

# ‘Miracle cures’ in psychiatry?

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“I take very small doses of it regularly against depression and against indigestion, and with the most brilliant success.... it is only now that I feel I am a doctor, since I have helped one patient and hope to help more.”

– Sigmund Freud (May 7, 1884)<sup>1</sup>

For a patient with a major mental illness, the road to wellness is long and uncertain. The medications commonly used to treat mood and thought disorders can take weeks to months to start providing benefits, and they carry significant risks for adverse effects, such as weight gain, sexual dysfunction, and movement disorders. Patients often have to take psychotropic medications for the rest of their lives. In addition to these downsides, there is no guarantee that these medications will provide complete or even partial relief.<sup>2,3</sup>

Recently, there has been growing excitement about new treatments that might be “miracle cures” for patients with mental illness, particularly for individuals with treatment-resistant depression (TRD). Two of these treatments—ketamine-related compounds, and hallucinogenic drugs—seem to promise therapeutic effects that are vastly different from those of other psychiatric medications: They appear to improve patients’ symptoms very quickly, and their effects may persist long after these drugs have been cleared from the body.

Intravenous ketamine is an older generic drug used in anesthesia; recently, it has been used off-label for TRD and other mental illnesses. On March 5, 2019, the

FDA approved an intranasal formulation of esketamine—the S-enantiomer of ketamine—for TRD.<sup>4</sup> Hallucinogens have also been tested in small studies and have seemingly significant effects in alleviating depression in patients with terminal illnesses<sup>5</sup> and reducing smoking behavior in patients with tobacco use disorder.<sup>6,7</sup>

These miracle cures are becoming increasingly available to patients and continue to gain credibility among clinicians and researchers. How should we evaluate the usefulness of these new treatments? And how should we talk to our patients about them? To answer these questions, this article:

- explores our duty to our patients, ourselves, and our colleagues
- describes the dilemma
- discusses ways to evaluate claims made about these new miracle cures.

## Duty: Protecting and helping our patients

The physician–patient relationship is a fiduciary relationship. According to both common law and medical ethics, a physician who enters into a treatment relationship with a patient creates a bond of special trust and confidence. Such a relationship

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The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.



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### Clinical Point

**As clinicians, we have a duty to evaluate the safety and efficacy of new treatments that are available, whether or not they are FDA-approved**

requires a physician to act in good faith and in the patient's best interests.<sup>8</sup> As physicians, we have a duty to evaluate the safety and efficacy of new treatments that are available for our patients, whether or not they are FDA-approved.

We should also protect our patients from the adverse consequences of relatively untested drugs. For example, ketamine and hallucinogens both produce dissociative effects, and may carry high risks for patients who have a predisposition to psychosis.<sup>9</sup> We should protect our patients from any false hopes that might lead them to abandon their current treatment regimens due to adverse effects and imperfect results. At the same time, we also have a duty to acknowledge our patients' suffering and to recognize that they might be desperate for new treatment options. We should remain open-minded about new treatments, and acknowledge that they might work. Finally, we have a duty to be mindful of any financial benefits that we may derive from the development, marketing, and administration of these medications.

### Dilemma: The need for new treatments

This is not the first time that novel treatments in mental health have seemed to hold incredible promise. In the late 1800s, Sigmund Freud began to regularly use a compound that led him to feel "the normal euphoria of a healthy person." He wrote that this substance produced:

...exhilaration and lasting euphoria, which does not differ in any way from the normal euphoria of a healthy person. The feeling of excitement which accompanies stimulus by alcohol is completely lacking; the characteristic urge for immediate activity which alcohol produces is also absent. One senses an increase of self-control and feels more vigorous and more capable of work; on the other hand, if one

works, one misses that heightening of the mental powers which alcohol, tea, or coffee induce. One is simply normal, and soon finds it difficult to believe that one is under the influence of any drug at all.<sup>1</sup>

The compound Freud was describing is cocaine, which we now know is an addictive and dangerous drug that can in fact worsen depression.<sup>10</sup> Another treatment regarded as a miracle cure in its time involved placing patients with schizophrenia into an insulin-induced coma to treat their symptoms; this therapy was used from 1933 to 1960.<sup>11</sup> We now recognize that this practice is unacceptably dangerous.

The past is filled with cautionary tales of the enthusiastic adoption of treatments for mental illness that later turned out to be ineffective, counterproductive, dangerous, or inhumane. Yet, the long, arduous journeys our patients go through continue to weigh heavily on us. We would love to offer our patients newer, more efficacious, and longer-lasting treatments with fewer adverse effects.

### Discussion: How to best evaluate miracle cures

To help quickly assess a new treatment, the following 5 categories can help guide and organize our thought process.

#### 1. Evidence

What type of evidence do we have that a new treatment is safe and effective? Psychiatric research may be even more susceptible to a placebo effect than other medical research, particularly for illnesses with subjective symptoms, such as depression.<sup>12</sup> Double-blinded, placebo-controlled studies, such as the IV ketamine trial conducted by Singh et al,<sup>13</sup> are the gold standard for separating a substance's actual biologic effect from a placebo effect. Studies that do not include a control group should not be regarded as providing scientific evidence of efficacy.



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## 2. Mechanism

If a new compound appears to have a beneficial effect on mental health, it is important to consider the potential mechanism underlying this effect to determine if it is biologically plausible. A compound that is claimed to be a panacea for every symptom of every mental illness should be heavily scrutinized. For example, based on available research, ketamine's long-lasting effects seem to come from 2 mechanisms<sup>14,15</sup>:

- Activation of endogenous opioid receptors, which is also responsible for the euphoria induced by heroin and oxycodone.

- Blockade of *N*-methyl-D-aspartate receptors. *N*-methyl-D-aspartate receptor activation is a key mechanism by which learning and memory function in the brain, and blocking these receptors may increase brain plasticity.

Therefore, it seems plausible that ketamine could produce both short- and long-term improvements in mood. Hallucinogenic drugs are thought to profoundly alter brain function through several mechanisms, including activating serotonin receptors, enhancing brain plasticity, and increasing brain connectivity.<sup>16</sup>

## 3. Reinforcement

Psychiatric medications that are acutely reinforcing have significant potential for abuse. Antidepressants and mood stabilizers are not acutely rewarding. They don't make patients feel good right away. Medications such as stimulants and opioids do, and must be used with extreme care because of their abuse potential. The problem with acutely reinforcing medications is that in the long run, they can worsen depression by decreasing the brain's ability to produce endogenous opioids.<sup>17</sup>

## 4. No single solution?

A mental disorder is unlikely to have a single solution. Rather than regarding a new treatment as capable of rapidly alleviating every

symptom of a patient's illness, it should be viewed as a tool that can be helpful when used in combination with other treatments and lifestyle practices. In an interview with the web site STAT, Cristina Cusin, MD, co-director of the Intravenous Ketamine Clinic for Depression at Massachusetts General Hospital, said, "You don't treat an advanced disease with just an infusion and a 'see you next time.' If [doctors] replace your knee but [you] don't do physical therapy, you don't walk again."<sup>18</sup> To sustain the benefits of a novel medication, patients with serious mental illnesses need to maintain strong social supports, see a mental health care provider regularly, and abstain from illicit drug and alcohol use.

## 5. Context matters

For a medication to obtain approval to treat a specific indication, the FDA usually require 2 trials that demonstrate efficacy. Off-label use of generic medications such as ketamine may have benefits, but it is unlikely that a generic drug would be put through a costly FDA-approval process.<sup>19</sup>

When learning about new medications, remember that patients might assume that these agents have undergone a thorough review process for safety and effectiveness. When our patients request such treatments—whether FDA-approved or off-label—it is our responsibility as physicians to educate them about the benefits, risks, effectiveness, and limitations of these treatments, as well as to evaluate the appropriateness of a treatment for a specific patient's symptoms.

## Tempering excitement with caution

Our patients are not the only ones desperate for a miracle cure. As psychiatrists, many of us are desperate, too. New compounds may ultimately change the way we treat mental illness. However, we have an obligation to temper our excitement with caution by

## Clinical Point

If a new compound appears to have a beneficial effect, it is important to consider the potential mechanism underlying this effect

remembering past mistakes, and systematically evaluating new miracle cures to determine if they are safe and effective.

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### Clinical Point

**We have an obligation to temper excitement with caution by remembering past mistakes and evaluating new miracle cures**