Neurobiología de la conducta suicida

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Suicide

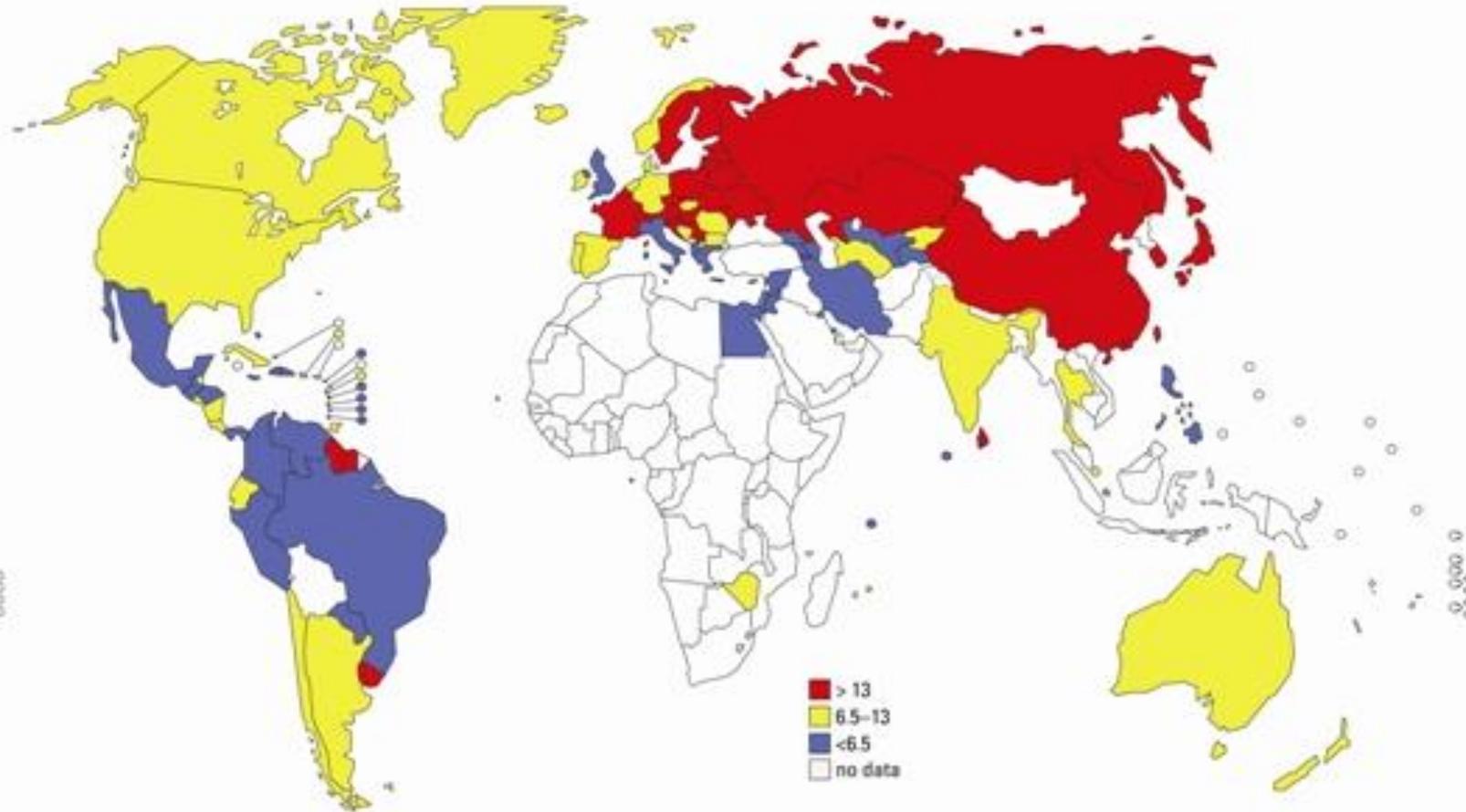every **40 seconds...**

somebody dies from suicide

The time to act is now

Provide support and restrict access to pesticides and other suicide means

World Health Organization

Map of suicide rates
(per 100 000; most recent year available as of 2009)

> 13
6.5–13
<6.5
no data

The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dashed lines represent approximate border lines for which there may not yet be full agreement.

WHO 06.160

Hay dos tipos de profesionales de la salut mental en esta reunion......

Aquellos a los que se les ha suicidado algún paciente y….

aquellos a los que se les suicidara…..

Investigacion en suicidio. Antecedentes

- Emile Durkheim "Suicide" 1897

- Factores de riesgo (Sifneos 1956)

  - Género, edad, intentos previos, religión, estado civil, climatología, enfermedad mental, discapacidad física, distocia familiar.

- Estudios de gemelos (Kallmann et al., 1949)

- 60' estudios neuroquímicos y postmortem en suicidas

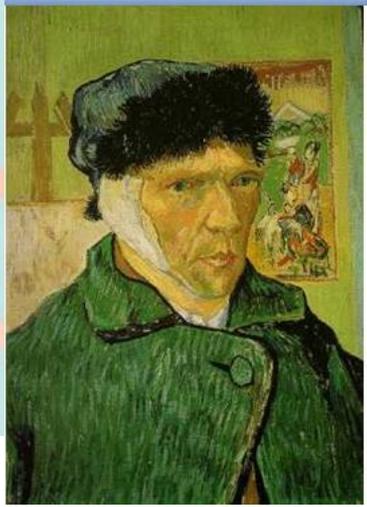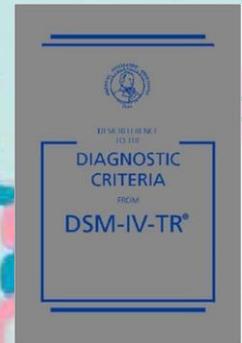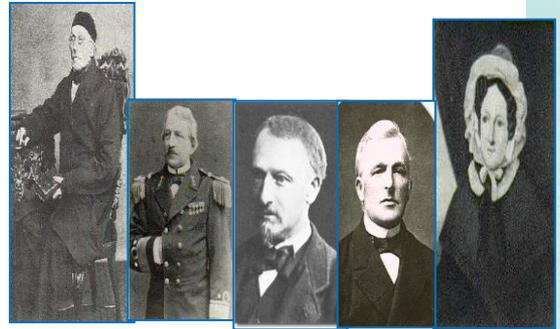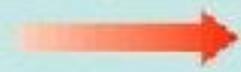- Autopsia psicológica (Barraclogh et al., 1974)

Ernst et al., 2009

Evolución

Genes

Experiencia

Organismo

DIAGNOSTIC
CRITERIA
FROM
DSM-IV-TR®
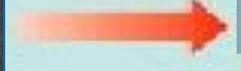
Suicidio

Historia/genética familiar

- Los familiares de sujetos suicidas tienes 4 veces más riesgo de suicidio.

- Los estudios con gemelos indican una mayor concordancia de la conducta suicida en MZ
    - MZ 11.3% vs 1.8% en DZ (Roy et al., 1991)

- Estudios de adopción: mayor riesgo de suicidio entre familiares biológicos que entre familiares adoptivos.
    - 12/269 F. biológica vs 2/269 en F. adoptiva
                                (Schulsinger et al 1979)

Conducta suicida y heredabilidad genética

- La contribución de factores genéticos se estima entre el 30% y el 50% para un amplio fenotipo de tendencias suicidas que incluye ideación, planes, e intentos, y es en gran parte independiente de la herencia de la enfermedad mental.

- **La conducta suicida, como rasgo complejo, es probablemente el resultado de una combinación de numerosos factores ambientales y el efecto de múltiples genes.**

Estudios genéticos de asociación

Endofenotipos de la conducta suicida
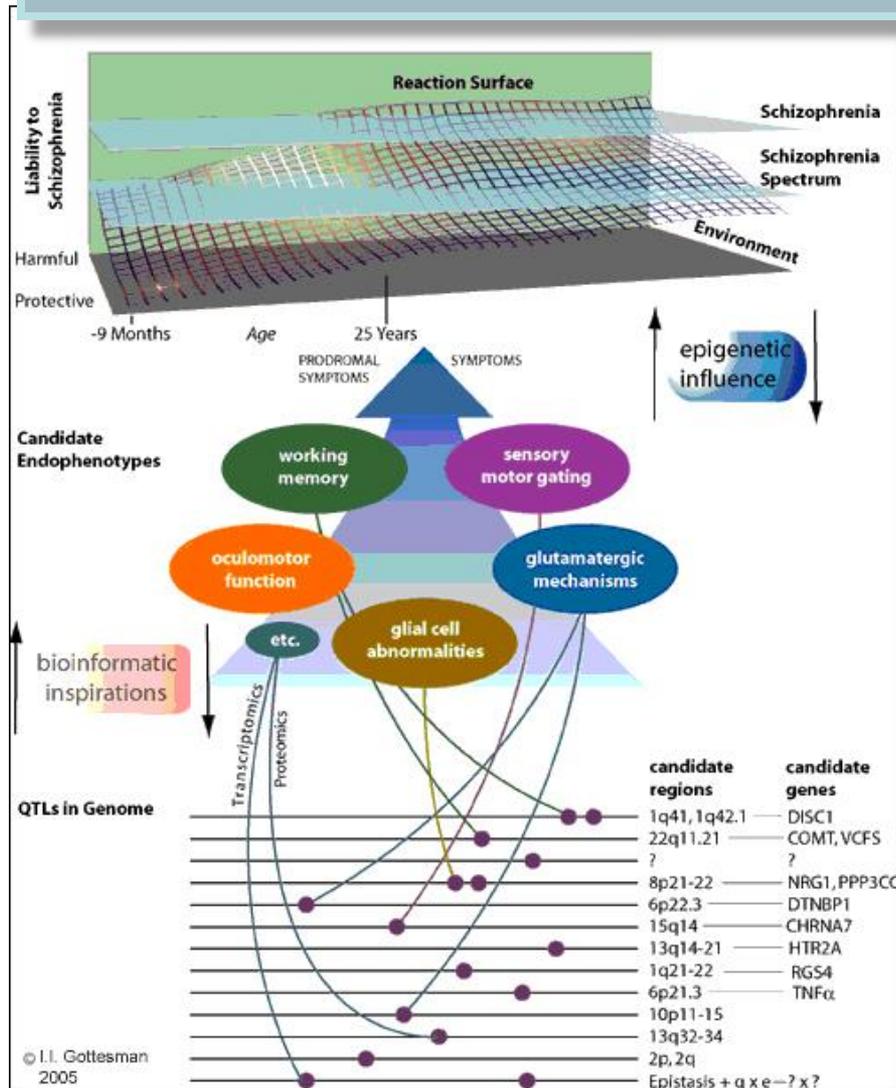
Criterios para un endofenotipo:

1) asociación con la enfermedad en la población

2) hereditario (> 20%)

3) independiente del estado primario

4) la enfermedad y el endofenotipo agregan intrafamiliarmente (vínculo entre rasgo y variante del gen)

5) Es más frecuente en familiares no afectados que en la población general

Gottesman and Gould 2003

Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach

AB Niculescu[1,2,3], DF Levey[1,2,9], PL Phalen[3,9], H Le-Niculescu[1,9], HD Dainton[1], N Jain[1], E Belanger[3], A James[3], S George[3], H Weber[3], DL Graham[1], R Schweitzer[1], TB Ladd[1], R Learman[1], EM Niculescu[1], NP Vanipenta[1], FN Khan[1], J Mullen[4], G Shankar[4], S Cook[5], C Humbert[5], A Ballew[5], M Yard[6], T Gelbart[7], A Shekhar[1], NJ Schork[8], SM Kurian[7], GE Sandusky[6] and DR Salomon[7]

Figure 1. Cohorts used in study depicting flow of discovery, prioritization, validation and testing of biomarkers from each step.

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IMMEDIATE COMMUNICATION

Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach

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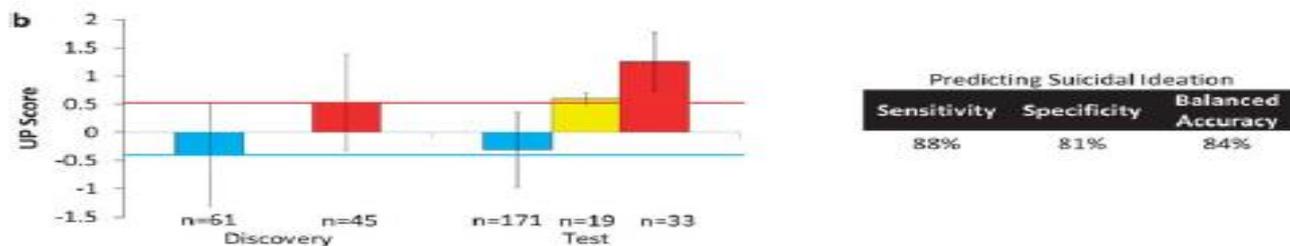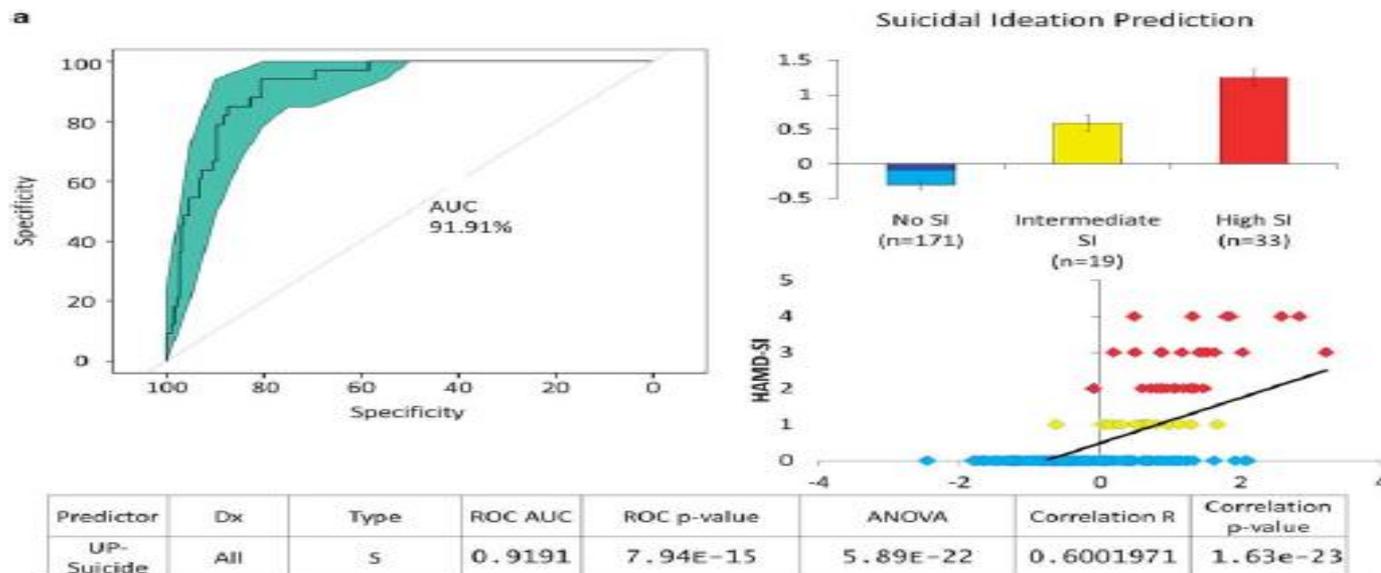**Table 2.** Top biomarkers for suicidality from discovery, prioritization and validation

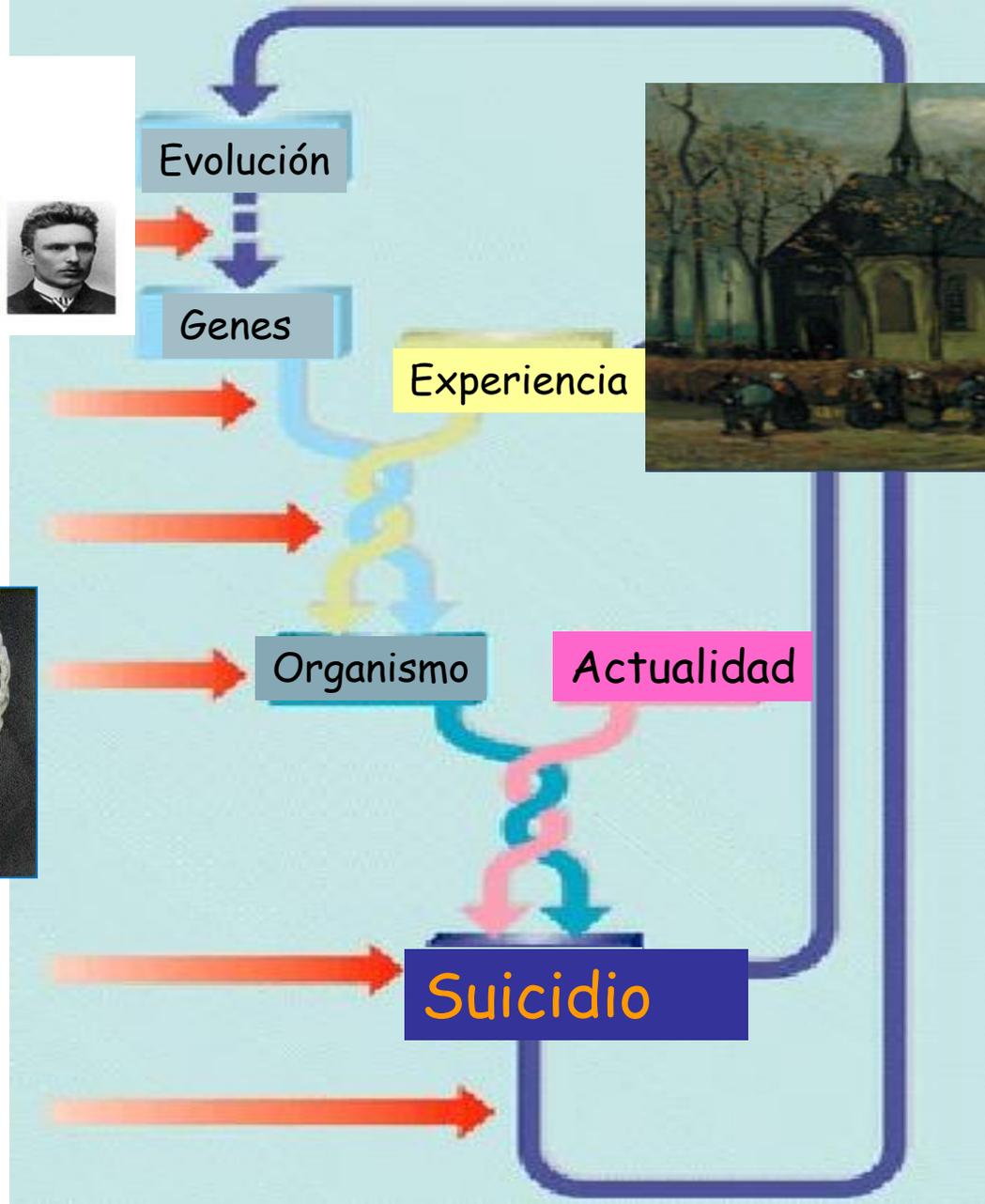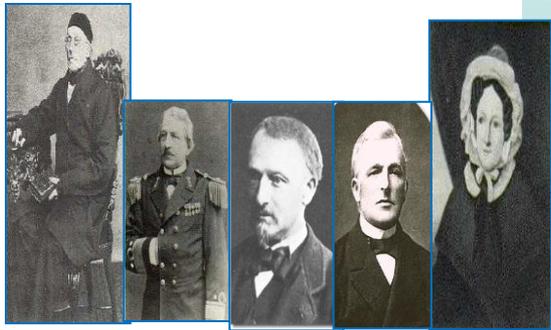| Gene symbol/gene name	Probesets	Discovery (change) method/ score	Prior human genetic evidence	Prior human brain expression evidence	Prior human peripheral expression evidence	Prioritization Total CFG score For suicide	Validation ANOVA P-value	Comment
SKA2 spindle and kinetochore associated complex subunit 2	225686_at	(D) DE/1 AP/1	Suicide[15]	(D) PFC[15]	(D) Methylation in blood[15]	9	0.006 0.027	Top Decreased BioM In prioritization from AP and DE
IL6 interleukin 6 (interferon, beta 2)	205207_at	(I) AP/2		(I) PFC[27] Hippocampus[28]	(I) CSF[29,10] (D) Blood[31]	8	1.44e−08	Top Increased BioM in Validation from AP
SAT1 spermidine/spermine N1-acetyltransferase 1	213988_s_at 210592_s_at 230333_at 203455_s_at	(I) DE/2 DE/1	Suicide[32,33]	(I) PFC BA46[12]	(I) Blood[1]	8	1.08e−44 1.24e−40 6.93e−12 3.09e−38	Top Increased BioM in Prioritization from DE Top biomarker in our previous work
SLC4A4 solute carrier family 4 (sodium bicarbonate cotransporter), member 4	211494_s_at 210739_x_at	(I) AP/2 DE/1	Suicide[34]	(D) PFC BA46/10[35]		8	5.84e−05 0.002	Top Increased BioM in Prioritization from AP
JUN jun proto-oncogene	201464_x_at 213281_at 201466_s_at	(I) DE/1 AP1		(D) HIP[36]		5	2.63e−51 1.02e−41 2.21e−08	Top Increased BioM in Validation from DE
MBP myelin basic protein	225408_at	(D) AP/1		(I) NAC[11]		5	6.74e−10	Top Decreased BioM in Validation from AP
CADM1 cell adhesion molecule 1	237259_at	(I) DE/4				4	NC	Top Increased BioM in Discovery from DE
CLIP4 CAP-GLY domain containing linker protein family, member 4	219944_at	(D) DE/4				4	NC	Top Decreased BioM in Discovery from DE
DTNA dystrobrevin, alpha	211493_x_at	(I) AP/4				4	NC	Top Increased BioM in Discovery from AP
KIF2C kinesin family member 2C	211519_s_at	(D) AP/4				4	0.00056	Top Decreased BioM in Discovery from AP
KLHDC3 kelch domain containing 3	214383_x_at	(D) DE/4			(D) Blood[1]	4	1.57e−17	Top Decreased BioM in Validation from DE A top biomarker in our previous study
MAOB monoamine oxidase B	204041_at	(I) DE/1		(I) PFC[37]	(D) Blood[38]	7	8.11e−08	Top Pharmacological Target
MARCKS myristoylated alanine-rich protein kinase C substrate	213002_at 201670_s_at	(I) DE/1		(I) HIP, PFC[39] PFC[40]	(I) Blood[1]	5	1.51e−06; 0.0004	A top biomarker in our previous study
PTEN phosphatase and tensin homolog	204053_x_at 222176_at	(I) DE/1		(I) PFC, HIP[41,42]	(I) Blood[1]	5	7.66e−17; 0.0003	A top biomarker in our previous study

Abbreviations: ANOVA, analysis of variance; AP, absent-present; CFG, convergent functional genomics; CSF, cerebrospinal fluid; DE, differential expression; SI, suicidal ideation. Bolded P-values are Bonferroni significant. NC—Non-concordant-not stepwise from no SI to high SI to suicide completers.

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Predictor	Dx	Type	ROC AUC	ROC p-value	ANOVA	Correlation R	Correlation p-value
UP-Suicide	All	S	0.9191	7.94E−15	5.89E−22	0.6001971	1.63e−23

Predicting Suicidal Ideation

Sensitivity	Specificity	Balanced Accuracy
88%	81%	84%

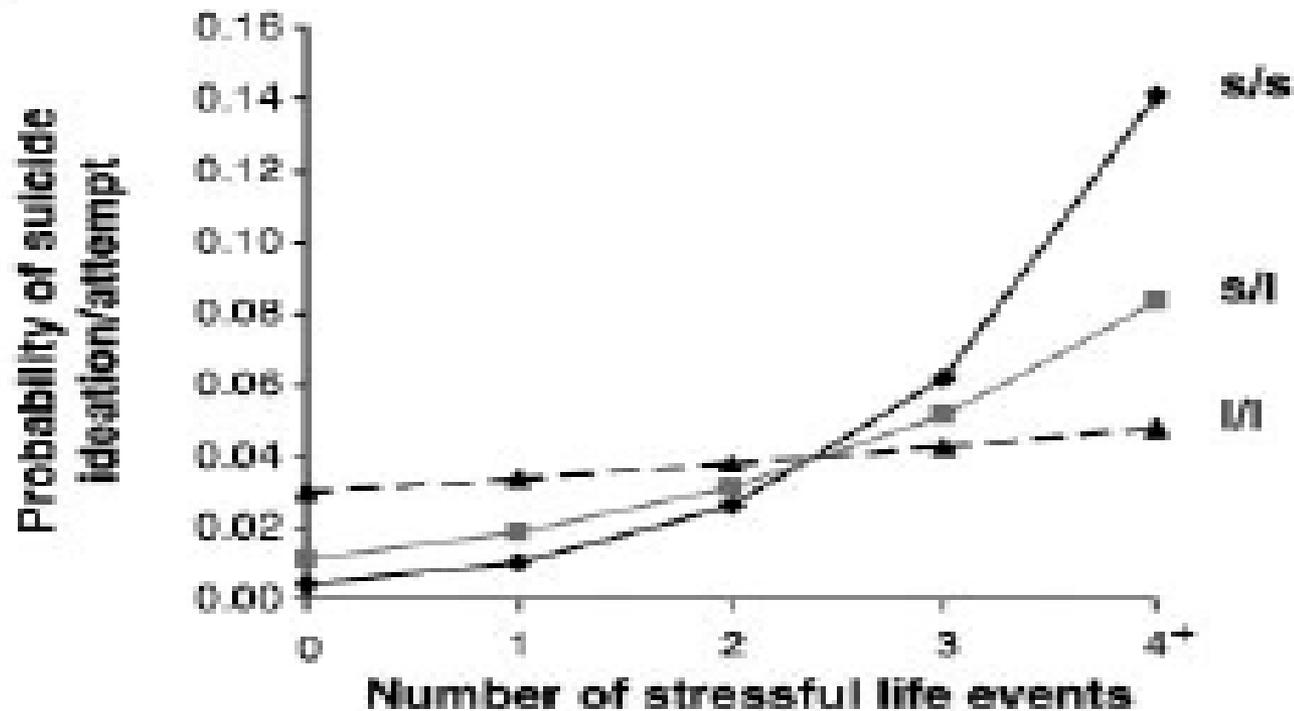Evolución

Genes

Experiencia

Organismo

Actualidad

Suicidio

Polymorphism in the 5-HTT Gene

Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*]
Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2]
Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3]
Antony Braithwaite,[4] Richie Poulton[3]

La interacción genes-ambiente podría tener un papel en la etiopatogenia de la conducta suicida

- Epístasis genética: interacciones complejas entre los genes "de vulnerabilidad", que hacen que se potencien o anulen los efectos entre sí

- Modulación epigenética: los acontecimientos vitales podrían influir en la expresión genética

- La diátesis sobre los trastornos del estado de ánimo es probablemente un producto de la compleja interacción de un gran número de genes con menores efectos individuales y factores ambientales
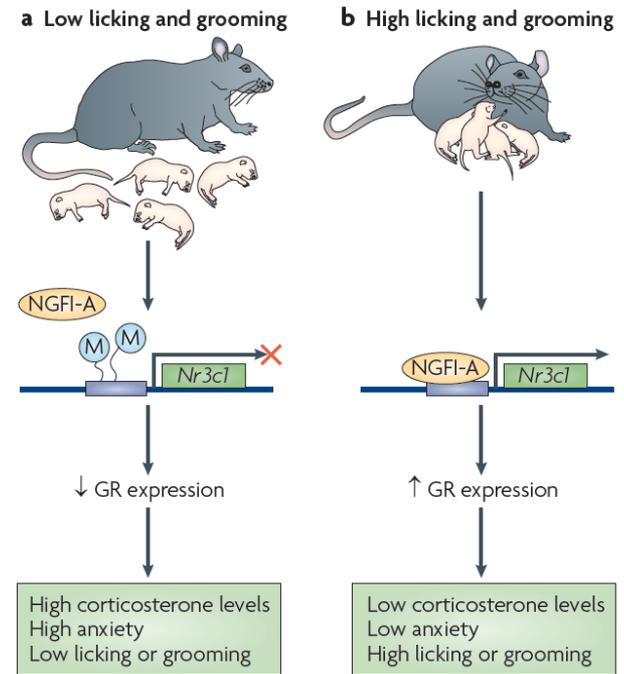

a Low licking and grooming   **b** High licking and grooming

NGFI-A

↓ GR expression   ↑ GR expression

High corticosterone levels
High anxiety
Low licking or grooming

Low corticosterone levels
Low anxiety
High licking or grooming

Figure 1 | **Epigenetic mechanisms of stress**

Maletic V, et al. *Front Biosci.* 2009;14:5291–5338

Evolución

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DIAGNOSTIC CRITERIA FROM DSM-IV-TR®
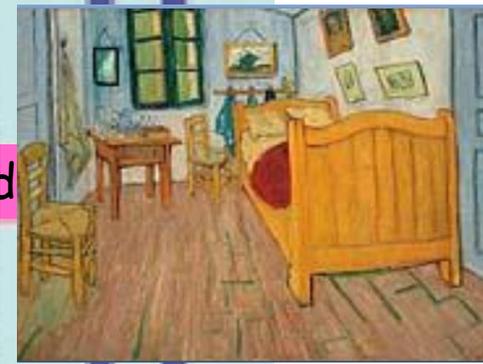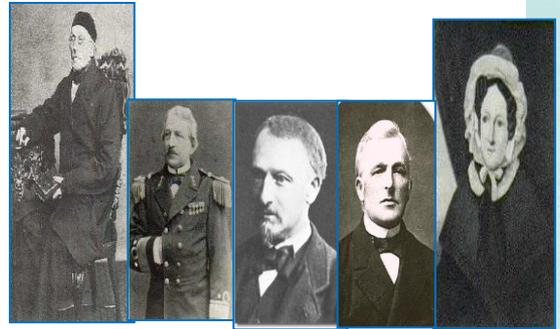
Suicidio

Comorbilidad

En general, a mayor número de diagnósticos, mayor es el riesgo de suicidio

Autopsia psicológica de 229 suicidas:

- 44% presentaban 2 o más diagnósticos de Eje I
- 31% presentaban diagnósticos de Eje I y Eje II
- 50% presentaban diagnósticos de Eje I y al menos uno de Eje III
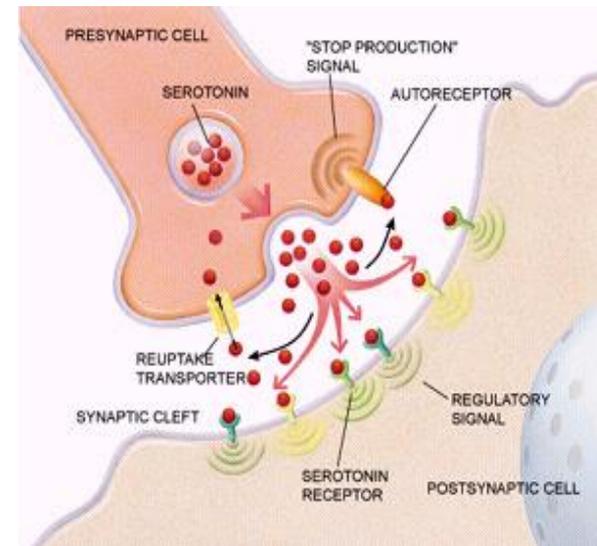- Solo el 12% presentaba diagnósotico de Eje I sin comorbilidad

Henriksson et al, 1993

Situación psicosocial: factores estresantes vitales

- Acontecimientos vitales grav... con el suicidio en sujetos vul...

- Los factores estresantes inc... problemas económicos, proble... 1993b, Lesage et al 1994, Ri...

- Factores estresantes de alto... (ej. ruina económica asociada... despedido, Hirschfeld and D... impulsivo.

- Identificar el factor estresante en relacion a la resilencia , la vulnerabilidad, la enfermedad y el sistema de apoyo.

Neurotransmisores y conducta suicida

El sistema neuromodulador en estudios sobre suicidas, tanto por suicidios consumados como por intentos de suicidio.

La idea de una disfunción en la transmisión 5-HT que provoca un humor depresivo y un posible suicidio surgió de los beneficios clínicos de los antidepresivos que actúan sobre la neurotransmisión serotonérgica, así como de los estudios que correlacionaban el CSF-5HIAA con la depresión y el suicidio (Asberg et al., 1976)

Serotonina y conducta suicida

- Disminución de los niveles de metabólitos del 5HT (5HIAA, HVA) en el líquido cefaloraquídeo (replicado en el 80% de los estudios)

- Disminución del transportador del 5HT en la corteza ventral prefrontal

- Sondas neuroendocrinas (fenfluramina)

- Polimorfismos genéticos en el gen para la hidroxilasa triptófano (TPH)
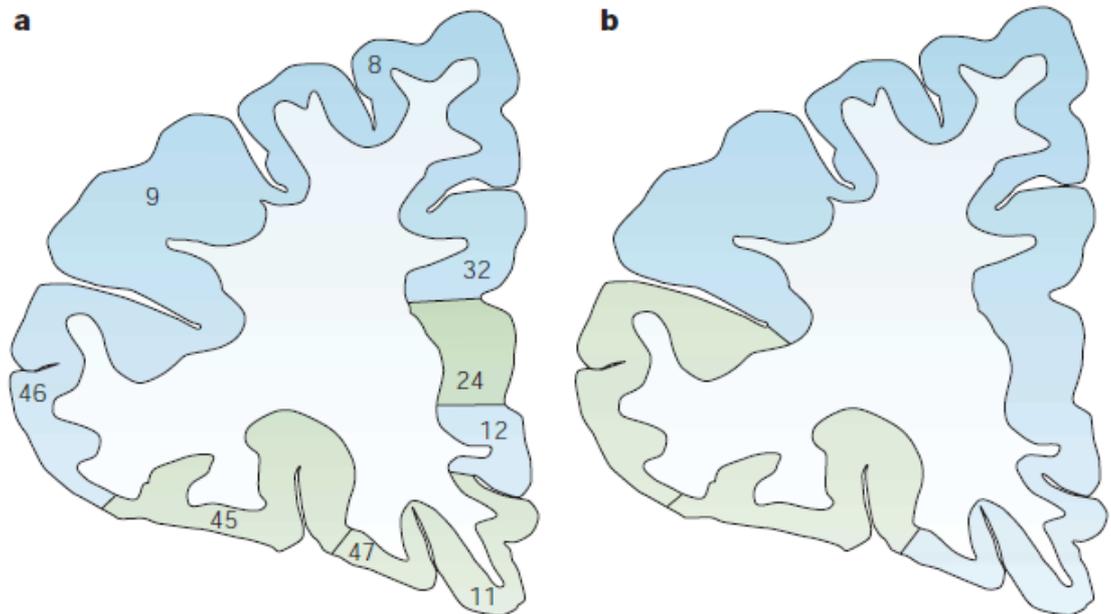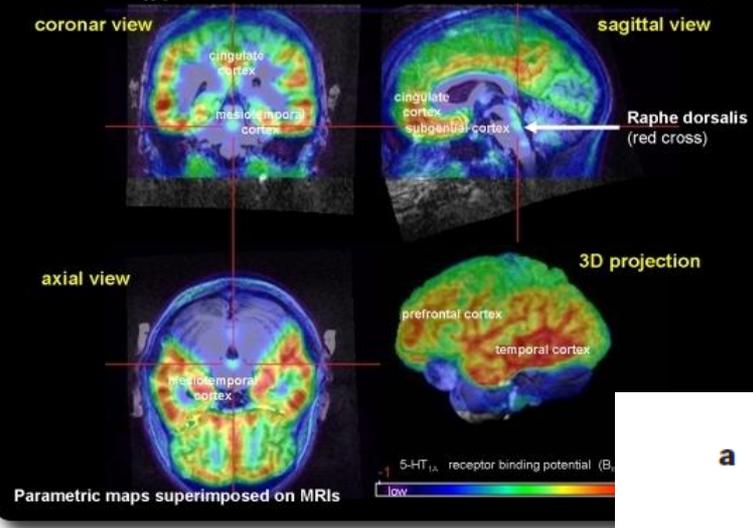
5-HT$_{1A}$ receptor distribution (single brain)

coronar view

cingulate cortex

mesiotemporal cortex

sagittal view

cingulate cortex

subgenual cortex

Raphe dorsalis (red cross)

axial view

mesiotemporal cortex

3D projection

prefrontal cortex

temporal cortex

5-HT$_{1A}$ receptor binding potential (B)

low

Parametric maps superimposed on MRIs


a

8

9

32

46

24

12

45

47

11

b

Figure 3 | **Serotonin and suicidal behaviour.** Post-mortem binding differences (green arrows) in serotonin transporter (**a**) and serotonin receptor 5-HT$_{1A}$ (**b**) in the prefrontal cortex of people who committed suicide. Whereas serotonin transporter binding was decreased in these subjects, 5-HT receptor binding was increased. The numbers correspond to the different Brodmann areas. (Image courtesy of V. Arango and M. Underwood.)

Mann JJ 2003

Regulación de los α2A-Adrenoreceptores plaquetares y postmorten en pacientes con conducta suicida:

Escibá et al., 2004
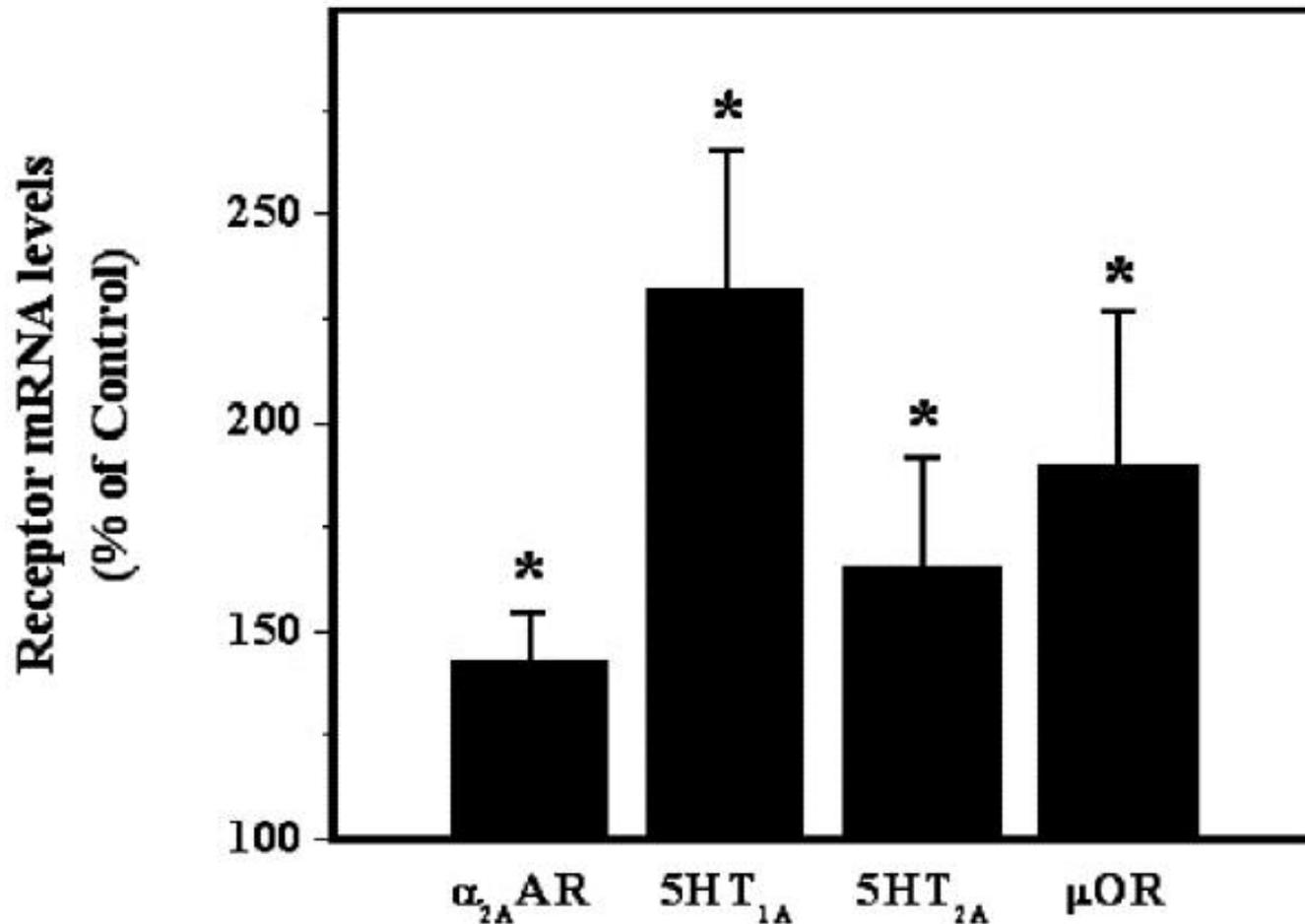
Suicidal Behavior Is Associated with Reduced Corpus Callosum Area

Fabienne Cyprien, Philippe Courtet, Alain Malafosse, Jerome Maller, Chantal Meslin, Alain Bonafé, Emmanuelle Le Bars, Nicolas Menjot de Champfleur, Karen Ritchie, and Sylvaine Artero
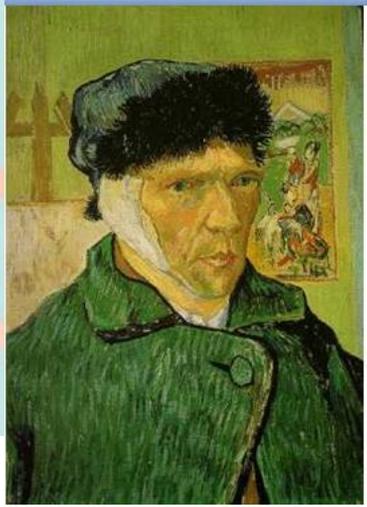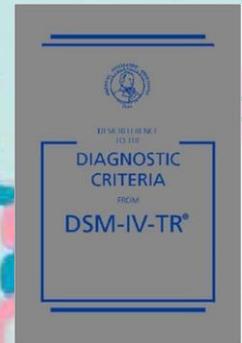
Evolución

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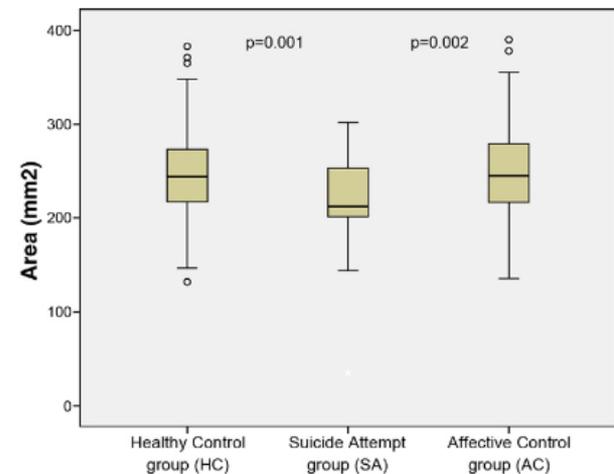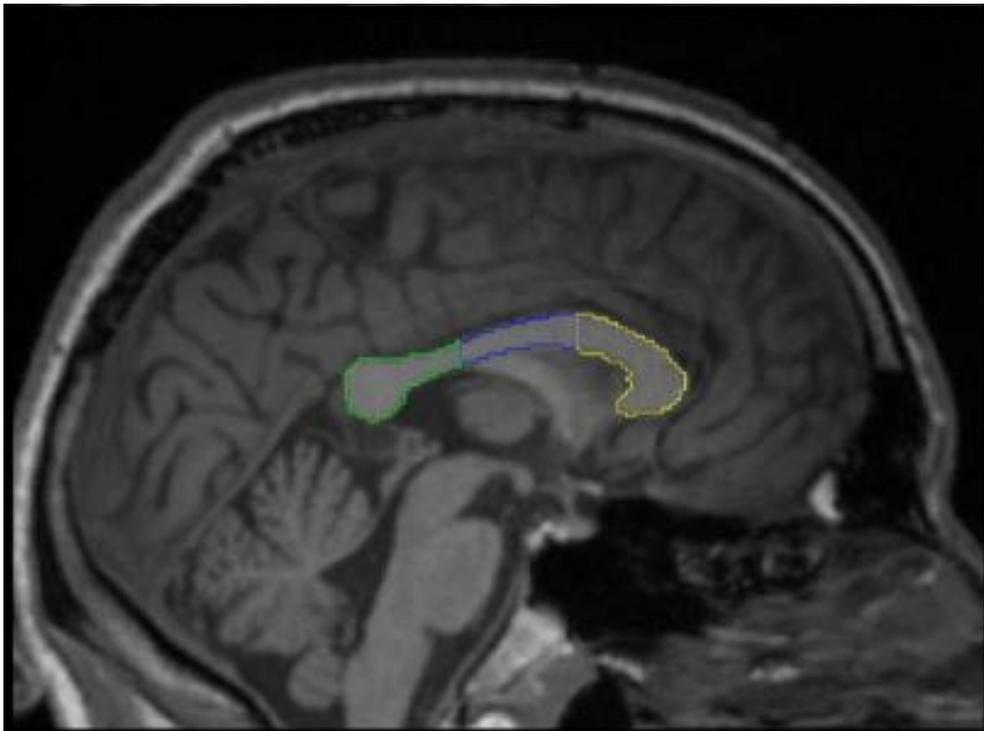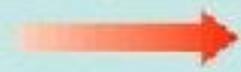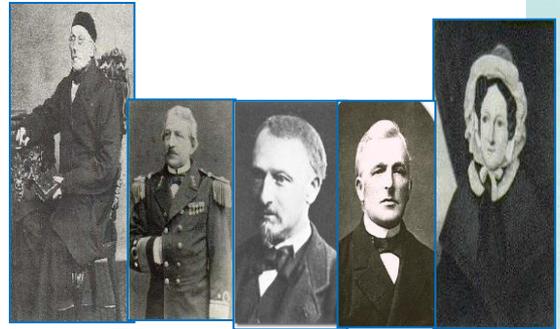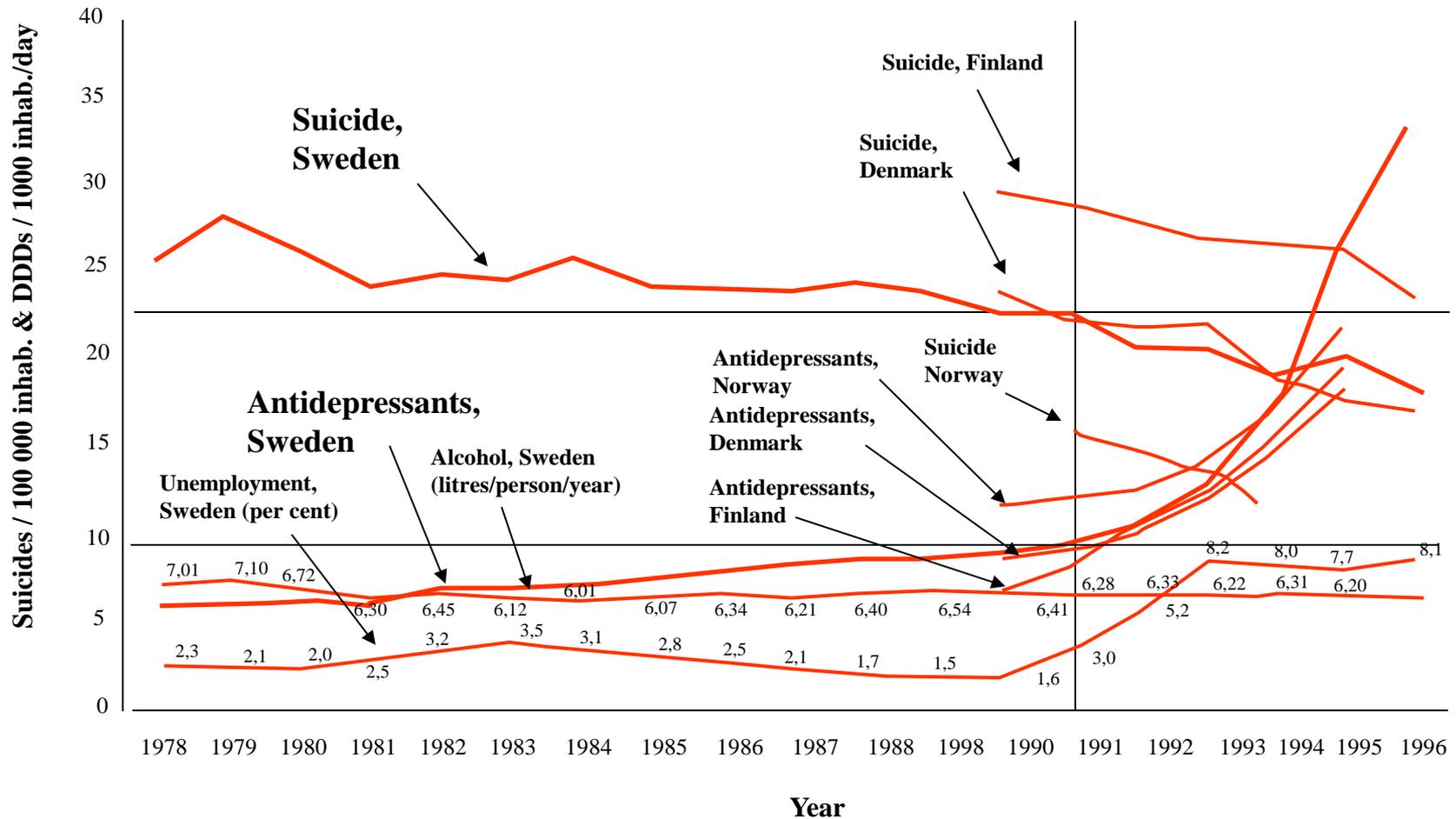
Suicidio

Psicoterapia – suicidio

2 técnicas psicoterapéuticas han demostrado eficacia

- Terapia Cognitivo Conductual

- Terapia Dialéctica –Conductual.

Suicide and sales of antidepressants

Isacsson et al 2000

Risk factors and impact of antidepressants in suicidal behavior in patients with depressive disorder: A general population study across all ages

Objective: To determine the risk factors for suicide-related events, suicide and suicide attempts, in patients with depression across all ages; specifically, to study the impact of different antidepressants on the risk of suicide across the life span.

Data sources: We performed the study using The Health Improvement Network data, which is representative of the UK general population.

Participants: Depression cohort that consisted of 1.129.080 patients.

Main outcomes and measures: Incidence rate (IR) per 100000 person-years of completed suicide and attempted suicide and the hazard ratios (HR) associated with several risk factors, including antidepressants.

Ayuso et al. under revision

Table 1. Demographic and clinical characteristics as well as the distribution of the risk factors of the cases with a diagnosis of depression.

| Risk factors	N Pts	%	Risk factors	N Pts	%	Risk factors	N Pts	%
Total	1129 009	100	Lithium use 6-m	2 401	0.2	Antidepressant drug exposure (in prior year)		
Males	386 990	34.3	In prior year	2 538	0.2	Fluoxetine	181 694	16.1
Age, M (SD)	45.0 (18.1)		In anytime prior	3 410	0.3	Citalopram	154 737	13.7
≤17	21 510	1.9	Drug abuse 6-m	434	0.03	Escitalopram	21 083	1.9
18-34	367 031	32.5	In prior year	579	0.05	Paroxetine	66 694	5.9
35-44	239 572	21.2	In anytime prior	2 652	0.23	Fluvoxamine	1 345	0.1
45-54	189 746	16.8	Diagnosed mental disorder 6-m	493 233	43.7	Sertraline	47 813	4.2
55-64	131 447	11.6	In prior year	530 541	47.0	Antidepressant drug category exposure (in prior year)		
65-74	85 464	7.6	In anytime prior	878 779	77.8	5HT	213	0.0
75-84	66 635	5.9	Alcohol abuse anytime prior	47 684	4.2	TCA	149 959	13.3
85+	27 604	2.4	Depression severity: Mild	423 819	37.5	TCA-NA	31 947	2.8
M (SD) of study years	6.10 (5,1)		Moderate	628 285	55.6	Dual	26 392	2.3
Antipsychotic use 6-m	40 564	3.6	Severe	76 905	6.8	MAOI	547	0.0
In prior year	44 225	3.9	Chronic disease score, M(SD)	0.97	1.28	SSRI	450 196	39.9
In anytime prior	64 703	5.7	0	556 061	49.3	NA	1 007	0.1
Antidepressant use 6-m	616 787	54.6	1	278 063	24.6	NaSSA	23 842	2.1
In prior year	638 267	56.5	2	157 854	14.0	Others	10 079	0.9
In anytime prior	731 824	64.8	3	78 389	6.9	RCT-5HT	12 953	1.1
Antiepileptic Rx use 6-m	26 555	2.4	4	34 861	3.1	RIMA	510	0.0
In prior year	28 793	2.6	5	14 788	1.3	Other drug exposure (in prior year)		
In anytime prior	40 992	3.6	6-9	8 962	0.8	Corticosteroids	127 499	11.3
BMI: Underweight (<18.5)	21 502	1.9	10+	31	0.0	Quinolones	23 327	2.1
Normal (18.5-25)	268 349	23.8	Townsend score: 1 (lowest)	224 111	19.9	Antipsychotics	44 225	3.9
Overweight (25-30)	186 813	16.5	2	211 649	18.7	Antiasthmatics	134 578	11.9
Obese (30+)	136 336	12.1	3	222 410	19.7	Antiinflammatories	218 273	19.3
Missing BMI	516 009	45.7	4	224 115	19.9	Prior history of suicide attempt	28 869	2.6
Family history of suicide anytime prior	656	0.1	5 (highest)	178 655	15.8			
			Unavailable/missing	68 069	6.0			

Note: M = Mean; SD = Standard deviation; BMI = Body Mass Index; 6-m = In prior 6-months. Risk factors on/prior to the study index date.

Figure 3

Suicide and suicide attempt adjusted HR
Antidepressant Rx categories vs SSRIs (AD Rx category)
among depressed patients in THIN database
Age ≥18
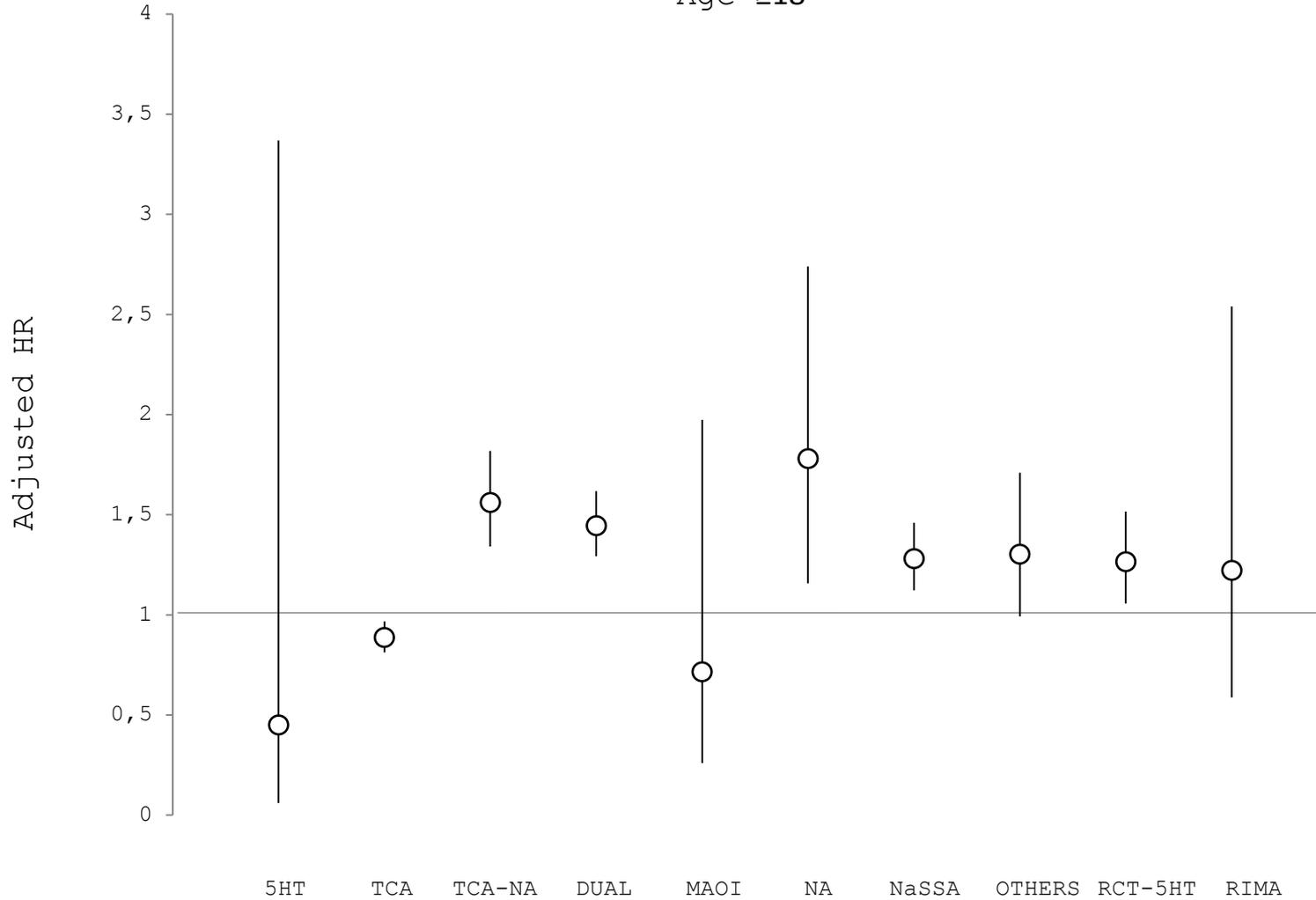
Suicide attempt adjusted HR Antidepressant Rx therapy vs non-Antidepressant among depressed patients in THIN database at each age category
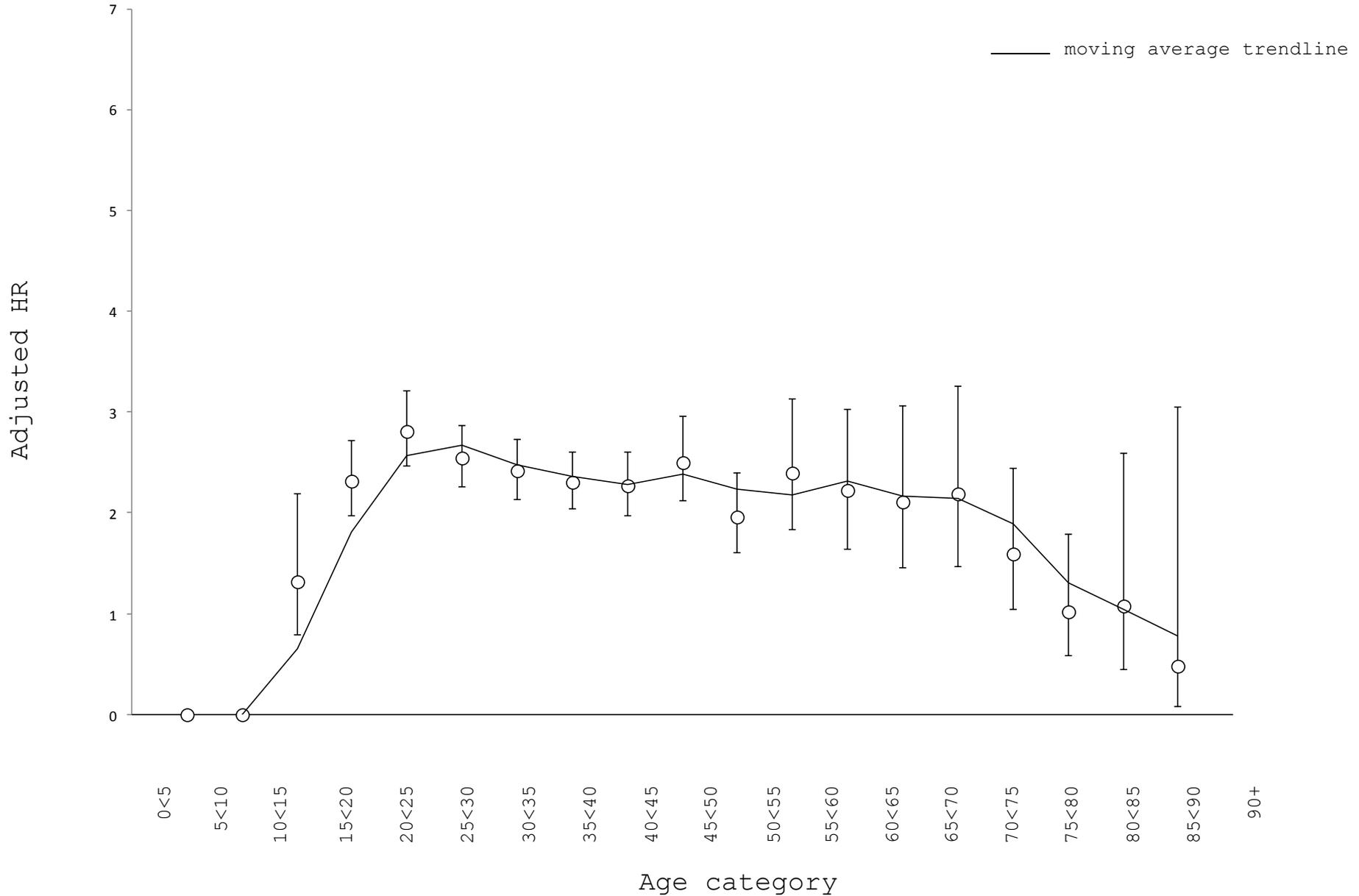
Existing and Novel Biological Therapeutics in Suicide Prevention

Joshua J. Griffiths, MD, Carlos A. Zarate Jr., MD, J. J. Rasimas, MD, PhD

We summa
been consid
attempts, a
lithium, an
stimulation.
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Study	Diagnosis	History of suicide attempt	Design/sample	Primary measures	Results
Grunebaum et al. (2012)[22]	MDD	Yes	DB, RCT, N=74, paroxetine (max 50 mg/day) versus bupropion (max 450 mg/day), 16 weeks	Suicidal attempt classification by weekly consensus; suicidal events by Columbia Suicide History Form; SSI	Depressed patients with greater baseline SI treated with paroxetine compared to bupropion appeared to experience greater acute improvement in suicidal ideation, after adjusting for global depression
Oquendo et al. (2011)[23]	BD	Yes	DB, RCT, N=98, lithium versus valproate, 2.5 years	Time to suicide completion; time to suicide attempt; time to suicide event; SSI	Intent-to-treat analysis showed no differences between treatment groups in time to suicide attempt or to suicide event
Khan et al. (2011)[24]	MDD	No	DB, RCT, N=80, parallel group; citalopram (20 mg/day) + placebo versus citalopram + lithium (300 mg/day), 4 weeks	At screening and trial end: suicidal thoughts/behaviors; S-STS; MADRS; CSSRS	No significant differences in primary outcome measures at 4 weeks; post hoc analysis showed patients assigned to citalopram + lithium had significantly higher S-STS remission rates
Rucci et al. (2011)[25]	MDD	No	Two-site, RCT, N=29, allocated to IPT or SSRI, 4 months	SI; Suicidality items from HDRS and QIDS	Time to suicidal ideation was significantly longer in patients allocated to SSRI compared to those allocated to IPT, even after controlling for treatment augmentation, benzodiazepine use, and comorbid anxiety disorders

Study	Diagnosis	History of suicide attempt	Design/sample	Primary measures	Results
Lauterbach et al. (2008)[26]	Affective spectrum disorders	Yes	DB, RCT, N=167, recent suicide attempts (<3 months), treatment with lithium or placebo, 12 months	Suicide attempt; SSI	Survival analysis showed no significant difference of suicidal acts between lithium and placebo; post hoc analysis revealed that all suicide deaths had occurred in the placebo group, with significant difference in incidence rate

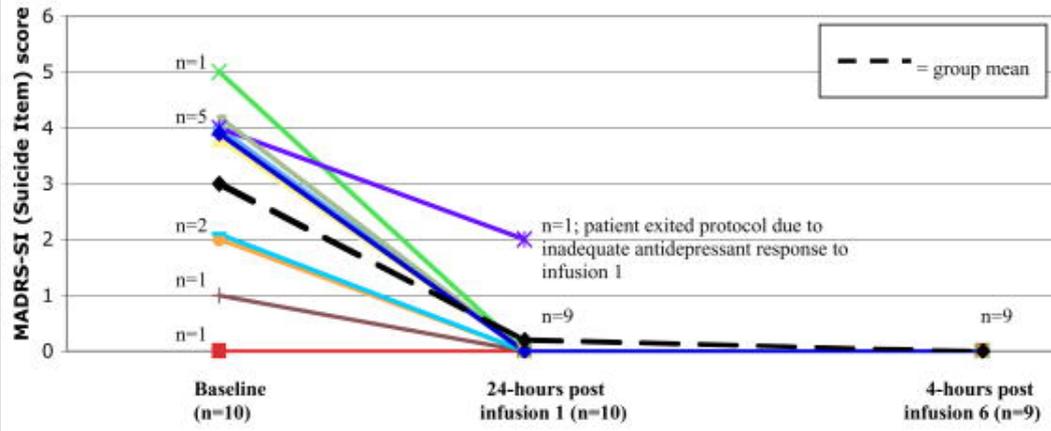| Study	Diagnosis	History of suicide attempt	Design/sample	Primary measures	Results
Meltzer et al. (2003)[16]	Schizophrenia/ schizoaffective disorder	Yes	Multicenter, RCT, N=980, international, clozapine versus olanzapine, 2 years	Suicide attempts/ completion; hospitalizations to prevent suicide; rating of "much worsening of suicidality" from baseline; CGI-SS	Clozapine therapy was superior to olanzapine therapy in preventing suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide
Verkes et al. (1998)[29]	No DSM diagnosis	Yes	DB, RCT, N=91, paroxetine (40 mg/day) versus placebo in patients who recently attempted suicide for at least a second time, 1 year	suicide attempt; self-rating scales for depressive symptoms, anger; Axis II diagnoses	With adjustment for the number of previous suicide attempts, paroxetine showed significant efficacy in the prevention of recurrent suicidal behavior

Ketamina y Conducta Suicida

Figure. Potential glutamatergic targets for novel antidepressants

NMDA antagonists: ketamine CP-101,606, AZD6765, Ro 25-6981, GLYX-13

Muscarinic antagonists: scopolamine, telenzapine

mGluR2/3 antagonists: LY341495, MGS0039

NMDA/MuscR

Spine synapse number and function

Biol Psychiatry. 2009 Sep 1; 66(5): 522–526

Repeated-infusions study

MADRS-SI (Suicide Item) score

- - - = group mean

n=1
n=5
n=2
n=1
n=1

n=1; patient exited protocol due to inadequate antidepressant response to infusion 1

n=9

n=9

Baseline (n=10)

24-hours post infusion 1 (n=10)

4-hours post infusion 6 (n=9)

Individual patient scores on the Montgomery-Asberg Rating Scale—Suicide item at baseline (Day 1; 150 minutes prior to infusion), 24-hours following a single subanesthetic infusion of ketamine (Day 2), and 4-hours following the final repeated infusion (Day 12 of study; Panel 2 only).

Conducta Suicida alguna dudas de futuro

✖ Problemas de conductas poco frecuentes o raras

✖ ¿Qué estamos valorando?

✖ Comorbilidad

✖ **Variable temporal**

✖ Falsos positivos "*post hoc*"

✖ Implicaciones para el tratamiento y prevención del suicidio

Comentarios al CRS
→Diciembre 201_

3. Consideracions específiques respecte al suïcidi

Creure que tot suïcida és un malalt mental, o que tot intent de suïcidi ja demostra la incompetència d'una persona, **pot ser una exageració**. Seria desconsiderar el que han mostrat grans personatges (reals o imaginaris) al llarg de la història i en diferents àmbits culturals; i seria menystenir el fet innegable que hi ha entre nosaltres qui contempla lúcidament el suïcidi com una sortida digna
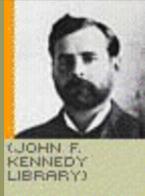
Gracias por su atención

EVERY 40
SECONDS
SOMEONE IN
THE WORLD
DIES BY
SUICIDE.

EVERY 41
SECONDS
SOMEONE
IS LEFT TO
MAKE SENSE
OF IT.