Beyond the Monoamine Hypothesis: Unraveling the Role of Ketamine in Major Depressive Disorder

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Learning Objectives:

1. Describe the current global health burden of Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD)
2. Discuss the role of current FDA-approved antidepressants and their clinical limitations
3. Analyze primary literature assessing the efficacy of ketamine in the treatment of MDD
4. Discuss the potential role of ketamine in the management of MDD and the potential barriers to access

Major Depressive Disorder

Background and Pathophysiology

Diagnostic Criteria[1]

- One or more major depressive episodes without a history of a manic or hypomanic episodes
- Criteria defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)
- During the episode, five or more symptoms must be met for at least 2 weeks

Table 1: DSM-5 Diagnostic Criteria for Major Depressive Disorder[1,2]

S	leep Disturbances
I	nterest deficit (anhedonia)
G	uilt
E	nergy deficit
C	oncentration deficit
A	ppetite disturbance
P	sychomotor retardation or agitation
S	uicidality

Assessing Severity of Depression[3–5]

- **Montgomery-Asberg Depression Rating Scale (MADRS)**
  - 10 item self or clinician rated
- **Beck Depression Inventory (BDI)**
  - 13 or 21 item self- rated
- **Hamilton Depression Rating Scale (HAM-D)**
  - 17 or 21 item clinician-rated
- **Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)**
  - 16 self-report or clinician rated

Figure 1: History of Advancements in Depression[6–12]

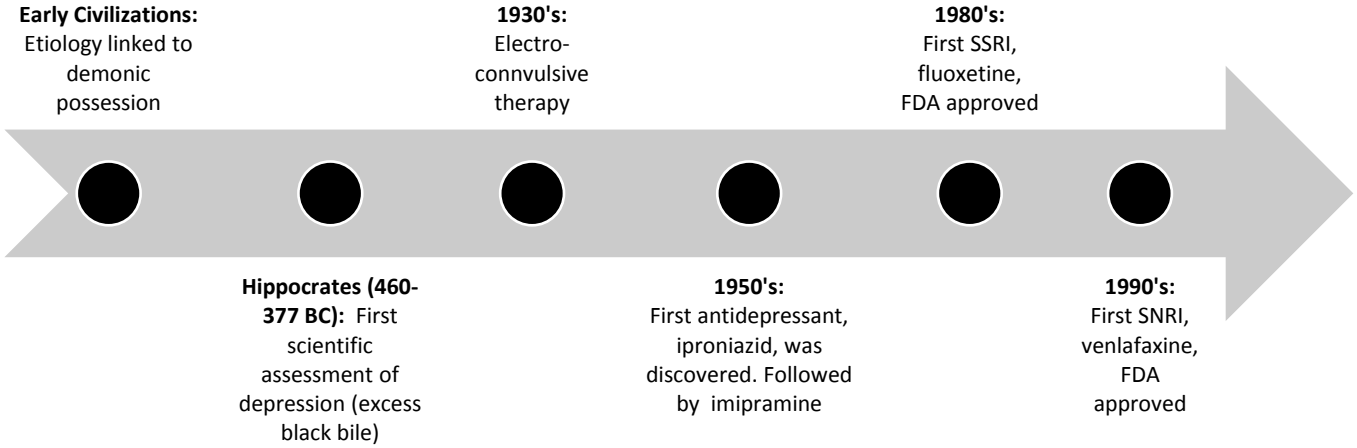
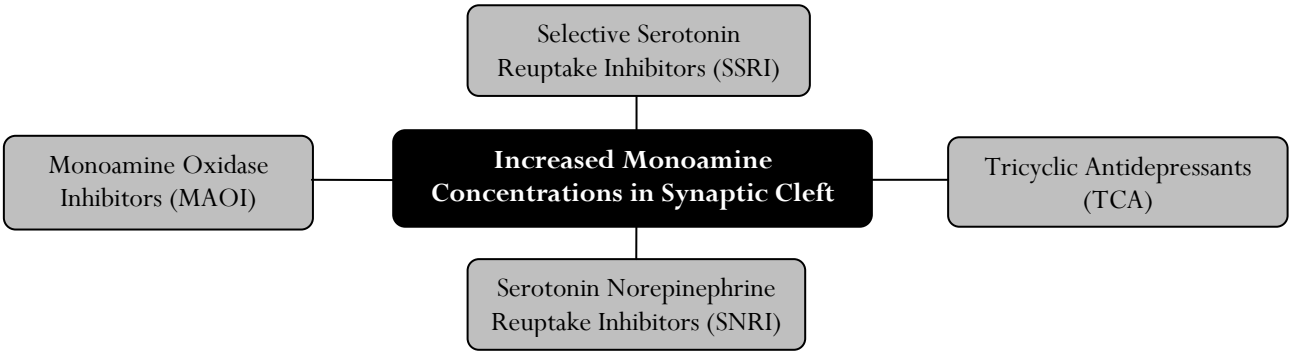
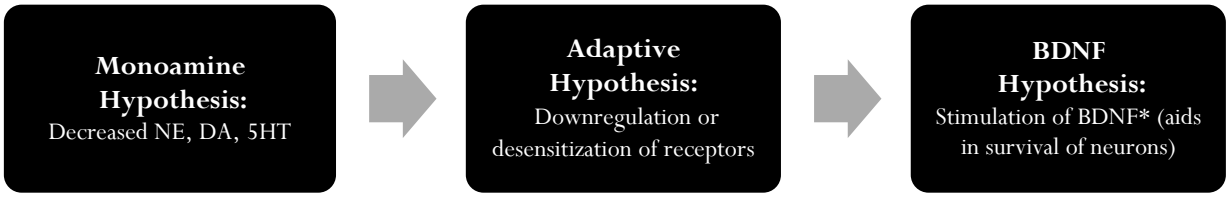


Figure 2: Shared Pharmacologic Mechanisms among Antidepressants[13]



Pathophysiology[11,13–15]



*Brain Derived Neurotrophic Factor

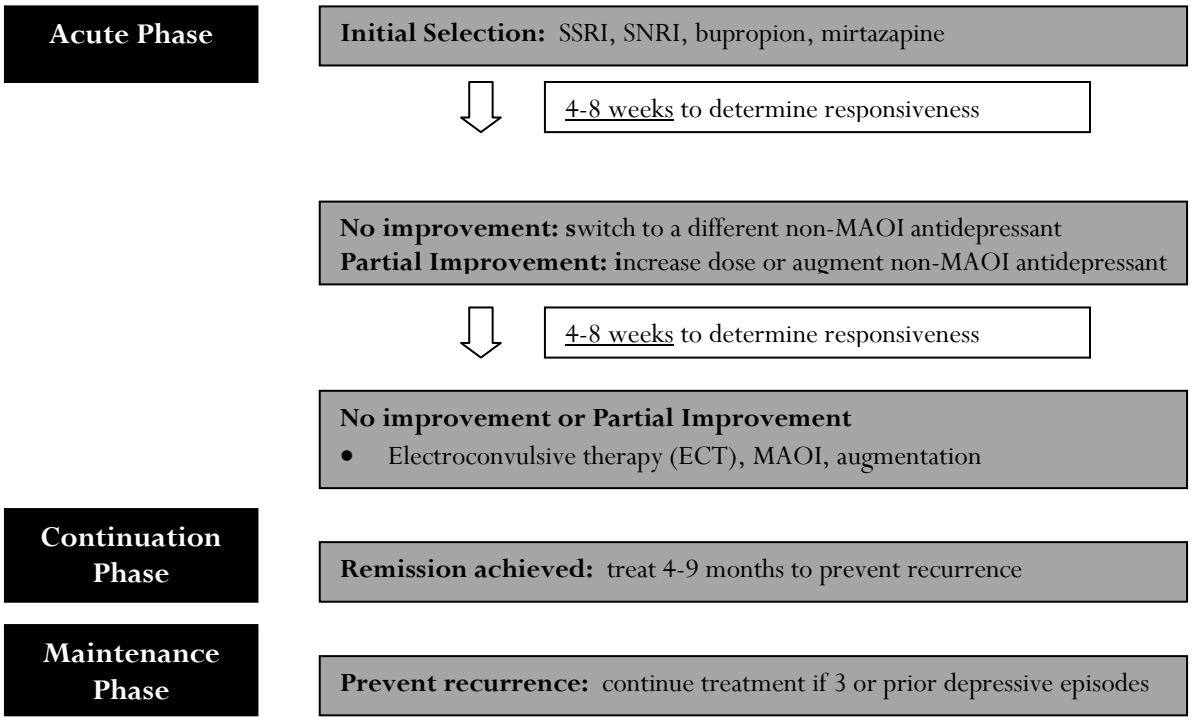
1977 FDA Guidelines for Antidepressant Drug Approval[12,16]

- Do not provide incentives for achieving greater levels of efficacy or targeting novel mechanistic pathways
- Response defined as ≥ 50% reduction in HAM-D, remission defined as a HAM-D score ≤ 7
- No specification of trial duration, assessment scales, or level of improvement needed to demonstrate efficacy
- Recent antidepressant approvals focused on safety improvements (enantiomers or various salt formulations)

Figure 4: Medications FDA Approved for Treatment of Depression

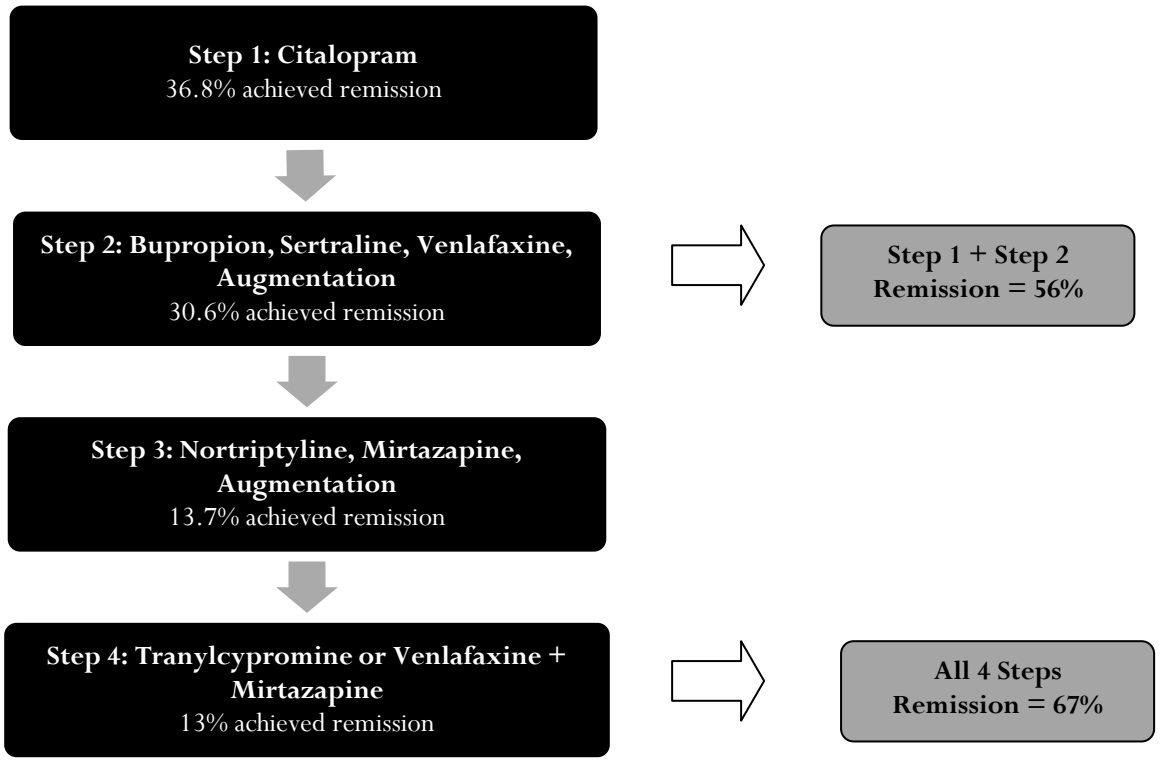
5HT	5HT + NE	5HT + NE + DA
Selective Serotonin Reuptake Inhibitors (SSRI) • Citalopram • Escitalopram • Sertraline • Fluoxetine • Paroxetine **Atypical Antidepressants** • Mirtazapine • Vortioxetine • Vilazodone • Trazodone	**Serotonin Norepinephrine Reuptake Inhibitors (SNRI)** • Venlafaxine • Desvenlafaxine • Duloxetine • Levomilnacipran **Tricyclic Antidepressants** • Amitriptyline, nortriptyline, doxepin, imipramine, desipramine	**Monoamine Oxidase Inhibitors (MAOIs)** • Isocarboxazid • Phenelzine • Selegiline • Tranylcypromine **Norepinephrine-Dopamine Reuptake Inhibitor** • Bupropion

Figure 3: Treatment Recommendations Based on Phase[17]



Efficacy of Antidepressants: Understanding the STAR*D Trial[18]

- 3,671 patients with major depressive disorder seeking acute treatment
- Treated in successive steps, moving on to the next step if remission was not achieved (QIDS-SR ≤ 5)



***Average treatment duration for each step = 9.3 weeks**

Treatment Resistant Depression

Treatment Options and Limitations

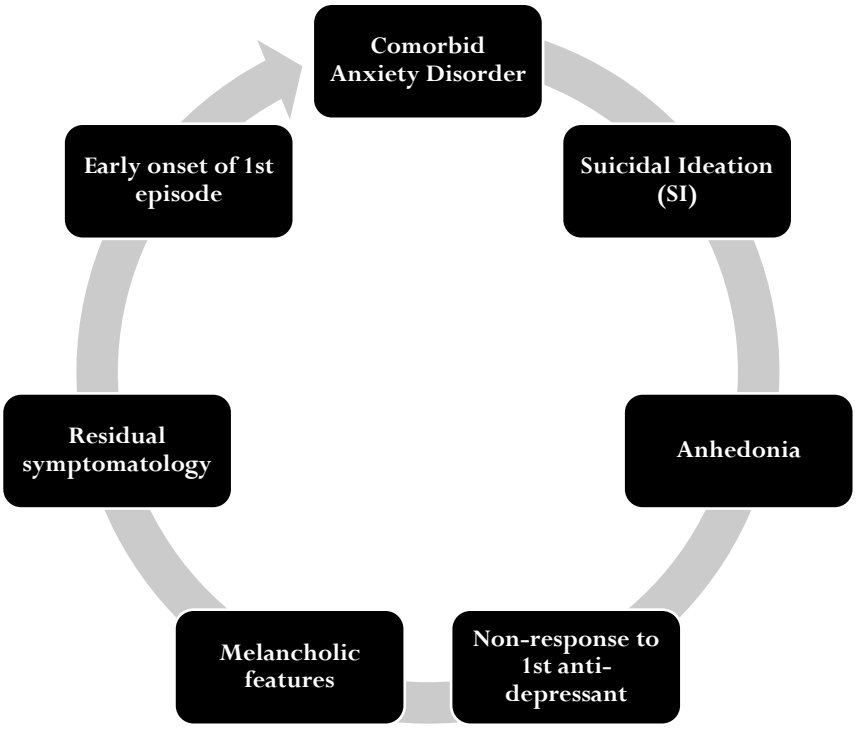
Definition of Treatment Resistant Depression[19,20]

- No universally accepted definition
- Frequently defined as failure to achieve remission following ≥ 2 antidepressant trials
- Trials must be of adequate duration to assess response and adequate dose

Prevalence and Epidemiology[19,21]

- WHO estimates 300 million people in the world with MDD
- Less than 50% of those with MDD are receiving treatment
- Estimated that around 20-40% of those receiving treatment are treatment resistant

Risk Factors for Treatment Resistant Depression[22–25]



National Institute of Mental Health (NIMH) Constructs of Depression[26]

- Research Domain Criteria (RDoC) is a research framework being prioritized by NIMH
- Research focus on physiologic constructs, grouped into domains of human behavior or functioning
- Those related to depression include anhedonia, negative and positive valence, cognition, working memory, and social processing

Global Impact of Treatment Resistant Depression[20,21,27]

Treatment Strategies for Resistant Depression[19,20]

Table 2: Treatment Strategies for Managing Resistant Depression

Strategy	Therapeutic Options
Optimize Antidepressant	• Increase dose • Treat for adequate duration
Switch Antidepressants	• Same or different class • MAOIs and TCAs
Augmentation	• Lithium, thyroid hormones, atypical antipsychotics (aripiprazole, quetiapine, olanzapine), anticonvulsants, mood stabilizers, buspirone
Other Treatments	• ECT, vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), direct brain stimulation (DBS)

Rates of Remission among Patients with Treatment Resistant Depression[19,28]

Optimizing and Switching
- Some estimates that as few as 11% of patients receive an adequate dose and trial of antidepressant therapy
- Switching classes may result in improvements in response of up to 70%

Augmentation Strategies
- Lithium: 30-65% response rates in TRD
- Fluoxetine + olanzapine: 40% improvement compared to 30% with fluoxetine alone
- Triiodothyronine (T3): about 25% remission rates in STAR*D

Electroconvulsive Therapy
- Generally considered to be the most effective option in TRD
- Response rates around 50-70%
- Relapse rates have been shown to be significantly higher following a successful ECT course

About 30% of patients with TRD do not respond to any treatment

Ketamine

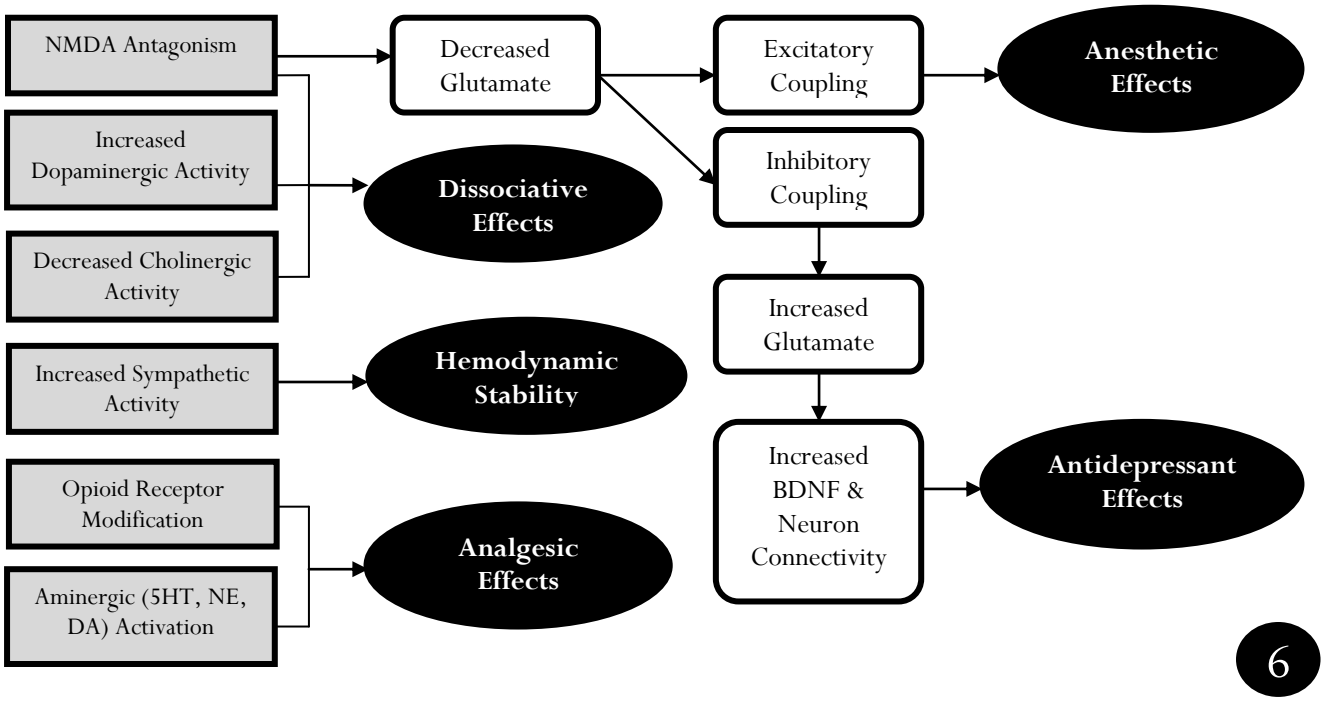
Medication Background and Uses

The Diversity of Ketamine use in Healthcare[29–31]

Anesthetic and Analgesic	• Developed in the 1960's; approved for human use in 1970
	• Lacks suppression of respiratory and cardiac function at therapeutic doses
	  ○ Battle field anesthetic in the Vietnam War
	  ○ Low-income countries where respiratory support is hard to obtain
	  ○ Veterinary medicine

Drug of Abuse	• Schedule III non-narcotic controlled substance under the DEA, not internationally controlled by the WHO • Abused for dissociative and hallucinogenic effects • Use is most common among teens and young adults as a "club drug" • Used to facilitate sexual assault
Novel Anti-depressant	• Studies have evaluated the role of ketamine in MDD • Investigated single-dose infusions, multi-dose infusion, and augmentation • Route of administration: IV infusions and intranasal (bioavailability of 35-50%) • Dosing: Low dose (sub-anesthetic) infusions ○ MDD dose of 0.5 mg/kg vs. anesthesia induction dose of 1-4.5 mg/kg

Mechanism of Action of Ketamine[32,33]



Single Dose Administration

Acute Reduction of Depressive Symptoms

Table 3: Murrough et al (2013)[34]
Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial.

Objective	To evaluate the antidepressant effects of a single ketamine infusion in patients with TRD
Methods	
Design	Two-site, randomized, double blind, placebo controlled (N= 73)
Patient Selection	**Inclusion criteria** • Age 21-80 • DSM-IV MDD diagnostic criteria • Inadequate response ≥ 3 antidepressant trials **Exclusion criteria** • History of psychotic illness or bipolar disorder • Alcohol or substance abuse within 2 years • Serious suicidal or homicidal risk • Score < 27 on Mini-Mental State Examination (MMSE)
Intervention	• Ketamine: 0.5 mg/kg IV infused over 40 minutes • Midazolam: 0.045 mg/kg IV infused over 40 minutes • Free of antidepressants for at least 1 week prior to intervention (4 weeks for fluoxetine)
Outcomes	**Primary Endpoint** • Reduction in depression severity 24 hours after administration (MADRS) **Secondary Endpoints** • MADRS response rate (50% reduction in baseline score) • Change in QIDS and CGI scores • Durability of benefit up to 7 days • Adverse effects and dissociative state at regular intervals
Statistical Analysis	• Modified intention to treat • Effect size estimates of MADRS response rates of 60% for ketamine vs. 15% for midazolam • 72 for 80% and 96% power to detect MADRS changes of ketamine and midazolam, respectively • General linear modeling and logistic regression, two-sided alpha of 0.05
Results	
Baseline	**Demographics** Age 45.5 Female gender 51.4% Caucasian 83.3% Unemployed 58.3% **Depression History** Duration of MDD (years) 21.4 Recurrent MDD 61.1% Index episode ≥ 2 years 68.1% Episode duration (years) 11.2 Prior suicide attempt 31.9% Prior hospitalization 50% **Baseline Severity** MADRS 32.1 IDS-30 48 QIDS-16 16.5 **Treatment Resistance** Previous trials 5.1
Study Outcomes	**Primary Outcome: (ketamine vs. midazolam)** • MADRS score at 24 hours: 14.77 vs. 22.72 ($p \leq 0.001$) **Secondary Outcomes:** **At 24 hours:** • MADRS treatment response: 64% vs. 28% ($p \leq 0.006$) NNT=3 • QIDS and CGI scores were significantly improved **Up to 7 days:** • MADRS scores collapsed across time: 16.93 vs. 23.19 ($p \leq 0.002$) • After adjustment for site and baseline scores, no significant difference at 7 days

	Adverse Events: • 17% receiving ketamine had significant dissociative symptoms; resolved by 2 hours post-infusion • No severe psychotic symptoms occurred in any patient • Transient blood pressure increases, hemodynamic changes required cessation in 2 patients
Critique	
Strengths	• Largest single-infusion trial to date • Use of midazolam as an active placebo to enhance blinding
Limitations	• Exclusion criteria limit applicability in practice (eg. substance abuse, psychotic symptoms) • Designed for patients able to tolerate a medication washout period (1 suicide attempts in trial) • Does not include most recent antidepressant regimen or other medications
Take Away Summary	
In patients with TRD after a washout of antidepressant therapy, low dose IV ketamine significantly reduced MADRS scores and increased response 24 hours. Adverse effects included transient dissociative symptoms and increased blood pressure.	

Other Trials Analyzing Single Dose Administrations of Ketamine

Table 4: Trials Assessing Symptom Reduction Following a Single Infusion

Study	Population	Intervention	Outcomes
Berman et al.[35] (2000)	• Double blind, randomized, crossover (N=7) • Inclusion: MDD (DSM-IV) • Exclusion: axis 1 disorder (eg. mood, psychotic), recent alcohol or substance abuse diagnosis	• Antidepressant free ≥ 2 weeks • Ketamine IV • Placebo	• Significantly reduced HAM-D scores for 72 hours (mean 14 point decrease) • 50% achieved response
Zarate et al.[36] (2006)	• Double blind, randomized, crossover (N=18) • Inclusion: MDD (DSM-IV), fail ≥ 2 antidepressant trials (average of 5.7), HAM-D score ≥ 18 • Exclusion: psychotic features, bipolar disorder, substance abuse or dependence within 3 months	• Antidepressant free ≥ 2 weeks • Ketamine IV • Placebo	• Significantly reduced HAM-D scores within 110 min maintained up to 7 days • 71% achieved response • 29% achieved remission
Lapidus et al.[37] (2014)	• Double blind, randomized, crossover (N=18) • Inclusion: MDD (DSM-IV), fail ≥ 1 (average of 4.1) antidepressant trials, IDS-C score ≥ 30 • Exclusion: psychotic features, bipolar disorder, substance abuse or dependence within 6 months	• Ketamine intranasal 50 mg over 20 min • Placebo	• Significantly reduced MADRS scores within 40 minutes, maintained up to 48 hours • 44% achieved response
Mathew et al.[38] (2010)	• Open label (N=26) • Inclusion: MDD (DSM-IV), fail ≥ 2 antidepressant trials (average of 6), IDS-C score ≥ 32 • Exclusion: psychotic or bipolar disorder, substance abuse or dependence within 6 months	• Antidepressant free ≥ 2 weeks • Ketamine IV	• Significantly reduced MADRS scores within 4 hours maintained up to 72 hours • 65% achieved response • 50% achieved remission
Ibrahim et al.[39] (2012)	• Open label (N=42) • Inclusion: MDD (DSM-IV), fail ≥ 2 antidepressant trials (average of 7.4), current episode ≥ 4 weeks, MADRS score ≥ 22 • Exclusion: psychotic features, drug induced hypomania or mania, substance abuse or dependence within 3 months	• Antidepressant free ≥ 2 weeks • Ketamine IV	• Significantly reduced MADRS scores within 240 minutes maintained up to 28 days • 62% achieved response

*All ketamine IV doses were 0.5 mg/kg administered over 40 minutes

Multiple Dose Administrations

Extended Reduction of Depressive Symptoms

Table 5: Singh et al (2016) [40]
A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression.

Objective	To evaluate the antidepressant effects of multiple ketamine infusions administered twice or thrice weekly in patients with TRD
Methods	
Design	Multi-center, randomized, double blind, placebo controlled (N= 67)
Patient Selection	**Inclusion criteria** • Age 18-64 • DSM-IV MDD diagnostic criteria • Inadequate response ≥ 2 antidepressant trials; 1 failure in current episode • Score ≥ 34 on IDS-CR **Exclusion criteria** • History of psychotic disorders, bipolar disorder, and other axis 1 disorders • Alcohol or substance abuse within 1 year • Serious suicidal or homicidal risk
Intervention	• Ketamine: 0.5 mg/kg IV infused over 40 minutes: given two or three times weekly for 4 weeks • Placebo: given two or three times weekly for 4 weeks
Outcomes	**Primary Endpoint** • Reduction in depression severity at 15 days (MADRS) **Secondary Endpoints** • Early onset response maintained through day 15 (MADRS) • Remission at day 15 (MADRS) • Change in MADRS scores from baseline to day 29 • Adverse effects and dissociative state at regular intervals
Statistical Analysis	• Intention to treat • 14 patients per group for 90% power (56 total), two-sample t test, one-sided alpha of 0.15 • Mixed-effect model with repeated measures for primary endpoint
Results	
Baseline	**Demographics** Age: 43.9 Female gender: 67.2% Caucasian: 79.1% **Depression History** # of Anti-depressants in current episode: 53.7% (1), 31.3% (2), 7.5% (3), 7.5% (≥ 4) Anxious depression: 28.4% **Baseline Severity** MADRS: 35.3 CGI-S (moderately ill): 31.3% CGI-S (markedly ill): 59.7% CGI-S (severely ill): 9%
Study Outcomes	**Primary Outcome: (ketamine vs. placebo)** • MADRS score at 15 days: significantly lower for both frequencies, but no difference between them ○ Twice weekly: -18.4 vs. -5.7 ($p \leq 0.001$); thrice weekly -17.7 vs. -3.1 ($p \leq 0.001$) **Secondary Outcomes:** significantly improved with ketamine, no difference between frequency groups, overall frequencies listed below: • MADRS response in week 1 maintained through day 15 (31% vs. 3.4%) • MADRS response at day 15 (62.1% vs. 10.3%) and remission at day 15 (31% vs. 3.4%) • MADRS score chance from baseline to day 29 (-22.2 vs. -3.8) • CGI-I and PGI-C scores significantly improved from baseline

	Adverse Events: • Higher in ketamine groups, most commonly headache, anxiety, dissociation, nausea, and dizziness. Dissociation occurred in 17.1% and resolved 3 hours post-infusion. Intensity reduced with repeated dosing (CADSS mean score of 7.5 on day 1 vs. 3.9 on day 15), 3 required discontinuation. • Mean changes in heart rate and blood pressure were within normal limits for all groups
Critique	
Strengths	• Largest multiple-infusion trial to date, only randomized placebo controlled trial • Did not require antidepressant washout phase • Assessed multiple dosing frequencies
Limitations	• Exclusion criteria limit applicability in practice (eg. substance abuse, psychotic symptoms) • Limited baseline characteristics provided (MDD history, suicide attempts, hospitalizations, etc.) • No use of an active placebo
Take Away Summary	
In patients with TRD on stable antidepressant therapy, low dose IV ketamine significantly reduced MADRS scores up to 29 days and increased response and remission rates at 15 days. Adverse effects included transient, dissociative effects.	

Other Trials Analyzing Multiple Dose Administrations of Ketamine

Table 6: Trials Assessing Symptom Reduction Following Multiple Infusions

Study	Population	Intervention	Outcomes
aan het Rot et al.[41] (2010)	• Open label (N=10) • Inclusion: MDD (DSM-IV), fail ≥ 2 antidepressant trials (average of 8.2), IDS-C score ≥ 32, response to single open label ketamine dose • Exclusion: psychotic features, mania or hypomania, substance abuse or dependence within 3 months	• Antidepressant free ≥ 2 weeks • Ketamine IV x 1 • If response at 24 hours, 5 additional doses for 12 days	• 90% achieved response at 24 hours, maintained through all infusions • Mean MADRS score reduction was 85% after 6th infusion • Average time to recurrence 19 days from last dose (range:6 to > 90 days)
Murrough et al.[42] (2013)	• Open label (N=24), • Extension of ann het Rot et al.that did not require response to a single open label ketamine dose	• Antidepressant free ≥ 2 weeks • Ketamine IV 6 infusions over 12 days	• Significantly reduced MADRS scores within 2 hours, maintained 12 days • 70% response following last infusion • Median time to recurrence 18 days, 4 with no recurrence by day 83
Diamond et al.[43] (2014)	• Open label , exploratory (N=28) • Inclusion: Bipolar (N-6) or unipolar (N=22) depression (DSM-IV), fail ≥ 2 antidepressant trials • Exclusion: schizophrenia, dementia or mild cognitive impairment	• Ketamine IV once a week for 3 weeks (N= 15) • Ketamine IV twice a week for 3 weeks (N= 13)	• 33% of completers achieved response based on BDI scores at 21 days • 50% of responders achieved remission • Median length of response of 70 days, range of 25 to 168.
Rasmussen et al.[44] (2013)	• Open label (N=10) • Inclusion: MDD or bipolar II disorder (DSM-IV), fail ≥ 2 antidepressant trials • Exclusion: psychotic or bipolar I disorder, substance or alcohol abuse within 12 months, dementia	• Ketamine IV over 100-minutes, twice weekly until remission (up to 4 doses)	• 50% MADRS remission (20% with 1 infusion, 60% with 2 , 20% with 4) • 40% sustained remission 4 weeks • 80% achieved response (37.5% after 1 infusion, 62.5% after 2)

*All ketamine IV doses were 0.5 mg/kg administered over 40 minutes unless otherwise specified

Ketamine and Electroconvulsive Therapy

Head-to-head Comparison and Augmentation Strategies

Direct Comparison of Ketamine to ECT

Table 7: Ghasemi et al. (2014)[45]
Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder

Objective	To evaluate the antidepressant effects of 3 ketamine IV infusions compared to 3 sessions of ECT in patients currently in an major depressive episode
Methods	
Design	Single-center, randomized, single-blinded (N= 18)
Patient Selection	**Inclusion criteria** • Age 18-75 • DSM-IV MDD diagnostic criteria • Currently experiencing an episode and scheduled to receive ECT **Exclusion criteria** • History of psychotic disorder, manic or hypo-manic episode, dementia, mental retardation • Substance dependence • Serious medical conditions
Intervention	• Ketamine: 3 doses of 0.5 mg/kg IV infused over 45 minutes every 48 hours • ECT: 3 sessions of bilateral ECT every 48 hours
Outcomes	**Primary Endpoint** • Reduction in depression severity based on BDI and HAM-D scores **Secondary Endpoints** • Change from baseline following each session or dose • Changes from baseline 72 hours and 1 week after the last session or dose • Response rates for each of the above time intervals
Statistical Analysis	• Mixed-design analysis of variance model for repeated measures • Independent t-tests for differences in depression scores, with alpha < 0.05
Results	
Baseline	**Demographics** Age: 37.6 Female gender: 55.6% Education (years): 9.2 **Depression History** Age of onset: 29.4 Length of current episode (weeks): 9 Time in hospital before study initiation (days): 12.9 Total number of hospitalizations: 2.1 Suicide attempts: 1.1 **Baseline Severity** BDI: 38.6 HAM-D: 33.1 **Current Medications** SSRI: 66.7% TCA: 33.3% Antipsychotic: 27.8% Anticonvulsant: 22.2% Benzodiazepine: 61.1%

Study Outcomes	**Primary Outcome: (ketamine vs. ECT)**
	• Both ECT and ketamine significantly improved BDI and HAM-D scores from baseline to 1 week post treatment
	• BDI and HAM-D scores in ketamine group significantly reduced following: the first and second treatment, and 7 hours post-treatment compared to ECT
	  ○ First treatment: BDI (20.22 vs. 36.5); HAM-D (16.88 vs. 31.44)
	  ○ Second treatment: BDI (18.22 vs. 31.3); HAM-D (15.55 vs. 24.55)
	  ○ 72 hours post-treatment: BDI (11.88 vs. 20.11); HAM-D (10.11 vs. 16.77)

	• Scores did not significantly differ following the third treatment or 1 week post-treatment. **Secondary Outcomes:** Percentage of patients meeting response criteria:

	Ketamine based on BDI	ECT based on BDI	Ketamine based on HAM-D	ECT based on HAM-D
First treatment	44.4%	11.1%	77.8%	11.1%
Second treatment	55.6%	11.1%	77.8%	22.2%
Third treatment	77.8%	44.4%	88.9%	66.7%
72 hours after	77.8%	44.4%	100%	88.9%
1 week after	77.8%	77.8%	100%	88.9%

Adverse Events:

- Both treatments well tolerated, no significant change in hemodynamic parameters in either group
- Temporarily increased systolic blood pressure and heart rate in 3 patients after the second and third dose of ketamine, not found to be clinically significant

Critique	
Strengths	• Only head-to-head comparison of ECT and ketamine • Did not require antidepressant washout phase • Reported current medications
Limitations	• Exclusion criteria limit applicability in practice (eg. substance abuse, psychotic symptoms) • Patients unable to be blinded in this comparison • Titration method for ECT and use of thiopental as an anesthetic could result in slower onset of action for ECT treatments

Take Away Summary

In patients with MDD indicated for ECT treatment, low dose IV ketamine significantly reduced BDI and HAM-D scores more rapidly than ECT with higher rates of response up to 72 hours post treatment. Both treatments were well tolerated.

Meta-analyses of Ketamine Augmentation with ECT

Table 8: Meta-analyses of Ketamine use as an Augmentation Strategy to Facilitate ECT

Study	Population	Intervention	Outcomes
Fond et al.[46] (2014)	• 4 trials (118 patients) • Search inclusion: randomized controlled trials evaluating ketamine in ECT, diagnosis of major depression or bipolar depression (DSM IV) • Population: 87% MDD, 13% bipolar disorder	• Ketamine doses ranged from 0.4 mg/kg to 0.8 mg/kg	• Ketamine use in ECT significantly improved depression scores compared to patients receiving thiopental or propofol • Driven by 1 of the 4 trials that found a significant improvements with ketamine
McGirr et al.[47] (2015)	• 5 trials (182 patients) • Search inclusion: randomized controlled trials evaluating ketamine in ECT, diagnosis of major depression or bipolar depression (DSM IV) • Population: 90.7% MDD, 9.3% bipolar disorder	• Ketamine doses ranged from 0.4 mg/kg to 1-2 mg/kg	• Ketamine use in ECT did not significantly improve clinical remission, response, or depressive symptoms • Augmentation was associated with significantly higher rates of confusion, disorientation, and prolonged delirium

Applications of Ketamine

Antidepressant Augmentation and Other Potential Uses

Single Ketamine Infusion Prior to Antidepressant Initiation

Table 9: Hu et al. (2016)[48]
Single IV ketamine augmentation of newly initiated escitalopram for major depression

Objective	To evaluate the antidepressant effects of a ketamine augmentation strategy with escitalopram
Methods	
Design	Single-center, randomized, double-blind (N= 30)
Patient Selection	**Inclusion criteria** • Age 18-60 • DSM-IV MDD diagnostic • Severe MDD (HAM-D ≥ 24) **Exclusion criteria** • History of psychotic, bipolar, or any other axis 1 disorder • Lifetime history of substance dependence • History of inefficacy or intolerance to escitalopram
Intervention	• Ketamine: single ketamine infusion of 0.5 mg/kg followed by escitalopram 10 mg po daily • Placebo: single saline infusion followed by escitalopram 10 mg po daily • Free of antidepressants for at least 2 weeks prior to intervention (4 weeks for fluoxetine)
Results	
Baseline	**Demographics** Age: 39 Female gender: 63% **Depression History** Age of onset: 34.4 Length of current episode (months): 5.1 Number of depressive episodes: 3.9 ≥ 2 failed antidepressant trials: 55.6% **Baseline Severity** History of Suicide Attempts: 11.1% MADRS: 34.3 QIDS-SR: 17.1

Study Outcomes	**Primary Outcome: (ketamine vs. placebo)**
	• Time to response was significantly shorter with ketamine: 6.4 days vs. 26.5 days ($p < 0.001$)
	  ○ By 4 hours post infusion 53.8% in ketamine group achieved response vs. 0 with placebo
	Secondary Outcomes:
	• Time to remission was significantly shorter with ketamine: 14 days versus 27 days ($p=0.001$)
	  ○ By 72 hours post infusion 38.5% in ketamine group achieved remission vs. 0 with placebo
	• Response rates higher with ketamine by 4 weeks: 92.3% vs. 57.1% ($p=0.04$) NNT = 3
	• Remission rates higher with ketamine by 4 weeks: 76.9% vs. 14.3% ($p=0.001$) NNT = 2
	• Ketamine group had significantly lower MADRS and QIDS-SR scores from 2 hours to 2 weeks
	• Ketamine group had significantly higher response rates for TRD: 88.9% vs. 33.3% ($p=0.02$)
	Adverse Events:
	• Ketamine had significantly higher mild and transient adverse effects, resolving by 24 hours post-infusion, with many resolving within 40 minutes post-infusion

Critique	
Strengths	• Only study looking at a single ketamine infusion for augmentation of conventional therapy • Only about half of the patients included were classified as TRD
Limitations	• Exclusion criteria limit applicability in practice (eg. substance abuse, psychotic symptoms) • Required a washout phase from current therapy
Take Away Summary	
In patients with MDD initiating escitalopram therapy, a single ketamine infusion significantly increased response and remission rates and significantly shortened time to response and remission.	

Reductions in NIMH Symptom Clusters and Suicidal Ideation[35,41–44,48–54]

Major Depressive Disorder

Anhedonia

Definition:

- Loss of interest or pleasure

Importance:

- Difficult to treat and not adequately addressed by current antidepressants
- Predictor of poor response

Effects of Ketamine

- Lally et al. found anhedonia was significantly reduced 40 minutes after a single infusion and maintained for 3 days.
- Murrough et al. found anhedonia was significantly improved within 2 hours of the first dose of ketamine

Cognition

Definition:

- Mental process of comprehension, judgment, memory, and reasoning

Importance:

- Difficult to treat
- Deficits can persist despite full or partial remission

Effects of Ketamine

- Murrough et al. found cognition was significantly improved within 2 hours of the first dose of ketamine
- Diamond et al. found improved memory testing following multiple ketamine infusions

Suicidal Ideation

Definition:

- Thoughts of suicide

Importance:

- High risk of mortality, not rapidly addressed by current antidepressants
- Predictor of poor response

Effects of Ketamine

- 4 trials of single-dose infusions have shown significant reductions in SI as early as 40 minutes post-infusion (N=127)
- 4 trials of multi-dose infusions have shown significant reductions in SI as early as 2 hours post-infusion (N=72)

Other Potential Applications for Ketamine in Depression[55,56]

Hospice and End of Life Care

Irwin et al. (2013)

- 28 day open-label trial looking at 14 hospice patients with symptoms of depression alone or depression plus anxiety
- Daily 0.5 mg/kg oral doses of ketamine significantly reduced both anxiety and depression scores (using the Hospital Anxiety and Depression Scale) by ≥ 30% in all patients who completed the study
- Anxiety scores were significantly reduced by day 3, depression scores were significantly reduced by day 14

Surgery Anesthetic in MDD

Kudoh et al. (2002)

- Randomized trial looking at 70 patients with MDD undergoing orthopedic surgery
- All patients were induced with propofol and fentanyl, and patients were randomized to receive an additional 1 mg/kg infusion of ketamine
- Ketamine was associated with significantly reduced HAM-D scores at 1 day post-op.
- Ketamine also had significantly improved post-operative pain, depressed mood, suicidal tendencies, and anxiety.

Limitations of Ketamine

The Controversy of Approving Ketamine for MDD

Safety[57,58]

- Ketamine Infusions
  - Adverse effects are transient, occurring during and immediately following infusions
  - Most common adverse effects include drowsiness, dizziness, poor coordination, blurred vision, and strange or unreal feelings
  - Estimated that about one third of patients experience transient hemodynamic changes (eg. tachycardia, hypertension)
- Chronic use
  - No trials looking at adverse effects of long term ketamine use in depression
  - Based on findings from ketamine abusers and chronic use in pain management, potential concerns of chronic use include hepatotoxicity, worsening of underlying cardiovascular disease, urological symptoms including cystitis, neurotoxicity and memory impairment

Cost[59,60]

- Estimated that over 60 private clinics provide ketamine infusions in the U.S.
- Administration requires continuous monitoring for transient effects
- The majority of ketamine infusion clinics are run by anesthesiologists

Cost of Ketamine

- Most commonly used dose = 0.5 mg/kg
- Cost of single dose for 70 kg patient = $3.78
- Cost of 6 doses = $22.68

Cost of Ketamine Infusion in Clinic

- Cost per infusion = $400 - $2000
- Cost per 6 infusions = $2,400 - $12,000
- Payment is out of pocket

Administration and Efficacy

- No trial data on long-term efficacy of ketamine infusions for MDD
- Most trials required that patients be taken off current antidepressant therapy
- Optimal number of ketamine infusions and frequency of infusions is unclear
- Limited data on novel routes of administration (eg. nasal, oral)
- Generic and inexpensive, unlikely that pharmaceutical companies will ever fund large studies

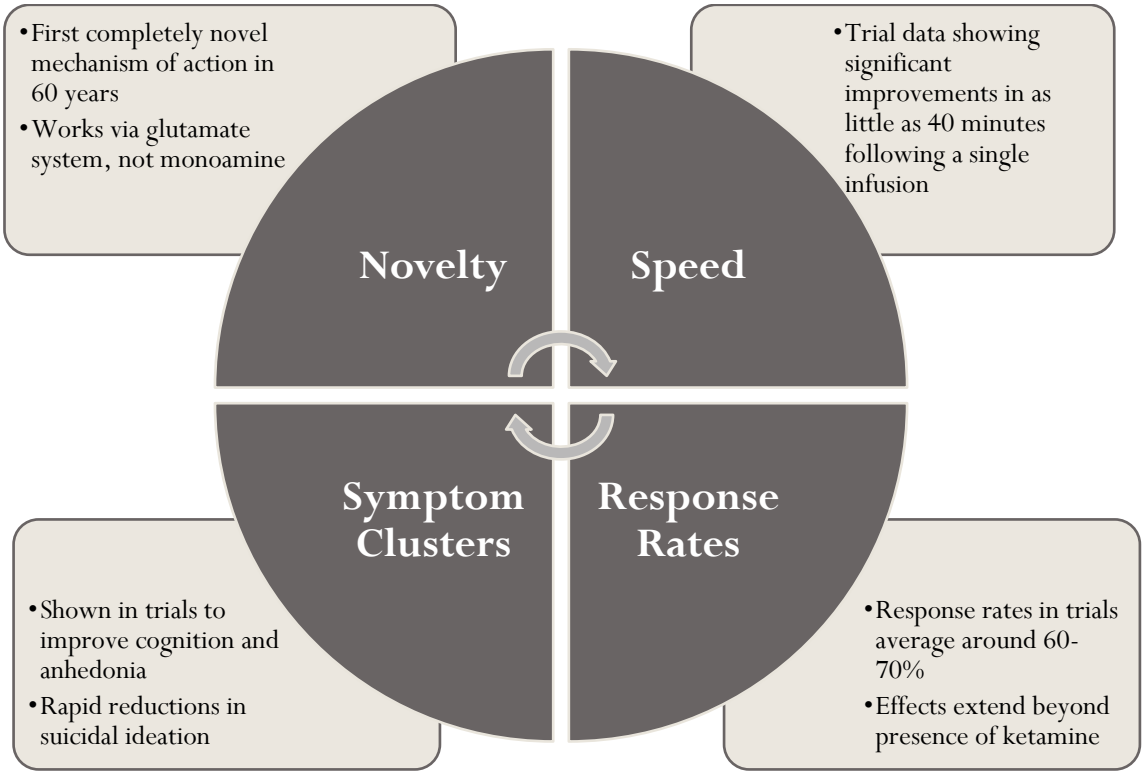
Abuse Risk[61–64]

- Around 8% of the general population has a substance use disorder; 33% of the MDD population
- Substance disorders associated with higher rates of suicide, impairment, and other psychiatric conditions
- Alcohol is the most commonly abused substance among patients with MDD
- Prevalence of lifetime ketamine use in the United States in 2006 estimated around 0.1%

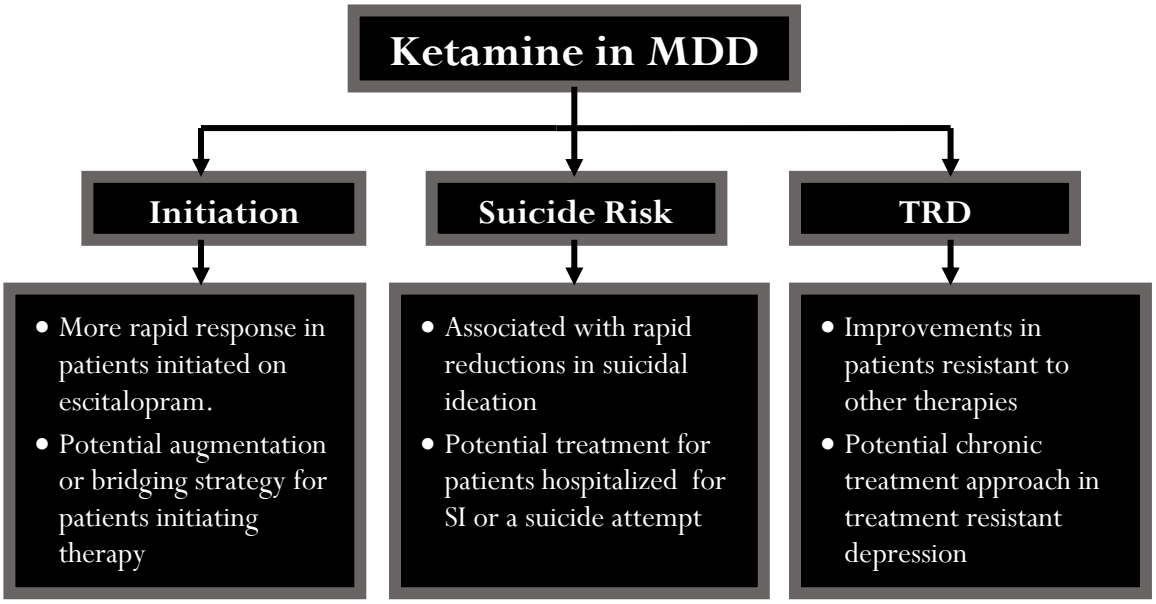
Conclusion and Recommendations

Summarizing the Role of Ketamine in MDD

Review of the Benefits of Ketamine in MDD



Summary of the Potential Role of Ketamine in MDD



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Appendices

Appendix A: Montgomery-Asberg Depression Scale (MADRS)		
Overview	**Scoring**	**Response & Remission**
• Severity assessment tool • Format: self-rated or clinician rated • Versions: 10-item	• Symptom absent = 0-6 • Mild depression = 7-19 • Moderate depression = 20-34 • Severe depression = 35-60	• Response = 50% reduction • Remission = ≤ 10 (varies)

Appendix B: Hamilton Depression Rating Scale (HAM-D)		
Overview	**Scoring**	**Response & Remission**
• Severity assessment tool • Format: clinician rated • Versions : 17-item and 21-item	21-item: • Normal = 0-7 • Mild depression = 8-13 • Moderate depression = 14-18 • Severe depression = 19-22 • Very severe depression = ≥ 23	21-item: • Response = 50% reduction • Remission = ≤ 7

Appendix C: Beck Depression Inventory (BDI)		
Overview	**Scoring**	**Response & Remission**
• Severity assessment tool • Format: self-rated • Versions: 13-item or 21-item	21-item: • Minimal depression = 0-13 • Mild depression = 14-19 • Moderate depression = 20-28 • Severe depression = 29-63	21-item: • Response = 50% reduction • Remission = ≤ 12 (varies)

Appendix D: Quick Inventory of Depressive Symptomatology (QIDS)		
Overview	**Scoring**	**Response & Remission**
• Severity assessment tool • Format: self-rated and clinician rated • Versions: 16-item	16-item: • No depression = 0-5 • Mild depression = 6-10 • Moderate depression = 11-15 • Severe depression = 16-20 • Very severe depression = 21-27	• Response = 50% reduction • Remission = ≤ 5