La ketamina como alternativa para el manejo de la depresión

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futuros residentes | sculapp

Introducción

Trastorno depresivo mayor: una de las principales causas de discapacidad en el mundo

Afecta alrededor de 300 millones de personas

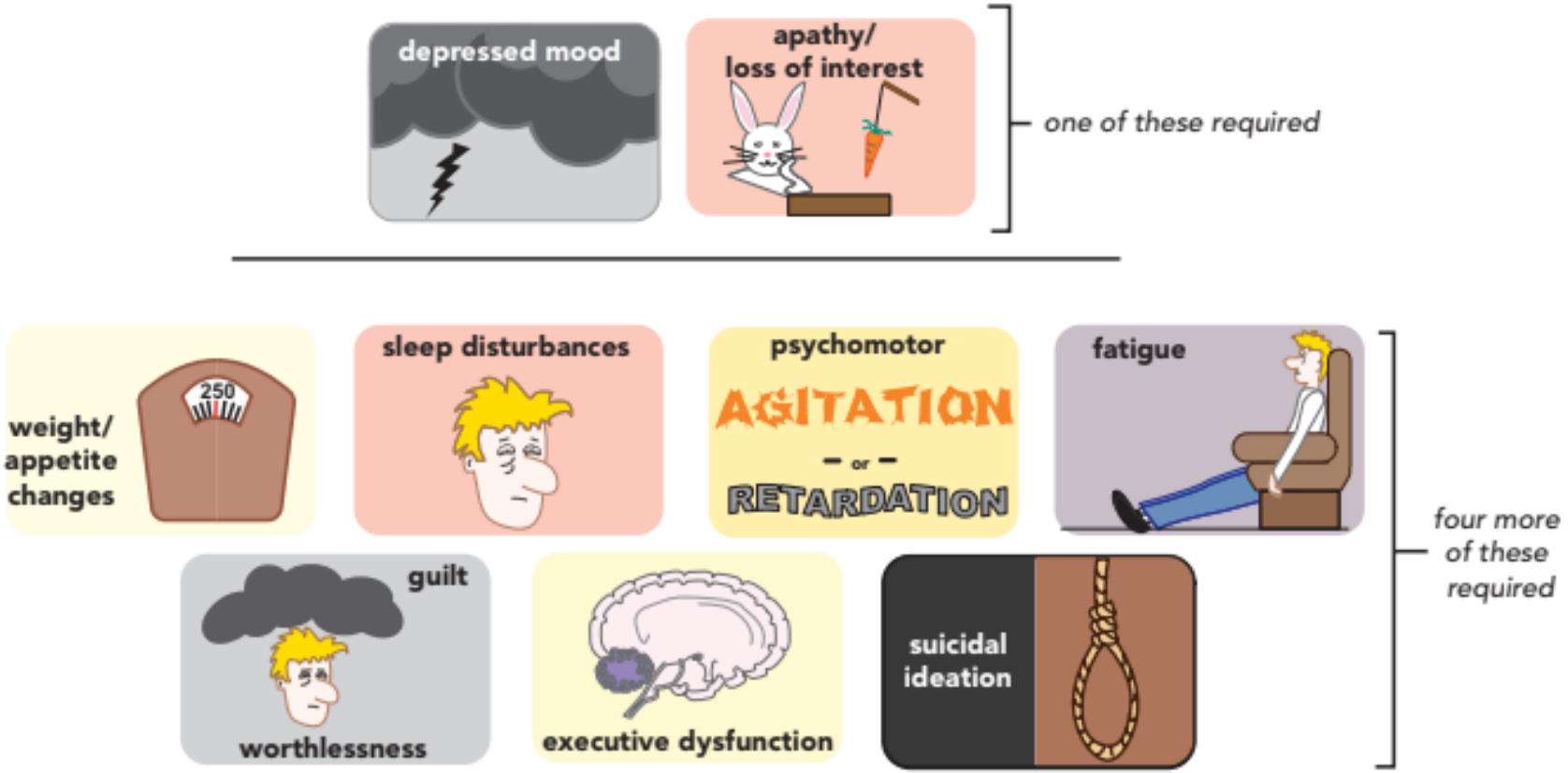
Suele mejorar unas semanas después del inicio del tratamiento farmacológico → 1/3 de los pacientes no lo harán

Se han buscado alternativas de tratamiento para la depresión resistente → Farmacológicamente se han visto beneficios en la ketamina y sus derivados

Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. J Affect Disord. 2021 Jan 1;278:542-555. doi: 10.1016/j.jad.2020.09.071. Epub 2020 Sep 23. Erratum in: J Affect Disord. 2020 Nov 20;. PMID: 33022440; PMCID: PMC7704936.

Síntomas de la depresión

Al menos dos semanas



Stephen M. Stahl. Stahl's Essential Psychopharmacology. Neurocientific Basis anf Practical Applications. 5 ed. 2021. Cambridge University Press. DOI: 10.1017/9781108975292

Tiempo de respuesta al tratamiento

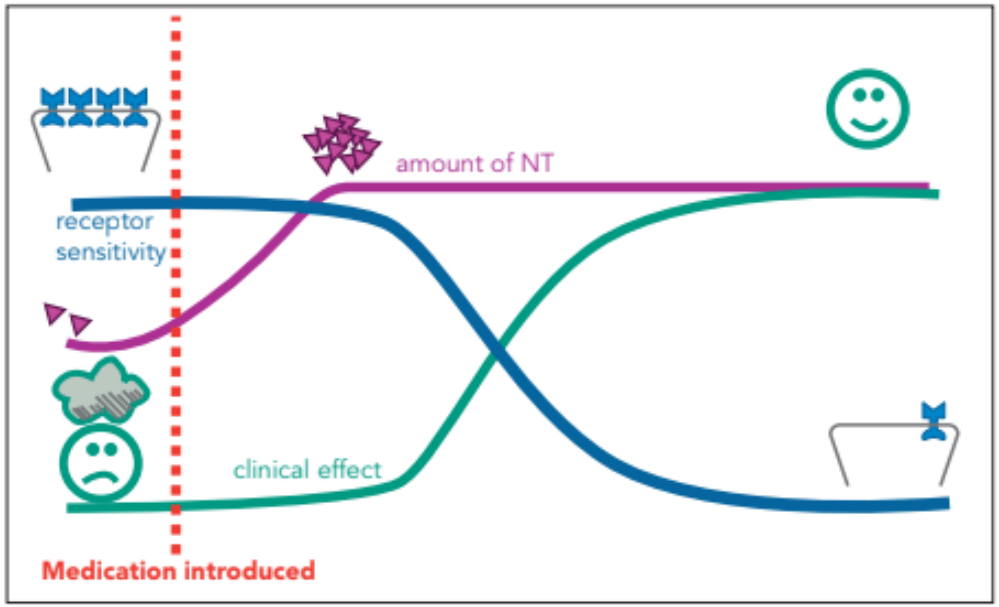


Figure 6-25 Time course of effects of drugs for depression. This figure depicts the different time courses for three effects of most drugs used to treat depression – namely, clinical changes, neurotransmitter (NT) changes, and receptor-sensitivity changes. Specifically, the amount of neurotransmitters changes relatively rapidly after a drug for depression is introduced. However, the clinical effect is delayed, as is the desensitization, or downregulation, of neurotransmitter receptors. This temporal correlation of clinical effects with changes in receptor sensitivity has given rise to the hypothesis that changes in neurotransmitter receptor sensitivity may actually mediate the clinical effects of drugs used for depression. These clinical effects include not only antidepressant and anxiolytic actions but also the development of tolerance to the acute side effects.

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Recaída y recurrencia

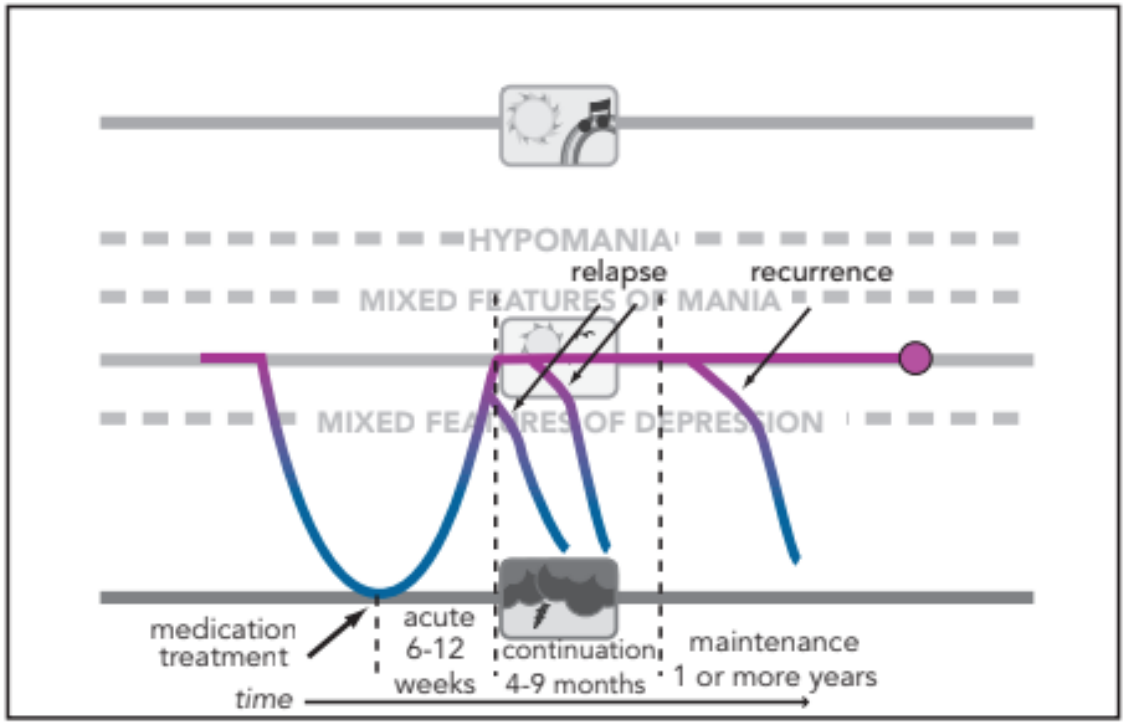

Figure 7-3 Relapse and recurrence in depression. When depression returns before there is a full remission of symptoms or within the first several months following remission of symptoms, it is called a relapse. When depression returns after a patient has recovered, it is called a recurrence.

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Tasas de remisión

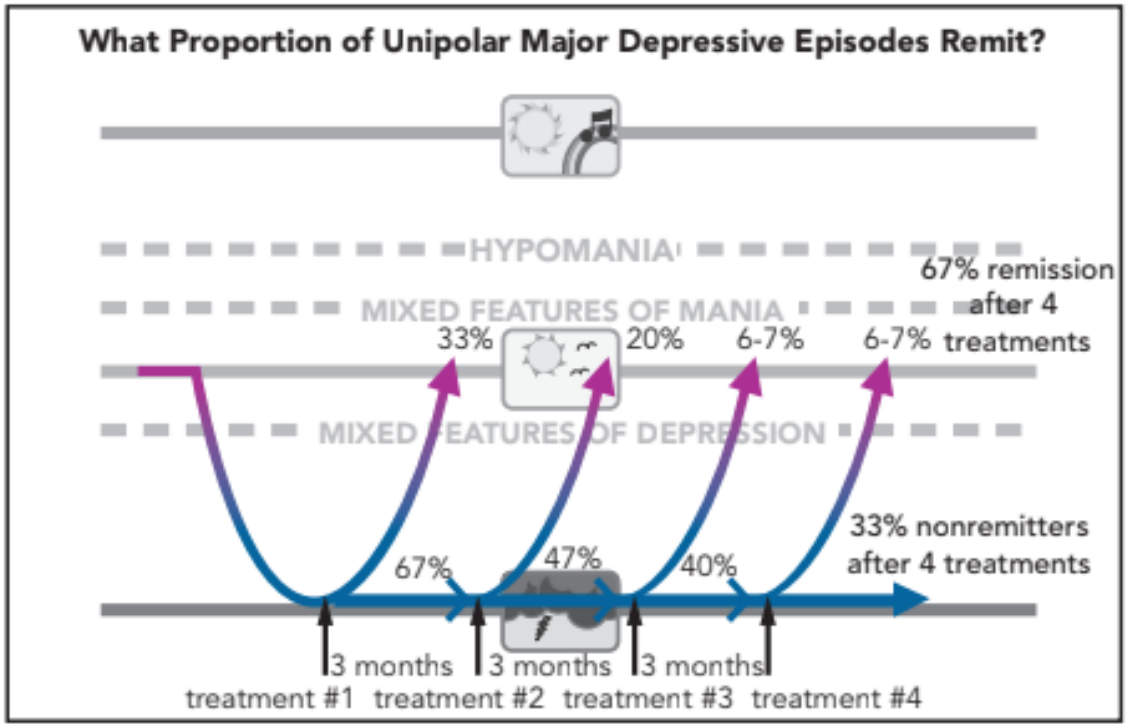

Figure 7-4 Remission rates in unipolar depression. Approximately one-third of patients with unipolar depression will remit during treatment with any treatment initially. Unfortunately, for those who fail to remit, the likelihood of remission with another monotherapy goes down with each successive trial. Thus, after a year of treatment with four sequential monotherapies taken for 12 weeks each, only two-thirds of patients will have achieved remission.

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Depresión resistente

No hay una definición estándar

Respuesta insatisfactoria a dos regímenes de tratamiento de dos clases de antidepresivo a dosis óptimas y por un tiempo suficiente

Indicadores de severidad → más riesgo de depresión resistente

- Tiempo de duración prolongado
- Alto riesgo suicida
- Comorbilidad con ansiedad
- Varias hospitalizaciones
- Altas dosis de antidepresivos

Pandarakalam JP. Challenges of Treatment-resistant Depression. Psychiatr Danub. 2018 Sep;30(3):273-284. doi: 10.24869/psyd.2018.273. PMID: 30267518.

Depresión resistente → antes de sospecharla:

Verificar adherencia

¿Dosis adecuada?

Niveles séricos (si disponibles)

Tratar psicosis si la tiene

Diagnósticos diferenciales:
- TAB
- Esquizoafectivo

Explorar dinámicas interpersonales y familiares

Evaluar comorbilidades físicas
- Alteraciones hormonales
- Malignidad
- Infecciones
- Deficiencias nutricionales

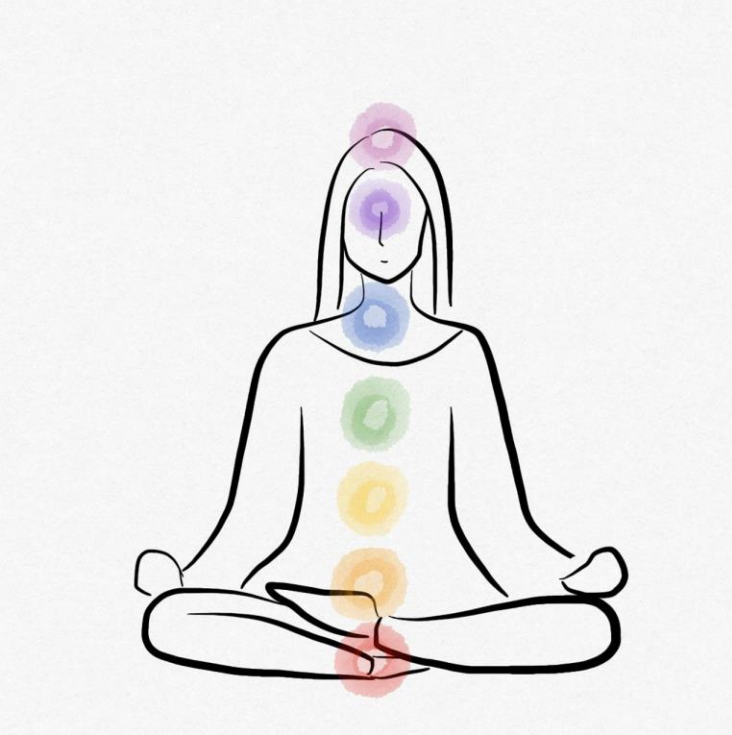
Evaluar comorbilidades psiquiátricas:
- Uso de sustancias
- Trastorno de ansiedad
- Trastorno de alimentación
- Trastorno de personalidad

Evaluar las expectativas del paciente

Pandarakalam JP. Challenges of Treatment-resistant Depression. Psychiatr Danub. 2018 Sep;30(3):273-284. doi: 10.24869/psyd.2018.273. PMID: 30267518.

Estrategias para el manejo de la depresión

- Si respuesta parcial: optimizar dosis
- Usar lo que al paciente le sirvió antes
- ISRS primera línea
  Otros: ISRSN, mirtazapina, tricíclicos
- Psicoterapia
- Realizar actividad física / meditación



Pandarakalam JP. Challenges of Treatment-resistant Depression. Psychiatr Danub. 2018 Sep;30(3):273-284. doi: 10.24869/psyd.2018.273. PMID: 30267518.

Historia de la ketamina

Sintetizada en 1962 por Calvin Stevens

Análogo estructural de la fenciclidina → Se desarrolló buscando propiedades anestésicas similares, con menos delirium asociado y menor tiempo de acción

- Analgésico y anestésico
- Alteración del estado de conciencia

→ Apareció el término “anestesia disociativa”

Luke A. Jelen & James M. Stone (2021): Ketamine for depression, International Review of Psychiatry, DOI: 10.1080/09540261.2020.1854194

Historia de la Ketamina: uso en psiquiatría

Irán 1973 (Khorramzadeh & Lotfy)
Uso 04-06 mg/kg + Psicoterapia para:
* Depresión, ansiedad, TOC, hipocondriasis

Argentina 1974 Fontana
Uso de la ketamina + psicoterapia para favorecer regresión

Krupitsky
- 1985: la usó como terapia psicodélica asistida en neurosis y T. de personalidad
- 1997: tratamiento alcoholismo

Luke A. Jelen & James M. Stone (2021): Ketamine for depression, International Review of Psychiatry, DOI: 10.1080/09540261.2020.1854194

Historia de la ketamina: uso en psiquiatría

Antidepressant effects of ketamine in depressed patients

R M Berman [1], A Cappiello, A Anand, D A Oren, G R Heninger, D S Charney, J H Krystal

Affiliations + expand

PMID: 10686270 DOI: 10.1016/s0006-3223(99)00230-9

Abstract

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 +/- SD 10 points vs. 0 +/- 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.

Primer ensayo controlado aleatorizado

Enantiómeros

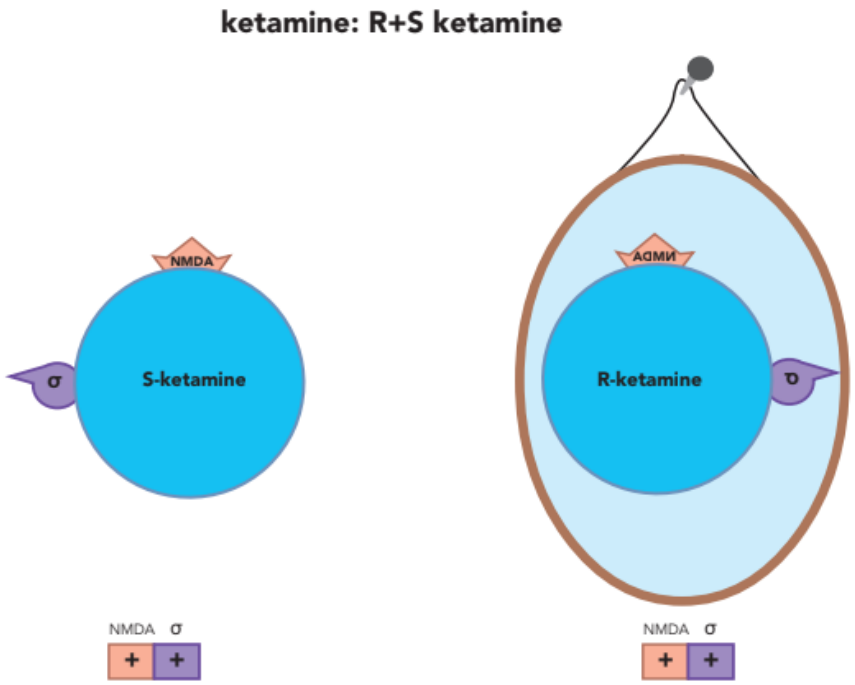


Figure 7-59 Ketamine. Ketamine is used off-label and is being studied for its potential therapeutic utility in treatment-resistant depression. Ketamine is an NMDA (*N*-methyl-D-aspartate) receptor antagonist, with additional weak actions at σ_1 receptors, the norepinephrine transporter (NET), μ-opioid receptors, and the serotonin transporter (SERT). Ketamine consists of two enantiomers, R and S.

Ketamina IV: enantiómeros R+S

Aprobado por la FDA como anestésico, analgésico y sedante

Uso off label en depresión

Esketamina IN: Enantiómero S

Aprobada por la FDA desde el 2019 para depresión resistente

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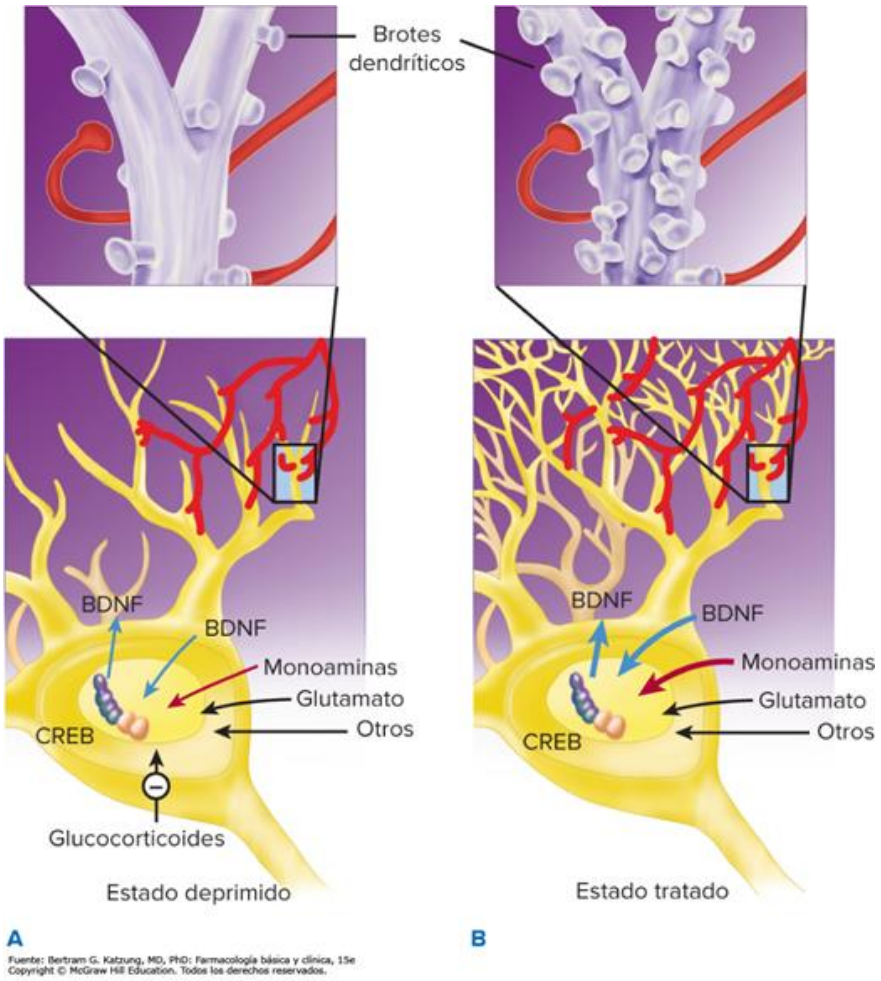
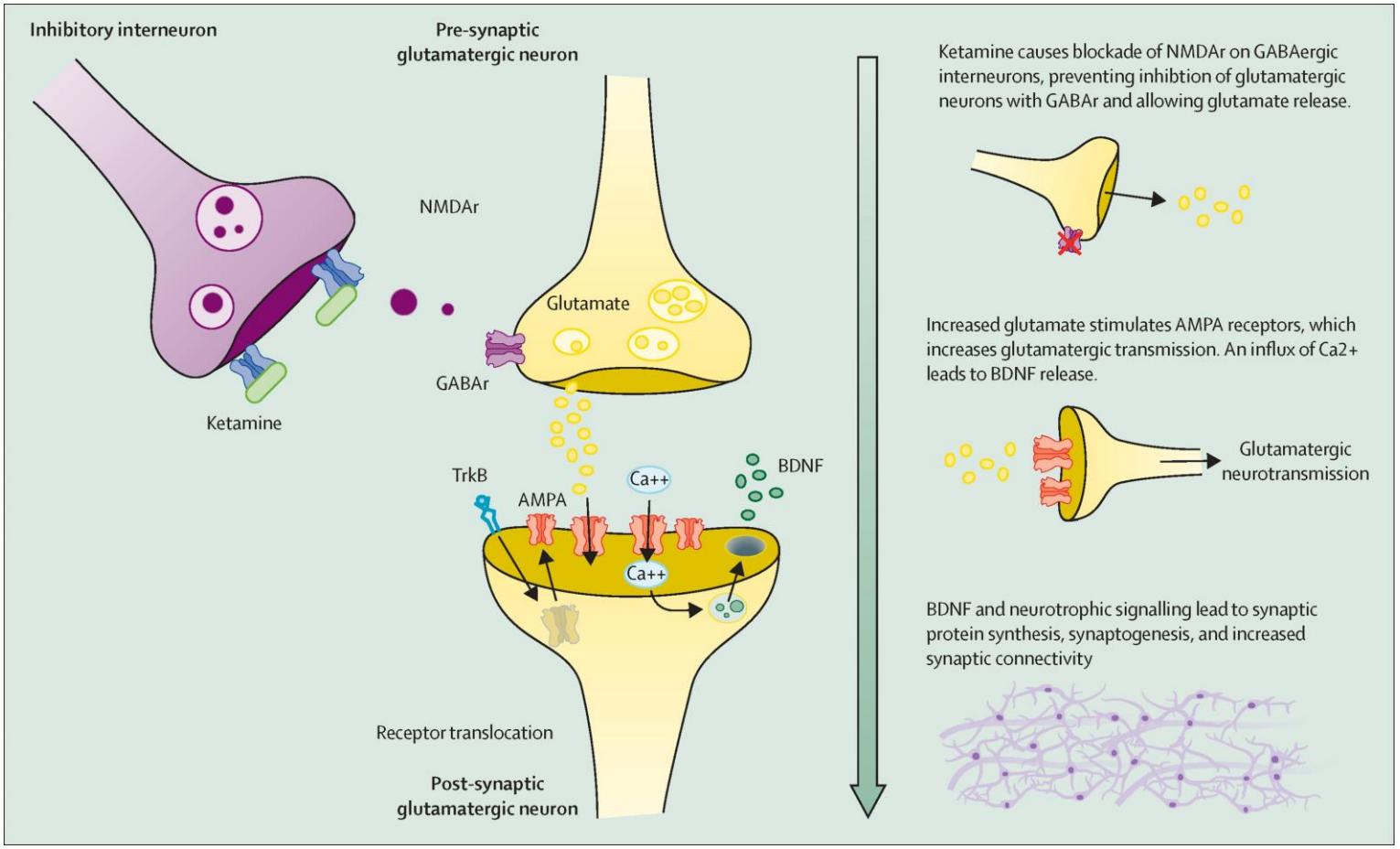
Hipótesis neurotrófica de la depresión



Bertram G. Katzung, Todd W. Vanderah. Farmacología básica y clínica, 15e. Capítulo 30: Fármacos antidepresivos. COPYRIGHT© 2020 por McGraw Hill Education Inc.

Mecanismo de acción de la ketamina



Mecanismo de acción de la ketamina

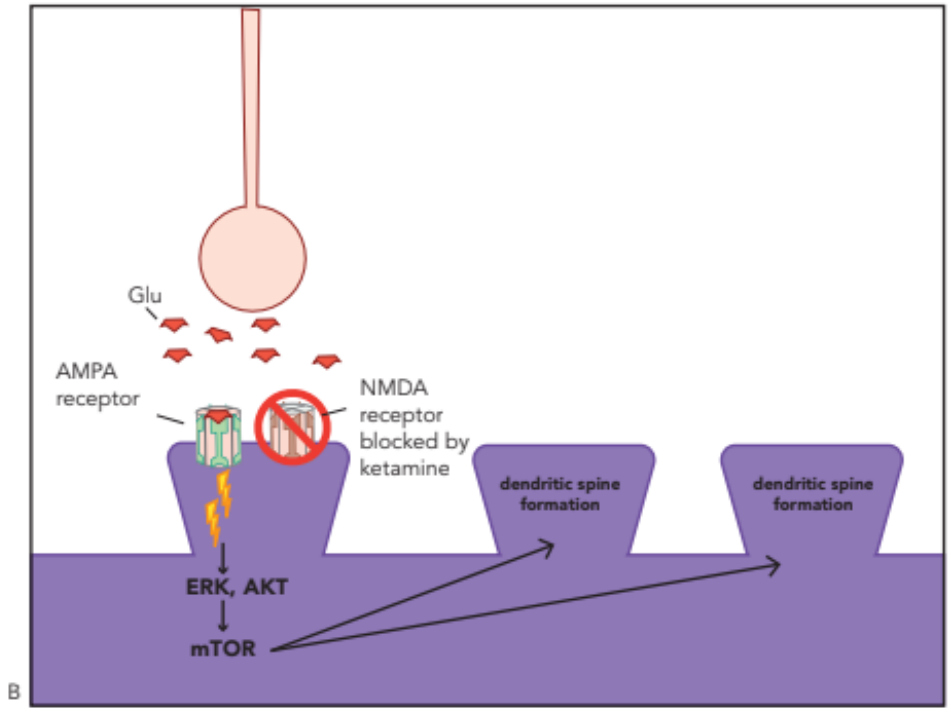


Figure 7-61 Ketamine, AMPA receptors, and mTOR. Glutamate activity heavily modulates synaptic potentiation; this is specifically modulated through NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors. Ketamine is an NMDA receptor antagonist; however, its rapid antidepressant effects may also be related to indirect effects on AMPA receptor signaling. (A) One hypothesis is that blockade of the NMDA receptor leads to rapid activation of AMPA, which triggers the ERK, AKT signal transduction cascade, which then triggers the mammalian target of rapamycin (mTOR) pathway. (B) This in turn would lead to rapid AMPA-mediated synaptic potentiation and increase in dendritic spine formation. Traditional antidepressants also cause synaptic potentiation; however, they do so via downstream changes in intracellular signaling. This may therefore explain the difference in onset of antidepressant action between ketamine and traditional antidepressants.

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TABLE 1. Key pharmacodynamic targets of ketamine and esketamine

Target	Pharmacodynamic Effect	Potential Clinical Effect[a]
Glutamate system		
N-methyl-D-aspartate (NMDA) receptor	Strong antagonist	Antidepressant and procognitive effects; acute dissociative effects
α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor	Indirect agonist (through increase glutamate release)	Antidepressant effects
D-Serine site	Antagonist	Antidepressant effects
Glutamate	Increased release	Antidepressant effects
Opioid system		
μ Opioid receptor	Weak agonist	Antidepressant and analgesic effect and potentially acute euphoric effect
μ Opioid 2 receptor	Antagonist	
κ Opioid receptor	Agonist	
δ Opioid receptor	Agonist	
Monoamine system		
Serotonin transporter	Weak inhibitor	Antidepressant effect
Norepinephrine transporter	Weak inhibitor	Antidepressant effect
Dopamine transporter	Weak inhibitor	Antidepressant effect
Dopamine 2 receptor	Agonist	Acute psychotomimetic effects
Serotonin (5-HT_3) receptor	Weak antagonist	Antidepressant effect
Cholinergic system		
Cholinesterase	Inhibitor	Procognitive effects
α7 Nicotinic receptor	Antagonist	Antidepressant effects
α4 β2 Nicotinic receptor	Antagonist	
Muscarinic receptors (M1–3)	Antagonist	Increased blood pressure and heart rate
Other		
σ_1 Receptor	Agonist	Antidepressant and cardiac effects
σ_2 Receptor	Agonist	Antidepressant and cardiac effects
Mammalian target of rapamycin (mTOR)	Downstream activation via glutamate system	Antidepressant effects
Brain-derived neurotrophic factor (BDNF)	Downstream from mTOR increasing BDNF levels	Antidepressant and procognitive effects
$GABA_A$ receptor	Agonist	Acute anxiolytic effects
mTORC1	Activation	Neuroplastic effects

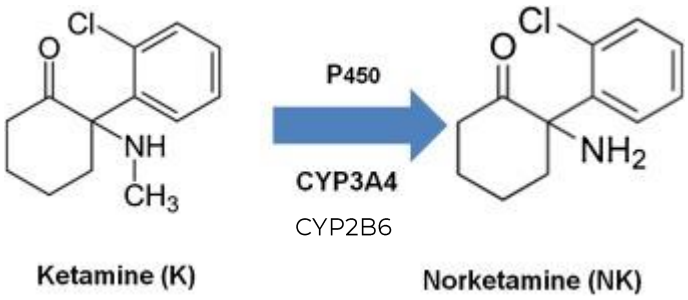
[a] The clinical significance of specific targets remains unclear, and results have been mixed. Potential proposed clinical effects are synthesized and summarized here.

McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399. doi: 10.1176/appi.ajp.2020.20081251.

Farmacocinética

TABLE 2. Comparison of routes of administration of ketamine and esketamine

Route	Bioavailability	Dose Range (Acute)
Intravenous	100%	0.5–1.0 mg/kg infused over 40–60 minutes twice weekly for 2 weeks
Intramuscular	90%–95%	Not established, likely similar to intravenous
Subcutaneous	90%–95%	Not established, likely similar to intravenous
Intranasal	30%–50% (significant differences between devices and solution)	Esketamine: 56–84 mg intranasally twice weekly for 4 weeks Racemic ketamine: 50–150 mg intranasally twice weekly
Oral	10%–20% (potential variability between capsules and liquid forms)	Highly variable (0.5–7.0 mg/kg daily to once weekly), with 100–250 mg 2–3 times per week most accepted
Sublingual	20%–30%	Not established, likely similar to oral
Transdermal	10%–50% (highly variable by vehicle used)	Not established



Ketamine (K) **Norketamine (NK)**

Vida media:
- Ketamina: 3 horas
- Esketamina 7 horas

Excreción renal
* <1% sin cambios

McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399. doi: 10.1176/appi.ajp.2020.20081251.

Bertram G. Katzung, Todd W. Vanderah. Farmacología básica y clínica, 15e. Capítulo 30: Fármacos antidepresivos.

Efectos adversos Ketamina

Psiquiátricos

- **Disociación**
  - ✓ Alteraciones sensoperceptivas
  - ✓ Desrealización y despersonalización
  - ✓ Pico alrededor de los 40 min de administración
  - ✓ Resolución en 1- 2 horas
- **Psicosis**

Neurológicos

- Mareo, somnolencia, aturdimiento
- No hay evidencia de deterioro cognitivo asociado

Abuso

- Puede relacionarse con el efecto en el sistema opioide
- A un año no hay evidencia de nuevo consumo de otras sustancias psicoactivas

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Efectos adversos Ketamina

Hemodinámicos

- Aumento de la FC y PA
- ✓ Palpitaciones, arritmias, dolor torácico
- Aumento PA dosis dependiente
- ✓ 10-50% de los pacientes
- ✓ 20-50 min de administración
- ✓ Se resuelve en 2 – 4horas

Monitorizar al menos 2 horas después de administrar ketamina o esketamina

Genitourinarios

- Daño del epitelio y de la unión neuromuscular vesical
- ✓ Nicturia
- ✓ Hematuria dolorosa
- ✓ Disuria
- ✓ Urgencia urinaria
- ✓ Incontinencia urinaria

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Forma de uso

Ketamina

- 05 mg/kg IV
- Infusión por 40 minutos
- No está clara la frecuencia de uso
- El efecto se ve durante el 1r día y dura alrededor de 7 días
- La mayoría de pacientes responde con 1 o 2 dosis

Esketamina

- Iniciar 1r día 56 mg
- Aumentar 56 – 84 mg 2 veces/semana por 4 semanas
- Luego 56-84 mg/semana por 4 semanas
- Luego cada 2 semanas

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Tener en cuenta

Monitoreo de signos vitales y del sensorio continuo durante la administración y posterior a esta

No deben manejar sin tener al menos una noche de sueño posterior a la administración

Se sugiere la administración concomitante de ketamina y esketamina con un antidepresivo oral (sertralina, escitalopram, duloxetina).

Contraindicaciones relativas

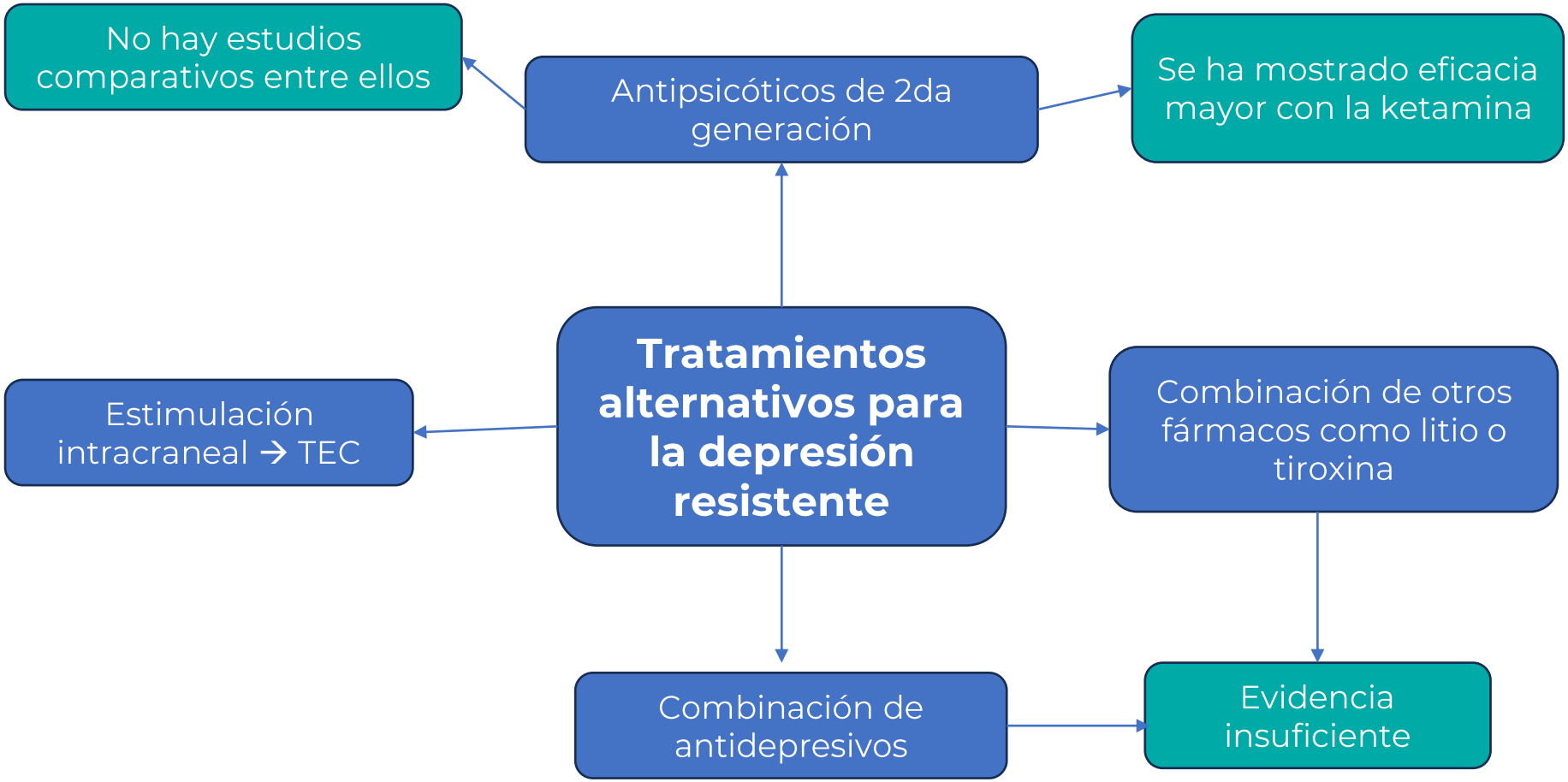
- Demencia
- Hipersensibilidad previa
- HTA no controlada
- Aneurisma cerebral
- Enfermedad valvular severa
- Evento cardiovascular <6 semanas
- Falla cardíaca

Precaución

- Pacientes con antecedente de psicosis

McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399. doi: 10.1176/appi.ajp.2020.20081251.

Ketamina/esketamina vs otros tratamientos



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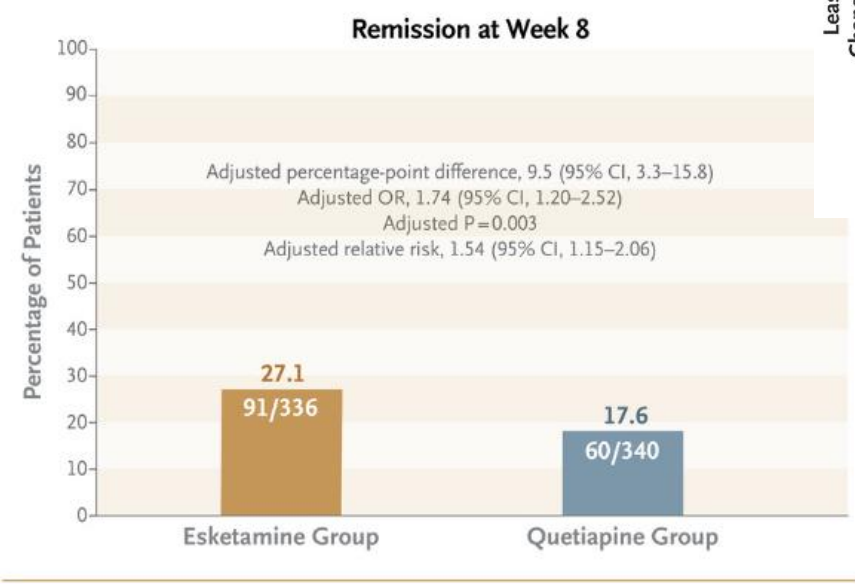
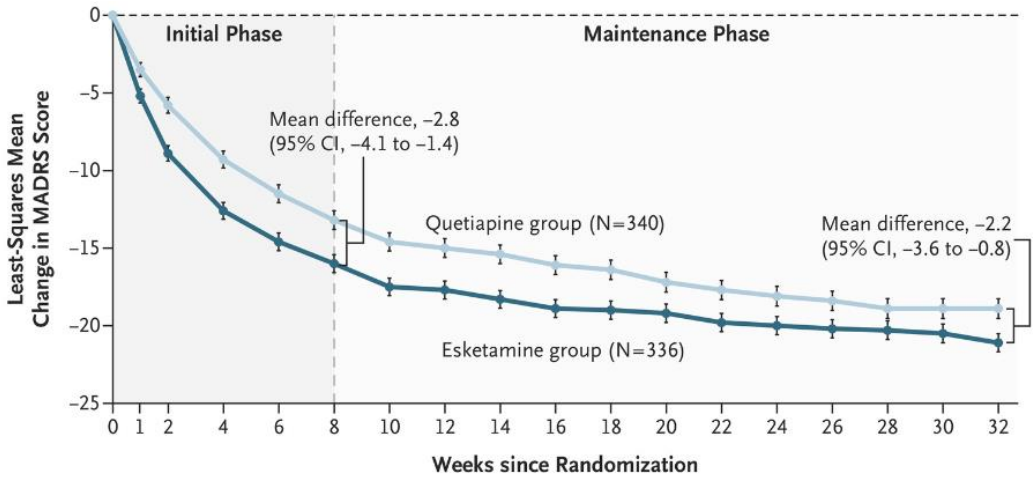
Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression

Andreas Reif, M.D., Istvan Bitter, M.D., Ph.D., D.Sc., Jozefien Buyze, Ph.D., Kerstin Cebulla, M.Sc., Richard Frey, M.D., Dong-Jing Fu, M.D., Ph.D., Tetsuro Ito, M.Sc., M.B.A., Yerkebulan Kambarov, M.D., Pierre-Michel Llorca, M.D., Ph.D., Albino J. Oliveira-Maia, M.D., M.P.H., Ph.D., Thomas Messer, M.D., Siobhán Mulhern-Haughey, Ph.D., et al., for the ESCAPE-TRD Investigators*

October 5, 2023
N Engl J Med 2023; 389:1298-1309
DOI: 10.1056/NEJMoa2304145





Estudio doble ciego aleatorizado

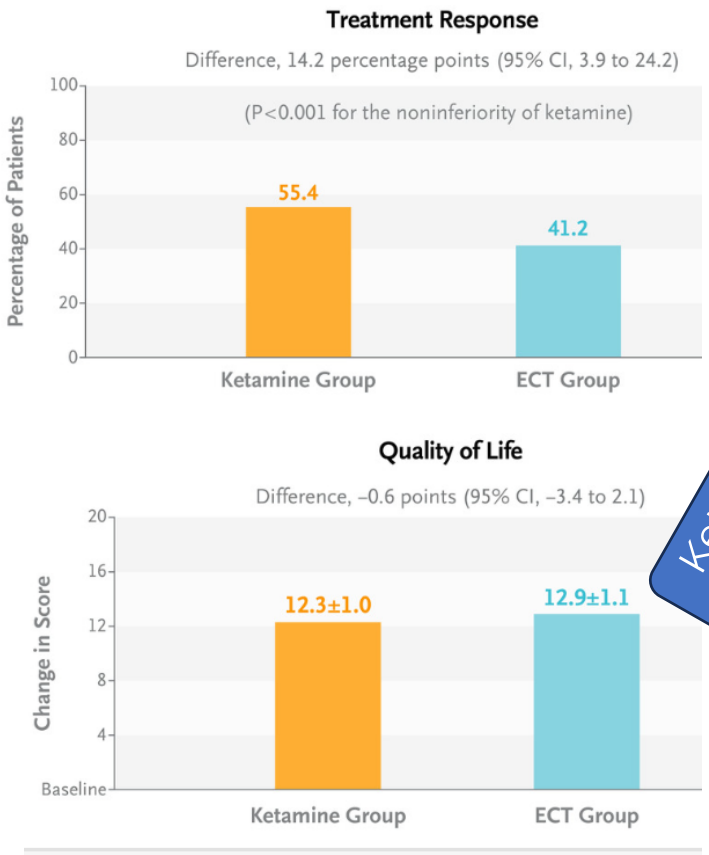
Combinado con ISRS o ISRSN

Eficacia se midió con:
- MADRS <10 puntos o mejoría >50% a las 8 semanas
- Sin recaídas a las 32 semanas de tratamiento

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

Amit Anand, M.D., Sanjay J. Mathew, M.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Fernando S. Goes, M.D., Murat Altinay, M.D., Amy S. Aloysi, M.D., Ali A. Asghar-Ali, M.D., Brian S. Barnett, M.D., Lee C. Chang, M.D., Katherine A. Collins, M.S.W., Ph.D., Sara Costi, M.D., et al.

June 22, 2023
N Engl J Med 2023; 388:2315-2325
DOI: 10.1056/NEJMoa2302399



Ketamina no es inferior al TECAR

Table 3. Moderate and Severe Adverse Events in the Modified Intention-to-Treat Population.*

Adverse Event	Ketamine	ECT
	no. of patients/total no. (%)	
Initial treatment phase		
≥1 Adverse event	49/195 (25.1)	55/170 (32.4)
Gastrointestinal adverse event	13/195 (6.7)	9/170 (5.3)
Muscle pain or weakness	1/195 (0.5)	9/170 (5.3)
Headache	16/195 (8.2)	12/170 (7.1)
Severe or prolonged hypertension	6/195 (3.1)	4/170 (2.4)
Suicidal ideation	4/195 (2.1)	2/170 (1.2)
Suicide attempt	0/195	0/170
Follow-up period		
≥1 Adverse event	17/108 (15.7)	10/70 (14.3)
Severe or prolonged hypertension	2/108 (1.9)	0/70
Suicidal ideation	4/108 (3.7)	1/70 (1.4)
Suicide attempt	1/108 (0.9)	0/70

* P>0.05 for all adverse events except muscle pain or weakness (P=0.01).

Otros usos

Ideación suicida
- Se considera como un efecto independiente del antidepresivo
- Mejoría en 1s 7 días posterior a la administración

En estudio
- Depresión TAB
- TOC
- TEPT

McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399. doi: 10.1176/appi.ajp.2020.20081251.

Conclusiones

- La depresión representa una alta carga mundial en múltiples esferas: económica, laboral, relaciones interpersonales y altos costos en salud → Importante su tratamiento.
- Se ha visto efecto favorable en la ketamina y en la esketamina; ésta última con un mejor perfil de seguridad y con el respaldo de la FDA para su uso.
- En nuestro medio, el uso de la ketamina como antidepresivo aún no es ampliamente usado, por lo que se requiere precaución y una buena selección del paciente para el manejo, además de una adecuada monitorización.
- Hay terapias con las que se tiene más experiencia en el medio, como la TECAR, y su efectividad puede compararse con la de la ketamina.
- Se sugiere el uso concomitante de antidepresivos orales para el mantenimiento.
- Requiere ampliarse los estudios para estandarizar la forma de uso de la ketamina.
- La elección del tratamiento depende de los gustos del paciente, los costos, el acceso y la disponibilidad.

GRACIAS