Psychedelic-assisted psychotherapy is one model of psychedelic medicine that could be used to treat some neuropsychiatric disorders.

NEUROSCIENCE

The therapeutic potential of psychedelics

The development of psychedelics as medicines faces several challenges

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Psychedelics are reported to have rapid-onset and long-lasting therapeutic benefits after a single or few doses. Sustained (1 year or more) clinical benefits have been reported in depression and smoking cessation studies after just two or three doses of psilocybin combined with psychotherapy (*1*, *2*). By contrast, conventional medications for neuropsychiatric disorders take days to weeks to begin working and need to be taken daily over prolonged periods and sometimes indefinitely. Other potential applications for psychedelics include treatment of cancer-related anxiety, obsessive-compulsive disorder, headache disorders, and phantom limb syndrome. Although arguably paradigm shifting, a number of unanswered questions remain about psychedelics as medicines, including the definition of a psychedelic drug, the mechanism of therapeutic effects, optimizing clinical benefit, and verifying safety.

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Lysergic acid diethylamide (LSD), psilocybin, *N*,*N*-dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), and mescaline are some of the agents collectively categorized as classic psychedelics. These drugs are all agonists at 5-hydroxytryptamine (5-HT; serotonin) 2A (5-HT_{2A}) receptors and produce characteristic acute psychedelic effects, which include alterations in perception, feeling, and consciousness (*3*). Although other compounds produce psychedelic-like effects as well as clinical benefits [such as ketamine and 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy")], they are pharmacologically distinct, and so the focus here is on classic psychedelics.

Narrowly defining a drug class by one set of its effects (psychedelic) can be problematic because it colors the perception and may ultimately limit the breadth of its application. For example, patients may be hesitant to take an antidepressant for a nonpsychiatric condition, such as peripheral neuropathy or migraine, simply because of the class name. Alternate terms offered for psychedelics include "psychoplastogens" or "neuroplastogens" (*4*), which remove prejudice and highlight the ability of these drugs to induce change, although not necessarily the distinct dosing regimen. Borrowing from headache medicine, transitional medications are those taken for a short time and that suppress headache for a prolonged period well beyond the treatment itself (steroid pulse). A compound term such as "transitional neuroplastogen" captures the notions of long-lasting change after a brief treatment period.

The mechanism of therapeutic effects of psychedelics is widely queried but remains unclear. 5-HT_{2A} receptor antagonists block acute psychedelic effects, but whether they also block therapeutic effects requires further investigation. To what extent the many other direct or indirect targets of psychedelics—such as 5-HT_{1A}, 5-HT_{2B}, and 5-HT_{2C} receptors; dopamine receptors; α-adrenergic receptors; monoamine transmission; and glutamatergic transmission—contribute to therapeutic effects is also not known (*3*). Once bound to a receptor, a ligand may also activate one or more intracellular processes. For example, the β-arrestin signaling pathway has been suggested to be relevant for antidepressant effects of 5-HT_{2A} receptor activation but not psychedelic effects (*5*). Psychedelics also have numerous physiological effects, including anti-inflammatory, hormonal, and epigenetic effects, which have pathological relevance in such conditions as depression, substance abuse, and headache disorders (*6*).

How any of these transient effects on receptors or biological systems might explain sustained therapeutic effects is unknown. The initiation of a cascade of events with en-

during neuroplastic effects at the cellular and network level is one plausible and popular theory. Classic psychedelics have been shown in cellular and in vivo preclinical models to promote synaptogenesis and increase cortical dendritic spine size, number, and complexity (*7*), with some effects lasting a month (*8*). In pigs, a single intravenous dose of psilocybin was shown to induce lasting (7 days) increases in cortical and hippocampal synaptic density (*9*). Interestingly, experiments identified some, but not other, cellular changes to be 5-HT_{2A} receptor-mediated. Whether these neuroplastic cellular changes are related to durable therapeutic effects could be investigated in models of human disease or human patients. For example, in patients with treatment-resistant depression, changes in brain resting-state functional connectivity the day after completing a two-dose regimen of psilocybin correlated with a lasting clinical improvement at 5 weeks (*10*). Moreover, various changes in brain connectivity persisted for 1 month after a single dose of psilocybin, as did increases in positive mood and decreases in anxiety (*11*). These postpsychedelic connectivity changes suggest an association with and perhaps a source for therapeutic effects. However, replication of findings in placebo-controlled studies, over a longer term, and with clearly delineated modeling and analytical parameters is necessary to show this more conclusively. In addition, comparisons with other drugs that also induce neuroplastic changes, such as ketamine (*8*), are necessary to characterize signature effects of psychedelics. Studies in different patient populations will also be required to identify the changes relevant to specific disorders, such as hypothalamic function in cluster headache (*6*).

The neuroplastic effects of psychedelics may serve to open a therapeutic window, allowing other drugs or treatments to take effect. For example, psychedelic drug studies in depression include a course of psychotherapy, a standard treatment used in depression. In a case of phantom limb syndrome, psilocybin mushrooms were reported to have synergistic and lasting therapeutic effects when used in conjunction with mirror therapy, a standard rehabilitative therapy used to reverse aberrant somatosensory cortex reorganization in that condition (*12*). These psychedelic-assisted therapies use the drug with an existing disease-specific therapy. However, psychedelics may also have independent treatment effects. Cluster headache patients have been self-administering them as standalone treatment for decades, and clinical trials in headache disorders have modeled this method. Ultimately, the independent and interactive effects of psychedelics with other disease-specific therapies must be investigated systematically. The type and duration of adjunctive treatment must also be considered (which form of psychotherapy for depression). The need to repeat drug treatment at certain intervals is also anticipated, although existing clinical trials are relatively short. Furthermore, some study protocols include curated decoration, music, and so on during drug dosing, as well as the presence of therapists to guide or enhance the experience. The specific settings and interactions that are necessary and optimal for therapeutic outcomes have not been systematically examined. Notably, whether additional treatments and procedures can be implemented on a large scale and reach all populations in need must be factored into the development of psychedelics as medicines.

Positive correlations between the magnitude of the psychedelic experience and therapeutic benefit have not been consistently observed. In headache disorders, acute psychedelic effects appear unrelated to therapeutic outcomes (*13*). Across studies, the scales (and subscales) used to measure psychedelic effects are not aligned, leaving the relationship between acute subjective effects and clinical effects unclear. Furthermore, different psychedelics produce distinct acute experiences. Seeking to understand the origin of specific acute perceptual and other subjective effects and their relevance in treating particular neuropsychiatric conditions could further optimize treatment. This could be done through a number of complementary experimental manipulations: comparing the therapeutic efficacy of subpsychedelic versus psychedelic doses, conducting wide dose-response studies, blocking the psychedelic effects with targeted receptor antagonists, using analogs that lack psychedelic effects [such as 2-bromo-LSD (BOL)], comparing classic psychedelics or using other psychotropic drugs with distinct pharmacological profiles (such as MDMA), or administering drugs to individuals while they are in natural or induced sleep. If the acute psychedelic effects of these drugs are central to some therapeutic effects, it will be critical to determine what level and duration are necessary. For example, intravenous DMT showed next-day (rapid) antidepressant effects and produced acute psychedelic effects for ~30 minutes (*14*), contrasting oral psilocybin's 6 hours or LSD's 12 hours of acute effects. A shorter psychedelic experience, if resulting in the same clinical benefit, would be more logistically feasible and palatable.

"The neuroplastic effects of psychedelics may serve to open a therapeutic window..."

Unlike the development of drugs in the pharmaceutical industry, there is a massive amount of information about psychedelics available to the public before their implementation as medicines. Media coverage is not bound by the standards of accuracy of scientific reporting and seems biased toward covering the "universally life-changing" abilities of psychedelics. This raises expectations for success in clinical trials, which may only partially be tempered by education (*15*). Study results are also affected by potential unblinding from the unmistakable acute effects of psychedelics and lack of acute effects with placebo (*15*). An active control that produces acute subjective effects may minimize unblinding, although identifying such an agent is challenging. A low dose of the psychedelic being investigated may be used, but this too may produce lasting therapeutic effects (*13*). A related drug with overlap in several dimensions of the psychedelic experience, such as ketamine, may be tried, although ketamine also has lasting clinical effects. The use of other nonclassic psychedelics with no known therapeutic effects (such as salvinorin A) might be considered. Other control agents that have been used include niacin and diphenhydramine, although these drugs do not entirely substitute for acute effects, particularly of higher doses of psychedelics. Additional methods for maintaining blinded conditions include recruiting psychedelic-naïve subjects, emphasizing interpersonal variability in the acute effects, and incomplete disclosure about drugs or doses that may be received (*15*).

Given the increase in psychedelic research, together with the surge in popular and commercial interests, the safety of psychedelics must not only be revisited but considered in the context of current and future use. Historically, the use of psychedelics has involved the infrequent consumption of moderate to high doses. In research, limited dosing (single or a few doses) is studied, and the drug is administered under controlled conditions with medical and psychiatric oversight to carefully screen and prepare participants. Such practices support safety and tolerability and deter misuse. However, practices that deviate from this model are emerging. One version of the practice of "microdosing" involves repeated exposure to low or subperceptual doses of a psychedelic over a prolonged period. Although "micro" might sound appealing and denote safety, there is no evidence that the frequent and long-term use of psychedelics (at any dose) is safe. As a case in point, the LSD-derivative methysergide, an effective migraine and cluster headache preventive (taken daily), was removed from the market after cases of cardiac valve fibrosis and other tissue fibrosis emerged.

The fibrogenic effects are related to 5-HT_{2B} receptor activation, and although psychedelics have varying affinities for this receptor (highest for ergot derivatives), frequency and duration of exposure must be considered in the pharmacodynamics of these new, unverified regimens.

Psychedelics may also have acute therapeutic effects (for example, aborting a headache attack). Although potentially acceptable for conditions that require infrequent use, the frequent consumption of these drugs for the acute management of a chronic and/or persisting condition is not only impractical but risks tolerance and loss of efficacy and has not been systematically studied for safety. Indeed, an ongoing challenge within pain management is the reliance on abortive rather than preventive treatment, which leads to sensitization and dependency. Psychedelics have historically failed to demonstrate addictive properties, but the neuropsychological impact of frequent (and potentially increasing) use needs further study. In addition to pharmacology and purpose of use, other factors that contribute to how a drug is used (or misused) include availability, perception, commercialization, and promotion. Furthermore, the idea that psychedelics may be used outside of a diagnosed medical condition—say, for general life enhancement or improved concentration—is intriguing but will also require formal investigation. Without dedicated study, new regimens and applications may have unexpected outcomes. The comprehensive investigation of psychedelics and their implementation as legitimate medicines remain valuable but substantial undertakings. ■

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PHOTO: JJ GOUIN/ALAMY STOCK PHOTO

Research using herbarium specimens collected over nearly 200 years demonstrates how the native North American weed waterhemp (shown here invading a soybean field) adapted to agricultural practices over space and time.

AGRICULTURE

Herbaria reveal cost of the Green Revolution

Rapid weed evolution is exposed by genome sequencing of natural history collections

By **Katherine Waselkov**[1] *and* **Kenneth M. Olsen**[2]

A visitor to the US Midwest will be immediately struck by the sheer scale of industrially farmed corn and soybean. These fields are intensively managed artificial ecosystems, from their planting and harvesting timelines to the fertilizers and pesticides that are continually applied. Evolutionary biologists have long presumed that weeds are under strong natural selection to adapt to this anthropogenic ecosystem, which first appeared in the mid–20th century's "Green Revolution" in agriculture. On page 1079 of this issue, Kreiner *et al.* (*1*) report that the selection pressure on weeds in modern agricultural fields is higher than estimates from most other natural systems (*2*). The authors leverage historical samples in natural history collections to temporally link the adaptation of the agricultural weed waterhemp to the Green Revolution.

The intensification of agriculture in the US and Canada has resulted in higher crop yields on less acreage in exchange for greater use of nitrogen-based fertilizers and pesticides. However, the maintenance of crop monocultures in these biodiversity-poor ecosystems spurred an arms race against weeds, insect pests, and microbial pathogens. To date, 267 plant species have evolved resistance to at least one chemical group of herbicides (a type of pesticide) meant to control their presence in agricultural fields (*3*). This intense, human-mediated selection pressure increased in the late 1990s with the widespread adoption of soy, cotton, and corn varieties that were genetically modified to resist glyphosate pesticides. This chemical (commercially known as Roundup) is currently the most popular herbicide in the US (*4*). Early fears about the escape of modified genes from genetically modified crops have largely been allayed through careful design and regulation. However, the proliferation of weeds that have evolved resistance to glyphosate largely through naturally occurring mutations has been an unanticipated consequence of the commercialization of glyphosate-resistant crops (*5*). As the continuous, exclusive use of Roundup leads to the emergence of more glyphosate-resistant weed populations and species (currently 56), farmers are resorting to older chemicals or more expensive weed-control methods. One of the most pervasive and damaging glyphosate-resistant weed species is the North American native waterhemp (*Amaranthus tuberculatus*).

Waterhemp is unusual among agricultural weeds in that individual plants are either male or female and thus must cross-pollinate to reproduce (unlike many weeds that self-pollinate). Encountering a mate is enabled by wind pollination and enormous popula-

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