Depressione Resistente

Nuove Prospettive Terapeutiche

Mario Amore, Costanza Giacomini

Dipartimento di Neuroscienze

Università di Genova

UNIVERSITÀ DEGLI STUDI
DI GENOVA

DiNOGMI

Depressione resistente al trattamento, un mito…? Evidenze a favore

Caspar David Friedrich, El caminante sobre el mar de nubes (1817–1818)

……The definition of TRD, was notably vague: ranging from 1 to as many as 8 failed antidepressant treatment trials…..

…..This lack of a consensual TRD definition creates enormous problems: it limits the ability to do comparative treatment research, to understand the biological underpinnings of TRD, and produces ambiguous medical insurance coverage issues……

*…..**This disparity** in defining TRD begs the question: When does major depressive disorder (MDD) become resistant?.....*

Conway, JAMA Psychiatry, 2017

Depressione Resistente

- Con Depressione Resistente (TRD) si intende l'assenza di risposta clinica dopo il trattamento con almeno due antidepressivi appartenenti a classi farmacologiche differenti, somministrati a un dosaggio e per un tempo adeguato

(European Medicines Agency, 2011)

Depressione Resistente
modelli di stadiazione

I) Fallimento di Trial adeguato con una delle principali classi di farmaci antidepressivi

II) Due fallimenti con due differenti classi

III) Resistenza di stadio due associata a fallimento con un TCA

IV) Resistenza di stadio tre associata a fallimento di un IMAO

V) Resistenza di stadio IV e fallimento di ECT bilaterale

Thase&Rush 1997

Nessuna risposta/risposta ridotta al trattamento iniziale:

- Dopo 3-4 settimane di terapia psicofarmacologica
- Dopo 4–6 settimane di psicoterapia o terapia combinata

Nice guidelines 2017

Depressione Resistente
La Pseudoresistenza

Pseudoresistenza: mancata risposta alla terapia per fattori esterni al trattamento.

DOSAGGIO INADEGUATO Sono state seguite le linee guida?

SCARSA ADERENZA TERAPEUTICA

BREVE DURATA DELLA TERAPIA

ETÀ, SESSO, PESO

Valutazione adeguata degli Stressors psicosociali

Valutazione livelli plasmatici METABOLIZZATORI RAPIDI

COMORBILITÀ MEDICHE

BIPOLARITÀ

Luchini et al 2014, Dold , 2017

ASSESSMENT CLINICO
Depressione Resistente e Storia Individuale

Storia familiare
di disturbo dell'umore (risposta terapeutiche di familiari)

Età d'esordio
Early onset si associa a cronicità e comorbidità psichiatrica
Late onset si associa a caratteristiche psicotiche e demenza (pseudoresistenza)

Genere
Da valutare come fattore di resistenza a particolari farmaci
(Il sesso femminile risponde in misura minore a triciclici, meglio a sertralina)

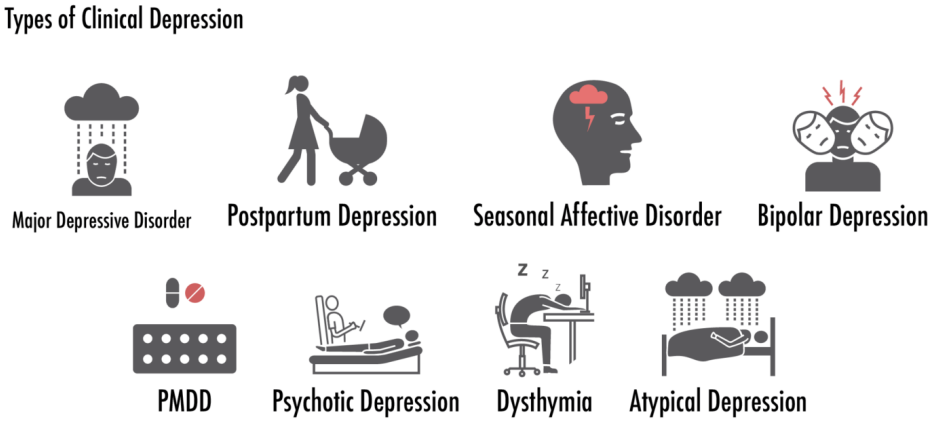
Depressione resistente e caratteristiche cliniche

- **Sintomatologia più severa** (disomogenea valutazione del concetto di «severità»)
- **Caratteristiche psicotiche e comorbidità** altre patologia psichiatriche e mediche
- **Maggiore rischio suicidario** (con ideazione suicidaria nel 80% dei casi)
- **Maggior numero di ospedalizzazioni**
- **Peggiore funzionamento psicosociale**
- **Cronicità:** pazienti con prolungati episodi di malattia > due anni con una remissione incompleta; il 20% dei MDD sviluppa depressione cronica che peggiora la prognosi del quadro depressivo; queste depressioni si associano più frequentemente a comorbidità; tempi di risposta più lunghi

Le depressioni croniche sono quelle con maggiore tasso di non-riconoscimento e sotto-trattamento (40% non trattati e solo 20% trattati correttamente, secondo lo studio di Keller et Al.)

Kornstein GS et Al., J of Psy (2001)

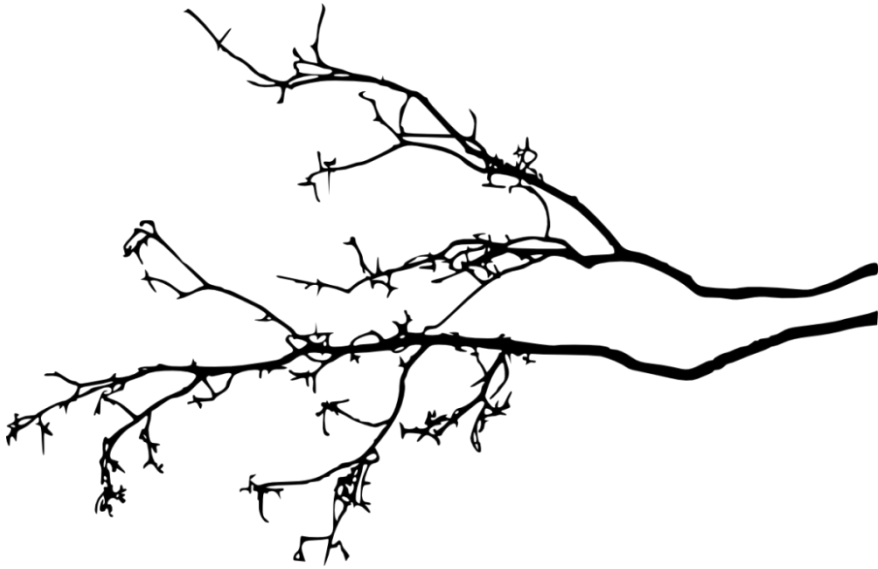
Le Depressioni
tra Sindrome e Malattia



Categoriale

Dimensionale

- Dimensione affettiva
- Dimensione cognitiva
- Dimensione somatica
- Dimensione spazio-temporale
- Dimensione anancastica



Comorbidità con altri disturbi psichiatrici

Disturbi d'ansia

Attacchi di panico → 29%

Ansia moderata → 62%

- Depressione più severa
- Maggiore rischio suicidario
- Frequenti ricorrenze
- Alto tasso di cronicizzazione
- Peggiore risposta al trattamento
- Maggiore collateralità
- Minore percentuale di recovery e remissione parziale

DOC *(22%)*

Disturbi del comportamento alimentare *(37%)*

Disturbo da dismorfismo corporeo

Disturbi di personalità

nel 50% dei casi (soprattutto dipendente, borderline e istrionico; evitante nel 25% e ossessivo-compulsivo nel 20%)

- Predisposizione/vulnerabilità
- Manifestazione attenuata del disturbo affettivo
- Modificatore dell'espressione clinica della malattia (modello patoplastico)

Disturbo da uso di sostanze → anche utilizzo moderato di alcol contribuisce a resistenza al trattamento, depressione predispone a uso di sostanze e quindi scompenso affettivo; quanto tempo di astinenza occorra per diminuire l'effetto di resistenza?

Kornstein GS et Al., J of Psy (2001)

Depressione resistente al trattamento e comorbidità con condizioni mediche

Diabete
TRD associata a un insufficiente controllo glicemico

Ipotiroidismo
Circa 50% dei pazienti con depressione resistente hanno ipotiroidismo subclinico rispetto al 8-17% dei depressi non sottocategorizzati

Morbo di Cushing

Patologie neurodegenerative

CAD

Fibromialgia

Patologie neoplastiche

HIV

Morbo di Addison

infezioni

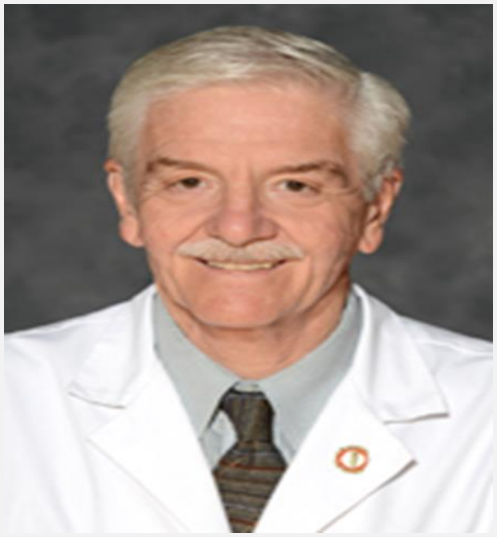
Farmaci
(e.g. anti-ipertensivi e steroidi)

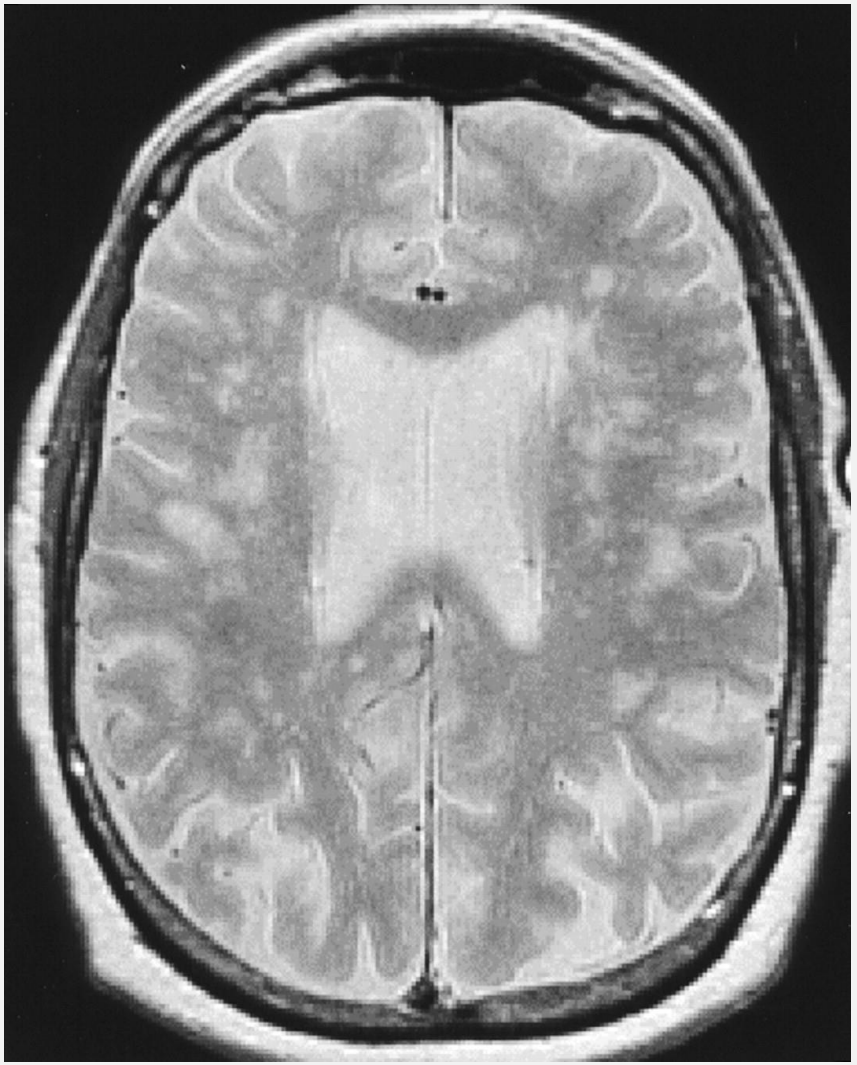
Sindrome da fatica cronica

Kornstein GS et Al., J Psy 2001

Depressione vascolare

- Fattori di rischio vascolare
- RMN - Iperintensità sottocorticale nella sostanza bianca o grigia profonda
- Esordio tardivo ***(late-onset)*** o dopo peggioramento di patologia vascolare
- Resistenza ai trattamenti





Modificata da: Alexopoulos GS, et al., 1997; Krishnan KR, et al., 1997

Fattori biologici nella depressione resistente

1. Predisposizione genetica (5HTTLPR)

2. Disfunzioni nei circuiti neuroanatomici *(e.g. default mode network)*
3. Attivazione del sistema infiammatorio

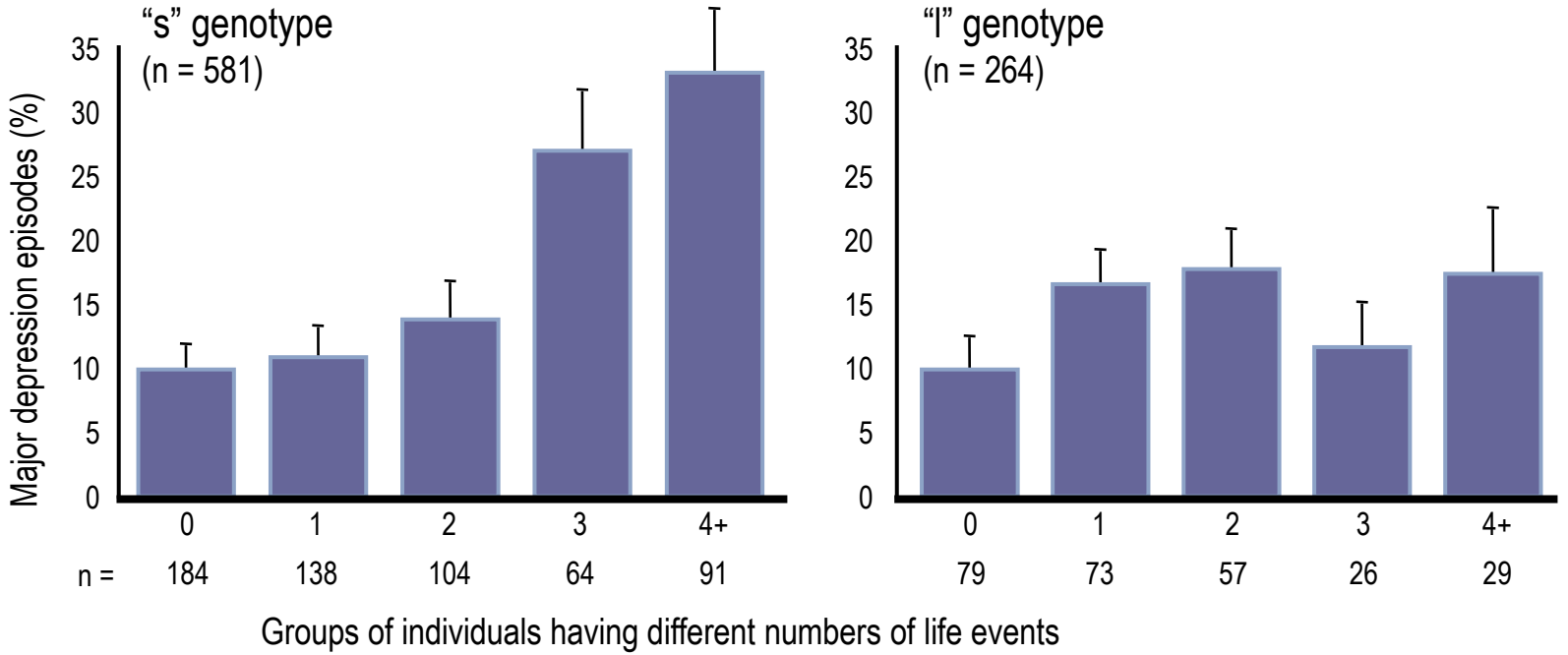
4. Alterazione dell'asse Ipotalamo-Ipofisi-Surrene

Kornstein GS et Al., J of Psy (2001)

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Caspi A, Sugden K, Moffitt TE, et al.

Science 2003;301:386-9



…"Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele"…

Depressione Resistente caratteristiche neuroanatomiche

- **Anomalie del "default mode network"**; con una iperattività più pronunciata rispetto a quanto osservato nella depressione maggiore.
- **Aumento della connettività funzionale** tra giro temporale mediale destro e giro frontale mediale destro, giro angolare, precuneo, giro superiore frontale e retto.
- **Elevata omogeneità** regionale a livello del giro temporale mediale destro e dell'insula.
- **Disomogeneità** del precuneo sinistro e giro frontale inferiore.

Alterazioni **immunitarie**: anormali livelli di citochine proinfiammatorie

Alterazioni **recettoriali**: eccitotossicità glutammatergica

Cattaneo et al; 2013

Minelli et al; 2015

Yong-Ku et al; 2016

Ma et al; 2012

Resting-State Functional Connectivity Bias of Middle Temporal Gyrus and Caudate with Altered Gray Matter Volume in Major Depression

Chaoqiong Ma[1], Jurong Ding[1], Jun Li[1], Wenbin Guo[2,3], Zhiliang Long[1], Feng Liu[1], Qing Gao[1], Ling Zeng[1], Jingping Zhao[2]*, Huafu Chen[1]*

Abstract

Magnetic resonance imaging (MRI) studies have indicated that the structure deficits and resting-state functional connectivity (FC) imbalances in cortico-limbic circuitry might underline the pathophysiology of MDD. Using structure and functional MRI, our aim is to investigate gray matter abnormalities in patients with treatment-resistant depression (TRD) and treatment-responsive depression (TSD), and test whether the altered gray matter is associated with altered FC. Voxel-based morphometry was used to investigate the regions with gray matter abnormality and FC analysis was further conducted between each gray matter abnormal region and the remaining voxels in the brain. Using one-way analysis of variance, we found significant gray matter abnormalities in the right middle temporal cortex (MTG) and bilateral caudate among the TRD, TSD and healthy controls. For the FC of the right MTG, we found that both the patients with TRD and TSD showed altered connectivity mainly in the default-mode network (DMN). For the FC of the right caudate, both patient groups showed altered connectivity in the frontal regions. Our results revealed the gray matter reduction of right MTG and bilateral caudate, and disrupted functional connection to widely distributed circuitry in DMN and frontal regions, respectively. These results suggest that the abnormal DMN and reward circuit activity might be biomarkers of depression trait.

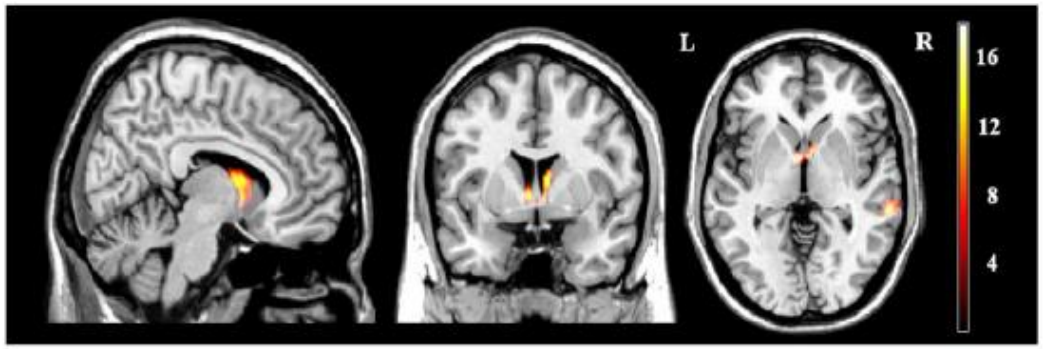


Figure 1. Statistical parametric images of voxle-based morphometry analysis among TRD,TSD and healthy controls. Significantly altered gray matter volume was detected in the right middle temporal gyrus and the bilateral caudate. Color scales represent T values using one-way ANOVA ($p<0.005$, AlphaSim corrected).
doi:10.1371/journal.pone.0045263.g001

Alterazioni significative nel volume a livello del giro temporale mediale e del caudato bilaterale.

Depressione Resistente

Strategie Terapeutiche

- Dose increase
- Switch
- Augmentation
- Combination

Incremento del dosaggio fino al massimo consentito, anche oltre se pz è metabolizzatore rapido

Cambio di classe di antidepressivo

Aggiunta di un farmaco appartenente a una classe differente: litio, aripiprazolo, olanzapina, quetiapina e risperidone

Combinazione di antidepressivi di due classi differenti

Caraci et al; 2018

Depressione Resistente: switching

- Da triciclico
- Da SSRI
- No SNRI se SSRI fallisce

A SSRI

Ad altro SSRI

Problemi:
- "DELUSIONE"
- WASH OUT
- LATENZA D'AZIONE

Il razionale:
- Possibile risposta con l'aggiunta del secondo farmaco
- Assenza di sintomi dovuti al termine del primo trattamento
- Mancanza di periodo di attesa per aver gli effetti del secondo trattamento
- Effetti del primo trattamento combinati con quelli del secondo
- Rapido raggiungimento dell'effetto antidepressivo

Combination e Augmentation

Combination

Table 5. Combination/augmentation

Patients unresponsive to the initial antidepressant may achieve clinical response when the second agent is added.
Discontinuation symptoms due to withdrawal of the original antidepressant avoided and patient does not have to cope with another waiting period for the substituted drug to produce desirable results.
The strategy builds on therapeutic gains obtained with the primary antidepressant and allows patients to continue to reap whatever benefits they have from the original drugs but with the additive or synergetic benefits of the augmentor or the additional combined antidepressant; switching has the disadvantage of losing the little gain already obtained.
Switching requires care in the changeover of drugs, which can cause delay and discontinuation reactions; these are avoided with the addition of a second drug.
Second compound is generally well tolerated and does not substantially alter the side effect profile of the first antidepressant.
Rapid onset of antidepressant action
Response rate is comparable or superior to substitution which involves tapering off the first drug wash out and delay in onset of the second drug.
Disadvantage is reduced concordance and increased side effect as a result of taking two agents than one.

SSRI + TCA

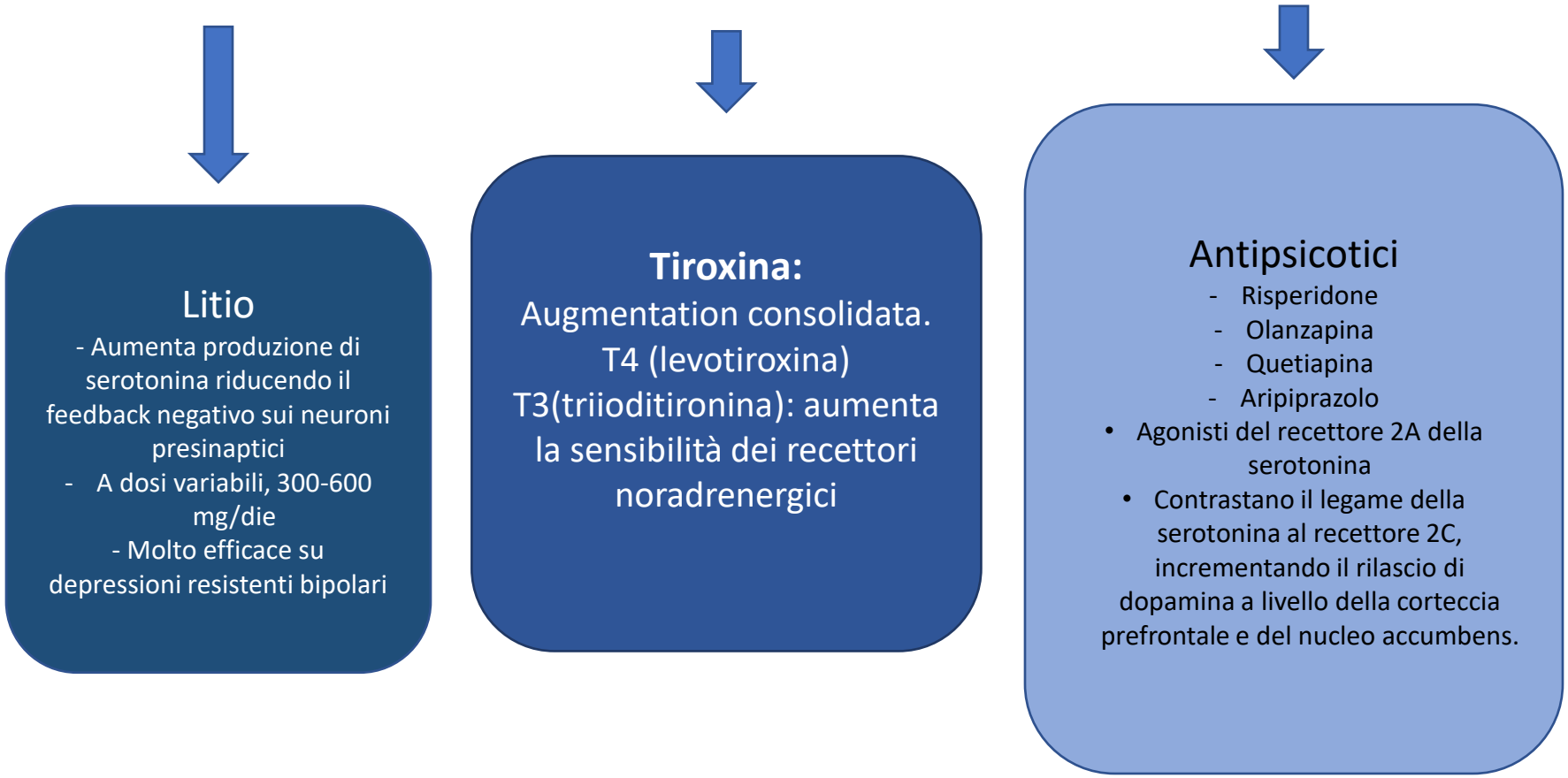
SSRI + SNRI

SSRI + NaRI: citalopram + reboxetina

SNRI + NaSSA: venlafaxina + mirtazapina

Depressione Resistente: augmentation

- Farmaci più spesso coinvolti:



Depressione Resistente
nuove terapie farmacologiche: sistema dopaminergico

Cariprazina: antipsicotico con azione di agonista parziale D2 e D3 ed antagonista 5-HT2B, su modelli animali ha azione antidepressiva ed antianedonica, proprio per la sua elevata selettività D3

(Duric et al., 2017).

Depressione Resistente
Trattamenti sul sistema dopaminergico

- Brexpiprazolo: agonista parziale D2 e 5 HT1A, antagonista 5 HT2A e del recettore noradrenergico alfa 1 B.

A dosi di 2-3 mg/die efficace come terapia aggiuntiva agli antidepressivi, in particolare nei soggetti con depressione con elevata quota ansiosa ed irritabilità.
Problemi: aumento di peso ed acatisia.
,

Hope et al, 2018

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane review, **2020**

Pharmacological interventions for treatment-resistant depression in adults (Review)

Davies P, Ijaz S, Williams CJ, Kessler D, Lewis G, Wiles N

One small study investigated changing current antidepressant treatment to a different antidepressant (mianserin) or adding mianserin to current treatment. We are uncertain about the effect changing treatment to mianserin has on depressive symptoms or the likelihood of dropping out of treatment. People who added mianserin to their current antidepressant treatment showed fewer depressive symptoms, but the likelihood of dropping out was not clear.

Adding the antidepressant mirtazapine to current antidepressant treatment had little or no effect on depressive symptoms or on the likelihood of dropping out of treatment.

The effect of adding an anti-anxiety medication (buspirone) to ongoing antidepressant treatment on depressive symptoms or dropping out is currently uncertain. These findings were based on one small study.

Most studies looked at the effects of adding an antipsychotic medication (cariprazine, quetiapine, ziprasidone or olanzapine) to current antidepressant treatment. These suggested that adding cariprazine results in a small reduction in depressive symptoms; adding quetiapine reduces depressive symptoms; and adding ziprasidone probably results in a small reduction in depressive symptoms. However, our results also suggest that adding these medicines to current treatment probably increases the likelihood of dropping out of treatment. The most common reasons for dropping out were side effects or adverse events. Adding olanzapine to ongoing treatment may reduce depressive symptoms, but the effects on dropping out are uncertain (findings based on one small study).

Nearly all (9/10) of the studies assessed the effects of treatment in the short-term – six or eight weeks after beginning the new treatment – so the longer term effects of most treatments are unknown.

VIEWPOINT

Evolving Issues in the Treatment of Depression

Ole Köhler-Forsberg, MD
Psychosis Research Unit, Aarhus University Hospital–Psychiatry, Aarhus, Denmark; and Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark.

Cristina Cusin, MD
Depression Clinic and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston; and Harvard Medical School, Boston, Massachusetts.

Andrew A. Nierenberg, MD
Harvard Medical School, Boston, Massachusetts; and Dauten Family Center for Bipolar Treatment Innovation, Department of Psychiatry, Massachusetts General Hospital, Boston.

…….New interventions are needed in this field…….

…….Several treatments for MDD have attracted increasing attention……with new pharmacological and non-pharmacological potential interventions for MDD that are now available…..

Andrew Nierenberg - Harvard Brain Science Initiative

However……further research is necessary to **determine how** to **provide the right intervention at the right time for each patient**

…..**While considering** individual **needs and preferences,** together with important factors such as: 1) **somatic and psychiatric comorbidities, 2) depression severity, 3) previous treatment trials, 4) patient adherence, 5) the availability of treatment options…….**

Köhler-Forsberg et al., JAMA 2019;321(24):2401-2402

Glutamate NMDA receptor modulators for the treatment of depression: trials and tribulations

James Murrough | Mount Sinai - New York

……Several decades of research have provided evidence for disturbances within the glutamate system in patients with depressive disorders……

…….several other NMDAR modulators are being investigated as candidate antidepressant agents…….

The failure of the low affinity **NMDAR antagonist memantine to separate from placebo in TRD**

The **glycine** site **partial agonist D-cycloserine at high doses preliminarly** showed **antidepressant efficacy in TRD**

The **NMDA** receptor **antagonist lanicemine** has **yielded only mixed results**

The **NMDAR antagonist dextromethorphan for potential therapeutic effects**

The NMDAR modulators **–NRX-1074 (apimostinel) – showed antidepressant efficacy only phase II**

However…..Will we wait fifteen years for the next breakthrough in depression treatment? Longer?.....

James W. Murrough, Psychopharmacology (Berl). 2015; 232(8): 1497–1499

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Esketamine for Treatment-Resistant Depression — First FDA-Approved Antidepressant in a New Class

Jean Kim, M.D., Tiffany Farchione, M.D., Andrew Potter, Ph.D., Qi Chen, M.D., M.P.H., and Robert Temple, M.D.

The FDA has approved esketamine, the first antidepressant in a new class, for treatment-resistant depression. The agency weighed the drug's rapid onset of effect against its abuse potential, which led to a Risk Evaluation and Mitigation Strategy.

Jean Kim, George Washington University

N Engl J Med. 2019;381(1):1-4

Depressione Resistente

nuove terapie farmacologiche: sistema glutammatergico

Ketamina:

- Anestetico dissociativo, somministrato a dosi sub anestetiche e.v., determina notevole riduzione dei sintomi depressivi.
- Antagonista non competitivo dei recettori NMDA
- 0,4-0,6 mg/kg infusi in 30-60 minuti hanno effetto antidepressivo su circa 40-60% dei soggetti, che si manifesta entro 24 ore e persiste per circa 7 giorni
- Sonnolenza, vertigini, cefalea, incremento della PA sono alcuni dei suoi effetti collaterali.
- Ha rapida insorgenza di azione; tuttavia sono necessari studi a lungo termine per consolidare I dati finora ottenuti.

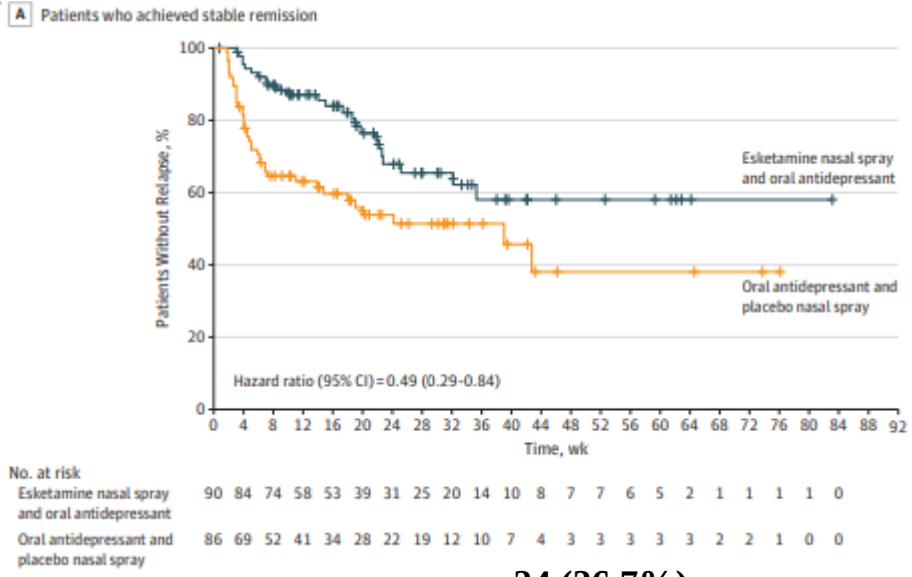
Thase; 2017

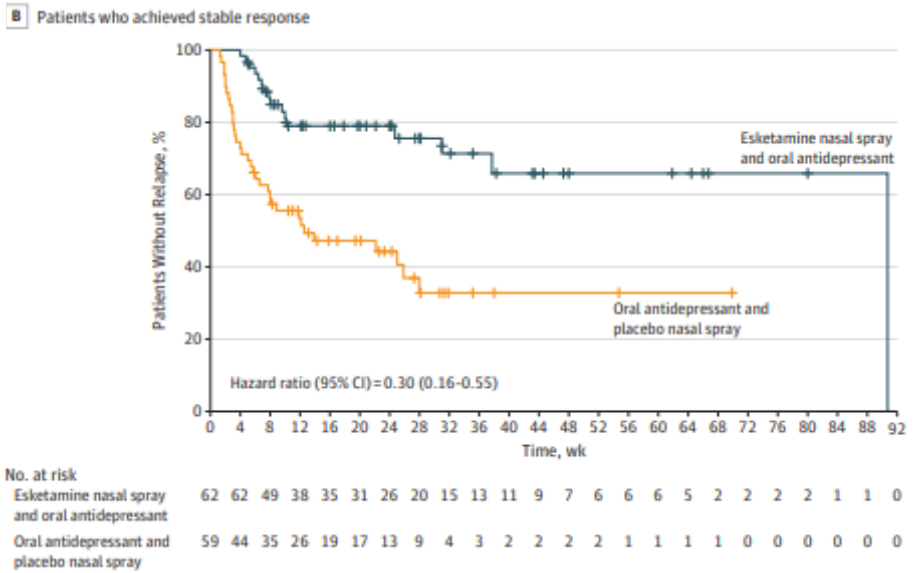
JAMA Psychiatry | Original Investigation

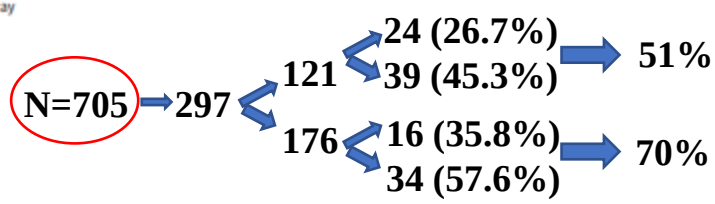
Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression
A Randomized Clinical Trial

Ella J. Daly, MD; Madhukar H. Trivedi, MD; Adam Janik, MD; Honglan Li, MD, PhD; Yun Zhang, PhD; Xiang Li, PhD; Rosanne Lane, MAS; Pilar Lim, PhD; Anna R. Duca, BSN; David Hough, MD; Michael E. Thase, MD; John Zajecka, MD; Andrew Winokur, MD, PhD; Ilona Divacka, MBA, MD; Andrea Fagiolini, MD; Wiesław J. Cubała, MD, PhD; István Bitter, MD, PhD; Pierre Blier, MD, PhD; Richard C. Shelton, MD; Patricio Molero, MD, PhD; Husseini Manji, MD; Wayne C. Drevets, MD; Jaskaran B. Singh, MD

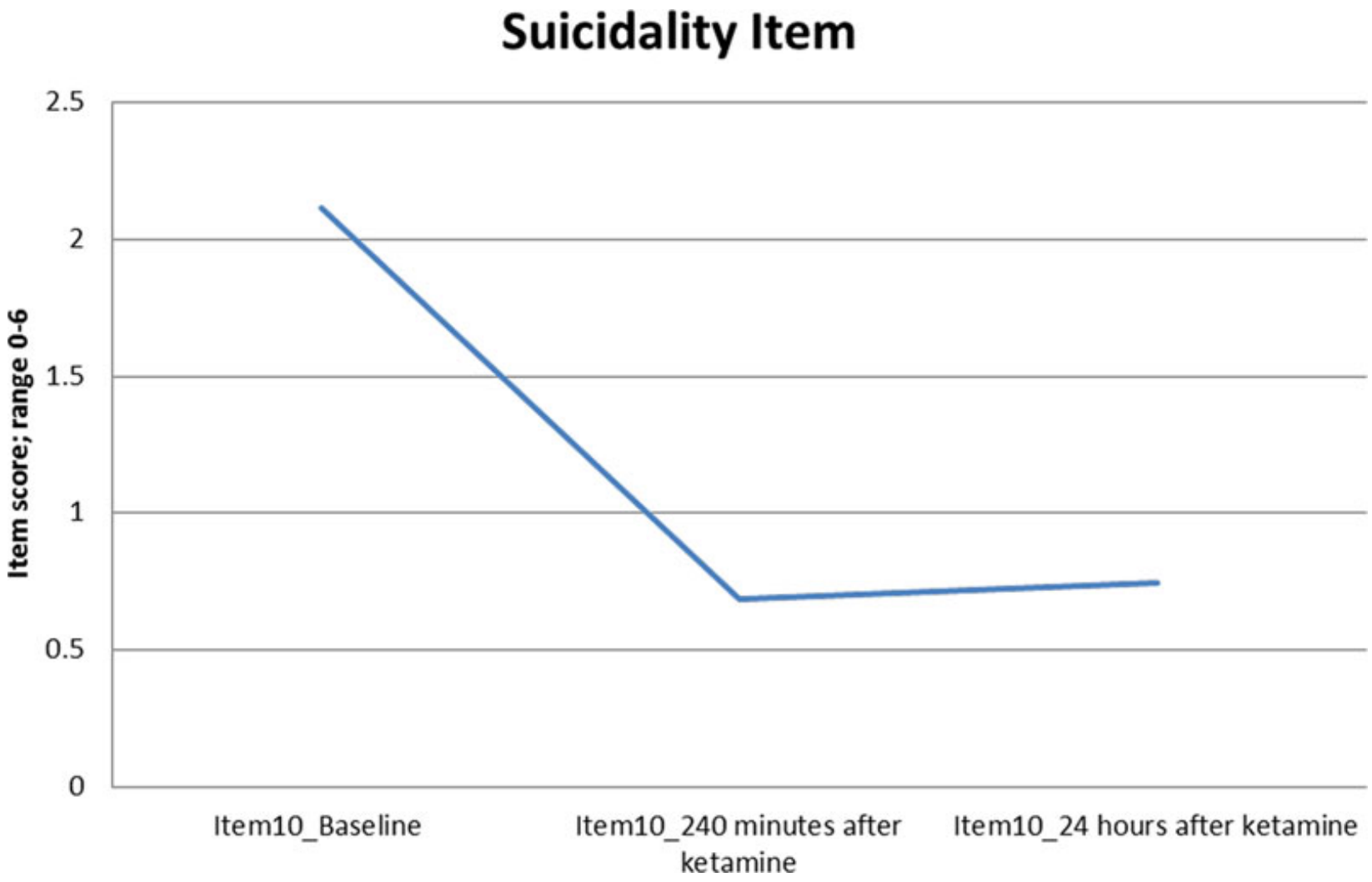
Kaplan-Meier Estimates of Time to Relapse







Daly et al., JAMA Psychiatry, 2018



Changes in suicidality. MADRS item score #10 showing improvements in suicidal ideation pre/post–ketamine infusion (percentage change from baseline to 24 h = −0.65). A lower score on the MADRS #10 signifies improved suicidal ideation. Data from an RCT of 72 patients with TRD.

Ketamine for depression: In What Dose, at What Rate, by What Route, for How Long, and at What Frequency?

1. Ketamine is most commonly dosed at 0.5 mg/kg. However, some patients may benefit from doses as low as 0.1 mg/kg. Patients who do not benefit at 0.5 mg/kg may respond at higher doses, such as 0.75 mg/kg. Higher doses may be associated with more adverse effects. These findings notwithstanding, parallel-group studies find no efficacy differences between different ketamine doses.
2. Ketamine is usually dosed across 40 min, especially when the dosing is by the IV route. However, benefits have been described even when infusion sessions are as short as 2 min or as long as 100 min. Ketamine is administered as a bolus when treatment is by the IM or SC route. Tolerability does not appear to be compromised by shorter treatment sessions or by bolus administration. Whereas ketamine has also been administered in best tolerated doses as a continuous infusion across 4–5 days, the case for such prolonged treatment remains unestablished.
3. Ketamine has been found effective when administered by oral, sublingual, transmucosal, intranasal, IV, IM, and SC routes. Whereas IV dosing has been the most extensively studied, intranasal, SC, and oral (despite low bioavailability) dosing are more convenient, but will require better study before they can be recommended over IV dosing.
4. Ketamine dosing can be repeated once in 2–3 days for 4–6 treatment sessions if the initial session elicits inadequate response; later sessions can be dosed at the same level or (preferably) at higher levels.
5. In patients in whom ketamine is required for continuation and maintenance therapy (because no other treatment is effective), sessions are best scheduled at an individualized frequency (typically once in 3–5 days) where each dose is administered a little before the effect of the previous dose wears off.

Abbreviations: IM = intramuscular, IV = intravenous, SC = subcutaneous.

Andrade, J Clin Psychiatry 2017;78(7):e852-7

Depressione Resistente

nuove terapie farmacologiche: sistema glutammatergico

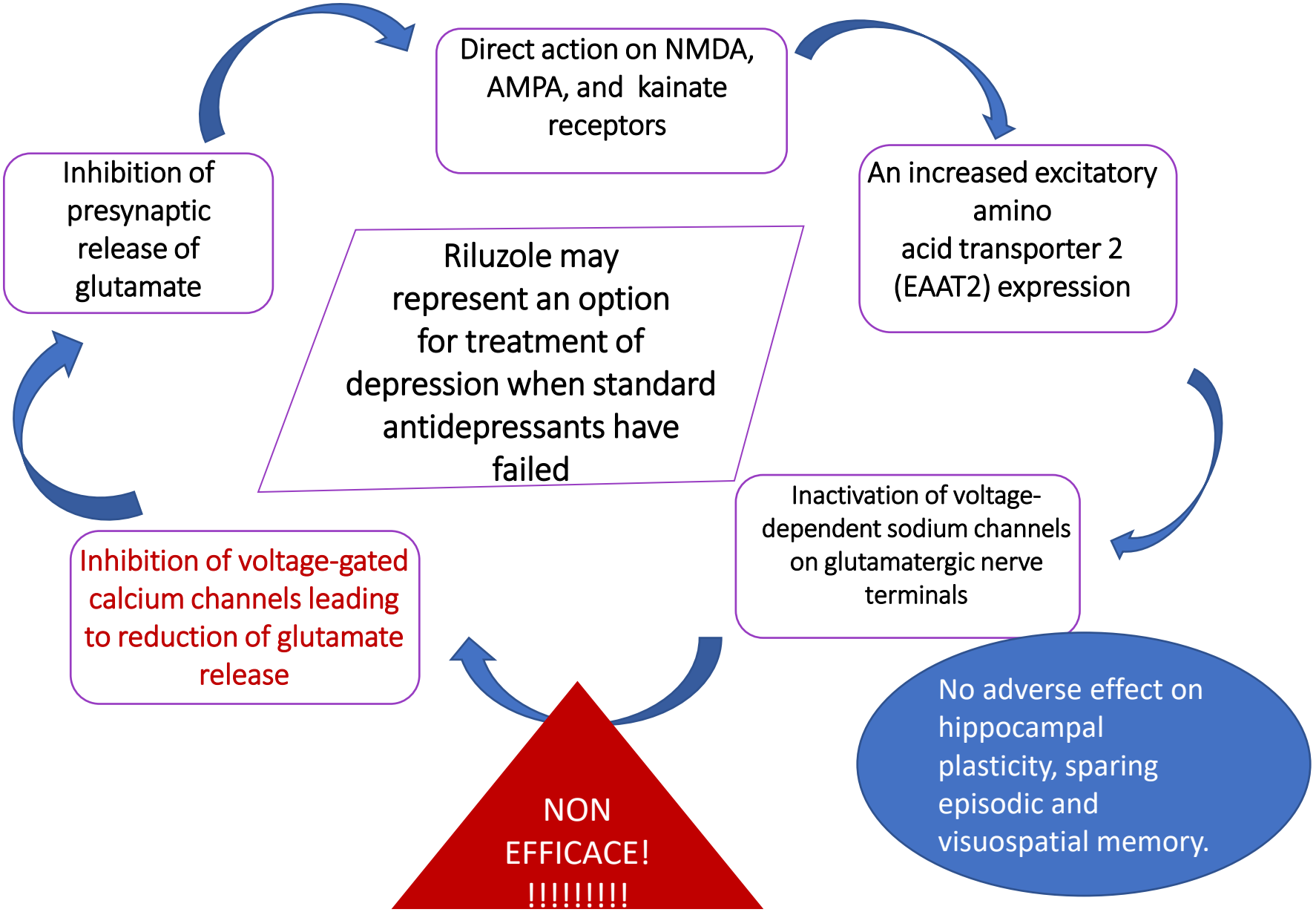
Alterazioni del glutammato presenti in soggetti MDD:
- A livello plasmatico
- Liquido cerebrospinale
- In studi post mortem

Il «ricircolo» del glutammato nelle cellule della glia: se alterato porta a una eccessiva **attivazione** e **tossicità**

In the current study, a CUMS rat model was employed to investigate the interrelationships between the glutamate system, glia, and depression, further, to probe into the underlying mechanism of astrocyte impairment in depression. Chronic stress might induce excessive glutamate release within the synapse, thus contribute to overstimulation of NMDA receptors, followed by the elevation of intracellular astrocytic calcium levels leading to subsequent mediation of the astrocyte apoptotic pathway. Calcium overload in astrocytes may be the underlying mechanism of astrocyte impairment in depression. Accordingly, further research with large samples and novel approaches is required to elucidate any specific interaction occurring between the intracellular calcium level and astrocyte impairment in depression.

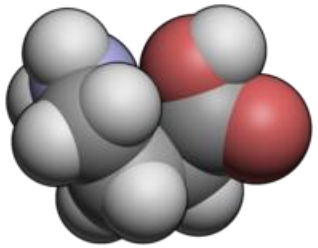
Jiang, 2019

Riluzole approved by the US FDA in 1994 for the treatment of amyotrophic lateral sclerosis



One hypothesis for the mechanism of depression implicates deficits in γ-aminobutyric acid (GABA)

Deficits in γ-aminobutyric acid and downstream alterations in monoaminergic neurotransmission



supported by evidence that:

↓ GABA levels

1. plasma
2. cerebrospinal fluid
3. cortical brain tissues

→ of patients with depression

↓ expression of **GABA-synthesizing enzymes**

→ in the **brain tissue of** persons who have **died by suicide**

↓ number of GABAergic interneurons

→ in the **brain tissue** of **patients with depression**

↓ mRNA for GABA type A (GABAA) α4 and δ subunits

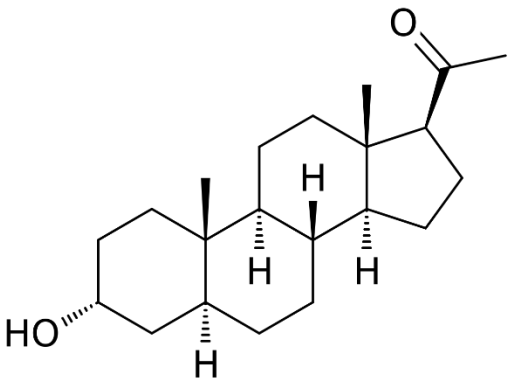
→ in the **brain tissue** of depressed subjects **who died by suicide**

Luscher et al., Mol Psychiatry 2011;16: 383-406

Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression (it may foster resilience)

Clinically **significant** antidepressant **activity in postpartum depression**

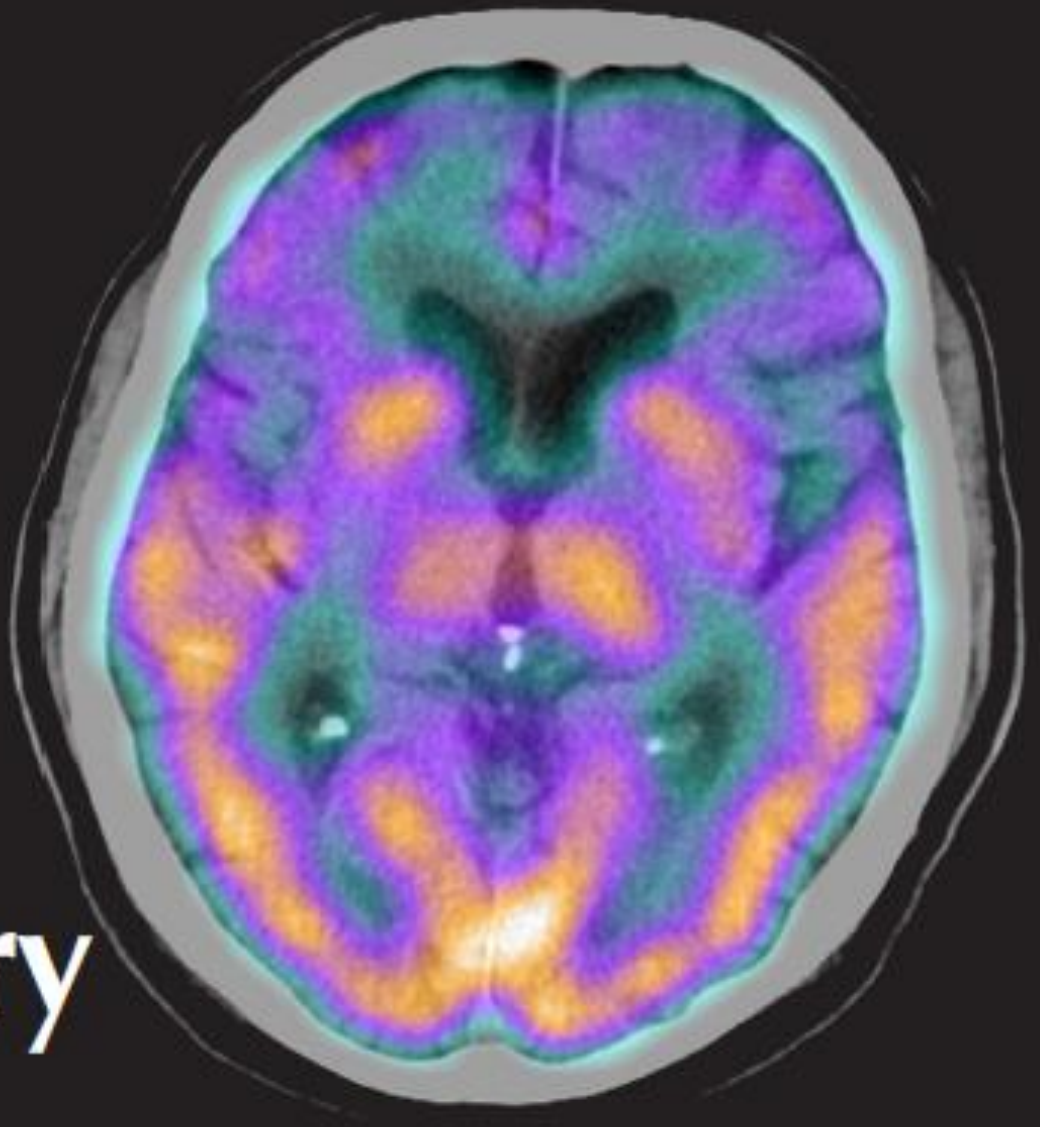
It may **enhance GABA-A receptor** function by increasing the GABAergic inhibition



It may **stabilize normal mood** by **decreasing** the activity of **stress-responsive dentate granule cells** and **sustain resilience** behavior

ClinicalTrials.gov, number NCT02614547

Kanes et al., Lancet. 2017;390(10093):480-489



Inflammatory illness:

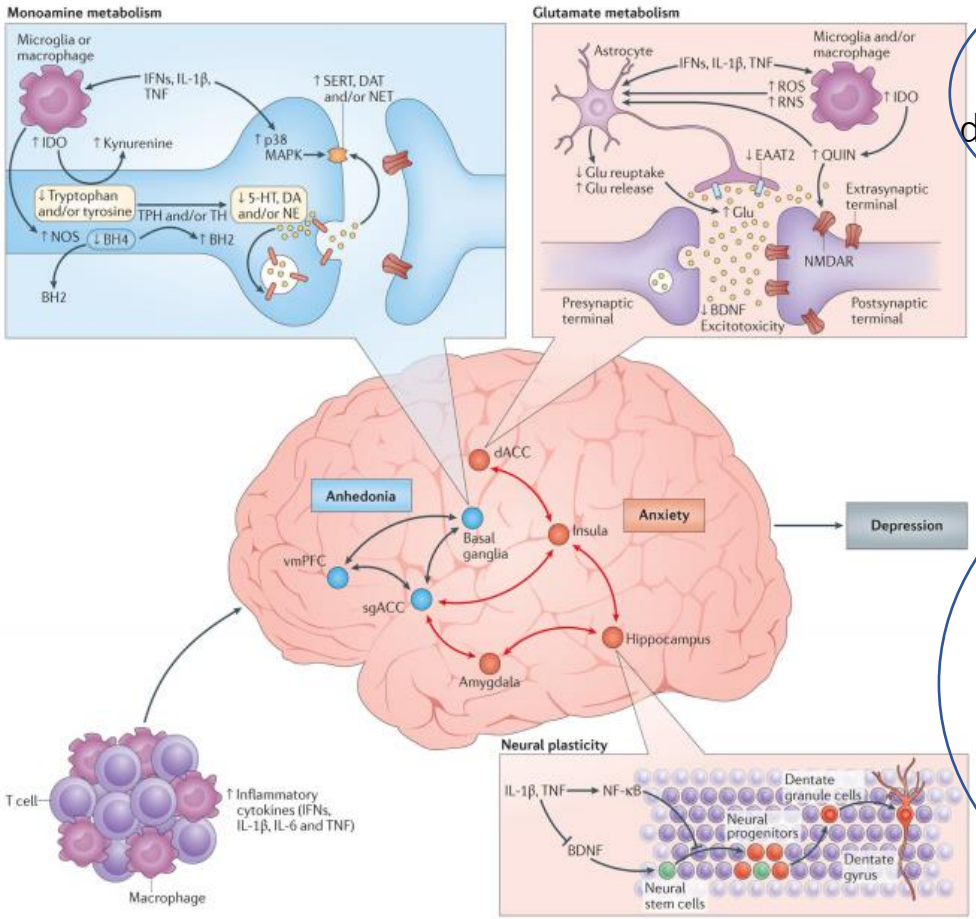
Why the next wave of antidepressants may target the immune system

By Nicole Wetsman

Steven Needell/Science Source

Antidepressivi e neuroinfiammazione

➢ Antidepressants:



Miller and Raison, Nat Rev Immunol 2016

1

reduce peripheral/central **inflammatory pathways** by decreasing **IL-1β**, **TNFα** and **IL-6** levels

2

stimulate neuronal differentiation, synaptic **plasticity**, axonal growth and **regeneration** through stimulatory effects **on** the expression of different **neurotrophic factors** (e.g. trkB, the receptor for BDNF)

3

attenuate apoptotic pathways by **activating Bcl-2** and **Bcl-xl** proteins, and suppressing caspase-3

External **stressors may provoke depression**-like behaviors **through activation of inflammatory, oxidative, apoptotic, and antineurogenic mechanisms. The clinical efficacy of antidepressants** may be **ascribed to** their **ability to reverse these** different **pathways**

M. Kubera et al. / Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 744–759

Depressione Resistente

nuove terapie farmacologiche: antinfiammatori

Systematic Review / Meta-analysis

Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials

CELECOXIB, FANS; STATINE E GLUCOCORTICOIDI in ADD-ON hanno evidenziato ottimi risultati

Una terapia di add-on con antinfiammatori, di breve durata (una settimana) migliora gli effetti antidepressivi senza incrementare gli effetti collaterali.

E' tuttavia necessario approfondire questo campo di studio, per individuare eventualmente sottogruppi di pazienti con sintomi depressivi e alterazioni infiammatorie specifiche, che potrebbero beneficiare ancor di più di terapie anti-infiammatorie.

Kohler-Forsberg et al, 2019

Systematic Review / Meta-analysis

Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials

Summations

- Among 36 RCTs including almost 10 000 patients, five out of six anti-inflammatory drugs improved depression scores compared to placebo.
- Short-term (i.e., weeks) anti-inflammatory add-on to antidepressants showed improved antidepressant effects in MDD without increasing the risk for side-effects.
- The effect size for anti-inflammatory add-on to antidepressants was similar to the effect size of antidepressants alone, indicating the potential clinical benefit.

Una terapia in add-on di breve durata è efficace e NON aumenta gli effetti collaterali

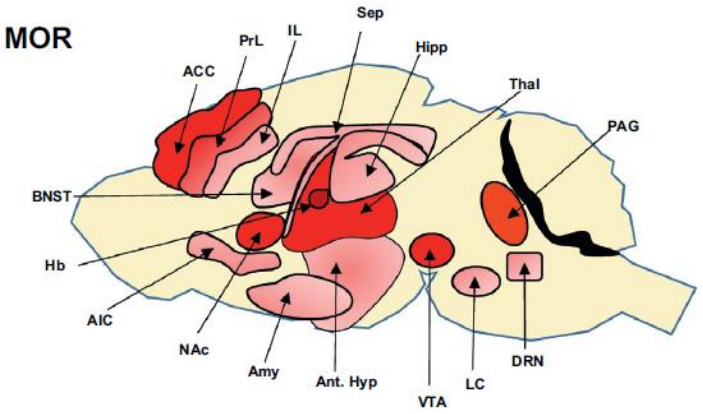
Kohler-Forsberg et al, 2019

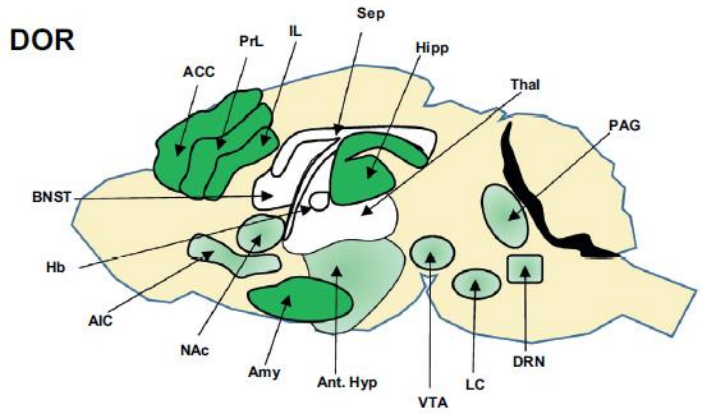
Nuove terapie: Antagonisti dei recettori oppioidi

Recettori mu- alta affinità per encefaline e beta-endorfine, bassa per dinorfina.

Modulating opioidergic tone at MORs has beneficial effects in models of aberrant emotional behavior. Antagonism at MORs could be useful for subjects displaying behavioral suppression due to anhedonia, social withdrawal and anxiety.

- The k-opioid receptor (KOR): new pharmacological target for the treatment of TRD. KOR has a central role in reward system and in mediating the effects of chronic stress on dopamine release in the mesolimbic pathway (Abraham et al., 2018). Activation of KOR receptor by dynorphin leads to a reduction in dopamine release, thus producing anhedonia and depressive symptoms.





Browne, Lucki, 2019

Depressione Resistente
nuove terapie farmacologiche: oppioidi

recettore k:

- target farmacologico della TRD
- centrale nel sistema del reward,
- effetti dello stress cronico

BUPRENORFINA: agonista parziale dei recettori μ e antagonista KOR, a basse dosi, è efficace, ben tollerata e sicura.

CeRC 501
Nuova molecola
ancora in fase di studio

Samidorphan: antagonista dei recettori μ, studiato da solo ed in combinazione con buprenorfina, migliora sintomatologia depressiva controllando il rischio di dipendenza.

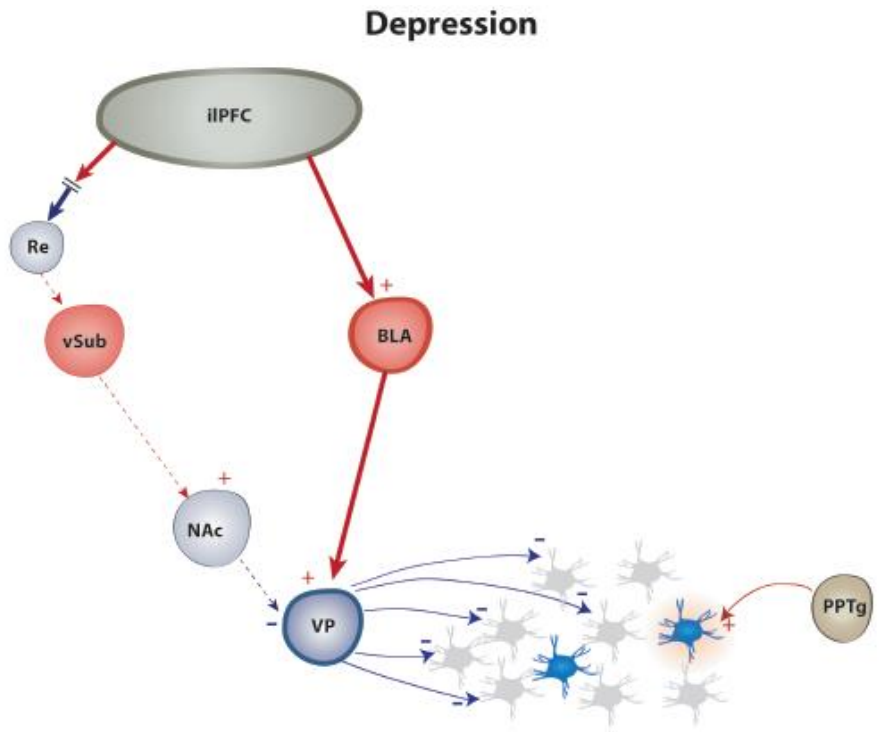
Browne, Lucki, 2019
Serafini, Amore et al, 2018

Depressione Resistente

nuove terapie farmacologiche: sistema dopaminergico

Il sistema dopaminergico ha un ruolo nella depressione variegato, diverso in base ai vari circuiti dopaminergici coinvolti (principalmente mesolimbico e del pathway mesolimbico-area tegmentale ventrale-nucleo accumbens).

AMANTADINA-BUPROPIONE



Sistema dopaminergico:
- Predizione del reward
- Motivazione
- Responsività a stimoli condizionati da incentivi

La dopamina contribuisce a dare salienza agli stimoli motivazionali, rendendoli desiderabili.

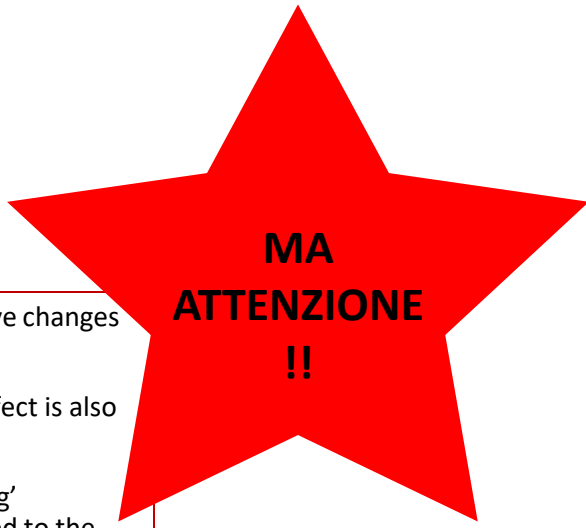
Figure 2. Afferent dysregulation of the dopamine (DA) system in major depressive disorder (MDD). In animal models of depression, the DA system is downregulated, as measured by a decrease in the number of DA neurons that fire spontaneously. This decrease is due to hyperactivity of the infralimbic subregion (ilPFC), driving activity in the inhibitory basolateral amygdala (BLA)-ventral pallidum (VP) pathway while attenuating excitation via the Re-ventral subiculum of the hippocampus (vSub)-nucleus accumbens (NAc)-VP pathway.

Belujon, Grace, 2017

Depressione e trattamento con sostanze psichedeliche

Psillocibina e TRD: nel corso di un trial farmacologico open label, 12 soggetti hanno ricevuto il farmaco oralmente in due dosi, a una settimana di distanza (in un setting ben preciso e con supporto psicologico e medico). Durante il follow up 8 pz hanno raggiunto completa remissione dei sintomi dopo una settimana, 7 l'hanno mantenuta a 3 mesi.

LSD e TRD: LSD potrebbe avere dei benefici in quanto
- Riduce l'attitudine ad una eccessiva difesa
- Aumenta le capacità di ridurre lo stress
- Stimola l'espressione dei sentimenti
- Aumenta le relazioni terapeuta-paziente
- Compare più materiale inconscio



- First, blinding is largely impossible. Therapeutic doses of psychedelics induce subjective and objective changes in feeling, thinking and behaviour that are usually obvious both to recipient and observer.
- Second, and on this basis, placebo control is problematic because the absence of the psychedelic effect is also obvious.
- Thirdly, and perhaps most pertinently to psychedelic trials, the 'set' (psychological state) and 'setting' (interpersonal and physical environment) within which the drug is experienced are inextricably linked to the therapeutic effect.

(Grinspoon and Bakalar, 1997).

Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomised placebo-controlled trial

Studio Brasiliano RANDOMIZZATO, PLACEBO CONTROLLATO, in DOPPIO CIECO a bracci paralleli.

I pz reclutati sono stati sottoposti a wash-out prima di iniziare lo studio.

Dose di ayahuasca contenente 0·36 mg/kg of DMT, o 1 ml/kg of placebo

N= 35 TRD patients

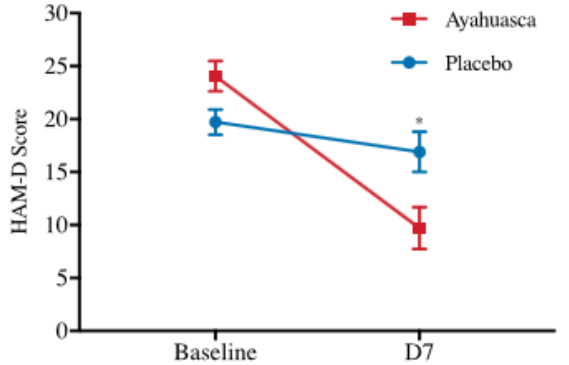


Figure 2. HAM-D scores at baseline and seven days (D7) after dosing.

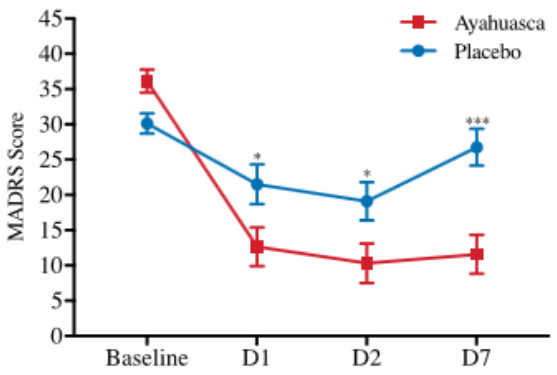


Figure 3. Average MADRS scores as a function of time.

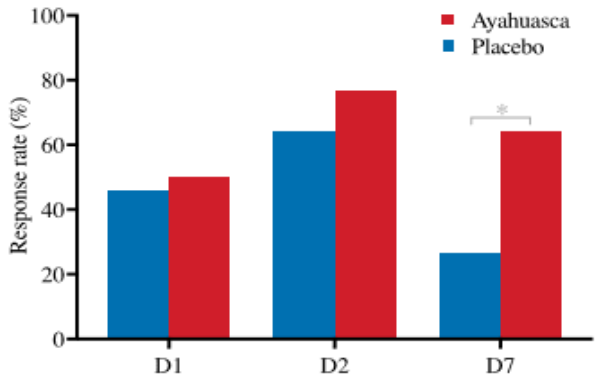
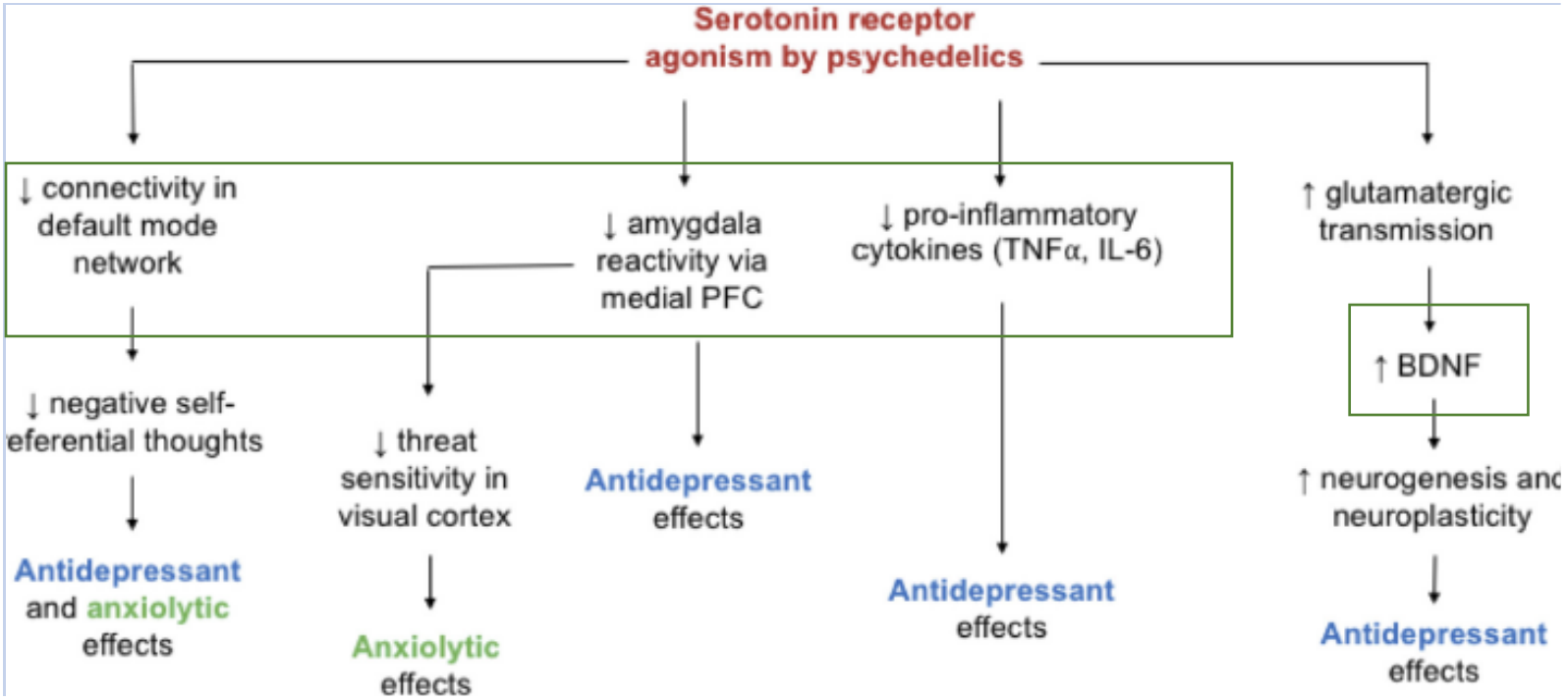


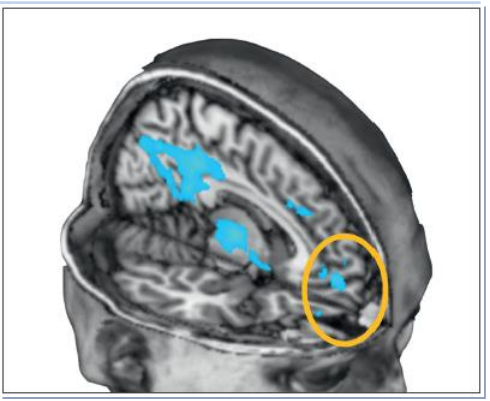
Figure 4. Response rate as a function of time.

Robust evidence of rapid antidepressant effects of a single dosing session with ayahuasca when compared to placebo was observed. Most frequently adverse effects: nausea (71%), vomiting (57%), transient anxiety (50%), transient headache (42%), restlessness (50%), transient dissociative symptoms

Viol et al., Sci Rep. 2017;7(1):7388

Neurobiological mechanisms mediating psychedelics' anti-depressant and anxiolytic effects





Muttoni et al., J Affect Disord, 2019

…..Psychedelic drugs—a new era in psychiatry? The resurrection of psilocybin research is still in its infancy….

David Nutt, Dialogues Clin Neurosci. 2019

Personalizing care: an amazing journey in depression

Roger McIntyre

- In 2015, **McIntyre** and his team **in Toronto initiated** a clinical trial **using infliximab**, to treat depression.

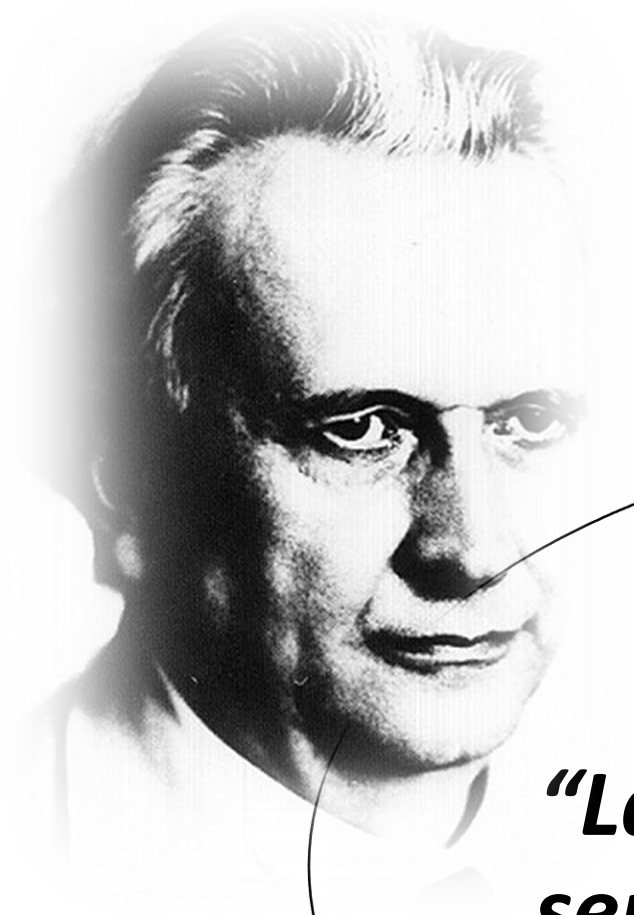
- However, in this study, **one of the criteria for participation is a CRP level above the value that predicted a reduction in depression in response** to the antibody drug **in the 2013 trial (Miller's study)**.

- **Another ongoing** clinical **trial**, **is dosing patients who have depression with** an antibody called **sirukumab** (**originally developed to treat rheumatoid arthritis**), which acts **to neutralize** the inflammatory protein **IL-6**. This study is **focused on how this drug will work in participants** with **higher CRP levels**.

- Another antibody to IL-6, **tocilizumab** (currently **indicated to treat rheumatoid arthritis**), is **being used** in a clinical trial **by a team at Brigham and Women's Hospital to treat depression**.

Unfortunately, **getting approval to use an anti-inflammatory medications** (that may be even expensive) for these disorders **could take years**

McIntrye, 2015



“La terapia è un’arte che si serve della scienza come di un nesso”