went to joy.

This is Exhibit D referred to in the
affidavit of Professor David Nutt
sworn before me, this 20th
day of April 20²⁴

A Commissioner, ETC

Sworn remotely by Professor David Nutt in the city of Bristol, England,
with commissioner Joanna Shaw in the city of Toronto, Ontario.

JOANNA KATHLEEN SHAW,
a Commissioner, etc., Province of Ontario,
for LEWIN & SAGARA LLP,
BARRISTERS AND SOLICITORS.
Expires October 16, 2026.



Drug harms in the UK: a multicriteria decision analysis

David J Nutt, L A King, L D Phillips, on behalf of the Independent Scientific Committee on Drugs

Objective Proper assessment of the harms caused by the misuse of drugs can inform policy makers in health, policing, and social care. We aimed to apply multicriteria decision analysis (MCDA) modelling to a range of drug harms in the UK.

Design Members of the Independent Scientific Committee on Drugs, including two invited specialists, met in a 1-day interactive workshop to score 20 drugs on 16 criteria: nine related to the harms that a drug produces in the individual and seven to the harms to others. Drugs were scored out of 100 points, and the criteria were weighted to indicate their relative importance.

Results MCDA modelling showed that heroin, crack cocaine, and metamfetamine were the most harmful drugs to individuals (part scores 34, 37, and 32, respectively), whereas alcohol, heroin, and crack cocaine were the most harmful to others (46, 21, and 17, respectively). Overall, alcohol was the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places.

Conclusion These findings lend support to previous work assessing drug harms, and show how the improved scoring and weighting approach of MCDA increases the differentiation between the most and least harmful drugs. However, the findings correlate poorly with present UK drug classification, which is not based simply on considerations of harm.

Centre for Crime and Justice Studies (UK).

Drugs including alcohol and tobacco products are a major cause of harms to individuals and society. For this reason, some drugs are scheduled under the United Nations 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. These controls are represented in UK domestic legislation by the 1971 Misuse of Drugs Act (as amended). Other drugs, notably alcohol and tobacco, are regulated by taxation, sales, and restrictions on the age of purchase. Newly available drugs such as mephedrone (4-methylmethcathinone) have recently been made illegal in the UK on the basis of concerns about their harms, and the law on other drugs, particularly cannabis, has been toughened because of similar concerns.

To provide better guidance to policy makers in health, policing, and social care, the harms that drugs cause need to be properly assessed. This task is not easy because of the wide range of ways in which drugs can cause harm. An attempt to do this assessment engaged experts to score each drug according to nine criteria of harm, ranging from the intrinsic harms of the drugs to social and health-care costs.¹ This analysis provoked major interest and public debate, although it raised concerns about the choice of the nine criteria and the absence of any differential weighting of them.²

To rectify these drawbacks we undertook a review of drug harms with the multicriteria decision analysis (MCDA) approach.³ This technology has been used successfully to lend support to decision makers facing complex issues characterised by many, conflicting objectives—eg, appraisal of policies for disposal of

nuclear waste.⁴ In June, 2010, we developed the multicriteria model during a decision conference,⁵ which is a facilitated workshop attended by key players, experts, and specialists who work together to create the model and provide the data and judgment inputs.

Methods

Study design

The analysis was undertaken in a two-stage process. The choice of harm criteria was made during a special meeting in 2009 of the UK Advisory Council on the Misuse of Drugs (ACMD), which was convened for this purpose. At this meeting, from first principles and with the MCDA approach, members identified 16 harm criteria (figure 1). Nine relate to the harms that a drug produces in the individual and seven to the harms to others both in the UK and overseas. These harms are clustered into five subgroups representing physical, psychological, and social harms. The extent of individual harm is shown by the criteria listed as to users, whereas most criteria listed as to others take account indirectly of the numbers of users. An ACMD report explains the process of developing this model.⁶

In June, 2010, a meeting under the auspices of the Independent Scientific Committee on Drugs (ISCD)—a new organisation of drug experts independent of government interference—was convened to develop the MCDA model and assess scores for 20 representative drugs that are relevant to the UK and which span the range of potential harms and extent of use. The expert group was formed from the ISCD expert committee plus two external experts with specialist knowledge of

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For more on the Independent Scientific Committee on Drugs see: <http://www.drugsociety.org.uk>

legal highs (webappendix). Their experience was extensive, spanning both personal and social aspects of drug harm, and many had substantial research expertise in addiction. All provided independent advice and no conflicts of interest were declared. The meeting's facilitator was an independent specialist in decision analysis modelling. He applied methods and techniques that enable groups to work effectively as a team, enhancing their capability to perform,⁷ thereby improving the accuracy of individual judgments. The group scored each drug on each harm criterion in an open discussion and then assessed the relative importance of the criteria within each cluster and across clusters. They also reviewed the criteria and the definitions developed by the ACMD. This method resulted in a common unit of harm across all the criteria, from which a new analysis of relative drugs harms was achieved. Very slight revisions of the definitions were adopted, and panel 1 shows the final version.

Scoring of the drugs on the criteria

Drugs were scored with points out of 100, with 100 assigned to the most harmful drug on a specific criterion. Zero indicated no harm. Weighting subsequently compares the drugs that scored 100 across all the criteria, thereby expressing the judgment that some drugs scoring 100 are more harmful than others.

In scaling of the drugs, care is needed to ensure that each successive point on the scale represents equal increments of harm. Thus, if a drug is scored at 50, then it should be half as harmful as the drug that scored 100. Because zero represents no harm, this scale can be regarded as a ratio scale, which helps with interpretation of weighted averages of several scales. The group scored the drugs on all the criteria during the decision conference.

Consistency checking is an essential part of proper scoring, since it helps to minimise bias in the scores and encourages realism in scoring. Even more important is the discussion of the group, since scores are often changed from those originally suggested as participants share their different experiences and revise their views. Both during scoring and after all drugs have been scored on a criterion, it is important to look at the relativities of the scores to see whether there are any obvious discrepancies.

Weighting of the criteria

Some criteria are more important expressions of harm than are others. More precision is needed, within the context of MCDA, to enable the assessment of weights on the criteria. To ensure that assessed weights are meaningful, the concept of swing weighting is applied. The purpose of weighting in MCDA is to ensure that the units of harm on the different preference scales are equivalent, thus enabling weighted scores to be compared and combined across the criteria. Weights are, essentially, scale factors.

MCDA distinguishes between facts and value judgments about the facts. On the one hand, harm

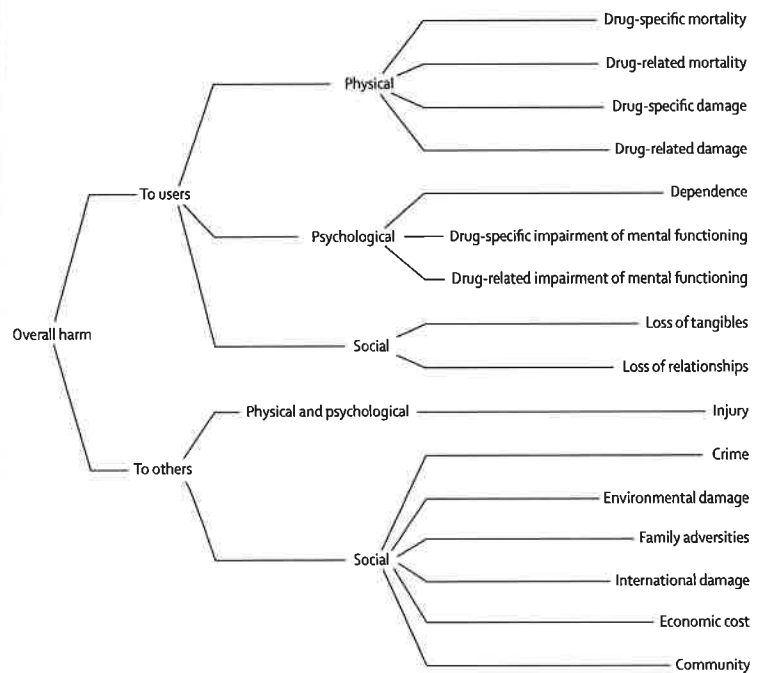


Figure 1: Evaluation criteria organised by harms to users and harms to others, and clustered under physical, psychological, and social effects

expresses a level of damage. Value, on the other hand, indicates how much that level of damage matters in a particular context. Because context can affect assessments of value, one set of criterion weights for a particular context might not be satisfactory for decision making in another context. It follows then, that two stages have to be considered. First, the added harm going from no harm to the level of harm represented by a score of 100 should be considered—ie, a straightforward assessment of a difference in harm. The next step is to think about how much that difference in harm matters in a specific context. The question posed to the group in comparing the swing in harm from 0 to 100 on one scale with the swing from 0 to 100 on another scale was: “How big is the difference in harm and how much do you care about that difference?”

See [online](#) for webappendix

During the decision conference participants assessed weights within each cluster of criteria. The criterion within a cluster judged to be associated with the largest swing weight was assigned an arbitrary score of 100. Then, each swing on the remaining criteria in the cluster was judged by the group compared with the 100 score, in terms of a ratio. For example, in the cluster of four criteria under the category physical harm to users, the swing weight for drug-related mortality was judged to be the largest difference of the four, so it was given a weight of 100. The group judged the next largest swing in harm to be in drug-specific

[Handwritten signature and initials]

Table 1. Harm criteria and their definitions

Drug-specific mortality

Intrinsic lethality of the drug expressed as ratio of lethal dose and standard dose (for adults)

Drug-related mortality

The extent to which life is shortened by the use of the drug (excludes drug-specific mortality)—eg, road traffic accidents, lung cancers, HIV, suicide

Drug-specific damage

Drug-specific damage to physical health—eg, cirrhosis, seizures, strokes, cardiomyopathy, stomach ulcers

Drug-related damage

Drug-related damage to physical health, including consequences of, for example, sexual unwanted activities and self-harm, blood-borne viruses, emphysema, and damage from cutting agents

Dependence

The extent to which a drug creates a propensity or urge to continue to use despite adverse consequences (ICD 10 or DSM IV)

Drug-specific impairment of mental functioning

Drug-specific impairment of mental functioning—eg, amphetamine-induced psychosis, ketamine intoxication

Drug-related impairment of mental functioning

Drug-related impairment of mental functioning—eg, mood disorders secondary to drug-user's lifestyle or drug use

Loss of tangibles

Extent of loss of tangible things (eg, income, housing, job, educational achievements, criminal record, imprisonment)

Loss of relationships

Extent of loss of relationship with family and friends

Injury

Extent to which the use of a drug increases the chance of injuries to others both directly and indirectly—eg, violence (including domestic violence), traffic accident, fetal harm, drug waste, secondary transmission of blood-borne viruses

(Continues in next column)

(Continued from previous column)

Crime

Extent to which the use of a drug involves or leads to an increase in volume of acquisitive crime (beyond the use-of-drug act) directly or indirectly (at the population level, not the individual level)

Environmental damage

Extent to which the use and production of a drug causes environmental damage locally—eg, toxic waste from amphetamine factories, discarded needles

Family adversities

Extent to which the use of a drug causes family adversities—eg, family breakdown, economic wellbeing, emotional wellbeing, future prospects of children, child neglect

International damage

Extent to which the use of a drug in the UK contributes to damage internationally—eg, deforestation, destabilisation of countries, international crime, new markets

Economic cost

Extent to which the use of a drug causes direct costs to the country (eg, health care, police, prisons, social services, customs, insurance, crime) and indirect costs (eg, loss of productivity, absenteeism)

Community

Extent to which the use of a drug creates decline in social cohesion and decline in the reputation of the community

ICD 10=International Classification of Diseases, tenth revision. DSM IV=Diagnostic and Statistical Manual of Mental Disorders, fourth revision.

final normalisation preserved the ratios of all weights, but ensured that the weights on the criteria summed to 1.0. The weighting process enabled harm scores to be combined within any grouping simply by adding their weighted scores. Dodgson and colleagues⁷ provide further guidance on swing weighting. Scores and weights were input to the Hiview computer program, which calculated the weighted scores, provided displays of the results, and enabled sensitivity analyses to be done.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the 16 identified harm criteria. Figure 2 shows the total harm score for all the drugs and the part-score contributions to the total from the subgroups of harms to users and harms to others. The most harmful drugs to users were heroin (part score 34), crack cocaine

mortality, which was 80% as great as for drug-related mortality, so it was given a weight of 80. Thus, the computer multiplied the scores for all the drugs on the drug-related mortality scale by 0.8, with the result that the weighted harm of heroin on this scale became 80 as compared with heroin's score of 100 on drug-specific mortality. Next, the 100-weighted swings in each cluster were compared with each other, with the most harmful drug on the most harmful criterion to users compared with the most harmful drug on the most harmful criterion to others. The result of assessing these weights was that the units of harm on all scales were equated. A

For more on Hiview see <http://www.catalyze.co.uk>

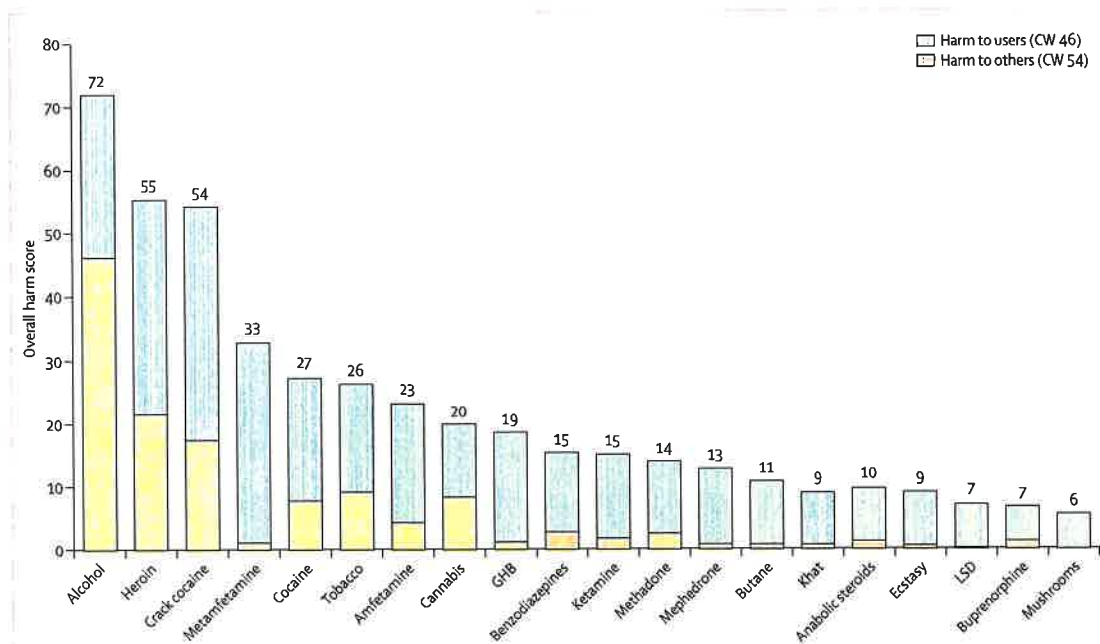


Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others
The weights after normalisation (0–100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 46; and for all the criteria to others, 54). CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide.

(37), and metamfetamine (32), whereas the most harmful to others were alcohol (46), crack cocaine (17), and heroin (21). When the two part-scores were combined, alcohol was the most harmful drug followed by heroin and crack cocaine (figure 2).

Another instructive display is to look at the results separately for harm to users and to others, but in a two-dimensional graph so that the relative contribution to these two types of harm can be seen clearly (figure 3). The most harmful drug to others was alcohol by a wide margin, whereas the most harmful drug to users was crack cocaine followed closely by heroin. Metamfetamine was next most harmful to users, but it was of little comparative harm to others. All the remaining drugs were less harmful either to users or to others, or both, than were alcohol, heroin, and crack cocaine (figure 3). Because this display shows the two axes before weighting, a score on one cannot be compared with a score on the other, without knowing their relative scale constants.

Figure 4 shows the contributions that the part scores make on each criterion to the total score of each drug. Alcohol, with an overall score of 72, was judged to be most harmful, followed by heroin at 55, then crack cocaine with a score of 54. Only eight drugs scored, overall, 20 points or more. Drug-specific mortality was a substantial contributor to five of the drugs (alcohol, heroin, γ hydroxybutyric acid [GHB], methadone, and butane), whereas economic cost contributed heavily to alcohol, heroin, tobacco, and cannabis.

Discussion

The results from this MCDA analysis show the harms of a range of drugs in the UK. Our findings lend support to the conclusions of the earlier nine-criteria analysis undertaken by UK experts¹ and the output of the Dutch addiction medicine expert group.⁸ The Pearson correlation coefficient between Nutt and colleagues' 2007 study¹ and the new analysis presented here for the 15 drugs common to both studies is 0.70. One reason for a less-than-perfect correlation is that the scores from Nutt and colleagues' previous study were based on four-point ratings (0=no risk, 1=some risk, 2=moderate risk, and 3=extreme risk). The ISCD scoring process was based on 0–100 ratio scales, so they contain more information than the ratings do.

Throughout Nutt and colleagues' 2007 paper, harm and risk are used interchangeably, but in the ISCD work, risk was not considered because it is susceptible to varying interpretations. For example, the British Medical Association defines risk as the probability that something unpleasant will happen.⁹ Thus, assessors from Nutt and colleagues' 2007 work might have interpreted their rating task differently from the scoring task of the ISCD experts. Furthermore, in Nutt and co-workers' 2007 study, ratings were simply averaged across the nine criteria (called parameters in the report), three each for physical harm, dependence, and social harms, whereas differential weights were applied to the criteria in this ISCD study, as is shown in the key of

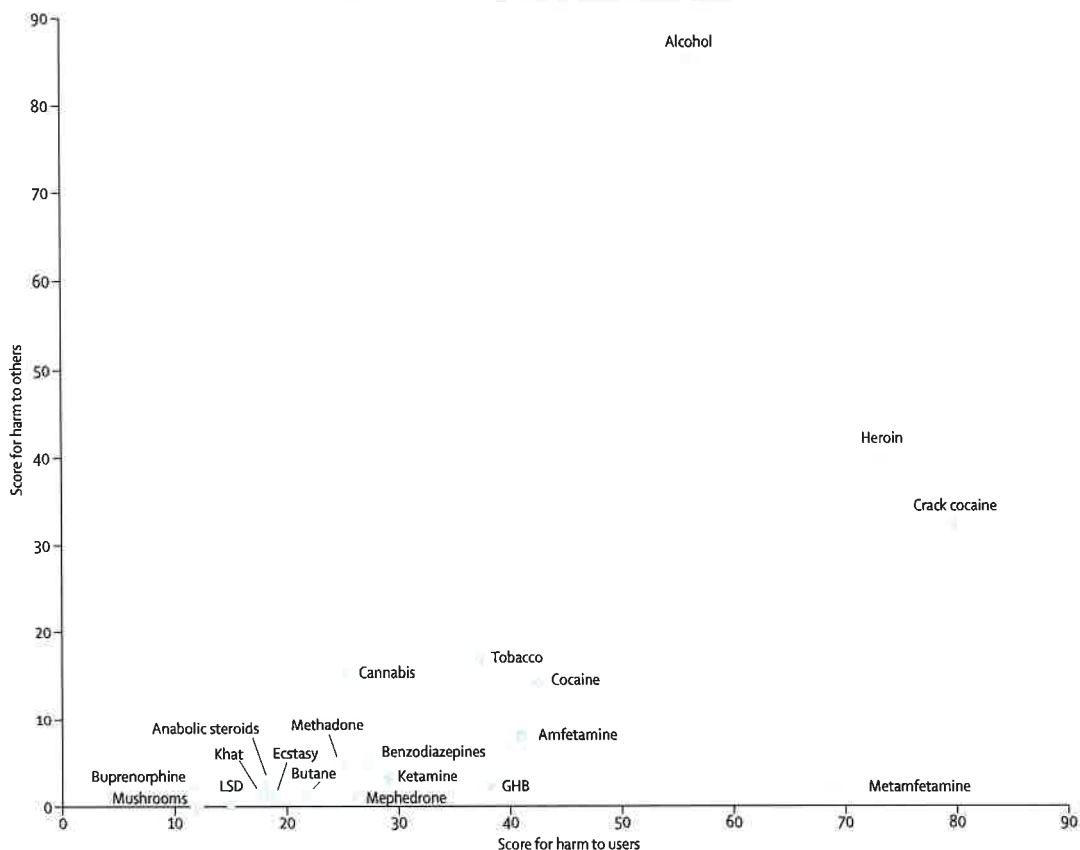


Figure 3: Drugs shown for their harm to users and harm to others
 LSD=lysergic acid diethylamide. GHB=γ hydroxybutyric acid.

figure 4. Despite these many differences between the two studies, there is some degree of linear association between both sets of data.

The correlations between the Dutch addiction medicine expert group² and ISCD results are higher: 0.80 for individual total scores and 0.84 for population total scores. As with Nutt and colleagues' 2007 study, the Dutch experts applied four-point rating scales to 19 drugs. However, they used five criteria: acute toxicity, chronic toxicity, addictive potency, social harm at individual level, and social harm at population level. Simple averages produced two overall mean harm ratings, one each for individuals and for populations. The probable explanation for the greater correlation between the ISCD and Dutch data lies in the greater relative ranges of the overall results than in Nutt and co-workers' 2007 study. The highest and lowest overall harm scores in the ISCD study are 72 for alcohol and 5 for mushrooms, which is a ratio of about 14:1; whereas in Nutt and colleagues' study it was a ratio of just over 3:1, from 2.5 for heroin to 0.8 for khat. The highest and lowest scores for the Dutch individual ratings were 2.63 for crack cocaine and 0.40 for mushrooms, which is a ratio of 6.6:1; and for the population ratings 2.41 for crack cocaine and

0.31 for mushrooms, which is a ratio of 7.8:1. The ratio scaling in the ISCD study spanned a wider range, making the three most harmful drugs—alcohol, heroin, and crack cocaine—much more harmful relative to the other drugs than can be expressed with rating scales, so that additional information stretched the scatterplot in one dimension, making it seem more linear. Additionally, because the Dutch scale attributes only a quarter of the scores to social factors, whereas in the ISCD scoring these factors comprise nearly half of the scores (seven of 16 criteria), drugs such as alcohol which have a major effect will rank more highly in the ISCD analysis, with tobacco ranked lower because its harms are mainly personal.

The correlations between the ISCD overall scores and the present classification of drugs based on revisions to the UK Misuse of Drugs Act (1971) is 0.04, showing that there is effectively no relation. The ISCD scores lend support to the widely accepted view^{10,11} that alcohol is an extremely harmful drug, both to users and society; it scored fourth on harms to users and top for harms to society, making it the most harmful drug overall. Even in terms of toxic effects alone, Gable¹² has shown that, on the basis of a safety ratio, alcohol is more lethal than many

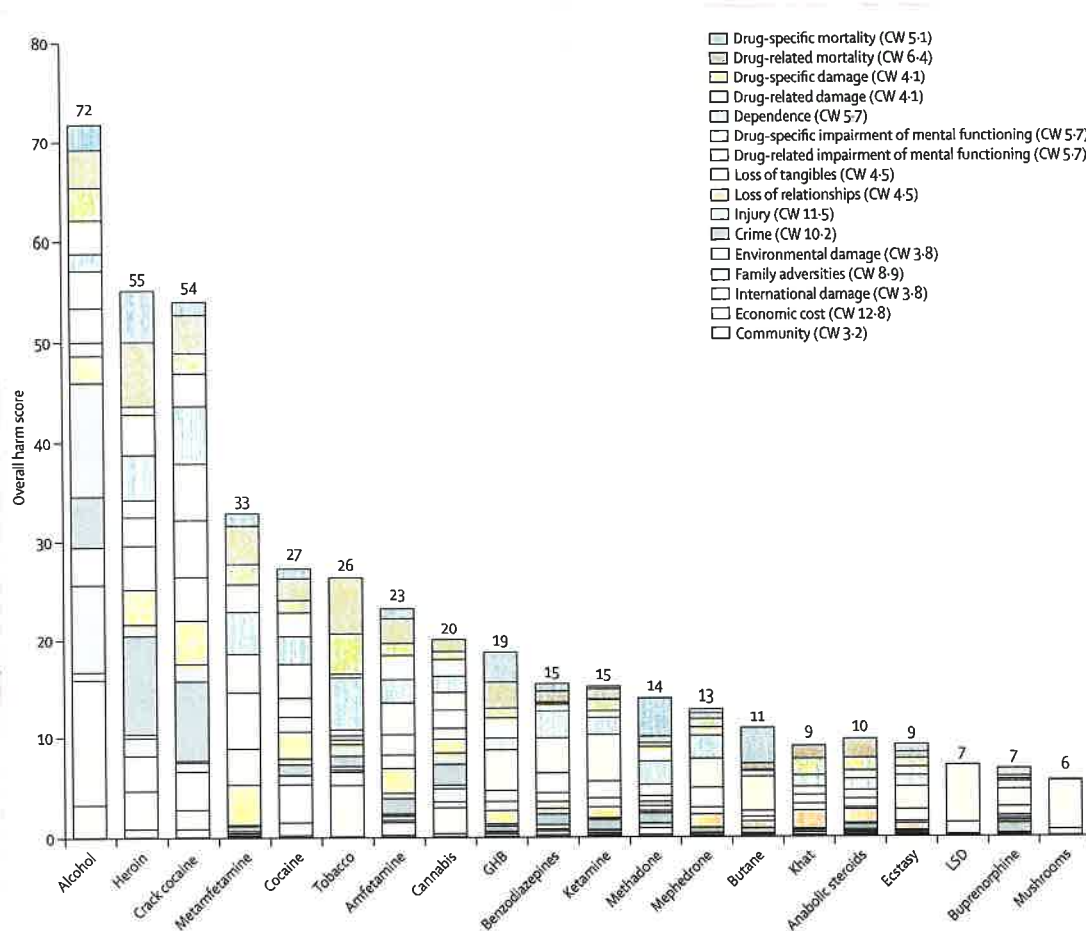


Figure 4: Overall weighted scores for each of the drugs

The coloured bars indicate the part scores for each of the criteria. The key shows the normalised weight for each criterion. A higher weight indicates a larger difference between the most harmful drug on the criterion and no harm. CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide.

illicit drugs, such as cannabis, lysergic acid diethylamide (LSD), and mushrooms.

The MCDA process provides a powerful means to deal with complex issues that drug misuse presents. The expert panel's scores within one criterion can be to some extent validated by reference to published work. For example, we compared the 12 substances in common between this study and those in Gable's study,¹² who for 20 substances identified a safety ratio—the ratio of an acute lethal dose to the dose commonly used for non-medical purposes. The log₁₀ of that ratio shows a correlation of 0.66 with the ISCD scores on the criterion drug-specific mortality, providing some evidence of validity of the ISCD input scores.

We also investigated drug-specific mortality estimates in studies of human beings.¹³ These estimates show a strong correlation with the group input scores: the mean fatality statistics from 2003 to 2007 for five substances (heroin, cocaine, amfetamines, MDMA/ecstasy, and

cannabis) show correlations with the ISCD lethality scores of 0.98 and 0.99, for which the substances recorded on the death certificates were among other mentions or sole mentions, respectively.

A comparison of the ICSD experts' ratings on the dependence criterion with lifetime dependence reported in the US survey by Anthony and co-workers¹⁴ showed a correlation of 0.95 for the five drugs—tobacco, alcohol, cannabis, cocaine, and heroin—that were investigated in both studies, showing the validity of the MCDA input scores for those substances.

Drug-specific and drug-related harms for some drugs can be estimated from health data and other data that show alcohol, heroin, and crack cocaine as having much larger effects than other drugs.¹⁵ Social harms are harder to ascertain, although estimates based on road traffic and other accidents at home, drug-related violence,¹⁶ and costs to economies in provider countries (eg, Colombia, Afghanistan, and Mexico)¹⁷ have been estimated. Police

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Systematic review

We analysed the data obtained from a multicriteria decision analysis (MCDA) conference on drug harms. The harms were assessed according to a new set of 16 criteria developed by the Advisory Council on the Misuse of Drugs (the UK Government committee on drug misuse). A panel of drug-harm experts was convened to establish scores for 20 representative drugs that are relevant to the UK and which span the range of potential harms and extent of use. Participants scored the relative harms of each drug on each of 16 criteria, and then assessed criterion weights to ensure that units of harm were equivalent across all criteria. Calculation of weighted scores provided a composite score on two dimensions, harm to the individual and harm to society, and an overall weighted harm score.

Interpretation

These findings lend support to earlier work from both UK and Dutch expert committees on assessment of drug harms, and show how the improved scoring and weighting approach of MCDA increases the differentiation between the most and least harmful drugs. On the basis of these data it is clear that the present UK drug classification system is not simply based on considerations of harm.

records lend support to the effect of drug dealing on communities and of alcohol-related crime.¹⁸ However, data are not available for many of the criteria, so the expert group approach is the best we can provide. The many high correlations (of our overall results with those of the Dutch addiction medicine expert group, and of some of our input scores with objective data) provide some evidence of the validity of our results.

The issue of the weightings is crucial since they affect the overall scores. The weighting process is necessarily based on judgment, so it is best done by a group of experts working to consensus. Although the assessed weights can be made public, they cannot be cross-validated with objective data. However, the effect of varying the weightings can be explored in the computer program through sensitivity analysis. For example, we noted that it would be necessary to increase the weight on drug-specific mortality or on drug-related mortality by more than 15 of 100 points before heroin displaced alcohol in first position of overall harm. A similarly large change in the weight on drug-specific damage would be needed, from about 4% to slightly more than 70%, for tobacco to displace alcohol at first position. And an increase in the weight on harm to users from 46% to nearly 70% would be necessary for crack cocaine to achieve the overall most harmful position. Extensive sensitivity analyses on the weights showed that this model is very stable; large changes, or combinations of modest changes, are needed to drive substantial shifts in the overall rankings of the

drugs. Future work will explore these weightings with use of other groups—both expert panels and those from the general public.

Limitations of this approach include the fact that we scored only harms. All drugs have some benefits to the user, at least initially, otherwise they would not be used, but this effect might attenuate over time with tolerance and withdrawal. Some drugs such as alcohol and tobacco have commercial benefits to society in terms of providing work and tax, which to some extent offset the harms and, although less easy to measure, is also true of production and dealing in illegal drugs.¹⁹ Many of the harms of drugs are affected by their availability and legal status, which varies across countries, so our results are not necessarily applicable to countries with very different legal and cultural attitudes to drugs. Ideally, a model needs to distinguish between the harms resulting directly from drug use and those resulting from the control system for that drug. Furthermore, they do not relate to drugs when used for prescription purposes. Other issues to explore further include building into the model an assessment of polydrug use, and the effect of different routes of ingestion, patterns of use, and context.²⁰ Finally, we should note that a low score in our assessment does not mean the drug is not harmful, since all drugs can be harmful under specific circumstances.

In conclusion, we have used MCDA to analyse the harms of a range of drugs in relation to the UK (panel 2). Our findings lend support to previous work in the UK and the Netherlands, confirming that the present drug classification systems have little relation to the evidence of harm. They also accord with the conclusions of previous expert reports^{11,18} that aggressively targeting alcohol harms is a valid and necessary public health strategy.

Contributors

DJN designed and participated in the study. LAK participated in the study. LDP participated in the running of the study and analysed data. All authors wrote the report and responded to referees' comments.

Conflicts of interest

DJN and LAK received travel expenses to attend the decision conference meeting. LAK is a consultant to the Department of Health and the EMCDDA. LDP is a director of Facilitations Limited, which paid him a consulting fee because it was the company engaged by the Centre for Crime and Justice Studies to run the study and analyse the data.


Acknowledgments

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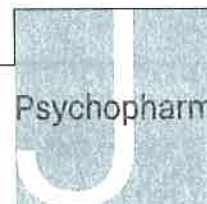
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This is Exhibit E referred to in the
 affidavit of Professor David Nutt
 sworn before me, this 29th
 day of April 20²⁴

 A COMMISSIONER, ETC

Sworn remotely by Professor David Nutt in the city of Bristol, England,
 with commissioner Joanna Shaw in the city of Toronto, Ontario.

JOANNA KATHLEEN SHAW,
 a Commissioner, etc., Province of Ontario,
 for LEWIN & SAGARA LLP,
 BARRISTERS AND SOLICITORS.
 Expires October 16, 2026.





The Australian drug harms ranking study

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Abstract

Background/Aim: The aim of the current study was to review drug harms as they occur in Australia using the Multi-criteria Decision Analysis (MCDA) methodology adopted in earlier studies in other jurisdictions.

Method: A facilitated workshop with 25 experts from across Australia, was held to score 22 drugs on 16 criteria: 9 related to harms that a drug produces in the individual and 7 to harms to others. Participants were guided by facilitators through the methodology and principles of MCDA. In open discussion, each drug was scored on each criterion. The criteria were then weighted using a process of swing weighting. Scoring was captured in MCDA software tool.

Results: MCDA modelling showed the most harmful substances to users were fentanyl (part score 50), heroin (part score 45) and crystal methamphetamine (part score 42). The most harmful substances to others were alcohol (part score 41), crystal methamphetamine (part score 24) and cigarettes/tobacco (part score 14). Overall, alcohol was the most harmful drug when harm to users and harm to others was combined. A supplementary analysis took into consideration the prevalence of each substance in Australia. Alcohol was again ranked the most harmful substance overall, followed by cigarettes, crystal methamphetamine, cannabis, heroin and pharmaceutical opioids.

Conclusions: The results of this study make an important contribution to the emerging international picture of drug harms. They highlight the persistent and pervasive harms caused by alcohol. Policy implications and recommendations are discussed. Policies to reduce harm from alcohol and methamphetamine should be a priority.

Keywords

Alcohol, tobacco, illicit drugs, drugs, ranking, harms

Introduction

The international landscape in relation to drugs is constantly changing. There are concerns currently about the escalating availability of new psychoactive drugs, crystal methamphetamine and high potency opioids – particularly fentanyl – in Western countries and tramadol in Africa and Asia (World Drug Report, 2018). World drug markets are expanding, with supply higher than ever recorded and geographic spread into regions previously not affected. Not surprisingly, drug treatment services globally are unable to keep pace with need, and health care systems and law enforcement agencies are under strain.

If alcohol and drug policies are to be efficient and limit the burden of the increasing prevalence of drug use, they must focus on the drugs causing the greatest harm in the community. Assessing such harm has been approached in a variety of ways. Most commonly, harms incurred by an individual through drug use are examined, and include methodologies that focus on Margin of Exposure (MOE) (European Food Safety Authority, 2005, p. 282; Lachenmeier and Rehm, 2015), Burden of Disease (BOD) (Degenhardt et al., 2013; Griswold et al., 2018; World Bank, 1993), and dependence liability (Anthony et al., 1994; United Nations Office on Drugs and Crime, 1972, p. 4). An alternative approach has been to put a monetary value on the social and economic costs associated with the use of particular drugs, including costs related to judiciary and law enforcement, health-care, loss of productivity, and road traffic accidents (Collins and Lapsley, 2008; Miller and Hendrie, 2008; Tait et al., 2018). While

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no single approach to assess harms related to drug use exists that encompasses both individual and societal costs, Multi Criteria Decision Analysis (MCDA), a decision support tool for consensus building and collaborative problem-solving, has been adopted to examine this issue in a number of countries, as it has been used successfully in a range of contexts beyond health or social harms. Examples include nuclear waste management in the United Kingdom, climate change by the United Nations, and in resource management in South America (Soma, 2003; Thokala et al., 2016; United Nations Framework for Climate Change, 2002). A major advantage of MCDA is that it brings together experts who contribute knowledge and understanding from a range of perspectives on a complex issue; especially where there are conflicting experiences or perspectives of stakeholders.

The aim of the current study was to review drug harms as they occur in Australia using similar MCDA methodology adopted in other jurisdictions, so as to ensure comparability of results. As such, the findings contribute to a series of investigations undertaken around the globe using MCDA to evaluate the harms associated with particular types of drug use. The initial study occurred in the United Kingdom (UK) in 2010 (Nutt et al., 2010), followed by others in Europe (Nutt et al., 2014; Van Amsterdam et al., 2010, 2015a). A study in South Africa focused on harms of nicotine based products (publication pending). We report on the results of this MCDA modelling for Australia as a contribution to the emerging international picture of drug harms across the world.

Methods

Study design

A facilitated workshop with 25 experts from across Australia, representing a range of professional domains, was held in April 2018, working together to input data and judgment into the MCDA model. The group was specifically convened to bring together not only research expertise, but also practice wisdom, and included a diverse range of sectors from across the community. Participants were selected to allow the broadest possible range of perspectives and opinions, reflected in their geographic spread across Australia and particular areas of expertise, encompassing treatment services, addiction medicine, psychiatry, pain medicine, academia and research, policy and planning, children and youth, aboriginal health, homeless services, judiciary, emergency services and police (Table 1). All participants provided independent perspectives and no conflicts of interest were declared. The process was facilitated by three independent, experienced individuals including the first author of the UK MCDA exercise (DN) and two specialists in MCDA (PS and PG) who ensured a consistent and rigorous process was followed and consensus was achieved. The facilitators did not take any part in the scoring.

The workshop followed standard decision conferencing processes, which have been previously reported (Nutt et al., 2010). In summary:

1. The substances to be evaluated were reviewed and confirmed by participants. The starting list was the same as that used in the UK study (Nutt et al., 2010) adapted to

include substances most relevant to the current Australian context (Table 2);

2. The criteria for harm employed in the UK MCDA (Nutt et al., 2010) were reviewed and adopted as applicable to the Australian context. The criteria fall into two groups, namely:

Harm to Users – the effect of misuse of a given drug to the average user, considering the harm to a single user (i.e. not taking prevalence of use of the drug into account) and including the harms associated with the impact of mechanisms of control, such as policing, criminalisation, etc.;

Harm to Others – the effect of misuse of that drug on people other than the drug user themselves (such as their family, community, etc.). These criteria consider the total harm to others in Australia (physical/psychological and social) (Figure 1).

Definitions of harms are included in Table 3.

3. In open discussion the drugs were ‘scored’ against the criteria – working through one criterion at a time, in the order of the list above. A process of ‘relative preference scoring’ was used:
 - a. For each criterion, the participants debated and ranked all the drugs on the list in order of most harm to least harm (with ‘NO DRUGS’ being consistently assessed as least harm);
 - b. The participants then debated the *relative* harm of each of the drugs, and ranked them on a scale from 0 to 100, where 0 represented ‘no harm’ and 100 represented ‘most harm’ against that criterion. For example, a drug which was assessed as half as harmful as the drug assessed as most harmful, would score 50;
 - c. Scores were frequently re-visited and reviewed by the group with the facilitator to ensure consistency.
4. Criteria were then weighted using a process of ‘swing weighting’, and a ‘bottom up’ approach:
 - a. First, all the ‘harm to users’ criteria were weighted against each other (swing weighting);
 - b. Then, all the ‘harm to others’ criteria were weighted against each other (swing weighting);
 - c. Finally, the highest weighted ‘to users’ criterion was weighted against the highest weighted ‘to others’ criterion (‘bottom up’).
 - d. The result of attributing these weights was that the units of harm for each substance were equated. A final normalisation preserved the ratios of all weights but ensured that the weights on the criteria summed to 1.0. The weighting process enabled harm scores to be combined for each substance by adding their weighted scores.
5. All scores and weights were captured in the MCDA software tool used for other MCDA analyses – Catalyze Hiview 3® (<http://www.catalyzeconsulting.com/software/hiview3/> accessed 12 October 2018).

During the Decision Conference, the participants noted these points of rationale and/or assumptions about specific drugs that impacted the assessment of harms:

Table 1. Expert panel membership and organisational affiliation.

Name	Sector/Specialty	Organisation
Yvonne Bonomo ^a	Addiction Medicine	St Vincent's Hospital Melbourne
Adam Pastor	Addiction Medicine	St Vincent's Hospital Melbourne
Jill Rundle	Treatment, Advocacy, Policy	Network AOD Agencies
Dan Lubman	Treatment, Research, Policy	Turning Point
Mark Daglish	Policy, Research	University of Queensland
David Castle ^a	Psychiatry	St Vincent's Hospital Melbourne
Simon Lenton ^a	Research, Policy	National Drug Research Institute, Curtin University
John Ryan	Research, Advocacy, Harm Minimization	Penington Institute
Raimondo Bruno ^a	Research	University of Tasmania
Adrian Reynolds	Addiction Medicine	President, Australian Chapter of Addiction Medicine
John Furler	General Practice	General Practitioner
Andrew Walby	Emergency Medicine	St Vincent's Hospital Melbourne
Diana Egerton-Warburton ^a	Emergency Medicine	Monash University
Charles Kim	Anaesthesia, Pain Management	Royal Melbourne Hospital
Jonathan Karro	Toxicology	St Vincent's Hospital Melbourne
Sharon Dawe	Families, Child Protection, Research, Policy	Griffith University
Clive Rust	Police	Victoria Police
Jenny Smith	Homelessness services, advocacy	Homeless Persons Council
Sam Biondo	Treatment, advocacy	Victorian Alcohol And Drug Association
Pauline Deweerdt	Aboriginal Health	St Vincent's Health Australia
Andrew Bruun	Treatment, Advocacy	Youth Support and Advocacy Service
Jennifer Bowles	Juvenile Justice	Magistrate, Children's Court of Victoria
Katharine Biffin	Forensic	Program Manager, Drug Court
Christine Watson	Policy, Treatment	Northern Territory Department of Health

^aMember of prevalence sub-group.

Table 2. Drugs evaluated by expert panel as most relevant in the Australian context (including explanatory notes as to definitions agreed by the panel).

Name	Description
Alcohol	Alcohol (consumed at levels beyond current Australian 'low risk' guidelines)
Crystal Meth	Crystalline methamphetamine (Referred to as Methylamphetamine in the UK study)
Heroin	Heroin (not prescribed)
Fentanyl	Fentanyl based substances (e.g. fentanyl, carfentanil, acetyl fentanyl, furanyl fentanyl)
Cigarettes	Cigarettes (Referred to as Tobacco in the UK study)
Methadone	Methadone (non-prescribed/extra-medical use)
Prescription Opioids	Strong pharmaceutical opioids (non-prescribed/extra-medical use), e.g. morphine, oxycontin
Solvents & Fuels	Fuel and solvent inhalation including 'chroming' (The practice of inhaling intoxicating fumes from chrome-based paint)
Synthetic Cannabis	Synthetic cannabinoid receptor agonists (e.g. AB-FUBINACA, XLR-11, 5F-PB-22)
Amphetamine	Meth/amphetamine (tablets, powder, base/paste, liquid – other than crystalline)
Cocaine	Snorted or smoked (excludes crack cocaine due to limited presence of this form in Australia)
Buprenorphine	Buprenorphine (non-prescribed/extra-medical use)
Cannabis	Excludes medicinal cannabis. Assessment of harm does not include the effects of any tobacco
Benzodiazepines	Benzodiazepines (non-prescribed/extra-medical use)
GHB	gamma hydroxybutyrate
PIEDs	Performance and Image Enhancing Drugs (including Anabolic Steroids and growth hormones)
Ketamine	Ketamine
Ecstasy	'Ecstasy', which may contain MDMA or a range of other psychostimulants
Anti-Psychotics	Anti-Psychotics (non-prescribed/extra-medical use)
LSD & Mushrooms	Lysergic acid diethylamide & natural psychedelic products
ENDS	Electronic Nicotine Delivery Systems (e-cigarettes containing nicotine)
Kava	Kava (Piper methysticum) is a depressant with a history of cultural use.
NO DRUGS	Baseline reference to represent 'no harm' on the criteria scales

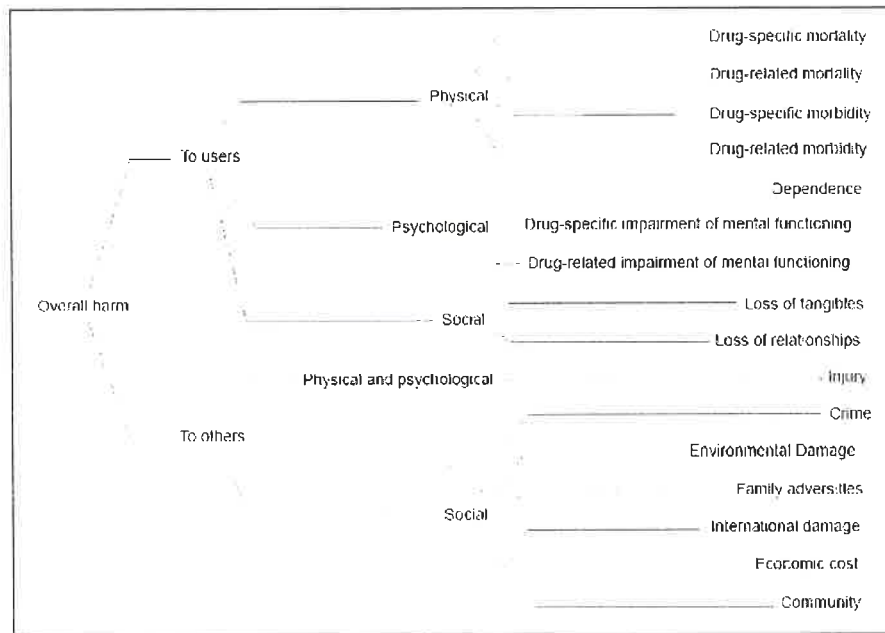


Figure 1. Evaluation criteria organised by harms to users and harms to others, and clustered under physical, psychological, and social effects.

- Fentanyl – these are currently low prevalence in Australia, but it is expected they may become more prevalent; hence, they were included in the exercise;
- Inhaled fuels – these are a particular issue in indigenous communities [for example sniffing of Avgas (aircraft fuel)];
- Tobacco was considered only as ‘cigarettes’, with ENDS (electronic nicotine devices or ‘e-cigarettes’) being rated separately (note that ENDS were not legal at the time of the decision conference);
- Cocaine – the ‘average user’ in Australia is generally of higher socio-economic status than the average user of other illicit substances, and most ‘average users’ do not inject the drug;
- Prescription medications such as benzodiazepines, buprenorphine, methadone and antipsychotics referred to diverted drugs for ‘street’ use;
- Each substance was assessed as if the user was using the substance alone, even when in practice it was acknowledged that multiple substances are frequently used together;
- Possible transition (‘gateway’) effects were not considered.

A supplementary analysis incorporating the prevalence of use of each substance in the assessment of harm to users was also undertaken as this had been a criticism of previous studies (Caulkins et al., 2011). The National Drug Strategy Household Survey 2016 (NDSHS) (Claydon et al., 2017) covers most, but not all, of the substances considered. Where there was no NDSHS data, the group referenced other data to determine prevalence, using the NDSHS as starting points (Table 4). Scores on each of the ‘harm to individual users’ criteria were multiplied by prevalence. Results were then normalised to a 0–100 scale for each criterion. Because the combining of the scores on the individual criteria was achieved through a swing weighting process, the

weights on these criteria also needed to be scaled to account for the impact of prevalence.

Results

Figure 2 shows the total harm score for all the drugs and the part-score contributions to the total from the subgroups ‘harms to users’ and ‘harms to others’. The most harmful substances to users were fentanyl (part score 50), heroin (part score 45) and crystal methamphetamine (part score 42). The most harmful substances to others were alcohol (part score 41), crystal methamphetamine (part score 24) and cigarettes/tobacco (part score 14). When the two part-scores were combined, alcohol and crystal methamphetamine were the two most harmful substances followed by heroin, fentanyl and cigarettes/tobacco. The least harmful drugs were kava, ENDS, LSD and mushrooms, antipsychotics and ecstasy. Overall, alcohol was ranked the most harmful drug, with a combined score of 77.

Figure 3 shows the contributions that the part scores for each criterion made to the total score for each drug. Alcohol, the substance judged to be the most harmful overall with a score of 77, scored highly on economic costs, family adversity, injury, drug related morbidity and drug specific morbidity. The major contributors to the overall harm score of crystal methamphetamine were crime, injury, loss of relationships, loss of tangibles, drug specific morbidity and drug related morbidity. Tobacco was rated the fifth most harmful substance, scoring highly on economic costs and drug related morbidity and drug-related mortality. Drug-specific mortality contributed substantially to the overall harm score of heroin and fentanyl while economic cost contributed heavily to the overall harm score of cigarettes and alcohol.

The scores from the supplementary analyses encompassing prevalence weighted harm to users, are shown in Table 5, normalised to 0 to 100 and sorted in decreasing harm. The top five

Table 3. Definitions of drug harms.

Name	Description
Harm to users	The effect of misuse of that drug on the 'average' user of that drug
Drug specific mortality	Intrinsic lethality of the drug expressed as ratio of lethal dose and standard dose (for adults). The likelihood of any single use killing the user
Drug related mortality	The extent to which life is shortened by use (excludes drug specific mortality). E.g. road traffic accidents, lung cancers, HIV, suicide
Drug specific morbidity	Drug specific morbidity to physical health e.g. cirrhosis, seizures, strokes, cardiomyopathy, stomach ulcers, emphysema
Drug related morbidity	Drug related morbidity, including consequences of e.g. sexual unwanted activities and self-harm, blood borne viruses
Dependence	Extent to which the drug creates a propensity to continue use despite adverse consequences and causes withdrawal symptoms on cessation.
Impaired mental function	Drug specific impairment of mental function e.g. meth/amphetamine induced psychosis, intoxication
Related impairment of function	Drug related impairment of mental functioning. E.g. mood disorders secondary to drug-users lifestyle or drug use.
Loss of tangibles	Extent of loss of tangible things (e.g. income, housing, job, educational achievements, criminal record, imprisonment) including product costs and health care costs
Loss of relationships	Extent of loss of relationships with family and friends
Harm to others	Harm as a consequence of the use of drugs to others both directly and indirectly – considering the total harm to Australia from misuse of the drug.
Injury	The extent to which use increases the chance of injuries to others both directly and indirectly, e.g. violence, rape, traffic accident, foetal harm, drug waste, secondary transmission of blood borne viruses
Crime	The extent to which use involves or leads to an increase in volume of acquisitive crime
Environmental damage	The extent to which use and production causes environmental damage locally, e.g. toxic waste from drug production, discarded injection equipment
Family adversities	The extent to which use causes family adversities, e.g. family breakdown, economic and emotional well-being, impact on children, child neglect.
International damage	The extent to which use in Australia contributes to damage at an international level, e.g. deforestation, international crime and new markets.
Economic cost	The extent to which use causes direct costs to Australia (e.g. healthcare, police, prisons, social services,) and indirect cost (e.g. productivity, absenteeism)
Community	The extent to which the use of this drug creates decline in social cohesion and decline in the reputation of the community.

most harmful drugs overall, considering prevalence-adjusted harm to users and harm to others, were (in rank order) alcohol, cigarettes, crystal methamphetamine, cannabis and heroin. This result is driven by the high prevalence of heavy alcohol consumption in Australia; the similar (high) weights of the first four 'to users' criteria (Drug-specific- and Drug-related mortality and Drug-specific and Drug-related morbidity); and the consistently high scoring for alcohol across all measures.

Discussion

This study highlights the persistent and pervasive harms of the most frequently used psychoactive substances in the Australian community. As in previous studies in other jurisdictions, alcohol was the drug ranked as causing the greatest overall harm. Alcohol had by far the highest score on harm to others (a score of 41 compared with the next highest score of 24 for crystal methamphetamine), reflecting its widespread negative impacts on broad sectors of our community. In contrast to other countries, crystal methamphetamine was found to be the next most harmful drug to the Australian community, with high scores in both harm to the user and harm to others. Notwithstanding this latter finding, there is striking consistency between the results of the studies

undertaken at different time points (the first study in the UK took place in 2010) and in different jurisdictions.

Alcohol consistently dominates harms in the MCDAs performed across the world (Nutt et al., 2010; Van Amsterdam et al., 2010, 2015a) and the most recent burden of disease study concluded that the level of alcohol consumption that minimises health loss is zero (Griswold et al., 2018). The harms associated with alcohol consumption cannot be ignored, and are particularly relevant to areas where per capita consumption is increasing, including South East Asia and the Western Pacific regions (World Health Organization, 2015). Recent data indicate per capita alcohol consumption in Australia has been declining. However, figures for alcohol-attributable deaths, alcohol-attributable hospitalisations (Lensvelt et al., 2018) and emergency department presentations (Lensvelt et al., 2015) have not followed this trend. The harm to others attributable to alcohol, is less easily quantified, but its pervasiveness is reflected in this study in that over 50% of alcohol's total harm score was contributed by harm to others. A 2011 study, the first to comprehensively examine the harms to Australians caused by the drinking of others (Laslett et al., 2011), found that 73% of respondents had been negatively impacted by someone else's drinking in the previous 12 months; women were more likely to be impacted by

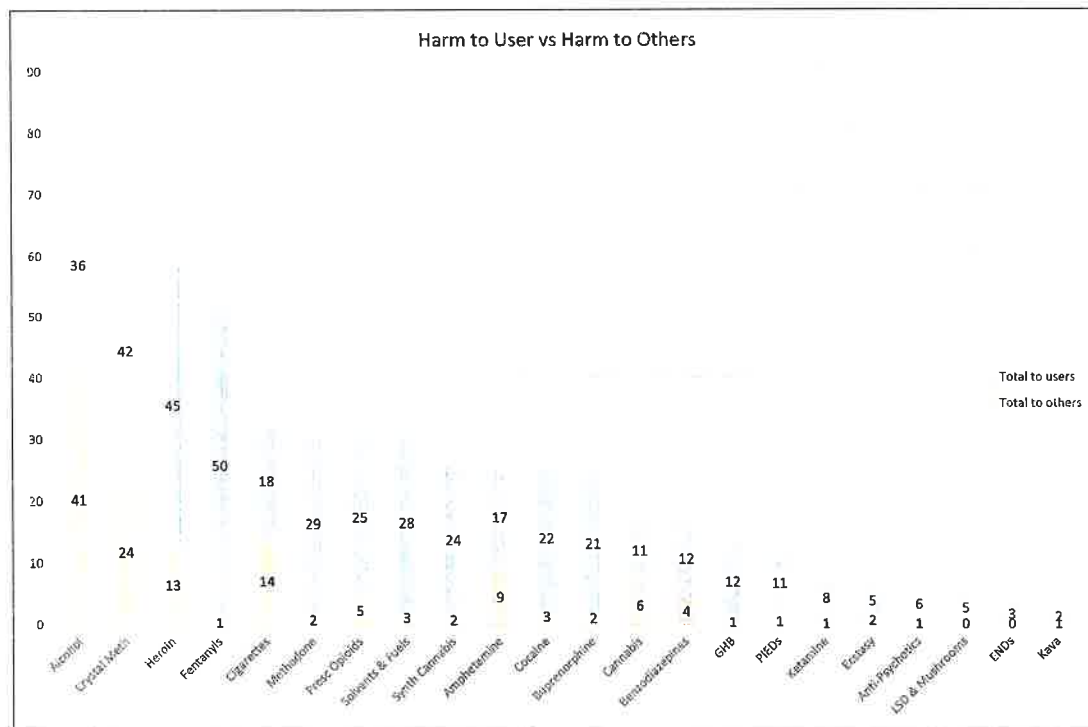
Table 4. Prevalence data based on National Drug Strategy Household Survey.

Substance	Prevalence ^a	Substance	Prevalence ^a
Alcohol	17.1% ^b	Buprenorphine	0.5%
Crystal Meth	0.8%	Cannabinoids	10.4%
Heroin	0.2%	Benzodiazepines	1.6%
Fentanyl	0.1%	GHB	0.1%
Cigarettes	12.2% ^c	PIEDs	0.1%
Methadone	0.5%	Ketamine	0.4%
Prescription Opioids	3.6%	Ecstasy	2.2%
Solvents & Fuels	0.1%	Anti-Psychotics	0.1%
Synthetic Cannabis	0.3%	LSD & Mushrooms	1%
Amphetamine (excl. Crystal Meth)	0.6%	ENDs	4.4%
Cocaine	2.5%	Kava	0.1%

^aDefined as any use in the last 12 month except^{b,c}.

^bPercentage with a Lifetime risk of harm due to risky drinking (1) On average, had more than two standard drinks per day, (2) Had more than four standard drinks on one occasion at least once a month.

^cDaily use.

**Figure 2.** Contribution of harm to user and harm to others to overall harm.

family members or intimate partners, while men were more affected by strangers, friends and co-workers. Of concern, young adults were the most negatively affected across a wide range of harms. This is reflected in the relatively high contribution of 'family adversities' and 'injury' to the overall harm ranking of alcohol in this MCDA. In Australia, the cost of the harms caused by the drinking of others was estimated to be approximately AUD\$6.8 billion in 2010 (Laslett et al., 2011). Yet, initiatives aimed at limiting alcohol harms, such as restrictions on the alcohol content of beverages at sporting events, despite their

effectiveness (Egerton-Warburton, 2018), draw complaints about the imposition of a 'nanny state' (<http://www.abc.net.au/news/2017-11-26/is-ban-on-full-strength-beer-at-perth-stadium-nanny-state-move/9190292>, accessed 12 August 2018). These data consistently and unequivocally indicate that alcohol and drug policies must prioritise investment in effective alcohol policies not only for the sake of the drinker but also the community. To this end, the WHO recommends quantifying the effects of alcohol on others in similar fashion to the effects of passive smoking (World Health Organization, 2015).

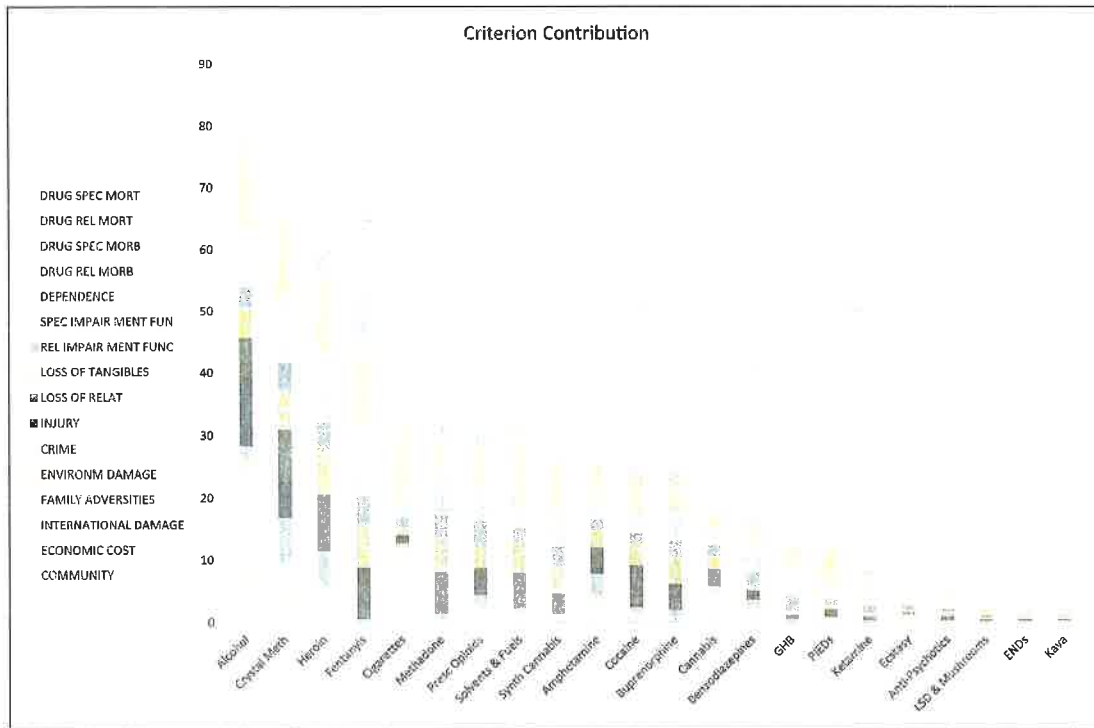


Figure 3. Contribution of criterion scores to overall harm.

Table 5. Overall relative harm score that combines prevalence weighted harm to users and harm to others.

Drug	Total (prevalence adj)
Alcohol	100.00
Cigarettes	37.1
Crystal Meth	32.0
Cannabis	17.3
Heroin	16.9
Prescription Opioids	13.6
Amphetamine	12.2
Cocaine	8.0
Benzodiazepines	7.3
Buprenorphine	3.8
Methadone	3.4
Solvents & Fuels	3.4
Ecstasy	2.8
Synth Cannabis	2.6
ENDS	2.1
PIEDs	1.7
Fentanyl	1.4
GHB	1.4
Ketamine	0.9
LSD & Mushrooms	0.9
Anti-Psychotics	0.7
Kava	0.7
NO DRUGS	0.0

In this study, crystal methamphetamine scored next highest in terms of overall harm. This contrasts with the UK and European Union (EU) where heroin was the next most harmful substance after alcohol (Nutt et al., 2010; Van Amsterdam et al., 2015a). The costs of methamphetamine to the Australian community are estimated at AUD\$5 billion annually, excluding the costs of Federal policing, Federal courts, and border protection (Tait et al., 2018). Methamphetamine death rates have doubled in Australia from 2009 to 2015, with direct toxicity being the most frequent cause but acceleration of natural disease, suicide and accidental death also feature highly (Darke et al., 2017). Regional and rural areas and younger drug users are disproportionately affected (Clayden et al., 2017). Globally, Australia is reported to have the highest prevalence of use of methamphetamine (O'Brien et al., 2017). In North America in 2016, methamphetamine was reported to be the second greatest drug threat after heroin (World Drug Report, 2018). In Europe, however, methamphetamine use is historically low, fairly stable and specific to the Czech Republic and Slovakia (European Monitoring Centre for Drugs and Drug Addiction, 2018).

A unique aspect of our study was the supplementary analysis, which took into account prevalence data to scale harm to user scores. Such analysis reflects that drug harms are not independent of prevalence of use. In this Australian MCDA, cannabis ranked 13th in harms prior to taking into account its prevalence of use. This contrasts with the UK and EU where it scored eighth position. However, once prevalence of use was taken into account, cannabis moved to the fourth rank. This is an important finding given the current debate in Australia and internationally

regarding the legalization of recreational cannabis. The harms associated with cannabis use are lower than other substances, but cannabis is not 'harmless' and this study indicates that an increase in use will be likely to result in an increase in cannabis-related harm to some individuals and the wider community. From a public health and policy perspective sensible approaches to access cannabis under one of a number of potential non-prohibition models (Kilmer, 2017) will reduce cannabis related health and economic burden.

There are public health concerns about the move to full commercial cannabis legalisation schemes being implemented in North America. In Colorado, for example, the emerging evidence suggests: impacts on rates of cannabis use is mixed, the black market continues; providing a product free of pesticides and other chemicals and of known purity is challenging; product diversity increases particularly in very high potency preparations; and the marijuana industry has strongly resisted regulations which might affect their profits and continues to target high frequency users which they see as the backbone of their industry (Parnes et al., 2018; Subritzky et al., 2016) Against this there is increased attention being focussed on 'mid-range' non-commercial models such as Cannabis Social Clubs, which are seen as more attractive from a public health perspective (Decorte, 2018).

Pharmaceutical opioids ranked sixth overall in the prevalence weighted rankings. This reflects the rapid increase in prevalence in Australia and internationally and the concomitant diversion for illicit use. The expansion of world drug markets and the continuing emergence of new drugs is reflected in the absence of fentanyl in the original MCDA analysis on drug harms in 2010 in the UK (Nutt et al., 2010), but its presence by 2015 in the EU MCDA (Van Amsterdam et al., 2015a) and in the UK opioid MCDA (Van Amsterdam et al., 2015b). In 2016, in the United States, there was a 21% increase in overdose deaths from the previous year largely due to a rise in deaths associated with pharmaceutical and synthetic opioids including analogues of fentanyl such as carfentanil (World Drug Report, 2018). Currently, the recreational use of fentanyls is far less prevalent in Australia than in North America, and cases of fentanyl contamination of street heroin deals are extremely rare. Consequently fentanyls are positioned at 17th in the prevalence weighted rankings (compared with 3rd in the primary analysis). It should be noted, however, that between 2002 and 2012, rates of fentanyl related deaths in Australia increased on average 40% per year (Roxburgh et al., 2017). Given their extremely high potency, and consequent high risk of harm to the user, and drug market trends in the United States and Canada, public health measures are needed in anticipation of any increase in the prevalence of misuse of fentanyls in Australia. These measures should include: sentinel site monitoring of potential fentanyl contamination of street heroin samples; access to supervised injecting facilities, education for injecting drug users; and ready access to the opioid antagonist naloxone.

In this study, the harms of GHB ranked relatively low when compared with similar studies in the UK (Nutt et al., 2010) and the Netherlands (Van Amsterdam et al., 2010, 2015a, 2015b). GHB use in Australia seems to have stabilised, with less than 1% of Australians aged over 14 years having used GHB at some stage in their life and 0.1% having used it in the previous 12 months (Claydon et al., 2017). Emergency department presentations continue, especially on weekends and public holidays in

inner city hospitals, with patients presenting mostly with varying levels of altered conscious state including coma (Dietze et al., 2014; Munir et al., 2008) but the rapid increase in presentations in the early 2000s has not been sustained. As well as the acute harms, there is emerging evidence of more chronic problems with memory and information processing in those users who experience recurrent episodes of coma (Raposo et al., 2018a, b) and delirium in acute withdrawal. As GHB use continues, the greater harms associated with GHB use will become apparent with time.

Limitations to the MCDA approach to assessing the drug harms have been discussed in previous publications (Nutt et al., 2010; Van Amsterdam, 2015a, 2015b). For example, some of the harms assessed in MCDA are unequivocally influenced by their legal status in the community, and it could be argued that the MCDA would be more accurate if only the harms resulting directly from the use of the drug – notwithstanding its legal status – were addressed. However, it was decided not to change these so that the findings could be compared with other international studies. In addition, rankings reflect only the current state of knowledge; for example, the harm status of ENDS in certain contexts remains to be determined, fentanyls or the more potent carfentanil may present greater risks if their prevalence, increases. Purity of crystal methamphetamine on the other hand may decrease, which may lower levels of harm over time (Scott et al., 2015). Also needing acknowledgement is that this exercise focused on the Australian population in general, and rankings within sub-populations of Australia would be different. Regional and rural communities, for example, have higher rates of use of methamphetamine and less access to treatment services, resulting in greater harms. Some remote indigenous Australian communities also have specific and significant problems with the recreational use of solvents and fuels. Another potential limitation is that the panel did not specifically include persons with a lived experience. It was deemed, however, that the diversity of our panel both in terms of extensive practice experience, skills, background and geography redressed these limitations.

International comparison of drug-related harms is essential. Comparing and contrasting trends between countries and regions to understand the most effective approach to a global problem, is a necessary step in understanding the impact of these drugs. Multi-criteria decision analysis is a useful approach to issues of concern for which there is no simple answer; using mathematical modelling to assess harms related to substance use that extend well beyond the traditional measures of drug-related morbidity and mortality, and that include assessment of harms that extend beyond the user to community. Application of this broad but detailed technique in different global regions enables useful international comparisons of trends in drug use and associated harms and hence informed debate by which to arrive at effective drug policy.

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Authors contributions

Yvonne Bonomo: literature search, study design, data interpretation, manuscript writing, expert panel member; David Castle: study design, data interpretation, writing, expert panel member; David Nutt: study design, data interpretation, writing; Amanda Norman: literature search, data interpretation, writing; Adam Pastor: data interpretation, writing, expert panel member; Simon Lenton: data interpretation, writing, expert panel member; Raimondo Bruno: data interpretation, writing, expert panel member; Dan Lubman: data interpretation, writing, expert panel member; Sharon Dawe: data interpretation, writing, expert panel member; Diana Egerton-Warburton: data interpretation, writing, expert panel member; Mark Daglish: data interpretation, writing, expert panel member; Sam Biondo: data interpretation, writing, expert panel member; John Ryan: data interpretation, writing, expert panel member; Jonathan Karro: data interpretation, writing, expert panel member; Charles Kim: data interpretation, writing, expert panel member; Jill Rundle: data interpretation, writing, expert panel member.





Declaration of conflicting interest

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This is Exhibit F referred to in the
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 sworn before me, this 29th
 day of April 20²⁴

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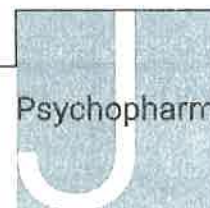
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 with commissioner Joanna Shaw in the city of Toronto, Ontario.

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Adverse effects of psychedelics: From anecdotes and misinformation to systematic science

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Abstract

Background: Despite an increasing body of research highlighting their efficacy to treat a broad range of medical conditions, psychedelic drugs remain a controversial issue among the public and politicians, tainted by previous stigmatisation and perceptions of risk and danger.

Objective: This narrative review examines the evidence for potential harms of the classic psychedelics by separating anecdotes and misinformation from systematic research.

Methods: Taking a high-level perspective, we address both psychological and psychiatric risks, such as abuse liability and potential for dependence, as well as medical harms, including toxicity and overdose. We explore the evidence base for these adverse effects to elucidate which of these harms are based largely on anecdotes versus those that stand up to current scientific scrutiny.

Results: Our review shows that medical risks are often minimal, and that many – albeit not all – of the persistent negative perceptions of psychological risks are unsupported by the currently available scientific evidence, with the majority of reported adverse effects not being observed in a regulated and/or medical context.

Conclusions: This highlights the importance for clinicians and therapists to keep to the highest safety and ethical standards. It is imperative not to be overzealous and to ensure balanced media reporting to avoid future controversies, so that much needed research can continue.

Keywords

Psilocybin, dimethyltryptamine, ayahuasca, mescaline, d-lysergic acid diethylamide, abuse liability/dependence, hallucinogen persistent perception disorder, toxicity, hypertension

Introduction

Psychedelic medicines are a rapidly developing area of clinical research (Nutt and Carhart-Harris, 2021) and public health policy. Clinical developments, together with changes in public interest, are increasingly leading to substantive changes at the regulatory level in the United States and Canada (Aday et al., 2020a). Within the past 3 years, psilocybin and other organic psychedelics have been decriminalised in Denver, Colorado; Oakland, California; Santa Fe, California; Ann Arbor, Michigan; Somerville, Massachusetts; Washington, D.C.; and the state of Oregon. Going beyond decriminalisation, Oregon voters recently passed a bill giving the Oregon Health Authority 2 years to develop a division to regulate the production, distribution, administration and possession of psilocybin.

In Canada, last year, the Minister of Health gave approval on a case-by-case basis for several terminally ill patients to receive psilocybin for the purposes of treating end-of-life distress (Lozano, 2020). Successful preliminary results led Health Canada to announce in December 2020 their intention to expand the Special Access Programme (SAP), so that practitioners could, on behalf of patients with serious or life-threatening conditions, request access to restricted drugs. This change would significantly broaden the number of individuals permitted to access psychedelic therapy. Subsequently, Health Canada granted exemption to 16 healthcare professionals to take psilocybin themselves for personal training (Dubinski, 2020), which is indicative of a rapidly

growing infrastructure for psilocybin-assisted therapy in Canada. In Europe, a special use programme for d-lysergic acid diethylamide (LSD) and psilocybin has been established in Switzerland to provide compassionate access to (mainly major depression and post-traumatic stress disorder (PTSD)) patients not responding to other treatments (Schmid et al., 2021).

Although these changes in regulation suggest that the stigma surrounding psychedelics may be dissipating, still many misconceptions exist. This narrative review aims to separate the anecdotes and misinformation from the systematic evidence. We cover the classic serotonergic psychedelics (5-HT_{2A} receptor

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agonists, referred to 'psychedelics' henceforth): these are plant-derived medicines; psilocybin, N, N-dimethyltryptamine (DMT), ayahuasca, mescaline and those synthesised in the laboratory, LSD. We exclude n-BOMEs, 3,4-methylenedioxymethamphetamine (MDMA), ketamine and ibogaine, as these are distinguished from classic psychedelics, both in their effects and in their pharmacology. We focus on the effects of full psychedelic doses; for an in-depth review on microdosing psychedelics, please see Kuypers et al. (2019). For more details on the pharmacology and neuroscience of the drugs we discuss, please see Nutt et al. (2020).

Assessing the risks of psychedelic use is challenging, as there are many different substances, applications, environments and population groups in this rapidly developing field. This article looks at the potential adverse effects of psychedelics, using the current science to outline risks as well as anecdotes surrounding harms. Many of these risk perceptions originate from the first wave of psychedelic repression in the middle of last century often with sensationalised media reports. Yet, these still contribute to their current stigmatisation.

Johansen and Krebs (2015) propose that modern anti-psychedelic legislation began over 100 years ago when rival religious groups campaigned against Native American peyote use, calling peyote 'addictive' as well as an 'insidious evil' (Newberne and Burke, 1922). Although evidence and human rights arguments led to exemptions for specific indigenous groups, the laws and biases against peyote remained in place and were then extended to other psychedelics.

Still today, psychedelics attract emotive and often polarised opinions (Rucker et al., 2018). It is essential to address this issue now as psychedelics are increasingly shown to treat a broad range of hard to treat disorders, with the potential to treat many more.

For our review, we gave precedence to randomised controlled trials (RCTs), systematic observational data collections and systematic reviews. Except where compelling, we avoided individual case reports for reasons outlined in detail by Krebs and Johansen (2013), such as the frequent failure to rule out pre-existing conditions or the use of other drugs, which could have contributed to adverse effects after psychedelic use.

LSD

First synthesised by Albert Hofmann in 1938, LSD is a semi-synthetic tryptamine derived from the naturally occurring ergot alkaloid ergotamine (Nichols, 2004). It acts primarily as a serotonergic receptor agonist and also acts at dopaminergic and adrenergic receptor sites (Nichols, 2004). Having been described as a 'problem child' (Hofmann, 1979), LSD became a major focus of negative public perceptions, many of which still prevail today.

By 1961, a large body of research with LSD in humans, incorporating over 1000 papers, including over 40,000 participants, had accumulated (Nutt et al., 2013). Although studies were small, they reported largely positive effects and a lack of adverse effects (as reported by the clinician). However, significant shortcomings were outlined in a review at that time (Savage et al., 1966), including lack of appropriate controls, small numbers of participants, inappropriate statistical analyses and importantly lack of follow-up, which has been rectified in recent trials. Unfortunately, for this promising field of research, however, the 1960s experimentation with LSD (and to a lesser extent, psilocybin), by

infamous Harvard psychologists Richard Alpert and Timothy Leary, and the emergence of 1960s counterculture led to a media frenzy and sensationalised representations of these substances, contributing to the halt of promising scientific research and national and international (under the 1971 UN Conventions) bans on LSD. Once LSD was banned, most countries made other serotonergic psychedelics illegal as well (Nutt et al., 2013; Rucker et al., 2018).

Psilocybin

Psilocybin is found in over 200 species of mushrooms. Psilocybin-containing mushrooms have been used for religious purposes throughout Mesoamerica for centuries (McKenna and Riba, 2016), with mushroom-shaped artefacts dating back to at least 500 BC (Guerra-Doce, 2015). In the West, psilocybin was first isolated in 1958 (Hofmann et al., 1958). While it was the lesser studied psychedelic in the 1960s in comparison to LSD, it has been the focus of much contemporary research, including as an efficacious treatment (combined with psychotherapy) for obsessive compulsive disorder (OCD) (Moreno et al., 2006), treatment-resistant depression (TRD) (Carhart-Harris et al., 2016), smoking cessation (Johnson et al., 2014) and alcoholism (Bogenschutz et al., 2015), leading to an increasing body of positive evidence being developed. The first RCT comparing psilocybin to a conventional selective serotonin reuptake inhibitor (SSRI) antidepressant found the former to be as efficient at reducing symptoms of depression, and with fewer side effects (Carhart-Harris et al., 2021). However, sample sizes remain small, and further research – using rigorous methodologies to address issues, such as blinding – is required to further understand the (long-term) effectiveness of these treatments.

Mescaline

Mescaline (3,4,5-trimethoxyphenethylamine) was first isolated from *Lophophora williamsii*, the peyote cactus, in 1896 by Arthur Heffter, making it the first naturally occurring psychedelic alkaloid to be isolated in the laboratory (Heffter, 1998). Peyote has a long history of religious use, dating back at least 5700 years (El-Seedi et al., 2005). Compared to the other classic psychedelics, contemporary research with mescaline has remained relatively limited to date and, despite its appearance in 'The doors of perception' (Aldous Huxley, 1954), it does not appear to be as prevalent in the public consciousness as LSD and psilocybin, potentially because of its lesser potency (Wolbach et al., 1962). However, recent naturalistic and online survey studies indicated that users report mental health benefits, such as reported improvements in depression and anxiety, related to its use (Agin-Liebes et al., 2021; Uthaug et al., 2021). In Basel, Switzerland, an ongoing clinical trial is directly comparing the effects of mescaline, psilocybin and LSD in healthy subjects (NCT04227756).

DMT and ayahuasca

DMT has become increasingly widely used in Western society in recent years (Winstock et al., 2013), both as the vapourised and inhaled form and as a psychoactive component of the hallucinogenic brew, ayahuasca. Although similar to LSD and psilocybin

Table 1. Potential adverse effects of psychedelics.

Psychological and psychiatric	Physiological
Hallucinogen use disorder	Toxicity, overdose risk
Abuse liability and dependence	Neurotoxicity
Hallucinogen-induced disorders	Hypertension, cardiovascular disease
Harms to self/others	Emergency medical treatment
Challenging experiences	
Hallucinogen persistent perception disorder	

in its molecular composition and affinity for the 5-HT_{2A} receptor (Rickli et al., 2016), DMT also possesses other unique characteristics (Garcia-Romeu et al., 2016), having been identified in human bodily fluids and in rats' pineal gland (Barker et al., 1981). Indolethylamine N-methyltransferase (INMT), the enzyme synthesising DMT from tryptamine, is widely found in the human body, although its physiological role is still unclear (Garcia-Romeu et al., 2016).

Used for millennia by Amazonian indigenous groups for medicinal and religious purposes, ayahuasca is a psychoactive plant tea, typically obtained from *Banisteriopsis caapi* and *Psychotria viridis* (Schultes and Hofmann, 1979). *B. caapi* contains beta-carboline alkaloids with monoamine oxidase inhibitor (MAOI) action, whereas *P. viridis* contains DMT. In addition to the traditional contexts, by now there is a large amount of anecdotal evidence of Western individuals having healed their depression, anxiety, addiction, PTSD and other trauma, and more through ayahuasca (e.g. Grob et al., 1996), highlighting the importance of further studying these promising effects scientifically. Palhano-Fontes et al.'s (2019) recent RCT supports the safety and therapeutic properties of ayahuasca, dosed within an appropriate setting, to help treat depression.

Adverse effects of psychedelics

Psychedelics have come a long way since the first wave of experimentation and research. However, their potential range of psychological and psychiatric, as well as physiological risks remains to be fully understood. Table 1 provides an overview of key potential adverse effects of psychedelics, focusing on those which still loom large in public perceptions. We explore the evidence base for these adverse effects to elucidate which of these are merely based on anecdotes versus those that stand up to close scrutiny with current scientific methods.

Psychological and psychiatric risks

Hallucinogen use disorder

In the 1960s, the perception that psychedelics cause a special type of dependence, defined as 'period use amongst arty types', contributed to their strict international scheduling. Psychedelics were considered to have high abuse potential simply because there were frequent reports of their use (Isbell and Chrusciel, 1970).

The *Diagnostic and Statistical Manual of Mental Disorders*, (5th edition; *DSM-V*) acknowledges psychedelic use only as it

pertains to hallucinogen persisting perception disorder (HPPD, outlined below), hallucinogen use disorders (HUDs) and hallucinogen-induced disorders (including psychotic and depressive disorders). HUDs fall under three broad categories: other HUD, hallucinogen dependence and hallucinogen abuse. HUD is described in *DSM-V* as a problematic pattern of hallucinogen use (other than phenylcyclohexyl piperidine; PCP) leading to clinically significant impairment or distress. Diagnostic criteria are summarised in Panel 1. (In *Diagnostic and Statistical Manual of Mental Disorders*, (4th edition; *DSM-IV*), this category was called HUDs.)

Panel 1: Other HUD – DSM-V diagnostic criteria

1. The hallucinogen is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control hallucinogen use.
3. A great deal of time is spent in activities necessary to obtain the hallucinogen, use the hallucinogen or recover from its effects.
4. Craving, or a strong desire or urge to use the hallucinogen.
5. Recurrent hallucinogen use resulting in a failure to fulfil major role obligations at work, school or home (e.g. repeated absences from work or poor performance related to hallucinogen use; hallucinogen-related absences, suspensions or expulsions from school; neglect of children or household).
6. Continued hallucinogen use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the hallucinogen (e.g. arguments with a spouse about consequences of intoxication; physical fights).
7. Important social, occupational or recreational activities are given up or reduced because of hallucinogen use.
8. Recurrent hallucinogen use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by the hallucinogen).
9. Hallucinogen use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the hallucinogen.
10. Tolerance, as defined by either of the following:
 - (a) A need for markedly increased amounts of the hallucinogen to achieve intoxication or desired effect.
 - (b) A markedly diminished effect with continued use of the same amount of the hallucinogen.

Dependence

Hallucinogen dependence is a separate category to HUD, based on generic substance use dependence criteria, several of which do not apply to hallucinogens. Withdrawal symptoms and signs are not established for hallucinogens, and so this criterion is not included. In hallucinogen abuse, hallucinogens are used but

much less often than in hallucinogen dependence. Diagnostic criteria include a pattern of pathological use, the impairment of social or occupational functioning due to use, and duration of disturbance of at least 1 month.

Psychedelic use does not conform to the profile of clinical features representing other types of dependencies, for example, opioids (Morgenstern et al., 1994). Very few hallucinogen users experience an inability to cut down or control use, a key indicator of dependence. HUD is relatively uncommon, with a low risk of development following exposure to hallucinogens (Shalit et al., 2019). The vast majority of hallucinogen users do not transition to hallucinogen dependence (Stone et al., 2006).

In Anthony et al.'s (1994) classic study on problematic drug use, based on representative data from the US National Comorbidity Survey, psychedelics had the lowest rate of abuse from all drugs analysed of users who qualified for a dependence diagnosis (4.9%). The Substance Abuse and Mental Health Services Administration (SAMHSA, 2017) also ranked psychedelic use at the bottom in terms of their dependence risk, although by their estimation up to 9% of psychedelic users may develop dependence (this higher percentage may be explained by the inclusion of MDMA and PCP). According to other studies using *DSM-IV* criteria, a far lower proportion of users develop hallucinogen dependence. For example, Kendler et al. (1999) provide a 0.2% estimate of hallucinogen dependence among hallucinogen-using female twins.

Today, research has repeatedly shown that psychedelics do not cause dependence or compulsive use (Halberstadt, 2015; Johnson et al., 2018; Morgenstern et al., 1994; Nichols, 2016). The effects of psychedelics are not universally euphoric (and can be dysphoric), tolerance develops quickly, cannot be overcome by dose escalation and there is no known withdrawal syndrome (Rucker et al., 2018), indicating a low risk of dependence in line with current *DSM-V* diagnostic criteria.

Tolerance – the decreased response with repeated administration of a drug – has been reported to develop rapidly to the euphoric and psychedelic effects of hallucinogens but not to the autonomic effects, such as pupillary dilation, hyperreflexia, increased blood pressure (BP), increased body temperature, piloerection and tachycardia. Cross-tolerance exists between LSD and other hallucinogens (e.g. psilocybin and mescaline). The fast build-up of tolerance and lack of withdrawal symptoms has been repeatedly shown in the literature (e.g. Krebs and Johansen, 2013; Liechti, 2017; Nichols, 2004), except for ayahuasca, which leads to minimal tolerance (Dos Santos et al., 2012).

Abuse liability

Johnson et al. (2018) reviewed the abuse potential of medical psilocybin according to the eight factors of the controlled substances act, highlighting its limited reinforcing effects. However, although low in comparison to other scheduled substances, psilocybin does have some limited potential for abuse. Using the Addiction Research Centre Inventory (ARCI), Johnson et al. (2018) found a major difference in the abuse potential associated with psychedelics, as compared with other substances that carry a high risk of compulsive pattern of repetitive use and abuse, as LSD and psilocybin were repeatedly found to have a substantially lower potential for use and abuse (Johnson et al., 2018).

Especially, the responses to the LSD scale contained a cluster of reported negative, unpleasant responses to LSD, such as 'I feel anxious and upset', that are associated with a lower propensity to frequently and repeatedly self-administer (Griffiths et al., 2008).

In comparison with other psychoactive drugs, psychedelics score consistently low in their abuse potential (Fábregas et al., 2010). Psilocybin has been evaluated, together with LSD in various preclinical models of dependence and abuse potential, yielding qualitatively similar results, with no physical dependence or withdrawal (Martin, 1973). Early studies showed that drugs commonly accepted as having hallucinogenic properties are not self-administered by laboratory animals (the gold standard test for dependence potential) supporting their low dependence in humans (see detailed analysis by Griffiths et al., 1979). Griffiths et al. (1979) show that the psychedelics mescaline, 2,5-dimethoxy-4-methylamphetamine hydrochloride (DOM), 2,5-dimethoxy-4-ethylamphetamine hydrochloride (DOET) and 4-methoxyamphetamine hydrochloride (PMA) did not maintain self-administration in laboratory animals, whereas other hallucinogens, for example, PCP (phencyclidine) did. This finding was further confirmed in a detailed review by Carroll (1990) who found that PCP is a highly effective reinforcer in animals, whereas LSD and other hallucinogens are not. Griffiths et al. (1979) concluded that the reinforcing effects of PCP are most likely unrelated to its hallucinogenic properties, and that the lack of self-administration in animals agrees with the finding that people use psychedelics at a very low level and that most discontinue use spontaneously. In support of this early work, a recent study in three baboons showed that, under daily schedules, they self-administered very low amounts of LSD, considerably less than cocaine. This did increase in two of these non-human primates under intermittent schedules, although still at a much lower level than cocaine (Goodwin, 2016).

Looking at psilocybin, Gable (1993) concluded that it carries a lower dependence risk than caffeine, and being among the lowest risks of death of all major substance abuse categories. In relation to ayahuasca, Gable (2006) found no evidence of abuse potential and compared its safety margin to codeine, mescaline or methadone. Rather, long-term psychological benefits have been documented when ayahuasca is used in a well-established social context. Yet, while Gable (2006) suggests that the dependence potential of oral DMT and the risk of sustained psychological disturbance are minimal, Winstock et al. (2013) argue that the very desirable effect profile of smoked DMT indicates a high abuse liability which may be offset by a low urge to use more. Similarly, administration of LSD results in high acute drug liking ratings but no craving (Holze et al., 2021; Schmid et al., 2015).

Investigating the potential abuse risk in regular ayahuasca users, Fábregas et al. (2010) used the addiction severity index (ASI) to assess addiction severity between rural and urban users in Brazil, concluding that the ritual use of ayahuasca, as assessed with the ASI in currently active users, was not associated with the negative psychosocial effects caused by other drugs of abuse.

In summary, although there have been isolated case reports of abuse (e.g. Modak et al., 2019), the characterisation of psychedelics as addictive is based on misinformation and misunderstanding. In fact, today these compounds are more often discussed in terms of their anti-addictive properties (e.g. Bogenschutz et al., 2015; Johnson et al., 2017).

A handwritten signature in black ink, followed by the initials '13' written in blue ink.

Harms to self and other

As emotional experiences can be intensified when under the influence of psychedelics, set and setting are crucial. Set and setting – the expectations and personal experiences of the users as well as the external environment – are established elements of psychedelic research and recognised as having a major impact on users' experience (Aday et al., 2021; Johnson et al., 2008). In unprepared individuals and/or in unsafe settings, effects of psychedelics may have the potential to escalate into dangerous behaviour (Johnson et al., 2008). Although very rare, there are reports of individuals jumping from buildings and ending their lives (e.g. Honyiglo et al., 2019; Keeler and Reifler, 1967). While these occurrences are uncommon compared with other psychoactive drugs – especially alcohol – they are widely reported in the media which contributes considerably to public perceptions of their risks.

In contrast, scientific research consistently assesses psychedelics as much less harmful to the user as well as to society compared to alcohol and almost all other controlled substances. In their seminal comparative drug harms studies, using Multi-Criteria Decision Analysis (MCDA), Nutt et al. (2010) ranked LSD among the drugs with the lowest harms, both for the individual and to society and 'magic mushrooms' received the lowest overall harm score (Nutt et al., 2010). These findings have been replicated in the Netherlands (Van Amsterdam and Van den Brink, 2010, Europe (Van Amsterdam et al., 2015) and Australia (Bonomo et al., 2019). Carhart-Harris and Nutt's (2013) survey of both substance users and other experts, again placed LSD and psilocybin in the lowest harm categories, and Morgan et al.'s (2010) survey of drug users further confirmed these findings.

In Carbonaro et al.'s (2016) online survey about challenging experiences after consuming 'mushrooms', 11% of users reported putting themselves or others at risk of physical harm. This was often related to greater (estimated) dosage, difficulty of the experience and lack of physical comfort and social support – all of which can be controlled under clinical conditions.

A challenging experience

An adverse reaction to psychedelics can include a 'bad trip' (in lay language) or a 'challenging experience' (in therapeutic language). Although there is no exact definition of such an experience, most involve feelings of fear, anxiety, dysphoria and/or paranoia, making it essential that the experience is prepared for, supervised and followed by extensive integration. These experiences are usually short-lived, that is, lasting the time of the experience, and are often found to be cathartic.

Recent qualitative research sheds light on some of these experiences, moving them away from their negative perception, highlighting their potentially positive outcomes (Gashi et al., 2021). In Carbonaro et al.'s (2016) survey, 39% of the respondents rated their 'worst bad trip' as one of the five most challenging experiences of their lifetime – yet the degree of difficulty was positively associated with enduring increases in well-being. Griffiths et al. (2006) found that in a controlled study of healthy volunteers, high doses of psilocybin created extreme fear in 30% of participants, yet 80% of these participants also reported subsequent improvements in well-being. Similarly, in healthy volunteers administered high doses of LSD of 100 and 200 µg in a controlled

setting, fear (with ratings > 50% on a visual analogue scale) is reported in approximately 20% and 30% of participants, respectively. Notably, more than 90% of the participants report good drug effects (> 50%) in the same session (Holze et al., 2021; Schmid et al., 2015). Recent clinical research also suggests that unpleasant reactions (such as anxiety, paranoia and confusion during the psychedelic experience) tend to be transient and do not diminish the therapeutic benefits of psychedelics in reducing depressive symptoms (Carhart-Harris et al., 2016).

Further research is required because the exact knowledge of what causes a challenging experience and who is susceptible to these experiences remains scarce. A recent systematic review found that individuals high in the traits of absorption, openness and acceptance as well as a state of surrender were more likely to have positive experiences with psychedelics, whereas individuals low in those domains or in a preoccupied/apprehensive state were more likely to experience acute adverse effects (Aday et al., 2021). Importantly, there were no sex differences, and increased age and experience with the drugs was related to slightly less intense effects. Similarly, effects of LSD were not influenced by sex or body weight in a pooled study of 81 healthy subjects. However, genetic polymorphisms of the CYP2D6 enzyme – responsible for breaking down many commonly used medicines – significantly influenced the pharmacokinetics and in part also the subjective effects of LSD (Holze et al., 2021).

Setting is likely a key influence of the progress of a psychedelic experience, as is the dose used, with a higher dose more likely to lead to these experiences (Johnson et al., 2014). Understanding the specific circumstances and individuals in which psychedelics may lead to challenging experiences will have important implications for future clinical research and harm reduction strategies.

Serious mental health effects, including psychosis and suicide

Fears of psychedelics leading to psychosis date back to the move to ban LSD, emphasising cases of 'acid casualties', which had a powerful impact on society's representations of psychedelics, although these instances are rare, especially in clinical use (see Table 2).

For example, Cohen (1960) found one single case of a psychotic reaction lasting more than 48 h, out of 1200 experimental, non-patient research participants administered LSD or mescaline. This individual was the identical twin of a patient with schizophrenia, who would have been excluded from the research under current conditions. McGlothlin and Arnold (1971) reported one case (out of 247 participants) in which an LSD-related psychotic episode lasted more than 48 h. Although very rare, it is important to be attentive to these negative experiences and to develop enhanced safety protocols accordingly.

Earlier studies sometimes neglected the importance of set and setting, contributing to the risk of adverse effects occurring (e.g. Malitz et al., 1960; Rinkel et al., 1960) and did not include the stringent control conditions or groups that are standard in today's clinical psychopharmacology research (Johnson et al., 2008). Adverse patient outcomes were often the result of unethical scientific methods, including restraining patients during the experience and administering high doses of LSD to unprepared, restrained patients (e.g. Smart et al., 1966). With present safety

Table 2. Pooled papers of serious adverse effects.

Reference	Drug and subjects	Relevant findings
Cohen (1960)	25,000 LSD drug sessions. 5000 subjects and 25,000 drug sessions.	Suicide attempts by 1.2/1000 LSD patients; completed suicides by 0.4/1000 patients with a mental health disorder. Mescaline patients experienced agitation and very low BP and pulse, but no serious adverse events.
Chandler and Hartman (1960)	700 LSD-25 sessions.	One case of prolonged psychosis
Ling and Buckman (1963)	350 outpatients over 4 years, using LSD.	One attempted suicide
Malleson (1971)	4000 LSD patients, 50,000 sessions.	Three suicides in patients with a mental health disorder. One death of a neurotic asthmatic male, 12 h after third LSD session (dose 100 µg) One sudden death after seventh LSD session (dose 200 µg) but no organic abnormalities.

LSD: d-lysergic acid diethylamide.

protocols for psychedelic research, such occurrences are significantly less likely, although individual cases of serious adverse effects can and do occur.

In non-clinical settings, there have been rare cases of psychedelics triggering psychotic episodes (e.g. Dos Santos et al., 2017; Tapia et al., 2021). In Carbonaro et al.'s (2016) survey, for three users (i.e. 0.15% of participants), the experience was reported to be associated with the onset of prolonged and distressing psychotic symptoms. However, this study specifically sought out individuals who had negative experiences with the drug.

This risk is greatly reduced with psychiatric screening. Those with a predisposition towards psychotic illnesses (i.e. personal or family history of schizophrenia or bipolar disorder) are generally excluded from clinical treatment with psychedelics (Johnson et al., 2008). With such screening, no psychotic episodes have been documented in modern clinical trials to the best of our knowledge.

In their systematic review, Zeifmann et al. (2021) examined the relationship between classic psychedelics and suicidality. Results suggest that psychedelic therapy can reduce suicidality in certain clinical psychiatric populations, and that classic psychedelic use may buffer against, and be associated with reductions in suicidality. However, in unsafe and unmonitored settings, psychedelic use can, on rare occasions, also lead to fatal consequences, including suicide, but Zeifmann et al. (2021) stress the highly limited nature of their source literature, with the majority of the included studies being case studies or small case reports using retrospective data.

Two large-scale population studies, each comprising over 130,000 US adults, and using data from the National Survey on Drug Use and Mental Health (NSDUH), found no evidence of an association between psychedelic use and mental health problems (Johansen and Krebs, 2015; Krebs and Johansen, 2013). Johansen and Krebs (2015) found that psychedelic users were no more likely to have experienced psychological distress, suicidal thoughts or behaviour, depression, anxiety or to have received mental health treatment in the past year than those who had not taken psychedelics. In contrast, people who had used psychedelics were less likely to have required mental health treatment in the past year than those who had not. Hendricks et al. (2015) report similar findings. The evidence for serious adverse events

remains low and recent RCTs using psychedelics in various non-psychotic psychiatric disorders are showing good evidence for both safety and efficacy (Carhart-Harris et al., 2021; Palhano-Fontes et al., 2019).

HPPD

A common perception linked to psychedelics is that they induce 'flashbacks' of the drug experience long after its acute effects have subsided. Although transient drug-free visual experiences resembling the effects of hallucinogens have been documented in psychedelic users (e.g. 40–60% of users; Baggott et al., 2011; Carhart-Harris and Nutt, 2010), they are not hallucinogen-specific, as they can also be caused by other psychoactive substances, for example, alcohol or benzodiazepines (Holland and Passie, 2011), and can occur in healthy populations (Halpern et al., 2016). In most cases, these side effects are mild and diminish in duration, intensity and frequency with time (Strassman, 1984).

If these symptoms are prolonged and distressing, the syndrome is known as HPPD. The *DSM-V* (American Psychiatric Association (APA), 2013) reports a prevalence rate for HPPD as 4.2% in hallucinogen users (Baggott et al., 2011) based on a single online questionnaire. Other studies have documented much lower prevalence rates of the disorder, some as low as 1/50,000 (Grinspoon and Bakalar, 1979). Furthermore, if approximately 1/25 users experience HPPD as suggested by Baggott et al. (2011), then it would be a near statistical certainty that some participants in the current era of psychedelic research, which has collectively included thousands of participants in trials since 2000 (Carhart-Harris et al., 2021; Ross et al., 2016), would have experienced HPPD by now; however, this has not been the case.

However, the emergence of large online fora dedicated to the discussion of HPPD on websites, such as Reddit (e.g. <https://www.reddit.com/r/HPPD/>, which has > 7000 members), suggests that cases can be identified at the population level, even if the prevalence is too low to be captured in clinical trials that typically use small sample sizes. While the large-scale data collection of online fora is helpful to gain insights into wider populations, samples are self-selected and likely to be biased, limiting the conclusions that can be drawn.

The incidence of HPPD appears to be much lower in the clinical context, perhaps as a result of efficient screening and preparation (Cohen, 1960; Johnson et al., 2008). Although Halpern and Pope (2003) suggest that there may be no identifiable risk factors for HPPD, a subsequent study of 19 individuals who developed HPPD found that all recalled anxiety and/or panic reactions during the triggering episode (Halpern et al., 2016). Thus, HPPD symptoms could potentially be conceived as a form of trauma response, similar to PTSD, or a form of health anxiety evoked by residual symptoms of the original experience.

Physiological risks

Neurotoxicity

A prevailing public belief about psychedelics is that they are neurotoxic (Presti and Beck, 2001). Much of this discourse has roots in the first era of psychedelic research in the mid-20th century, where several studies purported that users exhibited neurological or cognitive deficits (Acord, 1972; Acord and Barker, 1973); and others suggested that psychedelics (LSD in particular) damaged chromosomes (Cohen et al., 1967). Intriguingly and in contrast to this idea, Germann (2020) proposes the 'psilocybin telomere hypothesis' which states that psilocybin has a positive effect on leucocyte telomere length, which could reduce genetic ageing. In many cases, these earlier studies were refuted and retracted (e.g. Cohen et al., 1967; Dishotsky et al., 1971; Egozcue et al., 1968). Unfortunately, this did not generate the same media attention as the original work (Strassman, 1984), meaning that earlier studies played a major role in shaping media representations of psychedelics, ultimately shaping public opinion.

Most researchers now consider classic psychedelics to be non-toxic, that is, they do not damage mammalian organ systems, and as physiologically safe, even in very high doses (Gable, 2004; Halpern et al., 2005; Halpern and Pope, 1999; Malcolm and Thomas, 2021; Nichols, 2004). No long-term neurocognitive deficits have been reported by participants in the contemporary era of research (please see Aday et al., 2020b for a recent review). In a cross-sectional study, Doering-Silveira et al. (2005) compared adolescent ayahuasca users with matched non-user controls using a battery of neuropsychological tests and found no neurological deficits in users. Other studies comparing ayahuasca users with matched controls have documented *increased* working memory and executive functioning in users (Bouso et al., 2012), supporting the idea that psychedelics have neuroplastic and neurogenic properties (Catlow et al., 2013; Jepsen et al., 2020; Ly et al., 2018). DMT induces the proliferation of neural stem cells, migration of neuroblasts and generation of new neurones in the hippocampus of mice leading to improvements in working and recognition memory (Morales-García et al., 2017, 2020). These effects may explain why their therapeutic effects are so long-lasting (Carhart-Harris et al., 2016; Magaraggia et al., 2021) although further human mechanistic studies are required.

Overdose toxicity

Psychedelics are physiologically safe in humans when ingested at standard doses (Dos Santos et al., 2012; Gasser et al., 2014;

Nichols, 2004; Nichols and Grob, 2018). Overdose deaths have occurred due to ingestion of very large doses, that is, more than 23 times the previously recommended LSD human dose (Lim et al., 2012; Nichols and Grob, 2018; Van Amsterdam et al., 2011) or by mixing psychedelics with other drugs and/or alcohol (Gable, 2004; Van Amsterdam et al., 2011). For a summary of overdose and toxicity events reported in the literature, please see Table 3.

In rats, psilocybin has been reported to have an LD50 of 280 mg/kg (Cerletti, 1958, as cited in Passie et al., 2002). This is over 700 times the high dose of 25 mg used in clinical studies, for an average body weight of 70 kg. LSD has also been shown to be safe with very low physiological toxicity (Nichols, 2016). However, there have been cases of death by overdose of psychedelics with the majority from LSD (Fysh et al., 1985; Nichols and Grob, 2018) and psilocybin (Lim et al., 2012; Van Amsterdam et al., 2011) – probably because these are the most widely used. Supplemental Appendix 1 provides a summary of these and other case reports. Older reports of administration of LSD or mescaline in a clinically supervised setting have found adverse effects or death due to the person's underlying health conditions, such as, manic-depressive illness, acute asthma and depersonalisation syndrome (e.g. Cohen, 1960; Malleon, 1971). Yet, equally there are reports of ingesting large quantities of LSD with successful recovery and without long-lasting effects (Nichols and Grob, 2018).

Long-term ritual consumption of ayahuasca is not toxic or harmful to adults (Dos Santos, 2013) or in adolescents (Doering-Silveira et al., 2005). Doering-Silveira et al. (2005) also found no foetal deaths or abnormalities in mothers who used ayahuasca during pregnancy. However, large, well-conducted longitudinal trials in pregnant women would be needed to confirm these findings. One feature of ayahuasca, enhancing its safety profile, is the side effect of nausea and vomiting, especially at high doses (Dos Santos et al., 2012; Riba and Barbanoj, 2005; Van Amsterdam et al., 2011) which may prevent continued drug administration and overdose.

Cardiovascular pathology in human studies

Psychedelics can induce short-lived and non-clinically significant sympathomimetic effects, including on heart rate, BP, pupil size and body temperature, as shown in Table 4.

Most studies examined involved healthy subjects, some included patients with anxiety, or OCD, and in one large study of participants in ayahuasca ceremonies, a small number were taking antidepressant medication. Schmid et al. (2015) found that LSD induced a small but significant increase in BP, heart rate and body temperature in a sample of 16 healthy volunteers with normal values restored at 24 h post-dosing. Other studies reported similar results for LSD (Dolder et al., 2016; Gasser et al., 2014; Holze et al., 2020, 2021), psilocybin (Carbonaro et al., 2018), ayahuasca (Dos Santos et al., 2012) and DMT (Strassman et al., 1996). Combined results from Riba and Barbanoj's (2005) double-blind pilot study and clinical trial with ayahuasca found that 6 out of the 24 volunteers in their study met the diagnostic criteria for hypertension during drug administration and one volunteer had tachycardia. However, no medical assistance was required, and participants' symptoms subsided.

Table 3. Overdose and toxicity effects.

Reference	Design	Subjects	Drug	Relevant findings
Nichols and Grob (2018)	Case Studies	Five cases; 14-, 28- and 30-year-old males and a 20-year-old female. One gender and age unknown.	LSD	One death by an LSD overdose equivalent to 320 mg, two by asphyxiation and one from LSD toxicity – HR increased to 164 bpm, BP to 122/64 and temperature to 98.2°F, but toxicological report indicated 1 ng/mL of LSD which equates to only 100 µg of LSD. One female with an increase in temperature of 105°F – death by multi-organ failure, hyperthermia, and possible LSD intoxication.
Van Amsterdam et al. (2011)	Case Studies	10 cases; eight males and two females (aged between 18 and 33 years).	Magic Mushrooms (inc. <i>Psilocybe baeocystis</i> and Hawaiian psilocybin)	Three deaths from jumping of high buildings, three by overdose, one from cold temperature after large consumption of psilocybe subcubensis, one death presumed heroin overdose alongside consumption of 10 psilocybin mushrooms and one death after consumption of approx. 50, mostly raw magic mushrooms.
Cohen (1960)	Survey	Questionnaires from 44 of 62 clinicians who treated healthy 23 to 44-year-old subjects or patients with LSD or mescaline on more than 25,000 occasions	LSD doses ranged from 25 to 1500 µg and mescaline ranged from 200 to 1200 mg	Suicide attempts by 1.2/1000 LSD patients; completed suicides by 0.4/1000 patients with a mental health disorder. Mescaline patients experienced agitation and very low BP and pulse, but no serious adverse events.
Malleson (1971)	Survey	4300 patients with psychosis received approx. 49,000 sessions and 170 experimental subjects received 450 sessions – all aged between 21 and 41 years.	Doses ranged from 25 to 1500 µg; most received 100–200 µg	Three suicides in patients with a mental health disorder. One death of a neurotic asthmatic male, 12 h after third LSD session (dose 100 µg) One sudden death after seventh LSD session (dose 200 µg) but no organic abnormalities.

LSD: d-lysergic acid diethylamide.

Table 4. Hypertension and cardiovascular effects.

Reference	Subjects	Drug and design	Relevant findings
Schmid et al. (2015)	16 healthy participants (eight males/eight females), aged between 25 and 51 years Half were hallucinogen naïve; half had limited experience. No history of psychiatric disorders.	Single LSD (200 µg) or placebo. A double-blind, randomised placebo crossover trial.	Participants monitored for 24 h. BP peaked at 1.75 h to 140/83, HR peaked at approx. 1 h 60–80 (bpm) and body temperature peaked to 37.8°C at 3 h. No significant increase in adverse effects from 24 h post-dosage.
Holze et al. (2020)	28 healthy participants aged between 25 and 45 years (14 females/14 males).	LSD (0.1 mg), MDMA (125 mg), D-amphetamine (40 mg) and placebo. Double-blind, placebo-controlled, cross-over design.	At approx. 1 h post-LSD, BP increased to 135/81 mm Hg, HR to 86 bpm and body temperature to 37.3°C. Approx. 1.5 h after MDMA, BP increased to 140/85 mm Hg and HR to 80 bpm. Body temperature increased to 37.4°C at 4 h. D-amphetamine increased BP to 153/94 mm Hg at 0.5–1 h, HR rose to 72 bpm at 6 h and body temperature to 37.2°C at 3 h.
Gasser et al. (2014)	11 old patients aged 39–64 years (seven males/four females) with anxiety associated with life-threatening diseases (majority had cancer; one had Parkinson's disease, one celiac disease and one Bechterew's disease). One patient with previous LSD experience.	LSD 200 µg (experimental dose) and 20 µg (active placebo). A double-blind, active placebo-controlled, RCT.	LSD did not significantly alter BP or HR. At 0 h, post-LSD mean HR (bpm) was 74.8 and 73.3 at 8 h. Mean BP was 130.3/80.0 at 0 h and 126.3/77.5 at 8 h.
Holze et al. (2021)	16 healthy participants aged between 25 and 52 years (eight males/eight females).	LSD (0.025, 0.05, 0.1 and 0.2 mg) and placebo. Double-blind, placebo-controlled, cross-over design.	LSD significantly increased heart rate at 0.1 and 0.2 mg, reaching 81 bpm at highest dose. BP increased at doses of 0.05 mg or higher, approx. 134/83 mm Hg at dose 0.2 mg.

(continued)

Table 4. (continued)

Reference	Subjects	Drug and design	Relevant findings
Dolder et al. (2016)	24 healthy participants aged between 25 and 60 years (12 males/12 females).	LSD 0.1 mg and placebo	Compared with placebo, LSD moderately increased BP, heart rate and body temperature.
Carbonaro et al. (2018)	20 healthy participants aged between 22 and 43 years (11 females/9 males). All had history of psychedelic drug use.	Double-blind design. Single, acute doses of dextromethorphan (DXM) 400 mg/kg, psilocybin 10, 20, and 30 mg/70 kg and placebo.	BP increased to 138/80 mm Hg after 10 mg/70 kg psilocybin, 142/85 mm Hg after 20 mg/70 kg and 140/87 mm Hg after 30 mg/70 kg. BP peaked to 144/85 mm Hg after DXM. 30 mg/kg psilocybin increased HR at 94 bpm and DXM at 103 bpm. Max effects occurred between 2 and 4 h and decreased after 6 h.
Dos Santos et al. (2012)	Nine healthy male volunteers with experience in psychedelic drug use.	Double-blind cross-over placebo-controlled clinical trial. Dose 0.75 mg DMT/kg body weight and a placebo.	For approx. 15–30 min, SBP rose to 141 mm Hg in three volunteers after one dose and 146 mm Hg for two volunteers. In two volunteers, it rose after two doses of 147 and 142 mm Hg. DBP values did not reach above 90 mm Hg and HR rose to 105 bpm in one volunteer after one dose.
Strassman et al. (1996)	13 healthy 22- to 45-year-old experienced hallucinogen users (nine males/four females)	Randomised double-blind study design. Volunteers received four infusions of 0.3 mg/kg DMT fumarate IV or saline placebo at 30 min intervals on two separate days.	At D1 HR 99/bpm and at D4 77/bpm. Mean arterial BP peaked to 116 mm Hg at first DMT infusion and 112 mm Hg at fourth DMT infusion. Both resumed to normal within approx. 30 min.
Riba and Barbanoj (2005)	6 male volunteers in pilot study and 18 (15 males/3 females) in final double-blind trial. All healthy experienced psychedelic users.	Single-blind design for pilot, used doses of 0.5, 0.75 and 1.0 mg DMT/kg body weight. In final, double-blind randomised design doses used were 0.6 and 0.85 mg DMT/kg.	With results combined, 6 out of 24 volunteers experienced hypertension (SBP values over 140 mm Hg for two volunteers and DBP values over 90 mm Hg for four volunteers) after doses 1 mg/kg DMT in pilot and 0.85 mg/kg DMT in final study. One volunteer experienced tachycardia with HR increasing to 100 bpm.
Moreno et al. (2006)	Nine 26- to 62-year-old subjects (seven males/two females) with DSM-IV – defined OCD.	Four single doses of psilocybin; 100, 200 and 300 µg/kg. A very small dose of 25 µg/kg was administered randomly at any time after the first low dose. A double-blind, active placebo-controlled, randomised clinical trial.	One subject experienced transient hypertension 132/90, 135/90, 142/105, 142/95 and 116/78 mm Hg at 0, 1, 4, 8 and 24 h, respectively after 200 µg/kg of psilocybin.
Durante et al. (2020)	614 participants aged between 18 and 55 years (321 males/293 females). 50 self-reported a psychiatric disorder (commonly depression and anxiety). 31 reported using psychiatric medication – analysis considered only SSRIs and SSNIs	Cross-sectional study. Self-reported questionnaire of ayahuasca use in religious context.	Tachycardia occurred occasionally in 200 participants with higher frequency in patients with a psychiatric diagnosis (at least occasionally: 62% vs 40.07%, $p=0.003$). No significant difference in adverse effects between participants who used antidepressants and those who did not.
Olbrich et al. (2021)	24 healthy volunteers aged 20–34 years (19 males/5 females)	Double-blind placebo-controlled RCT. Volunteers were divided into three groups. Placebo + placebo (179 mg mannitol and aerosil 1 mg) or Placebo + LSD (100 µg) or LSD + Ketanserin (40 mg).	LSD intervention increased HR, Ketanserin decreased HR, compared to the placebo condition. HR increased to approx. 60 bpm for placebo + placebo condition. For Placebo + LSD, HR increased to 70 bpm and for Ketanserin + LSD, HR increased to approx. 56 bpm.
Hasler et al. (2004)	Eight healthy 22- to 44-year-old volunteers (four males/four females).	Within-subject study design. Each volunteer received placebo and four different doses of psilocybin in random order on five experimental days at least 2 weeks apart: very low dose 45 µg/kg; low dose 115 µg/kg; medium dose 215 µg/kg and high dose 315 µg/kg.	BP peaked at 60 min to approx. 150/93 mm Hg after exposure to high dose. DBP significantly elevated up to 90 min ($p < 0.05$) SBP increased significantly at 60 min ($p < 0.001$) following HD Psilocybin. No change in body temperature or cardiac from baseline up to 24 h after drug administration.

LSD: d-lysergic acid diethylamide; MDMA: 3,4-methylenedioxyamphetamin; DXM: Dextromethorphan; DMT: dimethyltryptamine.

However, 200 out of the 641 participants taking part in Durante et al.'s (2020) study experienced tachycardia, and frequency of occurrence was higher in patients with a psychiatric diagnosis than those without. However, it is unclear if this was due to direct effects of ayahuasca or a result of participants' underlying psychiatric disorder and/or medication. No difference in adverse effects was found between participants who used antidepressants and those who did not (31 participants reported using antidepressant medication). However, the combination of MAOIs, such as that found in ayahuasca, with SSRIs has the potential to lead to serotonin syndrome (Gillman, 2010), highlighting the importance of educating ayahuasca drinkers of this potential risk.

Overall, adverse effects are observed at higher doses (Cohen, 1960), risks are substantially increased when mixed with other substances (Gable, 2004; Van Amsterdam et al., 2011) and mortality is more common in patients with physical or mental health disorders, such as acute asthma and manic-depressive illness, than in healthy subjects (Cohen, 1960; Malleon, 1971). These risks are greater when drugs are used in unsupervised settings. With adequate inclusion and exclusion criteria and clinical supervision, adverse physiological reactions are minimal (Malleon, 1971; Muttoni et al., 2019).

Even in non-supervised setting, adverse effects remain rare. Looking at the self-reported incidence of emergency medical treatment (EMT) sought for LSD and 'magic mushrooms', EMT is consistently low, and less than 1% of users report seeking help (Global Drug Survey (GDS), 2019). In comparison to other recreational drugs, psychedelics rank as the lowest in the United States, with 1.9 emergency department visits per 100,000 in 2011 (Substance Abuse and Mental Health Services Administration (SAMHSA), 2017). In relation to hospital admissions, SAMHSA (2017) shows that the rate of 'hallucinogens' as the primary substance is at 0.1% of hospital admissions.

A recent Freedom of Information request to the Office for National Statistics (ONS, 2021) confirms the remarkably low overdose rate of LSD and psilocybin. Based on deaths registered in England and Wales (between 1993 and 2020), there were eight deaths where LSD was specified on the death certificate and two deaths where psilocybin was mentioned, with one death certificate reporting the presence of both substances. As mentioned above, mixing psychedelics with other drugs and/or alcohol can have detrimental effects, including death (Van Amsterdam et al., 2011). The dose (Gable, 2004), route of administration and likelihood of any underlying health condition/s (Malleon, 1971) also determine potential adverse effects, such as multi-organ failure, hyperthermia and intoxication leading to other risky behaviours (Nichols and Grob, 2018; Van Amsterdam et al., 2011).

The quality of available evidence

When evaluating the potential risks of psychedelic medicines as scientifically and objectively as possible, it is important to acknowledge that some of the evidence presented above (particularly studies conducted pre-prohibition) is not of the highest standard as described by Rucker et al. (2016) in their recent review. But today's scientific-technological approaches have advanced considerably since the early research. For an example of current techniques applied to enable our understanding of how

psychedelics produce their effects, please see Singleton et al. (2021). Most earlier shortcomings are being addressed in recent trials, that is, in randomised placebo double-blind studies (Carhart-Harris et al., 2021; Mitchell et al., 2021).

We have included evidence from both eras in an attempt to incorporate large evidence based on the safety of psychedelics. The approach of psychedelic-assisted psychotherapy (PAP) to psychiatric drug development is unique, a paradigm shift in fact. Therefore, this may not need to comply with the standard protocols required to enable a new chemical entity (NCE) to reach patients with a fully evaluated safety profile. Shahid et al. (2020) provide an extensive description of this process from drug target selection to testing in animal models, Phase I to Phase IV clinical studies to post-marketing surveillance and risk management. PAP drug development currently involves plant medicines that have been used safely by indigenous populations for thousands of years, by western populations over successive generations and currently in clinical trials for many psychiatric disorders in controlled situations. Such molecules do not require the same development steps as NCEs, as considerable information regarding their safety and efficacy already exists. However, as pharma becomes involved in PAP drug discovery to develop new psychedelic molecules with improved drug delivery systems, absorption, distribution, metabolism and excretion (ADME) profiles and reduced potential for toxicity in vulnerable populations, the processes described by Shahid et al. (2020) may become a requirement.

Furthermore, post-marketing surveillance and risk management, that is, pharmacovigilance, will likely gain in importance. As psychedelics are currently being given in non-clinical settings to patients and healthy volunteers (e.g. in retreats) and remain unlicensed as a medicine, pharmacovigilance currently rests with online for a qualitative investigations and organizations, such as the Psychedelic Experience (<https://www.psychedelicexperience.net/>). Once licenced formally, however, pharmacovigilance can proceed as for any new medicine to further assess patient safety (Shahid et al., 2020).

Summary

The physiological safety of psychedelics is by now relatively well established, and they have been described as 'one of the safest known classes of CNS drugs' (Nichols, 2016: 275). Psychological and psychiatric effects are less predictable and although rare, serious reactions can occur. Johnson et al. (2008) conclude that psychedelic use may involve unique psychological risks, the most common being participants having a challenging experience, while prolonged psychoses and HPPD are far less likely.

Table 5 summarises differences between clinical versus non-clinical uses and users. While categories are blurred and use and users might be overlapping between categories, and there are many similarities between medical and non-clinical uses (such as that neither are likely to be using daily or for users to become dependent), notable differences can be discerned in users' set and setting, as well as the pre- and aftercare experienced both areas where above adverse effects are potentially exacerbated. Psychedelics can induce a vulnerable state, not just during but also after use (Andersen et al., 2021).



Table 5. Clinical versus non-clinical use/users.

Clinical	Non-clinical
Safe and reliable dosing	Unknown dosing
Quality assurance of substance	Unknown quality of substance
Within controlled healthcare setting	Unknown setting
Full screening of patients	Screening limited or non-existent
Individual patients	Usually group setting
Medical support available	Medical support usually unavailable
Pre- and aftercare by trained psychologists, psychotherapists and so on.	Pre- and aftercare limited or non-existent. Fear of criminalisation may lead to unwillingness to seek medical help
No repeated dosing	More frequent dosing common
Aim to heal underlying disorder	Aim to heal/well-being/ spirituality/intoxicate/fun
Non-daily use	Non-daily use

Within the clinical environment, set and setting, as well as the overall care experienced, can be largely controlled (Rucker et al., 2018). Rapport between patient and therapist is vital as the patient is undergoing a potentially life-changing experience (for many, with a substance they have no previous experience with) especially as co-creating truly informed consent between providers and patient can be challenging (Andersen et al., 2021). Training and experience of the therapists (both during the dosing sessions and for the all-important integration sessions) is also essential (Tai et al., 2021).

The importance of preparation, supervision and integration work, as well as general emotional support – be that in a clinical or traditional ceremonial context – cannot be overestimated (e.g. Kettner et al., 2021) and a range of approaches to ensure psychedelic harm reduction and integration of challenging experiences are being developed (e.g. Gorman et al., 2021). Patient safety and well-being must always come first, together with a full appreciation of responsibility to develop outstanding standards of clinical training, quality assurance and peer review (Andersen et al., 2021).

Conclusion

Some of the perceived harms of psychedelics – for example, that they lead to addiction and are neurotoxic – are largely refuted by research of the past decades. Other risks, such as the risks of psychotic episodes or overdose, are rare and only reported in individual cases, but these risks still need to be minimised by careful patient selection and preparation. The past decade of research and clinical experience has increasingly demonstrated how psychedelics can be used safely under medical supervision, and safe use guidelines are progressively well defined (e.g. Griffiths et al., 2006).

Regulatory and legal hurdles of getting psychedelic medicines proven as mainstream medicines are still substantial, so overcoming historic misperceptions is vital. The past decade has seen an increasing focus on research on the therapeutic applications of psychedelics – a direct benefit for the public, which is positively represented in current media (Aday et al., 2019). A recent YouGov study (2017) indicates that public perceptions in the United States becoming more positive, with the majority (63%) being open to medical treatment with psychedelics if faced

with a pertinent medical condition, and a UK YouGov survey (2021) corroborates these results.

These changes in public interest are in line with the recent regulatory changes in the United States and Canada. Collectively, these changes in public perception and regulation suggest that the stigma surrounding psychedelics may be beginning to dissipate, and that society is moving away from previous negative narratives to a more scientific, evidence-based approach to risks and benefits of psychedelics as medicine.

Author contributions

A.K.S. developed the initial draft and wrote the introduction, and sections on dependence and abuse liability and challenging experiences; J.A. wrote sections on hallucinogen persisting perception disorder (HPPD) and neurotoxicity; I.S. and J.C.N. wrote sections on toxicity and cardiovascular risks; D.J.N. contributed to all sections. All authors reviewed, edited and accepted the article before submission.


Declaration of conflicting interests


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Supplemental material

Supplemental material for this article is available online.



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