



Role of psychotropics in suicide prevention

BCNBP Dutch Regional Meeting - Ghent
21/10/2016

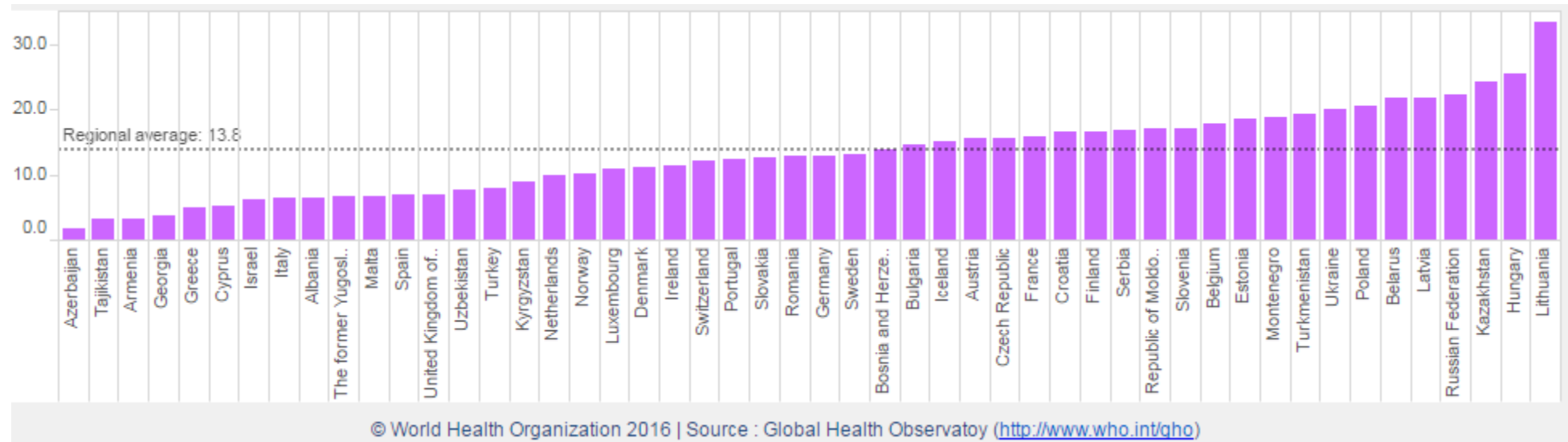
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University of Oxford

Overview

- Background & methodological issues
- Lithium
- Anticonvulsants
- Antipsychotics
- Antidepressants
- Ketamine
- Minor tranquilisers
- BPD

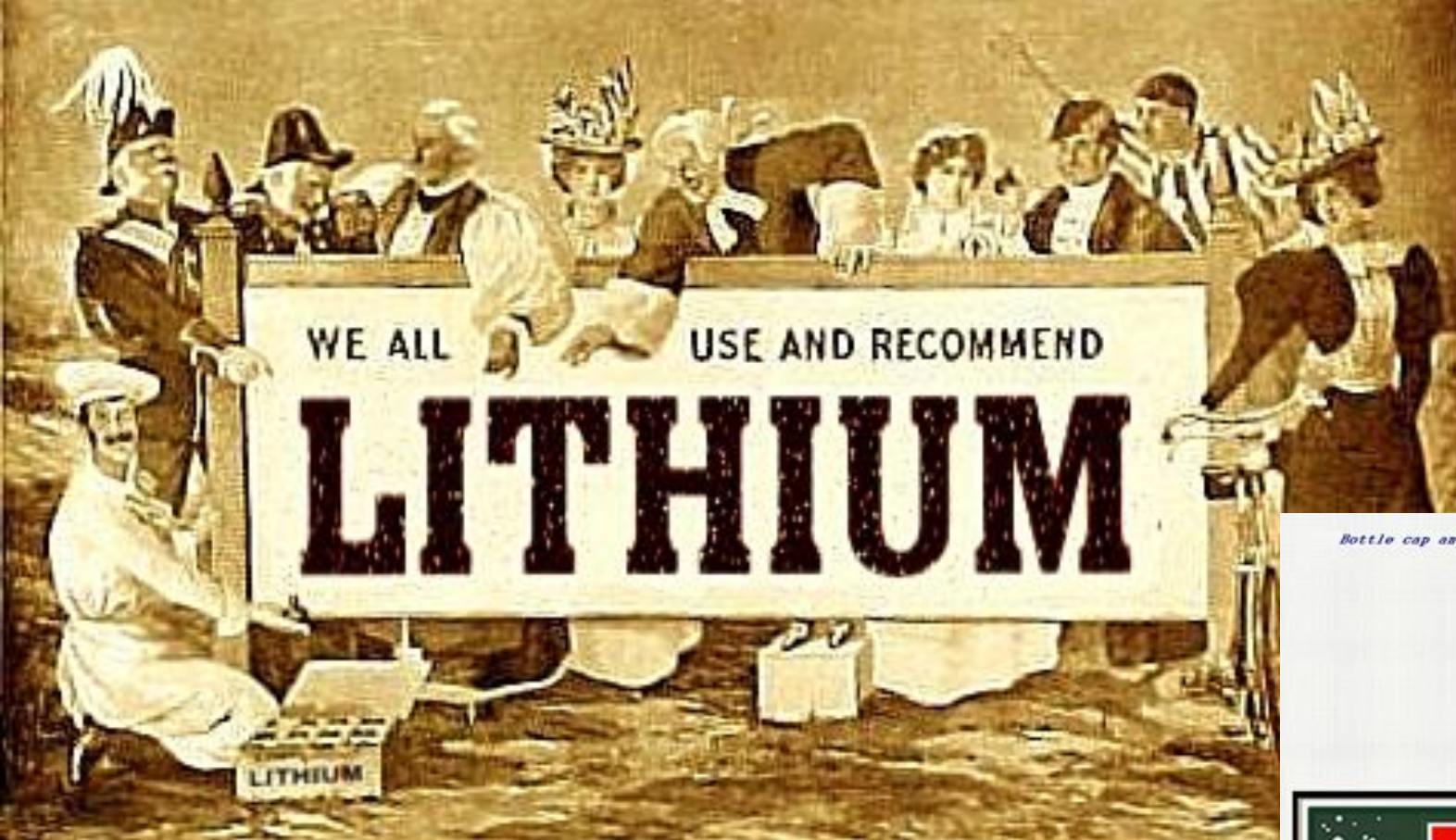
Background

- Suicide rare but devastating event
 - 11/100,000 /year internationally but rates vary considerably
- In the top three causes of death in those aged 15-44 (WHO)
- Suicide is strongly associated with mental disorder
 - Major affective disorders predominate
 - SMR = 10-20x general population



Methodological challenges

- Large numbers
 - Ethics of recruiting suicidal patients
 - Role of concomitant factors e.g substance misuse
 - Nomenclature
 - Need to control for frequency of clinical contact
 - Commercial considerations
-
- Evidence largely observational or from post hoc analyses



Bottle cap and label from 1930s era.



Seven Up
Settles the
Stomach
For Hospital
or home use.

**LITHIATED
LEMON SODA**

The added citrates neutralize free acid,
The sugar is inverted . . . burns clear.
7-Up is more than a mixer...It blends
out the harsh features. Disperses hang-
overs. Takes the "ouch" out of grouch.

Slenderizing

PRINTED IN U.S.A.

You Deserve
The Original

That's Your
Assurance

1955 print advertisement.



Why we have the youngest
customers in the business

This young man is 11 months old -- and he isn't our youngest customer
by any means.
For 7-Up is so pure, so wholesome, you can even give it to babies and
feel good about it. Look at the back of a 7-Up bottle. Notice that all
our ingredients are listed. (That isn't required of soft drinks, you know
-- but we're proud to do it and we think you're pleased that we do.)
By the way, Mom, when it comes to toddlers -- if they like to be coaxed
to drink their milk, try this: Add 7-Up to the milk in equal parts, pour-
ing the 7-Up gently into the milk. It's a wholesome combination -- and
it works! Make 7-Up your family drink. You like it . . . it likes you!

Nothing does it like Seven-Up!

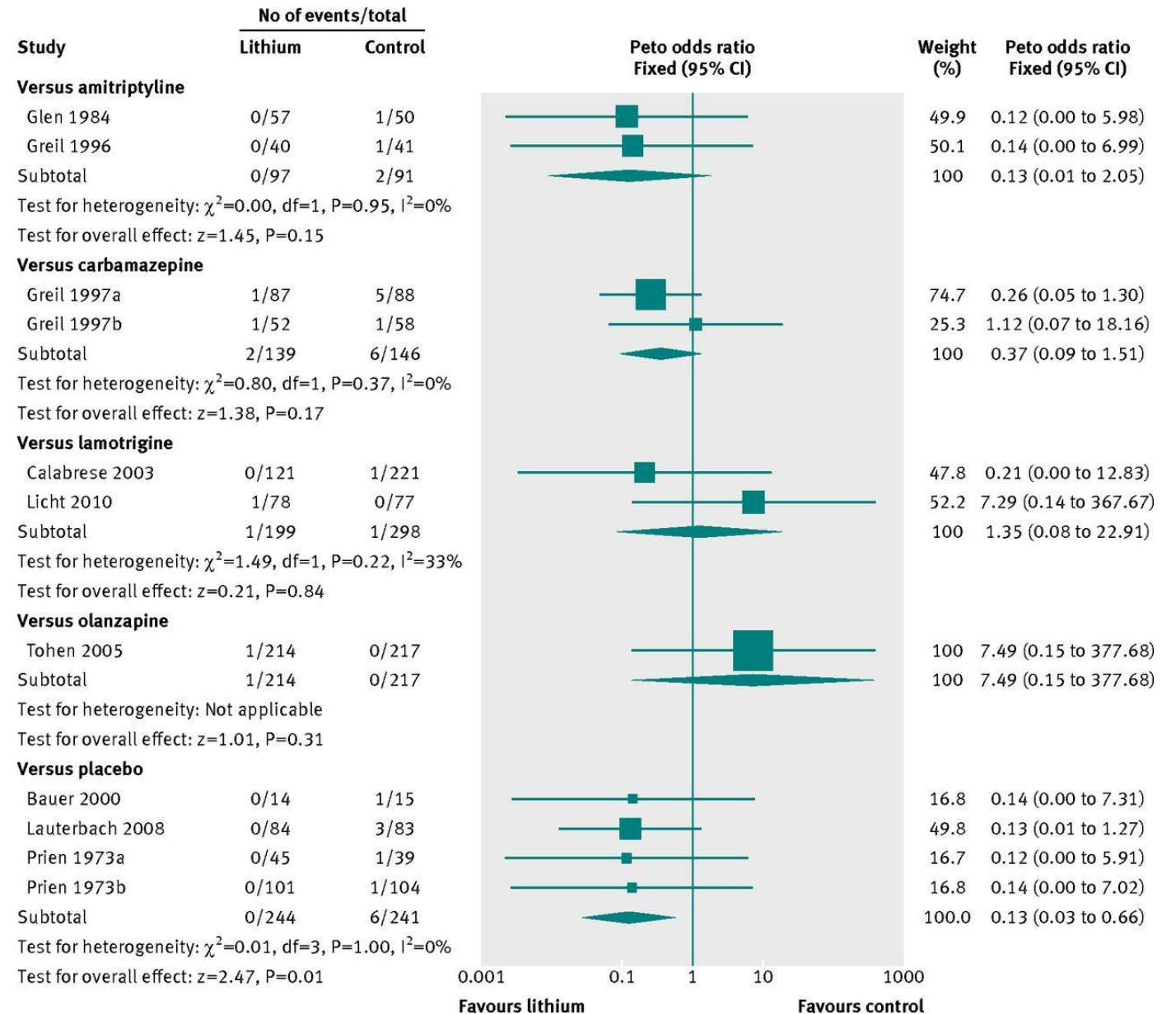
Lithium

Rx for bipolar disorder

Augmentation in UD

Meta analysis of RCTs

Cipriani 2013 BMJ





Research report

Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: A nationwide registry-based prospective cohort study



Elena Toffol^{a,*}, Taina Hättönen^{b,c}, Antti Tanskanen^d, Jouko Lönnqvist^{a,c},
Kristian Wahlbeck^{a,c}, Grigori Joffe^f, Jari Tiihonen^d, Jari Haukka^{a,g}, Timo Partonen^a

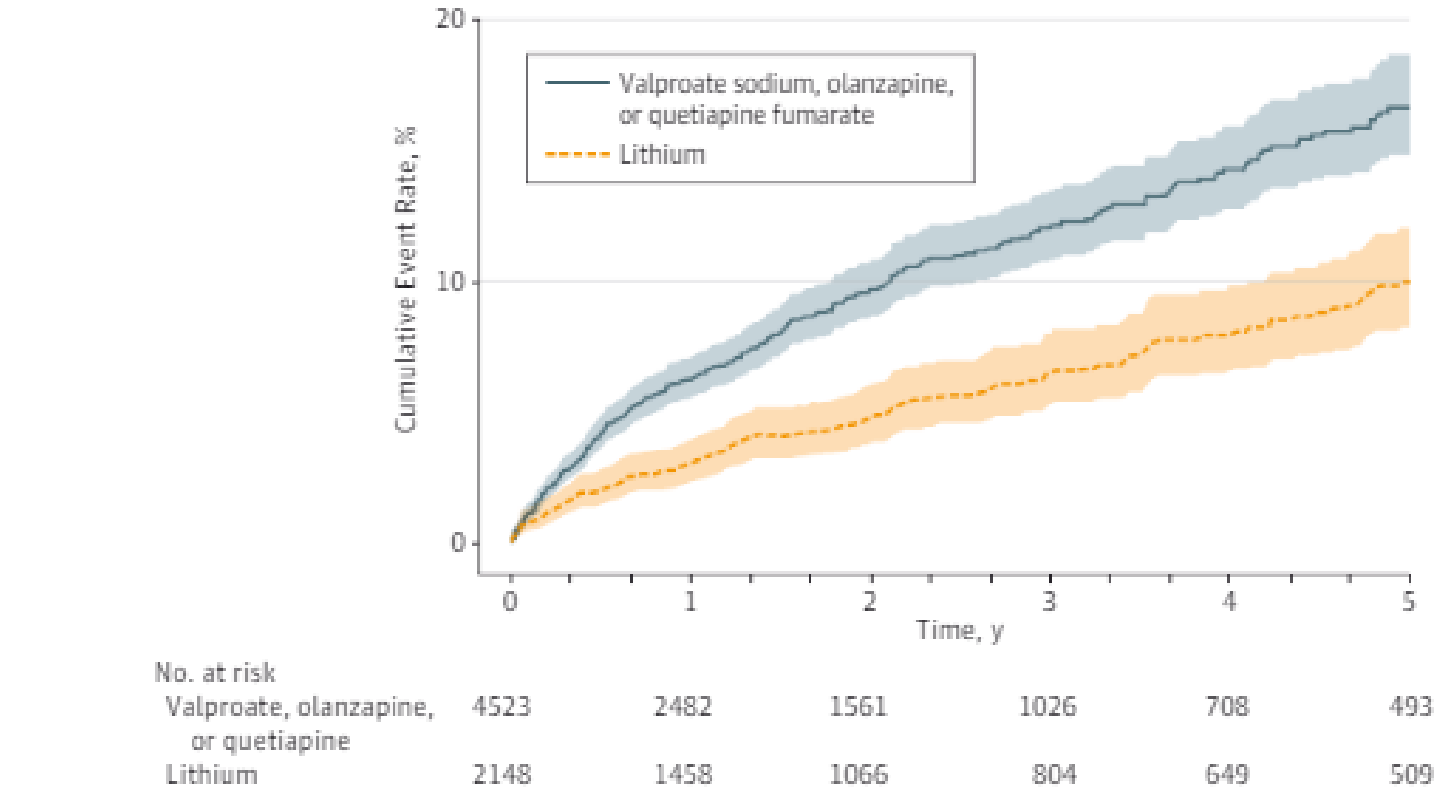
Suicide attempts

- Registry based study
- 826 hospitalised bipolar patients
- Lithium
 - Lower risk of suicide attempts (non significant)
 - Lower risk of suicide (univariate RR=0.39, p=0.03, cox HR=0.37, p=0.02)
 - Decreased all cause mortality by 49%

Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment

A UK Population-Based Electronic Health Records Study

Joseph F. Hayes, MSc, MBChB; Alexandra Pitman, PhD; Louise Marston, PhD; Kate Walters, PhD;
John R. Geddes, MD; Michael King, PhD; David P. J. Osborn, PhD



Shown are unadjusted Kaplan-Meier estimates of cumulative self-harm, with shaded areas showing 95% CIs.



Studies on the potential anti-suicidal effects of lithium as a trace element in drinking water

Year	Author	Measurement	Number of samples	Results
2009/Japan	Ohgami et al.	Li level in drinking water	18 municipalities	Standardized mortality ratio (SMR) negatively correlated with Li levels
2011/UK	Kabacs et al.	Li level in drinking (tap) water	47 samples from 47 subdivisions	No association between lithium levels in drinking (tap) water and mortality from suicide in the East of England
2011/Austria	Kapusta et al.	Li level in drinking water	6460 lithium measures of 99 Austrian districts	Suicide rate, SMR inversely associated with Li levels
2013/Greece	Giotakus et al.	Li level in drinking water	149 water samples from 34 prefectures	Tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water
2013/USA	Blüml et al.	Li level in public water	3123 lithium water samples, 226 counties	Higher lithium levels in the public drinking water were associated with lower suicide rates
2015/Italy	Vita et al.	Li level in drinking water	Review	Higher levels in drinking water may be associated with reduced risk of suicide in the general population

Li lithium

Lithium – mechanism of action

- Unknown
- Greater magnitude of effect on suicidality than depressive Sx

BUT

- Narrow therapeutic window
- Significant side effects
- Highly toxic in overdose

Anticonvulsants

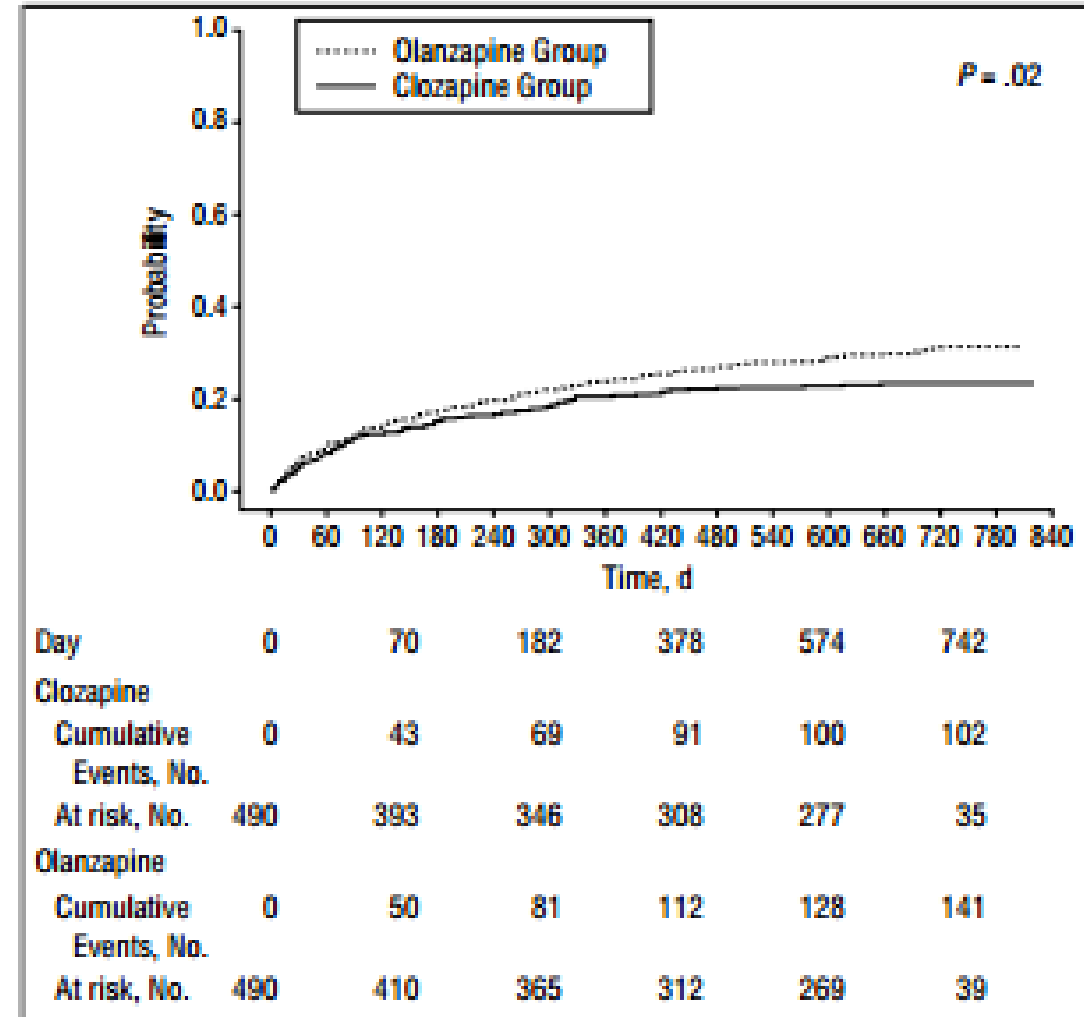
- Rates of suicide may be higher in those on sodium valproate (Goodwin 2003, Toffol 2015)
 - Confounding by indication
 - Increased risk associated with stopping lithium to switch to valproate
- No difference between anticonvulsants & lithium reported (Yerevanian 2003)
- Danish data suggest protective effect if compliant (Smith 2009)
 - Large sample
 - Healthcare records
 - Consistent collection of prescriptions associated with reduction in suicides
 - Similar reduction for lithium

Antipsychotics

- In RCTs little difference found when compared to placebo (Khan 2001)
 - All FDA registered trials of FGA or SGA v placebo
 - May simply reflect sample characteristics of those entering RCTs
- Retrospective database study suggested better compliance reduced risk
- Available data supports the protective effect of Clozapine
 - Those switched to clozapine demonstrated a reduction in suicide attempts (Meltzer 1995)
 - No follow-up data reported
 - Clozaril National Register (62,072 patients) – current users had lower mortality rate than past users
 - No control group
 - Discontinuation associated with poorer clinical outcome

Intersept (International Suicide Prevention Trial)

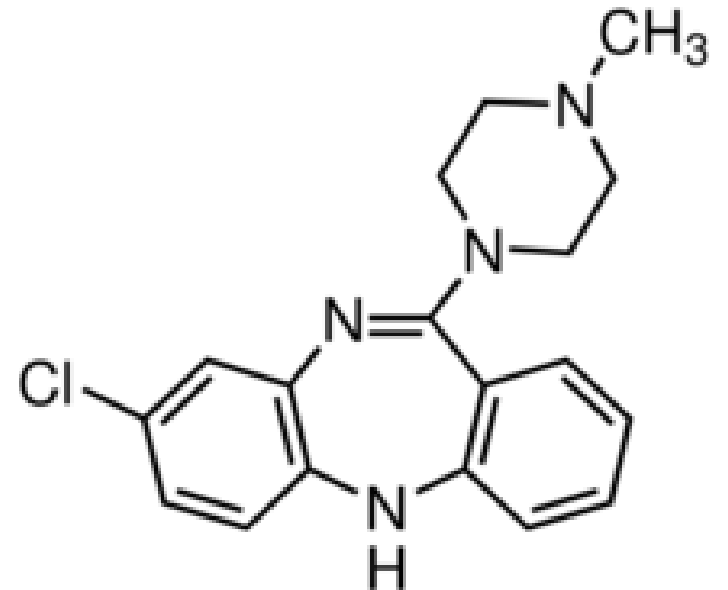
- Olanzapine v Clozapine
- Randomised multicentre trial
- Schizophrenia / Schizoaffective
- 980 patients
- 18 months
- Fewer suicides but small N



Kaplan-Meier estimates of the probability of a suicide attempt or hospitalization to prevent suicide.

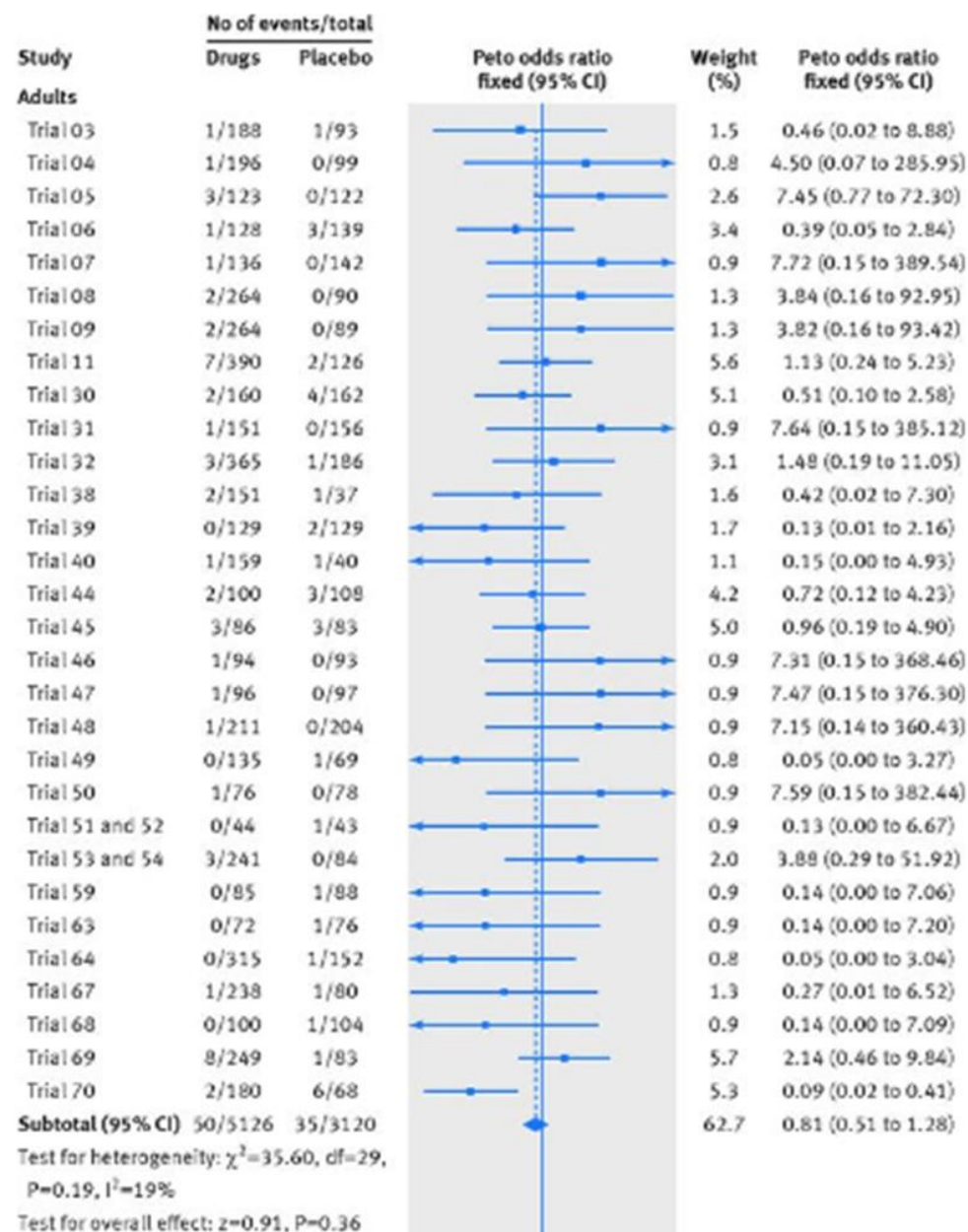
Clozapine - mechanism

- Closer follow-up due to monitoring for agranulocytosis
- Better symptomatic control
- Unique and complex pharmacology
 - Simultaneous modulation of multiple neurotransmitters
 - Hormones eg cortisol
 - Intracellular systems e.g NMDA receptor expression

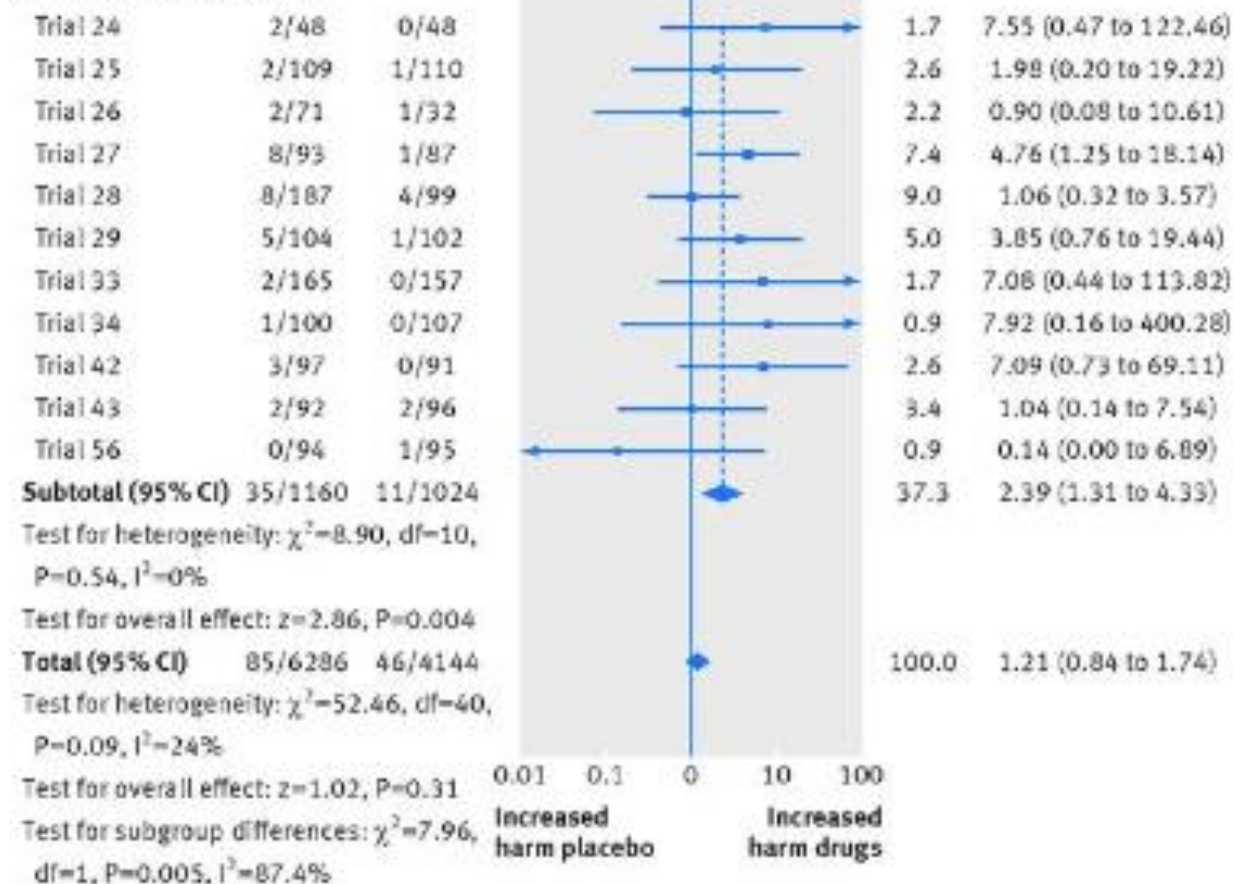


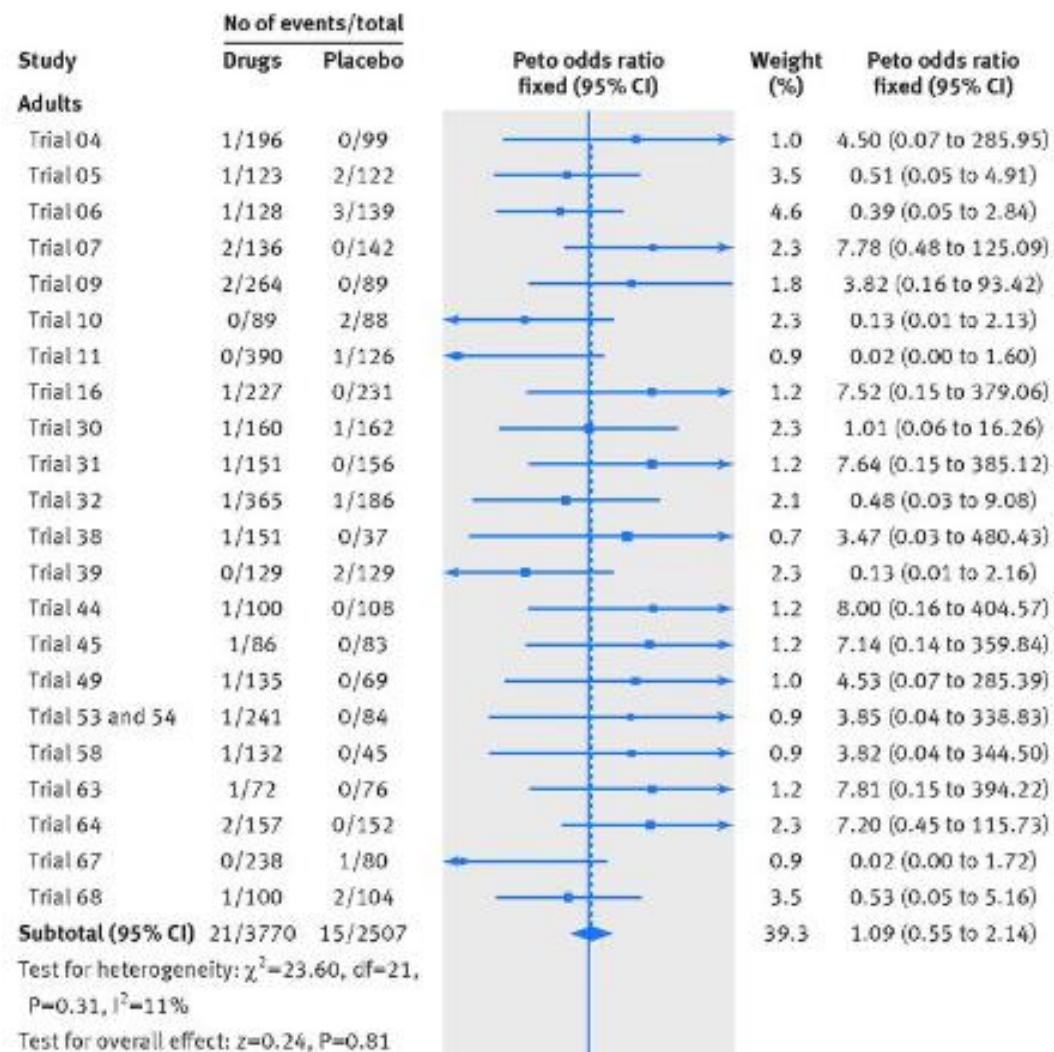
Antidepressants

- Controversial issue
- Ongoing debate especially in young people
 - Suicide 3rd leading cause of death in young people
 - 90% of depressive symptoms untreated at time of death (Leon 2004)

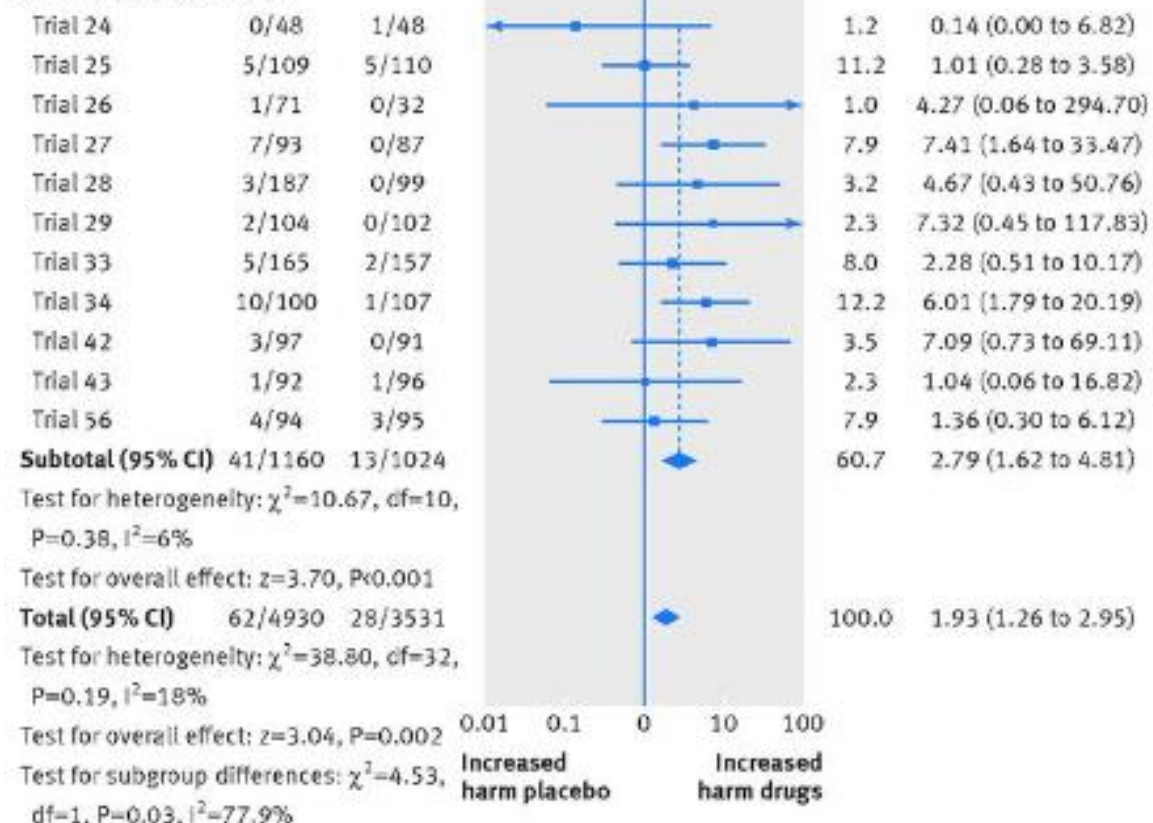


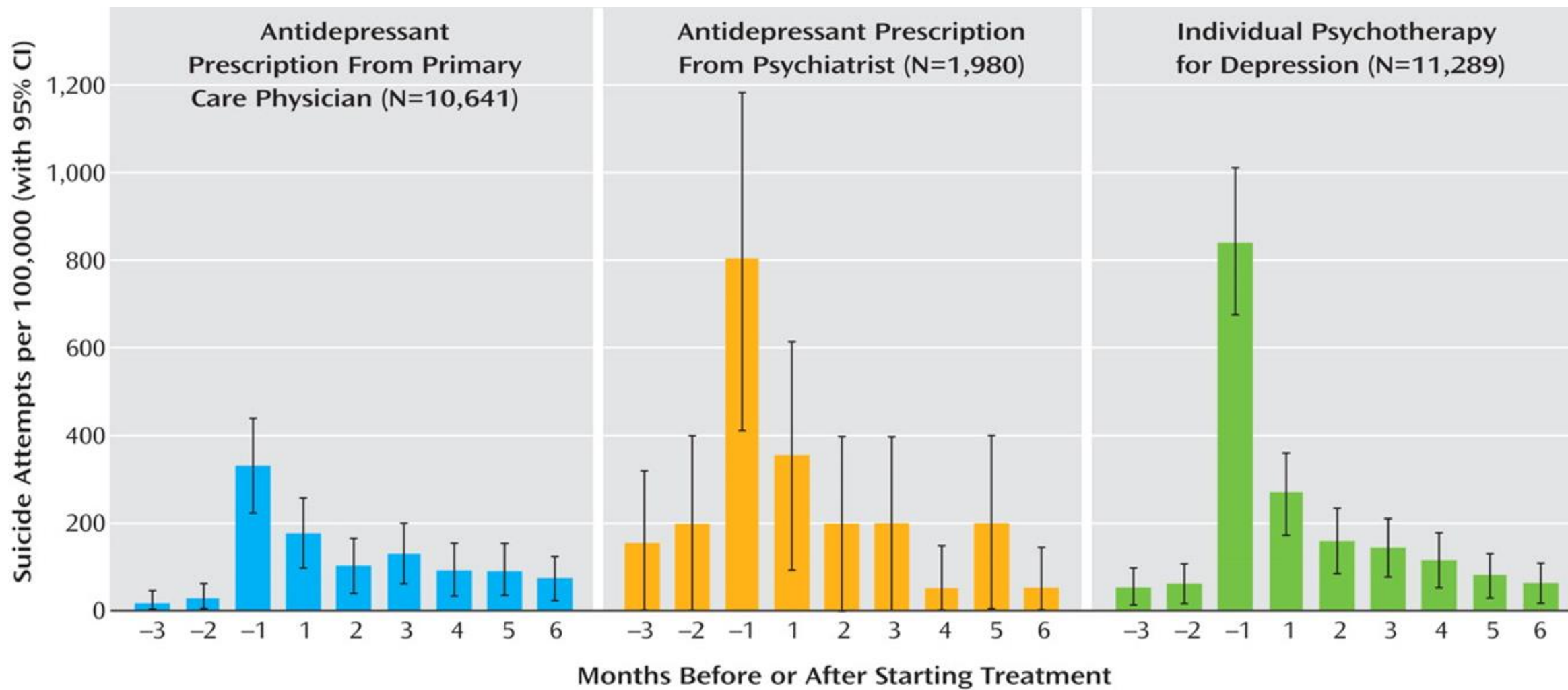
Children and adolescents



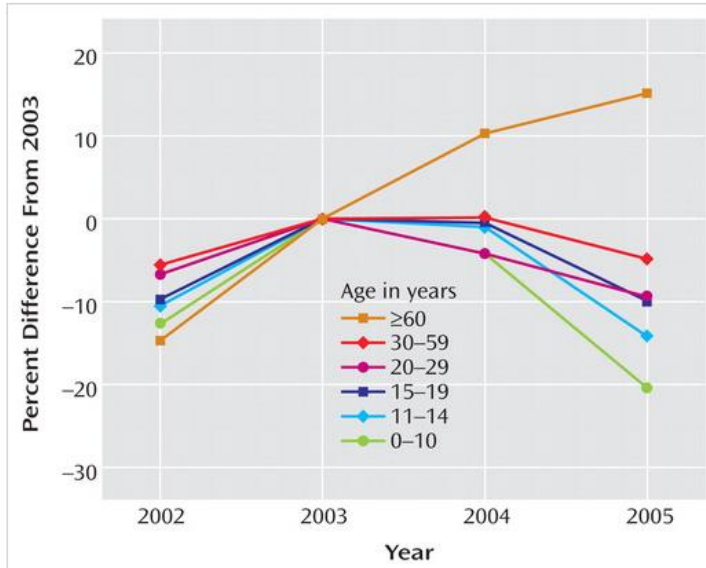


Children and adolescents



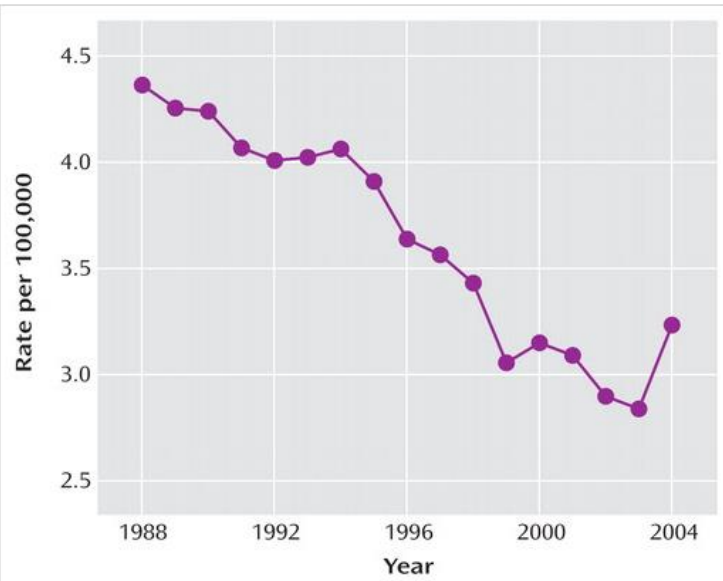
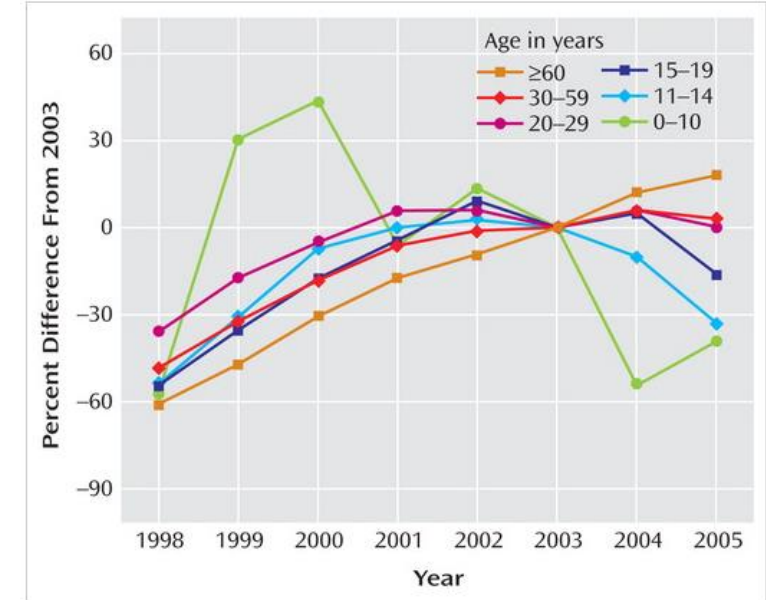


Impact of safety warnings

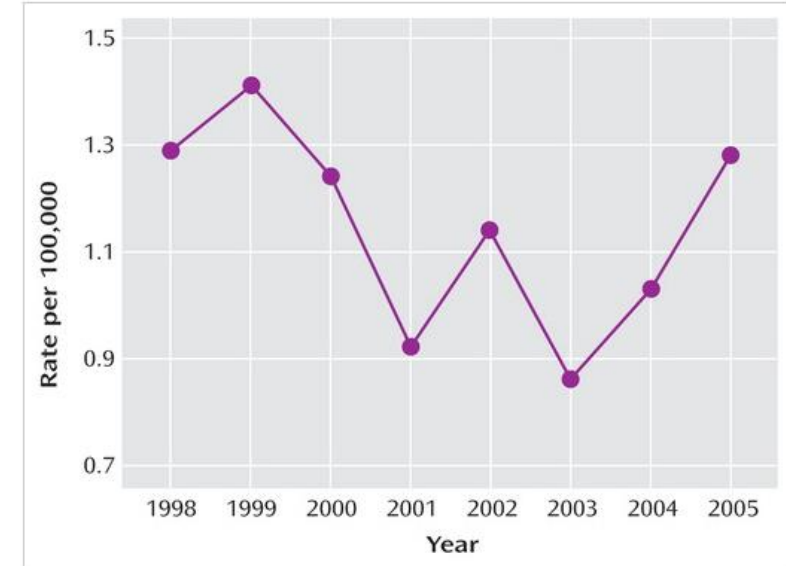


USA

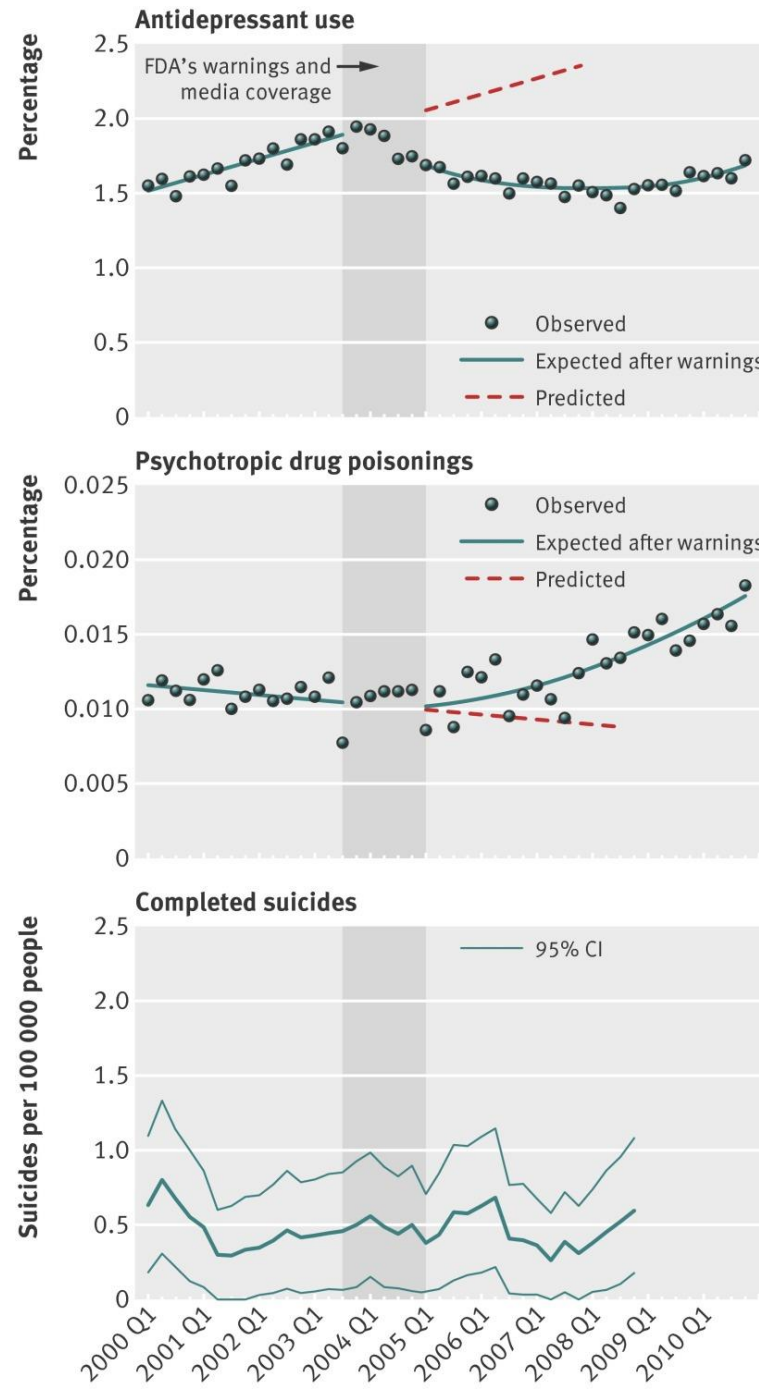
Netherlands



Gibbons AMJ Psych 2007



BMJ 2014
Healthcare claims data
11 health plans un the
US mental health
research network
Adolescents (10-17)



Antidepressants

Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose

Keith Hawton, Helen Bergen, Sue Simkin, Jayne Cooper, Keith Waters, David Gunnell and Navneet Kapur

Table 2 Fatal toxicity: rate ratios and relative toxicity indices for individual antidepressants based on rates of death (suicide and undetermined intent) in England and Wales, and prescription rates in the UK

	Both genders		Males		Females	
	Rate ratio (95% CI)	Relative toxicity index ^a	Rate ratio (95% CI)	Relative toxicity index ^a	Rate ratio (95% CI)	Relative toxicity index ^a
TCAs						
Amitriptyline	11.4 (10.3–12.6)	1.0	20.3 (17.7–23.2)	1.0	7.5 (6.5–8.7)	1.0
Clomipramine	14.1 (10.0–19.3)	1.2	15.9 (8.4–27.1)	0.8	13.3 (8.7–19.5)	1.8
Dosulepin	36.3 (33.4–39.3)	3.2	70.5 (62.9–78.8)	3.5	23.3 (20.6–26.2)	3.1
Doxepin	28.1 (17.6–42.6)	2.5	60.1 (32.0–102.7)	3.0	15.9 (7.3–20.1)	2.1
Imipramine	12.4 (8.1–18.4)	1.1	17.0 (8.5–30.4)	0.8	10.2 (5.6–17.2)	1.4
Nortriptyline	9.9 (3.2–23.2)	0.9	0	–	13.3 (4.3–31.0)	1.8
Trimipramine	15.0 (8.0–25.6)	1.3	35.1 (15.2–69.2)	1.7	7.8 (2.5–18.1)	1.0
All seven TCAs	18.8 (17.7–20.0)	1.7	33.7 (31.0–36.5)	1.7	12.6 (11.6–13.8)	1.7
SNRI: venlafaxine	5.3 (4.2–6.6)	0.46	8.7 (6.4–11.6)	0.43	3.5 (2.5–4.9)	0.47
NaSSA: mirtazapine	3.6 (2.1–5.7)	0.32	4.1 (1.8–8.1)	0.20	3.3 (1.6–6.0)	0.44
SSRIs						
Citalopram	1.7 (1.3–2.3)	0.15	3.3 (2.2–4.7)	0.16	1.0 (0.6–1.6)	0.14
Fluoxetine	0.5 (0.3–0.9)	0.05	0.6 (0.2–1.3)	0.03	0.5 (0.3–1.0)	0.07
Fluvoxamine	0	0	0	0	0	0
Paroxetine	0.5 (0.2–0.9)	0.04	1.1 (0.4–2.2)	0.05	0.2 (0.05–0.6)	0.03
Sertraline	0.7 (0.3–1.3)	0.06	1.1 (0.3–2.7)	0.05	0.5 (0.1–1.2)	0.06
All five SSRIs	0.9 (0.7–1.1)	0.08	1.6 (1.2–2.1)	0.08	0.6 (0.4–0.8)	0.08

TCAs, tricyclic antidepressants; SNRI, serotonin and noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; SSRIs, selective serotonin reuptake inhibitors.

a. Index of toxicity relative to amitriptyline.

Ketamine

- Widely used in anaesthesia
- Misused
- NMDA receptor antagonist
- Sub-therapeutic doses
- 6 treatment protocols of iv 0.5mg/kg (3 Rx) then 0.75mg/kg
- Emergent evidence base for treatment resistant depression
- Nasal administration currently being trialled.
- Side effects: dry mouth, tachycardia, hypertension, restlessness, visual disturbance, dissociation (usually short lived)

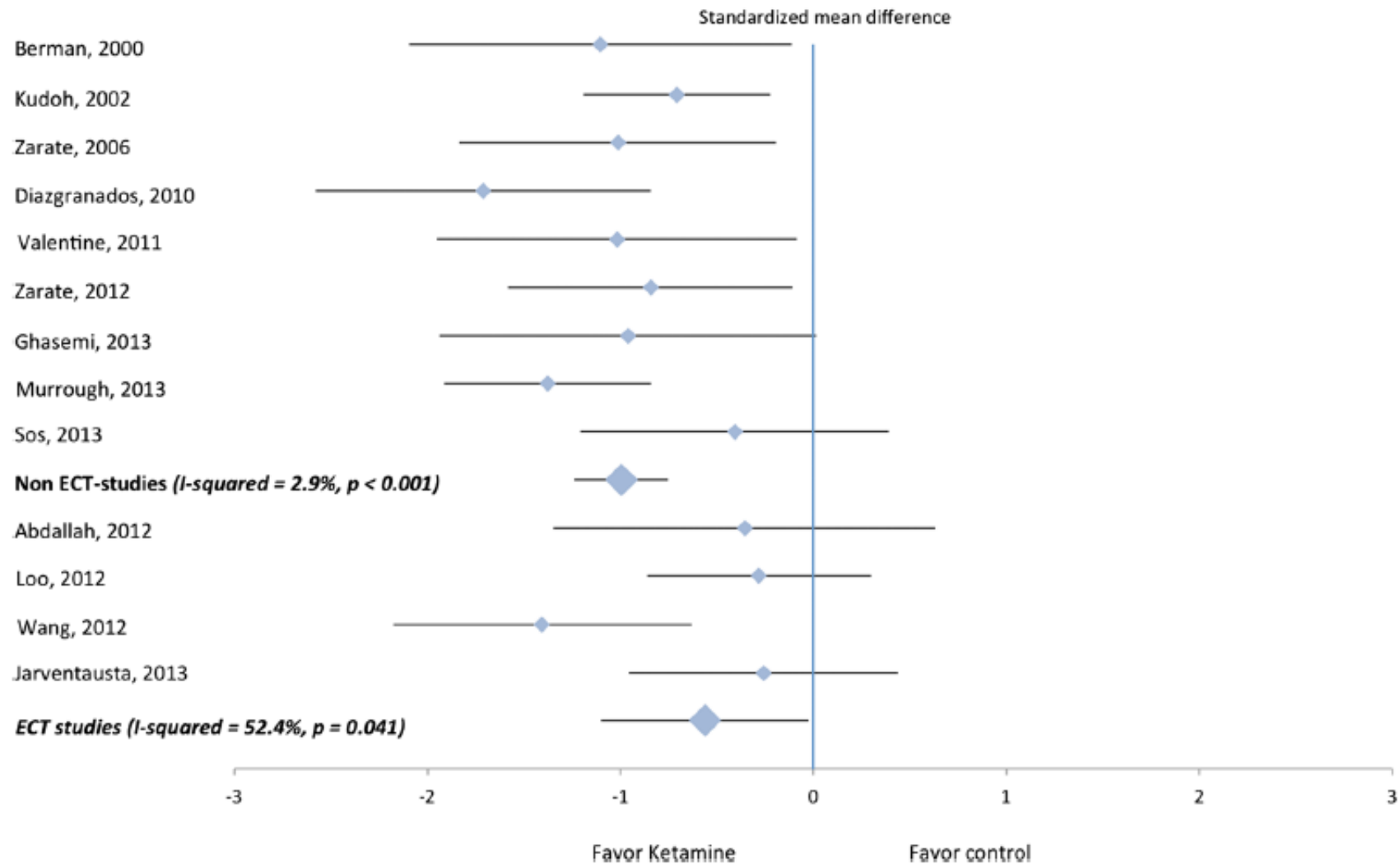
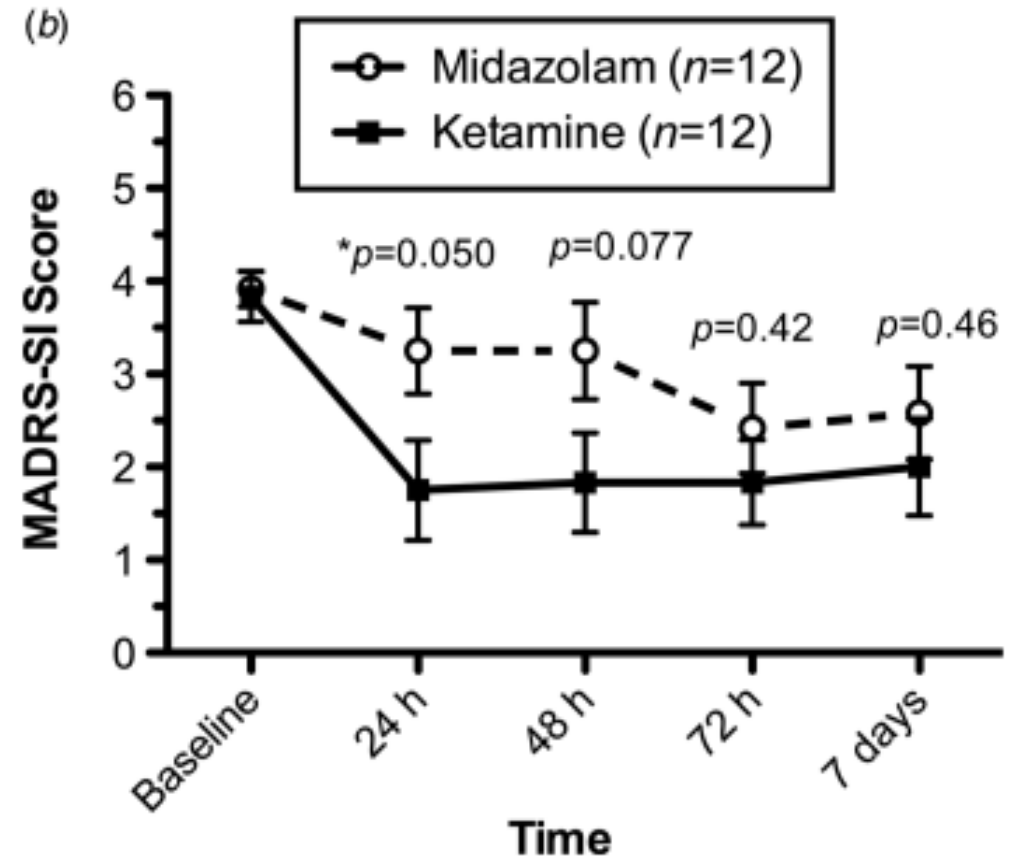
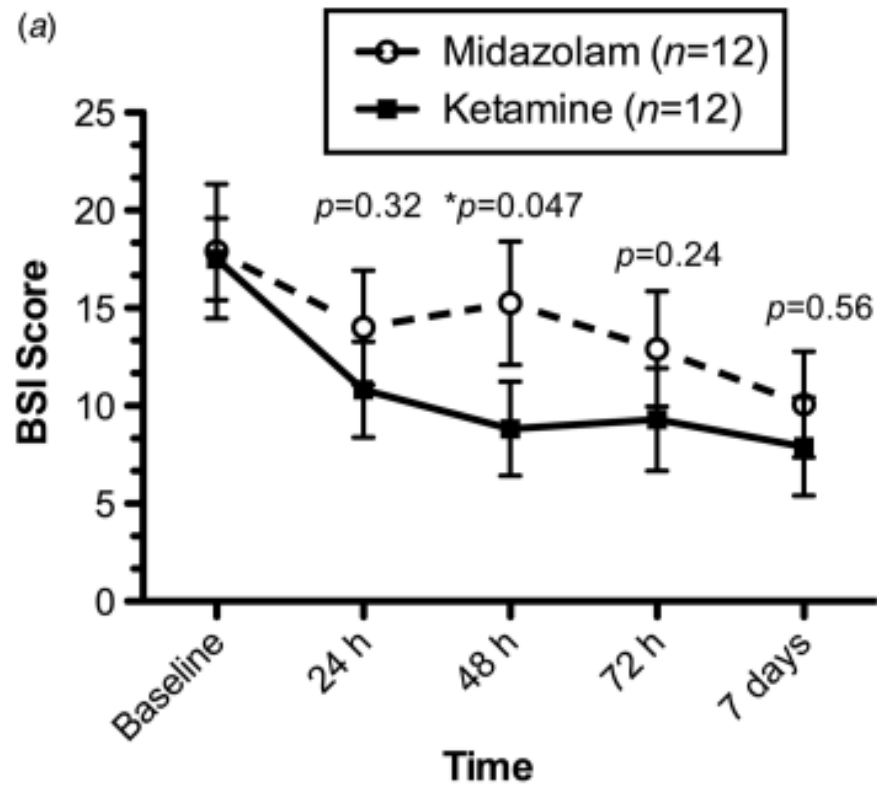


Fig. 2 Global ketamine's efficacy on depressive symptomatology in non-ECT and ECT studies. All depression assessments were made 24 h after administration in non-ECT studies

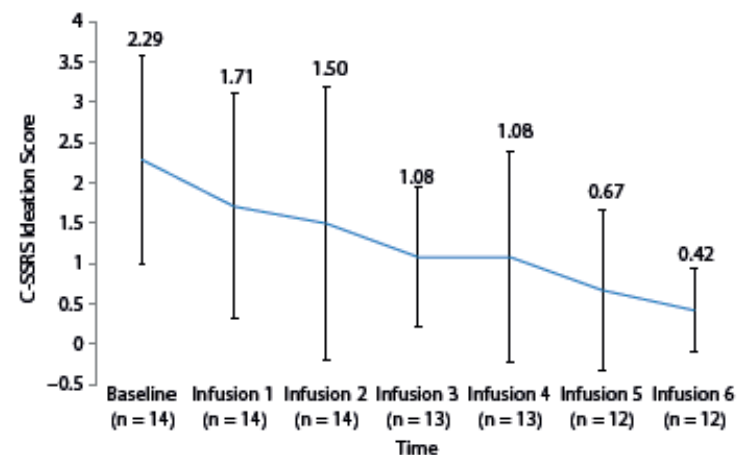
Single infusion (Murrough et al 2015)



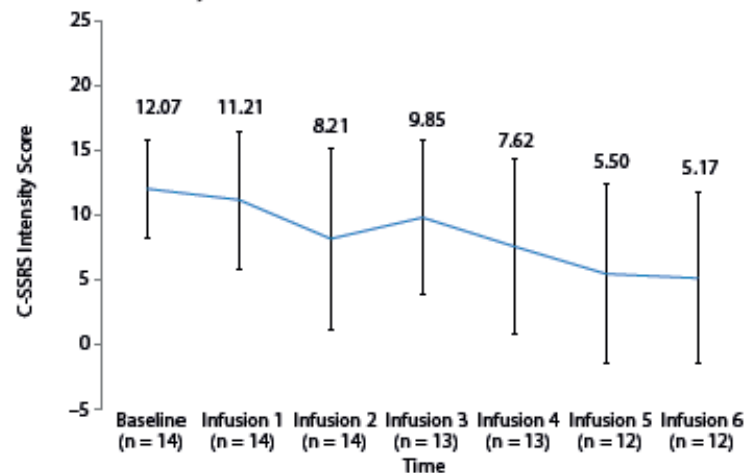
Ionescu et al 2016 J Clin Psych

- Open label study
- Intravenous ketamine
- 14 patients
- MDD with suicidal thoughts

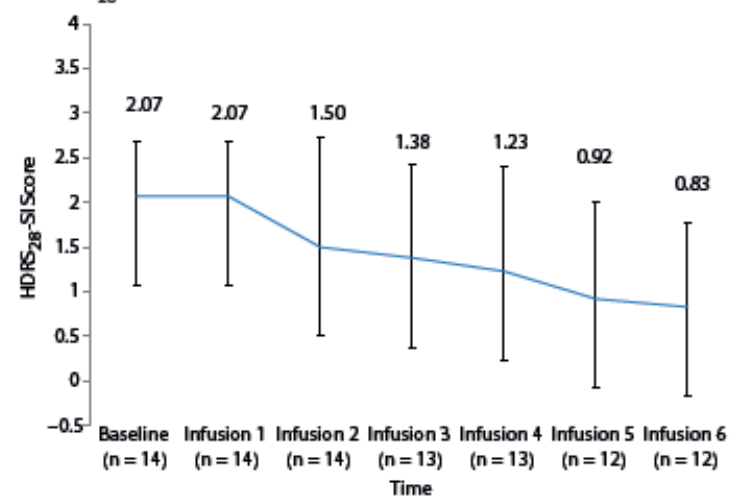
A. C-SSRS Ideation Scores



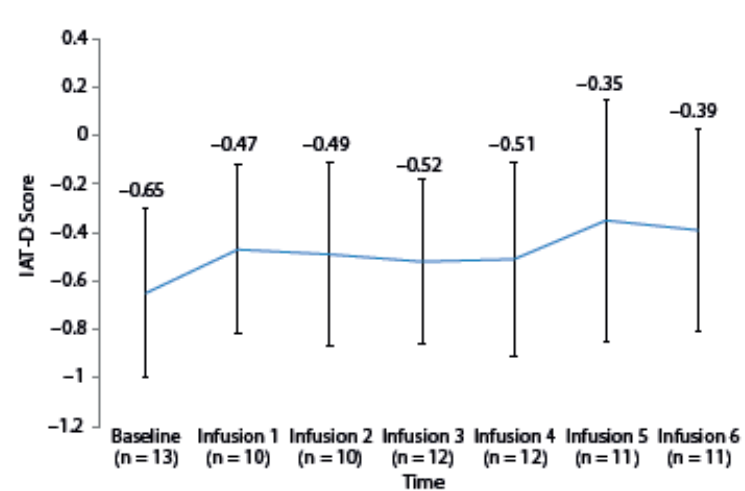
B. C-SSRS Intensity Scores



C. HDRS₂₈-SI Scores



D. IAT-D Scores



Mechanism

- Appears to alter a number of domains associated with suicidality
 - Anxiety
 - Anhedonia
 - Rumination – resting state DMN network data from healthy controls (DMN disruption associated with rumination)

Minor tranquilisers

- Epidemiological studies: increased risk of suicide
 - Poorly controlled for
 - Depression
 - Other psychiatric disorders associated with insomnia
- Suicides associated with single agent hypnotic overdoses

BUT

Insomnia is associated with suicidality

ECT

- No randomised evidence
- Expert consensus supports
- Limited role
 - Cost
 - Availability
 - Associated stigma
 - Involved process

Pharmacotherapy in borderline PD

- Flupenthixol (Montgomery & Montgomery 1982)
 - Reduction in self harm
 - Never replicated
- Paroxetine (Verkes 1998)
 - No difference in repetition of self-harm
 - In those with fewer than 5 past episode more effective
- Fluoxetine (Coccaro 1997)
 - May reduce aggression

Other possible compounds

Tiny doses of opioid could be first fast anti-suicide drug



- Double blind placebo controlled trial
- Suicidal patients(N=40)
- No hx of substance misuse
- sublingual administration
- 0.1 mg daily for 4 weeks
- in addition to current treatments
- Significant decrease in suicidal ideation

Yovel 2016 AJP

New scientist Feb 2016

Conclusion

- Good medication concordance is protective
- Lithium consistent protective effect
 - Largely limited to bipolar disorder
 - Side effect profile
- Relationship between antidepressants and suicidality remains contested
- Clozapine
- Ketamine
 - Promising findings
 - Duration of treatment effect unknown
 - May provide us with a tool to explore underlying biological mechanisms
 - IV administration limits use currently
- Buprenorphine

QUESTIONS