The Pharmacological Treatment of Suicidality – Where are we now?

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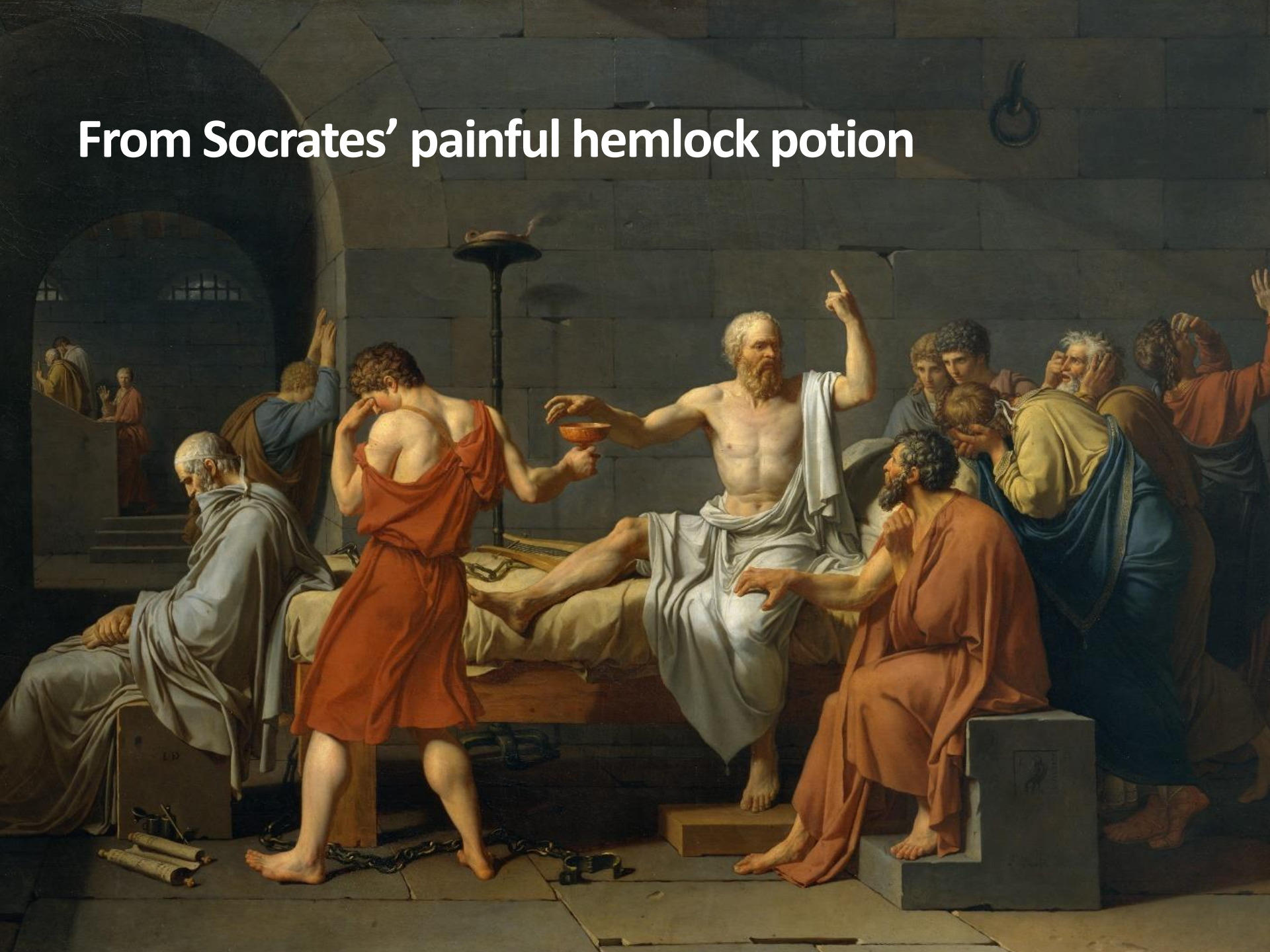

From Socrates’ painful hemlock potion

DIGNITAS

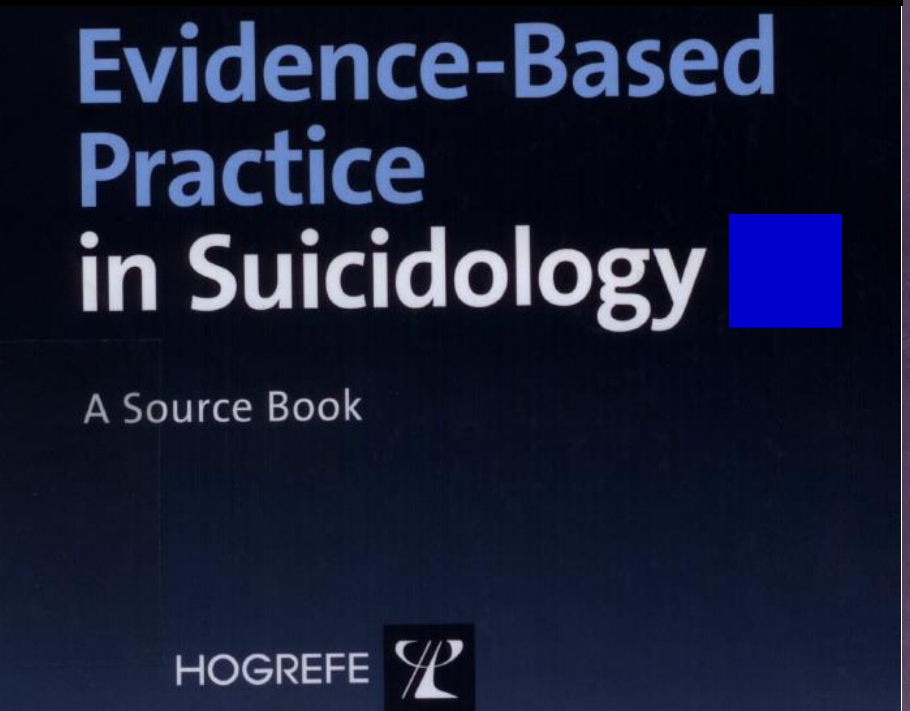
To live with dignity

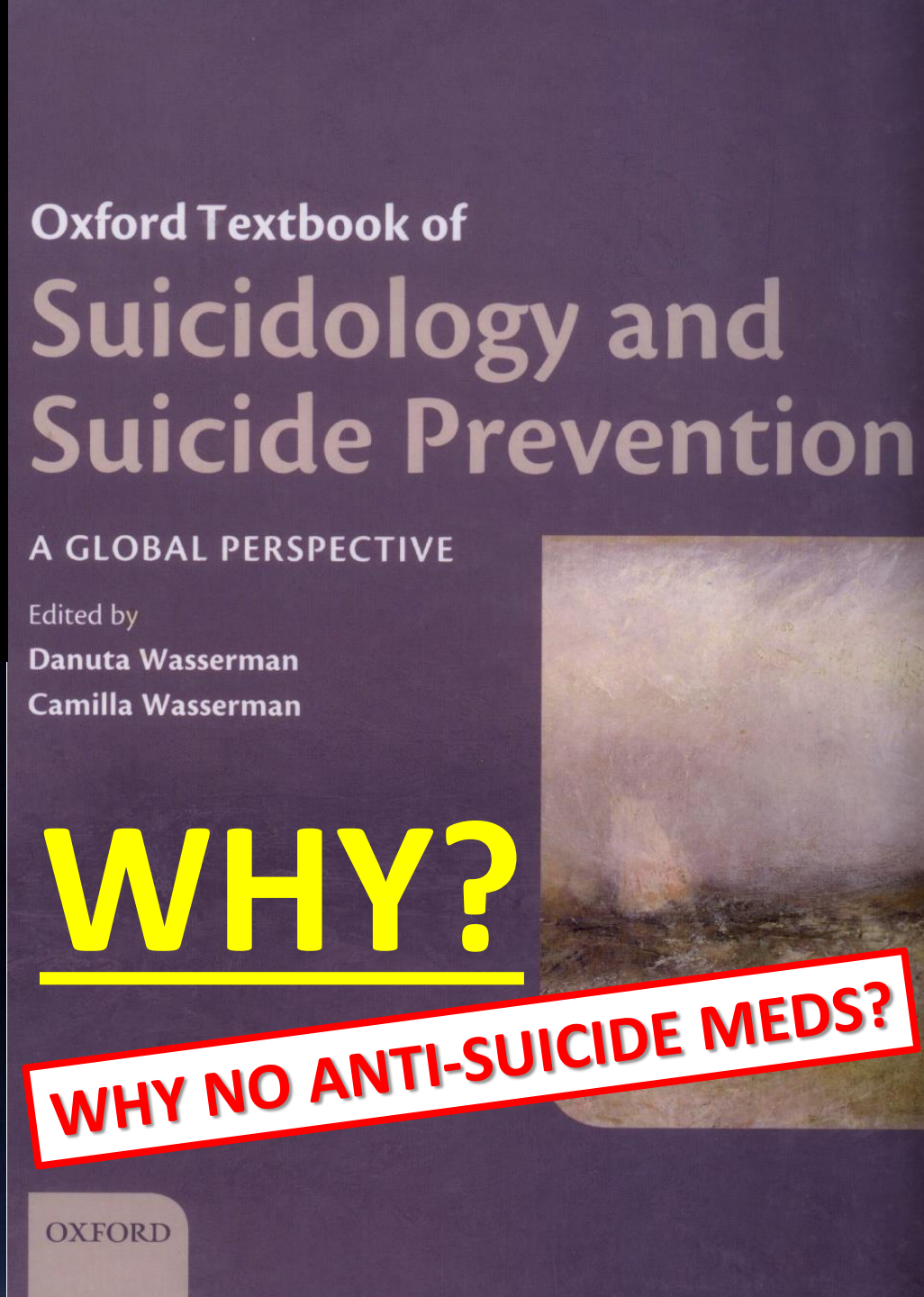
To die with dignity

To Dignitas' peaceful pentobarbital euthanasia

- People have used medications to end their lives
- -- May medications also be used to prevent suicide?

- Compared to –
  - -- the pharmacological treatment of most mental disorders
  - -- and the psychological treatment of suicidality
- **The pharmacological treatment of suicidality is still in its infancy**





WHY?

WHY NO ANTI-SUICIDE MEDS?

WHY NO ANTI-SUICIDE MEDS?

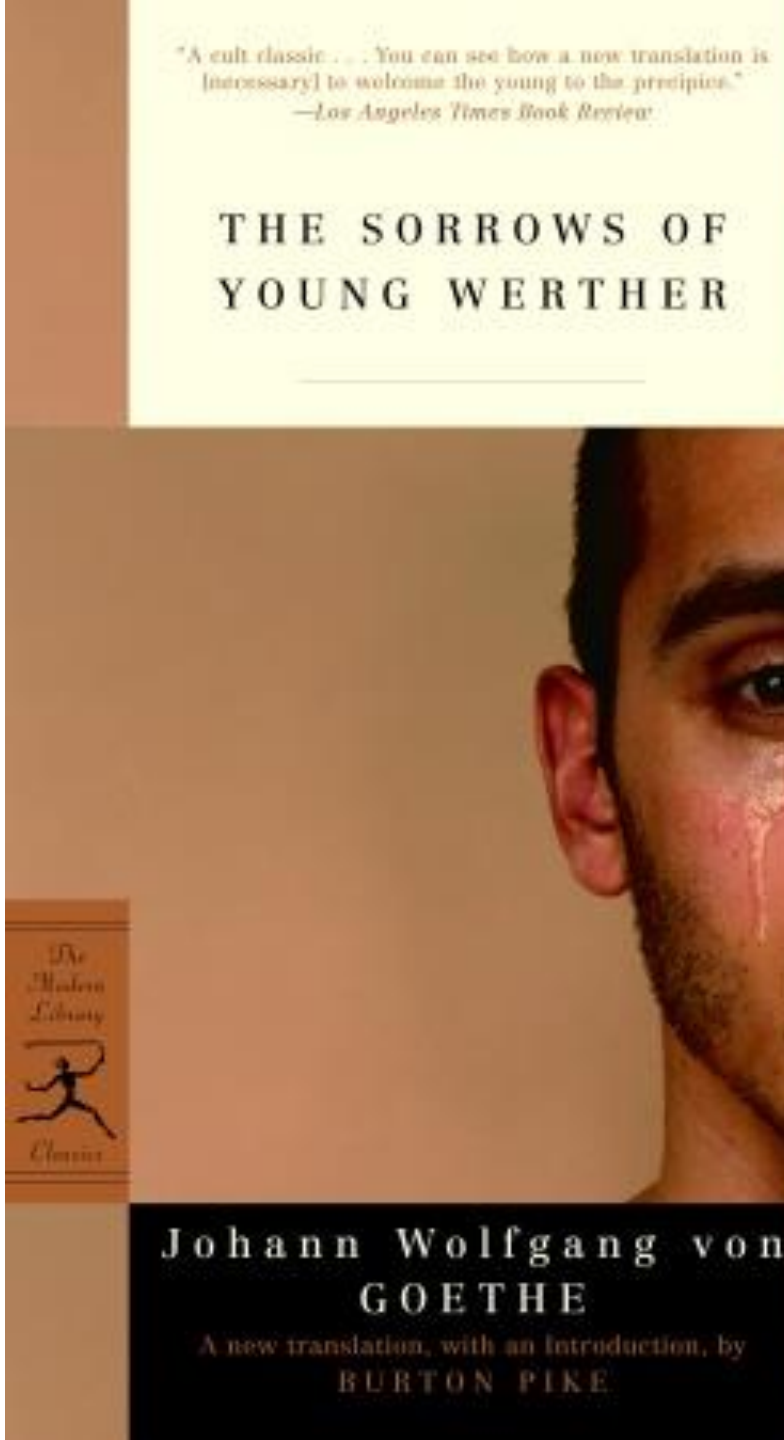
(1) No animal model

- Suicidality – the desire to kill oneself – is probably a heterogeneous, uniquely human phenomenon
- Suicidality requires complex cognitive capabilities:
- **Reflexive awareness**
  - "I exist, but I may also not exist"
- **An understanding of time as linear and unidirectional**
  - "I exist now, but soon I will not exist"

WHY NO ANTI-SUICIDE MEDS?

(2) "Lost in DSM"

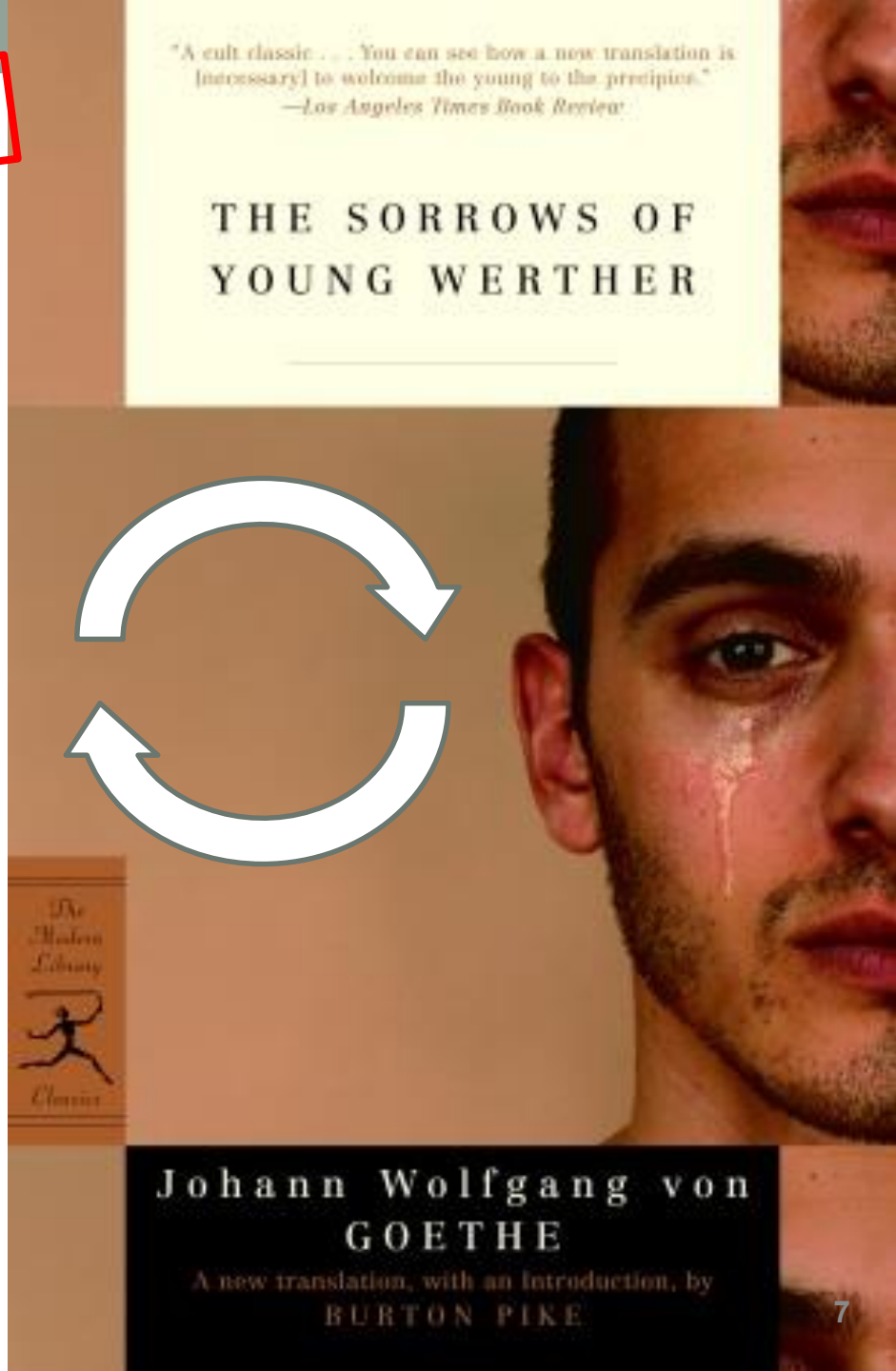
- Suicidality is **NOT** considered a clinical entity in its own right
- Appears only as a **SYMPTOM** of other DSM-5 disorders, like MDD and BPD
- In 696 pages of DSM-5 Section II text, **suicidality** is mentioned only **22 times**
- Even this is a vast improvement over previous DSM editions:
  - "DSM-5 shines a spotlight on suicide" David Kupfer MD, Chair, DSM-5 Task Force
- However, **suicidality** appears as a **SYMPTOM** of only **4** DSM-5 disorders
- **MDD, Bipolar I, Bipolar II, BPD**



WHY NO ANTI-SUICIDE MEDS?

- **Two pivotal questions:**
- (1) Is suicidality **only** a symptom of depression (or BPD)?
- (2) Can suicidality **only** be treated by treating depression (or BPD)?

- In my opinion, we have trapped ourselves and our patients in a vicious cycle:
- Until we view suicidality as **a problem in its own right**, how will we develop focused, effective treatments against it?



Even if you consider suicidality to be only a **symptom** of depression/BPD, rather than a clinical problem in its own right, "**symptomatic treatment**" may be life-saving

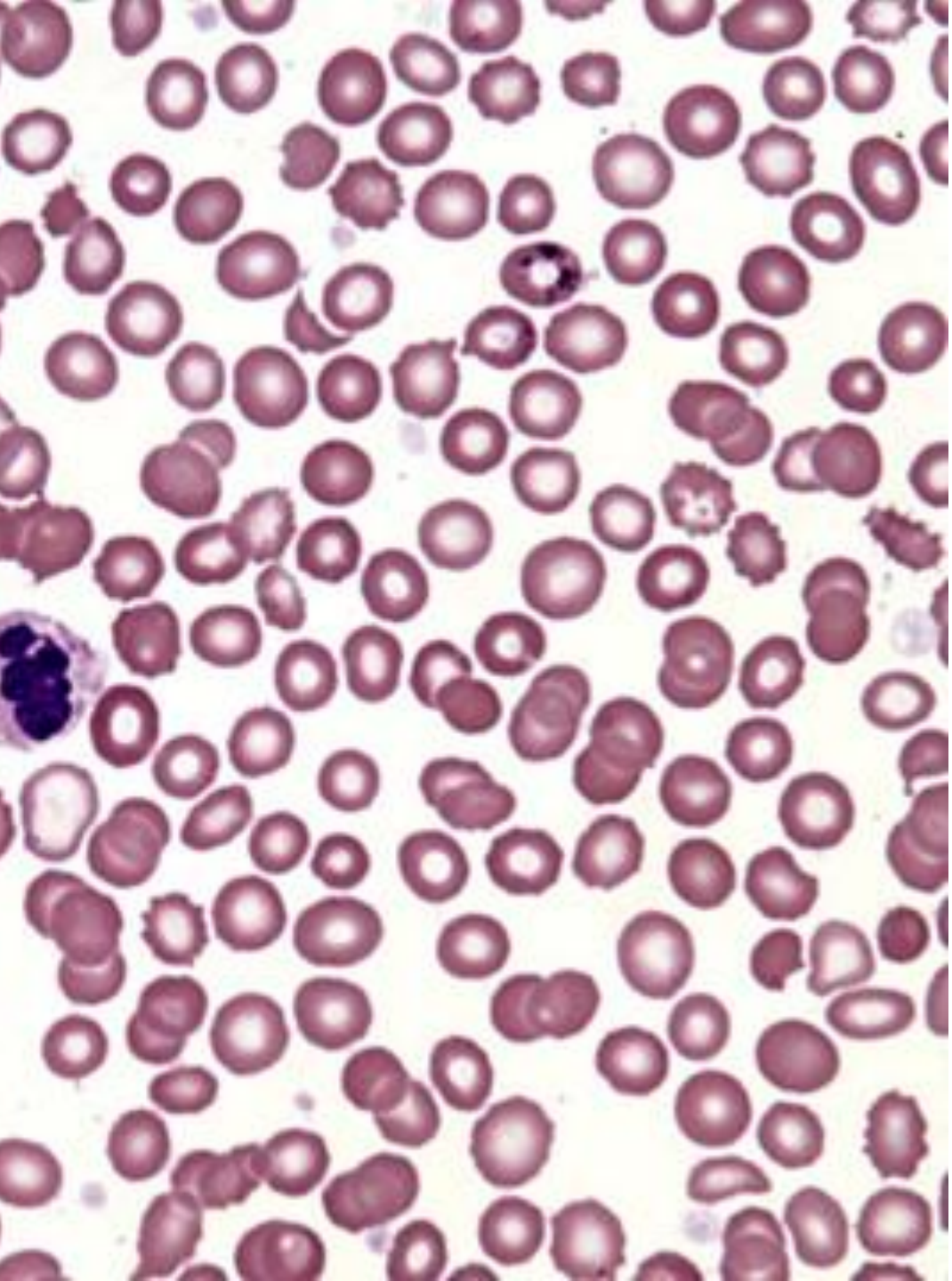
- It may not be enough to "treat the underlying disorder" (MDD/BPD)
- There are examples in medicine of **clinical problems** that are not disorders in their own right, but rather **symptoms** of other disorders/diseases
- Nevertheless, they are the targets of focused, short-term **symptomatic treatments** that can be life-saving
- Examples:

FEVER **ANEMIA**

Fever: a symptom, not a disease/disorder

- Fever is not a disorder but a symptom of --
  - Infections (viral, bacterial, fungal, parasitic…)
  - Inflammatory and auto-immune disorders
  - Neoplasms
  - Drugs, poisoning, FMF, PE…

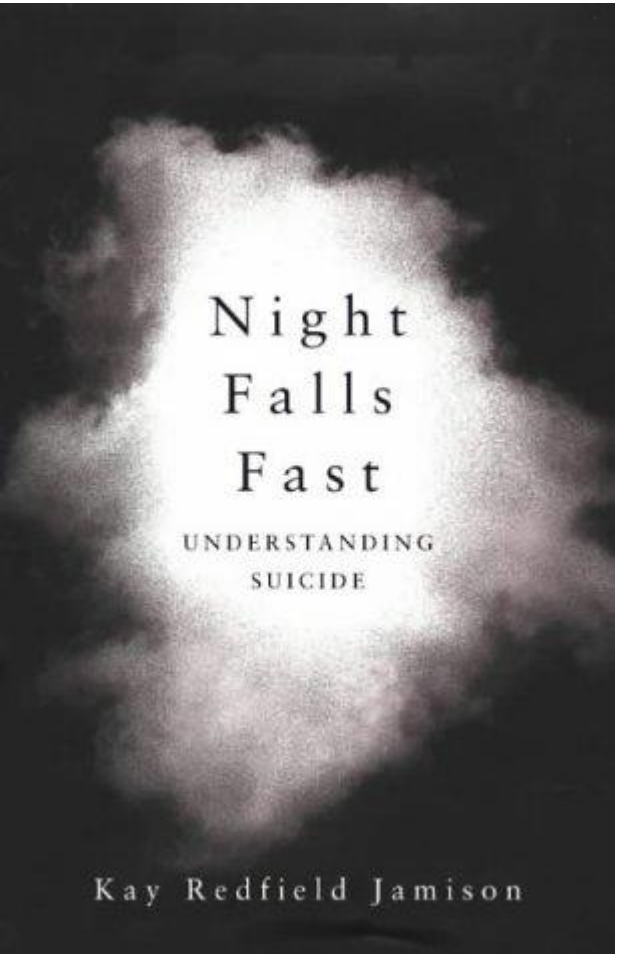
- But fever may become a life-threatening problem in its own right
- Symptomatic, sometimes life-saving Rx:
- **NSAID's, Acetaminophen**



Anemia: not a diagnosis

- Anemia is a symptom of --
  - Iron or B_{12} deficiency
  - Auto-immune disorders
  - Occult GI bleed
  - Neoplasms
  - Coagulopathies
  - Thalassemias, etc…
- But anemia may become a life-threatening problem in its own right
- Acute, symptomatic, sometimes life-saving Rx:
- **Blood transfusion**
- What about suicidality?

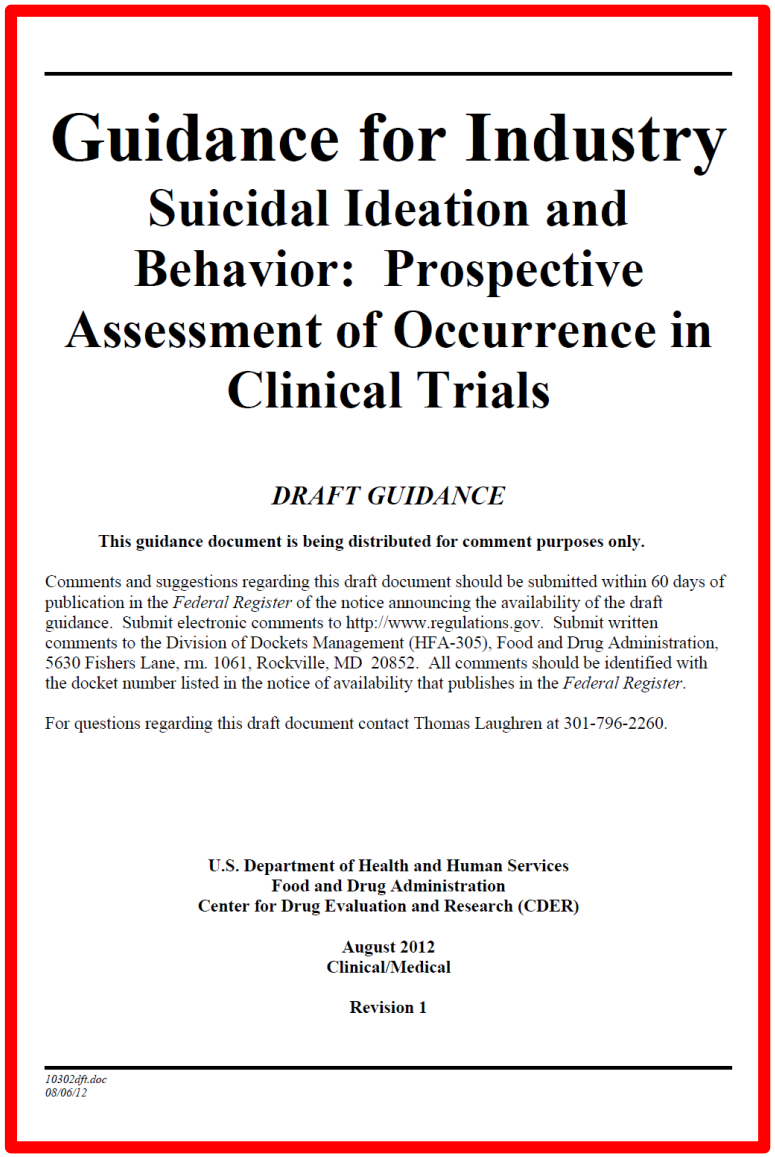
Suicide has many causes but only one outcome; to avoid that outcome, suicidality must be addressed as a problem in its own right



- "Suicide is a particularly awful way to die; the mental suffering leading up to it is usually prolonged, intense, and unpalliated…" (Kay Redfield Jamison PhD)
- Most suicide victims kill themselves not because they want to die, but because they want to stop their suffering
- There are many causes and risk factors for suicide, but among the most important are **mental pain** and **depression/hopelessness**
- Given the importance of depressive feelings and hopelessness in suicide –
- **Can antidepressant medications prevent suicide?**

Standard antidepressants and the risk of suicide

- **Most** suicide victims suffer from clinical depression on the day they die
- **2/3** of all patients with clinical depression struggle with suicidal ideation
- **Do standard antidepressants decrease the risk of suicide?**
- **--Well…**



Guidance for Industry

Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Thomas Laughren at 301-796-2260.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

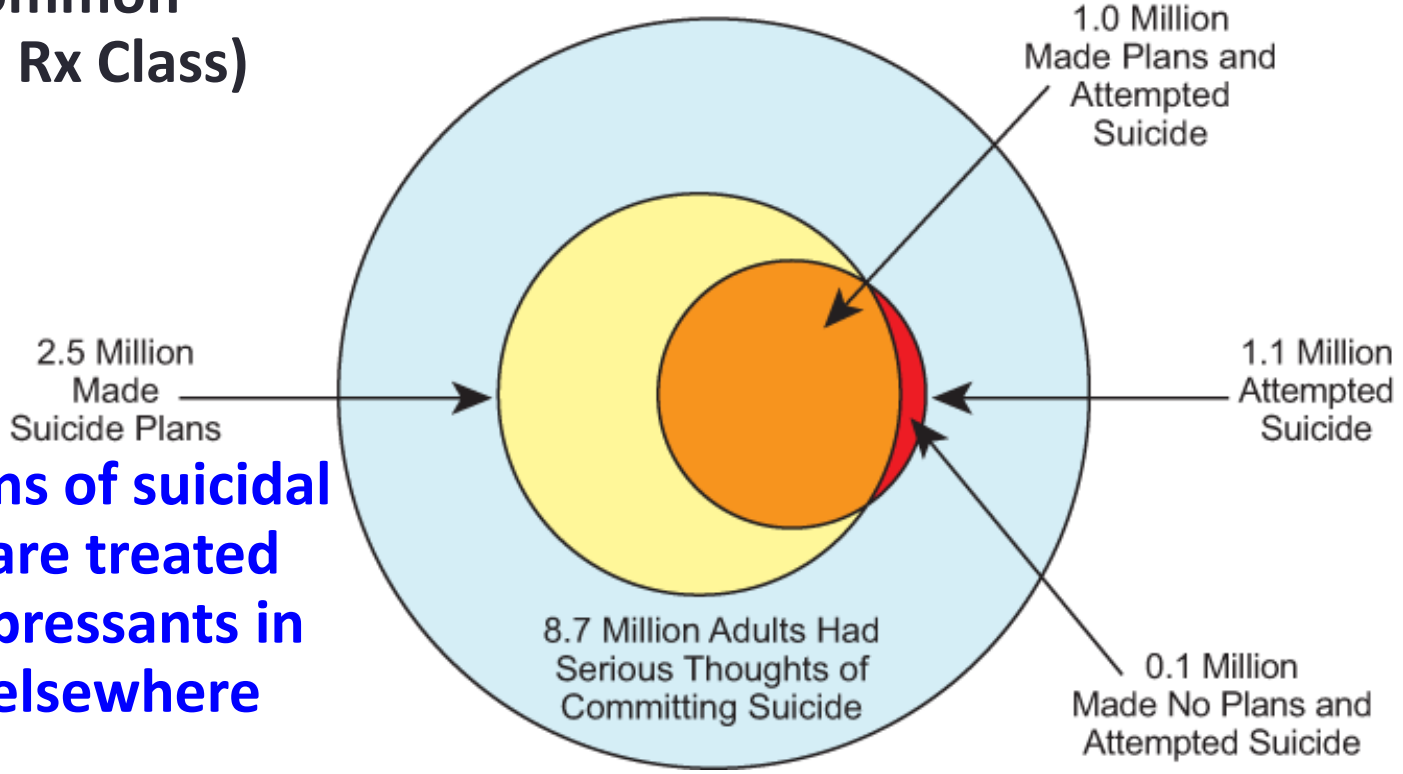
August 2012
Clinical/Medical

Revision 1

10302dft.doc
08/06/12

The incidence of suicidal ideation, suicidal behavior, and antidepressant use

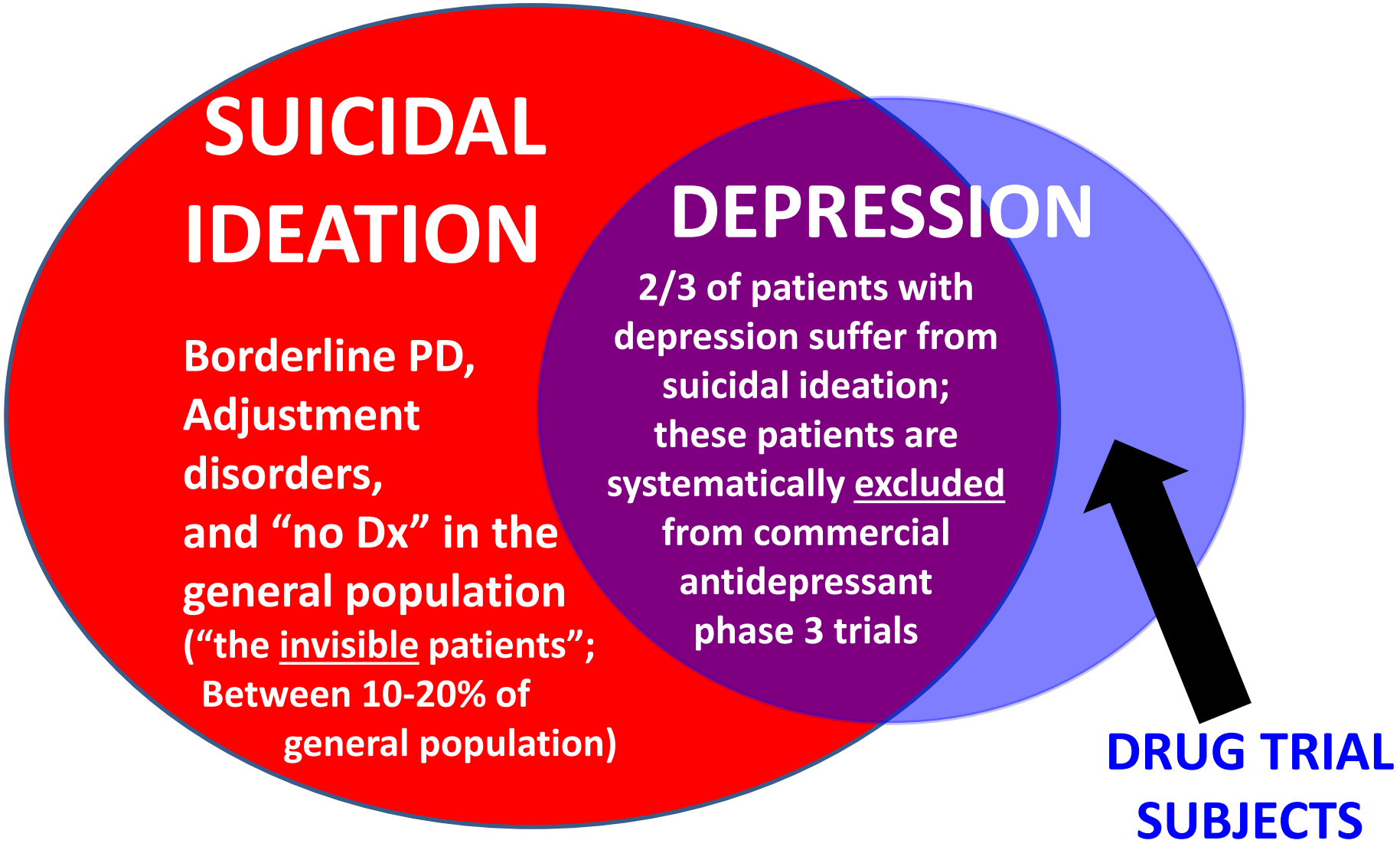
- > 35 Million people/year have some suicidal ideation in US
- > 8 Million people/year seriously think of committing suicide in US
- **> 25 Million people/year Take Antidepressants in US (3rd Most Common Prescription Rx Class)**



SAMHSA Report 2010

- **Thus, millions of suicidal individuals are treated with antidepressants in the US and elsewhere**
- **But…**

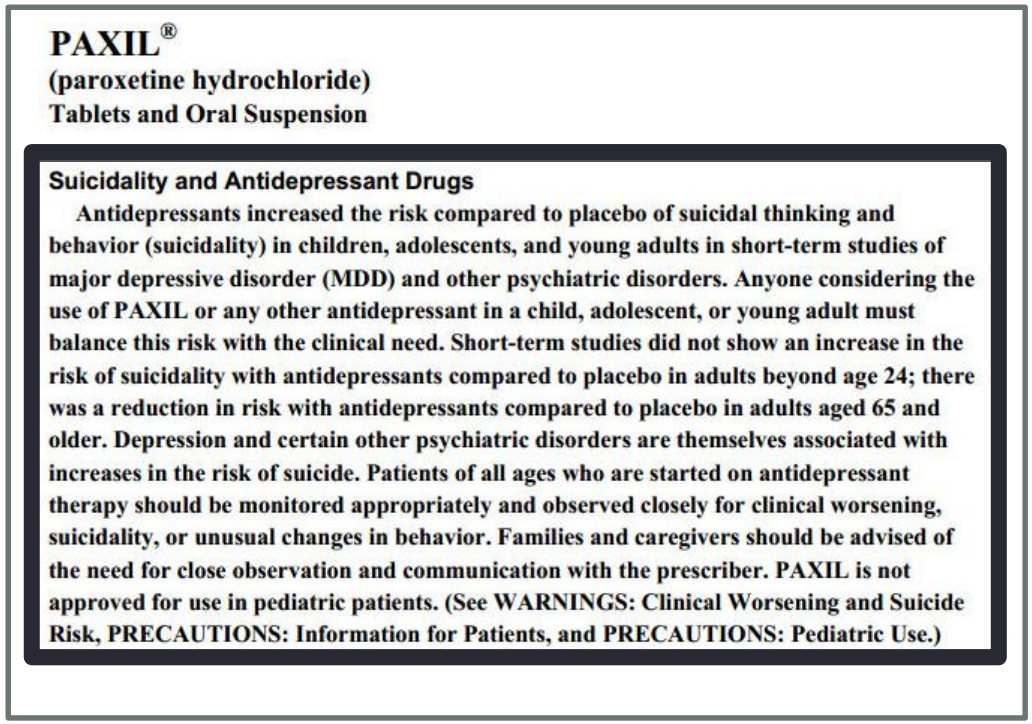
Standard antidepressant trials exclude most people who suffer from suicidal ideation



"THE BLACK BOX"

- Mandated by FDA
- On the package insert of all antidepressants since 2004

- **↑↑Suicidal ideation and behavior with <u>ALL</u> standard antidepressants in children, adolescents and young adults**
- Short-term studies
- Big media scare



PAXIL®
(paroxetine hydrochloride)
Tablets and Oral Suspension

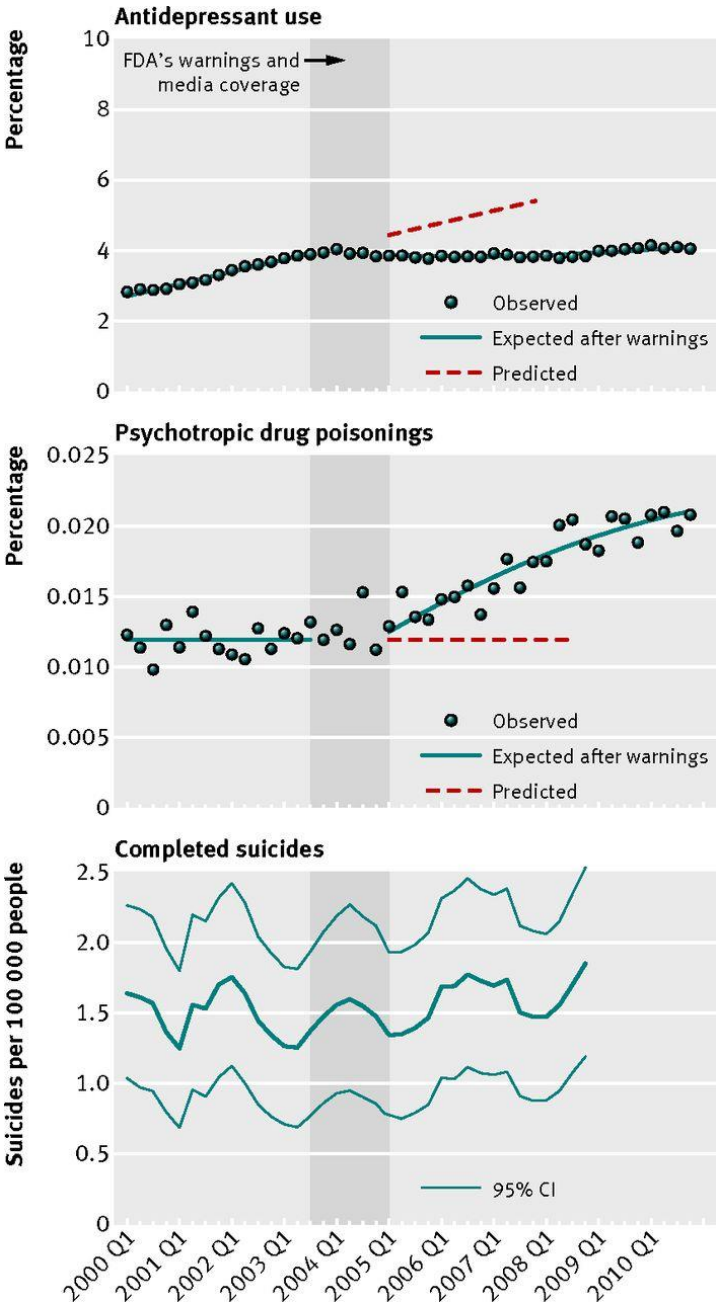
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

“Unintended consequences”

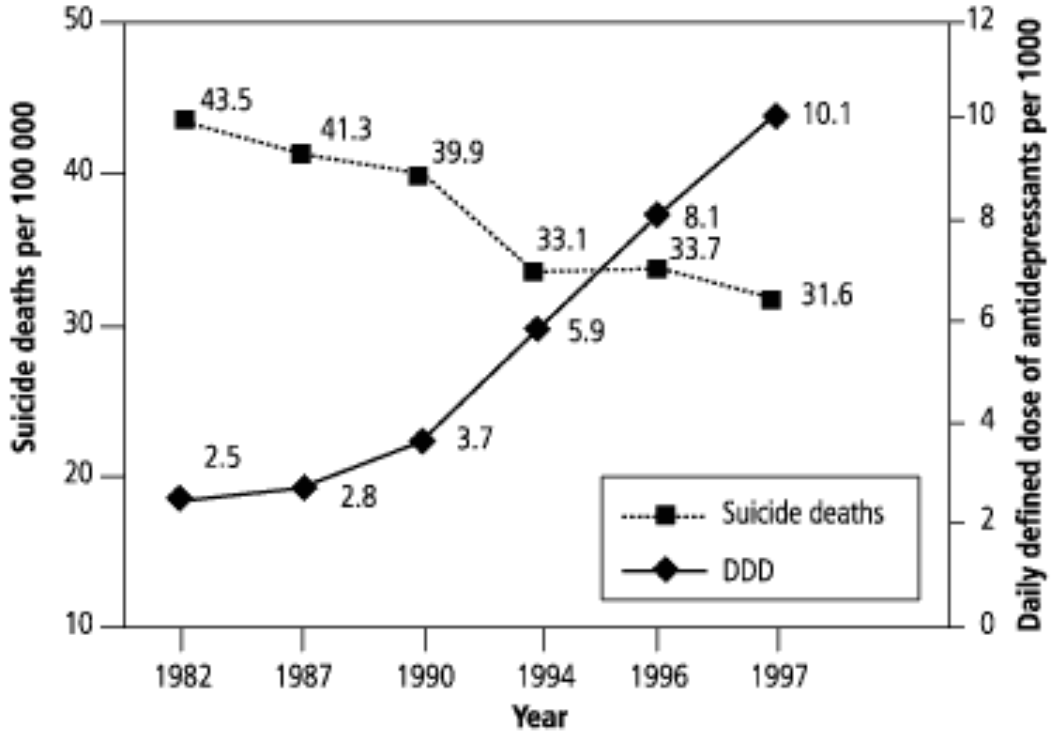
- **Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study** *Lu et al., BMJ* 2014

- Rates of antidepressant use, psychotropic drug poisonings, and completed suicides before and after the warnings, among adolescents enrolled in 11 health plans in nationwide Mental Health Research Network
- **“Safety warnings about antidepressants and widespread media coverage decreased antidepressant use, and there were simultaneous increases in suicide attempts among young people.”**



Current consensus:

Fig. 2. **Suicide deaths and daily defined dose (DDD) of antidepressants, Hungary**



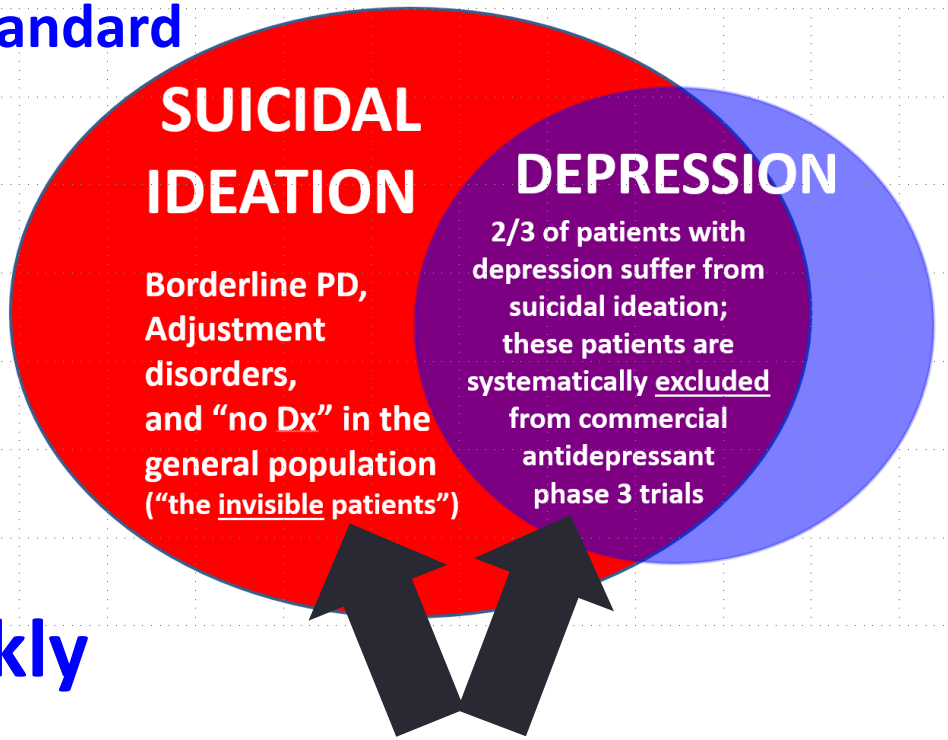
Source: data courtesy of Z. Rihmer

WHO 0085

- There is a difference between suicidal ideation and suicidal behavior
- There is a difference between short-term and long-term studies
- **Antidepressant Rx: Short-term risks, long-term benefits**
- **Overall, antidepressants improve both suicidal ideation and suicidal behavior in most patients**
- **but --**
- **Many exceptions**

Urgent need for quick-acting drugs that will decrease suicidal ideation and suicidal behavior

- In some cases, antidepressants do not decrease SI and SA
- In some cases, increases in SI and SA following antidepressant Rx
- **In almost all cases, at least a 3-week delay in antidepressant and anti-suicidal effects of standard antidepressant medications**
- **Therefore:**
- Urgent need for drugs that will **decrease** suicidal ideation and suicidal behavior **quickly**



WANTED: NEW DRUG TRIALS & NEW DRUG TRIAL SUBJECTS

HOWEVER: Very few randomized, double-blind placebo-controlled trials of drugs for decreasing SI and Suicide rates -- WHY?

- Difficult, dangerous trials – excluded subjects
- Ethical dilemmas
- Outcome measures
- "Lost in DSM" – our blind spot (conceptualizing and treating suicidality as a symptom of something else, not as a problem in its own right)

Only 4 medications currently recommended for decreasing suicide rates and suicidal ideation:

- **1. Lithium**
  - Long-term reduction in suicide rates of specific populations
- **2. Clozapine**
  - Long-term reduction in suicide rates of specific populations
- **3. Ketamine**
  - Short-term reduction in suicidal ideation in depression
- **4. Buprenorphine**
  - Short-term reduction in suicidal ideation

1. Lithium

- Well-established
- "Lithium is effective in the prevention of suicide, deliberate self-harm and death from all causes in patients with mood disorders"
- Especially in Bipolar-spectrum disorders
- The Sardinia study
- Also VPA?
- Usual maintenance/ augmentation doses
- Links to impulsivity?
- **VERY dangerous in OD**

Reviews and Overviews

Lithium in the Prevention of Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders: A Systematic Review of Randomized Trials

Andrea Cipriani, M.D.

Heather Pretty, M.L.I.S.

Keith Hawton, D.Sc.

John R. Geddes, M.D.

Objective: Observational studies suggest that long-term lithium treatment has a strong antisuicidal effect in mood disorders, but it is uncertain whether this association is a genuine therapeutic effect or is due to confounding factors in nonrandomized studies. The authors conducted a systematic review and meta-analysis of randomized trials to investigate the effect of lithium, compared to placebo and other active treatments, on the risk of suicide, deliberate self-harm, and all-cause mortality in patients with mood disorder.

Method: The data source was the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, incorporating results of searches of MEDLINE (1966–June 2002), EMBASE (1980–June 2002), CINAHL (1982–March 2001), PsycLIT (1974–June 2002), PSYNDEX (1977–October 1999), and LILACS (1982–March 2001). The Cochrane Central Register of Controlled Trials (CENTRAL) was searched with the term "lithium" for new records entered into the database from 1999 to 2003. Studies selected included randomized, controlled trials comparing lithium with placebo or all other compounds used in long-term treatment for mood disorders (unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling, diagnosed according to DSM or ICD criteria). Of 727 references identified in the search, 52 articles were marked as possibly relevant on the basis of the abstract, and 32 randomized, controlled trials were eligible for inclusion in the review. Two independent reviewers extracted the data, and disagreements were resolved by consensus with a third reviewer. Methodological quality was assessed according to the criteria of the Cochrane Collaboration. When the outcomes of interest were not reported, an attempt was made to obtain the required data from the original authors.

Results: In 32 trials, 1,389 patients were randomly assigned to receive lithium and 2,069 to receive other compounds. Patients who received lithium were less likely to die by suicide (data from seven trials; two versus 11 suicides; odds ratio=0.26; 95% confidence interval [CI]=0.09–0.77). The composite measure of suicide plus deliberate self-harm was also lower in patients who received lithium (odds ratio=0.21; 95% CI=0.08–0.50). There were fewer deaths overall in patients who received lithium (data from 11 trials; nine versus 22 deaths; odds ratio=0.42, 95% CI=0.21–0.87).

Conclusions: Lithium is effective in the prevention of suicide, deliberate self-harm, and death from all causes in patients with mood disorders.

(Am J Psychiatry 2005; 162:1805–1819)

2. Clozapine

- Well-established
- For the prevention of **suicide** and **suicide attempts** in patients with schizophrenia-spectrum disorders
- Much needed:
- 50% attempt suicide
- 10% die by suicide
- FDA-approved for this indication
- Underused?
- **Agranulocytosis, etc.**
- Other atypical antipsychotics (e.g. risperidone) may also decrease SI/SA, but less data

Herbert Meltzer and Clozapine

Making a Revolution in the Treatment of Schizophrenia

Herbert Meltzer recalls that as a doctor-in-training, in the 1960s, "within my first week on the psychiatry ward, I knew what I wanted to do for the rest of my life." His decision to devote himself to trying to improve the understanding and treatment of mental illness, and to personally treat patients with mental illness, resolved a question he had been pondering as to whether to pursue a career in clinical medicine or research. He did both. Shuttling between clinic and lab, he became, in the words of a colleague, "the driving force behind a revolution in the treatment of schizophrenia."

Now the Bixler/May/Johnson Professor of Psychiatry and professor of pharmacology at the Vanderbilt University School of Medicine, Dr. Meltzer is considered the world's foremost authority on atypical antipsychotic drugs. Antipsychotic drugs treat the psychotic symptoms, the delusions and hallucinations, of schizophrenia.

The so-called *typical* antipsychotics, in use for many years, are effective for the majority of patients. The *atypicals*, developed later, have offered rescue and respite to the 30 percent whose psychosis previously had been untreatable. These drugs were first called atypical because they are much less likely to induce the motor disturbances, the uncontrollable jerking and facial tics, that can occur with typical antipsychotics.

January 1, 2003, Vol 60, No. 1 >

< Previous Article Next Article >

Original Article | January 2003

Clozapine Treatment for Suicidality in Schizophrenia

International Suicide Prevention Trial (InterSePT) FREE

Herbert Y. Meltzer, MD; Larry Alphs, MD, PhD; Alan I. Green, MD; A. Carlo Altamura, MD; Ravi Anand, MD; Alberto Bertoldi, MD; Marc Bourgeois, MD; Guy Chouinard, MD; M. Zahur Islam, PhD; John Kane, MD; Ranga Krishnan, MD; J.-P. Lindenmayer, MD; Steven Potkin, MD ; InterSePT Study Group

[+] Author Affiliations

Arch Gen Psychiatry. 2003;60(1):82-91. doi:10.1001/archpsyc.60.1.82.

3. Ketamine

- Dissociative anesthetic
- NMDA antagonist
- Mu-opioid agonist
- **Rapidly** decreases suicidal ideation in patients with depression
- As early as 40 minutes
- IV, PO, SL, intranasal
- Repeated doses
- Effect not completely explained by decrease in depressive Sx
- **Doses:**
  0.5 mg/kg and less (sub-anesthetic)

Journal of Psychiatric Research 58 (2014) 161–166

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/psychires

Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety☆

Elizabeth D. Ballard*, Dawn F. Ionescu, Jennifer L. Vande Voort, Mark J. Niciu, Erica M. Richards, David A. Luckenbaugh, Nancy E. Brutsché, Rezvan Ameli, Maura L. Furey, Carlos A. Zarate Jr.

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ABSTRACT

Objective: Suicide is a psychiatric emergency. Currently, there are no approved pharmacologic treatments for suicidal ideation. Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that rapidly reduces suicidal ideation as well as depression and anxiety, but the dynamic between these symptoms is not known. The aim of this analysis was to evaluate whether ketamine has an impact on suicidal thoughts, independent of depressive and anxiety symptoms.

Methods: 133 patients with treatment-resistant depression (major depressive disorder or bipolar I/II disorder) received a single subanesthetic infusion of ketamine (0.5 mg/kg over 40 min). Post-hoc correlations and linear mixed models evaluated the relationship between suicidal ideation and depression and anxiety symptoms using the Hamilton Depression Rating Scale (HAMD), Scale for Suicidal Ideation (SSI), Beck Depression Inventory (BDI), and Hamilton Anxiety Rating Scale (HAMA) focusing on 230 min post-infusion.

Results: At 230 min post-infusion, correlations between changes in suicidal ideation and depression ranged from 0.23 to 0.44 ($p < .05$), accounting for up to 19% in the variance of ideation change. Correlations with anxiety ranged from 0.23 to 0.40 ($p < .05$), accounting for similar levels of variance. Ketamine infusion was associated with significant reductions in suicidal ideation compared to placebo, when controlling for the effects of ketamine on depression ($F_{1,587} = 10.31$, $p = .001$) and anxiety ($F_{1,567} = 8.54$, $p = .004$).

Conclusions: Improvements in suicidal ideation after ketamine infusion are related to, but not completely driven by, improvements in depression and anxiety. Investigation of the specific effects of ketamine on suicidal thoughts is warranted.

Published by Elsevier Ltd.

3. Ketamine

- Effective in treatment-resistant depression
- “Ketamine clinics” boom
- In higher doses – hallucinogenic, addictive?
- Many ongoing trials
- Can be used PO/SL in low doses
- Off-label use, but growing body of supporting data
- Probably safer than its reputation
- **May be formulated and obtained in Israel (details to follow)**

Ketamine Clinics of Los Angeles

Ketamine: The Future of Depression Treatment?

By Matt McMillen
WebMD Health News
Reviewed by Michael W. Smith, MD

Sept. 23, 2014 -- Every year, 13 million to 14 million Americans have major depression. Of those who seek treatment, 30% to 40% will not get better or fully recover with standard antidepressants.

That puts them at greater risk of alcohol and drug abuse, hospitalization, and suicide attempts. Now, though, a growing body of research shows there may be new hope: the anesthetic drug ketamine.

4. Buprenorphine

- Atypical opioid
- Mixed mu agonist-antagonist
- May be used in ultra-low, sub-analgesic doses
- Major advantages: **safe in OD; well-tolerated**
- Open trials and many case reports
- One recent randomized, double-blind, placebo-controlled trial found it effective in decreasing SI in patients with and without MDD, with and without BPD, who were and were not taking antidepressants
- Effect not completely explained by decrease in depressive Sx

Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial

Yoram Yovell, M.D., Ph.D., Gali Bar, Ph.D., Moti Mashiah, M.D., Yehuda Baruch, M.D., Irina Briskman, M.D., Jack Asherov, M.D., Amit Lotan, M.D., Amihai Rigbi, Ph.D., Jaak Panksepp, Ph.D.

Objective: Suicidal ideation and behavior currently have no quick-acting pharmacological treatments that are suitable for independent outpatient use. Suicidality is linked to mental pain, which is modulated by the separation distress system through endogenous opioids. The authors tested the efficacy and safety of very low dosages of sublingual buprenorphine as a time-limited treatment for severe suicidal ideation.

Method: This was a multisite randomized double-blind placebo-controlled trial of ultra-low-dose sublingual buprenorphine as an adjunctive treatment. Severely suicidal patients without substance abuse were randomly assigned to receive either buprenorphine or placebo (in a 2:1 ratio), in addition to their ongoing individual treatments. The primary outcome measure was change in suicidal ideation, as assessed by the Beck Suicide Ideation Scale at the end of each of 4 weeks of treatment.

Results: Patients who received ultra-low-dose buprenorphine (initial dosage, 0.1 mg once or twice daily; mean final dosage=0.44 mg/day; N=40) had a greater reduction in Beck Suicide Ideation Scale scores than patients who received placebo (N=22), both after 2 weeks (mean difference −4.3, 95% CI=−8.5, −0.2) and after 4 weeks (mean difference=−7.1, 95% CI=−12.0, −2.3). Concurrent use of antidepressants and a diagnosis of borderline personality disorder did not affect the response to buprenorphine. No withdrawal symptoms were reported after treatment discontinuation at the end of the trial.

Conclusions: The time-limited, short-term use of very low dosages of sublingual buprenorphine was associated with decreased suicidal ideation in severely suicidal patients without substance abuse. Further research is needed to establish the efficacy, safety, dosing, and appropriate patient populations for this experimental treatment.

Am J Psychiatry 2016; 173:491–498; doi: 10.1176/appi.ajp.2015.15040535

EDITORIALS

Opioids in Psychiatric Disorders: Back to the Future?

Alan F. Schatzberg, M.D.

An Opioid for Depression?

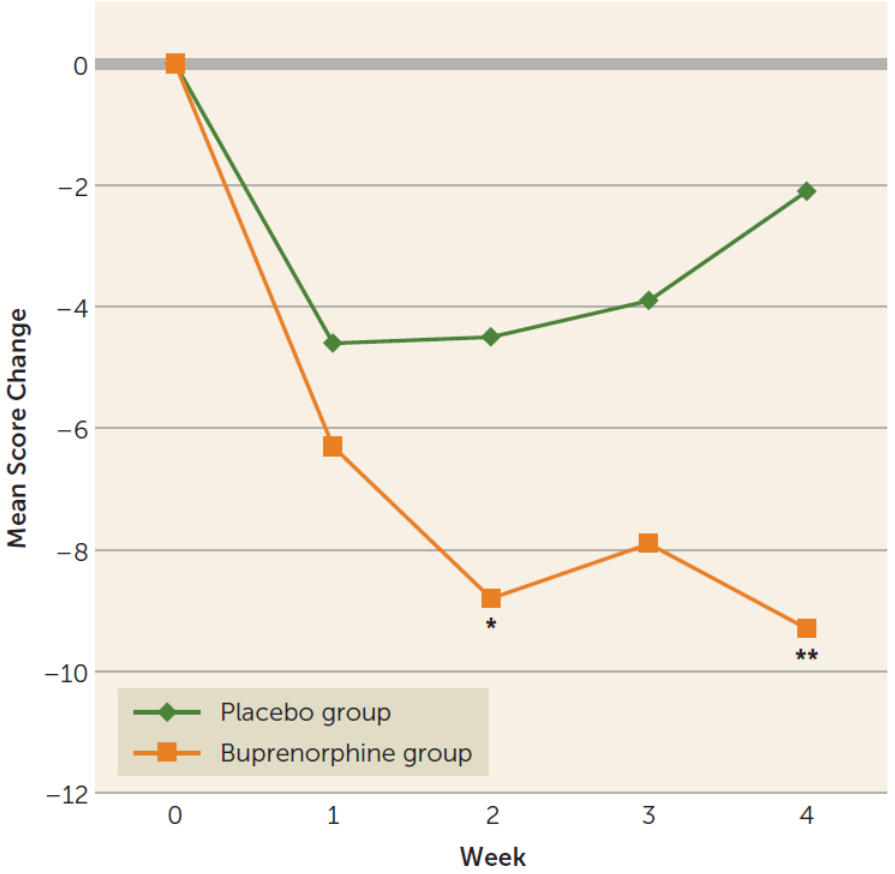
Thomas R. Kosten, M.D.

In contrast to the wildfire adoption of ketamine for acute depression, buprenorphine has excellent long-term safety data and has almost no possibility for overdose.

4. Buprenorphine

- **Doses:**
  0.1-0.3 mg SL bid
- Placebo-controlled effect seen by 2 weeks
- Short-term use
- Works by decreasing mental pain?
- Well-tolerated, no withdrawal symptoms
- Risk of addiction with prolonged use – not for patients with substance abuse Hx
- **May be formulated and obtained in Israel (details to follow)**

FIGURE 1. Changes From Baseline in Score on the Beck Scale for Suicide Ideation in Patients With Suicidal Ideation Who Received Buprenorphine or Placebo[a]



[a] Modified intent-to-treat group. Values are least square means. Lower scores are better.
*p<0.05. **p<0.01.

אפשר להזמין בארץ קטמין ובופרנורפין לטיפול באובדנות חריפה ו/או עמידה לטיפול, בנוסף לטיפול תרופתי "רגיל"

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Thank You!

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