MEDICINAL USE OF PSILOCYBIN

Reducing restrictions on research and treatment

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FOREWORD

Even before the Covid-19 emergency, global rates of depression were staggeringly high. It would be surprising if they did not rise further still in response to the measures taken to contain the virus. Since the advent of modern antidepressants in the late 1980s, the use of these medications has become so widespread that they are almost ubiquitous in the treatment of depression. This is despite their often severe side effects, and the fact that they are so regularly ineffective; usually working to minimise the symptoms of depression rather than alleviate the disease itself.

Psychedelic medicines such as psilocybin act in an entirely different way, being administered once or twice by a clinician in a clinical setting and getting to the root of the suffering. Patient access to this novel psychiatric intervention remains totally illegal in the UK, outside of the small sample sizes of the very few and hugely costly on-going clinical trials. The reports of those lucky enough to have received this treatment legally read as unequivocal endorsements, yet the possibility of scaling up the research necessary to roll out these treatments on the widespread scale so desperately needed remains at almost impossible reach.

The Misuse of Drugs Regulations 2001 deems psilocybin, along with many other potentially revolutionary medicines, harmful and lacking medical potential. This results in psilocybin, along with many other substances vested with therapeutic potentials, being erroneously perceived as such. Coupled with the Misuse of Drugs Act 1971, this absurd cross-hatching of prohibitive scheduling has led to a scientific blackout lasting nigh on fifty years, precluding new treatments and, with them, the prospect of a better life for millions of people.

A move of psilocybin from Schedule 1 to Schedule 2 of the 2001 Regulations, with restrictions strictly limiting its availability to registered clinical trials and experimental research studies, not only has the potential to deliver new treatments for patients, but also establish the UK as the world leader in psychedelic research, growing the UK drug development industry and advancing public health. Such a policy change also has the potential to significantly diminish the cost of research, reducing in turn the cost of the final product, which will no doubt translate into significant savings for the NHS later on.

Thousands of men and women from the armed forces, policing and front line medical staff are suffering today from psychological injuries incurred through service to their country. They are unable to find effective treatment in the UK. For these individuals to gain legal access to psilocybin, a substance deemed safe in humans with the potential to provide them with lifesaving psychotherapeutic relief, they are forced to break the law or travel abroad. This report makes the case for removing existing unnecessary blocks to research and drug development so we can unlock the evidence and deliver for them.

In the Netherlands, retreat centres with professional sitters already facilitate experiences with psychedelics for those seeking healing in safe and supportive environments. I am a trustee of Heroic Hearts UK, a charity run by and for UK veterans and ex-service staff, that provides preparation, access to and integration of the potentially psychotherapeutic psilocybin experience through such retreats. As a veteran myself, I am acutely aware of the urgent need for effective treatment options for this population, and for veterans to be able to access them closer to home at a fraction of the current costs. The wretched position those who have served with such courage are in, unable to alleviate their symptoms with current treatment and unable to benefit from new treatments due to a de facto block on the science, is unacceptable.

Psilocybin and other Schedule 1 substances must be put through the rigours of research and large scale randomised controlled trials for a fair demonstration of their medicinal potential, and the law must change to make that possible.

As we emerge from the social, economic and mental health effects of the Covid-19 pandemic, we have the opportunity to stimulate the UK economy, position ourselves as a world leader in the field of psychopharmacology and drug development, and facilitate the provision of treatment to those who need it most. We call for nothing more than this opportunity be taken. Doing nothing is senseless, morally wrong and frankly incomprehensible.

This report pays consideration to the ethical, medical, economic and criminal implications of psilocybin's current status as a Schedule 1 substance with the aim to move the UK into an evidence based, intelligent and reasoned position concerning this potentially revolutionary psychiatric intervention. An overdue move and one which

would enable the thousands, if not hundreds of thousands, currently in unnecessarily prolonged distress to access the treatment they both deserve and require.



Chairman, CDPRG

Crispin Blunt MP

EXECUTIVE SUMMARY

- **Psilocybin** is a compound found in over 100 species of fungi. In humans, it induces **temporary changes in mood, perception and cognition** via activation of serotonin receptors in the brain. It is associated with a **low potential for harm** relative to other classes of psychoactive drugs: it has very low toxicity, its use is not associated with the development of physical dependence, nor with acquisitive or other crime, and deaths attributed to its abuse are extraordinarily rare. It is listed in **Class A** of the Misuse of Drugs Act 1971 and in **Schedule 1** of the Misuse of Drugs Regulations 2001. There is overwhelming scientific consensus that **the current legal status of psilocybin is not evidence-based**, but rather grounded in overstated historical assumptions of harm.
- **Depression** is among the most significant social, economic and medical challenges in the UK. It is the greatest contributing factor to **suicide**, a leading cause of **disability**, and it costs the economy **£10 billion** annually. Existing therapies are not adequate for approximately 30% of patients; **1.2 million** British residents are estimated to be living with treatment-resistant depression. Since very few advances have been made in the treatment of depression in several decades, there is an

urgent need to support research into novel therapies for treatment-resistant cases.

- Psilocybin is being investigated as a **novel therapy for treatment-resistant depression** and other difficult-to-manage mental health conditions, including obsessive-compulsive disorder, substance misuse disorders, and end-of-life anxiety. In 2018, the British life sciences company Compass Pathways received **FDA 'Breakthrough Therapy'** designation for psilocybin. Evidence from completed early phase trials indicates that psilocybin can be used **safely** and **feasibly**, is **well tolerated** by patients, and that it is likely to have **lasting therapeutic benefits**. However, robust evidence on efficacy can only be generated by large-scale phase 3 controlled clinical trials. Compass intend to start phase 3 at UK sites in the near future. These trials will be greatly enabled by rescheduling.
- Although trials are successfully being undertaken, **Schedule 1 regulations are a major barrier**, increasing the **costs**, **difficulties** and **duration** of research. Schedule 1 research typically requires **multiple Home Office licenses** per study, incurring significant administrative costs and delays. Compliance with Schedule 1 **safe custody and security regulations** add further substantial burdens of cost and time. In practice, these requirements necessitate contracting specialised pharmacies to do what could otherwise be done by hospital pharmacies at trial sites. Additionally, **stigma** associated with Schedule 1 negatively impacts **funding, ethical approval, and collaboration**. These barriers, which are well known among the research community and have been recognised in Parliamentary reports for at least twenty years, **prevent many studies from taking place** and substantially complicate those that do.
- A scheduling review is undertaken as part of the normal process when a medicinal product achieves market authorisation, but **significant savings** could be made by **moving psilocybin**

to Schedule 2 prior to the commencement of phase 3 trials. This would have wide-ranging benefits: to legitimate commercial drug development through **reduced barriers to research**; to the taxpayer through **decreased expenditure of Government research grants**; and to the NHS and British patients through **lower end-costs of treatment** and **earlier completion of trials**. Greater regulatory support for psilocybin research will ensure the UK's reputation as a **global centre of excellence** in this area, attract **commercial investment and international expertise**, and **prevent a 'brain-drain'** of British research and innovation to other jurisdictions. **Immediate action will yield the greatest benefits** to the UK.

- In November 2018, a **precedent** was set for moving controlled drugs (cannabis-based products for medicinal use (CBPM)) from Schedule 1 to Schedule 2 prior to market authorisation as a medicine. At the time, the Home Office wrote: "*The rescheduling may lead to* ***increased UK research*** [...] *as these products can be tested more easily.*" "*This may lead to* ***economic benefits*** *for UK businesses and* ***health benefits*** *to patients if this research leads to new and improved* [medicinal products]." "*In principle, research is ongoing and could lead to* ***more effective treatment, lower costs, better understanding*** *and* ***management of risks,*** *and* ***improved health and wellbeing,*** *over the medium term.*" The current Chief Medical Adviser to the UK Government, Prof Chris Whitty, later stated that moving CBPM to Schedule 2 was "*the* ***single most important thing that could be done by Government***" to support the development of an evidence base.
- Likewise, rescheduling would be the most **significant and immediate way** that Government could **support ongoing research with psilocybin**. Psilocybin could be rescheduled with statutory limits **restricting access to ethically-approved research studies** only – unless a product has market authorisation – thus preventing wider prescribing on an unlicensed basis.

This would be unprecedented in UK law, but would serve to support scientific development **without risking inappropriate prescribing**.

- The major source of diverted medicinal drugs is by prescription prior to diversion. Moving psilocybin to Schedule 2 for research purposes **is unlikely to increase the risk of diversion** because the drug is administered to participants under clinical supervision, rather than being prescribed for use in the community. This is in line with ACMD advice that "the risk of diversion and misuse in a research setting is likely to be **minimal**."
- The proposed research-only model of rescheduling would **support legitimate scientific and commercial development** while **maintaining stricter controls** on psilocybin than on other controlled drugs associated with greater potential for harm, including diamorphine (heroin), methamphetamine, and cocaine. It would **not affect existing legal controls on criminal use** or supply. This model may also serve as a **basis for future scheduling decisions**; there are other Schedule 1 drugs under investigation as treatments for mental health conditions for which there are similar clinical arguments to support rescheduling, albeit with less immediate urgency.
- The ongoing ACMD review on barriers to research with Schedule 1 drugs is **vital**. We also welcome the current work to establish a Standard Operating Procedure (SOP) for scheduling decisions. However, the primary emphasis of the review on barriers to research is on **synthetic cannabinoids** and it is currently unclear whether the SOP will be used to review historical scheduling decisions. Since neither report is expected to be published until 2021, nor to directly provide recommendations on psilocybin, **there is no known work currently commissioned by the Home Office that addresses the urgent issues identified** in this report.

- We recommend that the Home Office **commission a high-priority ACMD review** into the access-restricted **rescheduling of psilocybin** under the Misuse of Drugs Regulations 2001.

ABOUT THE AUTHORS

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"There were times in the whole experience where I felt like I was being purged of self doubt, guilt and was being shown ways of handling all that was bringing me down. It was like having the best therapist in the world inside your mind, but all the answers were within. I cried at times, I laughed and afterwards felt totally moved by it all… My doctor was amazed also. I didn't want any more anti-depressants, nor have I taken any in 5 years now …

It is beyond ridiculous to think that this drug has no medicinal benefit, or that it causes harm. It is the polar opposite of that. It saddens me that others, who have also battled with or are still battling with depression can't benefit from this… It changed my life totally, and it has done for others. It needs to be made available soon."

- Clinical Trial Participant

INTRODUCTION

Psilocybin is a naturally occurring molecule found in almost 150 species of mushrooms in the genus Psilocybe.[1] It is psychoactive in humans and classified as a 'psychedelic' alongside lysergic acid diethylamide (LSD), 3,4,5-trimethoxyphenethylamine (mescaline) and N,N-dimethyltryptamine (DMT). Psychedelic drugs induce temporary alterations in mood, perception, and cognition ('psychedelic experiences') through activation of specific serotonin receptors in the cortex of the brain.[2] [3] The traditional use of psilocybin-containing fungi, mescaline-containing cacti, and DMT-containing plants, by geographically disparate cultures, is thought to date back hundreds, if not thousands, of years.[4] [5]

Psilocybin is the phosphate ester of psilocin and is thus listed, though not specifically named, under Class A of the Misuse of Drugs Act 1971, under Schedule 1 of the Misuse of Drugs Regulation 2001, and in Part 1 of the Misuse of Drugs Designation Order 2015. Accordingly, neither psilocybin or fungi containing psilocybin can lawfully be produced, prescribed or possessed, except under a license or other authority issued by the Home Office, and offences relating to the unauthorised use and supply of psilocybin may incur the most severe of the criminal penalties described in the 1971 Act.[6] [7]

Psilocybin is being investigated as a treatment for a range of mental health and substance misuse disorders, including depression, nico-

tine addiction, obsessive-compulsive disorder, and existential distress and anxiety in life-threatening cancer. Phase 1 (first-in-human) and phase 2 (first-in-patient) clinical trials in the UK, Europe and the US have provided preliminary evidence for the safety, feasibility and tolerability of psilocybin in research conditions. Early phase clinical trials are not designed to generate robust evidence of efficacy, but all published trials to date have reported positive findings on outcome measures of efficacy, justifying the need for continued research (Table 1). A systematic review that included historical clinical trials in unipolar mood disorders indicated that 80% of patients who received psilocybin showed clinical improvement.[8] Phase 2 trials are presently underway in the UK to investigate psilocybin as therapy for treatment resistant depression, a condition with an estimated 1.2 million British sufferers for which there have been no major advances in decades.[9]

There is also a recent upsurge in preclinical studies on psilocybin and related molecules for early stage drug discovery in animals and in in vitro systems. This work is essential to enable our understanding of how these substances produce beneficial and long-lasting effects in the brain. This work is mostly undertaken in higher education institutions (HEI) and will increasingly form part of that economy.

However, strict regulatory controls in the UK continue to slow the pace of the science. Schedule 1 regulations do not preclude legitimate scientific studies, but they do increase the cost, difficulty and duration of research in three main ways. Firstly, a single study will typically require multiple separate Schedule 1 licenses. It may take months or years for all license applications to be granted and the cumulative annual cost can have a substantial impact, particularly on smaller studies. Secondly, all study sites must meet extremely strict security standards, which, in practice, requires contracting external pharmacies to do what could otherwise be done by hospital pharma-

cies, at the cost of tens of thousands of pounds each year. The delays and costs associated with these regulations are particularly significant for large-scale, multi-site trials, and the increased expense of bringing a Schedule 1 drug to market may ultimately increase the end-cost of the treatment. Thirdly, the stigma of Schedule 1 negatively impacts funding, staffing, buy-in from collaborators, and ethical approval.

The burdens of Schedule 1 are well known in the research and commercial pharmaceutical communities; they prevent many studies from taking place – and substantially complicate those that do.[10] Large-scale phase 3 trials are exceptionally difficult to undertake under Schedule 1 controls, yet they must be done to determine the efficacy of psilocybin for market authorisation as a medicine, which will further develop its commercial potential. Acting swiftly to review the controls on psilocybin is the single greatest contribution that the Government could make to support research in this area.

The challenges posed to research with psilocybin are not unique. Clinical trials with other Schedule 1 drugs, such as methylenedioxymethamphetamine (MDMA), are subject to the same financial and practical obstacles. Until November 2018, when cannabis-based products for medicinal use (CBPM) were moved to Schedule 2 of the 2001 Regulations, there was no precedent for the rescheduling of a Schedule 1 drug prior to market authorisation. The rescheduling of CBPM was intended to permit their prescription as unlicensed medicines to treat patients with a special clinical need, but it was also recognised that it would be significantly easier for scientists to research CBPM under Schedule 2 controls.

The decision to reschedule CBPM came in response to several high-profile cases of children with treatment-resistant epilepsy in the British media.[11] Every year in the UK, almost three times more peo-

ple with depression or another mood disorder die from suicide than die from complications of epilepsy, which suggests a stronger clinical argument to support the rescheduling of psilocybin.[12] [13] [14] In the absence of Government action to review psilocybin, similar media campaigns are likely to increase the public and political pressure to do so.

This paper will outline the scale of the UK mental health crisis, the urgent need to support promising new therapies, and the ongoing clinical research into psilocybin as a potential treatment for depression and other mental health conditions. Qualitative testimonies from clinical scientists, industry, and scientific advisers to the Government are provided to illustrate the difficulties of research with Schedule 1 drugs. A quantitative cost-benefit analysis of rescheduling is to be published by the CDPRG in a subsequent report. Finally, this paper suggests routes to ease restrictions on psilocybin research while maintaining existing legal controls on non-medical or scientific use and minimising potential risks of diversion and inappropriate prescribing.

1. DEPRESSION AND OTHER MENTAL ILLNESS IN THE UK

THE BURDEN OF MENTAL ILLNESS

Depression and other mental illness remain among the most significant social, economic, and medical challenges of the modern world. Mental illnesses, including substance misuse, account for over 22% of disability in the UK – the largest of any medical illness category – with the leading cause being depression and anxiety.[15] Cancer and cardiovascular disease, by comparison, account for about 16% each.[16] In England, 1 in 6 people experience a common mental health problem – such as anxiety and depression – in any given week.[17] Fifty percent of mental illnesses are established by age 14, with this figure rising to 75% by age 24.[18] The personal and social burden to society is

thus cumulative throughout one's lifespan. Children and adolescents with mental illness have poorer educational outcomes and job prospects, while adults are less likely to be productive and more likely to receive government benefits. Public Health England has found that nearly 51% of those receiving the Employment Support Allowance list a mental and behavioural health problem as their primary condition.[19] Poor mental health has also been associated with increased health-damaging behaviour, including smoking, drug misuse and alcoholism, and less participation in community life.

Depression is the largest contributing factor to suicide, which remains the leading cause of death in men under 50 and women under 35, with men three times more likely to die from suicide than women.[20] Those with ongoing depression are twenty times more likely to commit suicide than the general population, and those with treatment resistant forms of the illness are, logically, at even higher risk.[21] Approximately 30% of people with treatment resistant depression attempt suicide at least once – ten times the incidence found in people with non-resistant depression.[22] Suicide and suicidality have a particularly devastating impact on families and communities. In 2018, there were 6,507 deaths by suicide in the UK, at a rate of just over 11 deaths per 100,000 people.[23] A reduction of approximately 10% on this metric would equate to preventing all the deaths caused by murder in England and Wales.[24] The link between suicide and mental illness is clear, with numerous studies concluding that a high number of people who survive a suicide attempt have suffered from mental illness.[25]

In 2010, the Centre for Mental Health estimated the combined cost of lost productivity, spending on health services and reduced quality of life as a result of mental health problems at £105.2 billion per annum, of which more than £53 billion was attributed to reduced quality of life alone.[26] [27] In 2013, Britain's Chief Medical Officer esti-

mated the annual cost of mental health problems at £70-100 billion.[28] 1 in every 10 pounds of the NHS budget is spent on mental illness.[29] A 2018 OECD report, which omitted the burden of reduced quality of life, concluded that mental illness costs the UK economy £94 billion per annum, or 4.1% of GDP, in line with the EU average of 4%. The indirect costs of mental illness also have a significant impact on individuals, reducing disposable income, financial security and workforce participation.[30] The toll is felt by business, too: a recent report by the Centre for Mental Health concluded that mental health problems cost UK businesses £34.9 billion in 2016/17, growing 34% since from 2006 (£25.9 billion).[31]

Depressive disorders are a major contributor to these costs. In 2007, direct treatment costs and costs of lost employment associated with depression in the UK were estimated at a total of £7.5 billion per year, rising to more than £10 billion by 2020.[32] These figures are likely to underestimate the true economic burden, since they do not include indirect costs due to morbidity and mortality, which have been estimated to contribute almost two-thirds of total healthcare costs.[33] A disproportionate humanistic and economic burden is associated with treatment resistant depression, which is associated with significantly lower quality of life, greater impairment to activity and work productivity, and increased healthcare resource utilization compared to non-resistant forms of the disease.[34] [35] [36]

EXISTING TREATMENTS FOR DEPRESSION

Selective serotonin reuptake inhibitor (SSRI) drugs and other structurally similar antidepressants offer a modest benefit for many patients; a rigorous 6-year evaluation by Oxford researchers found that about 60% of patients taking antidepressants responded within two months, and those who responded had a 50% reduction in their

symptoms.[37] However, approximately 10 – 35% of people with depression do not respond to at least two antidepressants.[38] [39] The National Institute for Health and Care Excellence (NICE) recommend that all treatment resistant patients should be referred to a specialist, but these targets are commonly missed.[40]

The prevalence of treatment resistant depression is difficult to estimate, partly due to inconsistencies in its definition and to differing findings of symptom response and remission after treatment with common antidepressants. A 2007 review of treatment-resistant depression in the United States estimated the 12-month prevalence of major depressive disorder (MDD) at 6.6%, of whom an estimated 35% do not respond to two courses of treatment.[41] Extrapolating these findings would result in an estimate of approximately 1.2 million adults in the UK with treatment-resistant depression. Estimates of prevalence based on the number of people who have been prescribed antidepressants are rather higher, at up to 2.7 million, but may be less accurate.[42] A Public Health England report found that approximately 7.3 million people in the UK had been prescribed an antidepressant between 2017-18.[43]

Progress in the treatment of depression has been slow. Prior to the approval of esketamine by the European Commission in late 2019, the last major advancement in the treatment of depression came over 30 years ago with the licensing of SSRIs.[44] A 2017 report by the UK Department of Health noted that "the pharmaceutical sector has undergone significant change with many larger companies scaling back mental health research portfolios." Recommendations were made for encouraging industry engagement in mental health research and for the streamlining of procedures for the regulation, governance and ethical oversight of research to expedite studies.[45]

2. PSILOCYBIN AS A MENTAL HEALTH TREATMENT

HISTORIC PSILOCYBIN RESEARCH

Psilocybin was first isolated and synthesized in 1958 and was subsequently marketed under the trade name Indocybin by the Swiss pharmaceutical company, Sandoz.[46] Throughout the late 1950s and 1960s, psilocybin and other psychedelic drugs were investigated as potential treatments in hundreds of clinical studies internationally, with tens of thousands of patients treated.[47] [48] Researchers noted that psilocybin showed negligible toxicity in animals and humans, and induced suggestibility, introspection and awe in the latter. While the evidence was mixed, these effects proved transformative in the context of psychotherapy for some patients who had otherwise been unwell

and unproductive for years.[49] [50] A 2016 systematic review of historical studies in unipolar mood disorders found that 80% showed clinically-judged improvement after treatment with psychedelic drugs.[51]

Research was primarily funded by pharmaceutical companies, the US National Institute of Mental Health (NIMH), and military and intelligence agencies – which retained interests in the application of psychedelics in espionage and warfare.[52] [53] [54] While studies often suffered from methodological limitations, they commonly identified a therapeutic potential of psychedelics – when delivered within safe and supportive settings – for sufferers of depression, anxiety, addiction, and obsessive disorders. They were ineffective in military and intelligence settings and unhelpful for those with pre-existing psychotic disorders.[55] [56] [57]

Regulations on clinical research were tightened in the early 1960s in response to the Thalidomide tragedy. In 1962, the Kefauver Harris Amendments to the US Federal Food, Drug, and Cosmetic Act strengthened regulations in drug research, enshrining a requirement for evidence of efficacy and, particularly, safety, to be established through controlled clinical trials. [58] [59] A consequent increase in the cost of clinical research, coupled with growing controversy and political disapproval regarding the non-medical use of psychedelic drugs, as well as the impending loss of patent for LSD, led Sandoz to cease production of psilocybin in 1965. [60] [61] [62] [63] [64]

The Misuse of Drugs Act was passed in 1971, swiftly followed by the Misuse of Drugs Regulations 1973, prohibiting the use of psilocybin and other psychedelic drugs unless specifically licensed by the UK Government.[65] [66] [67] The medical use of psychedelics, which had been well established in specialist hospitals, ceased as doctors were prohibited from prescribing outside of authorised clinical trials. The legal restrictions on the use of psilocybin did not reflect an absence of

therapeutic value, nor scientific evidence of harm, but rather a perception of harm by political leaders at the time.[68] In the face of sociopolitical opprobrium, institutional and grant support for psychedelic research dried up.[69] This previously vibrant and promising field entered a period of hibernation that lasted 25 years.

CONTEMPORARY PSILOCYBIN RESEARCH

Contemporary research with psilocybin and, to a lesser extent, other psychedelics, resumed with the publication of several Phase 1 clinical trials in Germany, the USA and Switzerland in the 1990s.[70] [71] [72] These, and successive studies, have established basic pre-clinical and in-human safety data.[73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90]

Phase 2 trials, necessarily small in scale, have also been completed. A number of groups have reported the safety and efficacy of psilocybin in patients with treatment resistant forms of depression, obsessive compulsive disorder (OCD), end-of-life psychological distress, and substance addiction. (Table 1). A meta-analysis of four trials testing the effects of psilocybin on symptoms of anxiety and depression found that, although sample sizes were small, both within-group and placebo-controlled effect sizes were large (Hedges' g=1.16-1.47 and 0.82-0.83 respectively).[91] The paradigm of therapy need not be restricted to these disorders: a wide variety of mental health disorders may theoretically be amenable to treatment with psilocybin, including post-traumatic stress disorder (PTSD), anorexia nervosa, and functional neurological disorders.[92] [93] [94]

TABLE 1 CONTEMPORARY CLINICAL TRIALS INVOLVING PSILOCYBIN*

Study	Indication and sample size (n)	Design	Main efficacy outcome
Moreno et al (2006)[95]	Obsessive compulsive disorder, n=9	Single-arm, within subjects, variable doses. Up to four doses of psilocybin	All patients showed improvements within 24 h of a treatment but no effect of dose.
Grob et al (2011)[96]	Anxiety and depression in end-stage cancer, *n*=12	DB-RCT, crossover, inert placebo. Single dose of psilocybin.	Significant reductions in trait anxiety at 3 months and depression at 6 months.
Johnson et al (2014)[97]	Long-term chronic tobacco smoking, *n*=15	Open-label. Up to three doses of psilocybin after four CBT sessions.	80% of sample abstinent at 6 month follow-up.
Bogenschutz et al (2015)[98]	Alcohol dependence, *n*=10	Open-label. Up to two doses after seven motivational therapy sessions.	Significant decrease in drinking behaviors for up to 9 months.

Carhart-Harris et al (2016a, b)[99] [100]	Treatment-resistant MDD, *n*=12 + study extension to *n*=20	Open-label. Two doses of psilocybin.	Significant decreases in depressive symptoms for up to 6 months.
Ross et al (2016)[101]	Anxiety and depression related to life-threatening cancer, *n*=29	DB-RCT, crossover, niacin=active placebo. Single dose of psilocybin.	Significant decreases in anxiety and depression *vs* niacin at 7 weeks (pre crossover) and sustained for 6.5 months.
Griffiths et al (2016)[102]	Anxiety and depression related to life-threatening cancer, *n*=51	DB-RCT, crossover, VLD psilocybin = control. Single dose of psilocybin.	Significant decreases in anxiety and depression *vs* VLD at 5 weeks (pre crossover). Effects sustained for 6 months.

*Abbreviations: DB-RCT, double-blind randomised controlled trial; VLD, very low dose; MDD, major depressive disorder; TRD, treatment-resistant depression. *Table adapted from Carhart-Harris and Goodwin (2017)[103]*

Interest in psilocybin research is growing rapidly across the world, with completed and ongoing studies undertaken by leading academic and research institutes in the US, Europe and Australia.[104] [105] [106] [107] [108] [109] [110] [111] [112] [113] In 2018, the US Food and Drug Administration granted 'breakthrough therapy' status to Compass Pathways Ltd – a British venture capital funded life sciences company – for psilocybin therapy in treatment resistant depression.[114] The following year, the FDA awarded the same status to the Usona Institute's psilocybin program for major depressive disorder.[115] Breakthrough therapy status is only

given to treatments that show early and substantial promise of a significant treatment advance in the field. Johns Hopkins University has recently announced the launch of its $17M donor-funded Centre for Psychedelic and Consciousness Research, which is currently studying the potential of psilocybin as a treatment in anorexia nervosa and in depression – including in patients with Alzheimer's Disease, for which there is currently no effective therapy to improve quality of life for patients and their carers.[116] [117]

Significant advances in the field are being accomplished by UK-based institutes and funders. King's College London recently launched 'The Psychedelics Trials Group,' led by Dr James Rucker, funded by a £1.2M grant from the National Institute for Health Research (NIHR) and contributions from industry (£600K annually). Aided by a £3 million grant from a number of entrepreneurial donors and charitable trusts, Imperial College London recently launched the 'Centre for Psychedelic Research.'[118] Imperial's Psychedelic Research Group was the world's first to investigate the effect of LSD on the human brain using modern brain imaging and to study psilocybin for the treatment of resistant depression.

Compass are now the first company in the world to manufacture psilocybin to the pharmaceutical quality required for a medicine – a notable achievement in the face of Schedule 1 restrictions. It is the sponsor of a late phase 2 trial of psilocybin in treatment resistant depression and recently completed the largest ever randomised study of psilocybin, in collaboration with Dr James Rucker and Professor Allan Young at King's College London.[119] [120] 89 healthy volunteers received psilocybin in a randomised, controlled trial that explored changes in cognitive and emotional processing before and after single doses of psilocybin and placebo. The study found that psilocybin caused no statistically significant worsening of cognitive and emotional measures, no serious adverse events and no adverse events that

led to withdrawal from the study. This is the strongest evidence yet for the basic safety profile of psilocybin, and the best evidence yet to justify ongoing, large scale research in patient populations.

THE IMPORTANCE OF PSILOCYBIN RESEARCH

Psilocybin therapy may be a novel and paradigm-shifting development in the treatment of mental health conditions. It works in a different way to traditional antidepressants and psychological therapies, by directly decreasing activity and changing patterns of connectivity in brain regions strongly associated with ongoing depression and anxiety.[121] This enables patients to challenge overly rigid, negative thought patterns and behaviours that often underlie psychiatric disorders like depression, particularly in treatment resistant cases.[122] [123] [124] Patient accounts of psilocybin therapy indicate two major psychological themes underpinning therapeutic change: (1) a movement from a sense of disconnection to connection - to self, others and the world; and (2) a movement from emotional avoidance to acceptance.[125] Clinical trial evidence suggests that psilocybin may be effective in groups where traditional treatments have failed (Table 1). This is where the clinical and health-economic problem lies, where new treatments are most needed, and where commercial potential exists.

Psilocybin therapy is likely to be cost-effective for health service providers, relative to existing therapies for patients with treatment resistant depression – such as electroconvulsive therapy (ECT), esketamine, and intensive talk therapy. Existing treatments have high costs related to the needs for dedicated personnel and treatment centres and for weekly or more than weekly repeat treatments. Psilocybin therapy, on the other hand, has a much longer duration of post-treatment efficacy.[126] [127] [128] [129] [130] In the most recent clinical

trial in treatment resistant depression in the UK, no patient required antidepressant treatment in the five weeks after treatment with psilocybin.[131] Significant effects on mood and function continued to be observed at 6 month follow up and some patients, with previously refractory illness, continue to be well 4 years later. Clinically, this is an intriguing and most unusual finding, underlining the potential health and socioeconomic utility, and commercial potential, of psilocybin.

Psilocybin therapy is practical. It is given to patients as a day case in a specialist day-hospital setting – in a similar manner to receiving outpatient dialysis or chemotherapy for cancer – in a carefully controlled environment designed to ensure safety and comfort.[132] Patients are supported by a therapist and psychiatrist throughout their treatment session to provide psychoeducation and psychological support, with medical care readily available if needed.[133]

Psilocybin therapy is acceptable to patients. Since it does not need to be taken regularly to produce clinical improvements, there are no direct side effect burdens or risk of relapse if patients forget to take their medication. This model of care has inherent benefits and is more acceptable to patients who reject forms of treatment that require daily medication and may result in dangerous side effects if not taken as prescribed.

Psilocybin therapy is empowering for patients. The drug acts as a form of psychological catalyst, helping patients work with their therapist to understand why they are suffering and how their own patterns of thinking and behaviour perpetuate this.[134] Patients who took part in the Imperial College open-label study reported that traditional medications and some short-term talking therapies tended to reinforce their sense of disconnection and avoidance, whereas treatment with psilocybin encouraged connection and acceptance. They iden-

tified themes of increased self-reflection, capacity for change, and motivation.[135] Psilocybin can induce deeply meaningful, personally transformative experiences that research participants rate as among the most significant in their entire lives.[136] These profound experiences 'sow a seed' that the patient can take away with them, enabling long-term therapeutic benefit.

Finally, psilocybin therapy has a low risk of harm and diversion. It is delivered in specialist hospital centres and the drug is not prescribed for the patient to take home.[137] Psilocybin is not known to cause addiction, dependence or overdose at typical doses and early phase studies indicate a low probability of serious adverse events when delivered in a controlled setting.[138] [139] [140] [141]

HARMS ASSOCIATED WITH THE USE AND MISUSE OF PSILOCYBIN

No drug is free of harms. Nonetheless, the safety profile of psilocybin compares favourably to other medicinal drugs, particularly to drugs in Schedule 2. Experimental and clinical data on the harms of psilocybin are broadly consistent with epidemiological data on the illicit use of psilocybin mushrooms. Users and experts consistently rate psilocybin mushrooms as having the lowest harms to society, public health and the individual of all recreational drugs, and as showing the most potential for benefit.[142] [143] [144] [145] [146] [147] [148] [149] [150] Psilocybin induces acute changes to perception, mood and thought – these effects have a potential for harm in non-medical use but are intrinsic to the therapeutic value of the drug in clinical settings.[151] [152] [153] Acute and chronic physiological toxicity is low and there is no evidence that psilocybin can cause dependence or withdrawals.[154] No serious adverse events have been reported in contemporary clinical trials with psilocybin to date. There is consistent evidence that psilocybin can cause transient

but potentially harmful experiences of overwhelming distress. These experiences typically resolve within hours and are both less frequent and less severe in research settings than in recreational use.[155] The social and wider criminal harms associated with the use of psilocybin are low.

Potential for addiction, dependence and abuse.

A 2018 academic review provides a thorough overview of the abuse potential of medical psilocybin, identifying low abuse and no physical dependence potential.[156] Psilocybin is neither habit-forming nor classically rewarding. Animal models of abuse potential suggest weak reinforcing effects of psilocybin, consistent with community level observations of non-medical use of psilocybin-containing mushrooms in humans, which suggest that the vast majority of individuals use psilocybin only a few times and do not develop compulsive patterns of use. Contemporary clinical trials with psilocybin that have included measures related to abuse potential showed acute elevations in fear and anxiety in some patients, as well as a subsequent sense of contentment, neither of which are predictive of a high potential for abuse. There is strong evidence of acute tolerance to the effects of psilocybin - decreased response with repeated administration - as well as cross-tolerance between psilocybin and other psychedelics. However, there is no evidence that repeated administration leads to physical dependence, nor to withdrawal symptoms on cessation. These conclusions are consistent with other reviews on the abuse potential of psilocybin.[157] [158] [159]

Physiological toxicity and overdose.

The acute lethal toxicity of psilocybin is extraordinarily low. The lethal dose has been estimated at 1,000 times the dose commonly used for non-medicinal purposes; by comparison, the lethal doses of the Schedule 2 drugs heroin, methamphetamine, cocaine and

codeine are approximately 6, 10, 15 and 20 times the non-medicinal doses respectively.[160] This low potential for overdose toxicity is reflected in official figures. The Office for National Statistics recorded only a single death associated with psilocybin use in the 20-year period from 1993-2014.[161] Whilst this may be an under-ascertainment, even highly granular registries of drug deaths that collate coroners' reports, toxicology analyses and medical histories have only recorded a handful of deaths in the UK in which psilocybin was implicated in the last 20 years, and fewer still where a causative chain of events between psilocybin and death was clear.[162] A 2010 review of the relative physical and social harms of alcohol, tobacco, and 17 other commonly used drugs ranked psilocybin mushrooms as having the lowest mean physical harm and chronic toxicity of all drugs reviewed, and the fifth lowest potential for acute toxicity, after cannabis, tobacco, anabolic steroids and khat.[163]

Intoxication and impairment

A UK multicriteria decision analysis reported that the largest contributing factor to the harms of psilocybin mushrooms – which, overall, were the lowest of all 20 drugs reviewed – was 'drug-specific impairment of mental functioning.'[164] Psilocybin induces dose-dependent changes in mood, sensory perception, and perception of time, space and self. It typically increases introversion and general inactivation; and causes impairments in alertness and cognitive performance. The onset of subjective effects of psilocybin is approximately 20-40 minutes after administration. Peak intensity is reached after 60-90 minutes and lasts for a further 60-120 minutes before subsiding, with effects typically absent at six hours after administration.[165]

The acute effects of psilocybin on time perception, synchronization, attention and working memory are likely to impair the ability to drive or handle machines.[166] [167] However, trends in US motor vehicle acci-

dents show that psychedelic drugs, unlike virtually all other classes of drugs, were not associated with fatal traffic accidents between 1999 - 2010.[168] Nonetheless, the behavioural, affective, perceptual and cognitive effects of psilocybin plausibly increase harms to the individual in uncontrolled non-medical environments. These harms are attenuated in the context of clinically supervised, dose-controlled psilocybin therapies, in which many of the subjective effects are intrinsic to the therapeutic potential of the drug.[169]

Acute adverse effects

Physiological side effects of psilocybin mushrooms may include dilation of the pupils, mild increases in heart rate and blood pressure, dizziness, nausea, abdominal discomfort, shivering, and headaches.[170] Acute psychological side effects include visual illusions, dream-like states, and anxiety. Non-serious side effects of psilocybin are relatively common in research settings.[171] Aside from headaches, which resolve over 24-48 hours, side effects are almost always resolved by the time the drug's effect has worn off, after 6-8 hours. Typically, these minor side-effects are not clinically significant. [172] [173] [174]

In clinical trials, a 'serious adverse event' is defined as an event that: is life-threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability, incapacity, or death; or consists of a congenital anomaly or birth defect. No such events have occurred in clinical trials with psilocybin to date. [175] [176] [177] [178] Psilocybin therapies are provided over a small number of sessions in a contained, safe and supervised setting. Patients are not given psilocybin to take home. Thus, any side effects are contained and not ongoing, unlike most other standard antidepressant therapies.

Acutely distressing psychological experiences

The use of psilocybin and other psychedelic drugs carries certain psychological risks in both recreational and clinical contexts – in particular, acute experiences of overwhelming distress known colloquially as 'bad trips.' While dysphoric experiences are rare and the majority do not result in dangerous or harmful behaviour, risks are increased in unprepared individuals or uncontrolled situations. A survey study on the single most psychologically difficult experience of almost 2000 individuals, after consuming psilocybin mushrooms in non-medical settings, identified risks to users of acute fear, putting themselves or others at risk for physical harm, and seeking medical help. Counterintuitively, 84% of respondents endorsed benefiting from these experiences.[179] In historical clinical and research settings and in uncontrolled non-medical settings, extreme panic or delusional reactions to psychedelic drugs have resulted, albeit rarely, in increased suicidality during the experience.[180] [181] [182] [183] This has not been reported in contemporary studies.

In research conditions, the incidence of dangerous behaviours or enduring psychological distress is extremely low and can be further minimised with participant preparation, clinical supervision and psychological support. Persistent and severe distress in medical settings can be managed with commonly available drugs, such as benzodiazepines and antipsychotics, that attenuate the effects of psilocybin.[184] Nonetheless, distressing experiences do still carry risks, such as research participants leaving the study site.[185] The acute effects of psilocybin therapy are rarely enjoyable for depressed patients, though most later consider such difficult experiences to be worthwhile.[186] Indeed, exposure to difficult experiences that may be driving depression is thought to be a necessary stage in the psychological process of change towards a more positive personal perspective, which logically may underpin the lasting positive outcomes seen in some patients

treated with psilocybin therapy.[187] [188] [189]

Long-term mental health effects

There have been no recorded incidences of prolonged psychosis in contemporary clinical or experimental trials.[190]

In rare cases, the administration of psychedelic drugs has been reported to precede prolonged perceptual disturbances or episodes of mental illness, including psychosis, that may last from days to several months or longer.[191] [192] [193] [194] These risks were reviewed in safety guidelines for psychedelic research published in 2008.[195] Prolonged effects are uncommon and it is still unclear how onset is linked causally to drug administration. It is particularly difficult to deduce causation when there is a considerable interval between the administration of the drug and the onset of the psychological change – a 1966 BMJ article, which highlighted potential risks of LSD, noted that events were separated by weeks or months in many cases of violent or otherwise aberrant behavior that had been linked to administration of the drug.[196] In such cases, pre-existing personal and social risk factors for such behavior are often identified, and much more likely to be aetiologically salient.

There is some evidence that psychedelics can exacerbate or precipitate symptoms in psychotic patients and individuals with a predisposition to psychosis, but little to no evidence of prolonged episodes induced in otherwise low-risk individuals.[197] [198] Only one case of a lasting psychotic reaction was documented in 1,200 non-patient research participants who took part in studies prior to 1960, affecting an individual whose identical twin was diagnosed with schizophrenia.[199] [200] It is now known that the concordance rates of schizophrenia for identical twins is approximately 40-50%.[201] The 1966 BMJ article hypothesized that "most of the patients who have developed these adverse reactions should not have been given the drug since they

were manifestly unstable or pre-psychotic."[202]

Enduring psychological symptoms of a non-psychotic nature have also been reported after difficult and distressing drug experiences, particularly in non-medical settings in which little or no psychological support may be available.[203] Historical and contemporary clinical observations suggest that particularly challenging psilocybin experiences can cause continued psychological difficulties if they are not worked through.[204] One patient in a recent open-label trial using psilocybin for treatment resistant depression in the UK was offered additional psychotherapeutic integration sessions to come to terms with an apparently repressed memory that surfaced during the treatment.[205]

Cases of persistent perceptual abnormalities have been documented following the use of psilocybin and other psychedelics.[206] 'Hallucinogen persisting perception spectrum disorders' (HPPSD) are a cluster of syndromes characterised by prolonged perceptual effects and clinical distress or impairment. The incidence is unknown but is thought to be extremely uncommon. Illicit drug use is associated with greater risks of HPPSD than administration in research or treatment settings.[207] It is more commonly diagnosed in individuals with a history of previous psychological issues or substance misuse, and more commonly precipitated by LSD, PCP and cannabinoids than by psilocybin.[208]

In a 1960 survey study of investigators who had administered the psychedelic drugs LSD or mescaline (which are pharmacologically similar to psilocybin), suicide attempts and completed suicides, occurring some weeks after treatment, were reported in 0.12 and 0.04% of patients respectively. There were no reports of attempted or completed suicides reported for 1,200 experimental (non-patient) research participants.[209] Nor have there been any incidents docu-

mented in or subsequent to contemporary clinical or experimental studies.

In clinical, laboratory and population-studies, the most common persisting effects of psilocybin seem to be beneficial.[210] Open-label and randomised controlled clinical trials consistently report reductions in measures of depression and anxiety for several months after administration.[211] [212] [213] [214] [215] Studies in non-patient research participants also report long-term increases in well-being, life satisfaction, interpersonal closeness, gratitude and life meaning.[216] [217] [218] Large survey studies have identified robust associations between the illicit use of psychedelic drugs and reduced odds of psychological distress, suicidal ideation, attempted suicide, opioid dependence, and antisocial behaviour.[219] [220] [221] [222]

Social and criminal harms of misuse

Psilocybin therapies are provided under clinical supervision for the duration of the drug effect and are, accordingly, unlikely to increase social harms related to acute intoxication. Nor are social harms likely to be affected by the diversion of medical psilocybin to the illicit market, since psilocybin is not prescribed for patients to take home and the major source of diverted medicinal drugs is by prescription prior to diversion.[223] This view is consistent with ACMD advice that "the risk of diversion and misuse [of controlled drugs] in a research setting is likely to be minimal."[224]

Psilocybin-containing mushrooms are not popular as a recreational drug in the UK, and psilocybin itself is rarely, if ever, used outside of medical research. Government estimates of the rate of non-medicinal use of psilocybin mushrooms are low relative to many other controlled drugs of abuse: from 2008/9 to 2018/19, the average proportion of 16 to 59 year olds who reported past-year use of psilocybin-containing mushrooms was 0.4%. In comparison, the average past-

year use rates were 6.7% for cannabis, 2.4% for cocaine and 1.5% for ecstasy over the same time period.[225]

Over half of all UK acquisitive crime is committed to fund drug misuse, primarily by low income dependent users of heroin and cocaine, costing society an estimated £13.9 billion annually.[226] [227] [228] [229] However, psilocybin and psilocybin-containing mushrooms do not cause dependence syndromes and, in 2005, the Home Office reported "no clear evidence of a link between psilocin use and acquisitive or other crime".[230] Conversely, there is some evidence that psilocybin may reduce the likelihood of criminal behavior. Survey data exploring the connections between drug use and criminal behaviour among almost half a million US adults over 13 years found that respondents who had used psychedelic drugs, such as psilocybin, had 27% decreased odds of committing larceny or theft, 22% decreased odds of past year arrest for a property crime, and 18% decreased odds of past year arrest for a violent crime. Lifetime use of other controlled drugs was associated with increased odds of criminal behaviour.[231]

A multicriteria decision analysis on drug harms in the UK found no evidence for substantial harms of psilocybin mushrooms related to loss of tangibles, loss of relationships, community, crime, environmental damage or economic cost. The overall rating of harm was the lowest of all drugs and there was no reported harm to others.[232] In 2000, a risk assessment of psilocybin by the Dutch Co-ordination Centre for the Assessment and Monitoring of new drugs (CCAM) found that the risk to public order was low.[233] The Dutch National Criminal Intelligence Service found no evidence of public nuisance related to the use of psilocybin mushrooms; though forensic physicians in Amsterdam, where psilocybin fungi are openly sold, have reported low numbers of arrests for public nuisance and violation of traffic laws.[234]

Healthcare costs of drug use are a major contributor to societal harms. Psilocybin mushrooms are not associated with any substantial burden of healthcare costs, based on a global survey of more than 12 million people, which found that approximately 0.2% of people required emergency medical attention after using psilocybin mushrooms recreationally – the lowest rate estimate of all reported drugs.[235]

3. LEGAL CONTROLS ON PSILOCYBIN

The legal controls on psychedelic drugs in the UK, and internationally, have been shaped by commitments made under three United Nations treaties on drug control, namely, the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 Convention Against Illicit Narcotic Drugs and Psychotropic Substances.[236] [237] [238] Shaped and influenced by the provisions of these treaties, the domestic laws of most countries currently enforce strict regulations with respect to the medical and scientific availability of psychedelic drugs, and impose severe criminal penalties for their unlawful production, supply and use, notwithstanding that such measures are, arguably, incommensurate with the scientific evidence as to their harms to society and to the individual.[239] In practice, the intensity of legal control concerning the production, distribution and use of drugs is a matter for each contracting

state. Furthermore, international treaties do not have a direct effect on the UK. Accordingly, the UK has room for manoeuvre under the Conventions, by which clinical research of psychedelic drugs might be facilitated by appropriate legislative action.

INTERNATIONAL DRUG CONTROL TREATIES

Various international drug control agreements, dating back to at least the 1912 Hague Opium Convention, were terminated and superseded by the 1961 UN Single Convention on Narcotic Drugs.[240] Though earlier treaties established prohibitions and limited certain actions to medical and scientific purposes, the 1961 Convention created a broader and more tightly controlled international approach and established the goal to eliminate non-medical opium use over a 15-year period and the use of cannabis and coca over 25 years.[241]

The Single Convention specifies four lists [schedules] of drug substances (with a total of more than 100 substances named) subject to control under the terms of the Convention, and a protocol was provided for adding new drugs without requiring amendments to the Convention.[242] The Single Convention was the first drug control treaty to focus on the cultivation of drug plants, putting the burden on producer countries to eradicate traditional use of those plants.[243] Contracting parties were required to introduce domestic drug control laws that give effect to its provisions and, in particular, to its primary aim to "limit exclusively to medical and scientific purposes the production, manufacture, export, import, distribution of, trade in, use and possession of drugs".[244] That aim remains the cornerstone of international drug policy.

Two further UN drug conventions have been ratified by the UK. The

1971 Convention applies to an even wider range of drugs including amphetamines, barbiturates, benzodiazepines and psychedelics.[245] According to a UN staff member of the Division of Narcotic Drugs at the time, the 1971 Convention consisted of two treaties, one outlining the strict controls for substances in Schedule I (i.e. psychedelic drugs), and the other covering weaker restrictions on pharmaceuticals in Schedules II, III and IV.[246] The disparity was, in part, a result of lobbying pressure from the European and American pharmaceutical industries.[247] As Schedule I drugs, psychedelics are subject to the following controls as outlined in art.7a: "Prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them". [248] This is more restrictive than the terms of art.4 of the Single Convention.

The 1988 Convention established additional legal mechanisms for enforcing the preceding treaties.[249] A key purpose of the convention was to promote international cooperation between consumer and producer countries to suppress trafficking. Parties agreed to establish the unlicensed manufacture, distribution or transport of psychedelic precursors as criminal offences.[250]

UK REGULATIONS ON THE USE OF CONTROLLED DRUGS IN SCIENCE & MEDICINE

The regulation of medicinal products - substances that are presented, used, or intended for the treatment or prevention of disease, modification of physiological function, or to make a medical diagnosis – has long been governed by legislation including the Therapeutic Substances Act 1925 (repealed and superseded by an Act of the same

name in 1956, which was itself repealed in 1993), the Medicines Act 1968, the Poisons Act 1972, and the Human Medicines Regulations 2012.[251] Oversight of medicines for human use is the responsibility of the Medical and Healthcare products Regulatory Agency (MHRA), the product of a merger of the Medicines Control Agency and Medical Devices Agency in 2003.[252] The MHRA performs a variety of functions in connection with medicinal products including the granting of marketing authorisations. As with its parent agencies, the MHRA is an executive agency of the Department of Health and Social Care (DHSC).[253]

The regulation of controlled drugs – drugs that are dangerous or otherwise harmful and liable for misuse – is laid out under the Misuse of Drugs Act 1971, which repealed and superseded the Drugs (Prevention of Misuse) Act 1964, and the Dangerous Drugs Acts of 1965 and 1967. The 1971 Act and its associated regulations constitute a mechanism by which the unauthorised supply and possession of controlled drugs is prohibited, whereas actions in respect of controlled drugs for medicinal or scientific use may be permitted. Medicinal drugs with a potential for harm may, therefore, be controlled under both medicines legislation and under the 1971 Act and its regulations. The 1971 Act was enacted and subsequently amended with consideration of the UK's treaty obligations under international drug conventions.[254] It lists controlled drugs in three classes (A, B, C) and defines criminal offences relating to their cultivation, production, supply, movement or possession. The classes are intended to be reflective of the relative potential harms of misuse. However, drug classification is a contentious issue and criticised for lacking scientific validation.[255] [256] [257] [258]

The 1971 Act and subsequent regulations provide various powers to the UK Home Office. Section 7(3) of the Act requires the Home Secretary to make regulations to permit the authorised medical

use of controlled drugs. The secondary legislation associated with Section 7(3), the Misuse of Drugs Regulations 2001, stipulates the conditions under which the professional use of controlled drugs can lawfully occur. The 2001 Regulations particularise controlled drugs into five schedules (see Box 1), and, alongside the Misuse of Drugs (Safe Custody) Regulations 1973, define the regulation of their supply, prescription, storage, destruction and record keeping.

Section 7(4) of the 1971 Act grants the Home Secretary power to designate certain drugs as being exempt from Section 7(3) if "it is in the public interest" to do so. Section 7(4) provides that, under such circumstances, the "production, supply and possession of that drug to be either wholly unlawful or unlawful except for purposes of research or other special purposes." The Misuse of Drugs Designation Order 2015 lists drugs to which this Section applies, and which may not be used lawfully except under a license or other authority issued by the Home Office.

Psilocin and its esters (including psilocybin) are listed in Class A of the 1971 Act, Schedule 1 of the 2001 Regulations and Part 1 of the 2015 Order. Accordingly, psilocybin cannot be produced, supplied or prescribed without specific Home Office approval. Amendment of the schedule of a drug under the 2001 Regulations does not require primary legislation and may be achieved through the use of a Statutory Instrument laid by the Home Secretary under the negative procedure after consultation with the Advisory Council on the Misuse of Drugs.

Box 1: Schedules of the 2001 Regulations

Schedule 1 includes drugs that are not available for scientific or medical use without specific approval from the Home Office. Schedule 1 drugs include psilocybin, LSD, MDMA, khat, coca leaf, raw opium, and cannabis other than 'cannabis-based products for medicinal use' (CBPM).[322] A controlled drug register must be used to record details of any Schedule 1 drugs received or supplied by a pharmacy.

Schedule 2 includes drugs that are available for prescription without specific Home Office approval, subject to special controls regarding safe custody and prescription. Schedule 2 drugs include opiates (e.g. diamorphine (heroin), morphine, methadone hydrochloride), major stimulants (e.g. amphetamine, methamphetamine), cocaine, ketamine and CBPM. A controlled drug register must be used to record details of the acquisition and use of Schedule 2 drugs.

Schedule 3 includes substances subject to special prescription regulations and safe custody regulations (with some exceptions). Schedule 2 requirements for record keeping and storage do not apply to Schedule 3 drugs, which include barbiturates and Flunitrazepam (also known as Rohypnol).

Schedule 4 (Parts 1 & 2) includes drugs that are not subject to special prescribing arrangements nor safe custody requirements. Predominantly, drugs in Part 1 are benzodiazepines, and those in Part 2 are steroids. Drugs in Part 2 are exempt from the prohibitions on importation, exportation and pos-

from the prohibitions on importation, exportation and possession when in the form of a medicinal product.

Schedule 5 is reserved for preparations with low concentrations of active ingredient, and therefore low strength. These substances are exempt from most of the requirements pertaining to controlled drugs.

4. THE SIGNIFICANCE OF SCHEDULES

SCHEDULE 1 REGULATIONS INCREASE COSTS, DURATION AND DIFFICULTY OF RESEARCH

The Schedule 1 status of psilocybin hinders research. This is particularly important to understand and rectify in view of the new Life Sciences Sector Deal. This has identified life sciences and pharma as a flagship UK industry post-Brexit. With the expertise that exists in the UK, we are well placed to lead the world in psychedelic research. However, Schedule 1 restrictions significantly impede this potential and reduce the economic impact of this research. Moving drugs with high research value from Schedule 1 to Schedule 2 will support medical and pharmaceutical research, while continuing to guarantee secure and responsible stewardship of substances in a small number of properly regulated organisations.

Although small clinical trials and limited animal studies with psilo-

cybin are being conducted in the UK, Schedule 1 regulations increase the costs, difficulties and duration of research. It is particularly important to highlight the added burden on universities, funders, personnel and patients in comparison with research into Schedule 2. Universities do not usually need a licence to possess and supply controlled drugs in Schedules 2 to 5 of the Misuse of Drugs Regulations 2001, but a controlled drugs (CD) licence is required to possess and supply controlled drugs listed in Schedule 1, including psilocybin. The issues described below do not apply to Schedule 2 drugs.

The barriers to research have been highlighted in peer-reviewed publications, including survey studies of researchers.[259] [260] A 2018 survey study of members of the British Association for Psychopharmacology concluded that "current UK legislation hampers research into the consequences, and potential therapeutic benefits of Schedule 1 drugs".[261] Respondents to the survey described the frustration vividly:

> "As it stands, it is so difficult to even contemplate research in this area as you almost have to think 'Right, we might, if all goes well, be able to start in two years'"

> "In short, I can tell you without hesitation that the current legislation surrounding controlled drugs is stifling research in this area: it has essentially dissuaded me from continuing my work. I no longer work on controlled drugs."

In comparison, working with Schedule 2 drugs was reported to be substantially easier:

> "We routinely use Schedule 2 drugs for experiments in animals. Processes for ordering and management work

> well. Schedule 1 drugs are much more difficult due to additional licensing which effectively precludes using these compounds despite potential value for preclinical research."

Most recently, an extensive analysis of UK University researchers has been conducted by academics at the University of Manchester (including the author JN), with a focus on psilocybin. Initial analysis shows significant and extensive barriers to research encountered by all personnel involved. This study included detailed interviews with a range of UK researchers, including clinicians, pharmacists, psychologists, imaging scientists, and animal researchers, and will be published in a peer reviewed scientific journal in Q4 2020. In 2020, the ACMD also conducted a survey of UK pharma and universities on Schedule 1 barriers to research with a focus on synthetic cannabinoids. Researchers in the US, where these drugs are also listed under the most restrictive schedule, face similar challenges.[262] [263] [264]

In summary, Schedule 1 regulations raise barriers at every stage of scientific inquiry from preclinical to late phase clinical research by adding costs, delays and stigma, thereby impacting funding, ethical approval, recruitment and collaboration. These barriers, which are well known among the research community and have been recognised in Parliamentary reports for at least twenty years, prevent many studies from taking place and substantially complicate those that do.[265]

Costs

The costs associated with Schedule 1 regulatory requirements, including licensing, negatively impact research at all stages, increasing the burden on large-scale clinical studies and effectively precluding many academics from conducting valuable experimental research. The authors JR and JN currently undertake clinical and

non-clinical research with Schedule 1 drugs in the UK and can thus attest to the costs and burdens as of 2020.

A controlled drugs licence costs approximately £3,000 and is renewable every 12 months, with a renewal fee of approx. £325, or £1,370 if an inspection is required. Separate Schedule 1 licenses are required at every stage of the supply chain, from the manufacture of the active substance (API), to the manufacture and preparation of the finished product, through to dispensing and administration. Mandatory import and export licenses for compounds that are moved between research partners and sites create additional costs and administrative burden, and limit opportunities for researchers to work internationally.[266] [267]

Schedule 1 regulations confer a particularly significant burden for large-scale, multi-site phase 3 clinical studies, which are already costly and administratively complex. These trials are essential to provide the safety and efficacy data required for regulatory approval of new drugs, and to guide future clinical research objectives.[268] Every site at every clinical trial must have a separate Schedule 1 'administer' license, which names medical personnel who can prescribe and nursing staff who can administer the drugs. Every pharmacy that dispenses Schedule 1 drugs must have a separate 'dispensing' license and every pharmacy that packages or otherwise handles Schedule 1 drugs must have a separate 'manufacturing' license.[269] In practice, the process of manufacturing the drug substance, ensuring quality and purity standards are met, and then encapsulating the drug substance are all undertaken by different pharmacies, all of which must have the relevant Schedule 1 licenses that, again, are renewed annually.

The burden imposed by license applications, however, pales in comparison to the practical and financial implications of Schedule 1. At

the time of writing, JR has just signed a contract with a pharmacy that holds a Schedule 1 manufacturing license to supply 120 doses of psilocybin and placebo for a clinical trial. The activity of the pharmacy is to put capsules of psilocybin or placebo in a plastic bottle, label them and then send them to the hospital pharmacy. This seemingly minor task is complicated by Schedule 1 regulations mandating extremely strict security standards, including specially designed safes, vetting of personnel and 24-hour CCTV coverage.

This contract is valued at £42,000, or about £400 per dose of psilocybin. A large proportion of this cost is directly attributable to Schedule 1 legislation and would not be required at all if psilocybin was a Schedule 2 drug, since the local hospital pharmacy would be able to undertake this task. It is germane to note that the UK Government will be paying the cost of this contract, since the money for this trial comes from UK Government itself via the National Institute of Health Research. This is a waste of the taxpayers' money and scarce grant funding that could be used for other research.

It is difficult to put an exact overall figure on the financial burdens of Schedule 1, partly as they are indirect and nebulous. Compass Pathways Ltd, which manufactures psilocybin in the UK and makes it freely available to researchers undertaking licensed, authorised research, have estimated that the cost of developing, manufacturing and encapsulating the first batch of psilocybin was in the region of £2,000,000, a significant proportion of which was due to the burdens imposed by Schedule 1 regulations. A health economic analysis of rescheduling is to be published by the CDPRG in a subsequent report, quantifying the additional costs of bringing a Schedule 1 drug to market.

> "In our first study of psilocybin in the treatment of resistant depression, I calculated that because of the

> extra costs incurred by the Schedule 1 status of psilocybin, each dose cost around £1,500 – more than ten times the amount if the restrictions were not in place. This money is taken from research grants and so undermines their financial viability and reduces their extent. It also took us over 2 years to get the permissions to conduct the research, which represents a huge lost opportunity cost."
>
> Professor David Nutt, Imperial College London [270]

Delays

Long delays related to Schedule 1 regulations are reported by research staff to occur at multiple stages in the research process, typically related to licensing, ethical approval and other administrative requirements. For instance, the ongoing University of Manchester analysis into barriers to controlled drug research identified delays associated with the Schedule 1 license application process, particularly for new applicants. One pharmacist reported difficulties with the online application form, which requires the applicant to enter information that can be time-consuming to gather, but which does not provide a list of required documentation at the beginning. The form does not permit going backwards to previous sections of the form and 'times out' after a certain period, meaning that applicants may have to restart the form numerous times before it can be completed.

> "The first screen might say you needed a list of who is responsible in your trust for security or governance or medicine, so you'd go away and try and find all this information, but it would take you a while. Then you would come back, click on the next screen and it would be talking about: "What is your alarm system; What is the response to your alarm system; When does it need test-

> ing; Who does the testing; What's your serial number?" So, you'd go away and try and find that, come back, click into the next screen and then it would say that somebody who's head of security needs to be DBS checked and your normal hospital DBS checks weren't applicable. They had to get a separate special DBS check for Schedule 1 drugs, which meant somebody quite senior in your trust had to go down to the post office with all their ID and get all that officially checked by the Post Office and sent off, and then that meant that form that you'd filled out gets cancelled [because of the time delay]. So then, because you didn't have the information you needed at hand you then had to then start the form all over again."

Research staff reported that once Schedule 1 license applications have been submitted, the validation and approval process (which may involve inspections from compliance officers) may add further delays of many months, or even years, for every necessary license to be granted. Previous survey data on barriers to research indicates that, in some cases, the Home Office has requested ethical approval before granting an initial licence, while ethics committees have requested Home Office licensing before considering the application - an impasse that causes further frustration, excess paperwork and long delays.[271]

At all stages of research, delays are caused by the additional background work that administrators and researchers must conduct to understand Schedule 1 regulatory requirements. Applicants may not be familiar with the licensing process, since universities do not require specific controlled drug licenses for research with other controlled drugs such as heroin, cocaine, and methamphetamine, all of which are in Schedule 2. According to the University of Manchester analysis, many research staff feel that there is limited available help

provided to applicants by regulators and that the rules and requirements can be challenging to understand. Indeed, current regulations regarding the use and storage of small quantities of Schedule 1 drugs for research have been described by the ACMD as 'problematic' and unclear.[272] Compound libraries are used by both industry and academia, containing small amounts of substances stored in multi-well plates in a computerized repository. It is problematic to store Schedule 1 drugs in such libraries, since regulations dictate that they must be stored in locked cabinets regardless of quantity.[273]

There are a wide range of further delays associated with Schedule 1 research, from contracting the specialist pharmacy services discussed previously, to the increased daily work involved with the added regulations on the storage, record-keeping and movement of Schedule 1 drugs at research sites. These delays will be addressed more comprehensively in the forthcoming analysis from the University of Manchester. In addition to the obvious impact on the speed of scientific progress, all delays also translate into higher research costs, since research staff must be employed for greater periods of time.

> "We had to wait one year to obtain our [Schedule 1] controlled drugs (CD) licence to investigate effects of cannabinoids in rats. This is an enormous delay. We cannot move the drugs outside of our building. This means that a colleague working on the same project in another building could not work under the permission of our CD licence. To have one licence for each building within an institution is very restrictive, expensive and time-consuming (for us and the Home Office) and does not enable academic collaboration which is essential for the success of research."

> Professor Joanna Neill, University of Manchester[274]

Stigma

Stigma is a huge issue with researching drugs in Schedule 1, even in animals. The stigma of Schedule 1 status perpetuates cultural biases against this category of controlled drugs and increases the difficulty of academic collaborations, obtaining ethics approval, and achieving institutional funding through research.[275] The impacts of stigma were recognised as early as 1998 in a Science and Technology Select Committee Report, which reported:

> "Transfer [of cannabis] to Schedule 2 would also go some way to removing the stigma which many of our witnesses believe hangs over research in this field, deterring researchers, funding bodies, pharmaceutical companies and local ethics committees alike from involvement in research which might turn out to be of great importance."
>
> Science and Technology Select Committee (1998)- Ninth Report: Cannabis[276]

The University of Manchester analysis has also identified negative impacts of stigma in both clinical and non-clinical research with psilocybin, clearly indicating that this issue has not been resolved in the past two decades:

> "There are several different people in a range of departments who all have to agree in order for Schedule 1 research to happen. Many of them have anxiety about engaging in research with a Schedule 1 drug because they are considered to be "high risk". This starts a bureaucratic process of oversight and audit, which does not hap-

pen for research with other drugs that are considered low-risk. Schedule 1 research is considered high-risk, politically sensitive, and that creates a lot more bureaucracy; different departments around the university that may not otherwise want to know about what is going on, suddenly want to know about the research."

Clinical trial example, University of Manchester analysis

"For preclinical research, each study is approved by a range of staff at the animal facility- (in addition to having a project licence from the Home Office for the programme of work, Animals Scientific Procedures Act 1986). To use psilocybin in animals we had to have extra precautions because it is a Schedule 1 drug. This included a meeting with the animal facility team, a report made to the Home Office and after the 1st safety study, an amendment to the project licence which can take up to 6 months. We have never had to do this for a schedule 2 drug. This is a good example of the stigma associated with schedule 1 research and the negative impact that has on the research."

Animal study example, University of Manchester analysis [277]

SCHEDULE 2 REGULATIONS SUPPORT LEGITIMATE RESEARCH WHILE MAINTAINING SAFEGUARDS

Researchers and other stakeholders, including the Home Office, have consistently reported that research is more easily conducted under

Schedule 2 regulations than under Schedule 1. The University of Manchester analysis on barriers to research identified a widespread belief among research staff that rescheduling psilocybin would facilitate scientific development while retaining the controls necessary to prevent unintended harms:

> "A lot of the regulations and practical security requirements surrounding the custody, transport & administration of the drug would be removed [if psilocybin were moved to Schedule 2]. Not all of them, because Schedule 2 drugs still have strict safe custody, security and administration requirements. But it would mean that we wouldn't need any of those Schedule 1 licences because you would have a specific exemption to do the research. In summary, re-scheduling would make the research easier whilst still maintaining the security and safe custody processes that are necessary."
>
> Representative excerpt from a clinician, University of Manchester analysis.
>
> "Research sites would be able to open up a lot quicker [if psilocybin were moved to Schedule 2]. There would be more sites willing to take on people who didn't have a high pharmacy presence. Mental health trusts don't often have a dedicated clinical trials pharmacist or access to a trials pharmacist.
>
> The licensing application itself is exceptionally time-consuming. I can understand why they need some of that information but if they sent you a pack just saying we need to know the basics of your security and your SOPs in advance then we will issue the license instead of this big

long process that we have to go through."

Representative excerpt from a pharmacist, University of Manchester analysis.

"My absolute view is that there should be no difference between Schedule 1 and Schedule 2. I don't think that there's a particular advantage to the process of Schedule 1 over Schedule 2. I would say that, if anything, the process for a Schedule 2 drug works fine, you can live with that level of management, the process off signing off all the paperwork [is not difficult], but Schedule 1 is pointless, it's bureaucratic and hinders good science.

It would be the speed in which science could react to things, e.g. many years ago, we had funding for a project in which we would have really liked to have looked at psychedelics. If it hadn't been for the restrictions, I could have tested psilocybin in a rodent model of depression, five to six years ago, which would potentially be really useful data to have to inform what is now happening. Not necessarily just the clinical trials, but the fact that you've got people microdosing and self-medicating with these compounds, and we don't know that data yet because it hasn't been done. I could have done that work five or six years ago if psychedelics were not in Schedule 1. Actually, the drugs that I routinely use that are probably the most dangerous are in Schedule 2, e.g. ketamine - people use it as anaesthetic, not just as a research tool. I personally think the risks are much greater with a compound like that than with psilocybin."

Representative excerpt from an animal researcher,

University of Manchester analysis.

Similar views were identified in the 2018 survey of members of the British Association for Psychopharmacology. This publication also reported concerns among the research community that the distinction between drugs in Schedule 1 and Schedule 2 was not based on scientific evidence on relative risks and harms:

> "The difference in regulations for using Schedule 2 drugs (e.g. PCP) and Schedule 1 drugs (e.g. cannabinoids), and difficulty in using Schedule 1 drugs is not evidence-based or scientific. The current UK drug laws are clearly hindering research at all levels."

A scheduling review is undertaken as part of the normal process when a medicinal product achieves market authorisation in the UK. In November 2018, however, a precedent was set for moving controlled drugs (CBPM) from Schedule 1 to Schedule 2 prior to market authorisation as a medicine. It was widely recognised that this change would result in improvements to the development of scientific research, thereby leading to various secondary benefits to public health and the UK economy. At the time, the Home Office wrote:

> "The rescheduling may lead to increased UK research [...] as these products can be tested more easily." "This may lead to economic benefits for UK businesses and health benefits to patients if this research leads to new and improved [medicinal products]." "In principle, research is ongoing and could lead to more effective treatment, lower costs, better understanding and management of risks, and improved health and wellbeing, over the medium term."[278]

The current Chief Medical Adviser to the UK Government, Prof Chris Whitty, later stated that:

> "[There] were four barriers to people getting cannabis products before the change in the law. The first and most important one at that stage was that all of those drugs were in Schedule 1, which made it difficult to build an evidence base, because, although it is possible to do trials under those conditions, it is extremely difficult. Removing that barrier is the single most important thing that could be done by Government at this stage. That has now happened, and it is a lot easier to do stuff on a schedule 2 basis. The next stage is to do the trials."[279]

In their written advice to the Home Office regarding the scheduling of CBPM, the ACMD wrote:

> "The research community has expressed concern that Schedule 1 acts as a 'barrier to research'. This is important to understand and is an issue with implications not just for Cannabis, but also for other Schedule 1 drugs where a potential therapeutic benefit has been proposed… The ACMD considers that it is important that Cannabis is not seen in isolation but as an example of a wider issue of potential 'barriers to research' associated with other drugs in Schedule 1."[280]

Evidently, there is widespread recognition across political and academic sectors that substantial challenges to conducting research are associated with Schedule 1, and that these challenges can be attenuated by moving a drug with high research value to Schedule 2.

JUSTIFICATIONS FOR RESCHEDULING PSILOCYBIN

We recommend that the Home Office urgently consult the ACMD with a view to rescheduling psilocybin to Schedule 2, with the option to impose special statutory limits on access to prevent prescribing outside of ethically approved research studies, unless a product has market authorisation as a medicine. A blueprint of how this could be achieved is provided in the subsequent section. Under this model, regulatory controls on legitimate research could be lessened without permitting the wider prescription of psilocybin as an unlicensed medicine. The scheduling of particular formulations that are brought to market would be reviewed in the normal way as part of the market authorisation process. The following section presents an overview of the arguments to support this recommendation.

1. There is an urgent need to support novel therapies in treatment-resistant mental health conditions, which constitute a vast social and economic burden in the UK. There is substantial commercial and scientific interest in researching psilocybin as a therapy, but Schedule 1 regulations obstruct research.

Schedule 1 controls substantially increase the cost, duration and difficulty of research at all stages of drug development, particularly in late-phase trials, which are already tightly regulated and expensive. Investment in new treatments for mental health has been significantly scaled back across the pharmaceutical sector, but improved regulatory support would expedite commercial progress in line with the Department of Health's 2017 'Framework for mental health research' and the 'Life Sciences Industrial Strategy' issued by Life Sciences Champion, Professor Sir John Bell.[281] [282] The need to re-

engage the pharmaceutical industry in mental health research is particularly salient at the current time, as the UK presently has no active pharmaceutical laboratories doing central nervous system research and development outside of universities since Eli Lilly closed their site in Surrey in March 2020. Accordingly, there are no psychiatric drug discovery laboratory jobs for PhD students, post-doctoral researchers, or technicians, nor industrial placements for undergraduates, posing a huge problem for UK scientific training.

The commercial potential of psilocybin therapies is considerable. The therapy is being developed for sufferers of treatment-resistant depression, a group which may comprise approximately one third of the 300 million sufferers of depression worldwide.[283] [284] Psilocybin therapies are also being investigated in a broad range of disorders related to depression, such as anxiety disorders, substance misuse disorders, eating disorders, functional neurological disorders, and other mental health problems associated with maladaptive habits of thinking and behaving for which there are few effective treatment options. There is not yet strong evidence for the use of psilocybin in these indications, but the broad scope of research reflects a substantial and growing commercial interest.

Compass Pathways, a UK company which holds a US patent covering the use of its psilocybin formulation (COMP360) in a therapy protocol for patients with treatment-resistant depression, is currently running a phase 2b clinical trial recruiting 216 patients across Europe and North America.[285] Subsequently, the safety and efficacy of COMP360 will need to be confirmed in large-scale phase 3 trials to support an application to the MHRA for market authorization. The normal process for market authorization will lead to a scheduling review for that specific formulation – however, significant savings could be made by moving psilocybin to Schedule 2 early, prior to the commencement of phase 3 trials.

In addition to supporting industry, rescheduling would save taxpayer's money by reducing wasted expenditure of Government research grants (such as the £1.2 million NIHR grant supporting psilocybin research at King's College London). Ultimately, reduced burdens on drug development would benefit public health through earlier completion of trials and lower end-costs of treatment, thereby widening access.

Schedule 1 controls on psilocybin also impede important non-clinical and preclinical research advancing scientific understanding in a wide range of biological systems, including the brain, the immune system and the endocrine system.[286 287 288 289] The UK is currently keeping pace with other leading countries in both clinical and non-clinical psilocybin research, but improved regulatory support will ensure the UK's reputation as a global centre of excellence in this area, attracting further commercial investment and highly-skilled workers, while preventing a 'brain-drain' of British research and innovation to other jurisdictions that may inevitably take place when other countries provide more favourable regulatory conditions.

Rescheduling psilocybin would be the most significant and immediate way that Government could support scientific and commercial development in this area.

2. There is no work currently commissioned by the Home Office that addresses the urgent issues identified in this report.

The ACMD are currently undertaking two relevant reviews: (1) to establish a Standard Operating Procedure (SOP) for scheduling decisions; and (2) to understand the barriers to research with controlled drugs. This work is vital, and we welcome it. However, it is currently unclear whether the SOP will be used to review historical scheduling

decisions, and the initial focus of the review on barriers to research is intended to cover synthetic cannabinoids. Neither report is expected to be published until 2021, nor to directly provide recommendations on psilocybin. Accordingly, it is not likely that either working group will address the urgent and specific issues identified in this report, nor lead directly to legislative change prior to the commencement of phase 3 trials in psilocybin. See Justification (1) for more details.

Immediate action is required to provide regulatory support to the development of psilocybin as a much-needed medicinal product.

3. There is conclusive evidence that the actual harms of psilocybin are substantially less than the assumed harms underpinning original scheduling decisions in the 1970s.

Almost half a century on from the Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 1973, there is little available information on the procedural basis of classification and scheduling decisions. According to the then Home Secretary, the 1971 Act was "drawn up on the basis of the lists of drugs controlled by the 1965 and 1964 Acts […] in the order in which we think they should be classified of harmfulness and danger."[290]

Psilocybin was never listed under the 1965 or 1967 Dangerous Drugs Acts. In 1965, it had been added to the 4th Schedule of the Pharmacy and Poisons Act 1933, and, in 1966, to the Schedule of the Drugs (Prevention of Misuse) Act 1964. Under the 1933 Act, it could only be sold under prescription, and under the 1964 Act, it could not lawfully be possessed except by certain exempted medical and scientific professions, nor could it be imported by any person except under Home Office license.[291] Hansard records show that the decision to move psilocybin under the Schedule of the 1964 Act reflected concerns of severe harms posed to society and the individual by the use of psy-

chedelic drugs, strongly influenced by accounts of LSD in the British media at the time.[292] [293] Little was known about psilocybin itself, which was mentioned only in association with LSD. Under the controls of the 1933 and 1964 Acts, psilocybin could be freely used without a license for medical and research purposes – it was not until the 1973 Regulations that specific Home Office authorization would be required. It is unclear why it was then placed under more restrictive controls than other Class A drugs with medicinal uses, such as heroin and cocaine.

With the benefit of several decades of epidemiological, experimental and clinical data, which were not available to the Government at the time of writing the 1971 Act and 1973 Regulations, the contemporary scientific consensus is that psilocybin does not pose a substantial risk to public health in the context of its scientific and medical use – or even as a drug of abuse.[294] [295] [296] [297] [298] [299] [300] [301] [302] [303] Early reports of suicide, violence and madness associated with psychedelic drugs in 1960s media were influential in policy decisions regarding their control, but population-level studies have since found decreased odds of suicidality, violent crime and psychological distress linked with their use.[304] [305] [306] A 2016 pharmacological review echoes this perspective: "For decades, the media have largely portrayed psychedelics as extremely dangerous drugs; in fact, the classic serotoninergic psychedelics are generally considered very physiologically safe, certainly compared with opiates and psychostimulants."[307]

In 2005, Professor Sir Colin Blakemore, former Chief Executive of the Medical Research Council, told the House of Commons Science and Technology Committee:

> "The placing of [psilocybin and other psychedelics] in category A [of the Misuse of Drugs Act] was a reaction to the concerns about drugs which were newly available

> on the street in the 1960s and 1970s with not much scientific evidence about their actions and certainly their long term consequences... The evidence of toxicity is very low. They are not addictive and I would rate them very low in their potential for harm... I would say they are in a classification that if one could look at all the evidence for harm available now, including social harms, one would say it is wrong."
>
> "I am sure [the Government] were using the evidence that was available to them at the time. The question is whether that evidence was fully formulated and was quantitatively organised in a way that would inform the decision well."

The Committee quoted Professor Sir Michael Rawlins, then-Chair of the ACMD as saying: "I have no idea what was going through the minds of the group who put [psilocybin] in Class A in 1970 and 1971 […] It is there because it is there."[308]

We make no recommendations on the classification of psilocybin under the Misuse of Drugs Act 1971, but we observe that its current inclusion in Schedule 1 of the 2001 Regulations follows an outdated assumption of harmfulness, implicit in its Class A status, which is not supported by the current evidence base.

4. There is a precedent for rescheduling Schedule 1 drugs prior to market authorization.

In 2018, CBPM were moved from Schedule 1 to Schedule 2 of the 2001 Regulations, with special statutory limits placed on supply and use. This allowed CBPM to be prescribed as unlicensed medicines to patients with a special clinical need, reduced the barriers to research,

and established additional checks and balances to prevent diversion and inappropriate prescribing. We propose special statutory limits that could be placed on psilocybin in a rescheduling instrument that would impose greater controls on prescribing than are currently in place for CBPM.

CBPM affected by the rescheduling are not licensed as medicines for any indication, in any patient group, either in the UK or internationally; with the exception of Epidyolex, which has since received been licensed for use in the UK. At present, there is no robust evidence of the safety and efficacy of any unlicensed CBPM from randomized-controlled trials (RCT).[309] Therefore, with multiple phase 2 RCT already completed, there is a stronger evidence base on the clinical use of psilocybin than on any of the currently-unlicensed CBPM formulations rescheduled by the Home Office in 2018.

Rescheduling psilocybin is possible and precedented.

5. A research-only rescheduling model for psilocybin will limit diversion and inappropriate prescribing, and act as a pilot intervention to guide the resolution of wider barriers to research.

Although there is a precedent for the rescheduling of Schedule 1 drugs prior to market authorisation, there is no precedent for the rescheduling of a drug for research purposes only. We propose that piloting this approach with psilocybin may serve to inform the resolution of wider issues affecting research on Schedule 1 drugs. Statutory research-only limits may reduce the well-recognised barriers to research without: (1) creating an unworkable administrative burden; (2) compromising the Home Office's commitments to report to the INCB; or (3) increasing the risks of diversion and inappropriate prescribing. An evaluation should be undertaken after 24 months

to assess the effectiveness of the model, with a view to applying it to other drugs in Schedule 1 for which there is substantial clinical, scientific or commercial interest, including MDMA, LSD, DMT, fentanyls, and synthetic cannabinoids. Urgent action in regard to psilocybin, specifically, is justified by the registration of a psilocybin formulation as an investigational medicinal product, currently being investigated in late phase trials as a therapy for treatment-resistant depression, a condition with no effective treatments – by definition – which affects an estimated 1.2 million people in the UK at significant social and economic cost.

The ACMD working group on barriers to research with controlled drugs is collecting evidence to inform an evaluation process that has already been underway for several years. In July 2017, the Home Office commissioned the ACMD to review what could be done to facilitate research involving Schedule 1 controlled drugs. In December 2017, the ACMD proposed the creation of a temporary 'research schedule' with reduced regulatory requirements.[310] Their recommendation was that Schedule 1 drugs proceeding into clinical trials could be moved to this novel schedule, provided that the drug sponsor issues a detailed investigator's brochure and ethical committee approval to the Home Office, showing evidence of safety and tolerability. Under this model, drugs that are not successfully brought to market would revert to Schedule 1 status.

However, in January 2019, a Home Office Minister of State, Nick Hurd, wrote to the Chair of the ACMD to reject the notion of a novel research schedule on the basis of a "heavy burden on legislative amendment time," since Ministers would be required to consult with the ACMD every time a drug was moved into or out of the proposed schedule.[311] He commented that there "may be some further legislative and non-legislative options which could be considered in further detail." We propose that the administrative burden identified by

Mr Hurd would be substantially less under research-only rescheduling model proposed in this paper, since, if it is effective in addressing the issues in regard to psilocybin, it can later be applied to multiple Schedule 1 substances in a single instrument without requiring subsequent consultations with the ACMD.

In their letter to the Home Office in December 2017, the ACMD also proposed a 'self-policing' approach whereby a research body would apply for a compound-specific exemption without disclosing the chemical structure, but using a unique identifier.[312] This proposal was unlikely to apply to psilocybin, but rather to compounds covered in the 2001 Regulations by generic chemical structures common to closely related drugs. The Home Office rejected this proposal on the basis that it would not be compatible with the obligations of the UK Government to report to the INCB, on a quarterly basis, on materials listed in Schedule I of the UN Conventions.[313] The proposed research-only rescheduling model would not compromise the Government's obligations in this regard, since Schedule 2 record keeping controls will be sufficient to inform the Government on the movement of drugs, as is currently the case with heroin, cocaine and amphetamines.

Academic reviews have found no instances of diversion of Schedule 1 or Schedule 2 drugs from research labs, consistent with ACMD advice that "the risk of diversion and misuse [of controlled drugs] in a research setting is likely to be minimal."[314] [315] In their comprehensive 2016 review of the diversion of controlled drugs from the medical sector to the illicit market, the ACMD concluded that the major source of diverted medicinal drugs is by prescription prior to diversion.[316] Since psilocybin is not prescribed to patients to take home, diversion by this route will effectively be prevented.

Rescheduling psilocybin on a research-only basis will provide

immediate benefits to scientific research and commercial drug development, while acting as a pilot to inform the ongoing evaluation of barriers to research with controlled drugs, without increasing the risks of inappropriate prescribing or diversion.

6. Rescheduling will not affect existing controls on the criminal use or supply of psilocybin or psilocybin-containing mushrooms.

Psilocybin can be moved from Schedule 1 to Schedule 2 of the 2001 Regulations and from Part 1 to Part 2 of the 2015 Order without requiring changes to its classification under the 1971 Act. Multiple high-profile reviews have found no convincing evidence that criminal penalties have any substantial 'deterrent effect' on drug offences, but in the presumption that such an effect may exist, rescheduling is not likely to reduce it, since criminal penalties for offences will be unaltered.[317] [318] [319]

PATHWAYS TO RESCHEDULING

Schedules of the UN Drug Conventions

Paragraphs 5-7 of Article 2 to the 1971 Convention outline a process for the rescheduling of a drug from one schedule of the treaty to another, whereby, in the light of new findings concerning a drug, the World Health Organization Expert Committee on Drug Dependence shall communicate its findings to the United Nations Commission on Narcotic Drugs (CND).[320] The CND may subsequently elect to transfer the substance between schedules, or delete it from them, requiring a 2/3 majority of their members according to Article 17. Any such decision made by the CND must be communicated by the Secretary General to all member States, to non-member

State parties to the 1971 Convention, the WHO and the INCB. The decision will come into effect for each party to the Convention 180 days following this communication. There are precedents of such a process being successfully applied, such as the movement of dronabinol from Schedule I of the 1971 Convention to Schedule II in 1991.[321]

Achieving rescheduling of psilocybin under amendments to the 1971 Convention through the process outlined above would support greater flexibility for signatory countries to adopt alternative legal controls on its production, supply and use. However, since international treaties do not have a direct effect on the UK, rescheduling at the UN level is not necessary for the UK to move the drug between schedules of the 2001 Regulations.

Schedules of the 2001 Regulations

The rescheduling of any drug listed in the 2001 Regulations requires amendments to that legislation by way of a Statutory Instrument laid by the Secretary of State under negative parliamentary procedure. The 1971 Act requires the Secretary of State to consult with the Advisory Council on the Misuse of Drugs (ACMD), a statutory advisory non-departmental public body established under the provisions of the Act, though it does not oblige the Government to follow ACMD advice. Under such a process, psilocybin may be rescheduled to a more appropriate schedule commensurate with its safety profile and clinical potential.

Special statutory limits can be provided in the instrument, as can be seen in Regulation 16A of the 2001 Regulations, which imposes special restrictions on the order and supply of CBPM. We note that Regulation 16A does not make allowances for the use of CBPM in non-clinical or preclinical research – a limitation that we strongly recommend against. However, we do propose that the Home Office consider statutory limits to prevent the order and supply of psilocybin

as an unlicensed medicine, as part of special checks and balances to avoid inappropriate prescribing and diversion. As an example, these restrictions could be worded in line with the following:

> 1) A person shall not order or supply (whether by issuing a prescription or otherwise) a product containing psilocin or esters of psilocin, unless that product is—
>
> > (a) a product without a marketing authorisation that is for use in a research study that has been approved by a research ethics committee;
> >
> > (b) an investigational medicinal product without a marketing authorisation that is for use in a clinical trial; or
> >
> > (c) a medicinal product with a marketing authorisation.

CONCLUSION

Schedule 1 regulations restrict the production, supply and use of harmful drugs to legitimate scientific and medical purposes under specific Home Office licenses or other authority granted by the Home Secretary. In practice, the regulations are a barrier to legitimate research and commercial drug development, leading directly to delays, additional costs and increased stigma. Clinical and epidemiological research has shown psilocybin to be a relatively safe drug and early phase trials indicate potential value as a therapy for treatment resistant mental health problems, including conditions associated with thousands of suicides annually in the UK.

Pharmaceutical investment in new therapies for mental health conditions has dried up and the UK Government has recognized the need to support and expedite research in this area. Psilocybin therapies are among the very few recent advances in mental health drug development with substantial commercial potential, but Schedule 1 controls obstruct research. The single most important thing that could be done by Government is the rescheduling of psilocybin under the 2001 Regulations.

Controlled drugs may be rescheduled by a Statutory Instrument implemented by the Home Secretary, on the advice of the ACMD, without affecting existing legal controls on non-medical or scientific use, and there is a precedent for rescheduling controlled drugs before

market authorization. The risks of diversion are low and Government have the option to introduce statutory limits to prevent inappropriate prescribing.

Swift policy change would immediately reduce the obstacles to scientific research and commercial development, shortening the time required to bring new drugs to market and reducing the end cost of therapies. Under a less restrictive regulatory framework, the UK would rapidly become the global centre of research in this area, attracting international investment and expertise. Immediate action will yield the greatest benefits to the UK.

We urge the Home Secretary to commission a high-priority ACMD review into the access-restricted rescheduling of psilocybin under the 2001 Regulations **and act swiftly on its recommendations.**

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