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The promises and perils of psychedelic pharmacology for psychiatry

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Abstract | Psychedelic drugs including psilocybin, *N*,*N*′-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD) are undergoing a renaissance as potentially useful drugs for various neuropsychiatric diseases, with a rapid onset of therapeutic activity. Notably, phase II trials have shown that psilocybin can produce statistically significant clinical effects following one or two administrations in depression and anxiety. These findings have inspired a 'gold rush' of commercial interest, with nearly 60 companies already formed to explore opportunities for psychedelics in treating diverse diseases. Additionally, these remarkable phenomenological and clinical observations are informing hypotheses about potential molecular mechanisms of action that need elucidation to realize the full potential of this investigative space. In particular, despite compelling evidence that the 5-HT_{2A} receptor is a critical mediator of the behavioural effects of psychedelic drugs, uncertainty remains about which aspects of 5-HT_{2A} receptor activity in the central nervous system are responsible for therapeutic effects and to what degree they can be isolated by developing novel chemical probes with differing specificity and selectivity profiles. Here, we discuss this emerging area of therapeutics, covering both controversies and areas of consensus related to the opportunities and perils of psychedelic and psychedelic-inspired therapeutics. We highlight how basic science breakthroughs can guide the discovery and development of psychedelic-inspired medications with the potential for improved efficacy without hallucinogenic or rewarding actions.

Psychedelics are drugs which have lysergic acid diethylamide (LSD)-like actions that alter perception, emotion and cognition without impairing memory or inducing delirium[1]. LSD is the prototypical psychedelic drug and produces a state of altered consciousness including prominent visual distortions, hallucinations and states of 'oceanic awareness'. The term 'psychedelic' was coined by Osmond in 1957 (REF.[2]) and is now defined as a drug that induces an LSD-like effect via activation of 5-HT_{2A} serotonin receptors. Such LSD-like psychedelics include numerous natural products such as *N*,*N*′-dimethyltryptamine (DMT), psilocybin, mescaline and various lysergamides[3] (FIG. 1). Other hallucinogenic natural products, such as the indole alkaloid ibogaine[4] and the diterpene salvinorin A[5], induce altered states in humans distinct from those caused by LSD-like psychedelic drugs[6] and are not discussed in detail here. In addition to naturally occurring psychedelics, a large number of synthetic and semi-synthetic drugs include ergolines such as LSD[7], various phenethylamines, tryptamines[3], N-benzyl phenethylamines[8] and others[3]. Thus, both naturally occurring and psychedelic compounds are represented by several chemical scaffolds (FIG. 1).

Historically, psychedelic plants and fungi have been used for millennia by humans (FIG. 1) for various purposes (as evidenced by their depictions in murals[9] and other artefacts) from between 3,000 and 5,000 years ago[10] across a wide variety of cultures[3]. There is extensive evidence for their use by indigenous cultures in pre-Columbian Mesoamerica[10]. In Western civilization, Heffter identified mescaline as the active ingredient of the psychedelic cactus *Lophophora* sp. in the 1890s[11,12], whereas LSD was rediscovered by Hoffman in 1945 (REF.[7]). Wasson was one of the first Western scientists to report on the properties of psilocybin-containing mushrooms[13] and the first to report on the effects of salvinorin A-containing plants[14]. Throughout the 1950s and 1960s there was considerable research on psychedelic drugs as potential adjuvants to psychotherapy for various conditions including depression and alcoholism (see for example REF.[15]). This trajectory of early psychedelic research explains, in part, how our understanding of the biology of neuropsychiatric conditions is convoluted with our understanding of the molecular mechanisms of drugs that impact the psyche. Early hypotheses on neuropsychiatric disorders were driven by experiments with psychedelic drugs that mimicked or ameliorated established symptoms[16]. As such, LSD and other psychedelics were originally annotated as 'psychotomimetics' for their ability to induce altered states of consciousness that shared some observable qualities with psychoses[17].

It was clear in the 1950s that psychedelic drugs such as LSD affected serotonergic function and neurotransmission[18,19], although it was not until the 1980s that a specific serotonin receptor subtype was determined to be the likely molecular target for psychedelic drugs[20,21]. Legislation to control the use and study of psychedelic drugs (BOX 1) may have hindered research. Despite these restrictions, a large number of psychedelic drugs have been synthesized based on the general scaffolds shown in FIG. 1, especially among the phenethylamine[22,23] and tryptamine[3,24,25] families. However, insufficient chemical diversity in compounds acting via the receptors known to underlie psychedelic drug actions has been generated to enable the kind of careful molecular pharmacology necessary to investigate the links between the drug mechanisms of action and the behavioural responses observed (both therapeutic and otherwise).

Renewed interest in the therapeutic potential of psychedelic drugs was becoming apparent in the mid-2010s. Some of the

earliest studies found significant positive effects with the use of psilocybin and guided therapy for anxiety and depression associated with life-threatening cancer. Subsequently, multiple trials have been completed or are in progress examining the potential therapeutic effects of psychedelic-adjuvanted therapy on other conditions, such as treatment-resistant mood disorders and substance abuse. In this Perspective, we review the current state of knowledge about the molecular mechanisms of action and critical receptor targets of psychedelic drugs, as well as the potential for the development of novel therapeutics based on those mechanisms and targets in the central nervous system. As psychedelic drugs represent a specific class, we will focus on their targets and associated mechanisms, and will not consider the ongoing studies with MDMA or other drugs which also can cause alterations in perception but are not considered to be psychedelic.

Basic science of psychedelics

Given the large number of molecular targets engaged by LSD and related psychedelics, it is perhaps surprising that, to date, only one molecular target has emerged as mediating psychedelic-like drug effects in humans and animals — the 5-HT_{2A} serotonin receptor[3]. It is well appreciated in behavioural pharmacology that psychoactive drugs produce phenotypes in animal models that only partially capture the effects observed in humans. This is particularly true for the psychedelic compounds, where the subjective perception and interpretation of the experience play major roles in both the acute and enduring effects. Moreover, the complex polypharmacology of psychedelic drugs makes direct comparisons and mechanistic inferences challenging. That said, evidence from structural studies is emerging that activation of 5-HT_{2A} receptors by psychedelics is capable of modulating multiple signalling pathways by virtue of interactions within the receptor binding site. Such actions likely underlie the observed impact of psychedelics on synaptic plasticity and spine dynamics.

Psychedelic receptor pharmacology. Virtually all classical psychedelic drugs have a complex in vitro receptor pharmacology. For instance, LSD has agonist activity at 12 of the 14 human 5-HT receptors (for example, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_4, 5-HT_5 and 5-HT_6)[26–30]. LSD is an antagonist

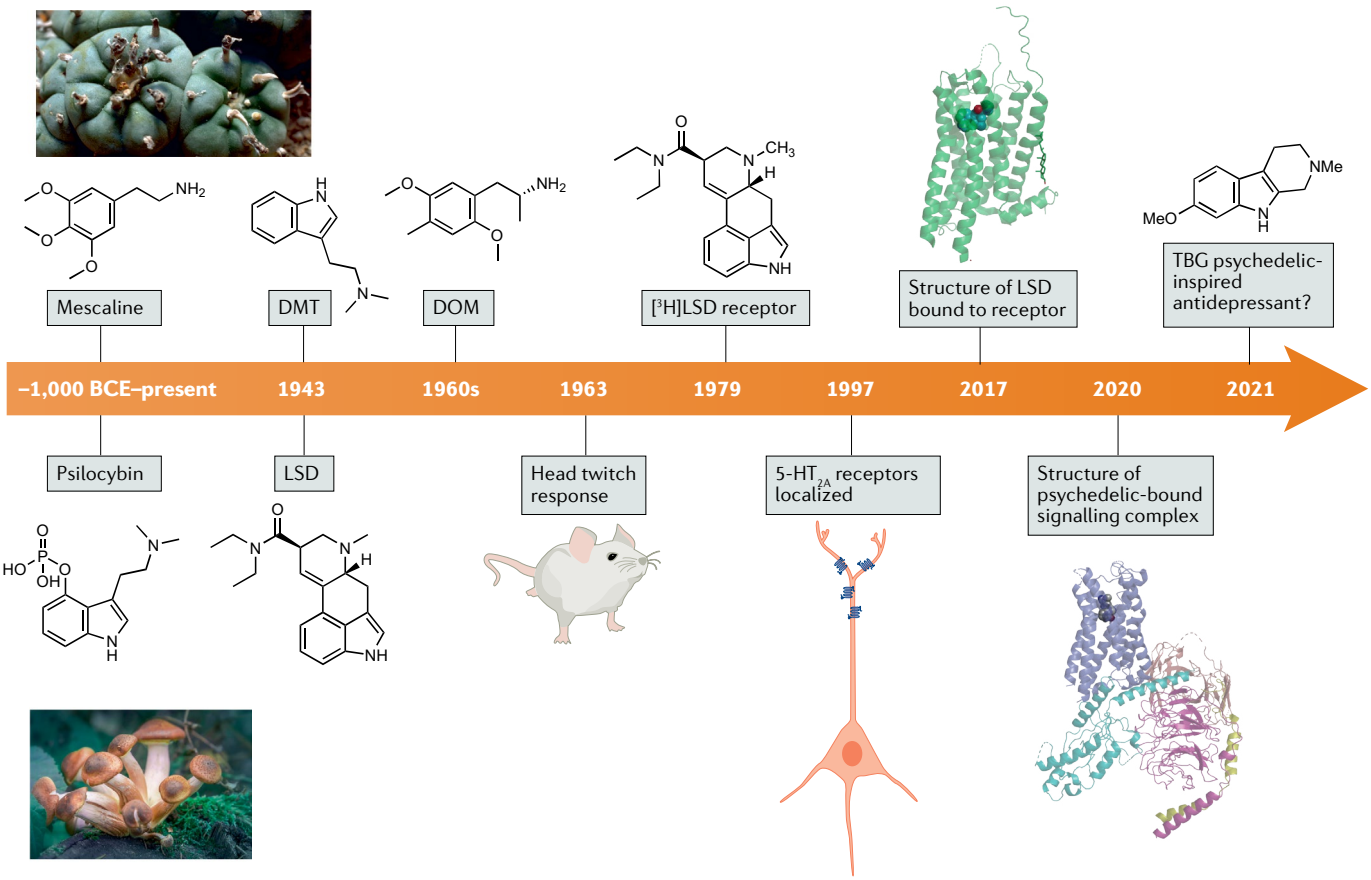

Fig. 1 | **Historical timeline of key events in psychedelic science.** Early ethnobotanical studies described use of naturally occurring psychoactive substances in various rituals and other practices, dating back thousands of years. Compounds such as mescaline from peyote cactus, psilocybin from various species of *Psilocybe* fungi and *N*,*N*′-dimethyltryptamine (DMT) in the multicomponent cocktail ayahuasca are 'archetypal' psychedelics with a long history of ascribed effects in humans. From the 1940s to the 1970s, more modern synthetic and medicinal chemistry efforts produced lysergic acid diethylamide (LSD) as well as several other psychedelic drugs based on phenethylamine (such as 2,5-dimethoxy-4-methylamphetamine (DOM)) and tryptamine scaffolds typified by mescaline and psilocybin, respectively. In 1963, the head twitch response (HTR), a behaviour in rodents caused by 5-HT_{2A} receptor activation, was developed as an important surrogate for psychedelic activity in animal studies. The late 1970s through the early 2000s introduced radioligand binding approaches to identify and quantify the neurotransmitter receptors engaged by LSD and other psychedelics. Subsequent studies with fluorescence microscopy helped localize these receptors to specific subpopulations of neurons in various brain regions. Most recently, advanced structural biology approaches have yielded atom-scale resolution of psychedelic drug-bound 5-HT_2 family receptors, enabling a fine-grained assessment of how these drugs engage their targets and what signalling pathways are responsible for their effects. TBG, tabernanthalog.

at the 5-HT_7 receptor[27] and inactive at the 5-HT_3 receptor[31]. LSD is also an agonist for α_1 and α_2-adrenergic receptors and for all five dopamine receptors (D_1, D_2, D_3, D_4 and D_5 dopamine receptors)[27,29,30]. LSD and other psychedelics have also been shown to activate TAAR1 trace amine receptors[30,32] (FIG. 2). Similarly, psilocin (the active metabolite of psilocybin), mescaline, DMT and their analogues have potent activity at many serotonin and other biogenic amine receptors[26,28,33,34]. By contrast, the N-benzyl phenethylamines have a more restricted pharmacology with their most potent agonist activities at 5-HT_2 family receptors[28], with 25CN-NBOMe being very selective for 5-HT_{2A} receptors[35,36]. Non-psychedelic hallucinogens do not activate 5-HT_{2A} receptors. Salvinorin A, for example, is a potent and selective κ-opioid receptor hallucinogenic agonist[37], whereas ibogaine is a weak partial κ-opioid hallucinogenic agonist with serotonin transporter inhibiting activity[38].

5-HT_{2A} receptor: a canonical target. Within the 5-HT_2 receptor family, psychedelics are generally non-selective agonists at 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors[26,29,35,39–41]. As mentioned above, it has long been known that activation of the 5-HT_{2A} receptor is essential for psychedelic drug actions[20,21,42–44]. 5-HT_{2A} receptors are expressed in several cortical and subcortical regions[45], and are concentrated in layer V cortical pyramidal neurons where they are localized to the apical dendrites[46,47] (FIG. 3). Activation of 5-HT_{2A} receptors by psychedelics in layer V cortical neurons enhances their excitability[48], presumably leading to the psychedelic experience. To mediate these actions, a 5-HT_{2A} receptor transduces its signal via a complicated network of signalling (FIG. 3) which initially relies on activation of G_q-family G proteins to induce phosphatidylinositol-4,5-bisphosphate hydrolysis and the liberation of inositol trisphosphate (IP_3) and diacylglycerol (DAG)[49–51]. In neurons, this leads to an enhancement of excitability and neurotransmitter release[48,52]. 5-HT_{2A} receptors also interact with arrestins[53–55], and both arrestin-dependent and arrestin-independent pathways have been linked to psychedelic drug actions[35,56–58]. Intriguingly, LSD and several psychedelic drugs display arrestin-biased signalling at 5-HT_{2A} receptors[40,55,59].

Although there appear to be many features shared between rodents and humans with regard to 5-HT_{2A} receptor signalling, there are differences. One of the most important distinctions is the species-specific amino acid difference at residue 242 in the binding pocket for LSD and related psychedelics[35] between the rodent (Ala) and human (Ser) 5-HT_{2A} receptors[60] (FIG. 4). Because of this difference, many hallucinogenic tryptamine and ergolines have reduced potencies at the rodent 5-HT_{2A} receptor[60]. This is potentially important because a Ser242Ala mutation in the human 5-HT_{2A} receptor greatly attenuates the receptor residence time of LSD due to a specific interaction between LSD and Ser242 (REF.[35]). Given that Ser242 is the only residue in the 5-HT_{2A} binding pocket which is unique to the human 5-HT_{2A} receptor, drugs targeting 5-HT_{2A} receptors may be expected to have different pharmacodynamic properties when tested in rodent models of psychedelic drug actions.

The off-target actions of psychedelics at 5-HT_{2B} and 5-HT_{2C} receptors engender potential therapeutic pitfalls. For instance, drugs with potent 5-HT_{2B} agonism induce life-threatening valvular heart disease in humans[61,62] when chronically administered. Thus, several anorectic drugs (fenfluramine, benfluorex)[63,64], various ergots (ergotamine, methysergide)[65,66] and some medications used to treat Parkinson disease[67] share a common mechanism by the parent drug (or active metabolites) in potently activating 5-HT_{2B} receptors[61]. Relevant to this is the observation that chronic administration of MDMA, which also can activate 5-HT_{2B} receptors[68], has been associated with valvular heart disease in humans[69–71]. It is currently unknown whether chronic administration of psychedelic drugs, as may occur with microdosing, increases the risk of valvular heart disease. As 5-HT_{2C} agonists induce anorexia[72,73], the agonist actions of psychedelics at 5-HT_{2C} receptors could explain why diminished appetite has been reported in clinical trials[74]. A final possible liability of psychedelic drugs as a class relates to their potential for inducing the occasionally fatal serotonin syndrome when co-administered with other serotonergic drugs including serotonergic antidepressants and anti-migraine medications[75–77]. Serotonin syndrome, broadly defined, is a collection of symptoms typically involving changes in mental, musculoskeletal and autonomic functions caused by excessive activation of serotonin receptors in multiple body systems[75–77].

Behavioural model studies. There are two major behavioural paradigms that are repeatedly cited as surrogates of psychedelic drug action in animal models: two-lever drug substitution and the head twitch response (HTR)[78] (BOX 2). Drug substitution is a useful paradigm for the comparative assessment of dose-dependent subjective drug effects and has been well validated for establishing which drugs are more or less 'LSD-like' and which receptor families are necessary for those actions[79]. Early drug discrimination studies in rodents showed that several psychedelic compounds were capable of fully substituting for others, whereas other psychoactive substances were not[80–82]. These studies were augmented by the discovery of drugs that modified 5-HT signalling, including 5-HT receptor subtype-selective antagonists. Drug discrimination studies that used subtype-selective antagonists in combination with psychedelics were among the first to establish that the 5-HT_{2A} receptor[20,83–85] was a common factor involved in the properties of LSD and other psychedelics[84]. Moreover, there is a linear correlation between binding affinity for cortical 5-HT_{2A} receptors and stimulus generalization in rats[86], indicating that a direct relationship exists between the extent of 5-HT_{2A} receptor occupancy and the effective dose that produces discriminative effects.

The HTR is another rodent behaviour originally demonstrated to be stimulated by LSD[87] and later shown to be a response

Box 1 | The Controlled Substances Act

Psychedelic drugs were made illegal in the United States and other countries in the latter half of the 1960s and early 1970s. In the United States, the 1970 Controlled Substances Act established certain regulatory and law enforcement oversights on the study and use of drugs. According to the Controlled Substances Act, drugs are listed in different categories (Schedules) based on the existence of any therapeutic utility and their abuse liability; drugs listed in Schedule I are viewed as those substances with the greatest risk for abuse and the least indicators of therapeutic activity. Most psychedelic drugs fall under Schedule I, and the Controlled Substances Act imposes formal restrictions on the use of federal funds to support research if it promotes their legalization without demonstrating therapeutic benefit. The impact of this legislation imposed certain specific barriers for research (for example, the need for investigators to acquire and maintain a separate Schedule I substances license), as well as more diffuse ones (for example, resulting from ambiguity over what constitutes research that 'promotes legalization'). Such restrictions are likely to have slowed the pace of research on the therapeutic potential of psychedelics.

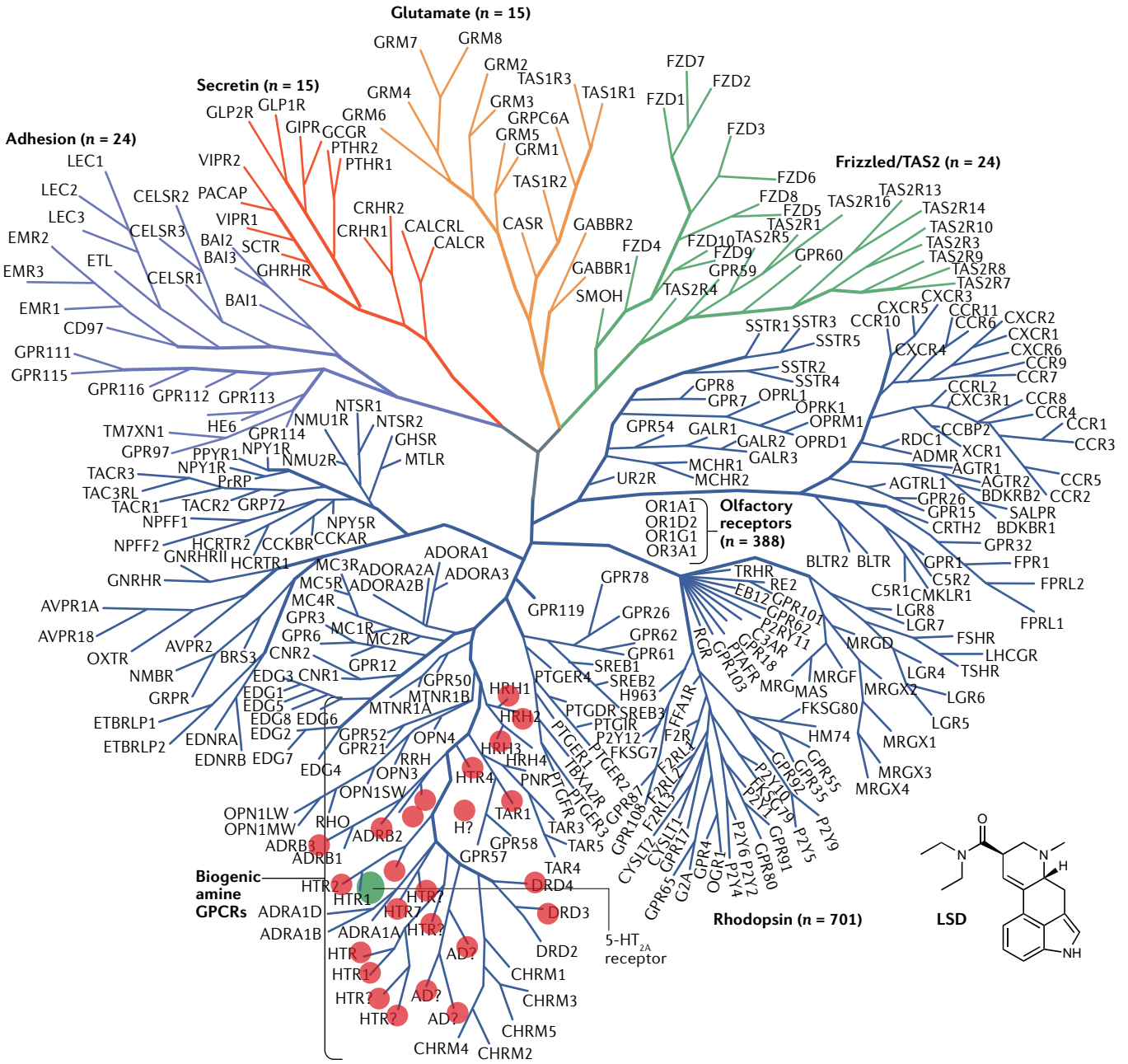

Fig. 2 | **LSD has a complex polypharmacology.** Phylogram of the human G protein-coupled receptor (GPCR) superfamily. GPCRS for which lysergic acid diethylamide (LSD) has high affinity (<100 nM) are indicated by red circles. The main target for LSD actions is the 5-HT_{2A} receptor (green circle). Figure adapted with permission from REF.[132], Elsevier.

induced by many other psychedelic drugs[88,89]. The involvement of the 5-HT_{2A} receptor was indicated by a strong correlation between the potencies of drugs for 5-HT_{2A} receptor binding and the induction of the HTR[20,21]. Subsequent studies showed that the HTR to psychedelics was abolished in transgenic mice that lack 5-HT_{2A} receptors (5-HT_{2A} receptor knockouts)[33,42]. Taken together, these studies supported the hypothesis that the 5-HT_{2A} receptor mediates the actions of psychedelics in rodents, at least to the extent of those reliable phenotypic measurements. In subsequent human studies, several well-controlled experiments have demonstrated that pretreatment with the 5-HT_{2A}-preferring (that is, a drug that has highest affinity for, but is not selective for, 5-HT_{2A} receptors) antagonist ketanserin blocks the psychedelic actions of LSD[90,91] and psilocybin[44,92].

It is clear that 5-HT_{2A} receptors represent the main molecular target for psychedelics, even though animal studies have shown that both psychedelic and non-psychedelic drugs can modify so-called 'classical' models of psychedelic drug-like actions. Moreover, although the HTR has long been used to profile psychedelic drugs in rodent models, the non-psychedelic compounds 5-hydroxytryptophan, tryptamine and serotonin induce robust HTR responses[57,93,94]. Additionally, some psychedelic drugs such as DMT induce modest 5-HT_{2A}-dependent HTR responses[33]. On the other hand, the non-psychedelic drugs lisuride and ergotamine, which are structurally and pharmacologically similar to

LSD, do not induce robust HTRs in mice[42]. Thus, although there is a linear correlation between drug potencies for inducing HTR and the in vivo hallucinogenic doses in humans[2], the magnitude of the HTR and whether a drug induces HTR is not, by itself, definitive evidence that a drug will have psychedelic drug-like actions in humans. Furthermore, the structural differences between rodent and human 5-HT_{2A} receptors may complicate the interpretation of both negative and positive findings for this and other behavioural assays.

For instance, psychedelics have also been shown to modulate other rodent behaviours including retrograde walking, nose-poking and locomotion, to name just a few[95], although the specificity of these behaviours for psychedelics has not been conclusively demonstrated. Similar to other psychotomimetic drugs, psychedelics also disrupt measures of sensory-motor gating such as pre-pulse inhibition in both humans and rodents[95]. Intriguingly, psychedelic drug-induced alterations in pre-pulse inhibition are attenuated in mouse models in which 5-HT_{2A} receptors cannot interact with synaptic scaffolding proteins[96,97]. These results indicate that not only are 5-HT_{2A} receptors involved in these actions of psychedelics but also that a specific synaptic complex is essential for their effects. Importantly, disruption of pre-pulse inhibition by psychedelics is blocked by specific 5-HT_{2A} antagonists in both mice and humans[95].

Induction of spine formation. Recently, we[98] discovered and others[99,100] confirmed that psychedelics can alter synaptic plasticity by enhancing dendritic spine formation on cortical neurons in vitro and in vivo (FIG. 3) by activating 5-HT_{2A} receptors. Furthermore, we have found that many of the biochemical and behavioural actions of psychedelics are dependent upon 5-HT_{2A} receptor interactions with synaptic scaffolding proteins that are enriched in dendritic spines and post-synaptic densities[93,97,98]. It is also well established that non-psychedelic, albeit clinically effective, antidepressants also induce spine formation and synaptic plasticity[101–103] and that this appears essential to their actions[103]. Taken together, these findings have supported a model for therapeutic actions of psychedelics that converge upon processes which enhance synaptic plasticity.

Insights from structural studies. Given the centrality of the 5-HT_{2A} receptor for psychedelic drug actions, key to understanding their mechanism of action is to reveal how they interact with and activate 5-HT_{2A} receptors. Recently both X-ray and cryogenic electron microscopy

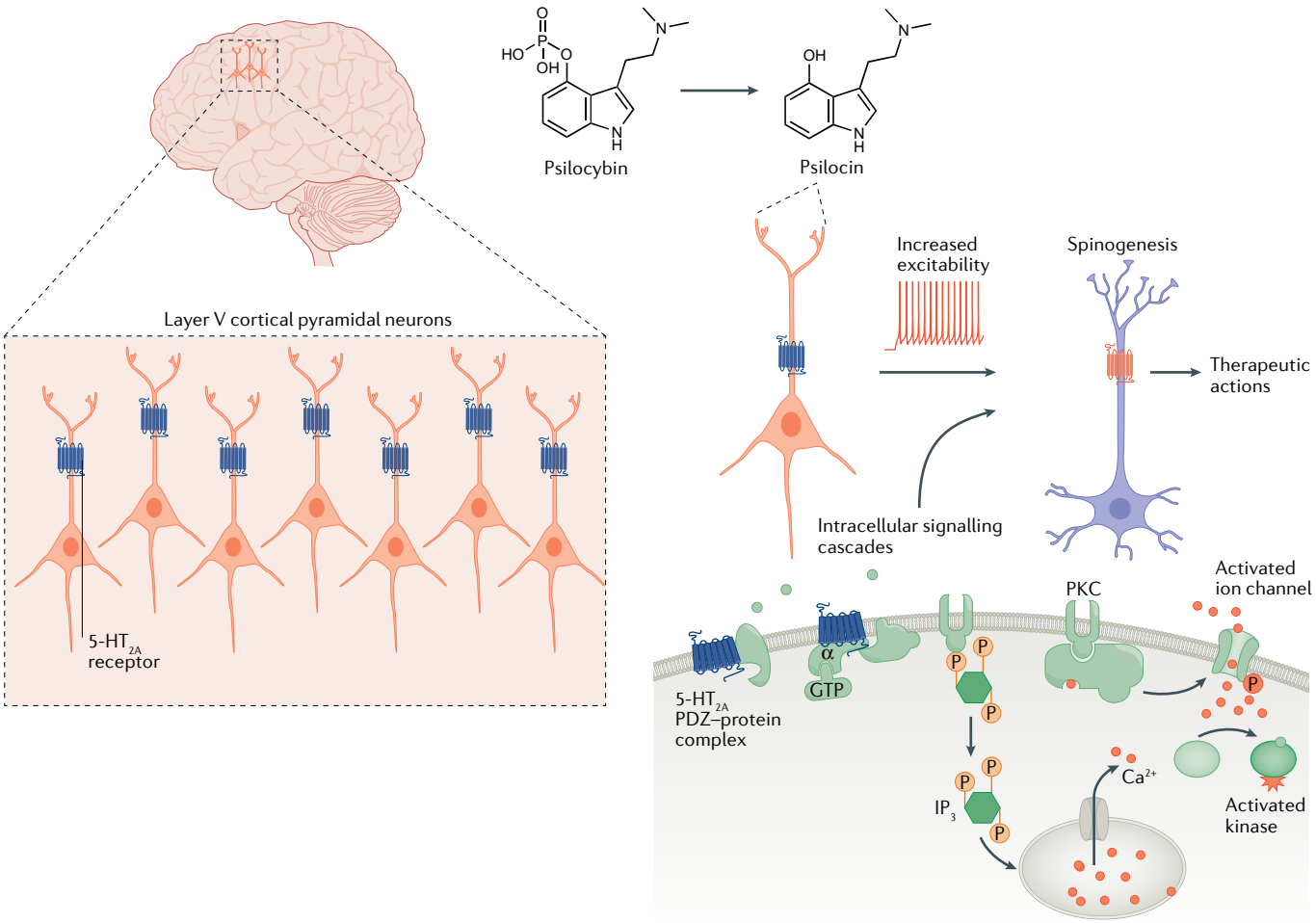

Fig. 3 | **Current model for psychedelic drug actions.** 5-HT_{2A} receptors are highly localized to apical dendrites of pyramidal neurons. Psychedelics such as lysergic acid diethylamide (LSD; not shown) activate 5-HT_{2A} receptor directly, whereas psilocybin is first metabolized to psilocin. Activation of 5-HT_{2A} receptor initiates a cascade of events leading to increased neuronal firing and activation of a large number of intracellular signalling cascades. Ultimately, various kinases, ion channels and transporters are activated. This leads to enhancement of synaptic plasticity and spine formation and, ultimately, a potential therapeutic effect. IP_3, inositol trisphosphate.

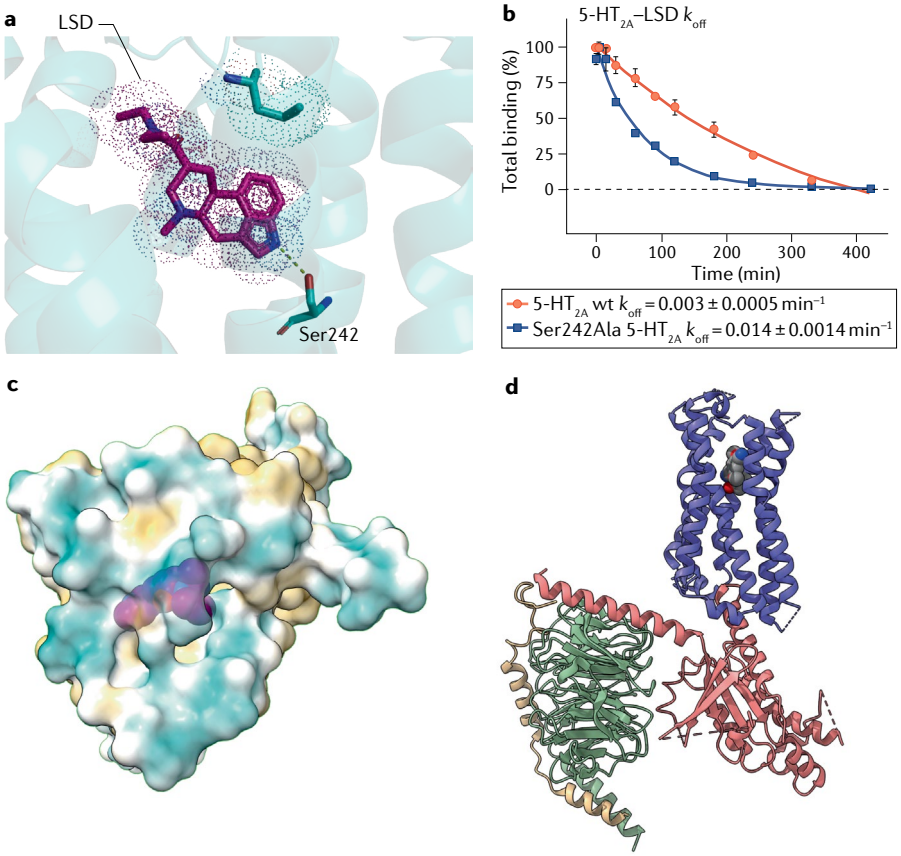

Fig. 4 | **A crystal-clear view of psychedelic drug actions.** X-ray crystallography and cryogenic electron microscopy studies illuminated the molecular mechanism of psychedelic drug binding at the 5-HT_{2A} receptor. **a** | Lysergic acid diethylamide (LSD) in its binding site stabilized by human-specific residue Ser242. **b** | Mutating Ser242 to the rodent residue Ala242 accelerates the dissociation rate (k_{off}) of LSD. **c** | A 'lid' is formed over LSD (purple) upon binding to 5-HT_{2A} receptor that prevents LSD from dissociating from the receptor. **d** | 5-HT_{2A}–G_q–psychedelic drug complex represents a snapshot of the initial event of psychedelic drug actions. wt, wild-type. Part **b** reproduced with permission from REF.[35], Elsevier.

studies have elucidated the modes of binding and activation of 5-HT_{2A} and related receptors by LSD[35,55] and the synthetic psychedelic 25CN-NBOMe[35]. The X-ray structures provided insights into how LSD interacts with 5-HT_{2A} receptors whereas the cryogenic electron microscopy structures clarified the mechanisms responsible for psychedelic-induced receptor activation (FIG. 4). To address controversies regarding which G proteins interact with 5-HT_{2A} receptors, an unbiased examination of G protein coupling[104] revealed interaction principally with G_q-like G proteins (for example, G_q, G_{11} and G_{15}) and minimal interactions with other G protein subtypes[35]. An examination of the structure revealed the determinants for selective engagement of G_q, verifying the hypothesis that 5-HT_{2A} receptors appear to selectively interact with G_q-like G proteins[35].

The structures also revealed a potential molecular mechanism for the long-lasting effects of LSD in humans. Here, it was found that in the LSD-complexed receptors, a 'lid' was formed over the binding pocket that greatly slows the dissociation of LSD from the receptor[35,55]. This specific interaction between the diethylamide moiety of LSD and Leu229 in extracellular loop 2 (EL2) of the 5-HT_{2A} receptor emerged as one key driver for LSD's long residence time in the receptor[55]. An additional 5-HT_{2A}-specific interaction with the human-specific residue Ser242 also mediates the slow kinetics of LSD dissociation from the human receptor[35].

Insights into how LSD and related drugs stabilize an arrestin-bound receptor complex were also provided by the structural studies. Again, the slow dissociation rate of LSD facilitated by interactions with Leu229 is key for arrestin interactions which occur with prolonged receptor binding[55]. Additionally, a 5-HT_{2A} residue which interacts directly with G_q is key for specifying G_q versus arrestin interactions[35]. As differential interactions with G proteins and arrestins have been postulated to be important for psychedelic drug actions[40,55,59], these studies could provide templates for future structure-guided drug discovery efforts.

The mechanisms by which non-psychedelic hallucinogens interact with their targets have also been clarified by high-resolution structures. Structures of activated κ-opioid receptors which mediate the actions of salvinorin A[105] have been reported. Also, a structure of ibogaine complexed with the serotonin transporter has clarified its molecular mechanisms of action at this target[106].

There has been a great deal of work conducted that indicates 5-HT_{2A} receptors are necessary for many of the observable phenotypic effects of psychedelic drugs, both behaviourally and molecularly. Despite the polypharmacology inherent in many (if not all) known psychedelic drugs, the 5-HT_{2A} receptor has emerged as a key enabler of their potent effects on perception and consciousness. As the majority of available model systems provide limited proxy measurements for very complex physiological processes, there is clearly a need to develop new tools for a careful mechanistic interrogation of 5-HT_{2A} receptor activation to determine the sufficiency of that receptor's actions in the phenotypic responses observed. More work must also be done on building chemical probes with selective receptor engagements and potencies to dissect the effects that are critical for therapeutic efficacy and ascertain whether they can be isolated from the other effects.

Psychedelics as therapeutics

Over the past several years there has been tremendous interest in re-examining the potential of psychedelics as transformative psychiatric therapies[107]. We use the term 'transformative' in the sense that the model for their use and integration into the therapeutic framework is distinct from how current standard-of-care psychopharmacologic medications are used. There are currently many clinical trials underway, with three phase II clinical trials demonstrating potential therapeutic actions of psilocybin for treating depression and anxiety[108–110]. An open-label extension arm for one of these studies revealed an apparently sustained action of psilocybin up to 6 months after a single administration[111]. A blinded comparison phase II study between the serotonin-selective reuptake inhibitor escitalopram and psilocybin revealed no difference in primary outcome measures for daily escitalopram (an approved antidepressant) versus

Box 2 | **Behavioural pharmacology paradigms for psychedelic drug action**

Drug substitution and the head twitch response (HTR) are two key behavioural approaches to study psychedelic drugs in animal models. The two-lever drug substitution paradigm involves training an animal to associate pressing one of two levers for a rewarding stimulus (usually a highly palatable food) with the effect of a co-administered drug. Once the animal has learned to associate the drug's effects with the reward presented by pressing the drug-paired lever, other drugs can be administered and the animal's lever-pressing responses are used to quantify the degree to which they resemble the drug used in the initial training (how well one 'substitutes' for the other). The HTR is a readily observable head-shaking motion produced in rodents following the administration of a psychedelic drug. It is an obvious behaviour that is readily quantifiable as the number of events within a given time window following drug dosing.

two doses of psilocybin[110]. As the study was not placebo controlled, it is unknown whether either treatment group would show superiority compared with placebo treatment. Taken together, these findings suggest a significant and enduring antidepressant and anxiolytic effect of one or two doses of psilocybin, although all are relatively small phase II trials. Although the secondary analysis of the single head-to-head comparison with escitalopram appeared to favour psilocybin, it is important to note that this study was underpowered to test the hypothesis of superiority of either treatment[110] and was not placebo controlled. Smaller controlled studies have supported the potential therapeutic actions of psychedelics for various other neuropsychiatric conditions[112]. Based on these favourable results collected within the experimental confines of the studies published thus far, psilocybin was granted FDA Breakthrough Therapy designation for these conditions.

How to construct clinical trials using psychedelics, or indeed any drug where an immediately perceptible effect is part of its panoply of actions, will face challenges in the use of placebo and comparator cohorts, and the degree of subject and investigator blinding that is possible. Recent reviews of these issues[113,114] have discussed some means of addressing the potential confounds. Being able to establish a dose–response relationship[115] with sufficient granularity to resolve the phenotypic effects (including therapeutic efficacy) would be highly informative, although it may be difficult to implement for practical reasons such as the sample sizes required and the associated costs. Including an arm with a lower-dose comparator group has been used, but does not allow for as much detailed comparison of effects and their magnitudes as a multilevelled dose escalation study. Similarly, whereas active placebos have been used in some studies with psychedelics (for example REF.[115]), the choice of what placebo to use and what aspects of the psychedelic experience to mimic (such that the results of the comparison capture the actual therapeutic effectiveness) are significant aspects to consider and remain open challenges.

TABLE 1 summarizes the results from well-controlled clinical trials to date. Although there is a clear efficacy signal in these trials, it is notable that high rates of disqualification of volunteers were reported, ranging from 90%[109] to 96.3%[116] of patients initially assessed. When examining only those who were deemed potentially eligible for the trial, inclusion rates ranged from 38 to 67%[109,116]. Exclusion criteria include having a first or second-degree relative with schizophrenia, psychotic disorder or bipolar I or bipolar II disorder; a current or past history of schizophrenia, psychotic disorder or bipolar I or II disorder; suicidal ideation or having "a psychiatric condition judged to be incompatible with establishment of rapport or safe exposure to psilocybin"; current antidepressant drug use; and routine medical exclusion criteria common for clinical trials[109,116]. In the most recent study[110], of the 1,000 patients who were initially screened by telephone, 891 were disqualified for not meeting the inclusion criteria. Of the remaining individuals, 59 were eventually randomized (5.9% of initially screened individuals)[110]. These stringent exclusion criteria, although justifiable in terms of optimizing safety, do risk constraining the size of the total number of subjects in a given trial as well as not accurately reflecting the diversity of the population that could potentially benefit from novel therapeutic intervention.

It is also important to note that there are no controlled studies demonstrating the safety or efficacy of psychedelic drugs in individuals currently on antidepressant medications. In all of the trials reported to date, individuals entering the trial were free of antidepressant drugs for several weeks prior to entry. There are also uncontrolled studies suggesting that the subjective effects of psychedelics may be attenuated by ongoing treatment with serotonin-selective reuptake inhibitors and other antidepressants[117,118]. As yet, the mechanism of this observed potential antagonism between psychedelic and other antidepressant drugs is not known and further studies will be necessary to determine how it impacts the practical utility of these drugs in the clinic.

Interestingly, the percentage of individuals who reported past psychedelic drug use ranged from 36 to 56% in one study[89], which is considerably higher than the general US population with the most recent estimate in 2019 being 44 million individuals (see Substance Abuse and Mental Health Service Administration — 2019 National Survey on Drug Use and Health Detailed Tables) out of a general population of 382 million, or 11.5%. In another study[92] a much lower rate of past psychedelic drug use was reported. These inconsistencies highlight some of the additional confounds presented by the current trial sizes and designs, particularly with respect to the degree of an individual's expectancy of drug

Table 1 | **Phase II trials of psilocybin**

Trial	Control	Outcome	*N*	Ref.
Psilocybin for anxiety and depression in individuals with life-threatening cancer	Niacin	Improvement in anxiety and depression[a]	29 (14 psilocybin; 15 niacin)	115
Psilocybin for anxiety and depression in individuals with life-threatening cancer	Low-dose psilocybin	Improvement in anxiety and depression[b]	51 (25 low dose; 26 high dose)	109
Psilocybin versus escitalopram in depression	Escitalopram	Improvement in depression for both psilocybin and escitalopram[c]	59 (30 psilocybin; 29 escitalopram)	110

[a]Clinical outcome measurements include statistically significant improvement in the Hamilton Depression Rating Scale and the Beck Depression Inventory for depression, and the Hospital Anxiety and Depression Scale for anxiety. [b]Clinical outcome measurements include statistically significant improvements in the Grid Scoring Hamilton Depression Rating Scale (GRID-HAM-D-17) for depression and the Hamilton Anxiety Rating Scale (HAM-A) for anxiety. [c]Clinical outcome measurements included statistically significant improvement in the six-item Quick Inventory of Depressive Symptomatology — Self-Report.

action afforded by previous experience with psychedelics, and the extent to which the trial population reflects the broader patient population intended to be modelled.

With regard to potential human genetic polymorphisms and variants that may affect the activity of psychedelic drugs at 5-HT_{2A} receptors, there are many reported non-synonymous protein-encoding single-nucleotide polymorphisms with non-rare population frequencies (Supplementary Fig. 1). Of these, the most frequent are T25N, I197V, A447V and H452Y variant 5-HT_{2A} serotonin receptors (see Genome Aggregation Database)[119]. A comprehensive analysis of the effects of these protein-encoding variants showed that agonist potencies or efficacies of prototypical psychedelics such as 2,5-dimethoxy-4-iodoamphetamine (DOI) or 5-methoxy-*N*,*N*′-dimethyltryptamine (5-OMe-DMT) were significantly attenuated in a drug × polymorphism-specific fashion for the T25N, I197V and H452Y polymorphisms[120]. There are currently no peer-reviewed published data examining the actions of LSD or psilocin at 5-HT_{2A} variants, although there are data showing differential actions of LSD at 5-HT_{2C} receptors where the receptor is subjected to RNA editing[121]. In this case, RNA editing involving adenosine→inosine substitution in the coding region leads to a change in the translated protein[121].

As previously mentioned, many psychedelic 5-HT_{2A} agonists including LSD and psilocin are potent agonists at 5-HT_{2B} receptors[29,55,122]. LSD displays unusual binding and activation kinetics at 5-HT_{2B} receptors[55] and has picomolar potency for activating both canonical and non-canonical 5-HT_{2B} receptor signalling[55]. As it is well established that 5-HT_{2B} receptor activation may be associated with drug-induced valvular heart disease in humans[61], there is the potential that chronic dosing as may be achieved with so-called 'microdosing' strategies could be associated with this serious and potentially life-threatening side effect. Other potential problems with psychedelics are the lack of known 'rescue' medications to abort unfavourable psychedelic experiences and potential long-term effects of psychedelic medications. Because of the potential for exacerbation of underlying psychosis, studies on psychedelic medications routinely disqualify individuals with personal or familial history of major psychotic disorders. As a consequence, subjects in future trials will continue to represent a restricted subset of the total patient population that could potentially benefit from novel drugs targeting the 5-HT_{2A} system.

In summary, evidence for the therapeutic effects of psychedelic compounds is mounting, at least under specific clinical settings and for select demographics of people with certain conditions. For the classical psychedelics gaining interest in the clinical domain, studies examining longer-term durability of therapeutic benefits and more comprehensive assessments of safety margins, particularly involving patient populations presenting with multiple comorbidities, will be highly valuable. Additional research and development is also required in the basic science domain to increase our understanding of the underlying mechanisms, and to diversify the chemical space of drugs that act via these mechanisms so that we may be able to benefit the greatest proportion of the affected population.

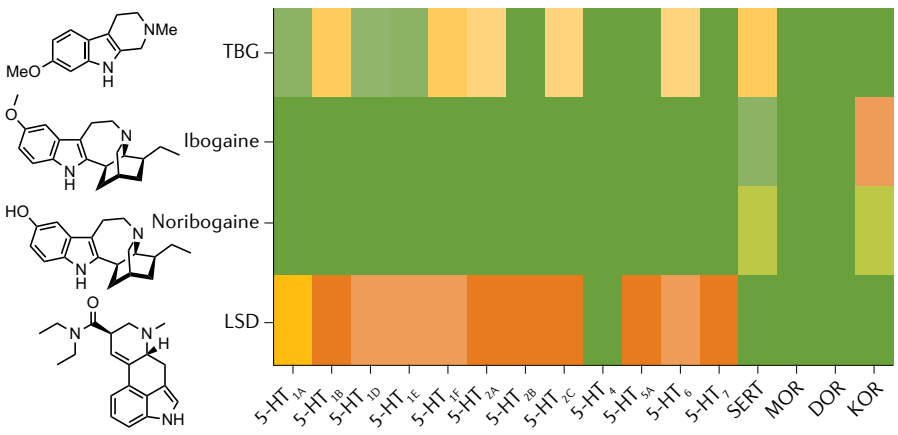

Fig. 5 | **The polypharmacology of the novel non-psychedelic drug TBG.** Heat map of nanomolar affinities of various drugs. Tabernanthalog (TBG) differs from the parental scaffolds ibogaine and noribogaine but shares much of its polypharmacological profile with lysergic acid diethylamide (LSD). SERT, serotonin transporter. DOR, δ-opioid receptor; KOR, κ-opioid receptor; MOR, μ-opioid receptor.

Potential for non-psychedelic drugs

It is currently unknown whether the subjective experience of a psychedelic drug is a necessary component of its ability to produce therapeutic benefits. The magnitude of the therapeutic effect correlates with several subjective qualities of the psilocybin experience[123,124]. The subjective intensity of the psychedelic experience elicited by psilocybin also correlates with the circulating plasma levels of psilocin and the degree of 5-HT_{2A} receptor occupancy in the brain[125]. Thus, a trivial conclusion is simply that the amount of drug administered recruits more receptor activity which results in more physiological effects, both quantifiable and subjective. Correlations, although robust and quantifiable according to the data collected, are not evidence of an underlying mechanism per se. We cannot say, with any certainty, anything beyond the existence of a relationship between these observations. Knowing what we do about the diverse constellation of signalling processes engaged by the 5-HT_{2A} receptor, and others implicated in the myriad effects of psychedelics, it is possible that a drug binding the receptor(s), but with different agonist activities and/or polypharmacology to psilocin, will have substantially different effects. Determining which receptor engagements and conformations contribute to which signalling processes and how those, ultimately, manifest as behavioural phenotypes requires additional experimentation and the application of both existing and new tools.

In this regard, a new paper[126] suggested that the psychedelic actions of psilocybin in mice could be blocked without affecting its antidepressant drug-like actions. Here the authors show that pretreatment with the 5-HT_{2A} receptor antagonist ketanserin attenuates, but does not abolish, psilocybin's HTR in mice without affecting psilocybin's antidepressant drug actions in two animal models. Although these findings are intriguing, given the non-translational value of many rodent models of antidepressant drug actions[127], and the substantial polypharmacology inherent with classical psychedelics, further investigation is warranted.

There have recently been preclinical reports that drugs which share at least some of the actions of conventional psychedelics may have antidepressant drug-like actions without psychedelic drug-like actions. Thus, in an intriguing study investigating ibogaine

Table 2 | **A comparison of measures of psychedelic drug actions**

Assay	True positive	False positive	False negative	Comments
Human administration	Yes	No	No	Gold standard
Head twitch response (HTR) assay	Yes	Yes	No	Several non-psychedelic compounds cause robust head twitch
5-HT_{2A}–G_q signalling assay	Yes	Yes	No	Some non-psychedelic compounds are agonists; all known pyschedelics are agonists
PsychLight biosensor	Yes	Yes	Yes	Some non-psychedelic compounds are active; some psychedelic compounds are inactive

derivatives, Cameron et al.[128] reported that tabernanthalog (TBG) (FIG. 1) had antidepressant and anxiolytic-like activity in several animal models but was devoid of activity in the HTR. TBG displayed a robust polypharmacological profile with potent agonist activity at several 5-HT receptors and the serotonin transporter (SERT). Even though TBG displayed quite modest potency at 5-HT_{2A} receptors, several of its actions in vivo were blocked by ketanserin[128]. TBG's pharmacological profile is quite distinct from the parent compound ibogaine (FIG. 5), which has negligible activity at 5-HT receptors and modest activity at various transporters and the κ-opioid receptor. TBG more closely mimics the polypharmacology of LSD, although LSD has appreciably higher potencies at most human 5-HT receptors[27] and lacks activity at the SERT.

Intriguingly, Dong et al.[129] recently reported that a biosensor (PsychLight) in which a circularly permuted GFP (cGFP) was inserted into the 5-HT_{2A} receptor was able to distinguish several psychedelic from non-psychedelic 5-HT_{2A} agonists in vitro. The sensor, however, was also potently activated by 5-HT and tryptamine (which are not psychedelic) whereas the psychedelic 2-(4-iodo-2,5-dimethoxyphenyl) ethan-1-amine (2C-I) was inactive (TABLE 2). The authors used this sensor to discover AAZ-134 — a tryptamine derivative — which displayed antagonist activity at the sensor and antidepressant drug-like actions in mice. Although the authors were unable to determine the molecular target(s) responsible for the actions of AAZ-134, the paper demonstrated the utility of the sensor for separating psychedelic from non-psychedelic compounds, at least for the majority of compounds tested. Going forward it will be important to examine the ability of other known psychedelic and non-psychedelic 5-HT_{2A} agonists to determine the fidelity of the sensor and to discover the molecular targets responsible for the actions of AAZ-134. 'Calibrating' such sensors to the gold standard of effects in humans (TABLE 2) will be an important step in preclinical evaluations of utility for progression into human trials with the appropriate expectations about the effects that may be produced.

Access to structurally diverse chemical matter may, ultimately, be key to the advancement of novel drug candidates targeted to the 5-HT_{2A} receptor with ranges of potencies, intrinsic activities and polypharmacology. As discussed previously, there are several discrete genetic polymorphisms in the primary target of interest already known to exist, with more likely present in our diverse population. It is certainly the case that a given psychedelic drug will elicit different interospective effects in different people. This is a consequence of the fact that genetic polymorphisms will influence both pharmacokinetic and pharmacodynamic effects, and because — although all psychedelic compounds share numerous molecular targets and intrinsic activities at those targets — the precise combination of polypharmacological effects will differ according to chemical structure. As such, the 'right' psychedelic-inspired medication may not be obvious for every individual seeking a pharmacological resolution to their specific condition. Rather, we need to expand the chemical space, both according to the subjective effects of the drugs as well as their structural diversity.

Discovering new chemical matter with beneficial actions at 5-HT_{2A} receptors will likely be accelerated by ultra-large-scale computational approaches[130]. In proof-of-concept studies we and others have shown that the ultra-large-scale docking of in silico enumerated molecules can afford the discovery of potent and selective compounds with biased signalling properties at prototypical G protein-coupled receptors (GPCRs)[130,131]. One can thereby envision a similar strategy aimed at 5-HT_{2A} receptors where, ultimately, billions of compounds might be interrogated computationally at relevant 5-HT_{2A} receptor complexes.

As of this writing, there are 40 public psychedelic medicine companies listed on the Psychedelic Stock Index, with numerous other ventures at varying stages of maturity pursuing psychedelic therapies as products and/or services. The majority of these commercial enterprises are pursuing formulations and/or specific integrated therapies with existing classical psychedelics, mostly psilocybin. As mentioned above, not every patient suffering from depression, anxiety, post-traumatic stress disorder and so on will be able to benefit from therapy including classic psychedelic drugs. As such, the emphasis at this stage should be on the discovery of new chemical matter with diverse target receptor engagements and intrinsic activities. Such efforts are active research pursuits and will be key to the longevity of effective psychiatric treatments inspired by psychedelic mechanisms of action. These areas of innovation should enhance the promise and minimize the peril of psychedelic pharmacology applications in psychiatry.

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https://doi.org/10.1038/s41573-022-00421-7

Published online: 17 March 2022

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Acknowledgements
B.L.R. was supported by grants from the National Institutes of Health (NIH), a cooperative agreement from the Defense Advanced Research Projects Agency (DARPA) and the Michael Hooker Distinguished Professorship. T.D.M.-B. is a programme manager in the DARPA Biological Technologies Office.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

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The views, opinions and/or findings expressed are those of the authors and should not be interpreted as representing the official views or policies of the US Department of Defense or the US Government.

Peer review information
Nature Reviews Drug Discovery thanks David Nutt, Harriet de Wit and Magali Haas for their contribution to the peer review of this work.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41573-022-00421-7.

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