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"THE SHAPE OF DISCOVERY: Ketamine for Treatment Resistant Depression"

American Society of Clinical Psychopharmacology

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Mount Sinai

DISCLOSURES

Dr. Dennis Charney is named as co-inventor on patents filed by the Icahn School of Medicine at Mount Sinai (ISMMS) relating to the treatment for treatment-resistant depression, suicidal ideation and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents for the treatment of treatment-resistant depression and suicidal ideation. Consistent with the ISMMS Faculty Handbook (the medical school policy), Dr. Charney is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO has received regulatory approval for treatment-resistant depression, ISMMS and thus, through the ISMMS, Dr. Charney, will be entitled to additional payments, beyond those already received, under the license agreement. Dr. Charney is a named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. The ISMMS has entered into a licensing agreement with Click Therapeutics, Inc. and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, Dr. Charney has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. Dr. Charney is a named co-inventor on a patent application filed by the ISMMS for the use of intranasally administered Neuropeptide Y (NPY) for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. Dr. Charney is a named co-inventor on a patent application in the US, and several issued patents outside the US filed by the ISMMS related to the use of ketamine for the treatment of post-traumatic stress disorder (PTSD). This intellectual property has not been licensed. Dr. Charney is a named co-inventor on a patent application filed by ISMMS for systems and methods for providing a resilience building application to support mental health of subjects. This intellectual property has not been licensed.

Abstract

The discovery of ketamine raises questions about the process of discovery. What types of environments facilitate discovery? What is the optimal size of research groups? How did the science come together that led to the initial trials? What opposition existed? What was the initial reaction?

Recent studies indicate that large teams develop and small teams disrupt science and technology. Smaller teams have tended to disrupt science and technology with new ideas and opportunities, whereas larger teams have tended to develop existing ones.

That was the case with our discovery of ketamine. The research groups at Yale, NIMH, and Mount Sinai were and are characterized by being small in size, encouraging bold scientific thinking in a psychological, safe, scientific environment that tolerated failure – as long as something was learned.

Large Teams Develop and Small Teams Disrupt Science and Technology

These results demonstrate that both small and large teams are essential to a flourishing ecology of science and technology, and suggest that, to achieve this, science policies should aim to support a diversity of team sizes.

Every once in a while a new idea comes along – a shift in thinking that challenges the status quo. These innovations require us to accept the change and adapt. This was true for ketamine.

Therapeutic discovery for mental illness needs a paradigm change consistent with Kuhn's conceptions of scientific revolution. As described by Kuhn, normal science begins, in which puzzles are solved within the context of the dominant paradigm, which in the case of depression was the monoamine hypothesis of depression and antidepressant action. There are similar dominant paradigms for other psychiatric diseases that have not resulted in breakthrough therapies.

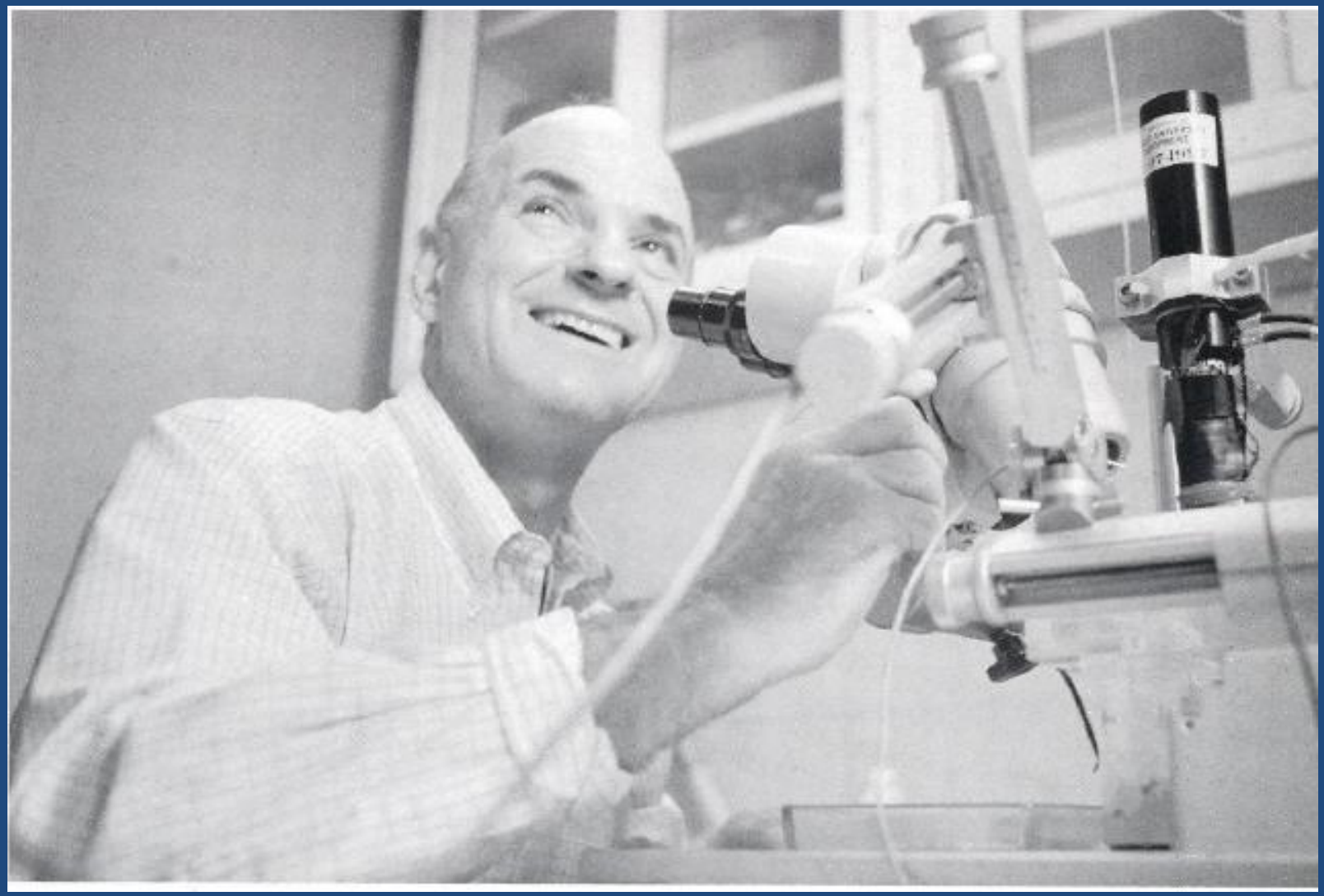
Over time, progress in "normal science" reveals facts that are difficult to explain within the context of the existing paradigm such as why don't existing therapies have better effectiveness and why haven't new medicines of novel mechanism and better efficiency been discovered.

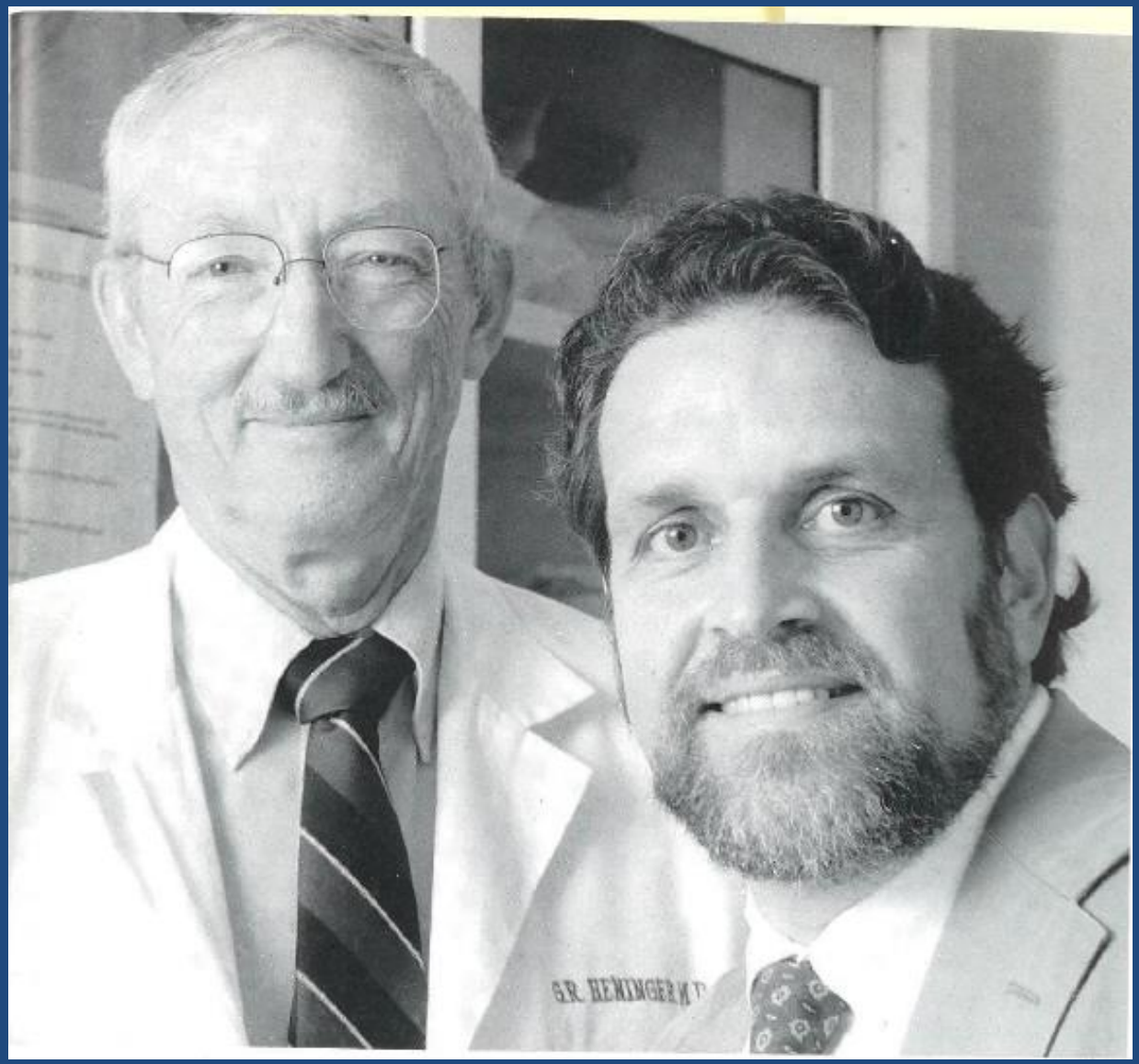
The major pharmacological treatments for major psychiatric disorders such as schizophrenia, bipolar disorder, multiple anxiety disorders, and attention deficit disorder are only partially effective and were discovered decades ago. We believe there needs to be an intense focus on drug discovery for these conditions. We suggest that multiple small groups of scientists, thinking out of the box, need to discover new hypotheses, moving beyond the long held traditional hypotheses. There have been too few novel treatment approaches and too little funding for innovative clinical trials. Progress has been too slow compared to other serious diseases such as cancer and heart disease, the lack of progress in treatment development for mental illness stands out.

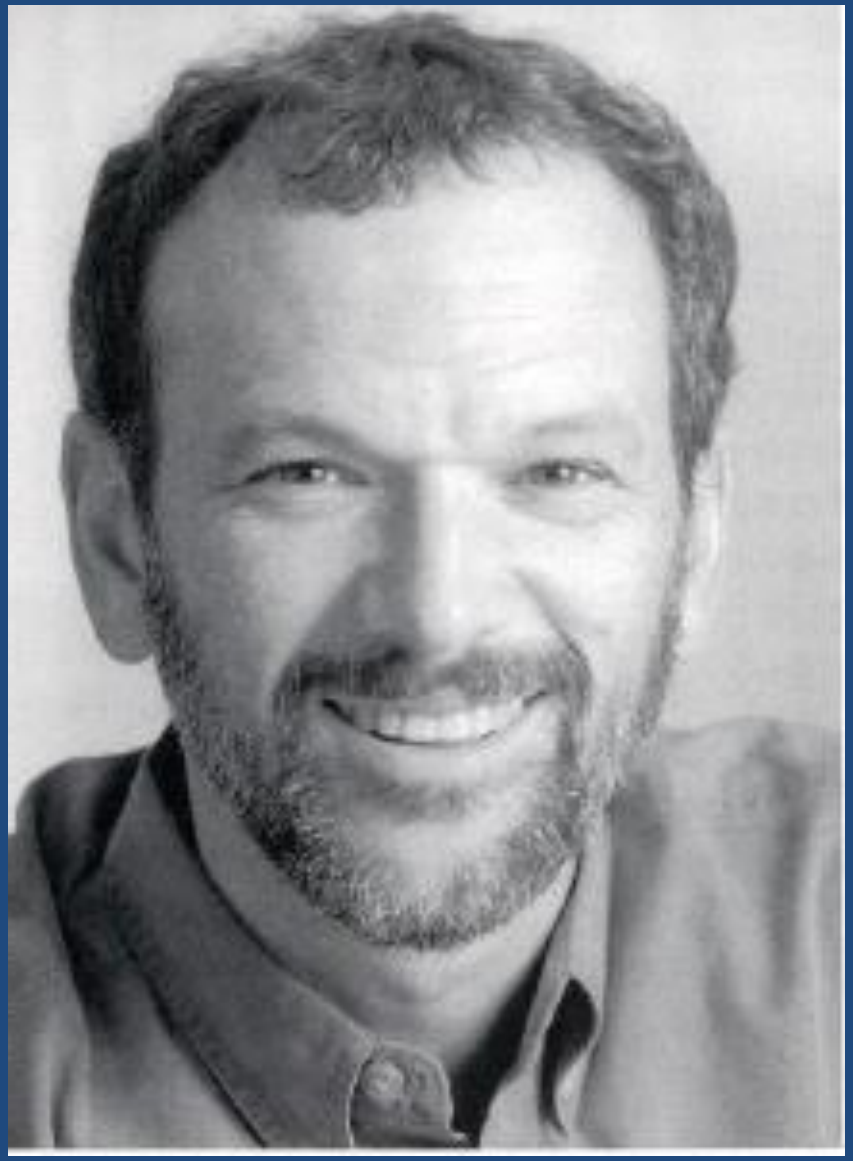
Learning Objectives

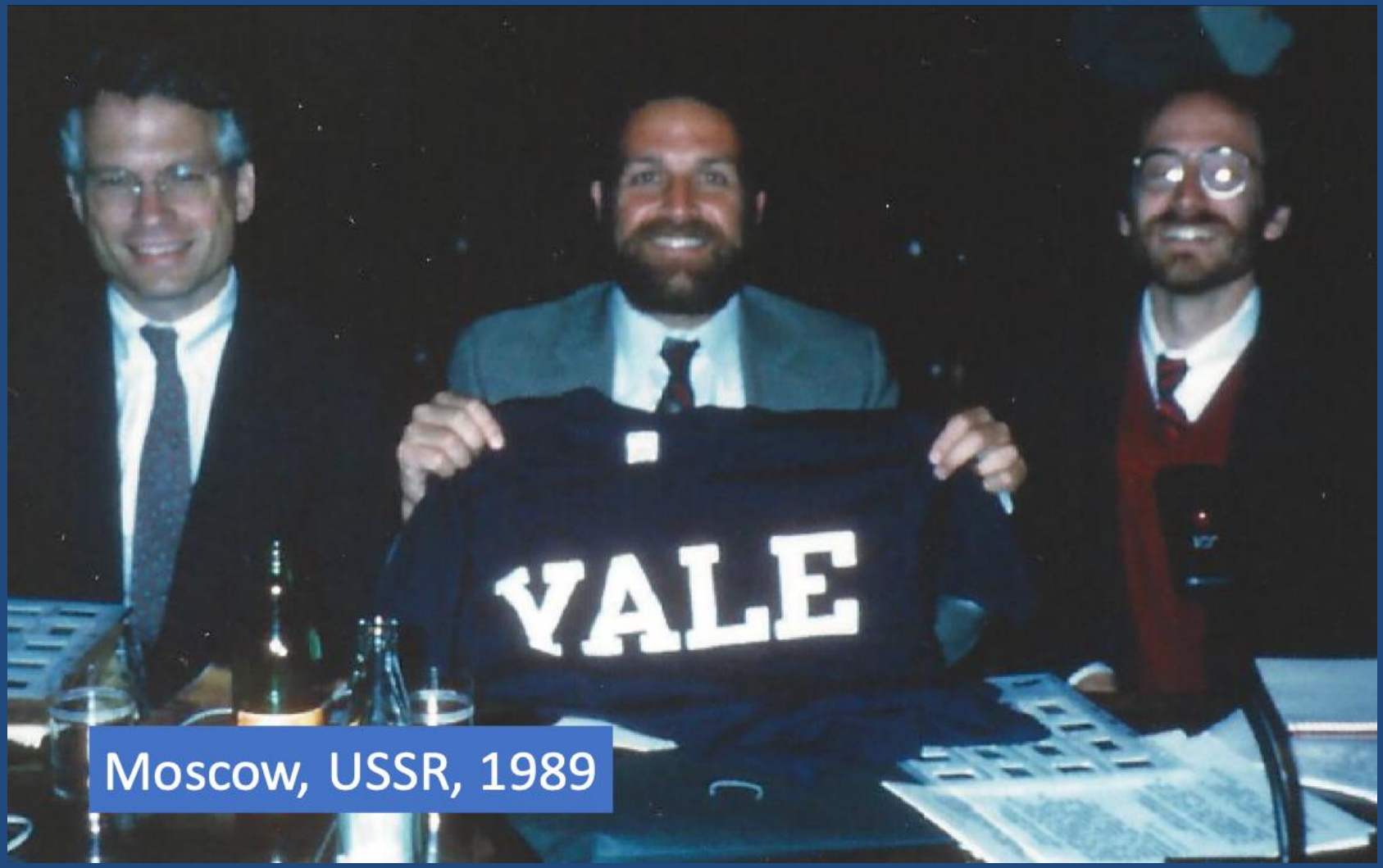
1) What processes facilitate major therapeutic discoveries

2) To have a good understanding of how ketamine for treatment resistant depression was discovered








YALE
Moscow, USSR, 1989


BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants
BRAIN &
BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

American Journal of Psychiatry
Published 1965

The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence

Joseph J. Schildkbaut, M.D.

https://doi.org/10.1176/ajp.122.5.509

During the past decade there has been a gradual accumulation of evidence suggesting a possible link between the affective disorders (depressions and elations) and changes in central nervous system catecholamine metabolism. Most of this evidence is indirect, deriving from pharmacological studies with drugs such as reserpine, amphetamine and the monoamine oxidase inhibitor antidepressants which produce affective changes in man (15, 16, 34, 43, 53,57,109).

Arch Gen Psychiatry 32:1357-1361, 1975

Biogenic Amines and Depression

Biochemical and Pharmacological Separation of Two Types of Depression

James W. Mass, MD

Recent research findings indicate that depressive disorders may be divided into two groups, A and B, using specific biochemical and pharmacological criteria. It is suggested that in the A group there is a disorder of norepinephrine metabolism or disposition, whereas serotonin and probably dopamine systems are not altered. Further, there is the possibility that B type patients have a disorder of serotonin, but not norepinephrine or dopamine systems. This biochemical heterogeneity of human depression has implications for both investigators and clinicians, and may account for disparate findings in biological studies of patients with affective disorders.

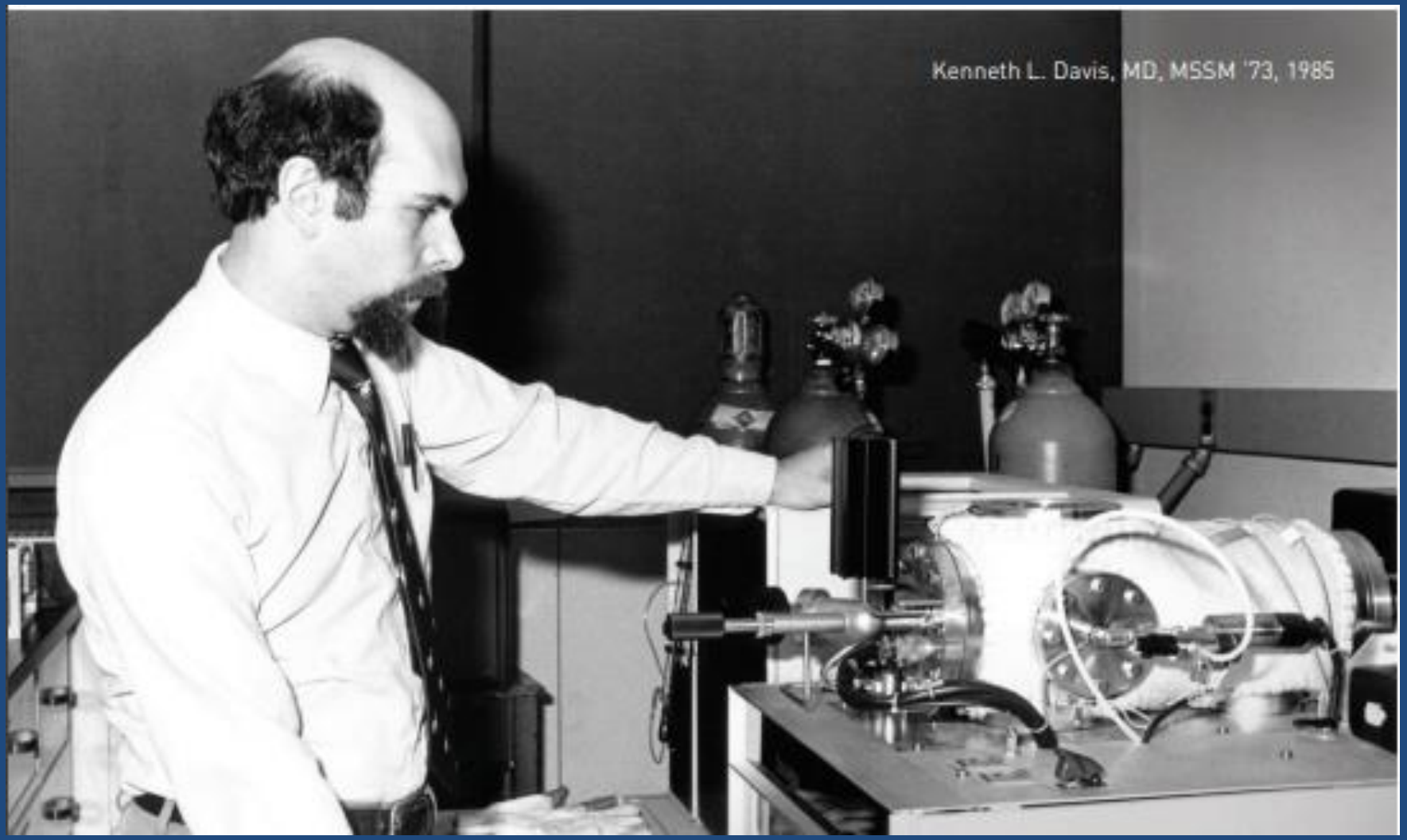
Arch Gen Psychiatry, 38 (10), 1160-80 Oct 1981

Receptor Sensitivity and the Mechanism of Action of Antidepressant Treatment. Implications for the Etiology and Therapy of Depression

D S Charney, D B Menkes, G R Heninger
PMID: 6271089 DOI: 10.1001/archpsyc.1981.01780350094011

Abstract

Considerable evidence suggests that the acute effects of antidepressant treatments on brain norepinephrine (NE) and serotonin (5-HT) systems cannot account fully for their delayed therapeutic action. This review evaluates the effects of long-term antidepressant treatment on biogenic amine metabolism and on various indexes of presynaptic and postsynaptic receptor function. In contrast to variable effects on NE and 5-HT turnover and on presynaptic receptor sensitivity almost all long-term antidepressant treatments produce consistent alterations in a number of measures of postsynaptic amine receptor sensitivity. Long-term treatment has been found to reduce beta-adrenergic sensitivity while enhancing responses to serotonergic and alpha-adrenergic stimulation, suggesting that modulation of receptor sensitivity may be a mechanism of action common to tricyclic antidepressants, "atypical" antidepressants, monoamine oxidase inhibitors, and electroconvulsive therapy. These findings provide support for hypotheses of amine receptor abnormalities in depression and indicate the need for expanded studies of amine receptor function in patients.


Kenneth L. Davis, MD, MSSM '73, 1985

J Clin Psychiatry, 53 Suppl, 28-35 Oct 1992

Acute Tryptophan Depletion: A Method of Studying Antidepressant Action

H L Miller 1, P L Delgado, R M Salomon, J Licinio, L C Barr, D S Charney

PMID: 1429482

Abstract

Serotonin (5-HT) has been implicated in the pathophysiology of depressive syndromes and in the mechanism of antidepressant drug action. Rapid dietary depletion of tryptophan (TRP) provides a paradigm for studying the role of 5-HT in depressed patients. Drug-free depressed patients do not show mood changes during TRP depletion but about one third have a clinically apparent, transient improvement in mood on return to normal TRP intake. Depressed patients in clinical remission after 6 to 8 weeks of antidepressant therapy experience a transient depressive relapse during acute TRP depletion. The significance of these findings will be discussed. Tryptophan depletion in other psychiatric syndromes will also be reviewed.

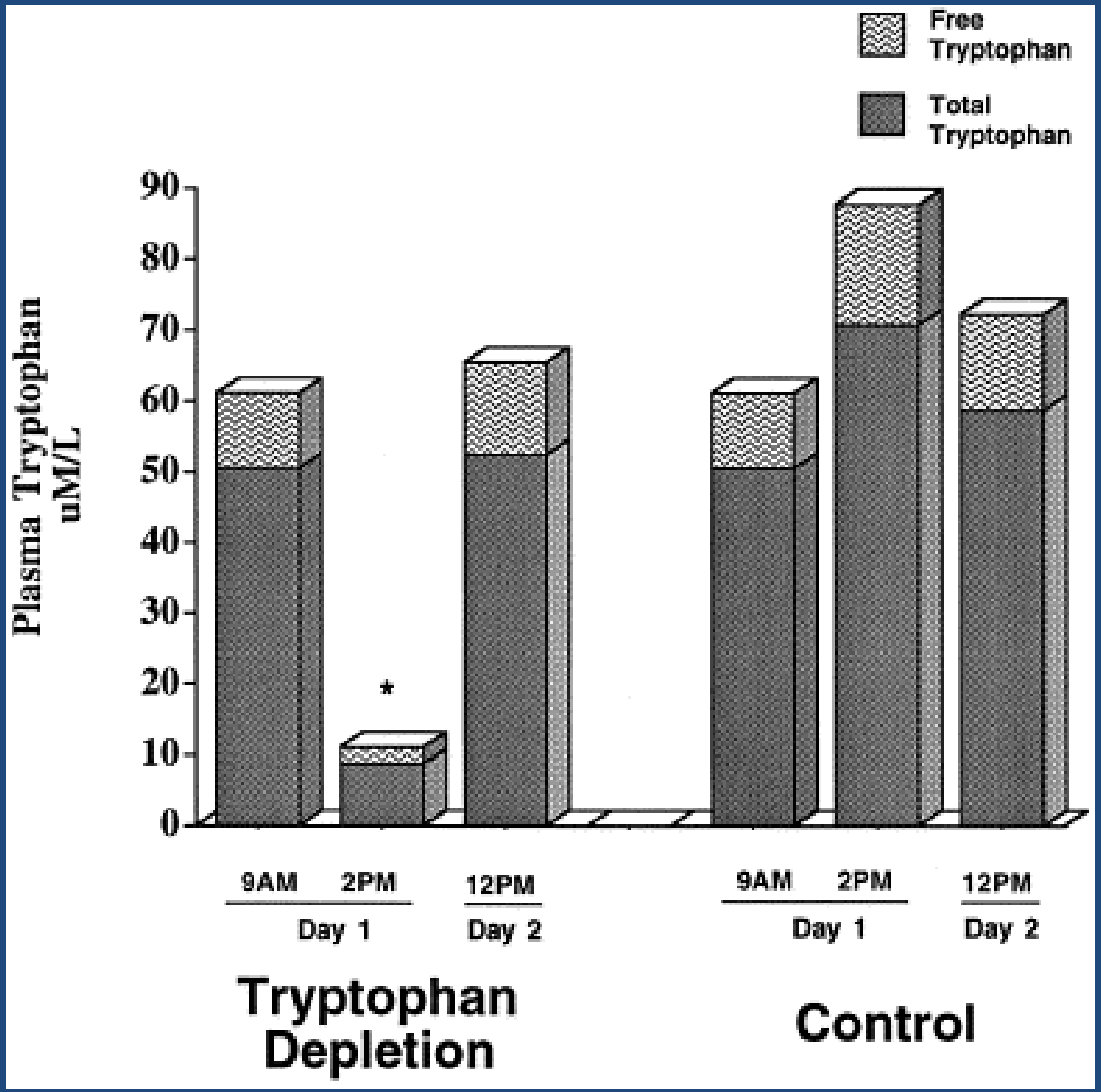


Figure 1. Plasma total and free tryptophan levels during depletion and control testing.
Day 1: 9 AM, 15 min prior to administration of the amino acid drink; 2 PM, 5 hours after the amino acid drink.
Day 2: Day after the TRP-depletion test.

Arch Gen Psychiatry. 1990;47(5):411-418

Serotonin Function and the Mechanism of Antidepressant Action
Reversal of Antidepressant-Induced Remission by Rapid Depletion of Plasma Tryptophan

Pedro L. Delgado, MD; Dennis S. Charney, MD; Lawrence H. Price, MD; et al
doi:10.1001/archpsyc.1990.01810170011002

Abstract
Brain serotonin content is dependent on plasma levels of the essential amino acid tryptophan. We investigated the behavioral effects of rapid tryptophan depletion in patients in antidepressant-induced remission. Twenty-one patients who were depressed by DSM-III-R criteria received a 24-hour, 160-mg/d, lowtryptophan diet followed the next morning by a 16—amino acid drink, in a double-blind, placebo-controlled (acute tryptophan depletion and control testing), crossover fashion. Total and free tryptophan levels decreased 87% and 91%, respectively, during acute tryptophan depletion. Fourteen of the 21 remitted depressed patients receiving antidepressants experienced a depressive relapse after the tryptophan-free amino acid drink, with gradual (24 to 48 hours) return to the remitted state on return to regular food intake. Control testing produced no significant behavioral effects. Free plasma tryptophan level was negatively correlated with depression score during acute tryptophan depletion. The therapeutic effects of some antidepressant drugs may be dependent on serotonin availability.

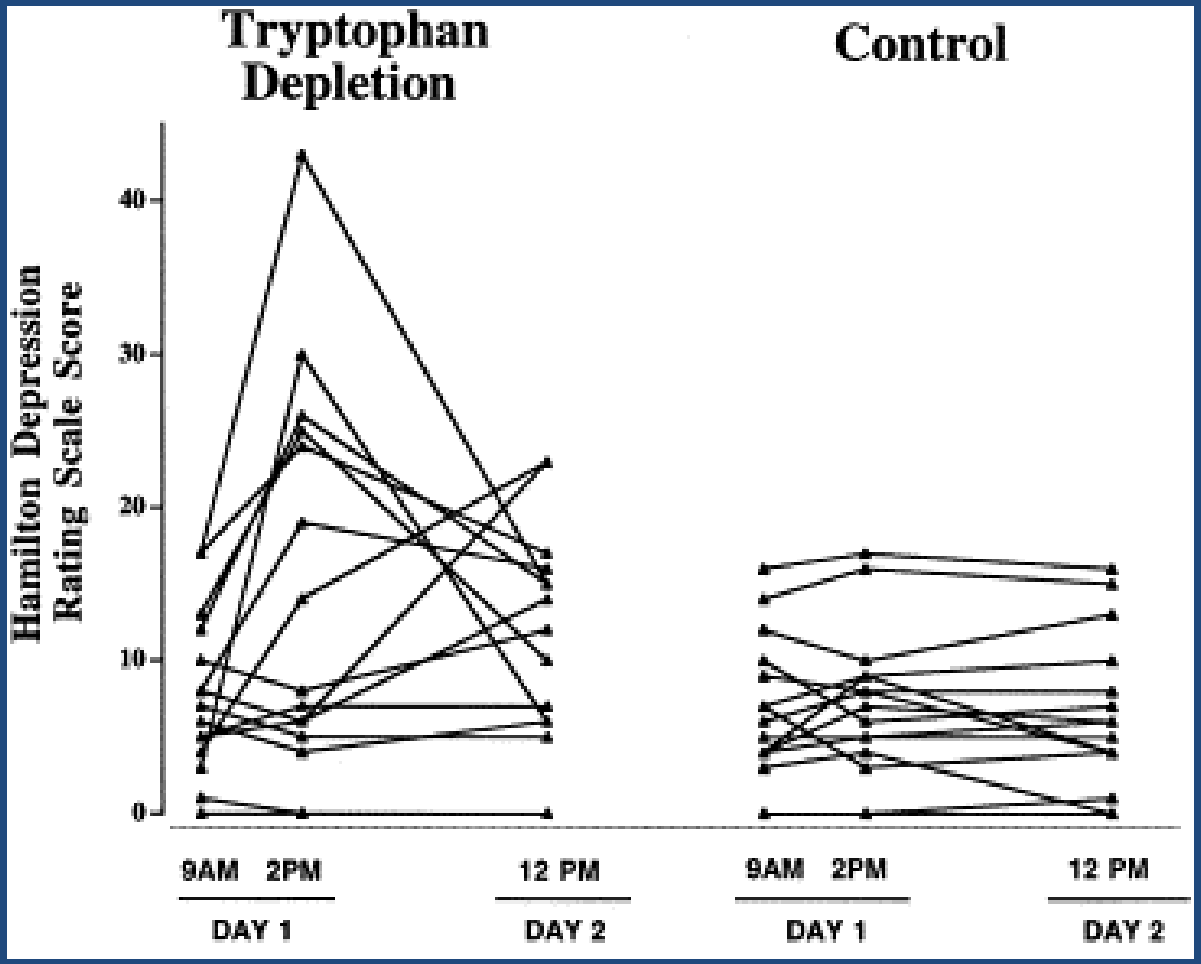


Figure 2. Hamilton Depression Scale Score in fluoxetine-responders during depletion and control testing.

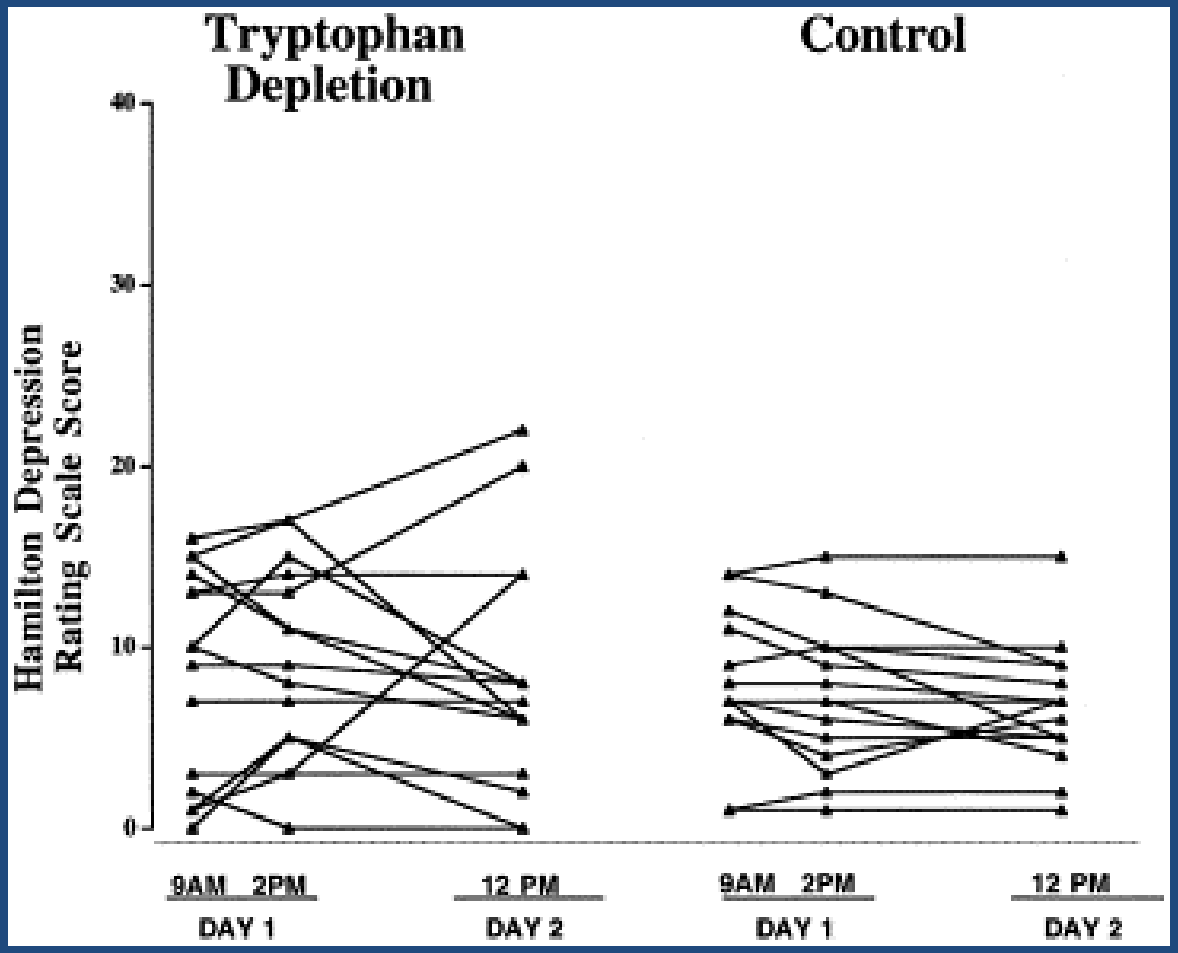


Figure 3. Hamilton Depression Scale Score in desipramine-responders during depletion and control testing.

Arch Gen Psychiatry. 1996;53:117-128

Clinical and Biochemical Effects of Catecholamine Depletion on Antidepressant-Induced Remission of Depression

Heien L. Miller, MD; Pedro L. Delgado, MD; Ronald M. Salomon, MD; Robert Berman, MD;
John H. Krystal, MD; George R. Heninger, MD; Dennis S. Charney, MD

Background: Most hypotheses of the therapeutic mechanism of action of antidepressant drugs have focused on the role of the monoamines. We examined the effect of catecholamine depletion on antidepressant-induced remission.
Method: The tyrosine hydroxylase inhibitor α-methyl-paratyrosine and the antihistamine diphenhydramine hydrochloride were administered, during separate test sessions, to depressed patients in remission maintained with either norepinephrine reuptake inhibitors (desipramine [n=7] or mazindol [n=2]) or serotonin reuptake inhibitors (fluoxetine hydrochloride [n=9] or sertraline hydrochloride [n=l]). Because of considerable sedation associated with α–methylparatyrosine testing, diphenhydramine was used as an active control rather than an inactive placebo. The effects of α-methylparatyrosine and diphenhydramine on depression, anxiety, and plasma catecholamine metabolites were assessed.
Results: α-Methylparatyrosine produced similar significant decreases in plasma 3-methoxy-4-hydroxyphenyl~ethyleneglycol and homovanillic acid levels in the treatment groups. α-Methylparatyrosine produced a robust increase in depressive symptoms on the Hamilton Depression Rating Scale, including depressed mood, decreased concentration, anhedonia, loss of interest, and feelings of worthlessness, helplessness, and hopelessness, in the desipramine-mazindol but not in the fluoxetine-sertraline group. Diphenhydramine had no effects on mood in either treatment group.
Conclusions: The therapeutic effects of norepinephrine reuptake inhibitors, but not serotonin reuptake inhibitors, are reversed by catecholamine depletion. Considered with previous reports that serotonin depletion produces depressive relapses in patients in remission maintained with serotonin reuptake inhibitors, but not norepinephrine reuptake inhibitors, these findings suggest that antidepressants may not work via a single monoamine-related mechanism

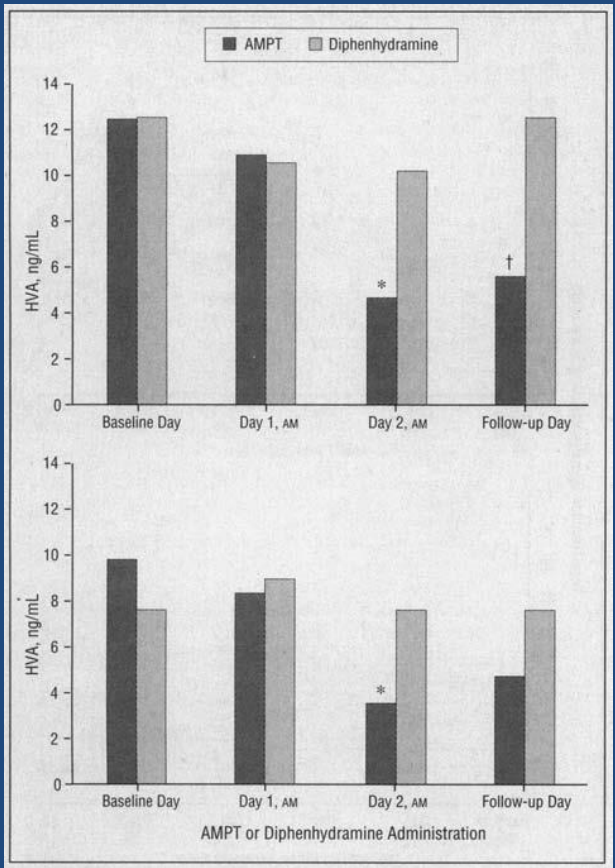


Figure 1. The effect of α-methylparatyrosine (AMPT) and diphenhydramine hydrochloride on plasma homovanillic acid (HVA) levels in patients who responded to fluoxetine hydrochloride (n=9) or sertraline hydrochloride (n=1) (top) and to desipramine hydrochloride (n=7) or mazindol (n=2) (bottom). There were significant decreases (asterisk, P<.001; dagger, P<.01) during and just after AMPT administration. There were no significant decreases in plasma HVA level during diphenhydramine administration. Values for baseline and day 1 reflect measurements before drug administration. Follow-up day values reflect measurements after discontinuation of drug administration.

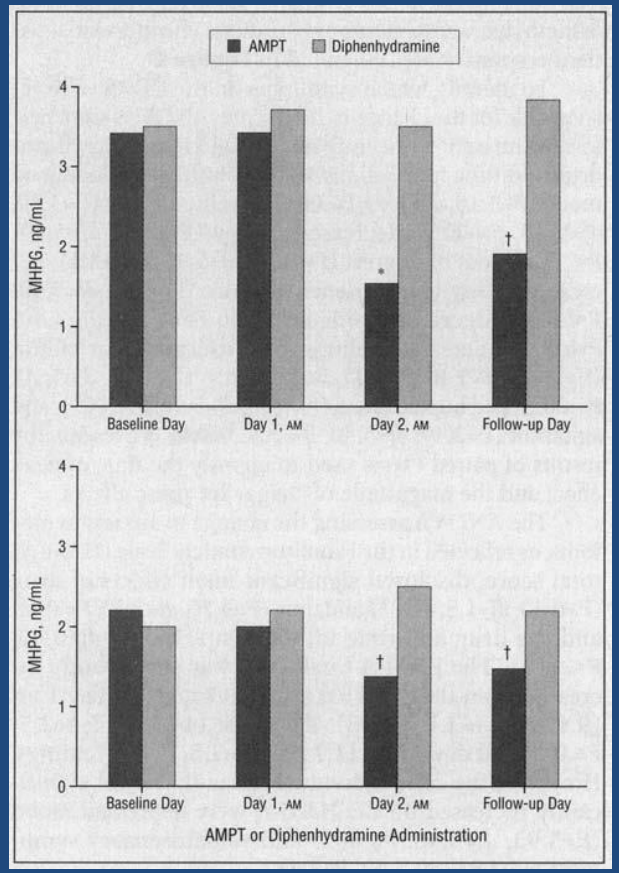


Figure 2. The effect of α-methylparatyrosine (AMPT) and diphenhydramine hydrochloride on plasma 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) levels in patients who responded to fluoxetine hydrochloride (n=9) or sertraline hydrochloride (n=1) (top) and to desipramine hydrochloride (n=7) or mazindol (n=2) (bottom). There were significant decreases (asterisk, P<.01; dagger, P<.05) in plasma MHPG levels during AMPT administration. There were no significant decreases in plasma MHPG level during diphenhydramine administration. Values for baseline and day 1 reflect measurements before drug administration. Follow-up day values reflect measurements after discontinuation of drug administration.

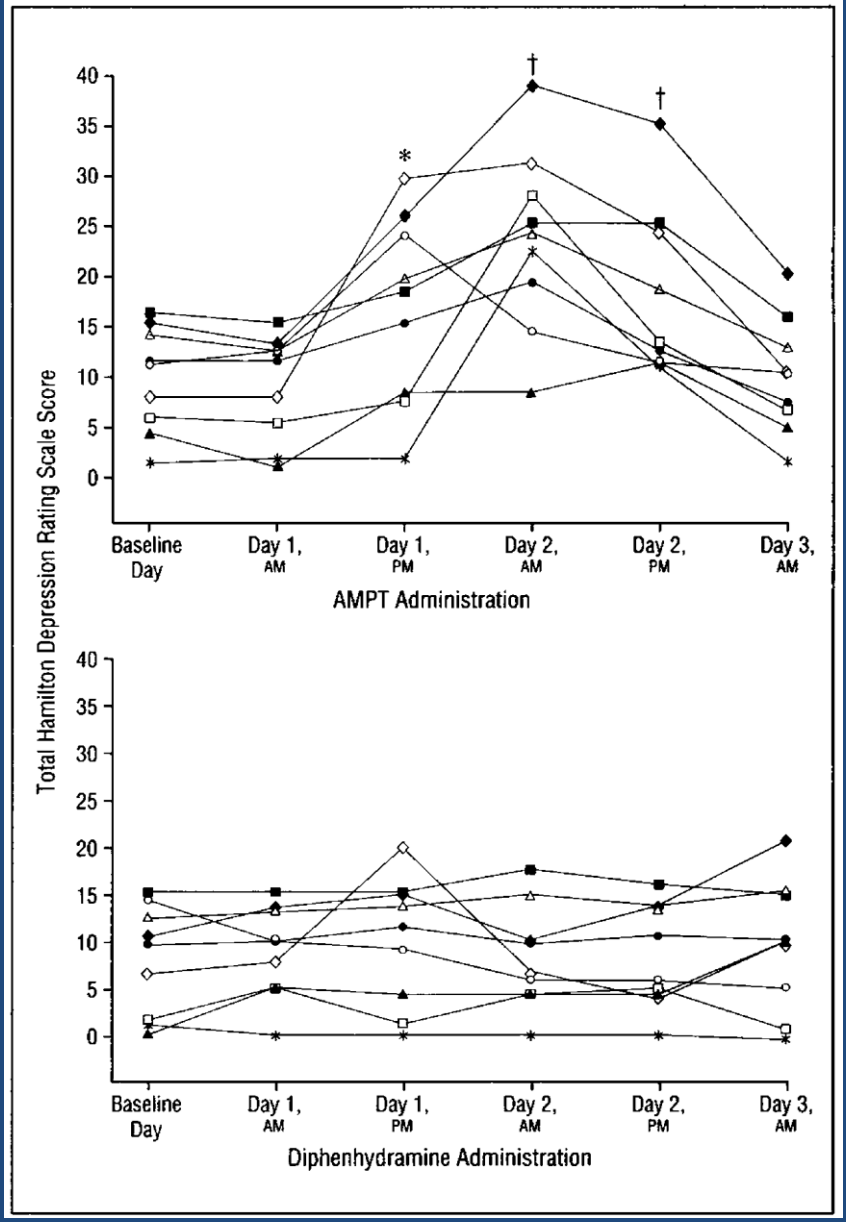


Figure 3. Scores on the 25-item Hamilton Depression Rating Scale for each of nine depressed patients in remission who were taking either desipramine hydrochloride (n=7) or mazindol (n=2) before (baseline and day 1 am ratings), during administration of either α-methylparatyrosine (AMPT) (1 g at 9 am, 1 pm, and 4 pm on day 1; 1 g at 9 am and 1 pm on day 2) or diphenhydramine hydrochloride (50 mg at 9 am, 1 pm, and 4 pm on day 1; 50 mg at 9 am and 1 pm on day 2), and at follow-up (day 3). Asterisk indicates P<.05 compared with day 1 am, paired t test, two tailed; dagger, P<.01 compared with day 1 am, paired t test, two tailed. Each of the nine patients is represented by a different symbol.

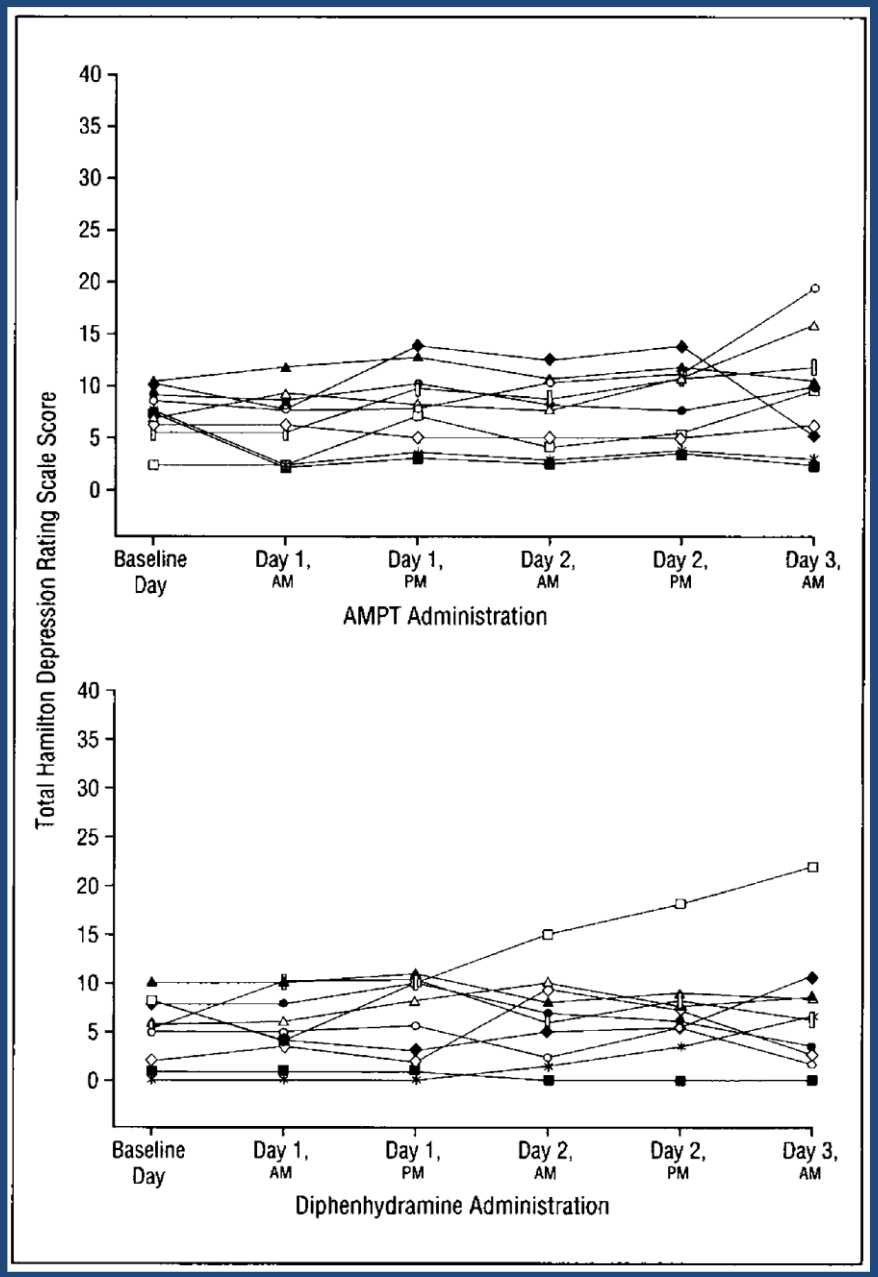


Figure 4. Scores on the 25-item Hamilton Depression Rating Scale for each of 10 depressed patients in remission who were taking either fluoxetine hydrochloride (n=9) or sertraline hydrochloride (n=1) before (baseline and day 1 am ratings), during administration of either α-methylparatyrosine (AMPT) (1 g at 9 am, 1 pm, and 4 pm on day 1; 1 g at 9 am and 1 pm on day 2) or diphenhydramine hydrochloride (50 mg at 9 am, 1 pm, and 4 pm on day 1; 50 mg at 9 am and 1 pm on day 2), and at follow-up (day 3). There were no significant changes in scores as a result of AMPT or diphenhydramine administration. Each of the 10 patients is represented by a different symbol.

THE REVISED MONOAMINE THEORY OF DEPRESSION: A MODULATORY ROLE OF MONOAMINES, BASED ON NEW FINDINGS FROM MONOAMINE DEPLETION EXPERIMENTS IN HUMANS

1. Healthy subjects do not become depressed (at most there are only mild increases in dysphoric mood) with the same procedures that do increase depressive symptoms in patients recently recovered from depression either on or off medications.

2. When depressed, patients do not have an increase in symptoms following either SD or CD.

3. The monoamine depletion methods appear to be valid, as evidenced by the selective effects of the **AA** drink and **AMPT** in producing relapse in patients responding to either SSRI's or CRI's.

Heninger, G., et al. “The Revised Monoamine Theory of Depression: A Modulatory Role for Monoamines, Based on New Findings From Monoamine Depletion Experiments in Humans.” *Pharmacopsychiatry*, vol. 29, 1996, pp. 2–11.

THE REVISED MONOAMINE THEORY OF DEPRESSION: A MODULATORY ROLE OF MONOAMINES, BASED ON NEW FINDINGS FROM MONOAMINE DEPLETION EXPERIMENTS IN HUMANS

An important modulatory role of monoamines in depression

Although the monoamines may not be a direct regulator of mood in depressed patients and healthy individuals, there is considerable evidence that they play a critical role in generating and maintaining the antidepressant response, as indicated by:

1. Depletion of monoamines in recently recovered patients on antidepressant treatment produced a rapid relapse which is specific to the type of depletion and type of treatment.

2. Recovered patients who are off medication either following drug treatment, light treatment. or spontaneous remission have a rapid relapse when depleted of monoamines.

3. All of the effective antidepressants known to date. Produce changes in monoamine receptor metabolism and receptor systems in laboratory animals consistent with the view that the antidepressant effects involve increased transmission in the monoamines systems.

Heninger, G., et al. “The Revised Monoamine Theory of Depression: A Modulatory Role for Monoamines, Based on New Findings From Monoamine Depletion Experiments in Humans.” *Pharmacopsychiatry*, vol. 29, 1996, pp. 2–11.

DESIPRAMINE-YOHIMBINE COMBINATION TREATMENT OF REFRACTORY DEPRESSION: Implications for the β-Adrenergic Receptor Hypothesis of Antidepressant Action

Preclinical investigations have shown that combined administration of the α_2-adrenergicreceptor antagonist yohimbine hydrochloride and the tricyclic antidepressant desipramine hydrochloride produces a reduction in brain β-adrenergic receptor function within four days.

This study provides evidence against the β-adrenergic receptor hypothesis of antidepressant action.

Charney, Dennis S, et al. “Desipramine-Yohimbine Combination Treatment of Refractory Depression. Implications for the β-Adrenergic Receptor Hypothesis of Antidepressant Action.” *Archives of General Psychiatry*, vol. 43, Dec. 1986, pp. 1155–1161.

DESIPRAMINE-YOHIMBINE COMBINATION TREATMENT OF REFRACTORY DEPRESSION: Implications for the β-Adrenergic Receptor Hypothesis of Antidepressant Action

Table 2.—Average of Depression Ratings During Desipramine and Desipramine-Yohimbine Treatment*

			Active Treatment†					
	Placebo Days −6-0		Days 1-3		Days 8-14		Days 22-28	
Treatment Group	SCRS-D+	HAM-D+	SCRS-D	HAM-D	SCRS-D	HAM-D	SCRS-D	HAM-D
Desipramine (N=11)	6.7±0.2	34±2	6.7±0.2	36±4	6.7±0.3	35±2	6.7±0.5	32±4
Desipramine-yohimbine (N=10)	7.1±0.4	34±3	7.1±0.5	34±3	6.8±0.4	37±3	6.4±0.5	30±3

*Patients in both treatment groups initially received placebo desipramine and placebo yohimbine for a minimum of two weeks. During treatment days 1 to 3, all patients were receiving active desipramine but continued to receive placebo yohimbine. During days 8 to 14, all patients in the desipramine-yohimbine group were receiving active yohimbine and desipramine, while the desipramine-alone group continued to receive placebo yohimbine. During days 22 to 28, patients in both groups were receiving active desipramine and placebo yohimbine. SCRS-D indicates the mean (±SEM) of the global depression rating item (range, 1 [none] to 15 [very severe] on the Short Clinical Rating Scale[16] done twice daily during the indicated time periods; Ham-D represents the mean (±SEM) of the total score on the Hamilton Depression Scale completed during the indicated time periods.[17]

†During none of the active treatment periods were the SCRS-D or Ham-D scores significantly different from the placebo treatment period.

Charney, Dennis S, et al. “Desipramine-Yohimbine Combination Treatment of Refractory Depression. Implications for the β-Adrenergic Receptor Hypothesis of Antidepressant Action.” *Archives of General Psychiatry*, vol. 43, Dec. 1986, pp. 1155–1161.

EFFECTS OF PINDOLOL IN HASTENING RESPONSE TO FLUOXETINE IN THE TREATMENT OF MAJOR DEPRESSION: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Objective: In two preliminary studies, pindolol produced robust results in hastening clinical response to antidepressant drugs in depressed patients. Validity of those pilot studies was limited by use of an open-label, unblinded study design, and so the authors conducted a double-blind, placebo-controlled trial to assess the effectiveness of pindolol in hastening response to fluoxetine.

Conclusions: These findings do not support the efficacy of pindolol in hastening clinical response in patients treated with fluoxetine.

Berman, Robert J, et al. “Effect of Pindolol in Hastening Response to Fluoxetine in the Treatment of Major Depression: a Double-Blind, Placebo-Controlled Trial.” *American Journal of Psychiatry*, vol. 154, no. 1, Jan. 1997, pp. 37–43.

EFFECTS OF PINDOLOL IN HASTENING RESPONSE TO FLUOXETINE IN THE TREATMENT OF MAJOR DEPRESSION: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

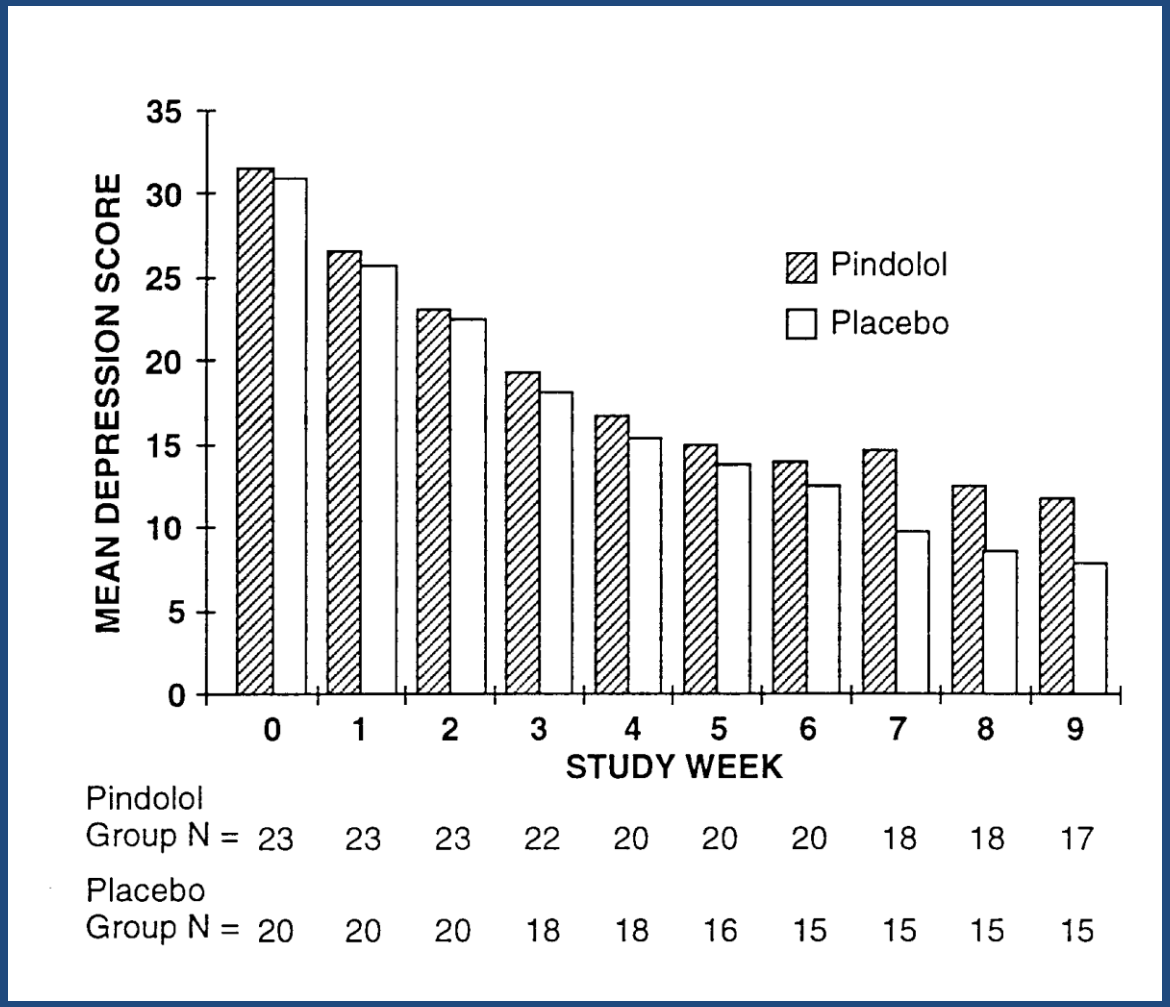


FIGURE 1. Mean Scores on the Hamilton Depression Rating Scale of Patients With Major Depression Who Received Fluoxetine Plus Either Pindolol or Placebo[a]

[a]Intergroup differences were not significant. All intragroup differences between baseline and subsequent weeks were significant (Student-Newman-Keuls Test, $p<0.05$).

Berman, Robert J, et al. "Effect of Pindolol in Hastening Response to Fluoxetine in the Treatment of Major Depression: a Double-Blind, Placebo-Controlled Trial." *American Journal of Psychiatry*, vol. 154, no. 1, Jan. 1997, pp. 37–43.

PINDOLOL AUGMENTATION IN DEPRESSED PATIENTS RESISTANT TO SELECTIVE SEROTONIN REUPTAKE INHIBITORS: A DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

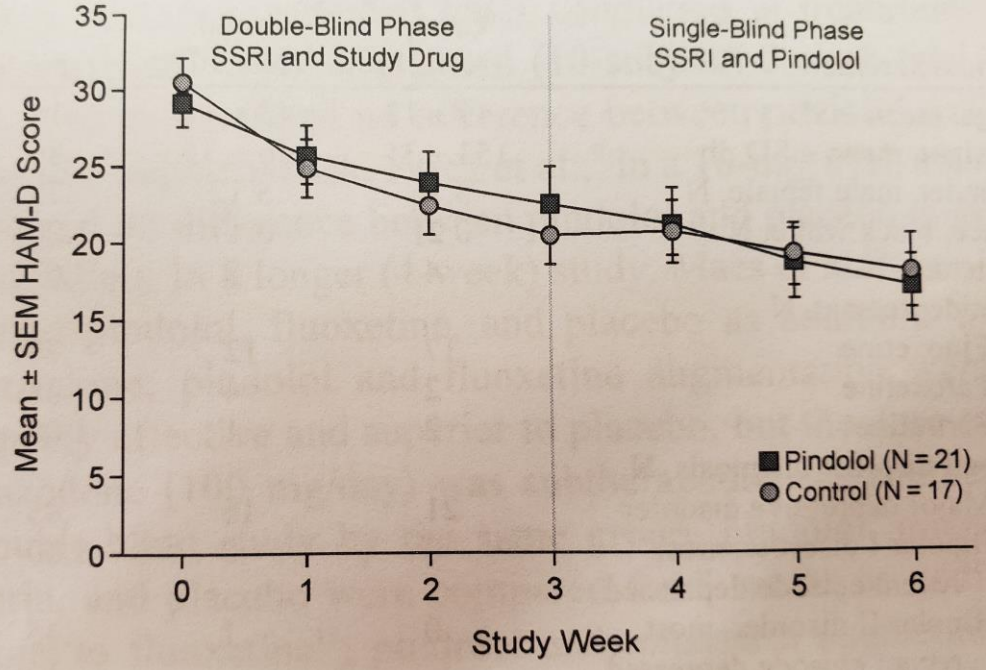
Background: Studies of pindolol augmentation of antidepressants in major depressive disorder have produced mixed results and data in treatment-resistant patients are limited.

Conclusion: These results do not support the efficacy of pindolol in augmenting clinical response to SSRIs in treatment-resistant depressed patients.

Perry, Edward B, et al. “Pindolol Augmentation in Depressed Patients Resistant to Selective Serotonin Reuptake Inhibitors: A Double-Blind, Randomized, Controlled Trial.” *J Clin Psychiatry*, vol. 65, 2004, pp. 238–243.

PINDOLOL AUGMENTATION IN DEPRESSED PATIENTS RESISTANT TO SELECTIVE SEROTONIN REUPTAKE INHIBITORS: A DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

Figure 1. HAM-D Scores for Pindolol and Control Groups (all subjects), Weeks 0–6



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

Perry, Edward B, et al. "Pindolol Augmentation in Depressed Patients Resistant to Selective Serotonin Reuptake Inhibitors: A Double-Blind, Randomized, Controlled Trial." *J Clin Psychiatry*, vol. 65, 2004, pp. 238–243.

THE REVISED MONOAMINE THEORY OF DEPRESSION: A MODULATORY ROLE OF MONOAMINES, BASED ON NEW FINDINGS FROM MONOAMINE DEPLETION EXPERIMENTS IN HUMANS

The glutamatergic neurotransmitter system.

Glutamatergic neurotransmission (specifically the interaction of glycine with the n-methyl-d-asparate receptor complex) may be one of the important "other systems being effected by changes in monoamine transmission. There are many know relationships between the monoamine systems and glutamatergic neural transmission.

Heninger, G., et al. “The Revised Monoamine Theory of Depression: A Modulatory Role for Monoamines, Based on New Findings From Monoamine Depletion Experiments in Humans.” *Pharmacopsychiatry*, vol. 29, 1996, pp. 2–11.

ADAPTATION OF N-METHYL-D-ASPIRATE (NMDA) RECEPTORS FOLLOWING ANTIDEPRESSANT TREATMENT: Implications for the Pharmacotheraphy of depression

Based on the consistency of these effects across antidepressant treatments, we propose that adaptive changes in NMDA receptors may be the final common pathway for antidepressant action.

Skolnick, P., et al. “Adaptation of N-Methyl-D-Asparate (NMDA) Receptors following Antidepressant Treatment: Implications for the Pharmacotheraphy of Depression.” *Pharmopsychiat.*, vol. 29, 1996, pp. 23-26.

INITIATION OF STUDIES WITH KETAMINE

We began human studies with ketamine as a strategy to deal with a conceptual and practical problem at the core of schizophrenia research at the time. One of us (JK) led a series of studies designed to move beyond the dopamine hypothesis of schizophrenia.

We began planning the ketamine study around 1988, about 5 years after the mechanism of action of ketamine in the brain was identified. Ketamine has been an FDA-approved anesthetic medication since the 1970s.

We thought that if we could recapitulate aspects of the signs and symptoms of schizophrenia by giving a single dose of a drug with a known mechanism of action, this would provide a simple research platform for probing the more complex biology of schizophrenia. Further, we thought that by evoking behaviors resembling schizophrenia in healthy people, we could use this as a “model psychosis” for testing the impact of novel therapeutics for schizophrenia.

INITIATION OF STUDIES WITH KETAMINE

The decision to move forward with a study of ketamine effects in depressed patients emerged from the ongoing dialogue between (DSC and JHK) at VA Connecticut in the 1990s. DSC occupied an office on the 9th floor and JHK's office was on the 8th floor. Both of us tended to work late. At the end of the workday, it was common for JHK to head up to DSC's office to discuss one or another research issue. We tossed around numerous research questions and generated projects related to several psychiatric disorders. In this case, we had the belief that the monoamine hypothesis did not reflect the primary causes of depression.

We hypothesized that alterations in glutamate signaling via NMDA receptors might play a role and that we could use the "standard" ketamine infusion (0.5 mg/kg, i.v., over 40 minutes) to probe NMDA receptor regulation in humans.

INITIATION OF STUDIES WITH KETAMINE

A particularly challenging issue was dose. Prior to initiating our first full study, we conducted unpublished pilot testing in a few healthy subjects that was quite informative. If we chose a dose that was too low, (0.1-0.2 mg/kg over 40 minutes), we missed seeing the behavioral effects we were seeking. If we chose a dose that was too high (0.5 mg/kg over 20 minutes), subjects were unable to meaningfully respond to the tests that we planned to administer. We settled on a dose of 0.5 mg/kg infused over 40 minutes. At this dose, we saw relatively prominent ketamine effects, but subjects were never so affected that they became disoriented or could not complete our testing. This dose worked well for our study and, remarkably, also turned out to be an optimal or near-optimal ketamine dose for the treatment of depression.

Arch Gen Psychiatry. 1994;51:199-214

Subanesthetic Effects of the Noncompetitive NMDA Antagonist, Ketamine, in Humans

Psychotomimetic, Perceptual, Cognitive, and Neuroendocrine Responses

John H. Krystal, MD; Laurence P. Karper, MD; John P. Seibyl, MD; Glenna K. Freeman; Richard Delaney, PhD; J. Douglas Bremner, MD; George R. Heninger, MD; Malcolm B. Bowers, Jr, MD; Dennis S. Charney, MD

Background: To characterize further behavioral, cognitive, neuroendocrine, and physiological effects of subanesthetic doses of ketamine hydrochloride in healthy human subjects. Ketamine, a phencyclidine hydrochloride derivative, is a dissociative anesthetic and a noncompetitive antagonist of the N-methyl-D-aspartate subtype of excitatory amino acid receptor.
Methods: Nineteen healthy subjects recruited by advertisements from the community participated in this randomized, double-blind, placebo-controlled study. Subjects completed three test days involving the 40-minute intravenous administration of placebo, ketamine hydrochloride (0.1 mg/kg), or ketamine hydrochloride (0.5 mg/kg). Behaviors associated with the positive and negative
symptoms of schizophrenia were assessed by using the Brief Psychiatric Rating Scale. Changes in perception and behaviors associated with dissociative states were assessed by the Perceptual Aberration Subscale of the Wisconsin Psychosis Proneness Scale and the Clinician-Administered Dissociative States Scale. Cognitive function was assessed by using the (1) Mini-Mental State Examination; (2) tests sensitive to frontal cortical dysfunction, including a continuous performance vigilance task, a verbal fluency task, and the Wisconsin Card Sorting Test; and (3) tests of immediate and delayed recall. Plasma levels of cortisol, prolactin, homovanillic acid, and 3-methoxy-4-hydroxyphenethyleneglycol were measured.
Results: Ketamine (1) produced behaviors similar to the positive and negative symptoms of schizophrenia;(2) elicited alterations in perception; (3) impaired performance on tests of vigilance, verbal fluency, and the Wisconsin Card Sorting Test; (4) evoked symptoms similar to dissociative states; and (5) preferentially disrupted delayed word recall, sparing immediate recall and postdistraction recall. Ketamine had no significant effect on the Mini-Mental State Examination at the doses studied. Ketamine
also had no effect on plasma 3-methoxy-4-hydroxyphenethyleneglycol levels, although it blunted a test day decline in plasma homovanillic acid levels at the higher dose. It also dose dependently increased plasma cortisol and prolactin levels. Ketamine produced small dose-dependent increases in blood pressure.
Conclusions: These data indicate that N-methyl-Daspartate antagonists produce a broad range of symptoms, behaviors, and cognitive deficits that resemble aspects of endogenous psychoses, particularly schizophrenia and dissociative states.

ANTIDEPRESSANT EFFECTS OF KETAMINE IN DEPRESSED PATIENTS

Background: A growing body of preclinical research suggests that brain glutamate systems may be involved in the pathophysiology of major depression and the mechanism of action of antidepressants. This is the first placebo-controlled, double-blinded trial to assess the treatment effects of a single dose of an N-methyl-D-aspartate (NMDA) receptor antagonist in patients with depression.

Methods: Seven subjects with major depression completed 2 test days that involved intravenous treatment with ketamine hydrochloride (.5 mg/kg) or saline solutions under randomized, double-blind conditions.

Results: Subjects with depression evidenced significant improvement in depressive symptoms within 72 hours after ketamine but not placebo infusion (i.e., mean 25-item Hamilton Depression Rating Scale scores decreased by 14 6 SD 10 points vs. 0 6 12 points, respectively during active and sham treatment).

Conclusions: These results suggest a potential role for NMDA receptor-modulating drugs in the treatment of depression. Biol Psychiatry 2000;47:351–354 © 2000 Society of Biological Psychiatry

Key Words: Major depression, N-methyl-D-aspartate antagonist, excitatory amino acids, randomized clinical trial

Berman, Robert M, et al. “Antidepressant Effects of Ketamine in Depressed Patients.” *Biological Psychiatry*, vol. 47, 2000, pp. 351–354.

Initial Demonstration of Antidepressant Effects of Ketamine in Humans

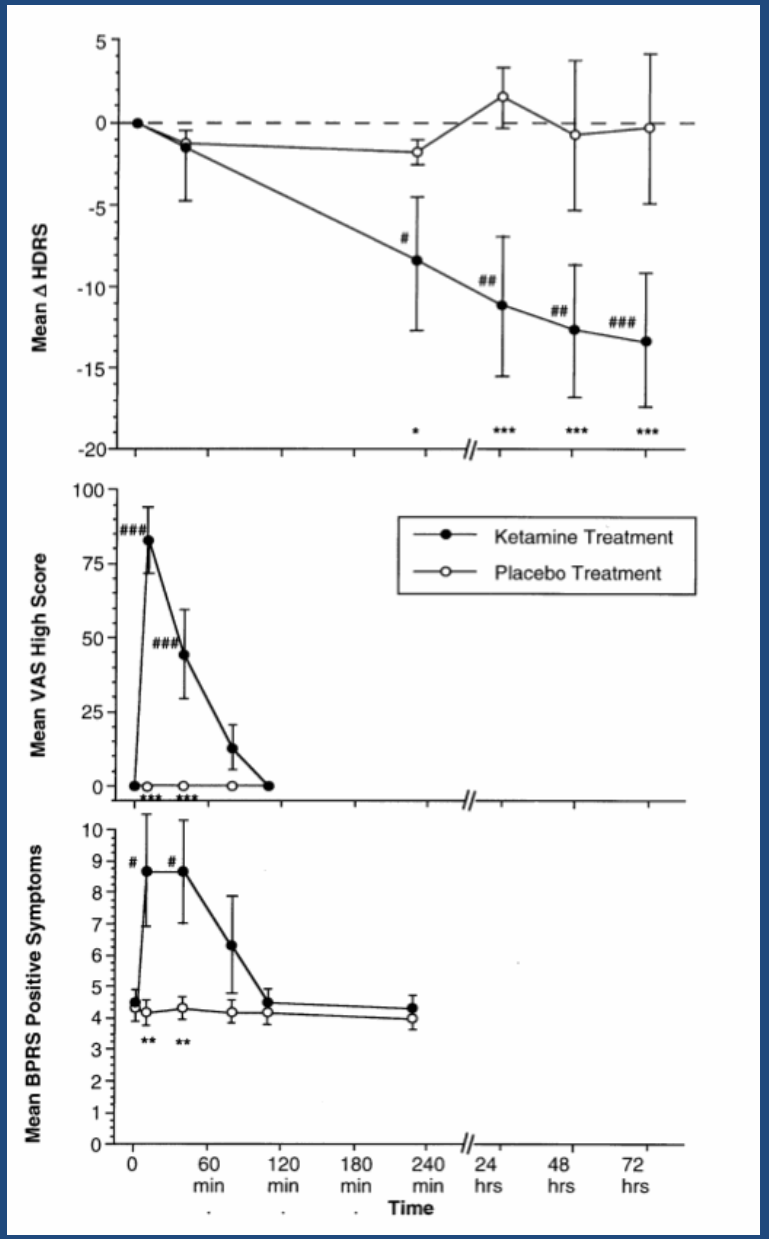
Patients (N=7) underwent two treatment days separated by one week in cross-over design

Ketamine (0.5 mg/kg) or saline administered IV over 40 min under double-blind conditions

Significant reductions in HDRS at 24, 48 and 72 hours following ketamine but not saline

Transient increases in “high” feeling and psychotomimetic symptoms resolved within two hours

No correlation between acute effects and antidepressant effects

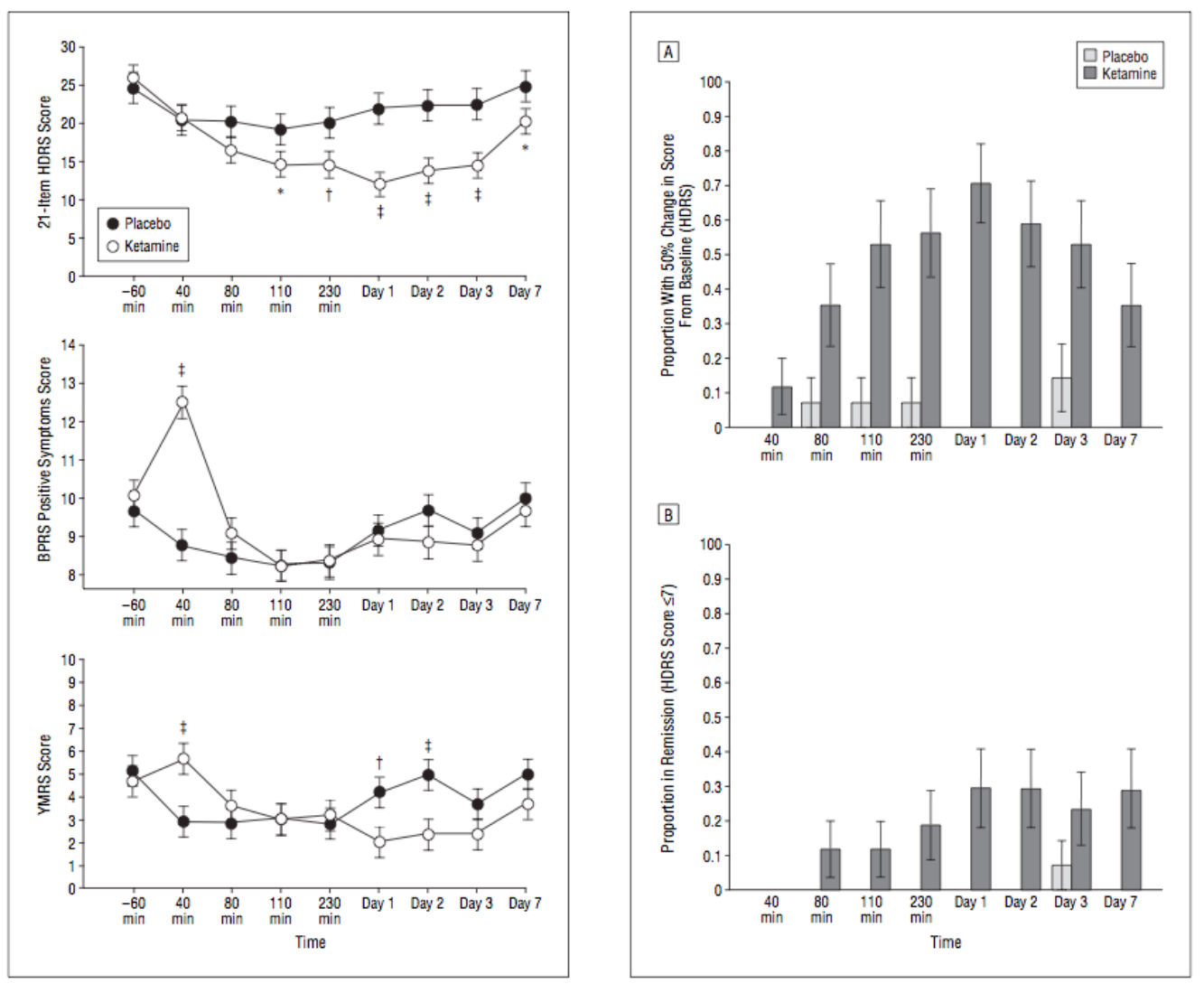


Berman et al. Biol Psych 2000

INITIATION OF STUDIES WITH KETAMINE

To our surprise, our initial presentation of the results in 1997 and the initial publication of the results in 2000, had very little initial impact on the field. Perhaps it was just not believed that an antidepressant effect within hours was possible. Also, there was concern about the abuse potential and psychotomimetic effects of ketamine. For many years, there was no attempt to replicate the antidepressant effects of ketamine. Subsequently, one of us (DSC) left Yale to lead the Mood and Anxiety Disorders Program at the National Institute of Mental Health (NIMH). He suggested to members of the research team, Carlos Zarate and Husseini Manji that an attempt should be made to replicate the original findings of the original study conducted at Yale.

REPLICATION OF RAPID ANTIDEPRESSANT EFFECTS OF KETAMINE IN TREATMENT-RESISTANT DEPRESSION



Zarate et al. *Arch Gen Psychiatry* 2006

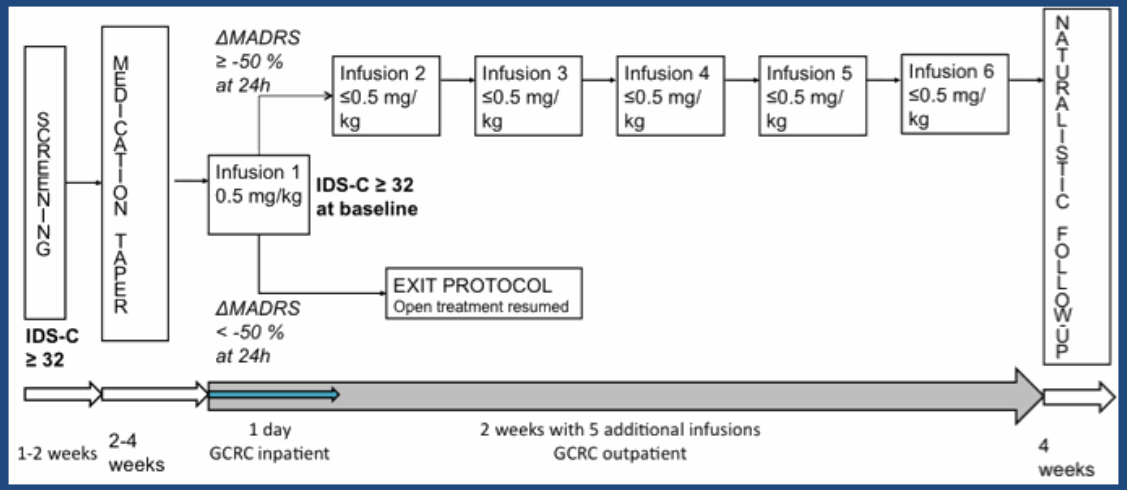
SAFETY AND TOLERABILITY OF REPEATED-DOSE KETAMINE IN TRD

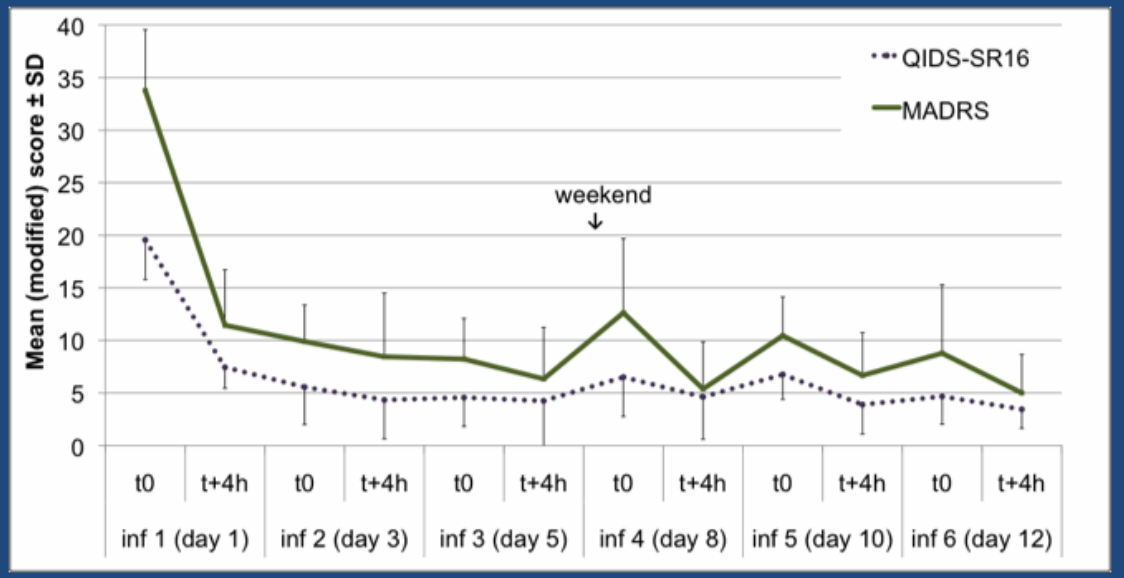
Table 1. Patient Demographic and Clinical Characteristics

Variable	Mean ± SD	Variable	*n* (%)
Age (yrs)	51.4 ± 14.6	Female gender	5 (50%)
Body Mass Index (kg/m^2)	30.1 ± 6.4	Ethnic minority	3 (30%)
Education (yrs)	15.6 ± 3.1	Received psychiatric disability	6 (60%)
IQ (WASI-2 score)	115.7 ± 11.8	Single MDE in lifetime[a]	5 (50%)
Adequate Antidepressant Trials (*n*)	8.2 ± 3.4	Comorbid anxiety disorder	7 (70%)
Age at First MDE (yrs)	20.9 ± 15.4	Past alcohol use disorder	0 (0%)
Duration of Current MDE (yrs)	21.7 ± 18.6	Family history of alcohol use disorder	4 (40%)
Baseline Depression ($IDS\text{-}C_{30}$ score)	44.3 ± 10.6	Past substance use disorder	2 (20%)
Patient Expectancy Rating (1 = lowest, 5 = highest)	3.9 ± .7	Family history of MDD	5 (50%)

Table 2. Numbers of Patients Who Endorsed Moderate-to-Severe Increases in Specific Symptoms on the SAFTEE-SI

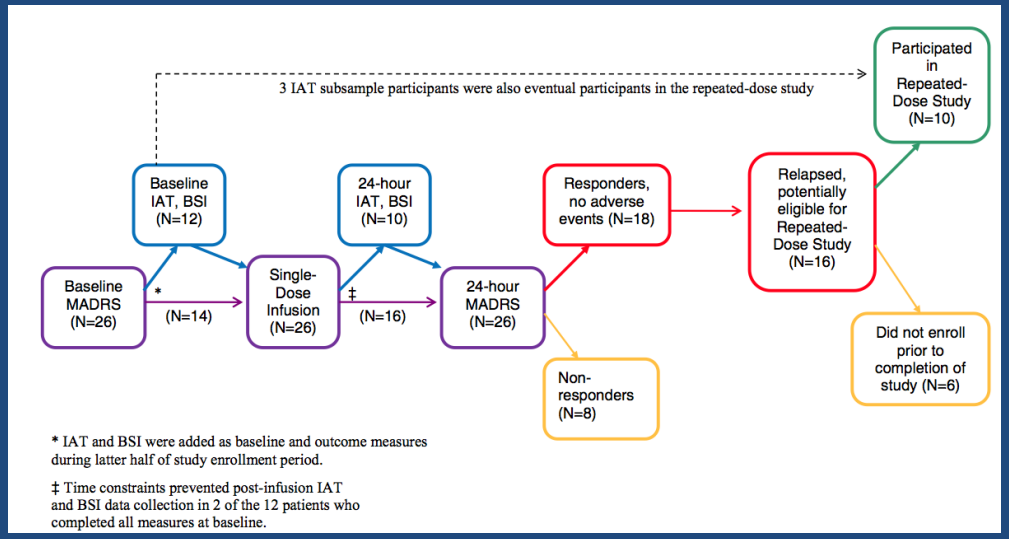
	Moderate		Severe	
Symptom	Week 1	Week 2	Week 1	Week 2
Abnormal Sensations	0	2	1	1
Blurred Vision	0	0	1	1
Diminished Mental Capacity	1	1	1	1
Dizziness or Faintness	1	0	0	0
Feeling Drowsy or Sleepy	2	0	0	0
Feeling Strange or Unreal	1	1	0	0
Headache	1	0	2	1
Hearing or Seeing Things	2	0	0	0
Numbness or Tingling	0	1	1	1
Poor Coordination or Unsteadiness	1	1	0	0
Poor Memory	1	0	0	0
Rapid or Pounding Heartbeat	1	0	0	0
Weakness or Fatigue	0	1	0	0





aan het Rot, Collins, Murrough et al, Biol Psychiatry 2010

INITIAL EVIDENCE FOR RAPID ANTI-SUICIDAL IDEATION EFFECTS OF KETAMINE



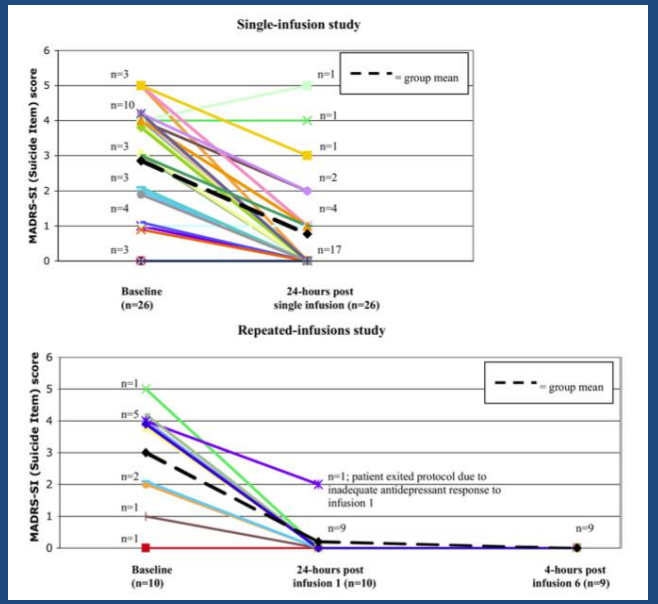
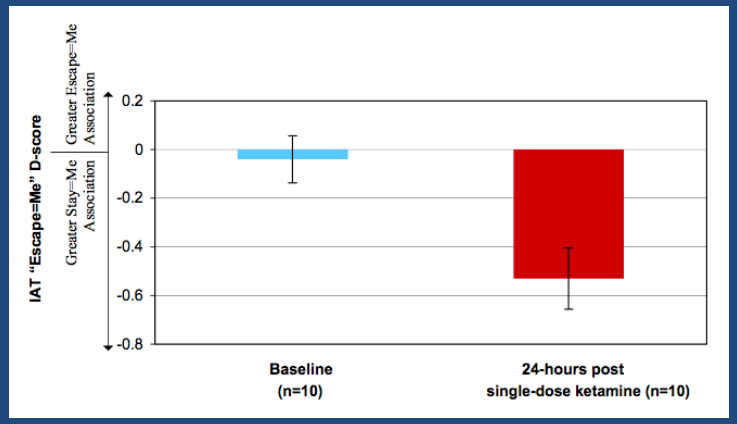


Table 1. Montgomery-Asberg Depression Rating Scale Scoring Guidelines for Item 10: Suicidal Thoughts

Score	Description
0	"Enjoys life or takes it as it comes."
1	(None provided)
2	"Weary of life. Only fleeting suicidal thoughts."
3	(None provided)
4	"Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention."
5	(None provided)
6	"Explicit plans for suicide when there is an opportunity. Active preparation for suicide."

Table copyright Stuart Montgomery 1978.



Price et al, Biol Psychiatry 2009

A RANDOMIZED CONTROLLED TRIAL OF INTRANASAL KETAMINE IN MAJOR DEPRESSIVE DISORDER

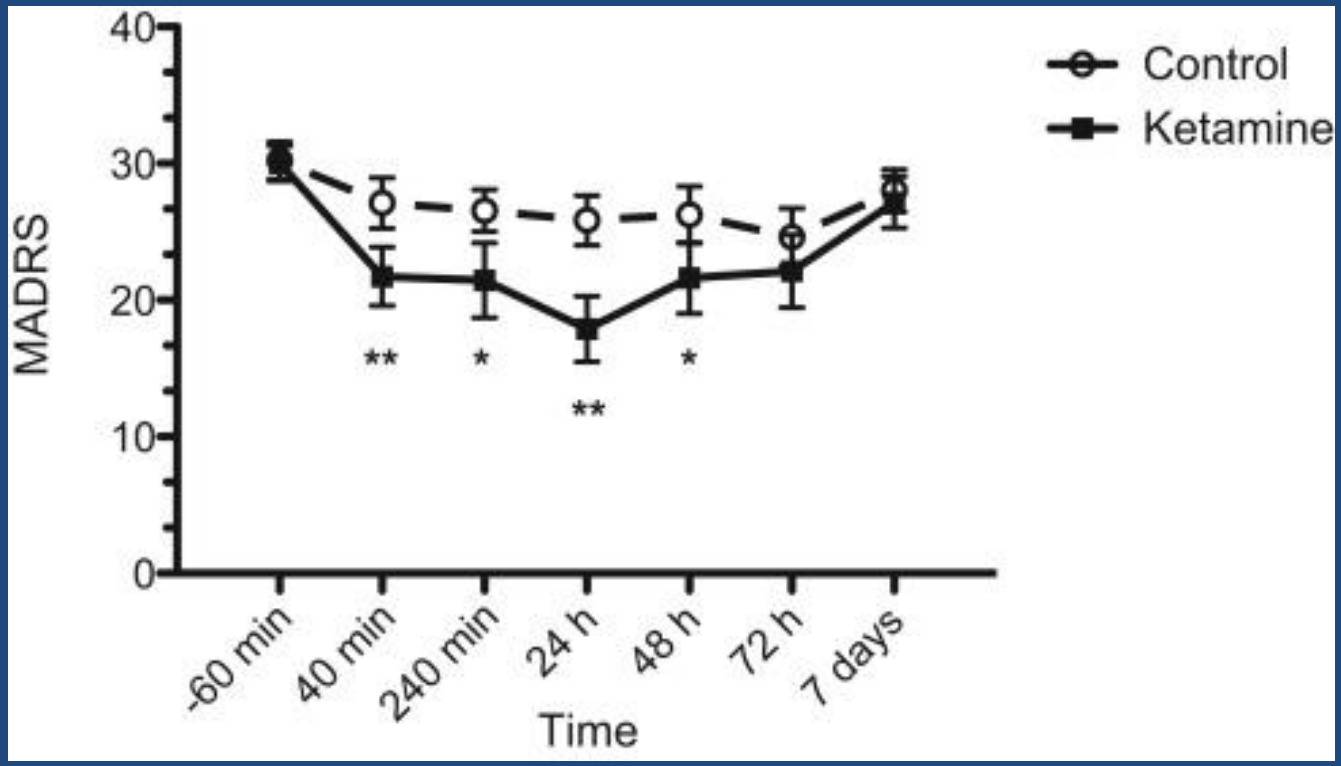
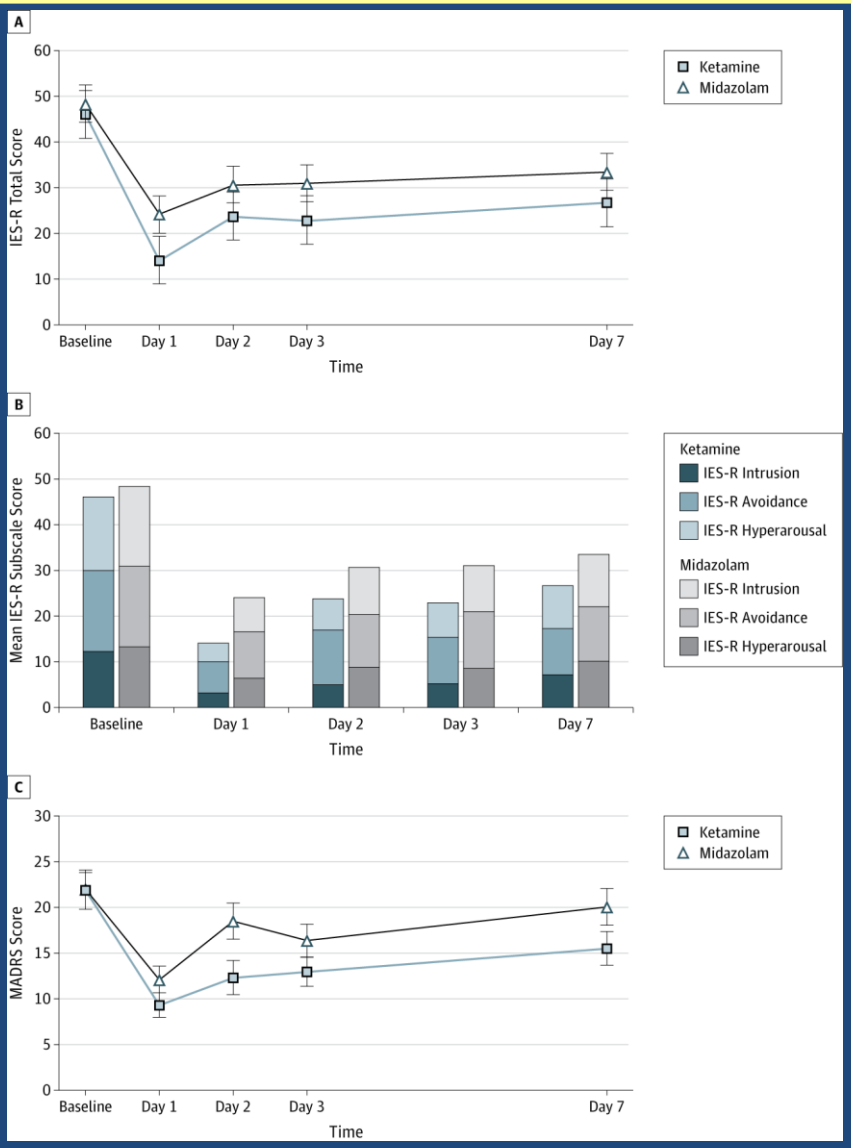


Figure 1. Change in depression severity in patients with treatment-resistant depression after intranasal administration of ketamine or placebo. Change in Montgomery-Åsberg Depression Rating Scale (MADRS) depression severity 24 hours after administration was the primary outcome measure and was significantly greater after intranasal ketamine than placebo in the modified intention-to-treat group (n = 18; $p < .001$). Range is 0–60 with higher scores indicating greater severity of depressive symptoms. *$p < .05$, **$p < .01$.

Lapidus, Kyle A.B., et al. “A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder.” *Biological Psychiatry*, vol. 76, 2014, pp. 970–976.

EFFICACY OF INTRAVENOUS KETAMINE FOR TREATMENT OF CHRONIC POSTTRAUMATIC STRESS DISORDER: A Randomized Clinical Trial



Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period Change in the Impact of Event Scale–Revised (IES-R) total score, the IES-R mean subscale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS) score over 1 week for the first period (n = 41). Error bars represent standard errors. For this study, the IES-R was modified to inquire about symptoms over the previous 24 hours (instead of the previous 7 days).

Feder, Adriana, et al. “Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder.” *JAMA Psychiatry*, vol. 71, no. 6, 2014, pp. 681–688.

THE SHAPE OF DISCOVERY

The discovery of ketamine raises questions about the process of discovery. What types of environments facilitate discovery? What is the optimal size of research groups? How did the science come together that led to the initial trials? What opposition existed? What was the initial reaction?

Recent studies indicate that large teams develop and small teams disrupt science and technology. Smaller teams have tended to disrupt science and technology with new ideas and opportunities, whereas larger teams have tended to develop existing ones.

That was the case with our discovery of ketamine. The research groups at Yale, NIMH, and Mount Sinai were and are characterized by being small in size, encouraging bold scientific thinking in a psychological, safe, scientific environment that tolerated failure – as long as something was learned.

THE SHAPE OF DISCOVERY

Large Teams Develop and Small Teams Disrupt Science and Technology

These results demonstrate that both small and large teams are essential to a flourishing ecology of science and technology, and suggest that, to achieve this, science policies should aim to support a diversity of team sizes.

Wu, Lingfei., et al. “Large Teams Develop and Small Teams Disrupt Science and Technology.” *Nature*, vol. 566, 2019, pp. 378.

THE SHAPE OF DISCOVERY

Every once in a while a new idea comes along – a shift in thinking that challenges the status quo. These innovations require us to accept the change and adapt. This was true for ketamine.

Therapeutic discovery for mental illness needs a paradigm change consistent with Kuhn's conceptions of scientific revolution. As described by Kuhn, normal science begins, in which puzzles are solved within the context of the dominant paradigm, which in the case of depression was the monoamine hypothesis of depression and antidepressant action. There are similar dominant paradigms for other psychiatric diseases that have not resulted in breakthrough therapies.

Over time, progress in "normal science" reveals facts that are difficult to explain within the context of the existing paradigm such as why don't existing therapies have better effectiveness and why haven't new medicines of novel mechanism and better efficiency been discovered.

THE SHAPE OF DISCOVERY

The major pharmacological treatments for major psychiatric disorders such as schizophrenia, bipolar disorder, multiple anxiety disorders, and attention deficit disorder are only partially effective and were discovered decades ago. We believe there needs to be an intense focus on drug discovery for these conditions. We suggest that multiple small groups of scientists, thinking out of the box, need to discover new hypotheses, moving beyond the long held traditional hypotheses. There have been too few novel treatment approaches and too little funding for innovative clinical trials. Progress has been too slow compared to other serious diseases such as cancer and heart disease, the lack of progress in treatment development for mental illness stands out.

THE SHAPE OF DISCOVERY

So, what is now needed for patients with serious mental illness are major paradigm shifts, a scientific research revolution in which underlying assumptions regarding the causes of psychiatric disorders are reexamined utilizing new data from molecular biology, genetics, neural circuitry, and other scientific domains leading to new and novel therapies for serious mental illness.