HOW KETAMINE BECAME AN ANTIDEPRESSANT

Vincent Joralemon[†]

TABLE OF CONTENTS

DOI: https://doi.org/10.15779/Z38W08WH8B

† J.D. Candidate, University of California, Berkeley, School of Law, Class of 2024; Petrie-Flom Student Fellow, Harvard Law School. This article benefitted from helpful comments from Peter Menell, Allison Schmitt, and Caressa Tsai.

I. INTRODUCTION

This Article examines the anomalous story surrounding the use of ketamine to treat depression. Although first discovered, developed, and patented half a century ago (albeit for use as an anesthetic), use of ketamine is now seen by many clinicians as "one of the most significant advances in the field of depression" in recent years.[1] Yet challenges related to intellectual property protection, regulatory exclusivity and approval, and insurance coverage are hampering further research on and deployment of ketamine for depression treatment. Despite these obstacles, access to ketamine is expanding. This expansion creates concerns about a lack of oversight, but also showcases the ingenuity of clinicians and researchers working to broaden access to the drug.

Part II of this Article traces the history of the recognition of depression as a treatable condition and the development of treatment approaches during the mid to late 20th century. Part III discusses the promises and pitfalls of ketamine as a depression treatment. Part IV explores the complex institutional impediments to ketamine's wider study and use for depression. Part V analyzes how entrepreneurs and clinicians are innovatively expanding access to ketamine, despite these obstacles.

II. THE HISTORY OF DEPRESSION AND DEPRESSION THERAPIES IN THE UNITED STATES

Depression is one of the most prevalent diagnosed conditions in the world. Yet, clinicians have protean views on a precise definition and what constitutes effective treatment. Over the centuries, clinicians have implemented a wide range of physical and psychological interventions with varying degrees of success. However, pharmacologic advances in the 20th century saw marked improvements in treatment, which culminated in the widespread adoption of selective serotonin reuptake inhibitors (SSRIs). Despite these advances, gaps in treatment persisted. Scientists thus looked beyond the monoamine focus that defined mid-1900s antidepressant pharmaceutical interventions, precipitating a shift towards glutamate-modulating drugs like ketamine.

1. Ronald S. Duman & George K. Aghajanian, *Neurobiology of Rapid Acting Antidepressants: Role of BDNF and GSK-3β*, 39 NEUROPSYCHOPHARMACOLOGY 233, 233 (2014).

A. DEFINING DEPRESSION

Depression has been defined in various terms since at least the time of Hippocrates.[2] While the first and second editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), DSM-I (1952)[3] and DSM-II (1968),[4] contained diagnostic criteria for "depressive reaction" and "depressive neurosis," respectively, the fourth edition (DSM-IV) codified the modern definition of depression in 1994.[5] The DSM-IV defined depression based on the presence of clinical features such as depressed mood, fatigue, and loss of interest or pleasure.[6] The DSM-IV diagnosis also acknowledged the possibility of both psychological and biological causes.[7]

Major Depressive Disorder (MDD) is now the most commonly diagnosed mood disorder in the United States and one of the most prevalent disabilities in the world.[8] According to the DSM-V (the fifth and current iteration of the DSM), individuals with MDD exhibit a minimum of five depressive symptoms nearly every day for at least two weeks, which are newly presented or clearly worsened prior to the onset of the depressive episode.[9] The symptoms include a depressed mood, loss of interest or pleasure, fatigue, feelings of worthlessness, diminished ability to concentrate, and suicidal ideation.[10] For a diagnosis of MDD, these symptoms must rise to the level of significantly impairing social or occupational functioning, and must also not be attributed to substance abuse or better explained by other psychological disorders (e.g., schizophrenia, bipolar, etc.).[11]

---

2. Eugene S. Paykel, *Basic Concepts of Depression*, 10 DIALOGUES IN CLINICAL NEUROSCIENCE 279, 279 (2008). Hippocrates characterized depression as "melancholia" defined by "fears and despondencies." HIPPOCRATES, APHORISMS § 6.23.

3. AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (1st ed. 1952).

4. AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (2nd ed. 1968).

5. Paykel, *supra* note 2, at 280; AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 339 (4th ed. 1994).

6. Paykel, *supra* note 2, at 280–81.

7. *Id.*

8. Todd M. Hillhouse & Joseph H. Porter, *A Brief History of the Development of Antidepressant Drugs: From Monoamines to Glutamate*, 23 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 1, 1 (2015); Anna Beyeler, *Do Antidepressants Restore Lost Synapses?*, 364 SCI. 129, 129–30 (2019).

9. AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (5th ed. 2013).

10. *Id.*

11. *Id.*

B. THE EVOLUTION OF MODERN DEPRESSION THERAPIES

Since the early diagnoses of "melancholia," clinicians have explored a wide range of interventions to treat depression. Early interventions included plant extracts from poppy (opium), nightshade (belladonna), hemp, and St. John's wort.[12] These were often used alongside other psychotherapeutic measures, such as music, dancing, theatre, and sleep therapies.[13] The 1800s saw the evolution of pharmaceutical interventions for depression, with documented uses of bromine salts (1826), codeine (1832), chloral hydrate (1869), and paraldehyde (1882).[14] Finally, barbiturates, which work primarily through sedation, gained popularity in the late 1800s as treatments for "agitated" patients suffering from depression.[15]

The late 1800s also saw the advent of Western modern psychotherapy and Freudian psychoanalysis. Early psychoanalysts such as Freud and Jung pioneered therapeutic interventions that aimed to improve patients' suffering from a range of mental disorders, including depression.[16] In the 1920s, behaviorism gained traction as a remedy for depression, based on theories outlined by B. F. Skinner and others researching operant and classical conditioning.[17]

In the 20th century, clinicians began implementing physiological interventions for patients suffering from mental illness.[18] These included recreational, occupational, and physical treatments, including electroconvulsive therapy.[19] Then, in 1944, penicillin demonstrated efficacy in a large-scale clinical trial, launching a new era of pharmaceutical interventions for psychiatric illnesses.[20] Researchers were soon on the hunt for novel drug therapies to treat depression.[21]

---

12. T. R. Payk, *Treatment of Depression*, 7 J. GERIATRIC PSYCHIATRY 3, 3 (1994).
13. *Id.*
14. *Id.*
15. *Id.*
16. Suzanne K. Haddad et al., *Depression and Internally Directed Aggression: Genetic and Environmental Contributions*, 56 J. AM. PSYCHOANALYTIC ASS'N 515, 515–18 (2008); Warren Steinberg, *Depression: A Discussion of Jung's Ideas*, 34 J. ANALYTIC PSYCHOLOGY 339, 339–42 (1989).
17. Paulo Roberto Abren & Carlos E. Santos, *Behavioral Models of Depression: A Critique of the Emphasis on Positive Reinforcement*, 4 INT'L J. BEHAV. CONSULTATION & THERAPY 130 (2008).
18. CHRISTOPHER M. CALLAHAN & GERMAN E. BERRIOS, REINVENTING DEPRESSION: A HISTORY OF THE TREATMENT OF DEPRESSION IN PRIMARY CARE, 1940–2004 88–89 (2004).
19. *Id.* at 89.
20. *Id.* at 92.
21. *Id.* at 92.

As the field of pharmacology developed, researchers synthesized more drugs that helped alleviate the symptoms of mental illness. By the second half of the 20th century, antidepressant medications became the primary tools to combat depression.[22] Drugs such as Prozac and Lexapro proved inexpensive, effective, and relatively safe.[23]

Understanding the development and progression of these drug therapies sets the stage for the use of ketamine as an antidepressant today. Many of the discoveries associated with ketamine's antidepressant qualities were made possible by attentive researchers, who followed up based on observations of their trial patients. Amidst these stories, a recurrent theme of clinical diligence emerges, highlighting the value of thorough observation and controlled experimentation to pursue curious scientific leads. The following Sections provide a history of seven notable 20th century therapeutics that preceded ketamine's ultimate discovery as an antidepressant.

22. Joshua Gordon, *New Hope for Treatment-Resistant Depression: Guessing Right on Ketamine*, NAT'L INST. MENTAL HEALTH DIRECTOR'S MESSAGES (Aug. 13, 2019), https://www.nimh.nih.gov/about/director/messages/2019/new-hope-for-treatment-resistant-depression-guessing-right-on-ketamine.

23. *Id.*

Table 1: Notable 20th Century Antidepression Pharmacologic Therapeutics.

Drug	Indication	Year Discovered	FDA Approval for Depression	Years Used as an Antidepressant
Lithium	Depression, bipolar disorder	1948	1970	1970 – present
Monoamine Oxidase Inhibitors	Depression	1952	1958 (iproniazid)	1972 – present
Tricyclic Antidepressants	Depression, neuropathic pain, migraine, etc.	1951	1959 (imipramine)	1957 – present
Meprobamate	Anxiety	1950	1959	1959 – present
Benzodiazepines	Anxiety, insomnia, seizures, muscle relaxant, etc.	1950	1960	1960 – present
Diazepam	Anxiety, sedation, etc.	1959	1963	1963 – present
Selective Serotonin Reuptake Inhibitors	Depression, OCD, panic attacks, etc.	1972	1987	1986 – present

1. Lithium

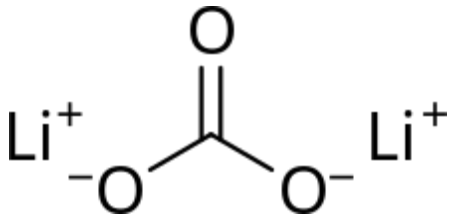
The discovery story of lithium as a therapeutic vividly demonstrates how coincidence followed by scientific diligence can lead to novel therapies. During World War II, Japanese troops captured and interned John F. Cade for over three years at a prisoner-of-war camp at Changi in Singapore.[24] A physician by training, Cade was put in charge of the camp's psychiatric section. While there, he noted a link between certain food deficiencies and diseases in some of the patients.[25] After the war, he homed in on one of those correlations to test his hypothesis that depression might result from "an abnormally low level" of uric acid in the bloodstream.[26]

24. Douwe Draaisma, *Lithium: The Gripping History of a Psychiatric Success Story*, 572 NATURE 584, 584 (2019).

25. *Id.*

26. Edward Shorter, *The History of Lithium Therapy*, 11 CAN. INSTS. HEALTH RSCH. 1, 2–3 (2013).

Figure 1: Lithium Carbonate, Used for Depression and Bipolar Disorder Treatments.[27]



Working out of an abandoned pantry in an under-resourced mental hospital near Melbourne, Cade explored his hypothesis by injecting uric acid into patients and monitoring the effects. Because uric acid is so toxic in the bloodstream, Cade used lithium urate (a known pharmacologic treatment for gout at the time) as an alternative in initial animal studies, because lithium can help modulate the toxicity of uric acid in humans.[28] Although his initial findings showed promise, Cade diligently sought to control for the additives he included in his treatments. To assess whether the lithium component of the treatment itself induced the positive results, Cade injected pure lithium into his subjects and observed a prolonged "placid state."[29] In 1948, after he experimented on himself and ten other patients with a range of psychiatric diagnoses, Cade reported significant improvements in the patients' "agitation."[30]

Cade's research spawned further investigation into the psychopharmacological effects of lithium, including a breakthrough random control study by Erik Strömgren in 1952, which showed that the drug served as a useful alternative to electroconvulsive therapy for patients with bipolar disorder.[31] The FDA approved lithium as a depression treatment in the 1970s, and today, millions of patients use it as a mood stabilizer for bipolar disorder.[32]

Lithium is largely credited with setting off the "psychopharmacological revolution" of the 1950s that eventually led to the discovery of numerous antipsychotics and antidepressants.[33] Although lithium is FDA-approved and primarily prescribed for patients with bipolar disorder, it is frequently used to

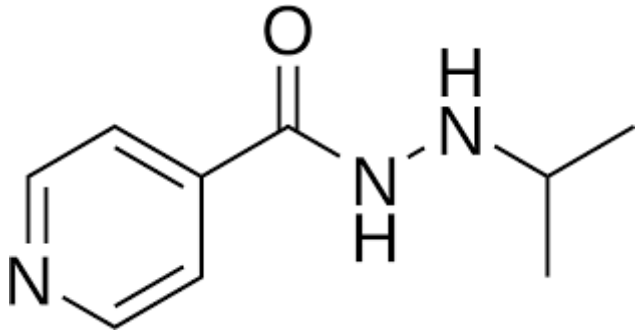
27. *Lithium (medication)*, WIKIPEDIA, https://en.wikipedia.org/wiki/Lithium_(medication) (last visited Nov. 1, 2023).
28. CALLAHAN & BERRIOS, *supra* note 18, at 95.
29. *Id.*
30. *Id.* at 95–96.
31. Shorter, *supra* note 26, at 3.
32. Draaisma, *supra* note 24, at 585.
33. *Id.*

treat depression.[34] Clinicians occasionally treat patients not responding to other antidepressants with lithium; some showcase promising results.[35] However, because of toxicity and efficacy concerns, it is typically not prescribed as an primary antidepressant.[36]

2. Monoamine Oxidase Inhibitors

The synthesis of monoamine oxidase inhibitors (MAOIs) follows a similar trajectory of observant clinicians exploiting unanticipated side effects of preexisting pharmaceuticals. In the aftermath of World War II, Germany had a large and inexpensive supply of hydrazine because the military used the compound as rocket fuel in the war.[37] Access to this compound led investigators to experiment with the use of hydrazine derivatives for a wide variety of applications, including treatment for tuberculosis.[38]

Figure 2: Iproniazid, the First MAOI Widely Used to Treat Depression.[39]



Clinicians using a hydrazine derivative for tuberculosis noted a peculiar side effect—many patients became euphoric when given the compound.[40] These unexpected effects motivated researchers to test the use of related compounds as a treatment for depression. Columbia University Professor Nathan Kline eventually established that these hydrazine derivatives—a class of drugs that came to be known as MAOIs—effectively treated depression in

34. Mark L. Ruffalo, *A Brief History of Lithium Treatment in Psychiatry*, PSYCHIATRIST (Oct. 12, 2017), https://www.psychiatrist.com/pcc/history-of-lithium-treatment-in-psychiatry/.

35. Tom Bschor, *Lithium in the Treatment of Major Depressive Disorder*, 74 DRUGS 855, 855 (2014).

36. Shorter, *supra* note 26, at 6.

37. CALLAHAN & BERRIOS, *supra* note 18, at 97.

38. *Id.*

39. *Iproniazid*, WIKIPEDIA, https://en.wikipedia.org/wiki/Iproniazid (last visited Nov. 1, 2023).

40. *Id.*

many patients.[41] One of these derivatives, iproniazid, was the first MAOI widely prescribed for depression.[42]

MAOIs help to alleviate depressive symptoms by blocking the monoamine oxidase enzyme responsible for breaking down neurotransmitters such as norepinephrine, serotonin, and dopamine.[43] Despite early promising treatment results, MAOIs caused undesirable side effects such as jaundice, headaches, and elevated blood pressure, causing the drugs to soon fall out of favor.[44] While doctors in the United States continue to prescribe MAOIs as antidepressants, these prominent side effects have prevented widespread adoption.[45]

3. Tricyclic Antidepressants

The discovery of tricyclic antidepressants (TCAs) continues this pattern of clinical diligence. The TCA story begins with chlorpromazine, a compound synthesized in 1951 as an antihistamine and potentiator for anesthetics.[46] As a medic in the French army, Henri Laborit discovered chlorpromazine's antidepressant effect while using the drug as a part of his "anesthetic cocktail."[47] Laborit observed that patients given chlorpromazine experienced "disinterest without loss of consciousness," and convinced his medical associates to try the drug with patients in a psychiatric setting.[48] Over repeated administrations, chlorpromazine effectively calmed "agitated" individuals. As a result, clinicians adopted the drug for a variety of psychiatric applications.[49]

Another researcher at an asylum in Switzerland, Roland Kuhn, also became interested in chlorpromazine. Faced with a limited budget, Kuhn contacted the pharmaceutical company Geigy to see if they had any available antipsychotic drugs to provide in exchange for his clinical data.[50] Geigy agreed, allowing Kuhn to commence experimental treatments for his schizophrenic patients with the chlorpromazine derivative imipramine.[51] Although

41. *Id.* at 98.

42. Hillhouse & Porter, *supra* note 8, at 4–5.

43. Tahrier Sub Laban & Abdolreza Saadabadi, *Monoamine Oxidase Inhibitors (MAOI)*, *in* STATPEARLS 1, 1 (2022).

44. CALLAHAN & BERRIOS, *supra* note 18, at 98.

45. *Id.*

46. *Id.* at 99.

47. Thomas A. Ban, *Fifty Years Chlorpromazine: A Historical Perspective*, 3 NEUROPSYCHIATRIC DISEASE & TREATMENT 495, 496 (2007).

48. *Id.*

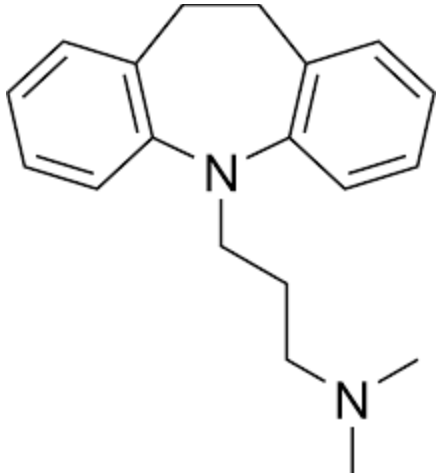
49. *Id.*

50. Charles Cahn, *Roland Kuhn, 1912–2005*, 31 NEUROPSYCHOPHARMACOLOGY 1096, 1096 (2006).

51. CALLAHAN & BERRIOS, *supra* note 18, at 99.

imipramine proved ineffective in his trials, he observed an excitatory effect that suggested to him that the drug might be used as an antidepressant.[52] In subsequent trials, Kuhn showed that imipramine was an effective antidepressant for many patients.[53]

Figure 3: Imipramine, the First FDA-Approved TCA.[54]

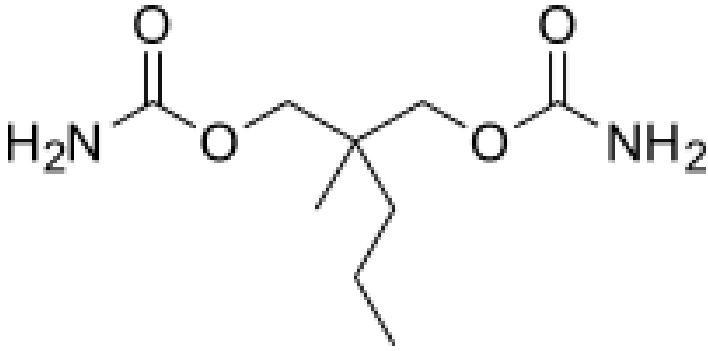


Imipramine established the class of "tricyclic antidepressants" (TCAs).[55] TCAs, like MAOIs, primarily aided the symptoms of depression through the reuptake inhibition of monoamines (namely, serotonin and norepinephrine).[56] The FDA approved imipramine for depression in 1959, and it—along with numerous other TCAs—is still prescribed for depression today.[57] Despite imipramine's efficacy, pharmaceutical companies did not aggressively market it or any other TCAs for depression because of concerns about time lag for efficacy and the narrow range of patients who might use the drug.[58]

52. *Id.*
53. *Id.* at 100.
54. *Imipramine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Imipramine (last visited Nov. 1, 2023).
55. Hillhouse & Porter, *supra* note 8, at 6.
56. *Id.*
57. *Id.*
58. Imipramine has dangerous interactions with other medications, is not recommended for patients with a history of heart problems, and can cause side effects such as blurry vision, dry mouth, and eye pain. For these reasons, it is seldom used as an appropriate treatment for depression. *See* CALLAHAN & BERRIOS, *supra* note 16, at 100.

4. Meprobamate, Benzodiazepine, Diazepam, and the Search for Effective Antidepressants for Wider Populations

Figure 4: Meprobamate, One of the First Widely Used GABA-Modulating Antidepressants.[59]



Despite promising results from lithium, MAOIs, and TCAs, none of these drugs dominated the depression market due to inadequate safety and efficacy profiles.[60] So, scientists continued their search for drugs that could treat depression for a wide range of populations with limited side effects. In the late 1950s, Wallace Laboratories began to market and sell meprobamate for patients with mild to moderate psychiatric conditions.[61] It soon became one of the most widely prescribed drugs in the world, inspiring other pharmaceutical companies to market competing drugs.[62] Unlike the MAOIs and TCAs, meprobamate binds to gamma-aminobutyric acid (GABA) receptors, modulating GABA levels.[63] GABA is a neurotransmitter that blocks specific signals in the central nervous system, producing a calming effect.[64]

59. *Meprobamate*, WIKIPEDIA, https://en.wikipedia.org/wiki/Meprobamate (last visited Nov. 1, 2023).

60. *Id.*

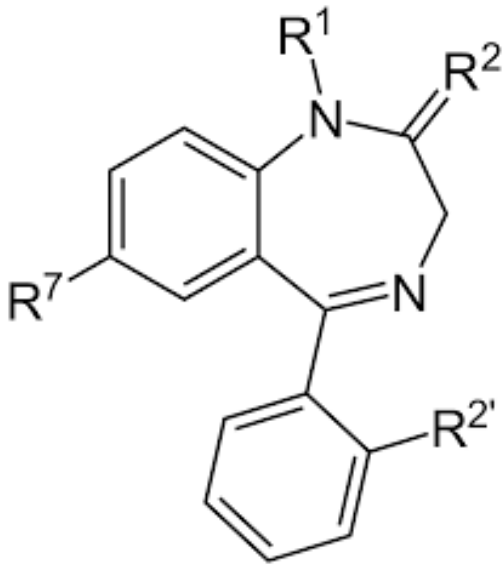
61. *Id.* at 106.

62. *Id.*

63. Manish Kumar & Glenn H. Dillon, *Assessment of direct gating and allosteric modulatory effects of meprobamate in recombinant $GABA_A$* receptor, 775 EUR. J. PHARMACOLOGY 149, 149 (2016).

64. Piril Hepsomali et al., *Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review*, 14 FRONTIERS IN NEUROSCIENCE 923, 923.

Figure 5: Benzodiazepine, the Most Frequently Prescribed Psychiatric Medication in the Late 1950s and Early 1960s.[65]



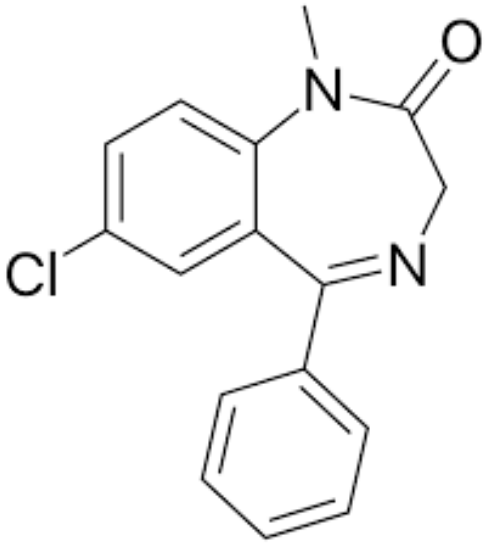
However, meprobamate was soon overtaken in popularity by another GABA-modulating drug—benzodiazepine. Leo Sternbach discovered benzodiazepine serendipitously, after accidentally leaving a meprobamate analog on the laboratory shelf for too long.[66] Benzodiazepine worked effectively to relax patients without sedation, and quickly overcame meprobamate as the most frequently prescribed psychiatric medication in the late 1950s and early 1960s.[67]

65. *Benzodiazepine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Benzodiazepine (last visited Nov. 1, 2023).

66. CALLAHAN & BERRIOS, *supra* note 18, at 107.

67. *Id.*

Figure 6: Diazepam (Marketed as Valium), Which Proved More Effective as a Tranquilizer than an Antidepressant.[68]



Sternbach continued researching antidepressants and developed diazepam in the 1960s.[69] This drug, marketed under the brand name "Valium," quickly overcame benzodiazepine as the most widely prescribed antidepressant in the United States, and the most commonly prescribed drug in the world.[70] Like benzodiazepine, Valium is a GABA modulator.[71] Valium hit a "sweet spot" for psychiatrists and primary care providers by proving effective for large populations of patients with relatively few side effects.[72] However, clinicians primarily used Valium as a tranquilizer rather than an antidepressant.[73]

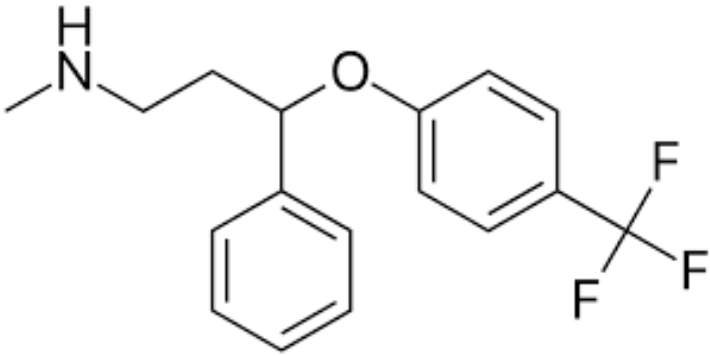
5. A Breakthrough Depression Treatment: Selective Serotonin Reuptake Inhibitors

Although physicians prescribed MOAIs, TCAs, and other pharmaceuticals such as Valium and lithium for depression through the 1970s, each drug

68. *Diazepam*, WIKIPEDIA, https://en.wikipedia.org/wiki/Diazepam (last visited Nov. 1, 2023).
69. *Id.*
70. *Id.*
71. Jaberpreet S. Dhaliwal et al., *Diazepam*, *in* STATPEARLS 1, 2 (Jan. 2022).
72. CALLAHAN & BERRIOS, *supra* note 18, at 107.
73. *Id.*

exhibited undesirable adverse effects or off-target pharmacological activity.[74] Researchers thus remained motivated to find a drug that could effectively treat a broad range of patients with depression while minimizing side effects.

Figure 7: Fluoxetine (Marketed as Prozac), Which Became the Most Prescribed Antidepressant in the United States by 1990.[75]



Inspired by the mechanisms of action of both the MAOIs and TCAs, pharmacologists at Eli Lilly spent much of the 1960s and 1970s searching for drug alternatives that might modulate neural serotonin levels.[76] At the time, various psychiatric conditions, including depression, were associated with reduced serotonin levels. So, the Eli Lilly researchers synthesized several compounds that they hypothesized might cause serotonin reuptake inhibition, which would lead to increased serotonin neurotransmission in patients suffering from depression.[77] Medicinal chemistry and animal studies eventually led to the discovery of a drug called fluoxetine, which served as a potent serotonin reuptake inhibitor with relatively few side effects in mice.[78]

Eli Lilly published the synthesis and activity of fluoxetine in 1974, and in 1983, Dista Products Company (a division of Eli Lilly) filed a New Drug

74. Laura Fitzpatrick, *A Brief History of Antidepressants*, TIME (Jan. 7, 2010), https://content.time.com/time/health/article/0,8599,1952143,00.html.

75. *Fluoxetine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Fluoxetine (last visited Nov. 1, 2023).

76. David T. Wong et al., *Prozac (Fluoxetine, Lilly 110140), the First Selective Serotonin Uptake Inhibitor and an Antidepressant Drug: Twenty Years Since its First Publication*, 57 LIFE SCIS. 411, 416 (1995).

77. *Id.*

78. *Id.*

Application for fluoxetine with the FDA.[79] The FDA approved fluoxetine for use in depression in 1987, and it hit the market under the brand name "Prozac."[80]

Prozac was immediately successful. By 1989, the drug brought in more money than had been spent annually on all antidepressants combined in 1987, adjusted for inflation.[81] By 1990, Prozac was the most prescribed antidepressant in the United States.[82] By 1993, clinicians prescribed the drug to over ten million people globally, and *Newsweek* noted that "Prozac has attained the familiarity of Kleenex and the social status of spring water."[83]

Several other SSRIs marketed for depression treatment soon entered the market: sertraline (Zoloft) in 1991; paroxetine (Paxil) in 1992; fluvoxamine (Luvox) in 1994; citalopram (Celexa) in 1998; and escitalopram (Lexapro) in 2002.[84] At last, scientists had developed antidepressants that safely and effectively worked on wide populations of individuals.

However, gaps in treatment remained. Although SSRIs presented relative improvements over prior treatment options, these compounds were not a "magic bullet" for all patients—many still failed to achieve depression remission even with SSRIs. Further, SSRIs come with a litany of potential side effects, with gastrointestinal disturbances, sexual dysfunction, weight gain, and sleep disturbances among the most commonly reported adverse events.[85]

79. David T. Wong et al., *The Discovery of Fluoxetine Hydrochloride (Prozac)*, 4 NATURE REVS. DRUG DISCOVERY 764, 770 (2005).

80. *Id.* at 770–71.

81. Fitzpatrick, *supra* note 74.

82. *Id.*

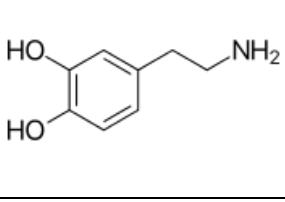
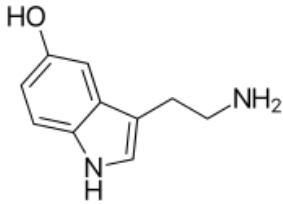
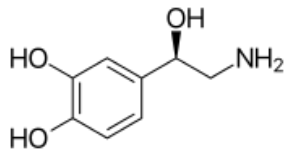
83. *Id.*

84. *See Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019839#3392 (Zoloft) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020031#3487 (Paxil) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020243#3660 (Luvox) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020822#4029 (Celexa) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021365#4290 (Lexapro) (last visited Oct. 6, 2023).

85. James M. Ferguson, *SSRI Antidepressant Medications: Adverse Effects and Tolerability*, 3 J. CLINICAL PSYCHIATRY 22, 24–25 (2001).

6. The Monoamine Hypothesis

Figure 8: The Primary Monoamines, the Target of Most 20th Century Antidepressants.[86]

		
Dopamine	Serotonin	Norepinephrine

In the wake of the SSRI explosion, clinicians solidified the "monoamine hypothesis" of depression.[87] By the 2000s, nearly all known antidepressants targeted monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine.[88] Proponents of the theory postulated that drugs targeting those neurotransmitters should be the primary means for treating depression.[89]

The post-SSRI world saw some novel antidepressant innovations, including changes to: dosing (e.g., extended release and sustained release mechanisms); monoamine targets (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs]); and receptor effect (e.g., serotonin agonism instead of reuptake inhibition).[90] But while scientists accomplished incremental improvements with the antidepressant efficacy of these drugs in the 1980s and early 1990s, by the early 2000s, researchers were unable to significantly improve on the efficacy of existing antidepressants.[91] There are several hypotheses for this stalled progress, and many believed that monoamine-targeting drugs had reached a ceiling in terms of antidepressant capacity.[92]

86. *Monoamine Neurotransmitter*, WIKIPEDIA, https://en.wikipedia.org/wiki/Monoamine_neurotransmitter (last visited Nov. 1, 2023).

87. Robert M. A. Hirschfeld, *History and Evolution of the Monoamine Hypothesis of Depression*, 61 J. CLINICAL PSYCHIATRY 4, 4–6 (2000). Monoamines are named for the single amine group in their structure.

88. These include serotonin-norepinephrine reuptake inhibitors (SNRIs), which inhibit reuptake of norepinephrine as well as serotonin. As a result, SNRIs have a more stimulating effect than SSRIs. *Id.*

89. Raleigh McElvery, *The Past, Present and Future of Using Ketamine to Treat Depression*, SMITHSONIAN (May 24, 2022), https://www.smithsonianmag.com/science-nature/a-brief-history-of-ketamines-use-to-treat-depression-180980106/.

90. Hillhouse & Porter, *supra* note 8, at 6–7.

91. *Id.*

92. *Id.* at 7.

Motivated by the desire to develop drugs that worked with a broader range of individuals, had increased efficacy, and threatened fewer side effects, researchers began to question the simplicity of the monoamine hypothesis.[93]

7. The Glutamate Hypothesis

In the 1990s, many scientists turned their attention to glutamate, an excitatory neurotransmitter, as a potential target for the next generation of antidepressants. Glutamate is the primary excitatory neurotransmitter in the brain.[94] It activates neurons that drive a wide range of behaviors and is also a necessary precursor to the synthesis of GABA. As a "calming" neurotransmitter involved in sleep, relaxation, anxiety regulation and muscle function, GABA seemed to be a promising drug target.[95]

Research starting in the 1990s showed that patients with depression had increased concentrations of glutamate in blood plasma and cerebrospinal fluid.[96] Additionally, patients who experienced successful remission through antidepressants exhibited decreases in glutamate concentration throughout their treatment.[97] These results suggested that while monoamine-based treatments like SSRIs and SNRIs impacted the glutamatergic system in some way, other drugs could likely treat depression through alternative approaches.

Scientists hypothesized that one of the receptors that glutamate binds, N-methyl-D-aspartic acid (NMDA), could be a promising drug target. Several studies indicated changes to the NMDA receptor in patients with depression, leading scientists to hypothesize that NMDA receptor-modulating antidepressants could revolutionize the monoamine-dominated paradigm of the post-SSRI clinical landscape.[98] A paper published by Robert Berman, Dennis Charney, John Krystal, and others at Yale University in 2000 showed that ketamine, an NMDA antagonist that had previously been used as an anesthetic, might be one such drug.[99]

---

93. *Id.* at 4.

94. Yun Zhou & Niels C. Danbolt, *Glutamate as a Neurotransmitter in the Healthy Brain*, 121 J. NEURAL TRANSMISSION 799, 799–800 (2014).

95. Cleveland Clinic Health Library, *Glutamate*, CLEVELAND CLINIC (Apr. 25, 2022), https://my.clevelandclinic.org/health/articles/22839-glutamate.

96. Hillhouse & Porter, *supra* note 8, at 10.

97. Amir Garakani et al., *Cerebrospinal Fluid Levels of Glutamate and Corticotropin Releasing Hormone in Major Depression Before and After Treatment*, 146 J. AFFECTIVE DISORDERS 262, 262 (2013).

98. *See, e.g.*, Michelle J. Chandley et al., *Elevated gene Expression of Glutamate Receptors in Noradrenergic Neurons from the Locus Coeruleus in Major Depression*, 17 INT'L J. NEUROPSYCHOPHARMACOLOGY 1, 1–2 (2014).

99. Robert M. Berman et al., *Antidepressant Effects of Ketamine in Depressed Patients*, 47 SOC'Y BIOLOGICAL PSYCHIATRY 351, 351–54 (2000).

C. TREATMENT-RESISTANT DEPRESSION: GAPS IN DEPRESSION TREATMENT

One of the chief issues facing depression researchers in the late 1990s and early 2000s was the prevalence of patients with treatment-resistant depression (TRD). Clinicians categorize patients with MDD who do not respond to one or more antidepressant treatment as having TRD.[100] Despite several treatment options like SSRIs, MAOIs, and TCAs, 34–46% of MDD patients still do not adequately respond to antidepressant treatment.[101] Even amongst those who recover from a depressive episode, 50–80% will experience symptom recurrence (usually within five years of the initial episode).[102] Likewise, even for patients who do respond to currently available treatments, most experience a delayed onset of four to twelve weeks before adequate symptom remission.[103]

The current method of treatment for patients with TRD is called Sequence Treatment Alternatives to Relieve Depression (STAR*D).[104] STAR*D is a four-step escalating treatment plan: patients start with SSRIs and move to other antidepressant drugs (e.g., TCAs) until they experience remission.[105] The vast majority of these antidepressants target only monoamine neurotransmitters (including serotonin, norepinephrine, and dopamine).[106]

Despite the range of possible treatment options, over 30% of patients do not sufficiently respond to these interventions.[107] The toll of such poor treatment efficacy is extraordinary. In the United States, 36.7% of individuals diagnosed with MDD are either unemployed or out of the labor force, and in 2018, the total economic impact of MDD was $326 billion.[108]

---

100. Hillhouse & Porter, *supra* note 8, at 2.

101. *Id.*

102. Stephanie L. Burcuso & William G. Iacono, *Risk for Recurrence in Depression*, 27 CLINICAL PSYCHOLOGY REV. 959, 960 (2007).

103. Hillhouse & Porter, *supra* note 8, at 2–3.

104. *Id.* at 3.

105. Step (1) of the STAR*D plan starts patients on an antidepressant for 12–14 weeks. If a patient does not achieve remission, they move on to step (2), where they either switch to a new antidepressant or take an additional antidepressant on top of their step (1) treatment. Those who do not achieve remission in step (3), where they again either switch to a new antidepressant or take an additional one on top of their existing treatment. Those who do not achieve remission through step (3) move on to step (4), and are considered to have TRD. These patients are moved on to a new antidepressant, often an MAOI or another treatment that has not yet been a part of their plan *See generally* Maurizio Fava et al., *Background and Rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study*, 26 PSYCHIATRIC CLINICS N. AM. 457 (2003).

106. McElvery, *supra* note 89.

107. *Id.*

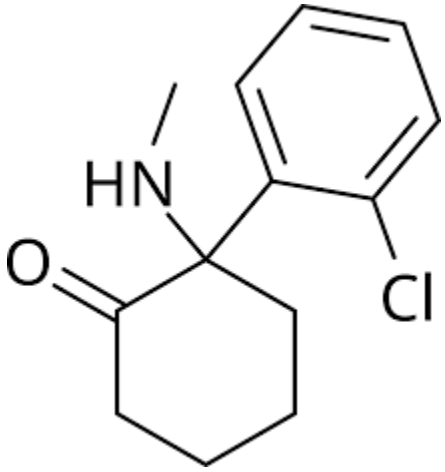
108. Paul E. Greenberg et al., *The Ecobonic Burden of Adults with Major Depressive Disorder in the United States (2019)*, 10 ADVANCES THERAPY 1, 2 (2023); Debra Lerner et al., *Research on the*

III. HISTORY OF KETAMINE

Discovered in the 1950s, ketamine's journey from a phencyclidine (PCP) derivative to a widely used anesthetic follows a similar pattern traced by many of the pharmaceuticals discussed in Part II, *supra*. The drug gained popularity as an anesthetic in surgical settings throughout the latter part of the 20th century. Researchers who observed ketamine's unexpected antidepressant effects in the 1990s helped to initiate an exploration into the drug's use outside of its previous analgesic purposes. This research led to what many clinicians heralded as "one of the most significant advances in the field of depression in recent years" as ketamine provided a much-needed leap forward for treatment of TRD.[109]

A. DISCOVERY AND INITIAL USE

Figure 9 Ketamine.[110]



Initially synthesized at Parke-Davis in 1956, ketamine proved to be an effective anesthetic. However, the drug's undesirable side effects limited the drug's widespread use. Ironically, these same dissociative side effects helped to propel ketamine's recreational use, leading to heightened government regulations.

Tufts Be Well at Work Program for Employees with Depression: 2005–2020, 72 PSYCHIATRIC SERVS. 1441, 1467–68 (2021).

109. Duman & Aghajanian, *supra* note 1, at 233.

110. *Ketamine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Ketamine (last visited Nov. 1, 2023).

1. Synthesis at Parke-Davis

On March 26, 1956, while working for the pharmaceutical company Parke-Davis, V. Harold Maddox first synthesized phencyclidine (PCP) through his discovery of a new chemical Grignard reaction.[111] Maddox shared his findings with his Parke-Davis colleague, Graham Chen. On September 11, 1958, Chen found that use of PCP created a drunken state in rodents but an immobilized state in pigeons.[112] This led to further animal experimentation with PCP, where scientists found similarly "unusual" results.[113] Curious to explore the compound further, the Parke-Davis researchers set about conducting more comprehensive animal studies to understand the full range of PCP's pharmacological impact.[114]

In the early 1960s, Chen and Maddox contacted Maurice H. Seevers, who was the Head of Pharmacology at the University of Michigan; Seevers agreed to be their pharmacology consultant.[115] Parke-Davis then collaborated with Ferdinand E. Greifenstein, who was the Chair of Anesthesiology at Wayne State University in Detroit, to conduct human trials of PCP at Detroit Receiving Hospital.[116] The clinical trials found PCP to be an effective and safe anesthetic, but some patients experienced severe and prolonged post-surgery emergence delirium.[117]

Although this prolonged delirium was not acceptable, PCP still proved an effective anesthetic, so Cal Bratton, Head of Pharmaceutical Research at Parke-Davis, approved further synthesis of related compounds.[118] Calvin Stevens—a Professor of Organic Chemistry at Wayne State University and a chemical consultant to Parke-Davis—synthesized a PCP derivative that proved an effective anesthetic in animal models without the long-lasting delirium side effects of PCP.[119] This chemical, known then as CI-581, was eventually named "ketamine."[120]

111. V. Harold Maddox et al., *The Synthesis of Phencyclidine and Other 1-Arylcyclohexylamines*, 8 J. MED. CHEMISTRY 230 (1965).

112. Edward F. Domino, & David S. Warner, *Taming the Ketamine Tiger*, 113 ANESTHESIOLOGY 678, 679 (2010).

113. Graham Chen et al., *The Pharmacology of 1-(1-Phenylcyclohexyl) Piperidine-HCl*, 127 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 241, 241 (1959).

114. *Id.*

115. Domino & Warner, *supra* note 112, at 679.

116. Ferdinand E. Greifenstein et al., *A Study of 1-Aryl Cyclo Hexyl amine for Anesthesia*, 37 ANESTHESIA & ANALGESIA 283 (1958).

117. Domino & Warner, *supra* note 112, at 679.

118. *Id.*

119. *Id.*

120. *Id.*

Edward Domino and Guenter Corssen, two University of Michigan professors working at the Parke Davis Research Unit at Jackson Prison in Michigan, intravenously administered the first human dose of ketamine on August 3, 1964.[121] The drug proved an effective anesthetic with minimal delirium side effects.[122] However, many subjects described feeling "spaced out" like they were "floating in outer space," with no feeling in their arms and legs.[123] Concerned about clinicians classifying these responses as "schizophrenomimetic" (hampering the drug's marketability), Parke-Davis researchers instead described ketamine as a "dissociative anesthetic."[124] The label stuck, and ketamine soon acquired approval for clinical trials.

2. Clinical Trials and FDA Approval

Clinicians published the first clinical study of ketamine as a human anesthetic in 1966.[125] The drug proved particularly safe because, as opposed to opiate-based anesthetics, patients in a ketamine-induced dissociative state maintained both an airway reflex and respiratory drive.[126] Corseen and Domino's initial human studies with ketamine showed that ketamine could produce rapid and effective anesthesia with a limited duration of effect that could safely be re-administered for prolonged surgical operations.[127]

The FDA approved the first preparation of ketamine in 1970 under the name "Ketalar" as a short-acting anesthetic in humans.[128] The drug was, and still is, widely employed in human and veterinary medicine.[129] In clinical settings, the drug is typically administered intravenously, although several alternate delivery routes exist.[130]

3. Recreational Use and Abuse Potential

Ketamine also became a popular recreational drug in the mid-1990s.[131] The drug is typically used at subanesthetic doses, which produces thirty to sixty

121. *Id.*

122. Linda Li & Phillip E. Vlisides, *Ketamine: 50 Years of Modulating the Mind*, 10 FRONTIERS HUM. NEUROSCIENCE 1, 2 (2016).

123. Domino & Warner, *supra* note 112, at 679.

124. *Id.* at 680.

125. Guenter Corssen & Edward Domino, *Dissociative Anesthesia: Further Pharmacologic Studies and First Clinical Experience with the Phencyclidine Derivative CI-581*, 45 ANESTHESIA & ANALGESIA 29 (1966).

126. Edward F. Domino et al., *Pharmacologic Effects of CI-581, A New Dissociative Anesthetic, in Man*, 6 CLINICAL PHARMACOLOGY & THERAPEUTICS 279, 319 (1965).

127. Li & Vlisides, *supra* note 122, at 2.

128. *Id.*

129. Domino & Warner, *supra* note 112, at 678.

130. Li & Vlisides, *supra* note 122, at 2–3.

131. Hillhouse & Porter, *supra* note 8, at 12.

minutes of perception distortion, mood and body image changes, and reality dissociation.[132] Its recreational use is limited; an estimated 0.19% of U.S. adults used ketamine in 2019.[133] However, as a result of its increased recreational use, ketamine became a Schedule III non-narcotic substance under the Controlled Substances Act in 1999.[134]

Studies indicate that ketamine can be addictive and can cause severe bladder damage if taken chronically in high doses.[135] Although ketamine (compared to other "club drugs" like MDMA and cocaine) has a relatively mild safety profile, high doses can cause cardiovascular and respiratory toxicity.[136] Likewise, ketamine's dissociative subjective effects can cause those taking the drug to experience physically traumatic events. Death by falls from height, driving accidents, and extended exposure are all major contributors to the drug's death rate.[137]

B. MECHANISM OF ACTION AND SAFETY PROFILE

David Lodge, of the Royal Veterinary College in London, initially proposed a theory for ketamine's mechanism of action in 1982. Lodge used feline models to assert that ketamine caused a selective depression of polysynaptic reflexes via antagonism of NMDA receptors.[138] Further research confirmed that ketamine binds to an ion channel site in the NMDA receptor complex.[139] Interestingly, ketamine has weak binding affinity for dopamine, norepinephrine, and serotonin transporters, which suggests a dramatically different mechanism of action than the monoamine modulators that previously defined the antidepressant landscape.[140]

Ketamine's overall safety profile and relatively low risk of overdose raises the question of why it is not more widely used as an anesthetic, especially

132. DEP'T JUST./DRUG ENFORCEMENT ADMIN., DRUG FACT SHEET KETAMINE (2020), https://www.dea.gov/sites/default/files/2020-06/Ketamine-2020.pdf [hereinafter Ketamine Fact Sheet].

133. R. Andrew Yockey, *Past-Year Ketamine Use: Evidence from a United States Population, 2015–2019*, 55 J. PSYCHOACTIVE DRUGS 134, 136 (2023).

134. Ketamine Fact Sheet, *supra* note 132.

135. Chris Hamby, *A Fraught New Frontier in Telehealth: Ketamine*, N.Y. TIMES (Feb. 20, 2023), https://www.nytimes.com/2023/02/20/us/ketamine-telemedicine.html.

136. John Martin Corkery et al., *Recreational Ketamine-Related Deaths Notified to the National Programme on Substance Abuse Deaths, England 1997–2019*, 35 J. PSYCHOPHARMACOLOGY 1324, 1329 (2021).

137. *Id.*

138. Domino & Warner, *supra* note 112, at 681.

139. Duman & Aghajanian, *supra* note 1, at 233.

140. Mitsuhiro Nishimura et al., *Ketamine Inhibits Monoamine Transporters Expressed in Human Embryonic Kidney 293 Cells*, 88 ANESTHESIOLOGY 768, 773 (1998).

considering the risks of addiction and overdose associated with analgesic and anesthetic opioids use. However, ketamine has a number of physiological side effects, including cystitis and urinary tract degeneration—although these are mostly seen with regular users.[141] More importantly, the psychoactive properties associated with ketamine are likely impeding its widespread adoption as an anesthetic.[142] Even at subanesthetic levels, patients given ketamine may experience unpleasant dissociative symptoms, including feelings of intoxication, somatosensory alteration, depersonalization, delusion, and disorientation.[143] While doctors attempt to mediate these effects with benzodiazepines or α_2-adrenergic receptor agonists (e.g., clonidine), clinicians remain unable to completely remove ketamine's psychotropic side effects.[144] Interestingly, ketamine's psychoactive effects, while undesirable for anesthetic applications, make the drug an interesting candidate for depression treatment.

C. KETAMINE AS AN ANTIDEPRESSANT

Researchers' discovery of ketamine's antidepressant qualities came about amidst frustration in progress towards improving antidepressant therapies. Through diligent follow-up of unexpected clinical results, researchers representing a wide range of public, private, and academic research initiatives helped to ascertain the drug's promise as a revolutionary depression therapy.

1. Discovery of Ketamine's Antidepressant Effects

Spurred by a desire to look beyond the monoamine-targeting drugs of the 20th century, researchers from a collaborative university and government effort began investigating unexpected antidepressant anecdotes from ketamine use in clinical settings. As a glutamate-modulating drug, ketamine proved an excellent target to spur an impressive leap in the field.

a) The Shift to Glutamate-Modulating Drug Targets

As discussed in Part II, *supra*, efficacy improvements for the SSRI, MAOI, and TCA classes of antidepressant therapies began to stall in the 1990s. In response, researchers at Yale School of Medicine, including Robert Berman, John Krystal, and Dennis Charney, hypothesized that pharmaceuticals needed

141. Peggy Sau-Kwan Chu et al., *The Destruction of the Lower Urinary Tract by Ketamine Abuse: A New Syndrome?*, 102 BJU INT'L 1616 (2008); Eric Kutscher & Richard E. Greene, *Ketamine Cystitis: An Underrecognized Cause of Dysuria*, 37 J. GENERAL INTERNAL MED. 1286, 1287 (2022).

142. *See* John H. Krystal et al., *Subanesthetic Effects of the Noncompetitive NMDA Antagonist, Ketamine, in Humans*, 51 ARCHIVES GEN. PSYCHIATRY 199, 200 (1994).

143. Edith Pomarol-Clotet et al., *Psychological Effects of Ketamine in Healthy Volunteers*, 189 BRITISH J. PSYCHIATRY 173, 176–78 (2018).

144. Marieke Niesters et al., *Ketamine for Chronic Pain: Risks and Benefits*, 77 BRIT. J. CLINICAL PHARMACOLOGY 357, 364 (2014).

to shift away from monoamine (e.g., dopamine, serotonin) targets.[145] Based on some promising studies and clinical anecdotes, the Yale researchers hypothesized that glutamate might serve as a catalyst for robust improvements in the fight against depression.[146] Many such drugs existed at the time, and although ketamine is a glutamate-modulating drug, it took a confluence of serendipitous findings and clinical diligence for researchers to hone in on the drug as an antidepressant.[147]

b) Yale Medicine / NIMH Collaboration: Early Antidepressant Findings

The National Institute of Mental Health (NIMH) funded much of glutamate-targeted antidepressant investigative work at Yale.[148] Starting in the 1990s, the NIMH established an Intramural Research Program (IRP) on the NIH campus in Bethesda, Maryland.[149] The IRP worked closely and continued funding the ketamine research work at Yale Medicine; clinicians from both organizations co-published much of their research in the 1990s and 2000s.[150]

At Yale, Berman, Charney, and Krystal recruited Husseini K. Manji and Carlos Zarate for the mood disorders research program with the IRP. Both researchers proved critical to the development of ketamine as an antidepressant.[151] The IRP program ultimately included researchers from several institutions, including clinicians from Mount Sinai Hospital in New York City.[152]

Throughout the 1990s, researchers in the IRP program used very low dose intravenous (IV) injections of ketamine as a potential model of schizophrenia, in order to develop treatments for the condition.[153] Unexpectedly, these subanesthetic doses of ketamine had antidepressant effects on patients with

145. Gordon, *supra* note 22.
146. *Id.*
147. *Id.*
148. *Id.*
149. *Id.*
150. *Id.*
151. *Id.*
152. *Id.*
153. *See* Krystal et al., *supra* note 142; John H. Krystal et al., *Interactive Effects of Subanesthetic Ketamine and Subhypnotic Lorazepam in Humans*, 135 PSYCHOPHARMACOLOGY 213 (1998); John H. Krystal et al., *Dose-Related Ethanol-Like Effects of the NMDA Antagonist, Ketamine, in Recently Detoxified Alcoholics*, 55 ARCHIVES GEN. PSYCHIATRY 354 (1998); John H. Krystal et al., *Interactive Effects of Subanesthetic Ketamine and Haloperidol in Healthy Humans*, 145 PSYCHOPHARMACOLOGY 193 (1999); John H. Krystal et al., *Dissociation of Ketamine Effects on Rule Acquisition and Rule Implementation: Possible Relevance to NMDA Receptor Contributions to Executive Cognitive Functions*, 47 BIOLOGICAL PSYCHIATRY 137 (2000).

depression.[154] Much like in the development of lithium, MAOIs, and TCAs, the observed antidepressant effects prompted further research into the impact that ketamine, an NMDA-receptor antagonist that impacted glutamate concentrations, might have in the treatment of depression.

In 2000, the Yale researchers showed in a small randomized, double-blind study that a single subanesthetic dose of ketamine improved depression in less than twenty-four hours, and in some cases led to a near complete recovery.[155] These results were particularly significant in light of the standard of care for depression—the available antidepressant drugs at that time required four to six weeks for their impacts to be measurable.[156] Importantly, this was also the first clinical study to demonstrate that glutamatergic drugs may be effective for the treatment of depression.[157]

In the wake of the Yale study, several other researchers reported similar antidepressant effects with ketamine administered to patients with depression. One study found an antidepressant impact in the postoperative period for surgical patients who received ketamine as an anesthetic.[158] Another reported promising results from low-dose ketamine infusions in two individuals who suffered from major depressive disorder.[159]

c) Ketamine for Treatment-Resistant Depression: Zarate (2006)

Despite these promising initial findings, skepticism persisted into the mid-2000s about whether ketamine's antidepressant effects could be used on patients suffering from TRD. Through the NIHM IRP collaboration, Zarate, Manji, and Charney planned the first study with ketamine in TRD.[160] The stakes were high—if the drug successfully treated TRD, that constituted a massive breakthrough for the millions of individuals suffering from TRD worldwide.

Zarate, Charney, and Manji conducted a randomized, placebo-controlled, double-blind crossover study from 2004 to 2006 on eighteen patients who previously failed to achieve success following treatment with at least six other

154. Berman et al., *supra* note 99, at 351–54.

155. *Id.*

156. Herbert C. Schulberg et al., *Treating Major Depression in Primary Care Practice: An Update of the Agency for Health Care Policy and Research Practice Guidelines*, 55 ARCHIVES GEN. PSYCHIATRY 1121, 1124 (1998).

157. Hillhouse & Porter, *supra* note 8, at 14.

158. Akira Kudoh et al., *Antidepressant Treatment for Chronic Depressed Patients Should Not Be Discontinued Prior To Anesthesia*, 49 CAN. J. ANESTHESIA 132 (2002).

159. Graeme E. Correll & Graham E. Futter, *Two Case Studies of Patients with Major Depressive Disorder Given Low-Dose (Subanesthetic) Ketamine Infusions*, 7 PAIN MED. 92 (2006).

160. Gordon, *supra* note 19.

antidepressant therapies.[161] The patients received two low-dose IV infusions of either saline (placebo) or ketamine infusions, administered one week apart.[162]

The study results, published in 2006 by Zarate and the other IRP researchers, were jaw-dropping. 71% of the patients experienced antidepressant effects after only one infusion, and 29% achieved full remission of TRD.[163] Adverse effects for patients receiving ketamine were relatively minor.[164] For patients with no otherwise-effective antidepressants available, this was a massive discovery.

d) Post-Zarate (2006) Research

Zarate's 2006 study prompted further research into ketamine's lasting effects on TRD.[165] Since the 2006 study, researchers funded by the NIMH IRP have conducted numerous studies to further understand the mechanisms by which ketamine may produce antidepressant effects. Several studies found that ketamine infusions provided an average of eighteen to nineteen days of relief from depression symptoms in TRD patients, with a number of patients experiencing remission that lasted through the months- or years-long publication of each study.[166] Several post-Zarate (2006) studies of ketamine's antidepressant effects are found in Table 2, *infra.*

161. Carlos A. Zarate Jr, et al., *A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression*, 63 JAMA PSYCHIATRY 856, 858 (2006).

162. *Id.* at 857.

163. *Id.* at 858–60.

164. *Id.* at 861.

165. *Dr. Carlos Zarate Carries the Torch toward FDA Approval of Rapid-Acting Antidepressant*, BRAIN & BEHAVIOR RSCH. FOUND. (Mar. 13, 2014) https://www.bbrfoundation.org/content/dr-carlos-zarate-carries-torch-toward-fda-approval-rapid-acting-antidepressant.

166. Marije aan het Rot et al., *Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression*, 69 BIOLOGICAL PSYCHIATRY 139–45 (2010); James W. Murrough et al., *Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression*, 74 BIOLOGICAL PSYCHIATRY 250, 254 (2013).

Table 2: Notable Studies on Ketamine's Antidepressant Effects, Post-Zarate (2006).

Study	Method of Treatment (Dosage)	Condition Targeted	Results
Matthew et al., 2010	IV Infusion (racemic[167] ketamine 0.5 mg/kg)	Major Depressive Disorder (MDD)	65% of patients experienced remission of depression symptoms within twenty-four hours of ketamine infusion; 50% experienced remission through the seventy-two-hour mark.[168]
Murrough et al., 2013	IV Infusion (racemic ketamine 0.5 mg/kg)	TRD	Antidepressant effect in 70.8% of patients for an average of eighteen days; four participants remained in remission through publication.[169]
Price et al., 2009	IV Infusion (racemic ketamine 0.5 mg/kg)	Suicidal Ideation	Rapid reduction in suicidal ideation/cognition in patients with TRD; reductions were sustained for twelve days by repeated-dose ketamine.[170]
Lally et al., 2014	IV Infusion (racemic ketamine 0.5 mg/kg)	Treatment-Resistant Bipolar Depression	Rapid reduction of depressive symptoms within forty minutes; remission persisted up to fourteen days.[171]
Irwin & Iglewicz, 2010	Oral (racemic ketamine 0.5 mg/kg)	Major Depressive Disorder (MDD)	Single oral dose of low-dose ketamine provided rapid and moderately sustained symptom relief for depressed patients receiving hospice care.[172]

167. "Racemic" refers to a mixture of ketamine with equal parts of the S- and R-enantiomer of the molecule. For a detailed explanation, see Section III.C.3.b *infra*.

168. Sanjay J. Mathew et al., *Riluzole for Relapse Prevention Following Intravenous Ketamine in Treatment-Resistant Depression: A Pilot Randomized, Placebo-Controlled Continuation Trial*, 13 INT'L J. NEUROPSYCHOPHARMACOLOGY 71, 76 (2010).

169. Murrough et al., *supra* note 165, at 254.

170. Rebecca B. Price et al., *Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression*, 66 BIOLOGICAL PSYCHIATRY 522, 522 (2009).

171. Níall Lally et al., *Anti-Anhedonic Effect of Ketamine and its Neural Correlates in Treatment-Resistant Bipolar Depression*, 14 TRANSLATIONAL PSYCHIATRY 1, 6 (2014)

172. Scott A. Irwin & Alana Iglewicz, *Oral Ketamine for the Rapid Treatment of Depression and Anxiety in Patients Receiving Hospice Care*, 13 J. PALLIATIVE MED. 903, 903 (2010).

Lara et al., 2013	Low-Dose Sublingual (racemic ketamine 10 mg)	Major Depressive Disorder (MDD), Bipolar Disorder	Sublingual (under the tongue) ketamine administration produced rapid, clear and sustained effects on bipolar and depressed patients' mood level and stability, cognition, and sleep quality.[173]
Lapidus et al., 2015	Intranasal (racemic ketamine 50 mg)	Major Depressive Disorder (MDD)	Intranasal ketamine administration showed significant improvements in depressive symptoms for eighteen patients.[174]
Daly et al., 2018	Intranasal (esketamine 28 mg, 56 mg, or 84 mg)	TRD	Patients with TRD experienced significant decreases in depression scores, and results were sustained for several weeks.[175]
Canuso et al., 2018	Intranasal (esketamine 84 mg)	Suicidal Ideation	Significant decrease in depression and suicidal ideation scores for patients receiving intranasal esketamine as compared to a placebo group.[176]

e) Confirming Ketamine's Antidepressant Mechanism of Action

Research published in 2014 confirmed that ketamine is an NMDA receptor antagonist.[177] This helped to explain the drug's antidepressant effects—one of the core pathophysiological changes underlying major depression is the loss of synaptic connectivity, and ketamine is thought to promote synaptogenesis.[178] This growth of new synapses suggests that ketamine may stimulate antidepressant effects that outlast initial drug actions.

173. Diogo R. Lara et al., *Antidepressant, Mood Stabilizing and Procognitive Effects of Very Low Dose Sublingual Ketamine in Refractory Unipolar and Bipolar Depression*, 16 INT'L J. NEUROPSYCHOPHARMACOLOGY 2111, 2111 (2013).

174. Kyle Lapidus et al., *A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder*, 76 BIOLOGICAL PSYCHIATRY 970, 970 (2015).

175. Ella J. Daly et al., *Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial*, 75 JAMA PSYCHIATRY 139, 146 (2018).

176. Carla M. Canuso et al., Effi*cacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study*, 175 AM. J. PSYCHIATRY 620, 620–21 (2018).

177. Duman & Aghajanian, *supra* note 1, at 233.

178. *Id.*

Likewise, preclinical studies of ketamine in patients with TRD demonstrate that the antidepressant actions of ketamine are mediated by the induction of synaptic proteins and increased number and function of new spine synapses in the prefrontal cortex.[179] Because of both its rapid antidepressant activity in treatment-resistant patients and potential for long-term therapeutic efficacy, experts hail ketamine as "one of the most significant advances in the field of depression in recent years."[180]

2. Alternative Methods of Administration

Since its first use as an anesthetic, medical professionals traditionally administered ketamine intravenously.[181] Researchers have since developed alternative routes of administration. For example, Stuart L. Weg patented intranasal administration of ketamine for pain management in 1996.[182] Today, ketamine can be safely administered intravenously, intramuscularly, orally, nasally, rectally, subcutaneously, and epidurally.[183]

The efficacy of each method is recorded in "bioavailability," which measures the proportion of the drug that enters the bloodstream when administered, and is therefore physiologically accessible.[184] As shown in Table 3, *infra*, ketamine administered through IV is far more bioavailable than ketamine administered by other treatment methods.

Table 3: Bioavailability of Ketamine by Administration Route.[185]

Route	Bioavailability	Time to Maximum Concentration
IV	100%	three minutes
Intramuscular	93%	five to ten minutes
Oral	17–29%	thirty minutes
Rectal	11–25%	thirty to thirty-five minutes
Intranasal	8–45%	ten to twenty minutes

Although IV or intramuscular (IM) ketamine administration routes result in far higher rates of bioavailability, such methods of treatment require

179. Ronald S. Duman & George K. Aghajanian, *Synaptic Dysfunction in Depression: Potential Therapeutic Targets*, 338 SCI. 68, 73 (2012).

180. *Id.*

181. Li & Vlisides, *supra* note 122, at 23.

182. U.S. Patent No. 5,543,434 (issued Aug. 6, 1996).

183. Li & Vlisides, *supra* note 122, at 2–3.

184. *Id.*

185. *Id.* at 3.

inpatient care and anesthesiologists present.[186] Oral, rectal, and intranasal delivery methods are much less bioavailable than IV delivery but are more amenable to outpatient use.[187]

A shift away from IV or IM administration presents many advantages to patients and medical professionals. IV and IM administration require hospital visits and a more extensive range of medical precautions; this presents a significant barrier to long-term patient compliance.[188] Unlike anesthetic ketamine use, which typically requires only a single large dose of ketamine over the period required for an operation or other medical procedure, antidepressant therapies may call for long-term repeated administration. As such, there are significant incentives for adopting a more seamless and frictionless means of delivery for antidepressant ketamine therapies.

In 2010 and 2012, two papers disclosed that orally administered ketamine effectively relieved depressive symptoms. One showed that a single oral dose of low-dose ketamine provided rapid and moderately sustained symptom relief for depressed patients receiving hospice care.[189] Another study showed that a daily oral ketamine solution created sustained antidepressant and antianxiety effects on a hospice patient with severe anxiety, fear, depression, and chronic pain.[190]

These findings prompted further research into oral administration of ketamine for the treatment of depression. A 2013 NIMH-sponsored study with eight patients found that daily oral ketamine administration alleviated depression symptoms for patients receiving hospice care.[191] Another study found that sublingual administration produced rapid, clear, and sustained effects on bipolar and depressed patients' mood, cognition, and sleep quality.[192] Notably, both the oral and sublingual administrations seemed to minimize some of the more undesirable side effects of ketamine, such as dissociation and psychosis.[193]

186. McElvery, *supra* note 78.

187. Li & Vlisides, *supra* note 122, at 2–3.

188. Gordon, *supra* note 19.

189. Irwin & Iglewicz, *supra* note 172, at 903.

190. Jack P McNulty & Kristian Hahn, *Compounded Oral Ketamine*, 16 INT'L J. PHARM. COMPOUNDING 364, 364 (2012).

191. Scott A. Irwin et al., *Daily Oral Ketamine for the Treatment of Depression and Anxiety in Patients Receiving Hospice Care: A 28-Day Open-Label Proof-Of-Concept Trial*, 16 J. PALLIATIVE MED. 958, 958 (2013).

192. Diogo R. Lara et al., *Antidepressant, Mood Stabilizing and Procognitive Effects of Very Low Dose Sublingual Ketamine in Refractory Unipolar and Bipolar Depression*, 16 INT'L J. NEUROPSYCHOPHARMACOLOGY 2111, 2111 (2013).

193. Lara et al., *supra* note 173, at 2111.

Researchers sought to identify a safe and easy method of delivery that could surpass oral bioavailability, spurring research into intranasal ketamine administration. A 2014 double-blind, crossover clinical study at the Mount Sinai Mood and Anxiety Disorders program provided the first controlled evidence for the antidepressant effects of intranasal ketamine, showing significant improvements in depressive symptoms for twenty patients.[194] A 2018 double-blind, placebo-controlled study showed rapid antidepressant relief for a large group of patients with TRD.[195] Like oral and sublingual methods, intranasal administration of ketamine also produced minimal undesirable side effects.[196] Another 2018 double-blind, placebo-controlled study co-sponsored by Janssen Pharmaceuticals and Yale Medicine showed a significant decrease in depression and suicidal ideation scores for patients receiving an intranasal ketamine enantiomer as compared to a placebo group.[197]

The encouraging results of these oral and intranasal treatments showed promise to researchers interested in using ketamine as an antidepressant therapy. Not only were such treatments effective at treating the symptoms of depression, but they were also safe and avoided the most undesirable dissociative side effects of IV ketamine administration. Most importantly, these methods allowed patients to potentially use ketamine in an outpatient setting, without the more cumbersome and expensive requirements of inpatient care.

3. Development of Spravato

Spravato was the first, and remains the only, FDA-approved ketamine treatment for depression. The development of the drug began with a wide-ranging NIH-backed collaboration but ultimately came to fruition when a researcher from that effort made a jump to the private industry. Spravato showcases how the motivations of patents can push private firms to develop novel, if dubiously beneficial, drug therapies.

a) Motivations and Contributions to the Development of Spravato

Even after the 2006 NIMH studies that found ketamine to be an effective treatment for patients with TRD, the predominantly used IV route of administration meant clinicians expended considerable resources (including

194. Lapidus et al., *supra* note 174, at 970.

195. Ella J. Daly et al., *Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial*, 75 JAMA PSYCHIATRY 139, 147 (2018).

196. Lapidus et al., *supra* note 174, at 970.

197. Canuso et al., *supra* note 176, at 620–21.

inpatient care and an on-site anesthesiologist) while delivering the drug.[198] As such, there were significant incentives for a private pharmaceutical company to develop a patentable, easy-to-deliver ketamine administration formulation. It took a decade of work until Janssen Pharmaceuticals, a Belgium-based subsidiary of Johnson & Johnson, could gain FDA approval for its solution, Spravato, which uses a far less cumbersome—but controversial—method of delivery for ketamine as an antidepressant.

The development of Spravato can be traced to Husseini Manji's arrival at Janssen in 2008. Before working at Janssen, Manji served as director of the Mood and Anxiety Disorders program at the NIMH.[199] At the NIMH, Manji co-authored the first study to replicate Zarate's seminal 2006 study (*see* Table 1, *supra*).[200] Inspired in part by a desire to develop new depression therapies and by similar leaps in cancer treatment spurred through private research, Manji left the NIMH to lead Janssen's Neuroscience Research & Development program in 2008, but continued to co-author ketamine research prodigiously through the 2010s.[201]

Because of this background, Manji understood the antidepressant promise of ketamine, but also the significant hurdles that IV administration created. So, he set about developing a more expedient delivery method for the drug.[202] Manji's team at Janssen worked to develop a nasal spray to deliver racemic ketamine because such a method of delivery did not require an anesthesiologist to be present, and allowed faster delivery to the brain.[203] But because the spray supplied much less of the drug than IV delivery, Manji's team searched for a more potent form of the drug.[204] They found their solution in the S-enantiomer of ketamine.

198. McElvery, *supra* note 78.

199. *Id.*

200. *Id.*; Zarate et al., *supra* note 161.

201. Intravenous ketamine administration requires an anesthesiologist to be present to address safety concerns; intranasal administration does not. Likewise, intranasal administration has a higher upper-range bioavailability than alternatives such as oral and sublingual ketamine. McElvery, *supra* note 89; Li & Vlisides, *supra* note 122, at 2–3.

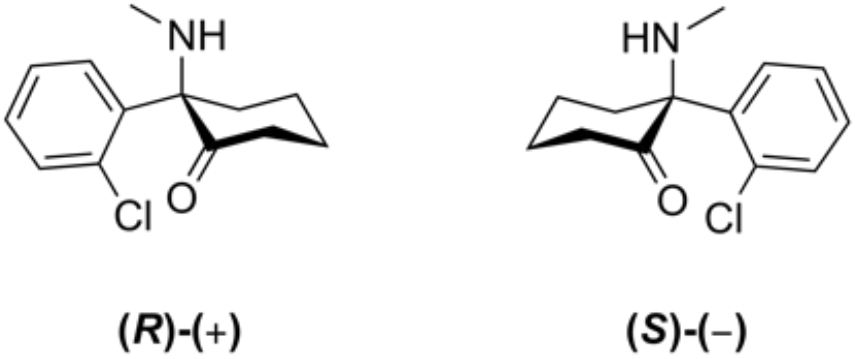
202. Ginny Graves, *The Mind Matters: This Johnson & Johnson Researcher is on a Mission to Change How We Treat Mental Illness*, J&J INNOVATION (May 16, 2017), https://www.jnj.com/innovation/johnson-and-johnson-researcher-on-a-mission-to-change-how-we-treat-mental-illness; Dana Talesnik, *Manji Develops Novel Treatment for Major Depressive Disorder*, NIH RECORD (May 17, 2019), https://nihrecord.nih.gov/2019/05/17/manji-develops-novel-treatment-major-depressive-disorder.

203. McElvery, *supra* note 89.

204. *Id.*

b) Ketamine's Enantiomers and Off-Label Treatment of Depression

Figure 10: Ketamine's R- and S-Enantiomers.[205]



Ketamine exists in two different enantiomer forms: R-ketamine and S-ketamine (often spelled "esketamine").[206] The form of the drug approved by the FDA for anesthetic purposes is equal parts of the R- and S-enantiomers ("racemic" ketamine).[207] Nearly all the influential early ketamine antidepression studies discussed *supra*, including Zarate's in 2006, utilized the racemic form.[208]

However, racemic ketamine is not currently FDA-approved for the treatment of depression. Though there is limited evidence available about the extent of ketamine's off-label use for depression, published records indicate antidepressant use since at least the early 2000s.[209] While in Europe, many countries follow the U.K. National Institute for Health and Care Excellence (NICE) recommendation that clinicians only use ketamine off-label for depression after attempting "all evidence-based antidepressant strategies"

205. *Ketamine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Ketamine (last visited Nov. 1, 2023).

206. *Id.*

207. *Id.*

208. *See* Table 2, *supra*.

209. Gerard Sanacora et al., *A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders*, 74 JAMA PSYCHIATRY 399 (2017); Samuel T. Wilkinson et al., *A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders*, 174 AM. J. PSYCHIATRY 695, 695–96 (2017).

outlined in clinical guidelines, in the United States, no such restriction exists.[210] Because of this, several startups have sprung up to provide U.S. patients with off-label racemic ketamine for depression, which can include IV, oral, or intranasal administrations of the drug.[211]

Likewise, retrospective studies analyzing clinical data reporting the off-label use of sublingual racemic ketamine found that the drug could be delivered safely at home with significant reductions in patient's depression metric scores.[212] However, alarmed at the extent of off-label use of racemic ketamine, the FDA released a warning to health care professionals in 2022 concerning potential side effects, including sedation, dissociation, and abuse or misuse.[213]

c) Spravato's Use of Esketamine

The clinical team at Janssen argued that the lower bioavailability and metabolism rate that resulted from nasal delivery of the drug (see Table 2) necessitated a more potent version of the ketamine formulation.[214] The patent that would ultimately cover Spravato cited evidence that isolated esketamine has a higher affinity to the binding site on NMDA receptors and is three to four times more potent than R-ketamine.[215] Additionally, research cited by Janssen showed that the esketamine enantiomer is associated with increased cardiac stimulation, decreased spontaneous motor activity, superior analgesia, faster recovery, and fewer psychological side effects.[216]

---

210. Álvaro López-Díaz et al., *Off-Label Use of Ketamine for Treatment-Resistant Depression in Clinical Practice: European Perspective*, 215 BRIT. J. PSYCHIATRY 447, 447 (2019).

211. Rebecca Heilweil, *Startups are Betting on a Psychedelic Gold Rush*, VOX (Oct. 13, 2021), https://www.vox.com/recode/22716491/psychedelics-ketamine-mental-health-research-fda.

212. Kazi Hassan et al., *Safety, Effectiveness and Tolerability of Sublingual Ketamine in Depression and Anxiety: A Retrospective Study of Off-Label, At-Home Use*, 28 FRONTIERS PSYCHIATRY 1, 7 (2022).

213. *FDA Alerts Health Care Professionals of Potential Risks Associated with Compounded Ketamine Nasal Spray*, U.S. FOOD & DRUG ADMIN. (Feb. 16, 2022), https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray#:~:text=Ketamine%20hydrochloride%5Ba%5D%20(tradename,and%20maintenance%20of%20general%20anesthesia [hereinafter FDA News Release, Ketamine].

214. McElvery, *supra* note 89.

215. *Id.*; *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Patent and Exclusivity for: N211243*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=211243&Appl_type=N; U.S. Patent No. 8,785,500 (issued Jul. 22, 2014);
Paul F. White et al., *Comparative Pharmacology of the Ketamine Isomers: Studies in Volunteers*, 57 BRIT. J. ANESTHESIA 197 (1985).

216. White et al., *supra* note 215.

Initial trials with esketamine for patients with TRD showed promise, with a single dose offering several days' worth of symptom relief for many patients.[217] So, Manji's team developed a treatment method where patients self-administered the intranasal esketamine formulation twice a week for the first month, then administered the treatments every one to two weeks thereafter (ongoing, or as prescribed by a physician) to maintain the drug's antidepressant effects.[218] Janssen thus moved forward with an intranasal formulation that contains only esketamine—and initiated the FDA approval process of the product that would come to be sold under the brand name "Spravato."[219]

d) FDA Approval

Janssen subsequently conducted a series of clinical trials on over 1,700 patients.[220] The initial success of Janssen's Phase II trials prompted the FDA to grant Janssen a "breakthrough therapy" designation, which allowed the company to "fast track" their Phase III trials.[221] In the approval process for Spravato, Janssen conducted roughly twenty-five different studies. In a pivotal Phase III trial, many patients with TRD saw a reduction in depressive symptoms after twenty-four hours when given Spravato in conjunction with an oral antidepressant.[222] The most common adverse side effects were dissociation, nausea, vertigo, dizziness, and an altered sense of taste.[223] In the clinical trials, many individuals required fewer treatments over time, often only requiring administration once every several weeks.[224] Due to the success of these trials, the FDA approved Janssen's S-ketamine intranasal administration as Spravato in 2019.

Spravato was the first, and remains the only, FDA-approved ketamine-based antidepressant for TRD.[225] It is also the only FDA-approved depression treatment with a glutamate-modulation mechanism of action.[226] In 2020,

217. Talesnik, *supra* note 202.
218. *Id.*
219. McElvery, *supra* note 89.
220. Talesnik, *supra* note 202.
221. Rebecca Bahr et al., *Intranasal Esketamine (Spravato™) for Use in Treatment-Resistant Depression in Conjunction with an Oral Antidepressant*, 44 PHARMACY & THERAPEUTICS 340, 340 (2019).
222. McElvery, *supra* note 89; Vanina Popova et al., *Efficacy and Safety of Flexibly Dose Esketamine Nasal Spray Combined with a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study*, 176 AM. J. PSYCHIATRY 428 (2019).
223. McElvery, *supra* note 89.
224. *Id.*
225. FDA News Release, Ketamine, *supra* note 213.
226. *Id.*

Janssen received FDA approval for use of Spravato for suicidal patients with MDD.[227] In 2021, Janssen implemented the Spravato Pilot Program to expand treatment for adults with suicidal ideation.[228]

e) Limitations and Drawbacks of Intranasal Esketamine

Esketamine, on its own, is not a panacea for depression. The claims of the U.S. patent cited in Spravato's FDA approval letter specify that the drug is to be taken in conjunction with one or more of the traditional antidepressants discussed in Part II (e.g., lithium, tricyclics, MAOIs, SSRIs).[229] Spravato is classified as an "augmentation strategy" to target depression treatment resistance, and so is administered in conjunction with (rather than in lieu of) these widely used pharmaceuticals.[230]

Likewise, despite Spravato's ease of use, the drug still has several downsides compared to other antidepressant therapies. Because of ketamine's potential side effects and abuse potential, Spravato must still be administered in a clinic under a health care professional's supervision.[231] However, much less clinical supervision is required for such ketamine therapies compared to traditional IV administration.[232]

Intranasal Spravato also shares some of the same side effects as IV racemic ketamine, including hallucinations and increased blood pressure.[233] Patients must also remain in the clinic for two or more hours after treatment for monitoring after esketamine administration, and are prohibited from driving for the rest of the day due to the drug's drowsy effects.[234]

With these barriers, Spravato is still far from reaching the accessibility of other antidepressant medications, such as oral SSRIs, which can be taken daily and at home relatively seamlessly. Notably, in the spring of 2020, the FDA waived the requirement that ketamine be administered only at a hospital, clinic, or medical office (due to the SARS-CoV-2 pandemic).[235] As of October 2023,

227. Jon Hamilton, *Nasal Spray Is a New Antidepressant Option for People At High Risk of Suicide*, NPR (Aug. 7, 2020), https://www.npr.org/sections/health-shots/2020/08/07/900272454/nasal-spray-is-a-new-antidepressant-option-for-people-at-high-risk-of-suicide.

228. *Greenbrook TMS Inc. Management's Discussion and Analysis of Financial Conditions and Results of Operation*, at 4, SEC (May 14, 2021), https://www.sec.gov/Archives/edgar/data/1735948/000110465921067010/tm2116020d2_ex99-3.htm.

229. U.S. Patent Application No. 2013/0236573, ¶ 1 (issued Sept. 12, 2013).

230. *Id.*

231. Talesnik, *supra* note 202.

232. Zarate et al., *supra* note 161, at 856–64.

233. Talesnik, *supra* note 202.

234. *Id.*

235. Am. Coll. Obstetricians & Gynecologists v. United States Food & Drug Admin., 472 F. Supp. 3d 183, 194 (D. Md. 2020).

this waiver was extended to at least the end of 2024.[236] This waiver appears to apply only to ketamine, but not Spravato; the former thus can be prescribed off-label via telehealth and taken at home, while the latter must still be taken in a certified treatment center.[237]

f) Criticisms

The FDA approval of Spravato has not been without controversy. In 2020, four Italian researchers working with the World Health Organization (WHO) published a scathing critique of the clinical trial evidence Janssen submitted to the FDA.[238] The researchers noted that, of three randomized trials submitted to the FDA, only one demonstrated the superiority of intranasal esketamine over a placebo.[239] Likewise, even aggregating these finds findings, critics argue the results were so narrowly above the threshold of statistical significance as to have dubious clinical consequence.[240]

Janssen's clinical trials also calculated the efficacy of esketamine against a placebo, instead of against an active and licensed comparator for TRD (such as fluoxetine).[241] Both the FDA and European Medicines Agency (EMA) had only required a placebo-controlled trial for regulatory approval in this case.[242] This brings into question the utility of esketamine, if it potentially did not provide superior results for improving TRD as measured against presently-available therapies.[243] Critics assert that Spravato's efficacy should be measured against existing, readily available, and affordable antidepressants like SSRIs, rather than compared to an inert placebo.[244] However, Spravato is specifically made for TRD patients—those who have *failed* to achieve remission in their depression symptoms with traditional antidepressants, so this specific criticism might be misplaced.[245]

236. Scott Brinks & Miriam E. Delphin-Rittmon, *Second Temporary Extension of COVID-19 Telemedicine Flexibilities for Prescription of Controlled Medications*, FED. REG. (Oct. 10, 2023), https://www.federalregister.gov/documents/2023/10/10/2023-22406/second-temporary-extension-of-covid-19-telemedicine-flexibilities-for-prescription-of-controlled.

237. *Id.*; SPRAVATO® FAQs, SPRAVATO (ESKETAMINE), https://www.spravato.com/patient-education#:~:text=You%20cannot%20take%20SPRAVATO%C2%AE,to%20help%20find%20a%20location (last visited Nov. 22, 2023).

238. Chiara Gastaldon et al., *Esketamine for Treatment Resistant Depression: A Trick of Smoke And Mirrors?*, 29 EPIDEMIOLOGY & PSYCHIATRIC SCIS. 1, 1 (2019).

239. *Id.* at 2.

240. *Id.*

241. *Id.*

242. *Id.*

243. *Id.*

244. *Id.*

245. *See* Hillhouse & Porter, *supra* note 8, at 2.

One of the selling points for the FDA approval of esketamine over the racemic mixture—in addition to its allegedly increased potency[246]—is that the S-enantiomer is supposedly safer than the racemic mixture, but other clinical trials call that assertion into question.[247] At least one analysis of intranasal ketamine treatment for depression argues that there has not been an adequately designed comparator of the esketamine enantiomer and racemic ketamine.[248] Moreover, recent mouse studies using ketamine as an antidepressant have shown the R-ketamine enantiomer to be more potent, with fewer side effects, than the esketamine enantiomer.[249] Another meta-analysis found that intravenously administered racemic ketamine more effectively treated TRD than intranasal esketamine.[250] While none of these results provide a conclusive rebuttal of esketamine's efficacy or safety over the racemic mixture, they nonetheless provide a basis for continued skepticism for the necessity of esketamine in Janssen's drug formulation.

Despite these criticisms, Spravato is proving a lucrative product for Janssen. While initial sales of the drug were somewhat lackluster, Spravato has experienced substantial growth—revenues in the second quarter of 2023 grew almost 100% compared to the same period in 2022, to $169 million worldwide.[251] This strong growth has continued; in the third quarter of 2023, sales increased over 80% compared to the same period in 2022, to $183 million worldwide.[252]

246. *See* White et al., *supra* note 215, at 201.

247. Gastaldon et al., *supra* note 238, at 1; Caroline Caddy et al., *Ketamine and Other Glutamate Receptor Modulators for Depression in Adults*, 9 COCHRANE DATABASE SYSTEMATIC REVS. 1 (2015).

248. Roger S. McIntyre et al., *Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation*, 178 AM. J. PSYCHIATRY 383, 386 (2021).

249. Ji-chun Zhang et al., *R (−)-ketamine Shows Greater Potency and Longer Lasting Antidepressant Effects Than S (+)-Ketamine*, 116 PHARMACOLOGY BIOCHEMISTRY & BEHAVIOR 137, 137–38 (2014).

250. Anees Bahji et al., *Comparative Efficacy of Racemic Ketamine and Esketamine for Depression: A Systematic Review and Meta-Analysis*, 278 J. AFFECTIVE DISORDERS 542, 542 (2021).

251. Benjamin A. Smith, *Sales of Johnson & Johnson Esketamine Drug Spravato Rise Nearly 100% Year Over Year*, DALES REP. (July 20, 2023), https://thedalesreport.com/psychedelics/sales-of-johnson-johnson-esketamine-drug-spravato-rise-nearly-100-year-over-year/; *Q2 2023 Results*, JOHNSON & JOHNSON REPS. (July 20, 2023), https://johnsonandjohnson.gcs-web.com/static-files/0d7dfa93-bb82-4fd9-af4d-5ccbd7478495.

252. *Q3 2023 Results*, JOHNSON & JOHNSON REPS. (Oct. 17, 2023), https://www.investor.jnj.com/files/doc_financials/2023/q3/Q3/3Q23-Press-Release_Final_With-Guidance_With-Attachments.pdf.

IV. THE COMPLEX ROLE OF PATENTS, FDA APPROVAL, AND INSURANCE MOTIVATIONS IN THE USE OF KETAMINE FOR DEPRESSION

Ketamine exists within a curious regulatory paradigm that likely impedes its widespread antidepressant use. It is widely available as an anesthetic drug in its racemic form but is only available as an FDA-approved depression therapy in its intranasal esketamine form. Combined with a high potential for abuse and clinical skepticism, ketamine's promise and widespread adoption as an antidepressant is currently falling short of its full potential as a "revolutionary" antidepressant.

A. PATENTS

In the United States, pharmaceutical inventions are patentable, and those that are filed with and granted by the U.S. Patent and Trademark Office (USPTO) are entitled to twenty years of patent protection.[253] Parke-Davis received the original patent for racemic (equal parts R- and S-enantiomer) ketamine in 1966, so that mixture of the drug is now off-patent.[254] Likewise, Stuart L. Weg patented intranasal administration of ketamine for pain management in 1996, and that patent expired in 2014.[255] The USPTO granted a patent for intranasal administration of ketamine to treat depression to Charney et al. in 2014.[256] While that patent is set to expire in 2030, the USPTO granted an additional 596 days for patent term extension associated with the FDA regulatory process of Spravato. On the patent, Mount Sinai School of Medicine, Yale University School of Medicine, and the NIH are named as assignees—these assignees licensed to Janssen for Spravato.[257] The USPTO granted Janssen a patent for their intranasal dosing method to treat suicidal ideation with esketamine on December 22, 2020.[258]

253. 35 U.S.C. § 154(a)(2).
254. *Id.*; Domino & Warner, *supra* note 112, at 679.
255. U.S. Patent No. 5,543,434 (issued Aug. 6, 1996).
256. U.S. Patent No. 8,785,500 (issued July 22, 2014).
257. *Id.*
258. U.S. Patent No. 10,869,844 (issued Dec. 22, 2020).

Table 4: Notable Ketamine Patents

Patent or Patent Application Number	Description	Approval and Expiration Dates	Owners/Assignees
US3254124	First compound ketamine patent; for racemic (equal parts R- and S-enantiomer) ketamine	May 31, 1966–May 31, 1983	Parke-Davis and Co LLC
US5543434	Method of self-administering intranasal ketamine for pain	Aug. 6, 1996–Feb. 25, 2014	Stuart L. Weg
US20070287753	Method of using intranasal ketamine to treat depression	July 22, 2014–Sept. 15, 2030	Yale University, U.S. Dept. of HHS, NIH, Icahn School of Medicine at Mount Sinai, Yale School of Medicine
US8785500	Method of using intranasal ketamine to treat depression in conjunction with an oral antidepressant	July 22, 2014–Sept. 15, 2030	Yale University, U.S. Dept. of HHS, NIH, Icahn School of Medicine at Mount Sinai, Yale School of Medicine
US10869844	Method of using intranasal administration of esketamine to treat depression in patents with TRD and/or suicidal ideation	Dec. 22, 2020–Sept. 14, 2035	Janssen Pharmaceuticals

Some have criticized the patents covering intranasal administration of esketamine for depression as "product-hopping"—a process where drug manufacturers swap subtly modified versions for existing treatments to extend their product monopolies.[259] According to critics, a classic example of "product hopping" occurs when a patent claims only one enantiomer of a

259. I. Glenn Cohen & Mason Marks, *Patents on Psychedelics: The Next Legal Battlefront of Drug Development*, 135 HARV. L. REV. F. 212, 224–226 (2022); Jennifer D. Claytor & Rita F. Redberg, *Product Hopping-An Expensive and Wasteful Practice*, 180 JAMA INTERNAL MED. 1154, 1154 (2021).

molecule that is previously available as a mixture of the right- and left-handed enantiomer of the molecule.[260] This was the case in the patent for treatment of depression using intranasal esketamine, where clinicians long treated depression with off-label racemic ketamine.[261] S-ketamine is present, in equal parts with R-ketamine, in the racemic ketamine formulation frequently used in anesthesia and psychiatry.[262] Critics fear this might reduce incentives for others to enter the market for fear of impeding Janssen's patent, which chills competition and innovation.[263]

Yet, these critiques may overlook the substantial benefits of Spravato's patents. Allowing Janssen to patent Spravato allows for reduced stigmatization through rebranding—which can in turn lead to broader acceptance and increased likelihood of insurance coverage.[264] And Janssen's patent provided the incentives for the considerable expenditures related to Spravato's FDA approval process.[265] Likewise, granting Janssen a patent on Spravato does not necessarily preclude competitors from entering the market with R-ketamine or another novel substance. Moreover, Part V, *infra*, argues that granting a patent to Spravato may, in many ways, *promote* innovation rather than stifle it.[266]

Notably, this patent paradigm shifts when looking to other jurisdictions. In Canada, drugs comprising a medical ingredient of a previously approved drug, such as an enantiomer of the original, constitute a "variation" on the original instead of an independent "innovative drug" worthy of patent-level protection.[267] In fact, the Canadian Federal Court of Appeal held that Spravato is not an "innovative drug" eligible for such protections.[268] Additionally, the United Nations recommends that enantiomers of existing inventions should be presumed unpatentable.[269] The United States does not presume that

260. Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167, 172 (2016).

261. Cohen & Marks, *supra* note 259, at 225.

262. Fernanda S. Correia-Melo et al., *Comparative Study of Esketamine and Racemic Ketamine in Treatment-Resistant Depression: Protocol for a Non-inferiority Clinical Trial*, 97 MED. 1, 1–2 (2018).

263. Cohen & Marks, *supra* note 259, at 226–28.

264. *Id.*

265. *See infra* Section IV.D.

266. *See infra* Section V.C.

267. Takeda Canada Inc. v. Minister of Health (2013) FCA 13, ¶¶ 13–14.

268. Janssen Inc. v. Minister of Health (2021) FCA 137, ¶¶ 2, 37–38.

269. Christopher M. Holman et al., *Patentability Standards for Follow-On Pharmaceutical Innovation*, 37 BIOTECH. L. REP. 131, 132–33 (2018) (describing efforts by the United Nations Development Programme to "protect public health and provide access to medicines" by heightening patentability requirements).

enantiomers of existing inventions are unpatentable, which is how Janssen successfully obtained a patent for a method of treatment using Spravato.[270]

B. FDA APPROVAL PARADIGM

Although clinicians frequently used racemic ketamine off-label for depression treatment before the FDA approval of Spravato, no formulation of the drug was authorized for depression treatment in the United States or any other country.[271] In the FDA approval process for Spravato, Janssen only needed to prove the drug's efficacy for the treatment of TRD over a placebo—a concept known as "absolute efficacy."[272]

Although controversial, clinical trials for antidepressants must only demonstrate efficacy against a placebo for marketing authorization.[273] Researchers have criticized this approval threshold, which is also the regulatory requirement in the European Medicines Agency (EMA), because it fails to compare Spravato's efficacy against other known effective treatments for TRD—utilizing the concept of "added value."[274] This is a disservice, the critics maintain, because it allows the marketing of a new drug that may be less effective, or more harmful, than others already in use.[275]

Despite evidence to support the use of racemic ketamine for the treatment of depression, only Janssen's intranasal esketamine administration is available as an FDA-approved therapy.[276] Additionally, in 2022, the FDA submitted an explicit warning to health care professionals of the risks associated with use of racemic ketamine for depression treatment (including IV, oral, and intranasal administrations).[277] It remains unclear whether these risks differ substantially from those of esketamine; the government likely submitted this warning because, unlike Janssen's safety trials with Spravato, no entity had produced sufficient safety evidence for racemic ketamine's use as an antidepressant.[278]

C. DEA CLASSIFICATION

Unlike other psychedelic drugs, ketamine is listed as a Schedule III drug, which is reserved for substances that have a potential for abuse less than those

270. U.S. Patent No. 10,869,844 (issued Dec. 22, 2020).
271. Gastaldon et al., *supra* note 238, at 1.
272. *Id.* at 2.
273. *Id.*
274. *Id.*
275. *Id.*
276. Olivia Goldhill, *Ketamine's Promise as an Antidepressant is Being Undermined by Its Lack of Profit*, QUARTZ (Aug. 6, 2020), https://qz.com/1889308/why-isnt-ketamine-approved-as-an-antidepressant/.
277. FDA News Release, Ketamine, *supra* note 213.
278. *See id.*

in Schedule I (which contains psychedelics such as LSD and MDMA) and Schedule II.[279] According to both the U.S. Department of Justice and the U.S. Drug Enforcement Administration, this schedule classification is also due to the fact that ketamine is currently approved for sedation, anesthesia, and (in the case of Spravato) TRD.[280]

However, because of its abuse potential and reputation as a "party drug," ketamine likely faces some clinical skepticism and regulatory hesitation for wider adoption. Ketamine's Schedule III classification makes it unique amongst other widely used antidepressants, most of which are either unclassified, or listed under Schedule IV (which is reserved for substances with a low potential for abuse and low risk of dependence).[281]

Table 5: DEA Classification for Common Antidepressants

Drug	Indication	DEA Classification
Lithium	Depression, bipolar disorder	N/A
MAOIs	Depression	N/A
TCAs	Depression, neuropathic pain, migraine, etc.	N/A
Meprobamate	Anxiety	Schedule IV
Benzodiazepines	Anxiety, insomnia, seizures, muscle relaxant, etc.	Schedule IV
Diazepam	Anxiety, sedation, etc.	Schedule IV
Fluoxetine (Prozac) (SSRI)	Depression, OCD, panic attacks, etc.	N/A
Ketamine	Anesthesia, sedation, depression	Schedule III

D. HOW THE PATENT SYSTEM, FDA APPROVAL PROCESS, AND INSURANCE COVERAGE HAVE HAMPERED KETAMINE'S PROMISE AS AN ANTIDEPRESSANT

The controversy surrounding ketamine's accessibility highlights a conflict between the incentives for patents, FDA approval, and insurance coverage in the United States. Currently, Spravato (intranasal esketamine) remains the only FDA-approved ketamine depression therapy. Yet, some speculate that racemic

279. *Controlled Substance Schedules*, DRUG ENF'T ADMIN, https://www.deadiversion.usdoj.gov/schedules/index.html (last visited Nov. 22, 2023).

280. Ketamine Fact Sheet, *supra* note 132.

281. *Id.*; Rick Stassman, *Should We Loosen the Restrictions on Psychedelics?*, SCI. AM. (July 17, 2018), https://blogs.scientificamerican.com/observations/should-we-loosen-the-restrictions-on-psychedelics/.

or R-ketamine is as safe or effective as esketamine. Racemic ketamine is off-patent, so would likely be much less expensive than Spravato. And the introduction of R-ketamine into this space would create an alternative therapy that ostensibly reduces costs through price competition. So, patients could enjoy a more affordable, and potentially equally effective, treatment if either was approved by the FDA as a depression therapy. But because of insufficient financial motivations to pay for clinical trials for either alternative formulation, patients and clinicians remain with a single FDA-approved treatment option in this space. Ideally, an alternate option would exist to decrease costs, but it remains unclear whether the incentive exists for any entity to expend the resources necessary for FDA approval (and, indirectly, insurance coverage) of racemic ketamine as an antidepressant.

1. Patent Monopolies and FDA Approval Incentives

The FDA approval process is extraordinarily expensive. The cost of clinical trials to support FDA approval typically ranges from $12 million to $33 million, with a median cost of $19 million.[282] In exchange for this expense, the FDA typically grants five (and sometimes up to six or seven) years of market exclusivity to applicants for "small molecule" innovator drugs like ketamine.[283] Companies require incentives to undertake such expenses; patents often provide such an incentive.

In the United States, inventors of new drugs receive twenty years of patent protection for their technological advances.[284] This twenty-year period can be extended for a maximum of five years for delays experienced in the FDA approval process.[285] After the patent (including any term extension) expires, the patent holder typically loses their monopoly on the sale of the drug. Companies, through clever "product hopping" or "evergreening" techniques that change formulation, method of treatment, or formulation claims, can continue blocking generics far beyond the original expiration date.[286]

282. Thomas J. Moore et al., *Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016*, 178 JAMA INTERNAL MED. 1451, 1451 (2018).

283. Aaron S. Kesselheim et al., D*eterminants of Market Exclusivity for Prescription Drugs in the United States*, 177 JAMA INTERNAL MED. 1658, 1658–60 (2017).

284. 35 U.S.C. § 154(a)(2).

285. *Id.* § 156 (providing statutory patent term extension).

286. "Product hopping" or "evergreening" involves a patent holder switching the market for a drug to a "reformulated version that has a later-expiring patent" but which offers little or no therapeutic advantage to its predecessor. Companies will spend heavily to convince clinicians and patients to switch to the new formulation, and may even pull the predecessor product from the market to avoid price competition with the newer product. *See, e.g.*, Gregory

Racemic ketamine was originally patented in 1963 and is long expired, even with any term extension.[287] While there are certain cases that provide an effective monopoly through "regulatory exclusivity" (such as for "orphan drugs" used for fewer than 200,000 patients), none of these seem to apply to the use of racemic ketamine for depression therapies.[288]

On the other hand, Janssen has achieved monopolization by cleverly navigating the patent and FDA exclusivity process. The earliest patent on Spravato expires in 2027; this is for the relatively broad "Intranasal administration of ketamine to treat depression" patent (the '207 patent).[289] In addition to two separate regulatory exclusivities, Janssen also acquired several patents that cover more specific dosage requirements, indications, and methods of treatments (such as simultaneous antidepressant therapies)—the latest of which (as of May 2023) expire in 2035.[290]

Janssen could potentially justify the lengthy expenses involved with FDA approval because they held the patent to intranasal delivery of esketamine. The company could conceivably recuperate their expenses through exploitation of their patent-reinforced monopoly on the sale of the drug. No such incentive exists for approval of racemic ketamine for depression treatment. Because racemic ketamine's patent expired in 1983, without a novel application or chemical modification, no company can acquire a patent on the compound. The only monopolization available would be three years of regulatory exclusivity for a "new indication" (here, racemic ketamine for the new indication of depression).[291] Thus, no company could receive the financial windfalls that monopolization from a patented drug confers, and the three years of exclusivity for a company that proves a "new indication" is probably not enough of an incentive to conduct the expensive clinical trials.

So, short of a non-profit or government initiative to assist with the enormous financial resources associated with the FDA approval process, it

H. Jones et al., *Strategies that Delay or Prevent the Timely Availability of Affordable Generic Drugs in the United States*, 127 BLOOD 1398, 1399 (2016).

287. Goldhill, *supra* note 276.

288. *Designing an Orphan Product: Drugs and Biological Products*, U.S. FOOD & DRUG ADMIN. (July 8, 2022), https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products.

289. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Patent and Exclusivity for: N211243*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=211243&Appl_type=N.

290. *Id.*

291. *Frequently Asked Questions on Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN. (Feb. 5, 2020), https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#:~:text=Patents%20can%20be%20issued%20or,have%20just%20one%20or%20neither.

seems unlikely that racemic ketamine will gain authorization to treat depression anytime soon. Any organization seeking to use their clinical trial data for FDA approval must publish their protocols to ClinicalTrials.gov; as of May 2023, the website lists several trials from nonprofit organizations (such as research hospitals and medical schools) who have run clinical trials for racemic ketamine use in depression. However, the majority of these have terminated, and the remainder are far from the multi-stage trial threshold required for FDA approval.[292]

2. FDA Approval and Insurance Coverage

Insurance coverage is often linked to FDA approval.[293] Medicaid must cover essentially all FDA-approved drugs (that are prescribed for a Medicaid patient by their physician), and Medicare has limited ability to decline to cover FDA-approved drugs.[294] Private insurance companies, similarly, are only ever *required* to cover a drug if it has FDA approval. And, if insurance companies do not have the FDA's stamp of approval that a drug works, they are more reluctant to pay for it.[295]

Without FDA approval, medical professionals can still prescribe racemic ketamine as an antidepressant, but this is considered "off-label" use of the drug, meaning it is for a clinical outcome not specified in the drug's FDA-approved indication(s).[296] Because the use of racemic ketamine to treat depression is an "off-label" application, it is less likely to be covered as an antidepressant by insurance than the patented Spravato, which is FDA approved as a depression therapy.[297]

Such off-label usage of a drug is difficult to reimburse through insurance, so patients and medical professionals are incentivized to favor the esketamine

292. *See Search Results*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/results?cond=depression&term=ketamine&cntry=&state=&city=&dist= (last visited Dec. 2, 2022) (providing a list of trials for ketamine use in depression treatment). While termination does not necessarily indicate that any issues occurred during the clinical trials, a terminated study will not lead to clinically relevant evidence to support an FDA application.

293. Rachel Sachs, *Your Weekly Reminder That FDA Approval and Insurance Coverage Are Often Linked*, HARV. L. PETRIE-FLOM CTR. BILL HEALTH BLOG (Nov. 30, 2016), https://blog.petrieflom.law.harvard.edu/2016/11/30/your-weekly-reminder-that-fda-approval-and-insurance-coverage-are-often-linked/.

294. *Id.*

295. *See, e.g.*, AETNA BETTER HEALTH, OFF-LABEL USE OF FDA-APPROVED DRUGS POLICY (2016).

296. *Understanding Unapproved Use of Approved Drugs "Off Label"*, U.S. FOOD & DRUG ADMIN. (Feb. 2, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label.

297. Steve Levine, *Ketamine: A Cautionary Tale*, PSYCH. TODAY (Nov. 30, 2021), https://www.psychologytoday.com/ca/blog/pathways-progress/202111/ketamine-cautionary-tale.

intranasal application of Spravato, despite the cheaper cost of racemic ketamine.[298] This can be a substantial expense—infusions of racemic ketamine for depression cost roughly $5–$15 per week for the drug alone, whereas Spravato costs $1,000–$1,600 per week.[299] Add that to the fact that, in 2022, the FDA submitted an explicit warning to health care professionals of the risks associated with use of racemic ketamine for depression treatment, and a rapid expansion of racemic ketamine antidepressant therapies in the near future grows unlikely.[300] Critics argue that this is deeply regrettable, given the affordability of racemic ketamine and the promise that the drug shows in treating depression.[301]

V. INNOVATIVE RESPONSES TO KETAMINE'S RESTRICTIVE REGULATORY LANDSCAPE

Given the current regulatory and public perception paradigm, ketamine faces an uphill battle towards increased widespread adoption. There are two promising avenues that might lead to more substantial use of the drug for depression therapies.

First is the budding psychedelic therapy space, which embraces drugs in spite of, and perhaps *because of*, their complex regulatory restrictions. Expansion in this space seems likely, especially given ketamine's promising initial antidepressant results and relatively safe use profile. Second, ketamine represents the immense untapped potential of glutamatergic/NMDA-reception modulating antidepressant therapies. Ketamine's ability to treat those who struggle to achieve depression remission on monoamine-targeting drugs will likely prompt significantly more research into the mechanistic understanding of the glutamatergic/NMDA-reception pathway. These insights may lead to novel drug therapies that avoid some of the obstacles facing ketamine.

Counterintuitively, constraints imposed by the existing regulatory landscape drive innovation in these spaces. In response to conditions that make the widespread antidepressant adoption of ketamine unlikely in its current distribution channels, both psychedelic therapy entrepreneurs and glutamatergic/NMDA-modulating drug researchers show that limitations can lead to *increased* innovation.

298. *Id.*

299. CADTH COMMON DRUG REVIEW, PHARMACOECONOMIC REPORT ESKETAMINE HYDROCHLORIDE (SPRAVATO) (2021) (providing cost information in Appendix 1, Cost Comparison Table) [hereinafter PHARMACOECONOMIC REPORT, SPRAVATO].

300. FDA News Release, Ketamine, *supra* note 213.

301. *See* Cohen & Marks, *supra* note 259, at 226–28.

A. PSYCHEDELIC THERAPY AND PSYCHEDELIC STARTUPS

Psychedelics have long been subject to draconian restrictions—scaring off researchers from investigating these drugs and their components.[302] As a result, little is known about these drugs' potential, but studies of drugs like MDMA, psilocybin, and ketamine suggest they could provide novel approaches to difficult psychiatric conditions.[303] Because of this untapped potential, entrepreneurs see immense upside despite the risks associated with this space.

More than a dozen psychedelic therapy start-ups have emerged in the past decade.[304] Notably, Field Trip Health, a Canadian company that operates high-end ketamine clinics, raised over $150 million to finance their expansion into the antidepressant therapy field.[305] Field Trip clinics offer ninety-minute ketamine "trips" with therapist-guided "integration sessions" to help patients process these experiences.[306]

Many companies like Field Trip are exploring more enduring therapies to treat MDD, TRD, and PTSD, using drugs such as psilocybin or MDMA. However, ketamine is primarily used in such facilities because it is legally available to patients outside a clinical study.[307] Despite this, those in the psychedelic therapy space are beginning to leverage the knowledge gained in ketamine depression studies to inform other unconventional depression treatments, such as those using psilocybin.[308] Spravato's success has even spurred other large pharmaceutical companies to invest in research using other psychedelics and their derivatives as antidepressants.[309]

These therapy channels, while auspicious, are also fraught with concerns about safety and oversight. During the pandemic, the Trump administration relaxed telehealth restrictions, and the Biden administration maintained this

302. Andrew Jacobs, *The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same*, N.Y. TIMES (Nov. 11, 2021), https://www.nytimes.com/2021/05/09/health/psychedelics-mdma-psilocybin-molly-mental-health.html.

303. *See, e.g.*, Jennifer M. Mitchell et al., *MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study*, 27 NATURE MED. 1025 (2021); Roland R. Griffiths et al., *Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety In Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial*, 30 PSYCHOPHARMACOLOGY 1181 (2016).

304. Jacobs, *supra* note 302, at 2.

305. *Id.* at 2–4.

306. *Id.* at 3.

307. *Id.*

308. McElvery, *supra* note 89.

309. Christoph Kraus et al., *The Influence of Ketamine on Drug Discovery in Depression*, 24 DRUG DISCOVERY TODAY 2033 (2019).

policy.[310] Telehealth increases access to off-label uses of racemic ketamine for depression but raises substantial concerns about a lack of clinical supervision. For example, Joyous, a ketamine telehealth startup, provides prescriptions of the drug in as short as a thirty-minute video call.[311] This shift away from clinics and towards at-home frequent use of ketamine alarms many public health officials because TRD patients, given their condition, are a particularly vulnerable population.[312] Additionally, telehealth channels might discourage patients from revealing adverse effects from ketamine, for fear that such disclosure inevitably results in (often prohibitively expensive) in-person care.[313]

This situation might be the reckoning of access issues caused by the very regulation that many public health officials advocate for. Because Spravato is the only FDA-approved antidepressant use of ketamine and insurance carriers are only likely to reimburse approved therapies, Janssen essentially has a monopoly on authorized ketamine depression treatments in the United States, which has led to exclusionary pricing of the drug.[314]

Many patients report that ketamine is "life changing" and "the only drug that ever relieved their crushing symptoms," but this paradigm means access to approved antidepressant administration of the drug is expensive and out of reach for many.[315] Thus, psychedelic therapy and telehealth startups are one promising alternative avenue to ketamine access for patients with depression, against the backdrop of an overly restrictive regulatory state.

B. MECHANISM OF ACTION: KETAMINE DERIVATIVES AND ALTERNATIVE GLUTAMATERGIC/NMDA-RECEPTION MODULATING DRUGS FOR DEPRESSION TREATMENT

Researchers remain unsure what precise mechanism of action causes ketamine's antidepressant effect, but discoveries into the method could prompt further breakthroughs in ketamine or ketamine-derived depression treatments. Recent proposals suggest that activation of α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid (AMPA) receptors by hydroxynorketamine, a ketamine metabolite, causes the rapid antidepressant-like properties observed with the drug.[316] Ketamine also acutely increases hippocampal brain-derived neurotropic factor, which some propose might cause antidepressant

310. Hamby, *supra* note 135.
311. *Id.*
312. *Id.*
313. *Id.*
314. *See* PHARMACOECONOMIC REPORT, SPRAVATO, *supra* note 299, at 20.
315. Hamby, *supra* note 123.
316. Panos Zanos et al., *NMDAR Inhibition-Independent Antidepressant Actions of Ketamine Metabolites*, 533 NATURE 481, 481 (2016).

effects.[317] Still others have postulated that ketamine may affect brain regions through epigenetic mechanisms. [318] Researchers continue investigating ketamine's impact on neural interconnectivity; one recent development suggests that subanesthetic ketamine administration (at a level used in depression treatment) disrupts functional connectivity between the subgenual anterior cingulate cortex (which is involved with mood modulation) and the thalamus, hippocampus, and retrosplenial cortex.[319]

A detailed mechanistic understanding of ketamine's antidepressant impact, at the very least, illuminates other potential drugs and targets in this pathway. Although much of the research around ketamine and depression pertains to increasing or prolonging ketamine's antidepressant effects, some researchers are working to manipulate the chemical composition of ketamine to reduce the drug's abuse potential.[320] Carlos Zarate, who was fundamental to the initial research into ketamine's antidepressant effects, is studying hydroxynorketamines (HNKs), ketamine metabolites which can offer rapid, sustained antidepressant effects without many of the drug's side effects.[321]

Recent efforts also focus on developing novel oral and sublingual formulations for ketamine, with an eye towards low-dose antidepressant use of the drug in an outpatient setting.[322] Death by ketamine overdose, in any delivery form, is rare and usually involves other intoxicants or physical trauma from accidents while under the influence of the drug.[323]

In a 2000 study on ketamine's antidepressant effects, Berman et al. suggested that other glutamatergic and NMDA receptor-modulating drugs might prove useful for patients with depression.[324] Many such drugs exist, and several are currently undergoing clinical trials as antidepressants.

317. Lêda S.B. Garcia et al., *Acute Administration of Ketamine Induces Antidepressant-Like Effects in the Forced Swimming Test and Increases BDNF Levels in the Rat Hippocampus*, 32 PROGRESS NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY 140, 140–41 (2008).

318. Miyeon Choi et al., *Ketamine Produces Antidepressant-Like Effects Through Phosphorylation-Dependent Nuclear Export of Histone Deacetylase 5 (HDAC5) in Rats*, 112 PROCS. NAT'L ACAD. SCIS. 15755, 15755–56 (Nov. 2015).

319. Jing J. Wong et al., *Ketamine Modulates Subgenual Cingulate Connectivity with the Memory-Related Neural Circuit—A Mechanism of Relevance to Resistant Depression?*, 4 PEERJ 1710 (2016).

320. Jaclyn N. Highland et al., *Hydroxynorketamines: Pharmacology and Potential Therapeutic Applications*, 73 PHARMACOL. REV. 763, 765 (2021).

321. *Id.*

322. Chui Chong et al., *Development of a Sublingual/Oral Formulation of Ketamine for Use in Neuropathic Pain*, 29 CLINICAL DRUG INVESTIGATION 317 (2009).

323. Brendon R. Lalonde & H. Rachelle Wallage, *Postmortem Blood Ketamine Distribution in Two Fatalities*, 28 J. ANALYTICAL TOXICOLOGY 71, 71 (2004).

324. Berman et al., *supra* note 99, at 351.

For example, the NMDA-receptor antagonist drug memantine displayed promising results as an antidepressant for patients who also suffered from alcoholism.[325] Lanicemine, an NMDA receptor open-channel blocker, also showed significant antidepressant effects with minimal side effects in a randomized, double blind, placebo-controlled study.[326] And D-cycloserine, an NMDA receptor agonist, worked to decrease depressive symptoms and suicidal ideation when used in conjunction with ketamine treatment.[327]

Manji, at Janssen, expressed a strong interest in the AMPA receptors as a promising regulatory pathway for future mental health therapeutics.[328] The AMPA receptors, which are ionotropic glutamate receptor subunits, exist throughout the brain and regulate excitability.[329] Manji hopes that the ubiquity of the AMPA receptors and the relatively few existing therapeutics in the field that target the pathway, might present opportunities for novel ways to treat mental illness conditions.

C. CONSTRAINTS AS A SOURCE OF CREATIVITY: REGULATORY RESTRICTIONS, PATENTS, AND CLINICAL SKEPTICISM AS INNOVATION DRIVERS

In 2015, Joseph P. Fishman published *Creating Around Copyright* in the Harvard Law Review, arguing that the *constraints* created by copyright law were themselves major sources of creativity.[330] Fishman's paper begins with the story of a filmmaker who devised a *Flash Gordon* remake. Unable to secure a license, the filmmaker cleverly worked around the *Flash Gordon* copyright, distilling visual thematic aspects of that story to construct a new universe of characters and settings. That filmmaker was George Lucas, and the galaxy far, far away eventually became the *Star Wars* universe.[331]

325. Leea H. Muhonen et al., *Double-Blind, Randomized Comparison of Memantine and Escitalopram for the Treatment of Major Depressive Disorder Comorbid with Alcohol Dependence*, 69 J. CLINICAL PSYCHIATRY 392, 392 (2008).

326. Gerard Sanacora et al., *Lanicemine: A Low-Trapping NMDA Channel Blocker Produces Sustained Antidepressant Efficacy with Minimal Psychotomimetic Adverse Effects*, 19 MOLECULAR PSYCHIATRY 978, 978 (2014).

327. Mu-Hong Chen et al., *Maintenance of Antidepressant and Antisuicidal Effects by D-Cycloserine Among Patients with Treatment-Resistant Depression who Responded to Low-Dose Ketamine Infusion: A Double-Blind Randomized Placebo-Control Study*, 44 NEUROPSYCHOPHARMACOLOGY 2112, 2112 (2019).

328. Talesnik, *supra* note 202.

329. *Id.*

330. Joseph P. Fishman, *Creating Around Copyright*, 128 HARV. L. REV. 1333 (2015).

331. *Id.* at 1336; J.W. RINZLER, THE MAKING OF STAR WARS 4 (2007).

Fishman's article describes how fears of copyright infringement can, paradoxically, result in imaginative creations.[332] Fishman and others note that this phenomenon occurs throughout the intellectual property landscape; constraints also promote innovation in the realm of patents and useful innovations.[333]

Impediments created by patent monopolies force inventors to look beyond the "default" and towards disparate applications and processes that might not initially appear promising.[334] A patentee's right to exclude triggers competitors to develop innovative creations that compete with and improve upon the patented invention.[335]

Ketamine provides a lucid illustration of this phenomena. The drug faces a litany of obstructions to widespread adoption as an antidepressant, from restrictive drug classifications to a misaligned patent and regulatory approval motivation paradigm. Although these conditions doubtlessly discourage many from entering the space, they also force those who wish to operate in this space to do so creatively.

1. *Psychedelic Therapy Startups and Telehealth: Creative Solutions to Restrictive Ketamine Access*

Psychedelic therapy startups rebelled against one framework by creating a new one, building a product that delivered treatment despite a restrictive regulatory landscape.[336] Companies such as Field Trip Health responded to clinical skepticism around ketamine's use as an antidepressant by creating a novel medical model for psychedelics. This creates a blueprint for others providing access to drugs, such as psilocybin and MDMA, that provide immense potential upside to patients facing difficult-to-treat conditions (such as TRD and PTSD), despite restrictive access issues.[337]

Likewise, those operating in the telehealth space are unquestionably serving as the type of "disruptors" that drive progress in ossified systems.[338] Access to pharmaceuticals, especially those that are not FDA-approved or used "off-label," can be incredibly cumbersome. Clinicians are skeptical about

332. Fishman, *supra* note 330, at 1336.

333. *Id.* at 1351.

334. *Id.*

335. *Id.* at 1339.

336. *Id.* at 1337; Philip N. Johnson-Laird, *Freedom and Constraint in Creativity*, *in* THE NATURE OF CREATIVITY 202, 212–13 (Robert J. Sternberg ed., 1988).

337. This is already happening. Companies are taking notice of ketamine's rollout in these psychedelic therapy startups and applying those learnings to increase access to other drugs and methods of treatment. *See, e.g.*, Jacobs, *supra* note 302.

338. Hamby, *supra* note 135.

prescribing such drugs, insurance companies seldom reimburse patients for them, and for those who have access, costs are often astronomical. Telehealth companies like Joyous provide relatively inexpensive access to drugs like ketamine cheaply, quickly, and to patients throughout the United States, regardless of their geographic proximity to clinics.[339]

There are certainly downsides to these approaches, discussed at length in Section IV.D, *supra*.[340] Nevertheless, these pathways are doubtlessly *innovative* in their approach to increasing access to novel therapies. In the oft-stagnate field of pharmaceutical access, this is the type of change that might inevitably prove immensely valuable to patients.

2. *Innovating Around Patents: Spravato and Novel Glutamate-Modulating Drugs*

Policy justifications for intellectual property protections in the United States typically focus on rewards for resource-consuming efforts while developing new inventions.[341] With the motivation of a government-sanctioned temporary monopoly, creators expend time and money designing products that benefit the public. This is a frequently discussed motivation for inventors; less examined is the impact that such monopolies have on *other* innovators.

Yet, courts and commentators recognize that "inventing around" patents creates a generative source of creativity.[342] For example, in *James P Marsh Corp. v. U.S. Gauge Co.*, Seventh Circuit Judge Evans noted that the patent system spurs competitors to "put forth their best effort to produce a product as good, yet different from the patentee's."[343] Others observe that innovation is improved through the patent system's "mandatory differentiation

339. *Id.*

340. *See id.*

341. *See, e.g.*, Fishman, *supra* note 330, at 1345; WILLIAM M. LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 69 (2003).

342. Fishman, *supra* note 330, at 1351.

343. 129 F.2d 161, 164 (7th Cir. 1942); *see also* Chicago Steel Foundry Co. v. Burnside Steel Foundry Co., 132 F.2d 812 (7th Cir. 1943). In *Chicago Steel Foundry*, Judge Evans again made a justification for the existence of the patent system, noting "instead of displaying monopolistic traits, the patent fosters competition among inventors and begets new and better products at lesser costs." *Chicago Steel Foundry*, 132 F.2d at 816.

mechanism."[344] In several decisions, the Federal Circuit cited "inventing around" as a major positive outcome of the patent system.[345]

Spravato is an example of the rewards that such diversified search routes promote. In attempting to "invent around" the existing ketamine landscape, Janssen developed a unique drug formulation and method of treatment. The USPTO granted Janssen a patent for their efforts in developing Spravato; in return, the public gained access to a novel drug therapy. Because Janssen's patent provided sufficient motivation to pay for the process, the company largely funded the otherwise prohibitively expensive FDA approval process for Spravato. So, when Janssen's patents ultimately expire, generic manufacturers will be able to provide a cheaply accessible *and* FDA-approved antidepression treatment.[346]

There is good reason to believe that similar motivations will drive novel glutamatergic/NMDA-receptor modulating drug therapies. With Spravato's existing patents and racemic ketamine's long-expired protections, companies might find that their best route to profitability in this space will be to develop completely new formulations of drugs. As discussed *supra*, this is already happening—several pioneers who established ketamine's antidepressant efficacy are now developing alternate drug formulations that modulate the glutamate/NMDA pathway, hoping to provide an alternative or improvement to ketamine.[347]

Antidepressant therapies are ripe for this type of divergent thinking. Depression treatments exist in a field where the optimal solution is not necessarily known ex ante—clinicians often must try numerous classes of drugs before a patient achieves remission.[348] A diverse set of solutions available in this space increases the chances of successful treatment.[349]

Research into this class of drugs might even open the floodgates to an entire new class of antidepressants. Scientists may soon develop drugs that harness ketamine's antidepressant power without its undesirable dissociative

344. *See, e.g.*, F. SCOTT KIEFF ET AL., PRINCIPLES OF PATENT LAW 70–71 (4th ed. 2008); Matthew J. Conigliaro et al., *Foreseeability in Patent Law*, 16 BERKELEY TECH. L.J. 1045, 1050 n.17 (2001).

345. *See, e.g.*, TiVo Inc. v. EchoStar Corp., 646 F.3d 869, 883 (Fed. Cir. 2011) (en banc); Hilton Davis Chem. Co. v. Warner-Jenkinson Co., 62 F.3d 1512, 1520 (Fed. Cir. 1995)

346. *See* Gastaldon et al., *supra* note 238.

347. *See, e.g.*, Berman et al., *supra* note 99, at 351–54; Muhonen et al., *supra* note 325; Sanacora et al., *supra* note 326; Chen et al., *supra* note 327.

348. Philip Royce & Cassandra Ma, *Choosing an Antidepressant*, 44 AUS. PRESCRIBER 12, 12–15 (2021); Richard R. Nelson, *Uncertainty, Learning, and the Economics of Parallel Research and Development Efforts*, 43 REV. ECON. & STAT. 351, 352 (1961).

349. *See* Fishman, *supra* note 330, at 1353; Nelson, *supra* note 348.

side effects. This might even lead to a class of drugs that, like SSRIs, patients can take daily with minimal adverse effects. Forced to explore realms outside of the current pharmaceutical mainstream, clinicians might develop a drug that becomes as powerful and as popular as Prozac was in the 1980s.

VI. CONCLUSION

The development story of ketamine follows the same track as many early antidepressant drugs (e.g., MAOIs, TCAs): researchers, using a drug for one therapeutic purpose, observe an unexpected side effect and follow through with clinical diligence to identify another useful purpose of the drug. Ketamine (and, potentially, its derivatives) holds immense promise for advances in antidepressant therapies. However, the current regulatory paradigm for ketamine in the United States also showcases a tension between the patent incentive system, the FDA approval process, and insurance carriers that might be limiting the otherwise breakthrough potential of ketamine as a depression treatment. For ketamine to truly achieve its prospect as "one of the most significant advances in the field of depression in recent years," regulators may need to rethink how novel uses of previously approved drug therapies can gain FDA approval for new indications and methods of treatment. Without such intervention, millions of individuals suffering from depression may not receive access to a potentially consequential intervention.