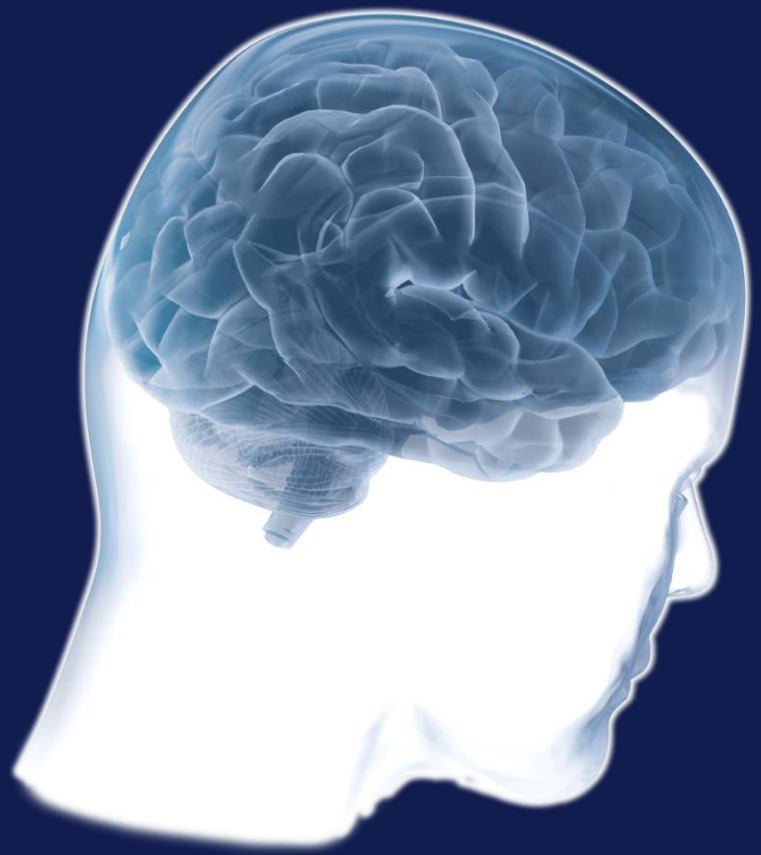
Glutamatergic agents for depression: historical perspective



Professor Siegfried Kasper

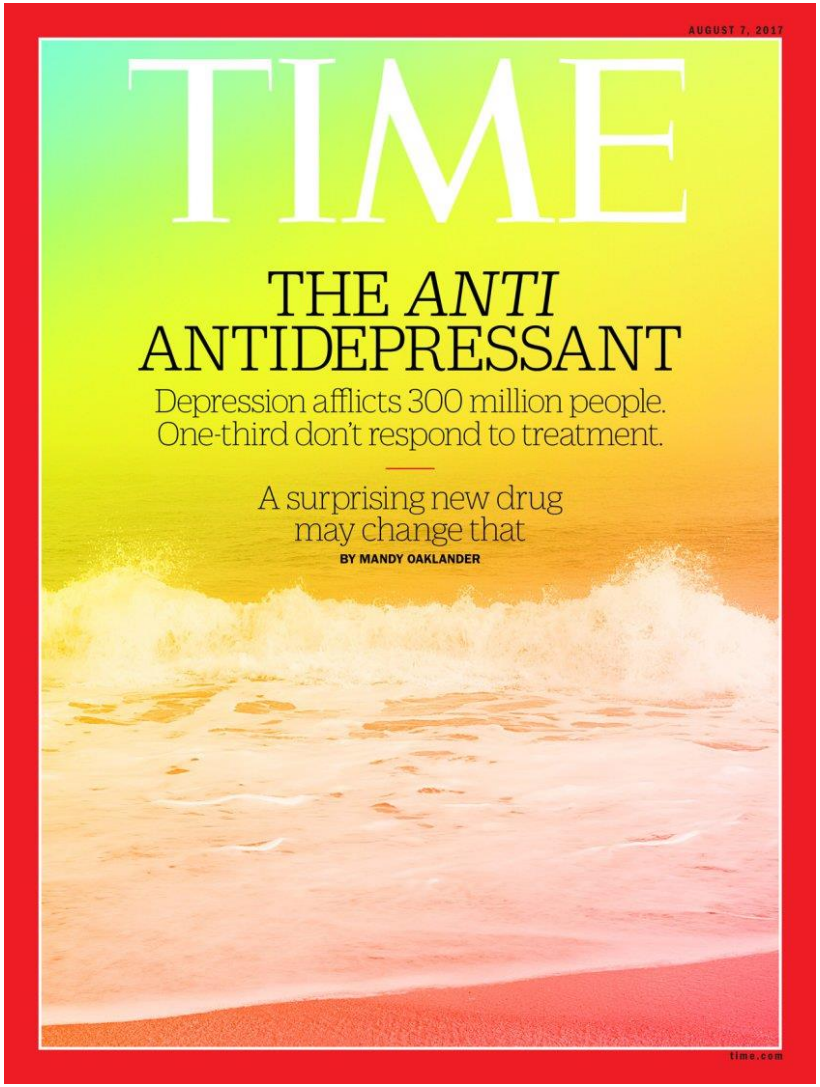
Chair

Department of Psychiatry and Psychotherapy

Medical University of Vienna (MUW)

Potential Conflicts of Interest (January 2015 to present)

Dr Kasper has received **grant/research support** from Lundbeck; he has served as a **consultant or on advisory boards** for AOP Orphan Pharmaceuticals AG, Eli Lilly, Janssen, Lundbeck, Schwabe and Takeda; and he has served **on speakers bureaus** for Angelini, AOP Orphan Pharmaceuticals AG, Eli Lilly, Krka Pharma, Lundbeck, Neuraxpharma, Pierre Fabre, Schwabe, Servier, Sun Pharma.


AUGUST 7, 2017
TIME
THE ANTI ANTIDEPRESSANT
Depression afflicts 300 million people. One-third don't respond to treatment.
A surprising new drug may change that
BY MANDY OAKLANDER
time.com

FDA News Release

FDA approves first treatment for post-partum depression

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release March 19, 2019

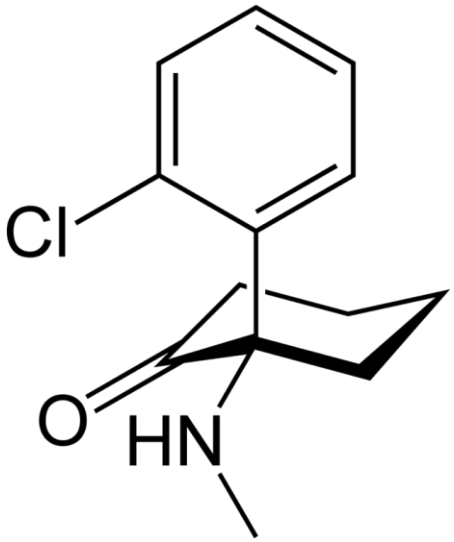
Release

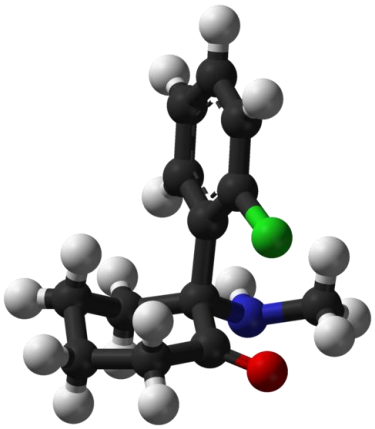
Español

The U.S. Food and Drug Administration today approved Zulresso (brexanolone) injection for intravenous (IV) use for the treatment of postpartum depression (PPD) in adult women. This is the first drug approved by the FDA specifically for PPD.

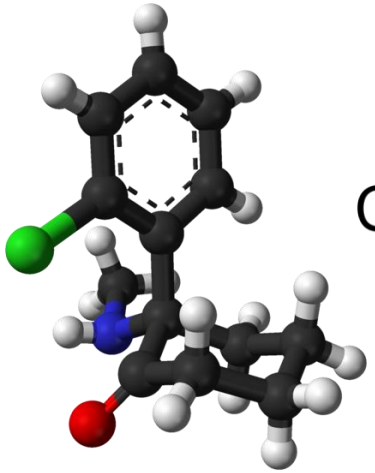
Neuropharmacology of NMDA Receptor Antagonist Ketamine

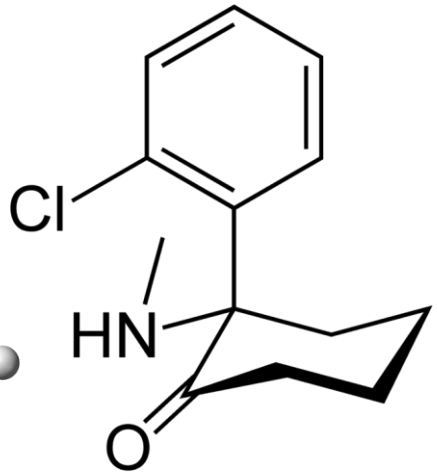
- **hypnotic**
- **amnesic**
- **analgesic**
- **psychotomimetic**





R(-) ketamine

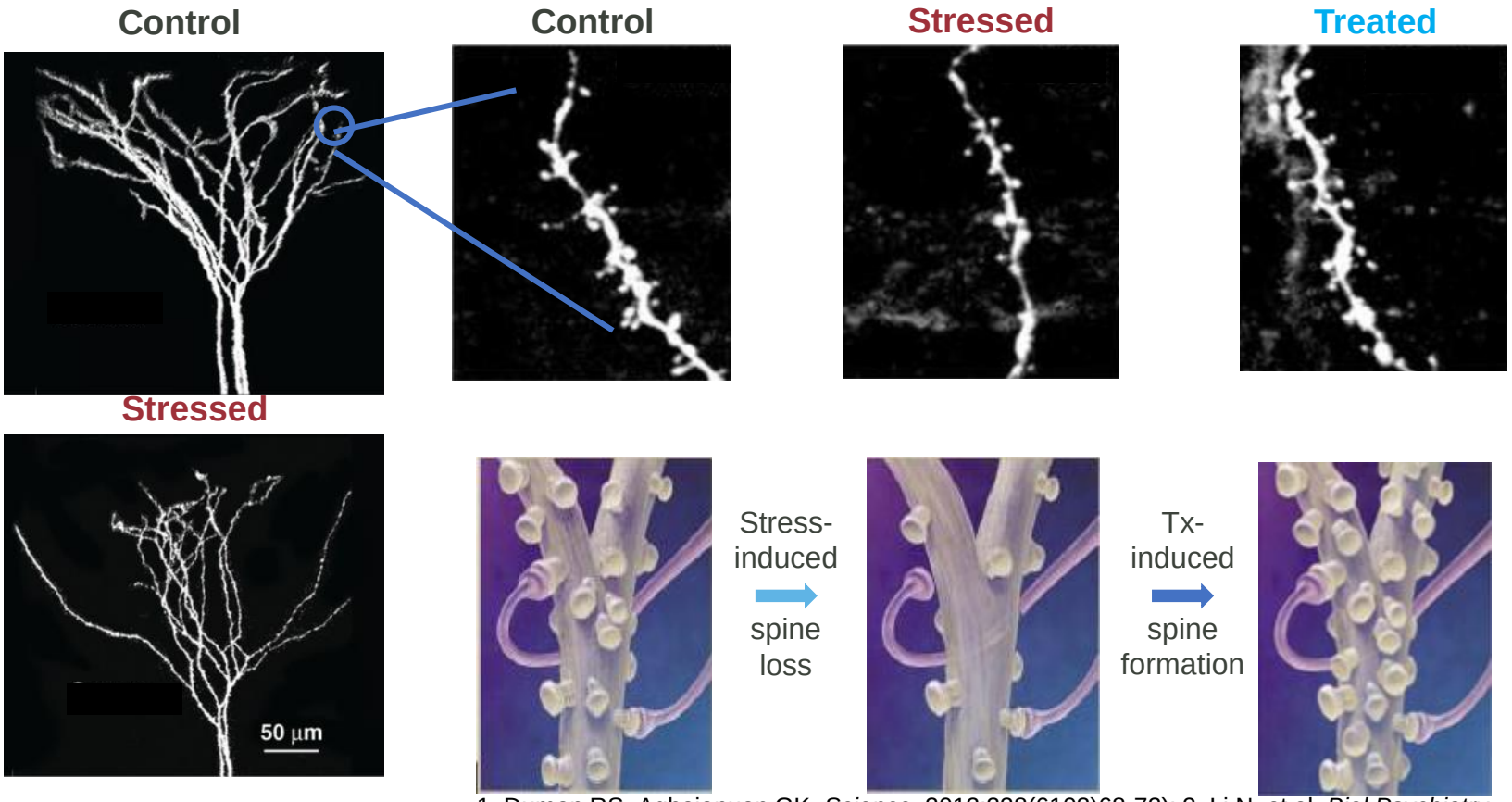




S(+) ketamine: 3-4 times higher affinity

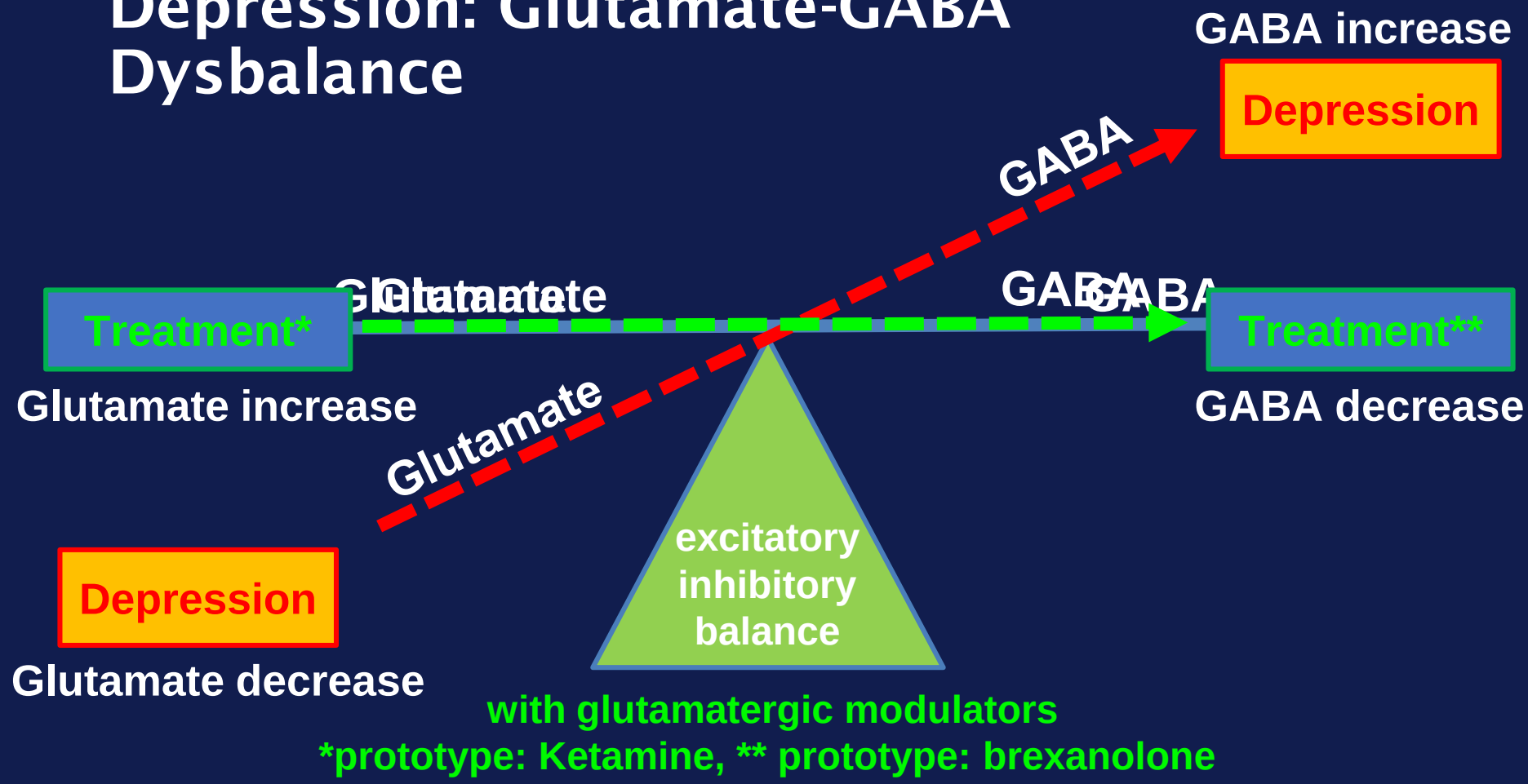
Major depression is a disorder of synaptic plasticity

Chronic unpredictable stress induces a depression-like phenotype in rodents which is associated with reversible decreases in the branching complexity[1] and spine density[2,3] of pyramidal neurons in the prefrontal cortex



1. Duman RS, Aghajanuan GK. *Science*. 2012;338(6103)68-72); 2. Li N, et al. *Biol Psychiatry.* 2011;69(8):754–761; 3. Nestler EJ et al. *Neuron*. 2002;34:13-25.

Depression: Glutamate-GABA Dysbalance



Modified from Wieronska & Pilic, Neurochem Int 2009

Proposed mechanisms of action of ketamine

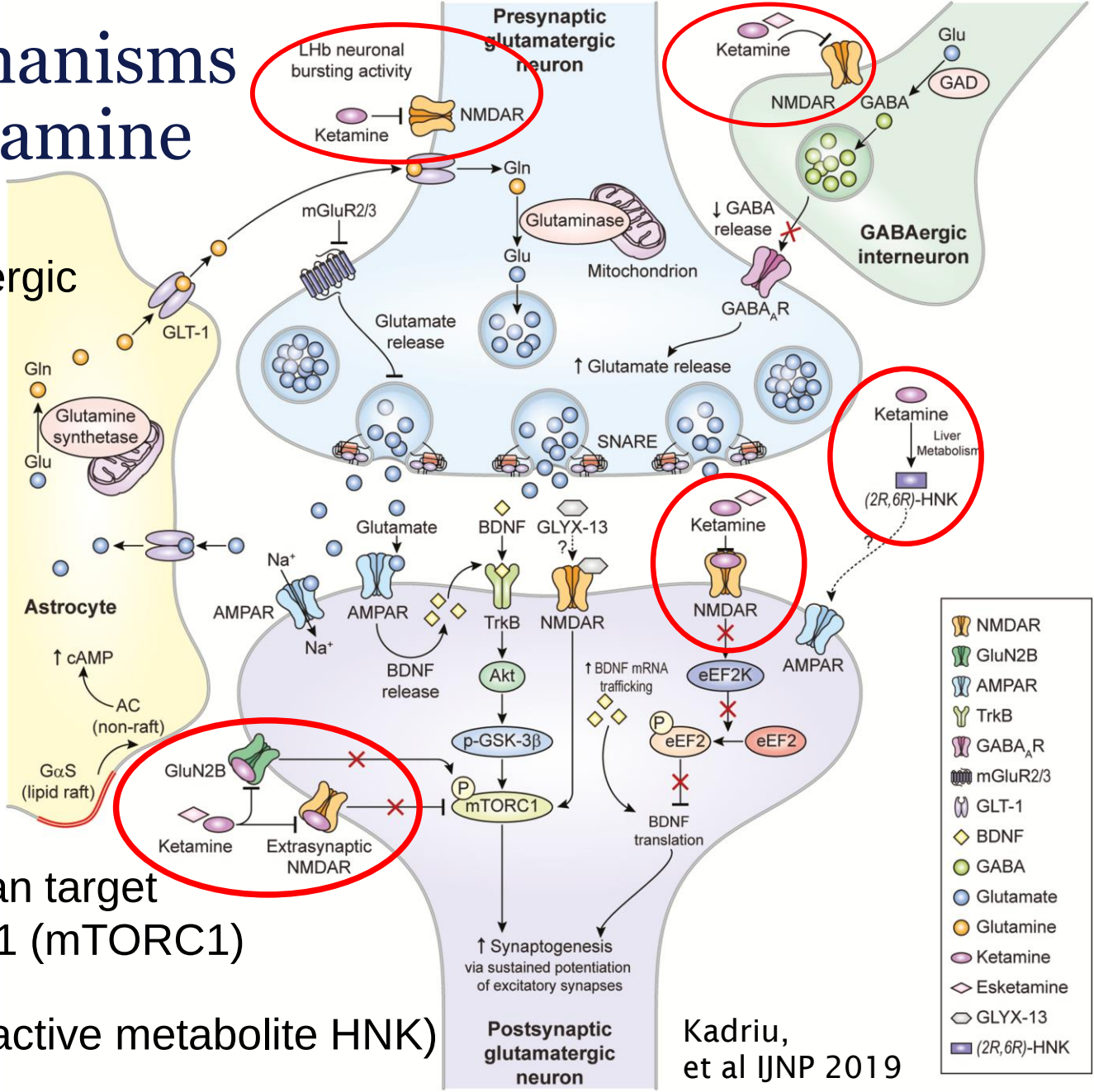
Disinhibition of GABA-ergic inhibitory interneurons

Rapid BDNF release

Inhibition of lateral habenula (LHb) neurons

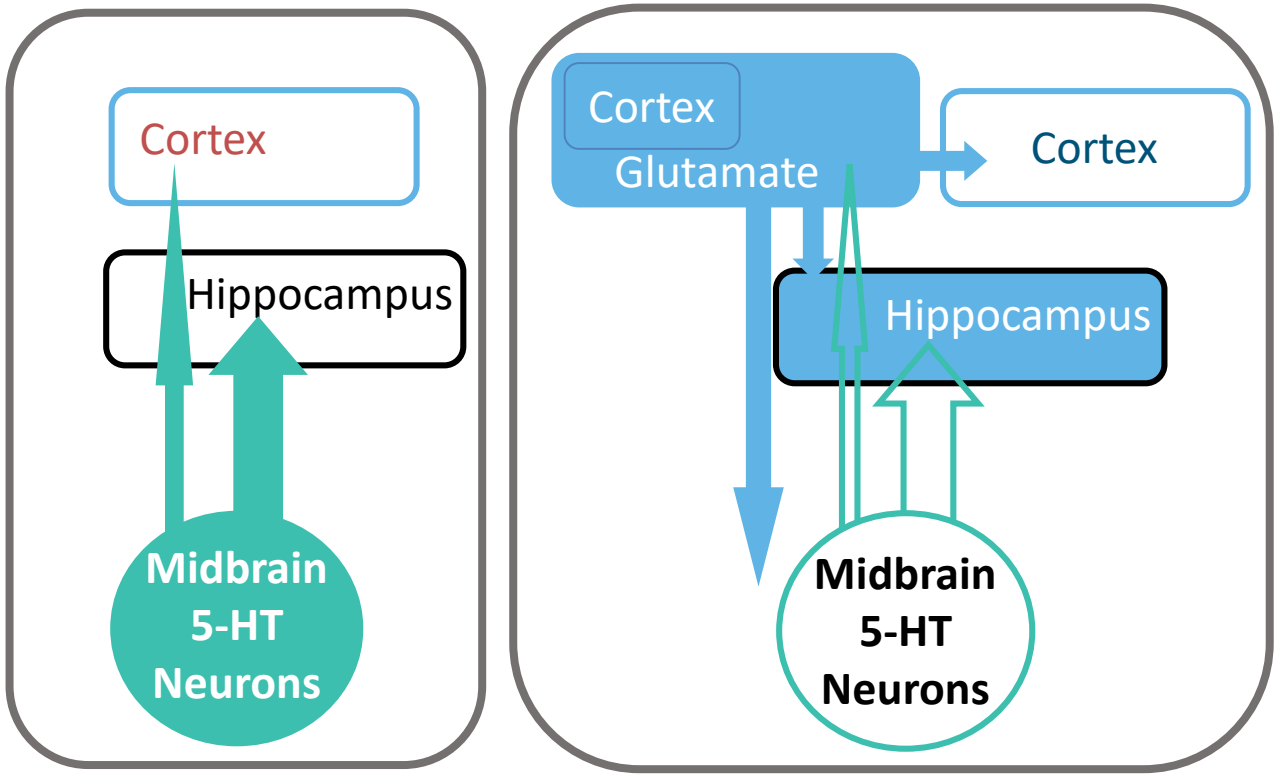
Activation of mammalian target of rapamycin complex 1 (mTORC1)

AMPA – Activation (by active metabolite HNK)



Kadriu, et al IJNP 2019

A shift in emphasis from serotonin/midbrain to glutamate and cortico-limbic circuits



5-HT, serotonin.

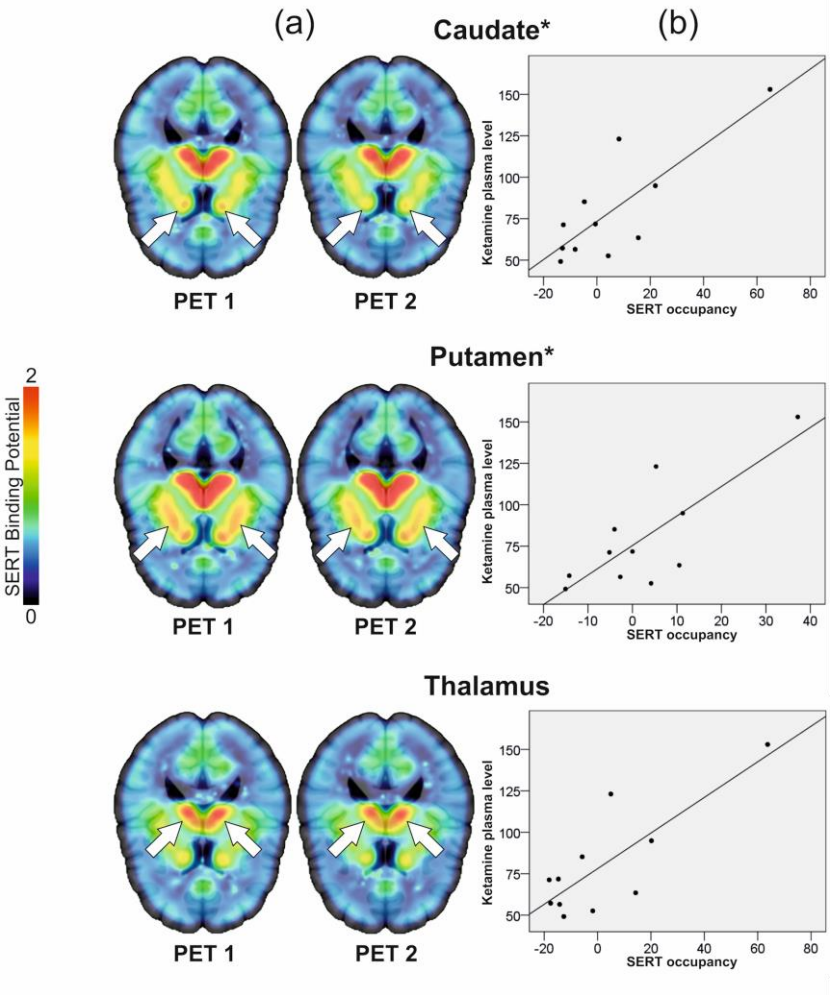
Image courtesy of J. Krystal.

Ketamine: Influence on serotonin system?

Does ketamine bind to the serotonin transporter in humans?

- WHY: Preclinical studies indicate 5-HT dependency of ketamine's AD effects
- THEREFORE: In-vivo human PET study
  - NO measureable binding to the SERT after 0.5mg/kg i.v.
  - BUT occupancy and ketamine plasma levels correlated

→ Does ketamine bind the SERT at higher doses?



Spies….Kasper Int. J Neuropsychopharm, 2017

Antidepressant Efficacy

What is the evidence…

INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE, 2017
VOL. 21, NO. 1, 2–12
http://dx.doi.org/10.1080/13651501.2016.1254802

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Administration of ketamine for unipolar and bipolar depression

Christoph Kraus[a], Ulrich Rabl[a], Thomas Vanicek[a], Laura Carlberg[a], Ana Weidenauer[a], Marie Spies[a], Lucie Bartova[a], Gregor Gryglewski[a], Konstantinos Papageorgiou[a], Rupert Lanzenberger[a], Matthäus Willeit[a], Dietmar Winkler[a], Janusz K. Rybakowski[b] and Siegfried Kasper[a]

[a]Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria; [b]Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Objective: Clinical trials demonstrated that ketamine exhibits rapid antidepressant efficacy when administered in subanaesthetic dosages. We reviewed currently available literature investigating efficacy, response rates and safety profile.

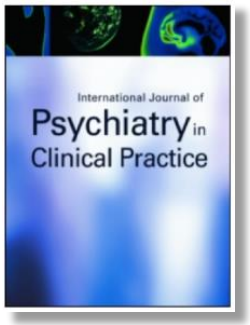
Methods: Twelve studies investigating unipolar, seven on bipolar depression were included after search in medline, scopus and web of science.

Results: Randomized, placebo-controlled or open-label trials reported antidepressant response rates after 24 h on primary outcome measures at 61%. The average reduction of Hamilton Depression Rating Scale (HAM-D) was 10.9 points, Beck Depression Inventory (BDI) 15.7 points and Montgomery-Asberg Depression Rating Scale (MADRS) 20.8 points. Ketamine was always superior to placebo. Most common side effects were dizziness, blurred vision, restlessness, nausea/vomiting and headache, which were all reversible. Relapse rates ranged between 60% and 92%. To provide best practice-based information to patients, a consent-form for application and modification in local language is included.

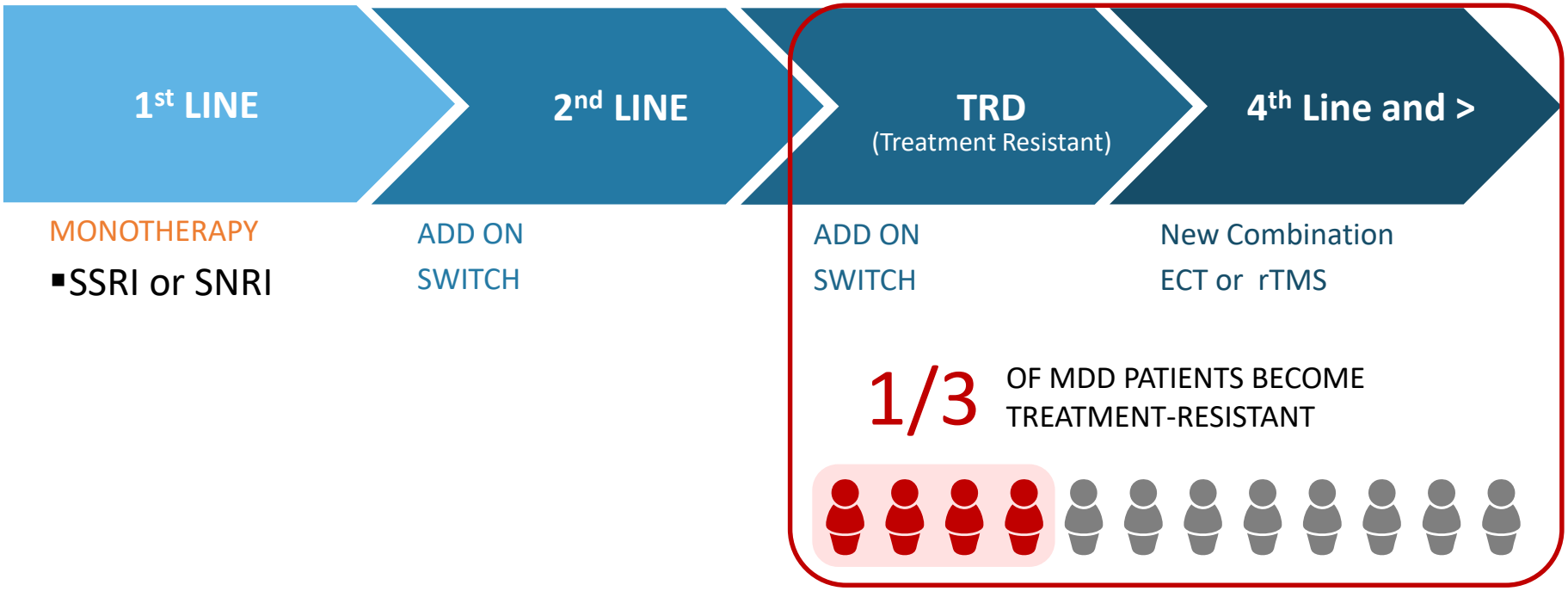
Conclusions: Ketamine constitutes a novel, rapid and efficacious treatment option for patients suffering from treatment resistant depression and exhibits rapid and significant anti-suicidal effects. New administration routes might serve as alternative to intravenous regimes for potential usage in outpatient settings. However, long-term side effects are not known and short duration of antidepressant response need ways to prolong ketamine's efficacy.

ARTICLE HISTORY
Received 16 March 2016
Revised 6 October 2016
Accepted 24 October 2016

KEYWORDS
Ketamine; depression; rapid antidepressant; glutamate; NMDA-receptor

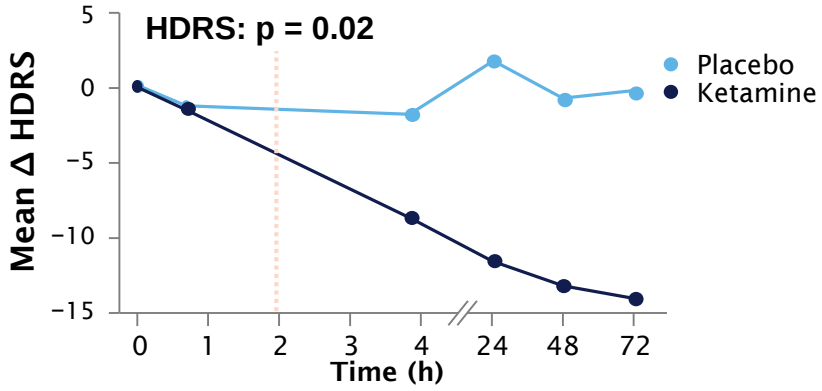


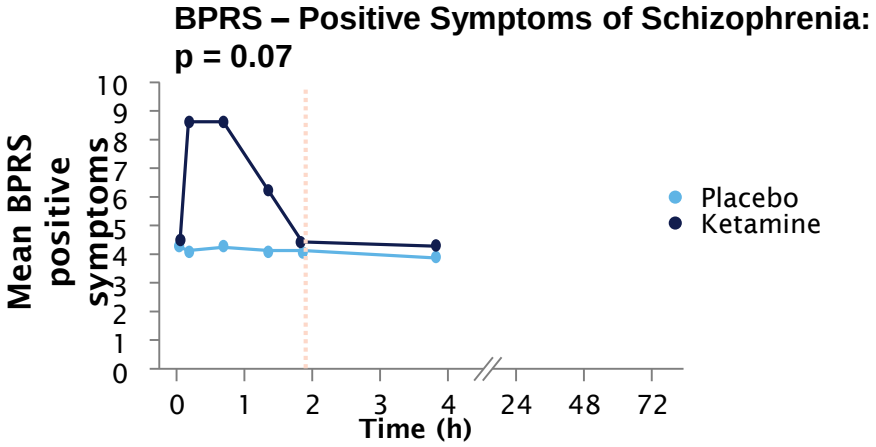
There is a need for effective treatment after 2 treatment failures

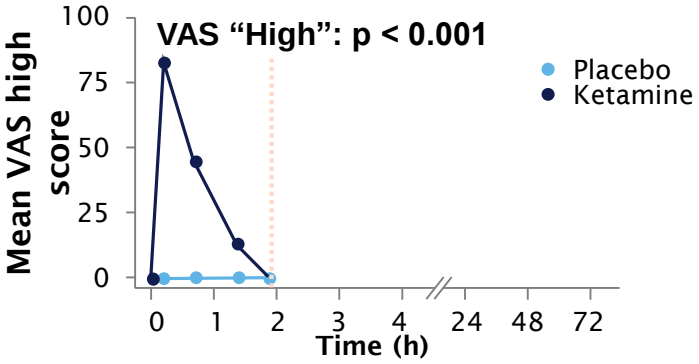


AD actions of ketamine (N = 9)[a]

Berman RM, et al.
Biol Psychiatry. 2000;47:351-4.







[a]2 participants terminated prior to the last treatment condition (1 each prior to placebo and ketamine treatment conditions).
BRPS, Brief Psychiatric Rating Scale; h, hour; HDRS, Hamilton Depression Rating Scale; VAS, visual analogue scale.

Ketamine – The First Rapid-acting Antidepressant

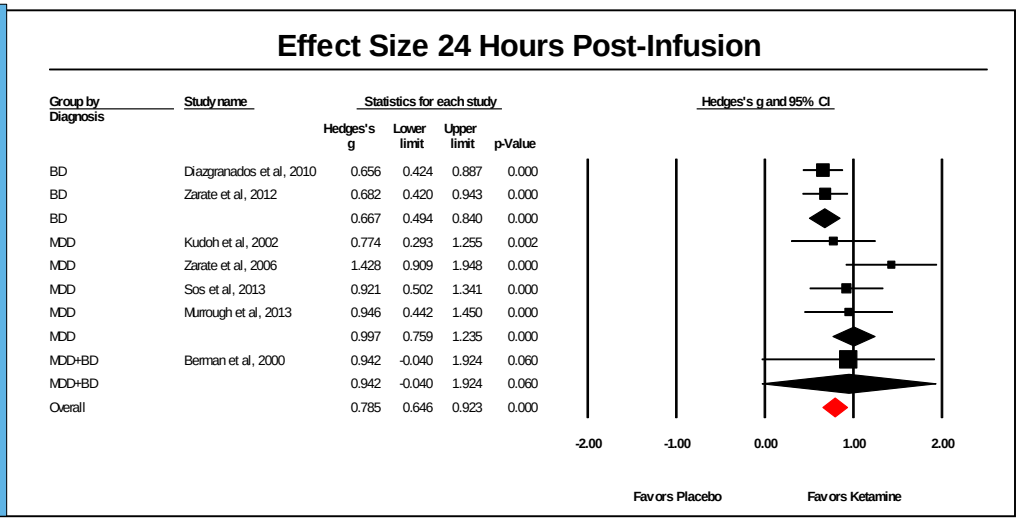
Psychological Medicine (2015), 45, 693–704. © Cambridge University Press 2014
doi:10.1017/S0033291714001603

REVIEW ARTICLE

A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes

A. McGirr[1]*, M. T. Berlim[2,3], D. J. Bond[4,5], M. P. Fleck[3], L. N. Yatham[1,5] and R. W. Lam[1,5]

- 7 Studies
- N=229 patients
  - RCT: N=142
  - Crossover: N=87
- Age: 46.5 ±1 0.4 years
- Sex:
  - 70 Unknown
  - 71/159 Male
  - 88/159 Female



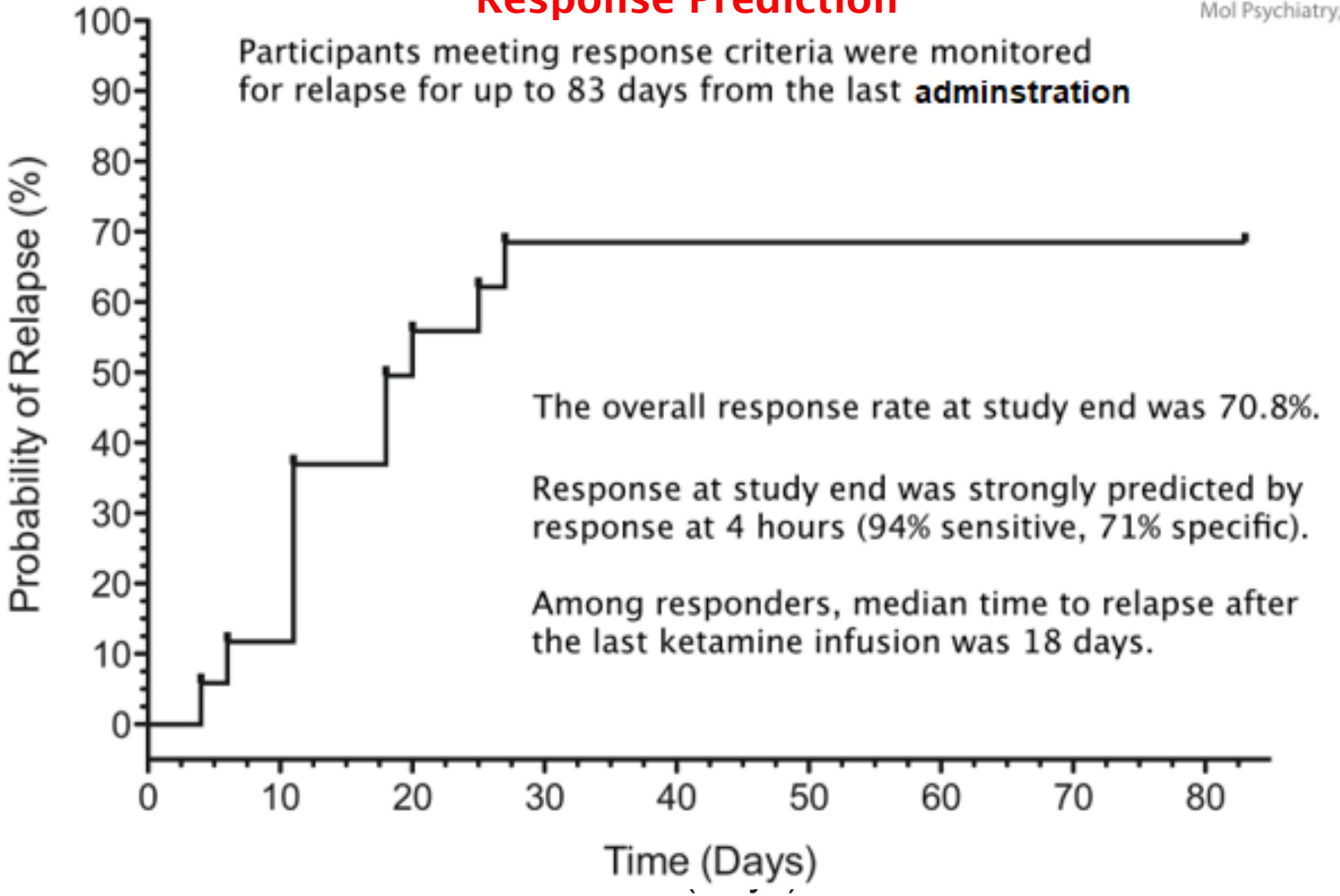
McGirr A et al. *Psychol Med* 2015;45:693-704. .

Longer-term antidepressant effects of repeated i.v. Glutamatergic treatment,

Sanacora et al.
Mol Psychiatry, 2013

Response Prediction

Participants meeting response criteria were monitored for relapse for up to 83 days from the last **adminstration**

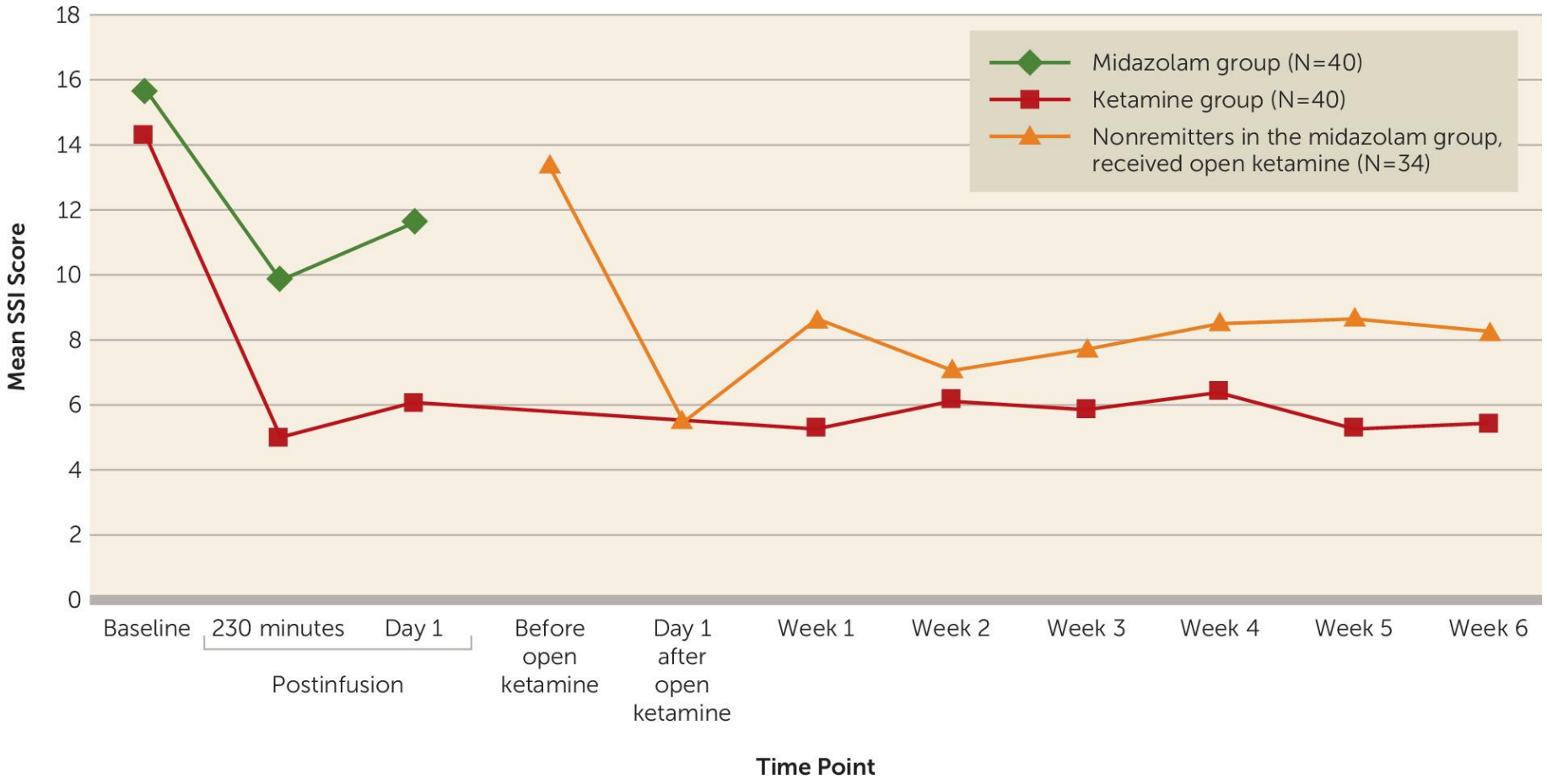


The overall response rate at study end was 70.8%.

Response at study end was strongly predicted by response at 4 hours (94% sensitive, 71% specific).

Among responders, median time to relapse after the last ketamine infusion was 18 days.

Ketamine reduces suicidal ideation



Grunebaum M et al. AJP 2017

European Neuropsychopharmacology (2015) 25, 2183–2184

www.elsevier.com/locate/euroneuro

SHORT COMMUNICATION

Combination of intravenous S-ketamine and oral tranylcypromine in treatment-resistant depression: A report of two cases

Lucie Bartova[a], Sonja E. Vogl[b], Mara Stamenkovic[a], Nicole Praschak-Rieder[a], Angela Naderi-Heiden[a], Siegfried Kasper[a], Matthaeus Willeit[a,*]

[a]*Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria*
[b]*Division of Gynecological Oncology, Department of Gynecology and Obstetrics, Medical University of Vienna, Austria*

Received 28 May 2015; accepted 28 July 2015

European Neuropsychopharmacology (2018) 28, 980-982

ELSEVIER

www.elsevier.com/locate/euroneuro

SHORT COMMUNICATION

Rapid antidepressant effect of S-ketamine in schizophrenia

Lucie Bartova[a], Konstantinos Papageorgiou[a], Ivan Milenkovic[a,b], Markus Dold[a], Ana Weidenauer[a], Matthaeus Willeit[a], Dietmar Winkler[a], Siegfried Kasper[a,*]

[a] *Department of Psychiatry and Psychotherapy, Clinical Division of General Psychiatry, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria*
[b] *Department of Neurology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria*

Received 28 February 2018; received in revised form 4 May 2018; accepted 17 May 2018

International Psychogeriatrics (2017), 29:7, 1223–1225 © International Psychogeriatric Association 2017
doi:10.1017/S1041610217000140

CASE REPORT

Electroconvulsive therapy with S-ketamine anesthesia for catatonia in coexisting depression and dementia

Zsuzsa Litvan, Martin Bauer, Siegfried Kasper and Richard Frey

Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

ABSTRACT

Information on efficacy and safety of electroconvulsive therapy in patients with dementia is sparse. The current case report describes a patient suffering from severe depression and dementia who received electroconvulsive therapy with S-ketamine anesthesia at our psychiatric intensive care unit for the treatment of her therapy-resistant catatonic stupor. The patient's condition improved remarkably through the treatment. By the end of 16 electroconvulsive therapy sessions, her catatonic symptoms remitted entirely, her affect was brighter and she performed markedly better at the cognitive testing.

Key words: electroconvulsive therapy, S-ketamine, dementia, catatonia, depression

Novel Medications in Development

Compound, Route of Administration	Pharmacology	Sponsor	Phase
Ketamine, various	Non-selective, non-competitive NMDA receptor antagonist	Multiple	--
Esketamine, IN	Non-selective, non-competitive NMDA receptor antagonist	Janssen	III
Lanicemine/AZD-6765, IV	Low trapping NMDAR antagonist	AstraZeneca/ Biohaven	IIb
Traxoprodil/CP-101,606, IV	NMDAR antagonist at NR2B subunit	Pfizer	II
EVT-101	NMDAR antagonist at NR2B subunit	Evotec/La Roche	II
Rislenemdaz/CERC-301/MK-0657, oral	NMDAR antagonist at NR2B subunit	Cerecor	II
AVP-786, oral	Non-selective antagonist of NMDAR	Avanir/ Otsuka	II
AXS-05, oral	Non-selective antagonist of NMDAR	Axsome	III
Rapastinel/GLYX-13, IV	Partial functional agonist at glycine site of NMDA receptor	Allergan	III
Apimostinel/NRX-1074/AGN-241660, oral	Reported to be a functional antagonist at Glycine B site of the NMDA receptor	Allergan	II

Wilkinson and Sanacora, *Drug Discov Today*. 2019 Feb;24(2):606-615

Novel Medications in Development, cont'd

Compound, Route of Administration	Pharmacology	Sponsor	Phase
AV-101, oral	Selective agonist at glycine site of NMDA receptor NR1 subunit	VistaGen	II
NRX-100/NRX-101, oral	Partial NMDAR agonist at glycine-site	NeuroRx	III
Basimglurant/RO4917523, oral	NAM of mGluR5	Hoffmann- La Roche	IIb
Decoglurant/RG1578/ RO4995819	NAM of mGluR2/3	Hoffmann- La Roche	II
Tulrampator/CX-1632/S-47445	PAM of AMPA receptor	RespireRx	II
Riluzole, oral	Glutamate release inhibitor/up take facilitator	NIMH, Tehran University of Med. Sc.	II
Brexanolone/ SAGE-547, IV	PAM of GABAA receptor	Sage	III Now with FDA indication
Ganaxolone, IV	PAM of GABAA receptor	Marinus	II
SAGE-217, oral	PAM of GABAA receptor	Sage	II

Wilkinson and Sanacora, *Drug Discov Today*. 2019 Feb;24(2):606-615