CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Translational Challenges in Psychedelic Medicine

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The role of serendipity in medical discovery is well known, including in psychiatry, in which it accounts for the discovery of most current major drug categories. This principle extends to ketamine and psychedelic drugs. The discovery of the psychoactive effects of lysergic acid diethylamide (LSD) in 1943 was a pivotal event in the history of psychedelic medicine in the West that catalyzed a wave of clinical research and application in the 1950s and 1960s, but it occurred because of human experience guided by educated chance after hundreds of years of human use of psychedelic fungi and plants for healing purposes.

In the first English-language publication about LSD, two American psychiatrists who were enculturated by a psychoanalytic perspective described LSD as "disturb[ing] the barrier of repression" in order to catalyze psychotherapy.[1] British psychiatrist Humphrey Osmond was also impressed by LSD and described the effects of the drug as "psychedelic" — combining the ancient Greek word for "soul" with a modified verb meaning "to reveal." Our understanding of the biologic action of psychedelic agents has been grounded in findings over the past decades that indicate a key signaling action at the serotonin 2A receptor (5-HT_{2A}).

Fast-forward to the present day, when there is a notable effort to identify what might playfully be called "nonpsychedelic psychedelics." Researchers, including Kaplan and colleagues,[2] have reported on the discovery of compounds that have 5-HT_{2A} receptor activity and produce rodent behavioral proxies of anxiolytic and antidepressant effects but do not produce behavioral analogues of psychedelic activity.

Kaplan et al. compiled, with the use of computer modeling, a vast library of billions of virtual molecules with a shared scaffold that were then screened for specific properties, including selective affinity for the 5-HT_{2A} receptor. The investigators chemically synthesized and tested 17 of these molecules and reported the effects of 2 of them on mouse behavior. These 2 compounds did not elicit effects that are assumed to reflect psychedelic activity (head-twitch or change in prepulse inhibition), and one of them, (R)-70, showed positive effects across various rodent tests of antidepressant or anxiolytic action.

Despite good sensitivity, head-twitch response and prepulse inhibition are nonspecific markers of psychedelic activity, and the former has negligible face validity for psychedelic activity in humans. Prepulse inhibition has better validity; however, it is nonspecific for serotonergic psychedelic agents, which remains a limitation. Although (R)-70 showed selective agonist properties at the 5-HT_{2A} receptor, it showed no preferential affinity for the 5-HT_{2A} receptor over the 5-HT_{2B} or 5-HT_{2C} receptor. This feature is important, since 5-HT_{2C} antagonism has been linked to antidepressant effects; in fact, this association was shown by Kaplan et al.[2]

Although I would not wish to single out the Kaplan et al. study, dismiss the impressive drug-discovery methodology used in that study, or devalue translational science outright, it seems necessary to draw attention to research findings in humans and ask whether they could inspire reverse translation for more valid and effective preclinical modeling (Table 1). For example, the entropy of spontaneous cortical activity maps closely to actual psychedelic experience in humans[3] and is proving to be predictive of therapeutically relevant processes. What if such indexes could read out in real time, inform dose–response adjustment, and predict downstream markers of heterosynaptic plasticity?

It is important to appreciate that all modern clinical trials involving classic psychedelic drugs

Table 1. Research on Psychedelic Drugs.*

Research Focus	Research Involving Humans	Research Involving Animals
Extrapharmacologic factors	Statistical modeling shows roles for interrelational,[5] experiential, epistemic,[4] and other extrapharmacologic factors that moderate and mediate therapeutic response.	There is a dearth of research on the role of extrapharmacologic factors (such as environmental enrichment vs. adversity) in moderating or mediating response to 5-HT_{2A} receptor agonists.
Principal marker	Subjective reports are taken as the principal psychological measure of psychedelic action.	Head-twitch is used as a principal behavioral marker of psychedelic action. Regarding behavior, learning and cognitive flexibility paradigms may offer superior face validity.
Electrophysiological markers	Electrophysiological markers index the intensity of acute psychedelic action according to robustness, reliability, apparent selectivity, and ease of use.[3]	Electrophysiological markers that show good validity and predictive utility in research in humans should be used in research in rodents (i.e., a reverse-translational approach).
Evidence of psychedelic effects	There is no evidence from controlled studies that a 5-HT_{2A} receptor agonist compound can produce therapeutic responses without also producing psychedelic effects (in brain or behavior).	Evidence exists of novel 5-HT_{2A} receptor agonists that produce no psychedelic effects in rodents (e.g., head-twitch response) at the tested dose range but result in rodent behaviors that suggest, for example, antidepressive and anxiolytic effects.[2]

* 5-HT_{2A} denotes serotonin 2A receptor.

(i.e., agonists of the 5-HT_{2A} receptor) have included psychological support and environmental manipulation. Why are analogous variables not being measured, controlled, or manipulated in the studies in animals? Interactions between nonpsychedelic serotonergic drugs and environment have been shown in mouse models, and the robust neuroplastic effects of psychedelic agents imply a similar, if not greater, context dependency of effects. Indeed, the latest response-modeling work involving humans has identified experiential and extrapharmacologic predictors of therapeutic response, such as emotional release, psychological insight, and therapeutic rapport.[4,5] These factors could be examined in rodent models — for example, by means of learning paradigms and environmental manipulation.

Why are we seeing human research evidence and approaches being lost in translation? Is it because psychedelic therapy is an "inconvenient shape" for conventional medical modeling? It is worth noting that the forward (e.g., rodent-to-clinic) translational effort has yielded little in terms of psychiatric drug discovery over the past few decades, accounting, in part, for pharmaceutical industry departure from mental health research.

Is it so illogical to suggest that we take our first lessons from human experience? Is phenomenology really the weaker science? If (R)-70 or other putative nonpsychedelic psychedelics make it to the clinic, will they bear any relevance to psychedelic therapy? Can we feel confident that mental health care by means of drugs alone will solve the mental health burden?

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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