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Disruptive Psychopharmacology

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The paucity of medications with novel mechanisms for the treatment of mental illnesses combined with the delayed response to currently available medications has led to great excitement about the potential therapeutic utility of previously demonized drugs, which offer the hope of generating rapid symptom reductions in some of the sickest patients. Within the past 2 years, the US Food and Drug Administration approved esketamine for treatment-resistant depression and 2 compounds that are still on the US Drug Enforcement Administration's most restrictive schedule, 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin, have received break-through therapy designation. If these latter drugs are approved, they will require a new mental health care infrastructure that is capable of administering powerful psychoactive substances while simultaneously incorporating appropriate psychotherapeutic support. The sheer prevalence of the conditions these drugs are meant to treat (depression and posttraumatic stress disorder among other emerging indications) will mean that clinicians will have to deal with safety issues, including appropriate patient selection, substance abuse potential, and emergent psychiatric and medical crises. These considerations justify investment in elucidating the detailed neural mechanisms by which these drugs work so that we might better control their safety and efficacy while simultaneously developing better treatments with fewer adverse effects.

Investigating Mechanism

Although ketamine, MDMA, and psilocybinare pharmacologically distinct, they share the ability to induce an acutely altered state of consciousness, which in the appropriate therapeutic context can lead to a rapid therapeutic onset and, to varying degrees, a durable treatment effect that persists well after the drug has been cleared from the body. Their effects are reminiscent of those of indigenous medicines such as ayahuasca, peyote, and ibogaine, which have been used for centuries across many cultures.[1,2] It is tempting to hypothesize that a common underlying physiological process is at play, given the similarity in these drugs' time courses and the common theme of acute psychological transformation. Conversely, it will be important to determine whether these drugs' benefits are specific to a given constellation of symptoms. A survey of currently registered clinical trials suggests

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otherwise, as ketamine, MDMA and psilocybin are each being tested for both affective and appetitive disorders.

How best to pursue the mechanisms of action for this next generation of therapeutics? We have argued for a circuits-firstapproach,[3] which involves using the armamentarium of modern neuroscience tools to define the circuit adaptations that contribute to a drug's behavioral and therapeutic effects. Once critical circuit nodes are identified, single-cell gene profiling can be performed in their key cell types based on their connectivity, yielding novel molecular targets for the development of next generation drugs with greater efficacy and fewer side effects. Modeling complex human behaviors in animals is particularly valuable when the structure and function of the involved neuroanatomy is highly conserved. This is likely the case for several neuromodulatory systems that contribute to a host of behaviors of direct relevance to psychiatry such as Pavlovian and instrumental conditioning, prosocial approach, aggression, cognitive flexibility, and responses to motivationally significant stimuli.

Of course, it is also critical to define the molecular targets of these new therapeutic agents. For ketamine, this has been more challenging than originally expected, with findings[4,5] suggesting a need to conceptualize its molecular mechanisms with more nuance than action at a single, broadly distributed glutamate receptor. The complexity of ketamine's actions emphasizes the critical importance of determining where in the brain it is exerting its therapeutic circuit effects. In contrast to the confusion surrounding ketamine's molecular targets, a prediction of preclinical studies of lysergic acid diethylamide (LSD), a drug with significant similarity to psilocybin, has been confirmed with the demonstration that LSD's subjective effects in humans could be blocked by a 5HT2a receptor antagonist.[6] Moreover, hallucinogen-induced changes in functional connectivity in human imagingstudies[2] suggest that reverse translation may be possible. For example, it will be advantageous to define the actions of 5HT2a receptors in the putative drug-modulated circuits in human brains in more experimentally tractable animal brains in which molecular and circuit targets can be manipulated with precision and detailed cellular level observations can be made. Identifying parallel circuitry that is influenced by classic hallucinogens in both humans and animals will be challenging. Nevertheless, the more we can define the relevance of evolutionary conserved behavioral parameters to the efficacy of the therapeutic intervention, the higher the probability of defining the causal neural mechanisms underlying the drug's therapeutic effects. In turn, more efficacious therapeutic interventions will follow.

Defining Clinical Variables

Great attention has been paid to the therapeutic setting itself in designing trials of MDMA and psilocybin because efficacy may well depend on both the drug and the therapeutic environment in which it is administered. In patients with posttraumatic stress disorder, MDMA, which enhances positive social interactions, may catalyze the extinction of aversive memories primarily by strengthening the therapeutic alliance.[7] Similarly, the vivid experiences during a psilocybin session that are revisited in subsequent therapy sessions may be central to its potential therapeutic action in addressing existential issues and sources of depression and anxiety.[1,2] It follows that we should characterize and test the

psychotherapeutic component as well as the necessity for the specific drug being tested. This rigor begins with developing appropriate placebo controls because expectancy bias in trials of this nature are likely to have strong effects. Indeed, despite laudable attempts using active placebos, both patients and therapists have been able to identify the treatment given.[1] Using dissociative drugs, such as dextromethorphan, as comparators for psilocybin or psychostimulants, such as meth- amphetamine, for MDMA warrants serious consideration. These psychoactive controls will help test whether the specific drug being evaluated is necessary for the consequent therapeutic effect.

We also need to understand the optimal dose and timing of therapy. What is the importance of preparatory and integrative therapeutic sessions relative to the drug session? Analyses of psilocybin trial data suggest that the mystical aspect of the acute drug experience scales with therapeutic benefit.[2] But are all patients capable of generating this kind of subjective state? We assume that the events during an acute drug experience are required for a treatment effect to occur. But perhaps, the conscious experience of a drug trip is an epiphenomenon relative to the therapeutic state the drug produces, an effect that would still occur, for example, if the drug of interest was administered during general anesthesia. These hypotheses are testable. Furthermore, using standardized measures of therapeutic alliance and operant tasks to assess cognitive flexibility and reward sensitivity could help establish what parameters are necessary and sufficient to achieve a treatment effect, thereby imbuing preclinical mechanistic studies with predictive utility.

Decades ago, the serendipitous discovery of iproniazid's antidepressant effect and chlorpromazine's antipsychotic efficacy led to the development of drugs that helped millions of patients. Preclinical behavioral screening models have had some success in predicting efficacy of drugs with pharmacology similar to already approved therapies, but have generally failed to yield new therapeutic principles or pathways. It is telling that the current wave of therapeutic innovation is based not on insights gained from studying established drugs, but rather on a disruptive new therapeutic approach involving compounds that have been known for quite some time in other contexts. By applying all the tools in our modern armamentarium to understand the mechanisms by which they work, it will be possible to develop better therapies, which will make up the next generation of disruptive psychopharmacology.

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REFERENCES

1. Bogenschutz MP, Ross S. Therapeutic applications of classic hallucinogens. Curr Top Behav Neurosci. 2018;36:361–391. doi:10.1007/7854_2016_464 [PubMed: 28512684]
2. Johnson MW, Hendricks PS, Barrett FS, Griffiths RR. Classic psychedelics: an integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacol Ther. 2018;S0163-7258(18)30215-8.
3. Monteggia LM, Malenka RC, Deisseroth K. Depression: the best way forward. Nature. 2014;515 (7526):200–201. doi:10.1038/515200a [PubMed: 25391955]

4. Williams NR, Heifets BD, Blasey C, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry. 2018;175(12):1205–1215. doi:10.1176/appi.ajp.2018.18020138 [PubMed: 30153752]

5. Abdallah C, Averill LA, Gueorguieva R, et al. Rapamycin, an immunosuppressant and mTORC1 inhibitor, triples the antidepressant response rate of ketamine at 2 weeks following treatment: a double-blind, placebo-controlled, cross-over, randomized clinical trial. 10.1101/500959v1. Published December 19, 2018. Accessed May 20, 2019.

6. Preller KH, Burt JB, Ji JL, et al. Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. Elife. 2018;7:7. doi:10.7554/eLife.35082

7. Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. Lancet Psychiatry. 2016;3(5):481–488. doi:10.1016/S2215-0366(15)00576-3 [PubMed: 27067625]