RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

PS02/25

Psychedelic and related substances (PARS) for medical use

(including pharmacologically assisted psychotherapy)

September 2025

POSITION STATEMENT

Contents

Authors and acknowledgements

This position statement on psychedelic and related substances for medical use (including pharmacologically assisted psychotherapy) was jointly created by the **Psychopharmacology Committee** and **Medical Psychotherapy Faculty**.

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Acknowledgement

We thank Professor Samuel R Chamberlain for helpful reviews of drafts.

How to cite this publication:
Royal College of Psychiatrists (2025) College Position Statement PS02/25 – Psychedelic and related substances for medical use (including pharmacologically assisted psychotherapy)

Executive summary

The term 'psychedelic' has been applied to a pharmacologically and phenomenologically diverse range of compounds including the serotonergic hallucinogens, ketamine and methylenedioxymethamphetamine (MDMA). There has been great interest in the use of these compounds to treat a range of mental health conditions, both in their own right and in the context of pharmacologically assisted psychotherapy, in which they are prescribed with a view to facilitate psychological change. Of these, ketamine, and its S-entantiomer, 'esketamine', have been the most studied in the rapid relief of depressive symptoms with evidence of efficacy including large randomised controlled trials.

Nonetheless, there is currently limited high-quality evidence for the efficacy of these compounds. Whilst the results of early clinical studies of the non-ketamine drugs to date have been encouraging, there is concern around the difficulties in conducting adequately blinded trials, as well as regarding side effects and whether any therapeutic benefits observed are sustained over time. These factors combined with questions regarding validity amongst clinical populations mean the current evidence base is limited, and it is not recommended that they are used in routine clinical practice other than where licensed.

Further evaluation of the clinical utility of these potential medications is needed, including in pharmacologically assisted psychotherapy, as well as research into their potential long-term adverse effects and safety. Psychiatrists should be involved in the future therapeutic use of these compounds if and when they have been licenced and as part of the clinical leadership of a multidisciplinary team, and anyone administering them and/or conducting any form of psychotherapy under their psychoactive effects must be an appropriately trained and competent registered clinician.

This statement refers to therapeutic use in clinical and research settings and not underground or recreational use of these drugs. Other than ketamine and esketamine, these treatments are not currently available in the UK on a legal basis outside of clinical research trials.

Section 1: Background

1.1 What are psychedelic and related substances (PARS)?

The term 'psychedelic', which loosely means 'to reveal the soul' from the Greek words psychē (ψυχή, 'soul') and dēloun (δηλοῦν, 'to make visible, to reveal'), has been applied to a range of compounds with diverse pharmacological and subjective effects. Originally, the term was applied to the classical hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin (the active ingredient in 'magic mushrooms'), which exert their hallucinogenic effects via the serotonin system.

However, over time, the term has also been used to encompass compounds with pronounced acute subjective psychopharmacological effects that do not have a marked hallucinogenic effect at the doses normally used, including methylenedioxymethamphetamine (MDMA, 'ecstasy') and the glutamatergic antagonists such as ketamine.

1.2 Why is there increasing interest in these compounds and which are the main ones being tested?

There has been a recent resurgence in research trials into the potential clinical utility of these compounds in the treatment of a range of mental health conditions. In the 1950s and 1960s, they were used as agents to potentially enhance psychotherapy for a wide range of presentations including mood and substance use disorders, and also in couples therapy. However, their classification as Schedule 1 substances "with no accepted medical use" in the mid-1960s effectively ended the majority of research programmes and their clinical use.

Renewed interest in the potential utility of these compounds has increased steadily since the 1990s. There have been several pilot trials and randomised controlled trials examining the effects of these compounds as medical interventions in their own right as well as in the context of pharmacologically assisted psychotherapy.

This field of research is fast moving, and we recognise that new research findings will likely emerge over the next few years and this position statement will require updating. For example, the Australian Government Therapeutics Goods Administration body legislated for MDMA and psilocybin to be prescribed for clinical use by approved psychiatrists from July 2023. Other countries such as Canada and Israel have regulatory pathways which allow the use of PARS for compassionate use. Some studies have provided encouraging evidence of safety and efficacy for some compounds[1]; although most studies to date have

not been appropriately designed to demonstrate this conclusively[2] and debate persists as to what the best design for these trials should be. These studies have understandably generated considerable excitement and publicity, as is often the case with medical innovations. However, the rigorous screening requirements of the research trials mean that it is not yet known if these results will be replicated within clinical settings where patients may have complex presentations, higher levels of clinical risk and diagnostic multimorbidity.

As an illustration, international research is ongoing with the following compounds and disorders:

- Psilocybin-assisted psychotherapy for end-of-life anxiety, treatment-resistant depression, obsessive compulsive disorders, tobacco smoking and alcohol dependence, anorexia nervosa and fibromyalgia.

- LSD 'microdosing' and LSD-assisted psychotherapy for substance use disorders, anxiety and depression.

- Methylenedioxymethamphetamine ('MDMA')-assisted psychotherapy for post-traumatic stress disorder (PTSD), eating disorders and social anxiety in adults with autism.

- Ketamine for treatment-resistant depression and ketamine-assisted psychotherapy for alcohol dependence.

1.3 Purpose and scope

This position statement seeks to capture the consensus views of the Psychopharmacology Committee and of the Working Group on Psychedelic Assisted Psychotherapy within the Medical Psychotherapy Faculty of the RCPsych after careful consideration of the available research evidence and to provide initial clinical and research recommendations based on current knowledge. This position statement draws on other similar documents, including a clinical memorandum by the Royal Australian and New Zealand College of Psychiatrists titled 'Therapeutic use of psychedelic substances'.

1.4 Psychopharmacology nomenclature

The British Association for Psychopharmacology and international psychopharmacology societies, such as the European College of Neuropsychopharmacology, are moving toward the neuroscience-based nomenclature, a classification of psychiatric medications based on their pharmacology and mode of action. The RCPsych Psychopharmacology Committee broadly supports this venture. There is no clear universally accepted definition of what a 'psychedelic' actually is, and using the term psychedelic may imply that psychedelic effects are linked to the therapeutic action of the drugs, but this remains an open question. This problem is compounded by the heterogenous subjective and pharmacological effects of these compounds. Given that the term 'psychedelic' can be

applied to compounds that are diverse in both their pharmacological and subjective effects, the RCPsych Psychopharmacology Committee suggests that it is avoided and instead recommend using a nomenclature based on the mechanism of action, i.e. in keeping with the Neuroscience-based Nomenclature such as 'serotonin receptor agonists' to refer to psilocybin and related compounds. Where a specific psychological effect of a drug is established through research as being a key mechanism of therapeutic change, it may be helpful in the future to refer to these specific effects. We recognise however that the Neuroscience-based Nomenclature has yet to be widely used in clinical settings and so, notwithstanding the scientific concerns of the Psychopharmacology Committee around the use of the term 'psychedelic', we use the term 'psychedelic and related substances' (PARS) in this guidance for ease of reference. The Medical Psychotherapy Faculty supports the use of this term.

1.5 Pharmacologically assisted psychotherapy (including psychedelic and related substance-assisted therapy)

We recognise that there is a lack of consensus on terminology for the combined use of a drug with psychotherapy. The term 'pharmacologically assisted psychotherapy' is used here to refer to the administration of a PARS within a psychotherapeutic process. This includes with psychotherapeutic input before and/or after the dosing session, and also during the dosing session, aiming to support the process of psychological change within a therapeutic relationship and setting. The terms 'psychedelic-assisted psychotherapy' and 'psychopharmacotherapy-assisted psychotherapy' have also been used in the literature.

We also note that other pharmacological treatments can facilitate psychotherapy, including, for example, serotonin reuptake inhibitors, which can facilitate cognitive–behavioural therapy. We use this term 'pharmacologically assisted psychotherapy' here to refer specifically to the deliberate combination of a pharmacologically active substance during a psychotherapeutic treatment session to facilitate psychological development and change.

A range of psychotherapeutic approaches have been used to date. Most of these approaches emphasise supporting the patient during the emerging therapeutic process rather than the application of a specific therapeutic treatment or technique. The psychological mechanisms of action are likely to include a lowering of psychological defences, increased cognitive flexibility and altered emotional state. Depending on the specific treatment, this may allow underlying issues, suppressed memories and traumatic material to emerge, as well as potentially suggestible states of mind.[11]

Other approaches have targeted specific psychological processes, for example, memory and emotional processing. Other common experiences can include perceptual changes, shifts in perspectives and altered bodily sensations. These experiences and the emergence of disturbing material may happen rapidly and be experienced as destabilising. Research trials have tended to utilise a 'psychedelic peak therapy' model using high doses of PARS to maximise the potential transformative nature of the experience

rather than lower doses used alongside psychotherapy in an ongoing way ('psycholytic therapy'). This means the participant is likely to have an intense response to the medication and to find themselves in altered states of thoughts, feelings and perceptions, emphasising the importance of skilled therapeutic input throughout the process.[8]

Key to containing and supporting this process is the quality of the therapeutic relationship and emotional attunement offered by the therapist/s. In most studies, the therapists are present for the preparation and follow-up sessions, and for the duration of the dosing session. Therapists can work in pairs for this.

During the dosing session, unconscious material akin to dreams may be freely expressed and intense transference and countertransference experiences and potential enactments may occur. Whilst these phenomena may occur within any clinical relationship, it seems likely that there is a heightened potential for these processes when working with the effects of these powerfully psychoactive substances. Therapeutic support should be available for the duration of the expected acute pharmacological effects, which may be up to 6–8 hours. There is evidence that the strength of the therapeutic rapport predicts the quality of the acute experience (i.e. the subjective experience after taking psychedelics) and ultimate clinical improvements.[71,72]

In keeping with the guidelines for good practice for any psychotherapy, key areas to consider include:

- Therapists' training, level of clinical experience and supervision with suitably qualified psychotherapy supervisors. Developing a therapeutic alliance with the patient in carefully considered preparation sessions.

- The provision of therapeutic integration sessions after the acute dosing sessions to consider the patient's experience, and the emotions and the material which have emerged in order to integrate and find meaning in the experiences.

- Managing expectations and preparation for ending treatment, with advice about further support and treatment if indicated.

- Recognition of the importance of working within therapeutic boundaries.

- Provision of a physical environment which adheres to the principles of any psychotherapeutic setting i.e. safe, confidential, comfortable and free from external intrusions/interruptions, whilst also giving access to adjuncts specific to this form of treatment if indicated (e.g. eye masks, headphones and music).

Further information about the recommendations for good therapeutic practice working with PARS as part of research is provided in the RCPsych guidance document *Psychotherapy assisted by psychedelic and related substances (PARS): Guidelines for psychiatrists taking part in research approved trials* (2025), which should be read alongside this document.

Further research is needed to elucidate the precise mechanisms of change associated with these interventions within a joint framework of evidence-based psychopharmacology and evidence-based psychotherapy. Given that pharmacologically assisted

psychotherapy involves the co-administration of psychoactive compounds with psychotherapy, there are risks of adverse drug–psychotherapy interactions.

As mentioned previously, experiences with psychedelic and related substances can be acutely destabilising, and emotionally challenging for both patients and clinicians (e.g. a 'bad trip' reaction). Therefore, anyone administering pharmacologically assisted psychotherapy should be a suitably qualified, competent, registered and regulated clinician who has undertaken rigorous training in psychopharmacology and/or psychotherapy by an accredited body such as the Royal College of Psychiatrists, and adheres to professional therapeutic boundaries, such as a suitably therapeutically trained and experienced psychiatrist.

As summarised by Dr Matthew W Johnson "psychedelic therapy is more psychotherapy than most pharma companies and neuroscientists know how to deal with, and more pharmacology than most psychotherapists know how to deal with".[55] A multidisciplinary team is therefore needed which includes psychiatrists with sufficient training in psychopharmacology and suitably trained and supervised therapists. Psychiatrists should also be involved in assessing who may benefit from treatment and the potential risks involved.

Within current treatment models, there is variability in the timing and number of sessions for therapeutic work. Some protocols involve psychotherapy during the drug session itself, others within 24 hours of the drug session, and others within days from the administration of the compound, contributing to a lack of consistency and comparability between studies.[73]

Whilst further research is needed to determine which intensity and duration of which pharmacologically assisted psychotherapy works best for whom, all interventions, regardless of modality, should adhere to the principles of good practice described in this paper, including the importance of the therapeutic relationship.

Section 2: Current evidence on effectiveness and potential harms

2.1 What is the evidence for their potential therapeutic use and efficacy in psychiatry?

A growing body of neuroimaging and psychopharmacology studies have established the scientific evidence base for the safe use of these compounds in humans, experimentally. Early-phase clinical trials have reported positive findings on the efficacy and tolerability of these compounds in the treatment of obsessive-compulsive disorder,[3] anxiety and distress in palliative care and life-threatening disease,[4–8] substance use disorder,[9, 10] depression particularly when refractory to conventional treatment[11–14] and post-traumatic stress disorder (PTSD).[74]

To date, different compounds are at various stages of the development pipeline. For example, ketamine now has an extensive evidence base. With MDMA, two phase 3 trials have been published confirming the efficacy and safety of MDMA-assisted therapy for severe PTSD (Mitchell et al., 2021). There is also evidence from phase 2 trials of LSD – for alcohol and opiate use disorders, anxiety symptoms including anxiety associated with life-threatening diseases – and trials are ongoing and have yielded mixed findings, with the strongest evidence in support of the use of LSD for alcohol use disorders.[16] Psilobycin has been used in a number of trials for treatment resistant depression and multisite phase 3 trials are in development. As most studies on these compounds have been low-powered and phase 1 or phase 2 in design, further high-quality phase 3 studies are required to fully understand the risks and benefits for these compounds in pharmacologically assisted psychotherapy. Multisite phase 3 trials are ongoing in the UK and internationally.

Taking the existing literature together, there is limited high-quality evidence on the use of these compounds. Whilst the results of clinical studies to date have been encouraging, there is concern around the difficulties of achieving adequate blinding of treatment allocations for both patients and researchers, as well as regarding side effects and whether any therapeutic benefit observed is sustained over time. There is clearly more to be learned and further evaluation of the clinical utility of these compounds, including in pharmacologically assisted psychotherapy, is needed. As an illustration, we describe some current areas of research relevant to clinicians.

2.2 5-HT$_{2A}$ agonists

Psilocybin

Psilocybin is a naturally occurring hallucinogen and the psychoactive ingredient of 'magic mushrooms'. Research is being conducted into doses that produce hallucinogenic effects both with and without psychotherapy, and also into using small, regular doses of psilocybin that do not have an acute psychotropic effect (termed microdosing) but without concurrent psychotherapy. Evidence for microdosing with psilocybin is currently limited.[17, 18]

Psilocybin, used as an adjunct to psychotherapy in controlled clinical environments, has shown variable outcomes in open label and placebo-controlled trials. Some studies have demonstrated clinically significant effect sizes and relative safety in the treatment of depression, anxiety, and addiction with phase 1 and 2 trials completed and phase 3 trials approved across North America and Europe.[1, 5, 6, 11, 12, 19] One review[19] found statistically significant efficacy in depression, existential anxiety (end-of-life distress), and alcohol use disorder – where across four double-blind studies and three open label studies with administration in 117 individuals, patient groups treated with psilocybin showed statistically significantly improved outcomes compared to control groups.

However, a more recent phase 2, double-blind RCT comparing psilocybin (n=30) with escitalopram (n=29) in the treatment of moderate to severe depression did not demonstrate statistically significant differences in therapeutic effect on primary outcome, but some benefits on secondary outcomes were observed.[20] Psilocybin-assisted psychotherapy for depression has been given 'breakthrough therapy' designation from the Food and Drug Administration (FDA) in the United States. This designation indicates that the FDA believes the treatment may offer substantial advantages over current therapies and is designed to expedite a treatment's transition to a prescribed medicine (subject to adequate phase 3 results), but this designation does not mean it has yet established efficacy. Australia has approved the use of psilocybin in the treatment of depression by approved psychiatrists.

This is a rapidly changing field, and it is possible that other countries will legalise psilocybin for medical use soon. Further research is needed into psilocybin-assisted psychotherapy before it can be recommended for use in routine clinical practice.

LSD

LSD is a hallucinogen with emerging evidence indicating utility as an antidepressant and anxiolytic. The majority of early psychedelic research was undertaken using LSD, generally supported by individual psychotherapy. This research looked at depression, anxiety, addictions, psychosomatic disorders and psychosis.[74] At the time this was divided into 'psychedelic' or high dose therapy and 'psycholytic' or lower doses.[75] The spectrum of the former to the latter ranged from experiences of ego dissolution, peak or mystical experiences and strong visual or dream like experiences to more typical psychotherapy processes of emotional processing, self-reflection, and working with the transference. Whilst these historic studies do not meet modern methodological requirements, they provided a framework for conceptualising therapeutic mechanisms and processes, as well as supporting the physiological and psychological safety profile of these substances.[76]

Modern research looking at LSD and recent systemic reviews[77] of recent and historic RCTs has shown potential utility in a range of disorders including end-of-life anxiety and depression, PTSD and complex trauma, addiction, and psychosomatic disorders. Systematic reviews[7, 16] have identified that in one double-blind randomised active placebo-controlled study in 12 patients, there were reductions in anxiety symptoms associated with life-threatening disease,[4] following LSD administration. These processes are generally supported with individual or group therapy. Mechanisms of action are similar to those described above. Like psilocybin, there has been research into the effects of microdosing LSD without psychotherapy on mental health but the evidence remains limited.[17, 18]

2.3 5-HT$_{2A}$ partial agonists

N,N-dimethyltryptamine (DMT)

Dimethyltryptamine (DMT) is the main active hallucinogenic ingredient in ayahuasca. Trials into the use of ayahuasca have evaluated its use in the treatment of depression.

One open-label study reported rapidly improving depressive symptoms; however, the study involved only 17 patients and highlights the need to assess replicability in larger randomised controlled trials.[14] Another open label trial of six patients found that a single dose of ayahuasca was associated with reduction of depression scores by up to a statistically significant average of 82% and significant reductions persisted for up to 21 days after administration; the study remains limited by sample size and lack of placebo or control groups.[13] In one RCT with 29 patients with treatment-resistant depression, ayahuasca was found to have a significant antidepressant effect at day 1 and day 7, when compared with placebo, with effect sizes increasing between day 1 and the final follow-up at day 7.[78]

There is evidence for potential roles for cortisol and brain-derived neurotrophic factor (BDNF) in ayahuasca's acute antidepressant effects.[79] It is also worth considering that

ayahuasca is an herbal preparation involving two botanic species both containing numerous psychoactive compounds, therefore the associated effects of it cannot be attributed only to DMT.[105]

The first DMT clinical trial in depression is ongoing in London. The phase 1 trial has been completed showing that this compound is safe and well tolerated, while the results of the phase 2 trial are not yet available.

2.4 Monoamine transporter inhibitors

Methylenedioxymethamphetamine (MDMA)

There is increasing evidence supporting the use of MDMA as a therapeutic agent. MDMA has been investigated in 17 phase 2 trials[2] with at least six of these trials focussing on its use in pharmacologically assisted psychotherapy for PTSD including in phase 3 studies. Applications for regulatory approval are in progress in the USA.

MDMA-assisted psychotherapy research has largely focussed on PTSD whereby MDMA may aid exposure to and semantic re-processing of traumatic memories which are key therapeutic targets across modalities of psychotherapy. The trial protocols of the Multidisciplinary Association for Psychedelic Studies (MAPS) emphasise the training and supervision required of the therapists and view the MDMA-induced state as a catalyst for the process of psychological change enhancing feelings of self-compassion and trust which can allow the revisiting of traumatic material previously experienced as unbearable within the container of the therapeutic relationship.

A phase 3 trial involving 90 patients found that MDMA-assisted psychotherapy for severe PTSD was effective, safe and well tolerated.[82] There is evidence that the therapeutic benefits of MDMA-assisted psychotherapy for PTSD may also persist to longer-term follow-up.[21] The long-term follow-up ranged from 17–74 months (mean = 45.4) after the final MDMA session for the Clinician Administered PTSD Scale (CAPS) and Impact of Events Scale Revised (IES-R) administration. A further multisite randomised double-blind phase 3 trial published in Sept 2023 confirmed the efficacy and safety of MDMA-assisted psychotherapy in reducing PTSD symptoms and functional impairment in a diverse population with moderate to severe PTSD and was generally well tolerated.[81] Potential therapeutic use of MDMA in PTSD has been further reported in other studies.[21–24]

There are also trials proposed to explore the use of MDMA in the treatment of autism-associated anxiety and alcohol use disorder[19] (table 1).

MDMA-assisted psychotherapy specifically for PTSD has also been given ‘breakthrough therapy’ designation from the Food and Drug Administration (FDA) in the United States.[25]

2.5 NMDA antagonists

Ketamine

Ketamine has been investigated in almost 70 phase 2 trials for psychiatric disorders and two phase 3 trials for depression.[19] As of 2018, there were 42 ongoing clinical trials investigating the effects of ketamine on depression (including major depression; treatment-resistant depression; bipolar depression; cancer depression; and suicidal depression) and 13 trials that had been completed. These trials included 3,813 patients and varied in oral (dose range: 0.5–1.0 mg/kg), intra-nasal (dose range: 0.2–0.5 mg/kg) and IV (dose range: 0.1–1.0 mg/kg) administration. The number of drug sessions range between 1–12 and used open label, single-blind, or double-blind designs. Control drugs used in these studies included placebo, lithium, saline, diphenhydramine, nitroprusside, midazolam, minocycline, and electro-convulsive therapy. At present, the effect size of these studies ranges from 0.99–1.67 (Cohen's d). There were also 31 ongoing or completed trials using ketamine for obsessive–compulsive disorder, post-traumatic stress disorder, and alcohol and cocaine use disorders.

The main evidence for the potential use of ketamine comes from depression (effect size: 0.99–1.67), but is also implicated in its use for obsessive–compulsive disorder (OCD) (effect size: 0.8), suicidality (effect size: 0.67–0.84), post-traumatic stress disorder, alcohol and cocaine use disorders[19] (Table 1) – the effect sizes for the latter three are at present unavailable. Nine meta-analyses of studies from open-label, single-blind and double-blind depression trials[26–34] reported short-term positive outcomes for patients. Reviews highlight methodological limitations in much of the relevant literature, as well as potential side effects and lack of longer-term data.

In one double-blind, randomised, cross-over trial comparing ketamine with an active placebo control (midazolam) in 41 patients,[35] ketamine infusion was associated with reductions in PTSD symptom severity compared with midazolam, 24 hours after infusion. This study provided the first evidence for rapid reduction in symptom severity following ketamine infusion in patients with chronic post-traumatic stress disorder.

Spravato is a proprietary formulation of ketamine's s-enantiomer (esketamine) in intranasal form. Most research has focussed on its use as an adjunct to established antidepressant therapy. Esketamine has shown antidepressant effects at 24 hours, lasting up to four weeks with repeated doses; whilst the effects of acute ketamine lasted up to one week and were absent after the second week.[92] Furthermore, esketamine is a licensed medication for major depressive disorder, although, in the UK, its use in the NHS was not approved by NICE in 2023 due to uncertainty about cost-effectiveness estimates.

We therefore recommend the use of ketamine in specialist settings with appropriate oversight and long-term monitoring arrangements in place (see below).

Most research and clinical use of ketamine has been as a pharmacological intervention without therapeutic support. There is increasing interest and research into ketamine as part of a pharmacologically assisted psychotherapy.

Ketamine-assisted psychotherapy may act through a range of mechanisms. Ketamine is thought to be able to block the reconsolidation of memories and therefore has potential in pharmacologically assisted psychotherapy by potentially weakening memory traces that may be contributing to psychopathology.[36] This blocking of fear memory reconsolidation is associated with protein downregulation in the CA1 segment of the hippocampus, and aberrant memory processing in this brain region is thought to be associated with psychopathology in PTSD.[37, 38]

Ketamine may also shift negative emotional states, foster self-acceptance and shift perspectives.[83] One large US-based study of three private practices reported reductions of depression and anxiety, especially for patients with complex PTSD or general exposure to developmental psychological trauma.[39] Additionally, preclinical studies suggest that ketamine may increase neurogenesis and synaptogenesis, which might enable more rapid learning associated with psychotherapy.[40]

Preliminary evidence also suggests that ketamine-assisted psychotherapy could be effective in those with alcohol use disorder (AUD). Individuals with AUD have impaired learning and planning, reducing the effectiveness of therapy.[42, 43] Neurogenesis and synaptogenesis could theoretically reduce these learning impairments.[40] A recent double-blind phase 2 placebo-controlled clinical trial of 96 patients with AUD, reported that three ketamine infusions were well tolerated, and ketamine-assisted therapy was associated with more days of abstinence from alcohol at six-months follow-up.[45] However, more phase 2 and phase 3 trials are required to establish treatment efficacy.

It has also been proposed that ketamine induces a dose-dependent sense of disembodiment and dissociation similar to mindfulness, which may enable patients to 'de-centre' from their thoughts and emotions during psychotherapy, thus potentially aiding shifts in perspective.[44]

2.6 Potential risks and safety considerations of PARS

To date, studies have found that when the compounds discussed above are given at therapeutic doses, the safety profiles are potentially acceptable, however side-effects are heterogenous across different compounds.[1, 19] Mild autonomic effects such as vomiting, diarrhoea, and increased blood pressure, as well as short lived anxiety, appear to be the most common immediate side effects and are usually short lived, whilst headaches seem to be the most common side effect manifesting in the post-acute phase.[1] There is a lack of long-term safety data on these compounds.

There remains an urgent need for further methodologically rigorous trials to understand the adverse effects associated with acute, prolonged and/or repeated use. Furthermore, there is emerging evidence of adverse effects when used in uncontrolled settings.[108] It will be important to investigate the risks of hallucinogen persisting perception disorder and adverse effects of distressing and potentially re-traumatising experiences involving hallucinogenic content, including 'bad trip' reactions, and a risk of PTSD in response to 'bad trip' reactions.

2.7 Risks and side effects associated with specific compounds

Dimethyltryptamine (DMT) – risks and side-effects

There is some literature reporting ayahuasca and other DMT-containing substances to be well tolerated,[46] although there is evidence of sympathomimetic effects such as increased heart rate and blood pressure, and temperature.[47, 48] DMT is thought to have little dependence potential.[49, 50]

Phase 1 of the SPL026 trial found that DMT is safe and well tolerated in healthy volunteers. This trial investigated the use of DMT fumarate in healthy subjects and patients with major depressive disorder. There were no drug-related serious adverse events, and of 20 drug-related adverse events, all were mild (85%) or moderate (15%) and resolved rapidly and independently. There were also no statistically significant negative effects on anxiety and wellbeing identified at any point during the three-month follow-up.

However, there is a need for further controlled trials in this area as these results were from the first clinical trial for DMT-assisted therapy in major depressive disorder.[93]

Lysergic acid diethylamide (LSD)– risks and side-effects

LSD appears to be relatively well-tolerated when used in controlled clinical settings with appropriate pre-screening of safety contraindications. A systematic review of 11 studies, involving 567 participants[16] reported two serious adverse effects (i.e. a tonic-clonic seizure and prolonged psychosis), however these were in patients with prior histories of seizures and recurrent psychotic episodes respectively. One trial found no persisting side effects following LSD administration but reported three participants requiring benzodiazepine administration to counter treatment-induced anxiety and/or emotional distress, which may have been related to acute hallucinosis.[4] In another trial, 50, 75 and 100 micrograms of LSD administration led to no serious adverse events in 91 participants, with 28% of patients experiencing at least one mild adverse event, and one expected moderate adverse event.

Future studies are needed to fully evaluate the safety and tolerability in clinical populations.[95]

Methylenedioxymethamphetamine (MDMA) – risks and side-effects

There is some evidence that frequent high-dose MDMA can be neurotoxic (damaging to the nervous system)[51] although such doses are well in excess of any clinical protocol. Indeed, several phase 1–3 clinical trials from have shown that clinical doses of MDMA have an acceptable safety profile relative to recreational MDMA use[52]: tolerable and

transient clinical side effects during these clinical trials include anxiety, fatigue, headache, jaw clenching, reduced appetite, and muscle tension. Serious adverse events are rare but there have been reported cases of suicidal ideation and behaviour (in the placebo arm of a phase 3 clinical trial).[81] However, drop-out rates during this trial were low with only five participants withdrawing (three due to COVID; one in the MDMA group due to distress from the CAPS assessment, and an adverse event of depressed mood during the experimental session; and one in the placebo group due to suicidal ideation).

The first randomised controlled pilot study[98] investigating the efficacy of MDMA-assisted psychotherapy for post-traumatic stress disorder was conducted in 2010. For 22 patients there were no drug-related serious adverse events or adverse neurocognitive effects and no medical treatment was required during any experimental sessions.

Several phase 2 clinical studies also documented similar findings of tolerable and transient side-effects. In one such trial of 28 patients, there were no drug-related serious adverse events reported and the treatment was well-tolerated.[101] In a separate trial of 26 patients, only one serious drug-related adverse event was reported to be associated with drug treatment: One participant "exhibited a premature ventricular contraction at baseline developed an acute increase in premature ventricular contractions during the third open-label session, detected on-site through routine heart rate readings".[81] Three other serious adverse events were reported but were deemed to be unrelated to the study drug treatment. Serious adverse events deemed unrelated were suicidal ideation in response to life events, major depression (same participant), and appendicitis.

Ketamine – risks and side-effects

Acute, self-resolving side-effects are common with ketamine treatment including mild distress and anxiety during and/or after treatment. Patients may experience dissociation, an increase in heart rate and arterial blood pressure, and cognitive impairments such as reduced verbal memory.[87, 103, 107]

However, high, repeated doses of ketamine have been associated with significant adverse effects[53] although the evidence remains uncertain due to longer-term risks of ketamine use having been extrapolated from a small population of people misusing ketamine/using ketamine recreationally at high doses, as well as from animal studies.

Important potential longer-term side effects include chronic cystitis, hepatoxicity, gall bladder pathology, and psychiatric symptoms of impaired cognition and persistent dissociative effects. Despite increasing use in clinical practice, the acceptability and tolerability of long-term ketamine use is uncertain.

The recreational use of ketamine appears to be increasing, and addiction specialists are seeing more people with ketamine dependence. Thus, there is the potential risk of diversion of ketamine from medical contexts for recreational use, and the potential risk of dependence following therapeutic use of ketamine. Further research is warranted to quantify these risks associated with ketamine's use for psychiatric disorders. Nevertheless, take-home ketamine dosing is not currently recommended due to its transient risks, potential long-term side effects, and risk of misuse,.[106]

Psilocybin – risks and side-effects

Psilocybin does not tend to have marked physiological effects and it does not induce dependence. It also has got a favourable therapeutic index of around 1,000 (the ratio comparing the blood concentration at which a drug becomes toxic and the concentration at which the drug is effective).[96, 100]

A pooled analysis of eight experimental studies involving 110 participants reported good tolerability with minimal subacute adverse effects and no serious adverse events in the short or long term when used in controlled clinical settings with appropriate pre-screening of safety contraindications.[54] Indeed, psilocybin has been shown to be safe and effective in patients with depression, obsessive compulsive disorder (OCD), end-of-life psychological distress, and substance use disorders.[9,99,91] A meta-analysis showed that four phase 2 clinical trials led to reductions in symptoms of anxiety and depression.[94] It should be noted that since 2016,[6] no long-term side effects have been reported in over 2,000 participants that have participated in contemporary trials.

However, these drugs should still be used with caution due to adverse effects reported in the literature from recreational use, such as hallucinogen persisting perception disorder.[97] There are some accounts of long-term side effects. One RCT for treatment-resistant depression compared 25mg and 10mg of psilocybin with psychological support to a control group of 1mg psilocybin. Worsening suicidal ideation was seen in 14%, 17%, and 9% of participants in each group, respectively. In the absence of statistical significance, authors suggested 'clinical vigilance' in future trials due to the higher proportion of suicidality in the higher dose groups.[84]

2.8 General risks and safety considerations

Risks of acute adverse effects

There are risks of acute sensitivity to hallucinogens resulting in 'bad trips' including aversive hallucinatory experiences and negative emotional states such as fear and panic, and the associated risks of (re-)traumatisation (Ungerleider 1968).

In research studies, practical steps, including patient screening to exclude patients with histories of psychosis (and other safety contraindications), concomitant medication management including checking for interactions and managing any dose changes, and psychiatrist oversight, have been taken to minimise these risks.[1, 56]

Distressing and traumatic material can emerge during treatment sessions which can be destabilising, but also, if worked with therapeutically, appropriately contained and re-processed, can foster psychological change. This highlights the importance of skilled and attuned therapeutic input, building a therapeutic alliance prior to the dosing sessions, containment of distressing experience, active support during and in

the aftermath of the dosing sessions, and adequate integration work provided over several sessions with the therapists after the dosing sessions.

Appropriate screening would need to consider patients predisposed to develop relevant medical and psychiatric complications. Psychiatric risk factors would include a personal or family history of psychosis or mania, and substance use disorder.[1] Significant medical comorbidities including cardiac, renal, hepatic, or neurological disease would also likely warrant exclusion and, for female participants, risk of or existing pregnancy will need to be considered due to lack of data in pregnancy.[1] Proper preparation and support of the person undergoing treatment, as well as an appropriate setting led by researchers with appropriate psychiatric and psychotherapy training is important to help mitigate risk.

Risk of delayed and/or chronic adverse effects with PARS

There is concern that hallucinogens can cause psychosis (hallucinogen-induced psychotic disorder) as well as hallucinogen persisting perception disorder (HPPD)[57, 58] in vulnerable patients. HPPD refers to persistent perceptual distortions after a previous hallucinogenic drug experience. The disorder can resolve within weeks to months, but more severe cases can become chronic and associated with significant impairment. Persistent perceptual disturbances can include pareidolia, micropsia, macropsia, palinopsia, visual fractals, and altered colour and motion perception.[56] It is notable however that this side effect is not recorded in the majority of trials of which we are aware, although this may be due to lack of long-term follow-up or other factors such as selection bias.

There has also been a theoretical concern that these compounds may increase the risk of psychotic disorder in people with underlying risk factors such as personal or family histories of psychosis; such people are therefore often excluded from research studies. Whilst research findings so far suggest there may be low risk of prolonged psychotic disorders in people treated with these compounds,[57, 59] data from a survey of investigators who had administered LSD at a rate of 1.8 per 1,000 of psychotic reactions lasting 48 hours or more in patients undergoing psychotherapy compared to 0.8 per 1,000 in non-patient participants.[60] There has been a lack of follow-up and further research is needed to investigate these risks, particularly in those individuals with a greater risk of psychosis.[1]

2.9 Limiting factors and considerations for assessment of risk associated with treatment in research trials

There remain many unknown factors, including potential long-term side effects, in the use of these compounds in psychiatric treatment. The selection of appropriate patients for research trials requires careful consideration. Patients should have the ability to provide valid consent and capacity to understand the risks and benefits of the treatment in the context of their disorder, the duration of the current episode, and previous treatment history. In addition to these diagnostic considerations, other considerations

include medical, psychological and/or social factors. Patients should therefore be offered a thorough biopsychosocial assessment and a comprehensive formulation towards understanding their vulnerabilities and potential triggers for worsening psychological difficulties in research trials to inform the consent process.

2.10 The relationship between recreational and medical use

There is a risk of confusion between the recreational and medical use of these compounds. Varying usage patterns may account for the range and severity of therapeutic and adverse effects observed in people who use such substances on a recreational basis. Additional studies are needed to address the concern that concurrent recreational and medical use may worsen clinical outcomes.[61]

However, studies often report minimal medical risks, and any longer-term psychological adverse effects are at risk of being underreported.[62] Evidence of this comes from Public Health England, whereby the proportion of adults (aged 16–59 years) who report typical use of these compounds in the last year was 0.9% in men and 0.5% in women – lower than all other drugs reported apart from amphetamines and new psychoactive substances.[63]

This parallels the number of adults in treatment for substance use disorders, which is the lowest for this group of drugs (n=1,913) compared to all other drug types, such as alcohol (n=12,9567), opiates (n=71,034), cannabis (n=52,006) and cocaine (n=33,6920).[64] Therefore, while there are no studies examining the relationship between recreational and medical use, there is less evidence of dependency or substance use disorder for recreational use of these drugs, compared to other dependence-forming drugs.

2.11 Summary of current risk–benefit analysis for PARS

There is evidence in support of the clinical efficacy and tolerability of some of these compounds for particular mental health conditions when used in controlled medical settings in carefully selected patient samples (i.e. unlikely to reflect people with those conditions in the general population). The strength and level of evidence varies due to heterogeneity in trial design and intrinsic difficulties with blinding, which mean that there may be marked expectancy effects, as well as other issues.

Whilst there is increasing understanding of the mechanisms of action of these compounds, the precise mechanisms of action are yet to be fully elucidated. It is likewise important to understand the synergies between pharmacological and psychotherapeutic aspects of the treatment.

There is also a need to better understand the longer-term effects of these drugs, both in terms of whether any beneficial effects observed are sustained, and in terms of adverse effects that may persist or emerge *de novo*.

With the exception of ketamine, we lack a high-quality evidence base on efficacy and side effects which means that the current risk–benefit profile is uncertain and cannot be recommended outside of research studies.

This is, however, a rapidly developing field, and other countries are moving towards legislating for potential compassionate and clinical use as previously described. For ketamine, there is higher quality evidence both regarding efficacy and side effects, but more evidence is still needed on long-term adverse effects and risks.

To further exclude longer-term risk, robust preclinical research is also needed, including the demonstration of negligible effects on the ventral tegmental area and ventral striatal reward pathways and no tendency for self-administration in addiction models. In addition, long-term longitudinal research in humans is needed to clarify the future long-term follow-up and monitoring requirements.

Section 3: Regulation of psychedelic and related substances (PARS)

3.1 What is the current legal status of these compounds?

The international legal status of these compounds is a rapidly changing area. It is possible these substances could soon be legalised for clinical use in various jurisdictions.

The main legal framework in the United Kingdom for these compounds is the Misuse of Drugs (Safe Custody) Regulations 1973 (as amended), which details the storage and safe custody requirements for Controlled Drugs[65] and the Misuse of Drugs Regulations 2001 (and subsequent amendments) which defines who is authorised to supply and possess Controlled Drugs and the conditions under which these activities may be carried out.[66] In the 2001 regulations, drugs are divided into five Schedules, each specifying the requirements governing such activities including prescribing and record keeping which apply to them. The most restrictive Schedule is Schedule 1, which is applied to compounds deemed by government to have little or no medicinal value. The Misuse of Drugs Act 1971 (as amended) contains different categories of drug called 'Classes' based on their perceived harm and respective criminal penalties, such that the supply, possession and use of Class A drugs may result in more punitive penalties then Class B or Class C drugs.[67] The table below gives examples of the current UK Classes and Schedules.

Drug	DMT	Ketamine	LSD	MDMA	Psilocybin
Class	Class A	Class B	Class A	Class A	Class A
Schedule	Schedule 1	Schedule 2	Schedule 1	Schedule 1	Schedule 1

3.2 Monitoring arrangements

There has been a rapid proliferation of ketamine clinics and there is likely to be a proliferation of clinics offering treatments with the other compounds outlined in this statement. It is important to consider how we monitor their use before it becomes more widespread, as now seems likely. We do not know the optimal dosing schedule, or even the best route of administration for these compounds. There are almost no data on the long-term safety of repeated use. Conventional pharmacovigilance alone will not be sufficient, given that there are no

established optimal dosing schedules, notwithstanding the potential for underreporting. The clinical use of these compounds should therefore be carefully monitored via centralised systems including dose, indication, therapeutic response and adverse effects. These systems should also be capable of gathering information on any adverse consequences arising from self-medication. Such multi-drug monitoring systems are not without precedent, as is the case with controlled drug prescription surveillance or clozapine monitoring, for example. There is a clear need for multi-agency collaboration within the UK agreement between the Medicines and Healthcare products Regulatory Agency (MHRA), the National Institute for Health and Care Excellence (NICE), the National Health Service (NHS), private providers, the British Association for Psychopharmacology (BAP), and the relevant royal colleges.

3.3 Regulatory framework for medicine licensing and prescribing in the UK

Marketing authorisations, also referred to as licences, confirm the health condition the medicine should be used for and the recommended dosage. Licences for medicines are granted if strict safety and quality standards are met.

In the UK, licences are granted by the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). It is possible to prescribe medications 'off-licence' as occurs in routine psychiatric practice. Different rules on off-label prescribing apply in National Health Service (NHS) and private healthcare settings.

We advise against the off-licence use of PARS without a clear evidence base outside the context of research trials.

3.4 Usual criteria for Early Access to Medicine Schemes (EAMS)

The early access to medicines scheme (EAMS) seeks to provide patients who have life threatening or seriously debilitating conditions access to medicines that do not yet have a licence (marketing authorisation) when there is a clear, unmet, medical need. EAMS is run by the Medicines and Healthcare products Regulatory Agency (MHRA) which provides an opinion on the benefits and risks of the drug. The opinion lasts for a year and can be renewed. EAMS does not replace the normal licensing procedures for medicines. EAMS involves a two-step evaluation process:

- **Step 1:** Promising innovative medicine (PIM) designation that a compound may be eligible for EAMS based on early clinical data.
- **Step 2**: EAMS scientific opinion.

3.5 Potential socio-political implications that need to be considered when carrying out research into PARS

There are a range of factors which need to be considered when carrying out research into these compounds. One of the current socio-political barriers to conducting this research lies in the scheduling of many of these compounds under Schedule 1 (see table above). Factors to consider include the sale of prescribed medicines on the black market (referred to as one form of 'diversion'), as can occur with opiates, or patients resorting to the black market and therefore potentially unsafe preparations, if they are unable to obtain a compound they are seeking through legally permitted channels. Stigma associated with recreational use also requires consideration. Patients may be less willing to consent to the use of drugs in pharmacologically assisted psychotherapy if they have not previously used them.

Section 4: Current uses

4.1 In what kind of settings should PARS be administered?

Prescribing for mental health conditions is a highly specialist skill due to clinical complexity, drug interactions, assessing response, risks of harm, adverse effects and other factors including psychological processes and dynamics within the doctor–patient relationship. As such, these compounds should only be administered in specialist settings by registered clinical professionals competent in psychiatry and psychotherapy (if there is co-administration with psychotherapy), with suitable knowledge of the psychopharmacology of the relevant medications.

As these compounds can induce transient physiological effects, an understanding of physical health parameters and how to monitor these is therefore essential.[68] These clinical settings must have access to healthcare professionals who, as outlined above, are suitably qualified and regulated and have undertaken training for these circumstances.

4.2 The role of psychiatrists and MDTs in potentially screening, assessing, and delivering pharmacologically assisted psychotherapy

The safe and effective use of pharmacotherapy and pharmacologically assisted psychotherapy requires thorough biopsychosocial assessment, formulation and treatment planning. Therefore, we recommend:

- a multidisciplinary team (MDT) approach is taken regarding the use of these compounds, with clinical leadership involving a consultant psychiatrist.
- the involvement of psychiatrists in collaboration with other health professionals such as clinical psychologists and/or nurses to help determine who would access this treatment and help deliver it.
- the MDT screens referrals for suitability for treatment
- a psychiatrist carries out a comprehensive assessment, including biopsychosocial and medical assessment to identify any possible physical or mental health contraindications.

Previous studies into the use of psilocybin can be used to help determine indications and contraindications.[69]

A psychiatrist is also required to confirm the patient's psychiatric diagnosis and determine whether it is consistent with a likely response to treatment. A safety and clinical risk assessment must be completed prior to starting treatment, with consideration of both mental and physical health.

4.3 What should be the training requirements for psychotherapists?

In pharmacologically assisted psychotherapy, psychotherapists are sometimes referred to as 'guides'. Just as is the case with any treatment, including all types of pharmacotherapy and psychotherapy, the principles of primum non nocere (first do no harm) must apply. It is also essential to understand the biopsychosocial processes, including the relational aspects, of the treatment. Pharmacologically assisted psychotherapy should be no exception. We recommend that the psychotherapy delivered with these compounds be evidence-based[70] and follow guidance for good practice in keeping with other psychological therapies. Professionals delivering pharmacologically assisted psychotherapy have been referred to in the literature as both 'therapists' and 'guides'.

We recommend that the Royal College of Psychiatrists, in collaboration with other relevant professional bodies, take a leading role in developing specific training standards for the safe and effective delivery of this form of therapy.

A defined set of competencies should be established and achieved to ensure professionals are equipped to deliver pharmacologically assisted psychotherapy safely and effectively, and to enable appropriate monitoring of practice. Regular supervision with a suitably qualified supervisor should be a core requirement, including the presentation and review of detailed session process notes. A dedicated curriculum would also be necessary, covering psychopharmacology, alongside other relevant skills and knowledge in psychotherapy and of psychedelic experiences.

4.4 Recommendations for College members if asked to prescribe these drugs

If members of the Royal College of Psychiatrists are asked to prescribe these compounds, they should be aware of the licensing of individual drugs for individual indications.

With the exception of ketamine and esketamine, for which there have been large RCTs, we recommend against the unlicensed use of these drugs outside of research trials.

4.5 Self-treatment

This joint position statement discourages self-administration as an attempt to treat mental health conditions with these compounds and the usual General Medical Council (GMC) guidance should be followed with regards to self-prescribing. It must be acknowledged that their use can be associated with harm.

There are further risks associated with the use of compounds obtained illegally (i.e. not in a regulated clinical setting with trained professionals), with increased risk of contamination from other substances being more likely. Individuals have previously described both immediate and longer-term negative effects with the use of these compounds, which is why this treatment should be carried out with the support of registered healthcare professionals.

Under circumstances in which someone may have experienced adverse or destabilising psychological effects after self-administration, they should be encouraged to seek psychotherapeutic support towards processing their experiences, to try to avoid potential long-term/traumatising effects of their usage in an unsupported setting.

Section 5: Challenges and future use of PARS

5.1 In what kind of settings could these compounds be administered in the future?

Ketamine and esketamine: these are already used in specialist settings in the UK and some other countries. There must be appropriate clinical input, supervision and leadership/co-leadership from psychiatrists in clinics that use these compounds. Appropriate psychotherapeutic input and supervision must be in place where these compounds are used to assist psychotherapy.

Other PARS: The other drugs should only be used initially in highly specialised clinical settings with appropriate medical cover due to the lack of robust long-term harm–benefit data. We recommend against the use of these compounds in settings which lack supervision by a consultant psychiatrist specialised in the relevant areas of practice.

5.2 What are the current challenges and limiting factors in research into the use of these compounds?

As described above, research into the therapeutic potential of these controlled substances has been limited by legal restrictions and practical difficulties. Due to the illegal nature of the substances and the fear of harm, research trials often involve lengthy ethics approvals and complicated access pathways, which act as significant barriers to advancing new therapeutic options, and evidence-based practice.

5.3 Summary of key gaps in knowledge

There is emerging evidence for the use of some of these compounds in the treatment of particular mental health conditions in carefully selected adult samples. Further research is required in the following areas:

- The efficacy and safety (including long-term safety) of these compounds to inform future potential use in patients with symptoms that are refractory to existing treatments.
- Assessment of the safety for individuals with psychotic disorders, as there is a theoretical risk of greater adverse effects.
- Studies specifically assessing the impact of these compounds on the potential long-term risks of hallucinogen-induced psychotic disorder and hallucinogen persisting perception disorder. Research should only occur under research trial conditions that include oversight by an institutional research ethics committee and careful monitoring and reporting of effectiveness and safety outcomes. Such trials should be led by researchers with appropriate psychiatric and psychotherapeutic training. These studies may complement ongoing naturalistic studies.

5.4 Recommendations for the field, including research, audit, and practice guidelines

There is an ongoing need to collect adverse event data systematically and accurately, in a manner that allows aggregated analysis. There is also a need to collect data on the long-term risk of hallucinogen-induced psychosis and hallucinogen persisting perception disorder (HPPD) following PARS.[18, 19] Further research is also needed towards elucidating common therapeutic factors and how emerging challenging experiences and consequences can be safely managed.

Summary of recommendations

- The early evidence base from research trials shows the promise of a number of PARS for a range of psychiatric presentations and further research is warranted on this basis.

- The Psychopharmacology Committee encourages using nomenclature based on neuroscience-based mechanisms of action. A compromise has been reached referring to psychedelic and related substances (PARS) for this paper which links more closely to other research nomenclature whilst acknowledging the heterogeneity of these compounds.

- Further high-quality studies are required to understand therapeutic mechanisms and processes, and risks and benefits for these drugs in pharmacologically assisted psychotherapy and within clinical populations outside the selection criteria of research trials.

- The therapeutic effects of many of these compounds are likely to be due to the interplay between the pharmacological effects of the substance and the therapeutic relationship. Training, supervision and adherence to good therapeutic practice for the psychological aspects of the treatment should be provided and adhered to in keeping with other psychological treatments.

- There is an urgent need for further methodologically rigorous trials to understand the putative mechanisms of action and adverse effects associated with prolonged and/or repeated use of these drugs.

- Further longitudinal research is required to investigate the risk of persistent psychotic and perceptual disorders, as well as other untoward consequences.

- A psychiatry-led (or co-led) multidisciplinary team should be involved in the administration of these compounds. These compounds should only be administered in highly specialised settings by registered clinical professionals competent in psychiatry and psychotherapy (when used in combination with psychotherapy), with suitable knowledge of the psychopharmacology of the relevant medications.

- All patients should be offered a thorough biopsychosocial assessment to carefully identify relevant physical and psychological risk factors when conducting research trials and receiving treatment under such settings.

- The use of these compounds should be monitored via centralised systems that can monitor the inadvisable strategy of self-treatment, and wider harms.

Disclosures and potential conflicts of interest

- Dr Bloomfield's research is funded by a UKRI Future Leaders Fellowship. He is a shareholder of Bloomfield Health Holdings Limited.

- Dr Lennox reports institutional funding from Johnson and Johnson, Angelini, Arialys therapeutics and Argenx for scientific advice, investigator initiated research, and/ or participating in educational events.

- Dr Howes has received research funding from and/or participated in advisory/ speaker meetings organised by Abbvie, Alkermes, Angellini, Autifony, Biogen, BMS (Karuna), Boehringer-Ingelheim, Delix, Eli Lilly, Elysium, Heptares, Global Medical Education, Invicro, Jansenn/Johnson and Johnson, Karuna, Lundbeck, Merck, Neumora, Neurocrine, Ontrack/ Pangea, Otsuka, Sunovion, Teva, Recordati, Roche, Rovi and Viatris/ Mylan. He was previously a part-time employee of Lundbeck A/v.

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