

Suicidal ideation and behavior as rare
adverse events of antidepressant
medication. New findings from AMSP.
The potential role of lithium

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Ref. Stübner S et al. Int J Neuropsychopharmacol 2018

Three modes of causal relation between drugs and suicide

- After hanging intoxication by tablets is the second most frequent way to commit suicide in Germany.
- Can the risk of suicide and the excess mortality of patients with affective disorders be lowered by psychotropic drugs ?
(Tranquilizer, neuroleptics, antidepressants , lithium , anticonvulsants ?)
- Is there a potential increased risk of depression, suicidal ideation and suicidal acts by regular medication with various compounds ? If so, which compounds ?

Is there any scientific evidence that antidepressants can lower the risk of suicide ? No !

Six negative controlled studies:

- 1. Gunnell D, Saperia J, Ashby D (2005) Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 330:385-389**
- 2. Hammad TA, Laughren TP, Racoosin JA (2006) Suicide rates in short-term randomized controlled trials of newer antidepressants. J Clin Psychopharmacol 26:203-207**
- 3. Khan A, Khan S, Kolts R, Brown WA (2003) Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 160:790-792**
- 4. Khan A, Khan SR, Leventhal RM, Brown WA (2001) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database. Int J Neuropsychopharmacol 4:113-118**
- 5. Khan A, Warner HA, Brown WA (2000) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry 57:311-317**
- 6. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B (2005) Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 330:396-402**

Consumption of antidepressants and suicide rates in Spain

(Arias et al. 2010)

A pharmacoepidemiological study in Castilla y Leon (Central Spain)

Objective: evolution of description of antidepressants and lithium 1992 – 2005, based on DDD

Results: antidepressant consumption increased 7-fold; the corresponding increase in costs was more than 10-fold. SSRI comprised 77% of total consumption. Lithium consumption increased by 76%, but plateaued in 2000.

No association was observed between antidepressant consumption and suicide rates.

Lithium in bipolar High-Risk-Patients

Toffol et al. 2015

- 826 bipolar pats. from Finland, hospitalized between 1996 and 2003 because of suicide attempt. Follow-up over 3.5 years. Focus : Suicide attempts, suicides, mortality related to treatment with either lithium vs. antidepressants, vs. valproate vs. benzodiazepines.

Findings:

- Lithium patients in comparison to non-lithium pats ::
 - much lower risk to die from suicide
(RR 0,39. CI 95% :0,17-0,93 ; li vs. Non-li)
 - non significantly lowered risk of suicide attempts.
- Lithium diminished the mortality from all causes by 49 % . (ref. Cipriani and IGSLI)
- Valproate, antidepressants and BDZ were associated with a comparatively increased risk of suicide attempts. (RR: 1,53.. 1,49...1,49)

Overview

- **Lithium** beyond any doubt **lowers the suicide risk and the excess mortality in all groups of affective disorders** down to the level of the normal population.
- **Valproate possibly lowers somewhat the risk of suicide attempts.** Suicides were prevented much less than by lithium.
- **Antidepressants do not lower the suicide risk** in patients with affective disorders.
- **Antipsychotics do not lower the suicide risk** .(Exception :Clozapin lowers the incidence of suicide attempts in schizophrenic patients.) Suicidal acts occur more frequently during neuroleptic medication than in lithium-or valproate medicated patients.

Does lithium save lives? ...Yes– but how many ?

(Joffe RT: J Psychiatry Neurosc 2004; 29: 9)

We calculated the potential reduction of suicides in Germany on the basis of data from the Epidemiological Catchment Area Study (ECA; Weissman et al. 1991) und epidemiological data from Denmark (Weeke 1979) and the findings of the IGSLI MORTA studies.

Assumption :

- ca. 50.000 persons received lithium prescriptions in 2001 within the German health scheme. (most likely a massive undertreatment.)
- 60 % of all suicides are observed in people with a depression. .

Result : 1,34 Suicide are to be expected for 827 persons of the general population matched as to gender and age with the 827 patients from the IGSLI study. **34 suicides are to be expected in a matched sample of untreated patients with affective disorders.** .In the **IGSLI sample** we observed 7 **suicides**, i.e. 27 of the 34 expected suicides did not occur..

Conclusion: 5 suicides per 1000 patients/ year can be prevented by regular lithium treatment. Thus, 250 suicides could be prevented year by year in Germany .

Induction of depressive symptoms and
„suicidality“ by legal medication ?

FDA lists nearly 60 compounds....



Potentially depressiogenic und suicidogenic compounds (FDA :n = 58)

In order of strength of evidence. (**convincing** - moderate evidence or case reports.)

Interferon alfa

Hepatitis B und C etc.

Mefloquin

Malaria-Prophylaxis

Efavirenz

HIV-Infektion

Finasterid

BPH, alopecia in men

Fluoroquinolones

Infectious diseases

e.g. . Ofloxacin®,

Isotretinoin

Severe acne

SSRI-Antidepressants

Depression, Anxiety etc.

Topiramate, Vigabatrin

Epilepsy

Bupropion, Vareniclin

Tobacco withdrawal

Statines

Hypercholesterinaemia

Kortikosteroids

Rheumatic disease etc.

„Suicidality“ as ADR of fluoroquinolones (FQ) .

54 cases of depression / suicidality reported to the Drug Commission within the German Spontaneous Reporting system.

	N
„Suicidality „	17
Observed for the first time under FQ medication in those patients	17
Suicidal ideation, wish to die.	11
Suicide attempt	2
Sucide	4

Wolfersdorf und Müller-Oerlinghausen, 1998



Suicidality induced by particularly SSRI antidepressants Long lasting controversy.

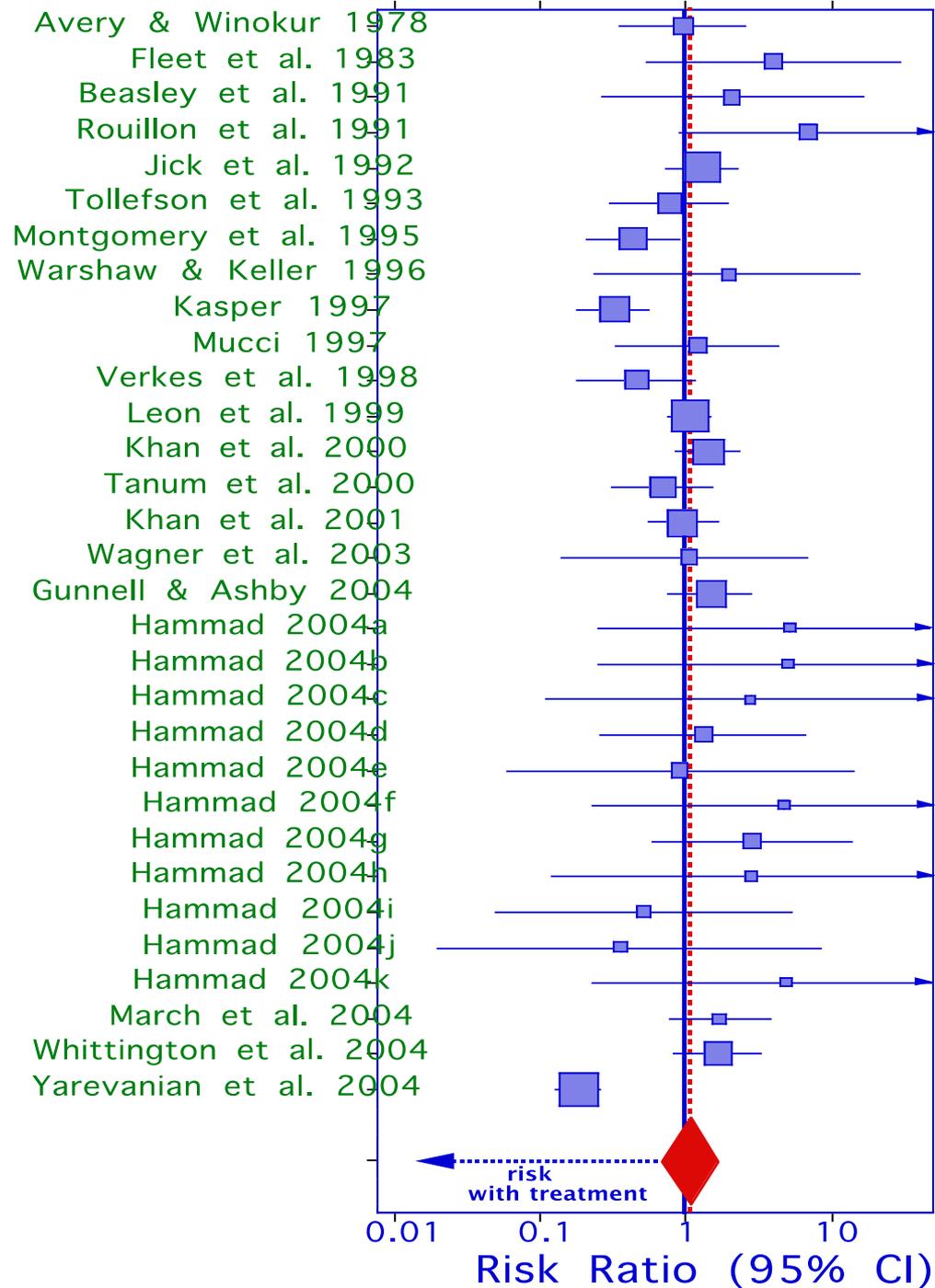
- Since the intriguing observations published by David Healy et al. in 2003 a long-lasting controversy originated .
- Possibly a rare event , difficult to be observed in medium sized RCTs. (particularly if study monitors are not made aware of such a potential causal relationship.
- However : Companies encountered difficulties when seeking approval for their new compounds. Agencies : Not sufficient evidence for clinical efficacy AND : suggestions of increased suicidality.
- FDA paper: risk might only be present in children and adolescents
- Meta-analyses inconclusive. (Ref. Braun et al. 2018 , IGSLI meeting)

Antidepressiva RCTs

Meta-Analysen Suizide und SV Erwachsene + Jugendliche

Pharmaka vs Kontrolle:
RR=1.06 [0.74–1.52]

Baldessarini et al. 2006





Suicidal behaviour possibly induced by antidepressants, in particular SSRI und SNRI

Report and Recommendations by the Drug Commission 2005:

ADR committee has discussed suicidal acts reported by German doctors between 1993 and 2004. In total 1.588, among them 111 related to tricyclics, 337 related to SSRI / venlafaxin

Unter allen Meldungen zu psychiatrischen Reaktionen von SSRI war Suizidalität häufigst genannt, gefolgt von Nervosität, Agitiertheit, Verwirrung, Angst. Nur 4% der Meldungen betrafen Altersklasse unter 19 Jahren. (Altersgipfel zwischen 30 und 49 Jahre)

In vielen Fällen zuvor niemals Suizidalität beobachtet. Sie wird als ausgesprochen ich-fremd und dranghaft erlebt. Typisches Prodrom ist psychomotorische Unruhe.

AMSP = Arzneimittelsicherheit in der Psychiatrie (Drug Safety in Psychiatry)

- Since 1993 continuous prospective monitoring for ADR caused by psychotropic and other drugs
- Assessment of severe and unusual ADR
- Mostly psychiatric inpatients are monitored
- Findings refer to everyday clinical practice.
- 63 hospitals mainly from Germany (44), Switzerland (10), Austria (9) participating
- Up to 25.000 patients monitored yearly.

AMSP

Main methodical features of AMSP.

- Monitoring by specialized psychiatrists.
- Continuous training of monitors
- „Severe event“ defined by our own manual.
- Hierarchical, sophisticated system of establishing the **causal relationship between imputed drug and adverse event.** (regional and central conferences
- Classification of likelihood of causal relationship grade1 –6.
- Special consideration of potential pharmacokinetic-genetic interaction
- Complete and detailed **assessment of total medication** in all AMSP centres, **twice per year.**

First AMSP Study

Stübner et al. J Clin Psychiatry, 2010

- **33 cases** (1993 – 2008) of suicidal ideation and suicidal acts,- evaluation whether event possibly or most likely be caused by imputed drug extremely conservative. Only if all other causes could be excluded with sufficient certainty.
- **Very few cases caused by tricyclics**. Mostly SSRI/SNRI
- Prominent clinical features : restlessness, impulsiveness ,**ego-dystonic thoughts or urges** preceded suicidal act or accompanied it.
- **First published study in which single cases have been prescribed in detail.**

Antidepressants and Suicidality. .

Replication study within AMSP

(Stübner et.al., Int J Neuropsychopharmacol , 2018)

- Within the AMSP system 220.000 documents of psychiatric patients hospitalized between 1993 and 2013 and having been treated with antidepressants were screened for the occurrence of most likely drug related suicidality. .
- 83 such cases acc.to extremely conservative criteria were found in the data bank. Suicidal ideation : 44; suicide attempts : 34 ; suicides : 5 cases had been consented and documented. The proportional incidence was much higher under SSRI/SNRI (63 cases) than under tricyclic medication (3 cases)
- *It can be assumed that in spite of prospective monitoring there exists an unknown dark figure. True incidence might be much higher. T*

AMSP Replication Study. Contd.

- **Time course** of adverse events : 71 % of the events of suicidality occurred during the first 7 days after start of medication or increase of dosage.
- **Prodromal symptoms**: Unrest , increased impulsivity.
- As in the former study and in the cases described by the Drug Commission suicidal ideas were often be described as **urging, ego-dystonic and they occurred often in patients who never before had experienced such symptoms.**

Protective role of lithium within the AMSP cohort ?

- Division of all cases of antidepressant treated patients with any kind of ADRs into cases (83 cases of suicidality) and „non-cases“ (4.294 = patients with any kind of ADR except suicidality.) ref. Moore et al. 1997) Calculation of reporting odds ratio as a measure of disproportionality.
- To note : There is no patient with antidepressant plus lithium only medication in the cases group, whereas there are 45 patients with such combination in the non-cases group.--- Furthermore: there is only one case (1.2 %) of lithium with polypharmacy in the cases group whereas there are 395 such cases (9.3 %) in the non-cases group.
- This could be interpreted as a potential suicidality preventing effect of lithium , even in drug combinations.

Finis

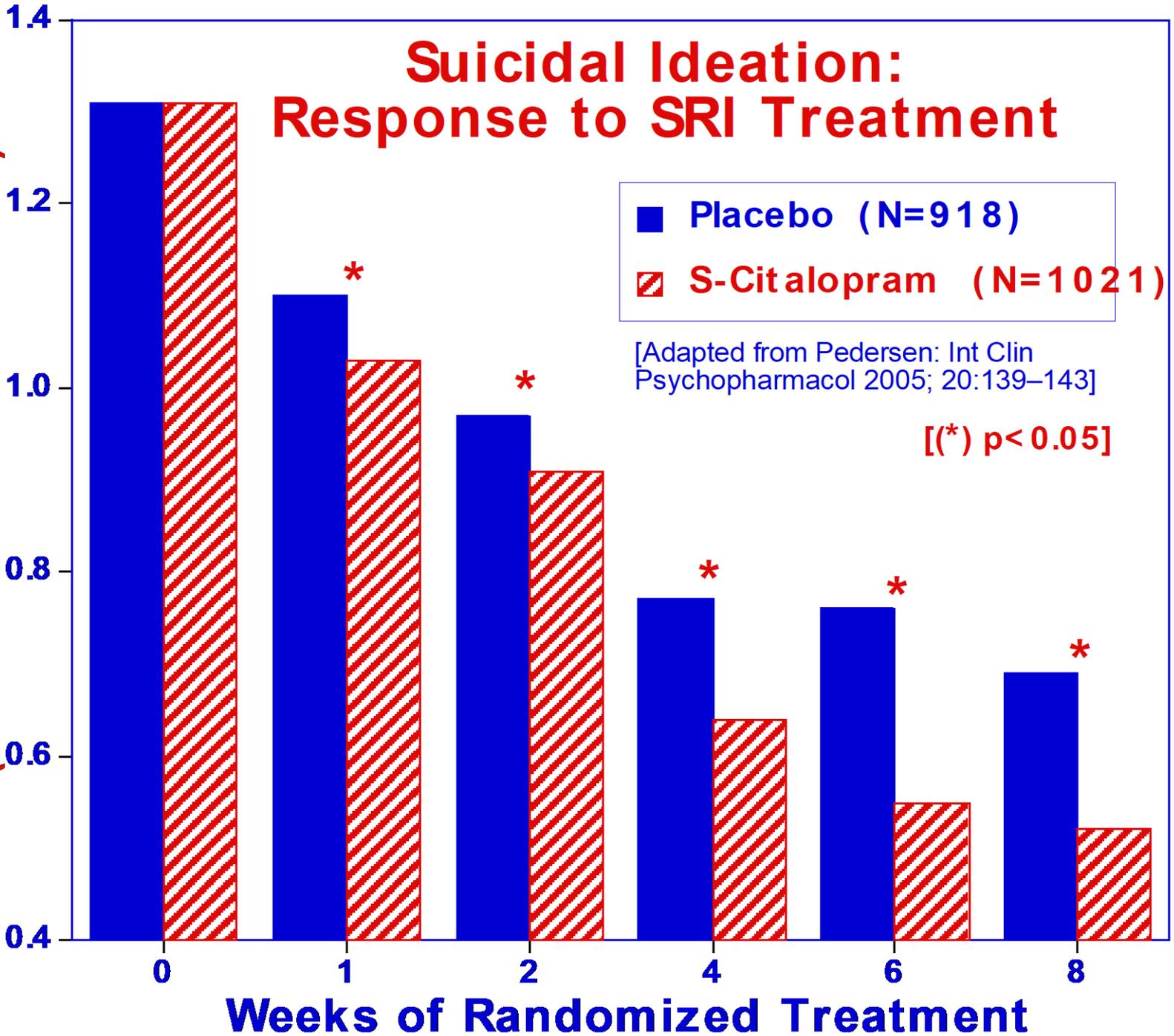
Antidepressants and Suicide: What is the balance of benefit and harm?

(Gunnell D and Ashby D: Br Med J 2004; 329: 34-38)

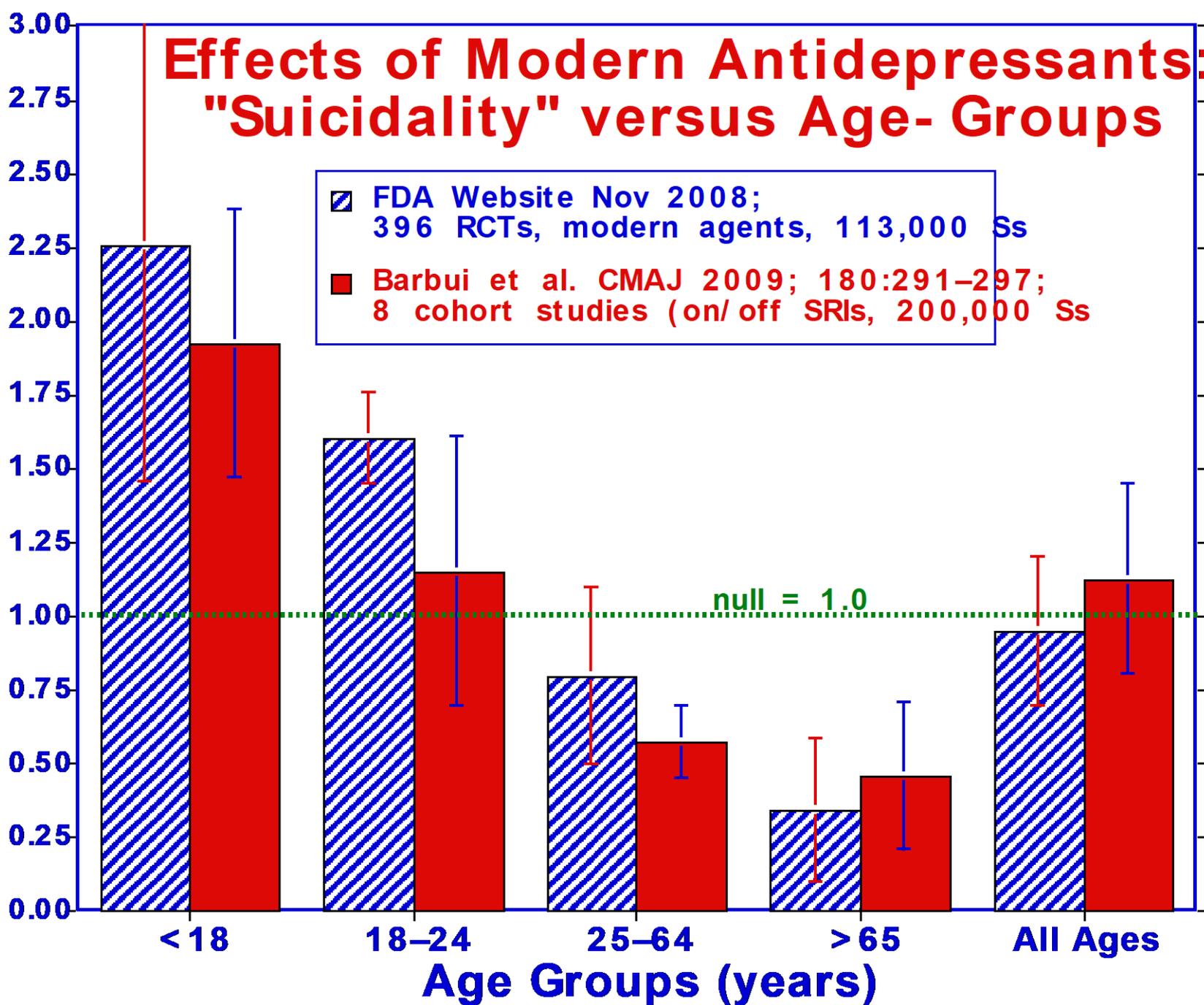
- „Direct evidence that antidepressants prevent suicide is hard to find!“
- Some „studies conclude that recent rises in AD prescribing have contributed to falls in suicides. Interpretation of these findings is not straight forward.“
- Toxicity: „Increased SSRI prescribing has not been accompanied by a fall in use of tricyclics.“
- Suicidality induced by antidepressants? „Any antidepressant induced suicides maybe offset by the beneficial effects of antidepressants on depression and long-term suicide risk associated with untreated depression. The balance of risks and benefit may vary depending on an individual underlying suicide risk. For patients with conditions that have a high risk of suicide, such as severe depression, the risk-benefit balance maybe more favourable than for patients with conditions such as anxiety and mild depression in which suicide is rare. It is in these lower risk conditions, however, that much of the recent rise in prescribing has probably occurred.
- „Long-term studies are required to assess the effect on population health of recent rises in antidepressant prescribing.“

Suicidal Ideation: Response to SRI Treatment

Suicidal Ideation
(Mean MADRS Item-10 Score)



Effects of Modern Antidepressants: "Suicidality" versus Age-Groups





Lithium – Mortalitätssenkende Wirkung: Naturalistische und kontrollierte Studien der 90er Jahre

IGSLI-Studien (Müller-Oerlinghausen et al. 1992, 94, 96; Ahrens et al. 1995; Wolf et al. 1996):

- suizidbedingte Mortalität im 1. Jahr noch 16-fach erhöht
ab 2. Jahr nicht mehr erhöht

M.A.P.-Studie (Thies-Flechtner et al. 1996):

^ Li* vs .CBZ vs.AT :

- Lithium: während 2,5 Jahren keine suizidalen Handlungen
- Carbamazepin: 4 Suizide, 5 Suizidversuche

Metaanalyse (Tondo et al. 1997) über 17.000 bipolare Pat.:

- ohne Lithium 8,6-fach erhöhte Mortalität als unter Lithiumtherapie