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## Ketamine—Its History, Uses, Pharmacology, Therapeutic Practice, and an Exploration of its Potential as a Novel Treatment for Depression

Philip E. Wolfson  
*Center for Transformational Psychotherapy*

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# INTRODUCTION TO SPECIAL TOPIC SECTION ON PSYCHEDELIC KETAMINE AS ANTIDEPRESSANT

## **Ketamine—Its History, Uses, Pharmacology, Therapeutic Practice, and an Exploration of its Potential as a Novel Treatment for Depression**

The origins of this special section on ketamine and ketamine assisted psychotherapy and an overview and deliberately controversial discussion of depression and ketamine's putative efficacy as an anti-depressant arise from two sources. The first is a fairly widespread and historical appreciation of ketamine's power as a transformative agent, especially when embedded in a psychotherapeutic context. Ketamine is after all the only legal psychedelic in use—as a Schedule III substance with an indication as a dissociative anesthetic and a long history of safe and effective use for anesthesia and analgesia, this without significant respiratory depression. Other uses have occurred, for example in the control of agitated, suicidal, and aggressively psychotic individuals in the ER setting, and as a transformational, psychedelic experience at low to moderate dosages—pre-anesthetic levels—inspired by the work of Roquet, Jansen, Krupitsky, and others.

More recently, ketamine has come into exploration as an anti-depressant, based on an adventitious finding of effect in subjects being assessed for the cognitive impact of ketamine (see Kolp et al. in this section for a more thorough description of this history). The original and early work with ketamine using low to moderate transformational medication levels with psychedelic

impact noted anti-depressant responses related to an overall psychological benefit and an “afterglow” that could last for up to two weeks time, very similar, and seemingly longer than single dose IV drip administration in the current dominant application. This burgeoning of interest in ketamine as an anti-depressant with a unique mechanism of action that differentiates it from the existing and limitedly efficacious static psychiatric arsenal that includes SSRIs, SNRIs, and others is the second source of this section.

Much of the current research focused on depression appears to be an attempt to administer ketamine intravenously at rates that are slow enough and doses that are low enough to avoid much of the psychedelic effect that occurs at higher moderate dosages. If an experience of psychedelic or dissociative effects interferes with an antidepressant outcome, then such an approach would be sensible. On the other hand, if higher dosages or the psychedelic experiences that they typically produce are both entirely safe and also associated with greater antidepressant effect, it is difficult to understand the logic of attempting to avoid psychedelic dosages. Surely it is time to set aside the old War on Drugs narrative, and embrace the use of ketamine for depression if there is evidence that it can have significant efficacy

in treatment resistant depression and other indications without concern for the fact that a psychedelic experience may be inseparable from effective therapeutic dosages, and may well contribute to the therapeutic effect. In this section, Kolp et al. review the numerous new ketamine related substances being examined for human use—substances that are based on the same mechanism of action as ketamine but without its psychedelic effects. Yet, as Ryan et al. (this issue) note, thus far no new relative of ketamine that lacks its dissociative effects has yet to show antidepressant efficacy. Still, research is in an early stage, and more such work is planned or in process at pharmaceutical houses. It remains to be seen whether the glutamate/NMDA hypothesis that has emerged around the anti-depressant effects of ketamine will be separable from its psychedelic effects.

Can a single chemical have remarkably dissimilar effects at different concentrations, or is there a continuum? Certainly with regards to dose related anesthetic effect, an escalation of effect corresponds to increasing dosage. Could there be an anti-depressant effect at very low ketamine dosages that disappears as psychedelic effects occur? Not very likely! If dosage is reduced in an attempt to preclude psychedelic effects, at what level is that achieved, and how does benefit, such as anti-depressant effect, wane or somehow, paradoxically increase? Where, if there is such a thing, does a boundary lie between anti-depressant effect and interference by psychedelic effect—this being implied by much of the research that promotes anti-depressant efficacy? Does investigator bias, the War on Drugs, the desire for status and acceptability effect research and promulgation? Whatever the answer to that may be, what is presented herein is evidence for ketamine's use to create transformational experiences at low to moderate, pre-anesthetic dosages that when embedded in a psychotherapeutic approach have great potential for emotional healing and the amelioration of human suffering and confusion.

As an introduction to this section, it may be useful to consider a broader discussion of depression and the implications of phenomena under that heading.

#### **Depression, Anti-Depressants, and Transformation**

Depression is as old as mammalian life itself. Grief, the sensations of loss, aloneness, frustrated desire, hopelessness, resignation, despair come along with mothering—as do attachment, affection, education, empathy, protectiveness, and connection. These are

inherent to nurturing and raising young to adulthood. They are the heart—positive and consequent—of live birthing of young—of children—who cannot survive on their own. From this perspective, the negative emotional consequences of a particular individual's life are systemic—culturally and situationally conditioned within a matrix of local and disparate social formations—family, band, tribe, species, interrelated and interacting other species in the broad sense of the biological community, and its resources—embedded in nature and its individual and group potentialities for creative engagement. The vectors and interactions—the symbioses, dependencies, obligations, potentialities, adaptations and threats go in all directions.

Human consciousness has tended towards an individual orientation as a distortion—connections and connectivities being more unconscious and built into the stored complexes that are the substrates of our interactive capacities, what in earlier times were inadequately termed instincts. We look out from our insides and interpret our inputs inside. This inevitably leads to self-absorption and ego formation. But life, our life, is far more complex and interrelated than we appreciate—and much of our sensational realm never makes it to consciousness, whether it is about our own complex multicellular integrations, or our relationships externally. What is exciting about the evolution of systemic thought and exploration is that it has opened us to the vast web of integrations and effecting influences and relationships, and our awareness of this is growing exponentially, ever-widening the complexity of our understanding, yielding new conceptual schemas that are continually being updated, expanded or abandoned.

Psychiatry, as an evolving solidifying guild, now too coupled with Big Pharma and compensation through the insurance industry, has rubricized and rigidified step by step. Emphasizing consensuality to enable a replicable conceptual and compensable schema, it has tightened its grip on how mental health practitioners think and afflicted the public's consciousness as well. How often does one use the word "depression" mindlessly to compress feelings, or hear, "She's bipolar," as if that expresses the essence of a person. We have become all too comfortable and accepting of diagnostic terminology as if it were real and expressive of our realities. This extends to how depression is measured and formalized into a few codes that are supposed to cover the vast array of human responses.

Such an approach tends to understate the overlap between conceptually discrete DSM entities that are really not separable. Take, for example, a continuum of anxiety-grief-trauma-poverty-gender-ethnic-racial-oppressions-depression-torpor-fatigue-insomnia-agitation-confusion-interpersonal struggle-divorce-child abuse-hopelessness-lovelessness and many more linkages. These are all embedded in the term depression but not visible, as is so much of what occurs to cause depression and is depression is not endogenous and not brought on by those who suffer with depression. But this is not in the discussion format, for in this respect causation is linked directly to culture and outside the dominant culture's acceptable boundaries for change—and therefore of psychiatrists'/psychotherapists' responsibilities. Antidepressants may reduce suffering and improve functionality to some degree for some people and may have an impact on their perspectives as well, but going to the “shrink” often has little impact on the chain of interlinked contributors to depression. Spuriously rigid diagnostic entities do not help the matter, as if, for example, PTSD is not a form of depression/agitation, and as if most depressions are not trauma or PTSD driven and are not linked to anxiety; they are. Psychiatric drugs are not all that specific, nor often that helpful, yet they have been tied to the development of this constricted view. One only has to recall the relationship between certain drug companies' push for the bipolar II category linked to the anticonvulsant Lamictal. With the patent expired and the availability of the generic lamotrigine—without all the hype and the profits, promotion of attention to bipolar II has largely gone away.

Adding to this tendency to confine views of depression is its measurement as per the indices that give the diagnosis—a circularity to be sure—such as the Beck Depression Inventory, the Hamilton, the MADRS. Those measures used to assess the effect of drugs that are in development are constrained by the instruments themselves to narrow measures of change. Yet even when administered by blinded researchers, assessment is generally obtained by self-report, since subjective reporting is truly the only means to obtain information on consciousness outside of guesswork by observation, or questioning, which are again inevitably self-report based. The instruments used tend contain narrowing and often confusing questions about how the person feels within a very circumscribed framework. One doesn't ask, for example, how they feel about going back to their difficult circumstances; or how they feel about living with that

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person with whom they may be having difficulties; or their careers; or being laid off; or about sexuality—the latter being especially conspicuous as an omission when most of the drugs in use tend to suppress it.

The following papers on ketamine and its use in therapeutic contexts represent a bit of defiance of all that conventionality, for its use challenges one to understand on a broader level what they are truly about as practitioners and human beings. There are those who practice psychiatry/psychotherapy to improve symptoms, which may well improve lives. There are also those who practice psychiatry/psychotherapy to change lives. Invariably, practitioners do both, or certainly the latter group must do both. At this game, in true modesty, mental health practitioners are partly successful at best. Our aspiration in producing this section is to assist practitioners a bit in improving the practice of helping humans to grow, connect, prosper, and reduce their suffering.

#### The Ketamine Papers

I am truly honored to be the guest editor for this Special Topic Section of the *International Journal of Transpersonal Studies* on ketamine—exploring its history, uses, pharmacology, therapeutic practice, and its potential as a new and novel treatment for depression. To call this collection of papers seminal is to understate its contribution to the subject. This section assembles the core of investigators who have used the substance in a variety of therapeutic contexts for over 40 years, and whose experience with the transformative and therapeutic properties, risks, and clinical successes and failures constitutes what is likely the largest body of information available on the subject. The reader is invited to take time moving through the long and detailed contours of this comprehensive undertaking. Later this year, these papers will be republished in book form by the Multidisciplinary Association for Psychedelic Studies (MAPS), together with several additional articles, as *The Ketamine Papers*.

The section begins with what is to date the most thorough review in the literature of the use of ketamine for the treatment of depression. Wesley C. Ryan, Cole J. Marta, and Ralph J. Koek's paper, “Ketamine and Depression: A Review,” analyzes and segregates studies into meaningful categories that enables a thorough review of this new field, its claims, and its limitations. From this perspective, it is more feasible to evaluate that which appears to be plausible, or overstated,

or an indication of a vector for further exploration. Additionally, the tendency to strip ketamine practice of its psychedelic actuality—through adjustment of dosage and administration—is also made clear. This paper constitutes a pivotal reference point for evaluating the view presented in other papers contained in this section: that the transformative nature of ketamine as a dissociative agent with psychedelic properties is key to its therapeutic potential, including its antidepressant efficacy.

Next in the section is my own study of experienced users replicating the “NIMH protocol,” as I have called it after the National Institutes of Mental Health studies that posited a very low dose antidepressant effect. The subjects in my study compared the NIMH protocol experience that was duplicated with their prior transpersonal experiences of larger IM doses. This represents an attempt to understand and feel the effects of the low dose as it might pertain to the reported experiences that have been called antidepressant. Positing a psychological mechanism of action, this paper also discusses antidepressant treatment in a novel framework.

The following paper, “Ketamine Psychedelic Psychotherapy: Focus on Its Pharmacology, Phenomenology, and Clinical Applications,” by Eli Kolp, Harris Friedman, Evgeny Krupitsky, Karl Jansen, Mark Sylvester, M. Scott Young, and Ana Kolp, offers a comprehensive overview of the development of psychedelic ketamine therapy. Eli Kolp’s work with ketamine in a full program that he unabashedly entitles Ketamine Psychedelic Psychotherapy (KPP) is a thorough approach to working with many different diagnoses, addictions, and trauma. Kolp’s treatment experience is extensive and his use of a variety of supportive and essential techniques, and methodologies including MAOIs, diet, meditation, and an orientation towards the successful induction of transpersonal experiences as healing and transformative is unique, daring, and well worth understanding. Evgeny Krupitsky began groundbreaking work with ketamine in the former USSR, focusing on alcoholism and addiction in inpatient settings using a single and, later, two and three administrations of ketamine embedded in an intensive abstinence/therapy program. Krupitsky has remained in Russia and has had his singular and promising work disrupted by a change in the scheduling of ketamine to the equivalent of Schedule I claimed to be due to a dangerous accelerating street use of the drug. As a co-author of this article, Krupitsky brings the perspective

of his extensive and pioneering experience. Karl Jansen is the author of *Ketamine: Dreams and Realities*, published in 2000, which remains the single most thorough and intelligent overview of the ketamine experience. Harris Friedman is Senior Editor of this journal and a significant contributor to the understanding of altered states and psychedelic psychotherapy. The remaining authors each bring an additional facet of expertise to this compelling perspective on ketamine psychotherapy.

Terrence S. Early offers an in-depth look into his practice using ketamine, along with a discussion of its history, political issues, and relationships to other treatments, in his paper, “Making Ketamine Work in the Long Run: The Basics.” Dr. Early’s practice model involves primarily the use of intramuscular ketamine—often with multiple sessions over time—embedded in an extensive therapeutic program. His comprehensive psychiatry practice, situated on the interface between psychiatry, anesthesiology, and psychotherapy, had its origins in academia and has continued in an intensive clinical practice in the Santa Barbara area that is most likely unique in the United States and internationally. His work may serve as a guide to the possibilities for using this substance, and as a specific reference manual for others interested in entering this field of practice. Often treating the most damaged and suffering individuals with commitment and heart, Early is one of those rare lions of medicine who exemplify for all practitioners the best efforts to assist and heal those in need.

Jeffrey Becker practices psychiatry/psychotherapy in the Los Angeles and Santa Barbara areas. His paper, “Regarding the Transpersonal Nature of Ketamine Therapy: An Approach to the Work,” describes his use of ketamine as an enfolded part of an overall therapeutic method. Combining Edinger’s ego-Self axis with aspects of Jungian thought, Becker has created his own approach to treating depression with intramuscular ketamine and its attendant experiences. He offers an explicitly transpersonal perspective for practitioners in this clinical field.

A conversation with Richard Yensen brings the reader into the realms of Carlos Castaneda, and of Salvador Roquet, with whom he had a close and enduring relationship. In dialogue with me (Wolfson), Yensen shares rich accounts from the history of ketamine therapy in the piece, “Psychedelic Experiential Pharmacology: Pioneering Clinical Explorations with Salvador Roquet.” Roquet left his mark on psychedelic

psychotherapy in which ketamine came to play a significant part as an ego-lytic and then reconstitutive agent along with other psychedelics. It was Roquet who principally introduced ketamine practice into the small world of psychedelic practitioners, of which Richard Yensen was a part along with such luminaries as Stanislav Grof and Stanley Krippner. Yensen provides the details of Roquet's art form, which to this day influences many practitioners. The psychedelic world has always had a bell shape to it: There are the heroic take-it-as-far-as-you-can-go dissolutionists, or psychotomimeticists bent on crushing ego and then reassembling; and the step-by-step cautionists who build the experience and practice a more classical psychotherapy approach. In between, there are those of all stripes. Over time and with experience, practitioners will shift positions and modify their practices. A second continuum that may occur to readers is the "hard-head to vulnerable" spectrum—on the one hand a sense of anxiety about going too far, and on the other a sense of loss from not going far enough. There are two aspects: Each person is built differently with different tolerances and physical vulnerabilities. Each tends to either exaggerate or understate these. Most have a fear of losing their minds; of their minds betraying them; of madness lurking if they do too much of something or other; of a distrust of their core sanity. These too change with time and experience, albeit we humans are often best served by recognizing our limits and limitations. Yensen offers an intimate view of Roquet as a man who pushed limits, and seemed without fear of going too far.

On a more personal and anecdotal level, the next paper is a collection that offers three first-person reports entitled, "Ethnographic Accounts of Ketamine Explorations in Psychedelic Culture," by Kenneth Ring, Ralph Metzner, and Philip E. Wolfson. Ken Ring, one of the great progenitors of research on the near death experience (NDE), regales with an account of his first powerful ketamine experiences in a way that also recollects the culture of Esalen Institute in the 1980s. In fact, there was a significant underground use of ketamine that paralleled on a smaller scale the then legal exploration of MDMA for psychotherapy and peaceful transformation of interpersonal relationships. Ken's personal account serves as an in-depth exemplar of the feel of a first time experience—though certainly not the only feel, as the breadth of ketamine experience is not subject to compartmentalization. This was also the

era when John Lilly made his appearance in the Esalen circles, and Ralph Metzner shares a brief account of Lilly as he both exhilarated us with the possibilities of ketamine's psychedelic properties for transformation and transpersonal experiences, and horrified us at its addictive potential. Viewing ketamine's potential for dependency through John Lilly, I provide brief closing remarks as a warning of the possibility of the poison path arising from ketamine use. Ketamine's putative mechanism of action(s) does not reside in the usual self-reward dopaminergic path; instead, its allure may well be of a different nature, a possibility that is discussed.

Included in the section is, "Ketamine (IM) Assisted Psychotherapy (KAP): A Model for Informed Consent," which potentially may serve others as they consider including ketamine in their own clinical work. This sample informed consent form is intentionally comprehensive and lengthy. Though it builds on the prior work of Eli Kolp and Terry Early, this consent form reflects my own engagement with the challenges of effectively providing informed consent for KAP and is my responsibility.

The final piece in the Section presents my own schema for conceptualizing transformation—a topic of some relevance since a major claim of this Section is that Ketamine Assisted Psychotherapy's value is inextricably linked with the psychedelic experiences that ketamine induces—experiences that are often reported as psychologically transformative processes. My hope is that this piece will serve as a fulcrum for discussion, amplification, and healthy controversy. . Included in the paper is a taxonomy offered as a meta-structure for examining transformation with psychedelics, the formats presented being derived principally from ketamine experiences, but also having wider applicability. A 'transformation codex' is included as a matrix for characterizing one's own personal histories of transformational experiences.

As you read these papers, here are some points to consider:

- The complexity of our evolved brain/mind/consciousness/connectivity makes reductionist and narrow concepts and explanations for complex and varied states of mind like depression unhelpful, off the mark and superficial. DSM diagnoses are circular and tautological defining depression as a cluster of the symptoms that in turn define depression. They

take the complexity of human beings out of the analysis and create deep mystification in all of us as we think about ourselves and others.

- The concept of antidepressants is at its core complex and varied and the restriction in thinking primarily about drug interventions serves the pharmaceutical industry and the officials who are in charge of the self-interested fabrication of depression as disease.
- Within the realm of psychiatric medicine there are many types of drugs said to be antidepressants and the fact that 20% to 50% of people do not respond to drugs based on the neurotransmitter model of depression strongly suggests that this approach has serious flaws. The chemical imbalance that is theorized as the source of depression is elusive, and though it sounds empirical, there is no actual evidence that such an imbalance exists in actual individuals.
- A very partial list of antidepressants includes multiple types of chemical antidepressants with very different neurotransmitter actions and myriad other means to obtain antidepressant effects: anticonvulsants, stimulants, marijuana, exercise, meditation, hedonism, temporary satisfaction of cravings, elimination of cravings, oxytocin, sexuality, spiritual practice, money, love, children, activism, justice, a good job, respect, friendship, education, a good book, a bad book, and so on.
- Most depressive episodes come to an end without psychiatrists and without therapy. Some depressions begin with psychiatrists and psychotherapists.
- There appears to be a continuum between anxiety, trauma, and depression, and most often they are mingled.
- There are so many aspects of being and being in the world, and they all reflect and infect mood. All evaluations are oversimplifications. Even a partial evaluation of related parameters and aspects must include: energy-enthusiasm-motivation-sexuality-engagement-learning-intellect-spirit-love/hate-trauma-grief/loss-failure/success-pleasure/displeasure-hopefulness/hopelessness-health-age-intelligence-blocks/phobias-social/environmental context-the cultural affect-religion-gender-education-origins and history of oppression-parenting-grief and loss-responsibilities-family-addictions, and so on.

Humans are complex, and “character,” though it is tempting to see it as evanescent, not essential, and malleable, has its rigidity and implacability in all of us. After all, being a “shrink” is really a scholarship to watch oneself, as well as others. The argument here is that transformative work generally trumps symptom relief—and contains the latter within its effect size. In other words, in my humble view, ketamine really is not very promising as a low-dose anti-depressant. Low dose ketamine treatment does not do much, and it does not do it for very long. Embedded in a repetitive psychotherapy format, its success rate for depression increases. In most studies, it appears impossible to reliably strip ketamine of some element of mild dissociative experience, as if they were merely some undesirable “side effect.” Even at a low dose, its effect is felt as being mildly “stoned.” If even that minimal change of consciousness does not occur or is deliberately stripped from administration of ketamine, I believe there is then no therapy and no possibility of even a modest anti-depressant effect. After all, this is not homeopathy!

This section sets out the history, the practice, the pharmacology, the effects, various therapeutic contexts, and the literature on ketamine as a psychedelic and as an antidepressant. I hope you enjoy the controversy. You be the judge

*Philip E. Wolfson*

Center for Transformational Psychotherapy  
San Francisco and San Anselmo, CA

### **About the Author**

*Philip E. Wolfson, MD*, is the Principal Investigator for the MAPS sponsored FDA approved Phase 2 clinical trial of MDMA Assisted Psychotherapy for Individuals Suffering with Anxiety Due to Life Threatening Illnesses. Practicing psychiatry/psychotherapy in the Bay Area since 1977, Dr. Wolfson has been on the faculties of UCSF School of Medicine, JFK and CIIS and has been at the forefront of the development of alternative, progressive psychotherapies. Writing on politics, medicine, psychiatry, psychedelics, consciousness, Buddhism, and bereavement, he is the author of *Noe—A Father/Son Song of Love, Life, Illness and Death*. In creation is The Center for Transformational Psychotherapy, established as a base for offering Ketamine Assisted Psychotherapy and progressive psychotherapy in general.

## **About the Journal**

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