Science to Practice

Top Ten Research Findings of 2018-2019

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NORTH CAROLINA
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Science to Practice

Top Ten Research findings of 2018-2019

Objectives

By the end of this session, the participant should be able to. . .

- Recognize that the current best evidence about a given treatment must be considered and applied to clinical practice wherever possible.
- Describe the methodology used in this presentation for identifying the top research findings for clinical psychiatry.
- Identify the most important* research findings of 2017-2018 that have a direct bearing on the practice of clinical psychiatry.

*As identified by the methodology utilized for this presentation.

Disclosure

Neither I nor any member of my immediate family have any relevant financial relationship with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

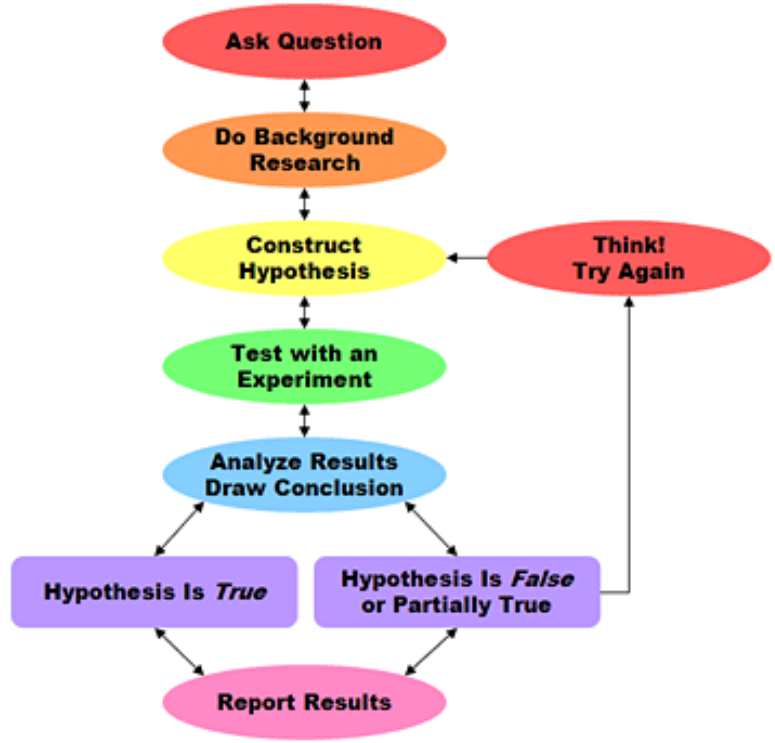
How much information in our midst is useful?
How much of it gets in the way?

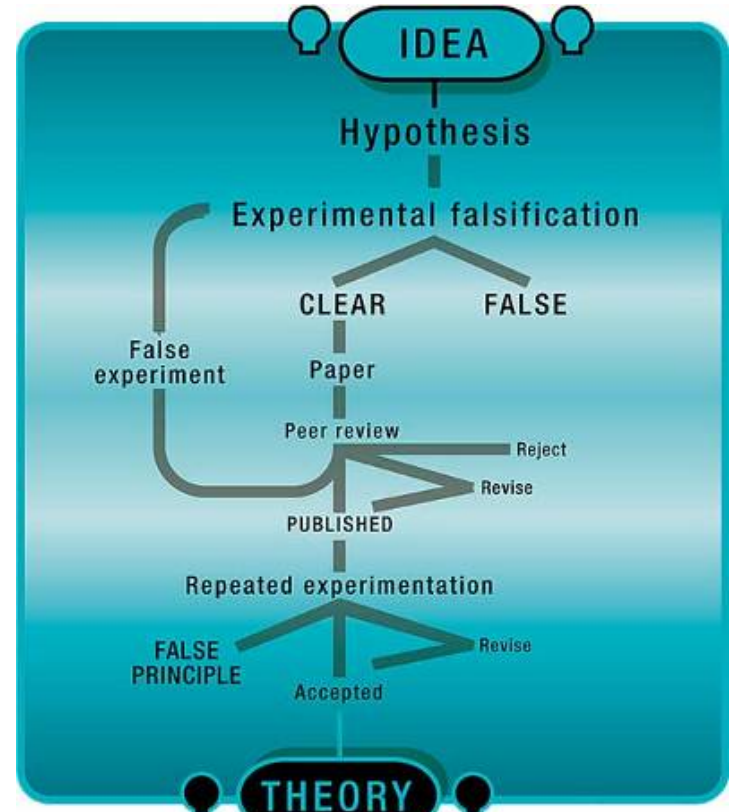
As we accrue more and more of it, information has emerged not only as a currency, but also as a pollutant.

David Shenk. Data Smog: Surviving the Information Glut. San Francisco: Harper, 1998: 30.

There is a long tortuous road to a "Scientific Truth"

YOU MUST ALWAYS OFFER EVIDENCE TO SUPPORT YOUR STATEMENTS.





All scientific truths are provisional!

Methodology

- **Primary Literature Search**
- **Survey** [Question: *Amongst the papers published in the period July 1, 2018 to June 30, 2019, which ones in your opinion have (or likely to have or should have) impacted/changed the clinical practice of psychiatry?*].
  - AACDP
  - GAP
  - AACP
  - AAPA
  - NCPA
  - Other Colleagues
- **Secondary Literature**, e.g. Faculty of 1000 Factor, Cochrane, NEJM Journal Watch, etc.

Disclaimers

- Selection of an article
  - Clinical relevance/applicability
- Order in which the articles appear in the list is arbitrary.
- The notion that these are definitively the “top” papers cannot be defended.
  - It is likely that others would choose different papers to include or exclude
  - However, these are papers of high quality with direct clinical application


The NEW ENGLAND JOURNAL of MEDICINE
JAMA
JAMA Psychiatry
THE AMERICAN JOURNAL OF PSYCHIATRY
The Journal of Neuropsychiatry and Clinical Neurosciences
nature
BJPsych
PSYCHOSOMATICS
nature medicine
Science
BMJ
SUBCLINICAL vCJD: How common is it?
The American Journal of Psychotherapy
Journal of Abnormal Psychology
Journal of Clinical Psychopharmacology
PNAS
Potential Energy Landscapes
Clinical Neuropharmacology
THE LANCET
ACADEMIC PSYCHIATRY
Journal of Psychotherapy Integration
The Journal of Neuroscience
PSYCHOLOGICAL MEDICINE
Neuropsychopharmacology
Biological Psychiatry
BJP
PLOS ONE
Psychological Bulletin
Behavioral Neuroscience
Journal of Consulting and Clinical Psychology
PERSONALITY DISORDERS
Theory, Research, and Treatment
Psychotherapy
Theory, Research, Practice, Training
Journal of the American Academy of Child & Adolescent Psychiatry
Behavioural Pharmacology
Psychiatry Research
Psychiatric Quarterly
Psychiatric Services
International Clinical Psychopharmacology

F1000 | FACULTY of 1000
POST-PUBLICATION PEER REVIEW

NEJM Journal Watch

Cochrane Library
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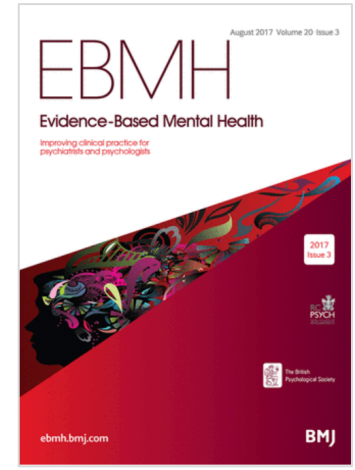
CEBM | UNIVERSITY OF OXFORD
Centre for Evidence-Based Medicine

ESSENTIAL EVIDENCE PLUS

BMJ Best Practice



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AHRQ
Agency for Healthcare Research and Quality

BMJ Journals
Evidence-Based Mental Health

Science to Practice

Top Ten Research Findings of 2018-2019

Association of Antipsychotic Treatment With Risk of Unexpected Death Among Children and Youths

Wayne A. Ray, PhD; C. Michael Stein, MB, ChB; Katherine T. Murray, MD; D. Catherine Fuchs, MD; Stephen W. Patrick, MD, MPH; James Daugherty, MS; Kathi Hall, BS; William O. Cooper, MD, MPH

IMPORTANCE Children and youths who are prescribed antipsychotic medications have multiple, potentially fatal, dose-related cardiovascular, metabolic, and other adverse events, but whether or not these medications are associated with an increased risk of death is unknown.

OBJECTIVE To compare the risk of unexpected death among children and youths who are beginning treatment with antipsychotic or control medications.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted from 1999 through 2014 and included Medicaid enrollees aged 5 to 24 years in Tennessee who had no diagnosis of severe somatic illness, schizophrenia or related psychoses, or Tourette syndrome or chronic tic disorder. Data analysis was performed from January 1, 2017, to August 15, 2018.

Association of Antipsychotic Treatment With Risk of Unexpected Death in Children and Youths

Question Are antipsychotic medications prescribed for children and youths without psychosis associated with increased risk of unexpected death or deaths other than from injuries or suicides without prolonged hospitalization?

Association of Antipsychotic Treatment With Risk of Unexpected Death in Children and Youths

EXPOSURES Current, new antipsychotic medication use at doses higher than 50 mg (higher-dose group) or 50 mg or lower chlorpromazine equivalents (lower-dose group) as well as control medications (ie, attention-deficit/hyperactivity disorder medications, antidepressants, or mood stabilizers) (control group).

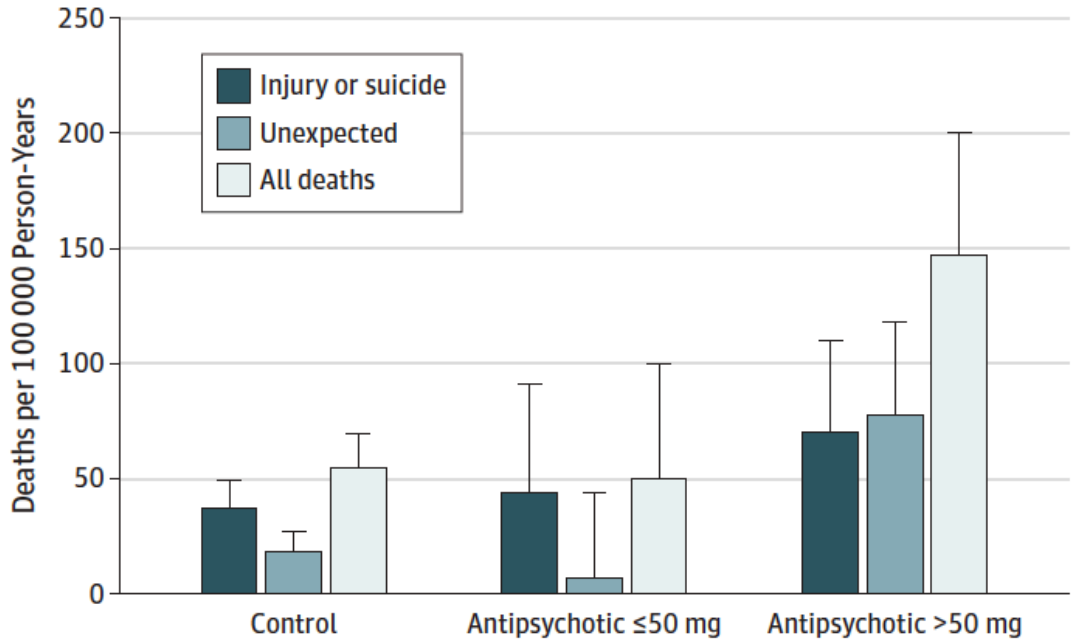
MAIN OUTCOMES AND MEASURES Deaths during study follow-up while out of hospital or within 7 days after hospital admission, classified as either deaths due to injury or suicide or unexpected deaths. Secondary outcomes were unexpected deaths not due to overdose and death due to cardiovascular or metabolic causes.

RESULTS This study included 189 361 children and youths in the control group (mean [SD] age, 12.0 [5.1] years; 43.4% female), 28 377 in the lower-dose group (mean [SD] age, 11.7 [4.4] years; 32.3% female), and 30 120 in the higher-dose group (mean [SD] age, 14.5 [4.8] years; 39.2% female). The unadjusted incidence of death in the higher-dose group was 146.2 per 100 000 person-years (40 deaths per 27 354 person-years), which was significantly greater than that in the control group (54.5 per 100 000 population; 67 deaths per 123 005 person-years) ($P < .001$). The difference was primarily attributable to the increased incidence of unexpected deaths in the higher-dose group (21 deaths; 76.8 per 100 000 population) compared with the control group (22 deaths; 17.9 per 100 000 population). The propensity score–adjusted hazard ratios were as follows: all deaths (1.80; 95% CI, 1.06-3.07), deaths due to unintentional injury or suicide (1.03; 95% CI, 0.53-2.01), and unexpected deaths (3.51; 95% CI, 1.54-7.96). The hazard ratio was 3.50 (95% CI, 1.35-9.11) for unexpected deaths not due to overdose and 4.29 (95% CI, 1.33-13.89) for deaths due to cardiovascular or metabolic causes. Neither the unadjusted nor adjusted incidence of death in the lower-dose group differed significantly from that in the control group.

Findings In this cohort study of 247 858 Medicaid-enrolled children and youths in Tennessee who were new users of antipsychotic or control medications, the group that received a higher dose of antipsychotic medication had a significantly increased risk of unexpected death compared with the group that received control medication.

Meaning This study suggests that antipsychotic treatment may be associated with increased mortality among children and youths and appears to underscore recommendations for careful medication use and monitoring in this population.

Figure. Unadjusted Incidence of Study Deaths According to Cause of Death and Study Medication



There were 123 005 person-years for the control group with 45 deaths due to injury or suicide and 22 unexpected deaths, 16 159 person-years for the group receiving 50 mg or less of antipsychotic treatment with 7 deaths due to injury or suicide and 1 unexpected death, and 27 354 person-years for the group receiving more than 50 mg of antipsychotic treatment with 19 deaths due to injury or suicide and 21 unexpected deaths. Bars indicate upper 95% confidence limits.

Conclusions

Children and youths beginning antipsychotic therapy who received doses higher than 50-mg chlorpromazine equivalents had a 3.5-fold increased risk of unexpected deaths but no increased risk for deaths from injuries or suicides. This finding suggests that the increased unexpected death risk was associated with the use of antipsychotics. These results appear to reinforce recommendations for careful prescribing and monitoring of antipsychotic regimens for children and youths and the need for larger antipsychotic safety studies in this population.

CONCLUSIONS AND RELEVANCE The findings suggest that antipsychotic use is associated with increased risk of unexpected death and appear to reinforce recommendations for careful prescribing and monitoring of antipsychotic treatment for children and youths and to underscore the need for larger antipsychotic treatment safety studies in this population.

What Is the Risk for Unexpected Death Among Children and Youths Taking Antipsychotics?

All medications carry risks, but these data are particularly sobering because with the exception of autism, the population was being treated off-label.

As with all association studies, no direct line connects cause and effect. In this analysis, the lower- and higher-dose groups differed in diagnoses, age, and antipsychotics prescribed.

Examining risks associated with particular drugs will require larger datasets but will be critical for our understanding of the risks and benefits.

NEJM Journal Watch PSYCHIATRY

Bryan H. King, MD, MBA, (Jan 4, 2019)

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

IMPORTANCE Controlled studies have shown short-term efficacy of esketamine for treatment-resistant depression (TRD), but long-term effects remain to be established.

OBJECTIVE To assess the efficacy of esketamine nasal spray plus an oral antidepressant compared with an oral antidepressant plus placebo nasal spray in delaying relapse of depressive symptoms in patients with TRD in stable remission after an induction and optimization course of esketamine nasal spray plus an oral antidepressant.

JAMA Psychiatry Published online June 5, 2019

DESIGN, SETTING, AND PARTICIPANTS In this phase 3, multicenter, double-blind, randomized withdrawal study conducted from October 6, 2015, to February 15, 2018, at outpatient referral centers, 705 adults with prospectively confirmed TRD were enrolled; 455 entered the optimization phase and were treated with esketamine nasal spray (56 or 84 mg) plus an oral antidepressant. After 16 weeks of esketamine treatment, 297 who achieved stable remission or stable response entered the randomized withdrawal phase.

INTERVENTIONS Patients who achieved stable remission and those who achieved stable response (without remission) were randomized 1:1 to continue esketamine nasal spray or discontinue esketamine treatment and switch to placebo nasal spray, with oral antidepressant treatment continued in each group.

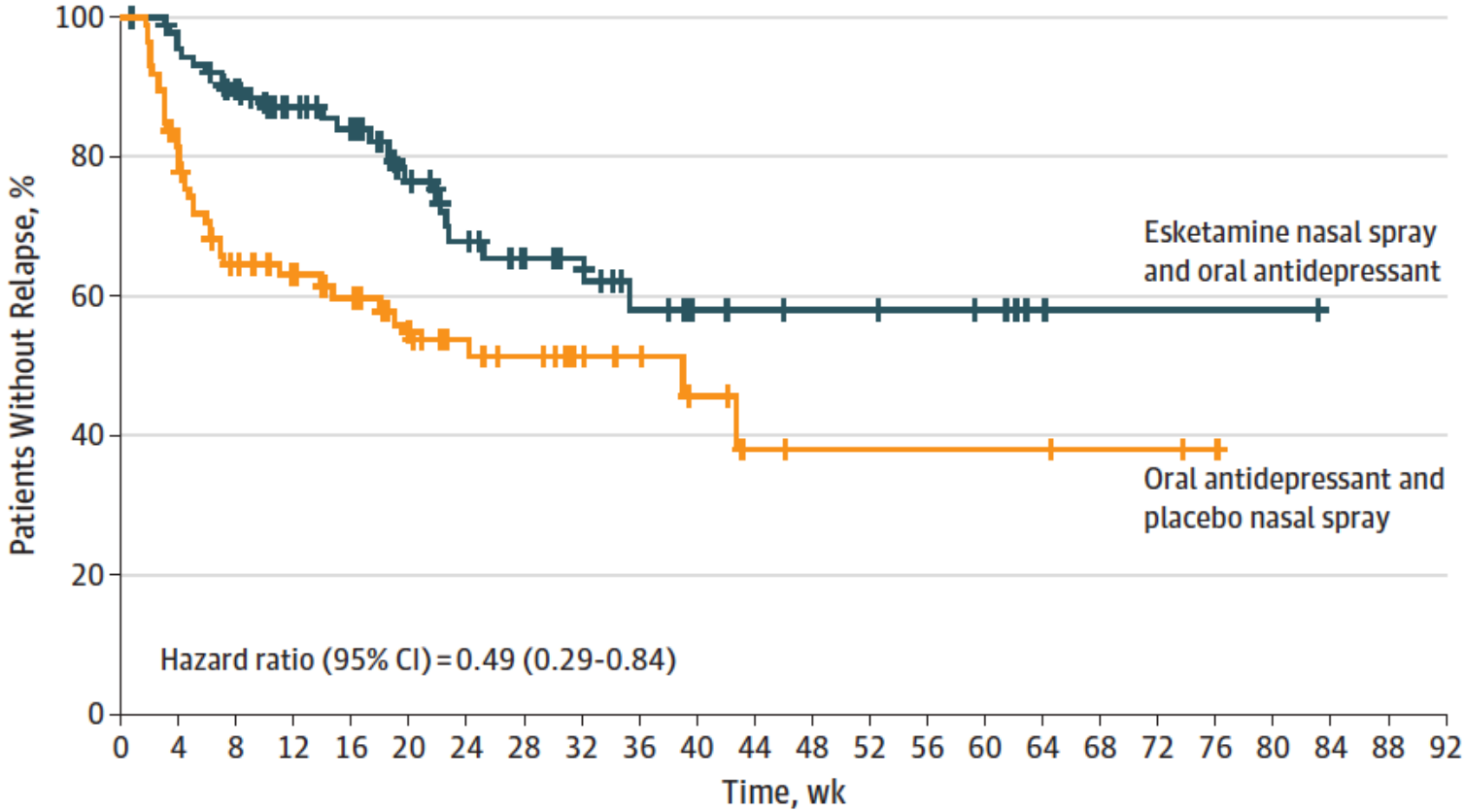
MAIN OUTCOMES AND MEASURES Time to relapse was examined in patients who achieved stable remission, as assessed using a weighted combination log-rank test.

RESULTS Among the 297 adults (mean age [SD], 46.3 [11.13] years; 197 [66.3%] female) who entered the randomized maintenance phase, 176 achieved stable remission; 24 (26.7%) in the esketamine and antidepressant group and 39 (45.3%) in the antidepressant and placebo group experienced relapse (log-rank $P = .003$, number needed to treat [NNT], 6). Among the 121 who achieved stable response, 16 (25.8%) in the esketamine and antidepressant group and 34 (57.6%) in the antidepressant and placebo group experienced relapse (log-rank $P < .001$, NNT, 4). Esketamine and antidepressant treatment decreased the risk of relapse by 51% (hazard ratio [HR], 0.49; 95% CI, 0.29-0.84) among patients who achieved stable remission and 70% (HR, 0.30; 95% CI, 0.16-0.55) among those who achieved stable response compared with antidepressant and placebo treatment. The most common adverse events reported for esketamine-treated patients after randomization were transient dysgeusia, vertigo, dissociation, somnolence, and dizziness (incidence, 20.4%-27.0%), each reported in fewer patients (<7%) treated with an antidepressant and placebo.

Esketamine Nasal Spray Plus Oral Antidepressant Treatment in Patients With Treatment-Resistant Depression

Kaplan-Meier Estimates of Time to Relapse

A Patients who achieved stable remission



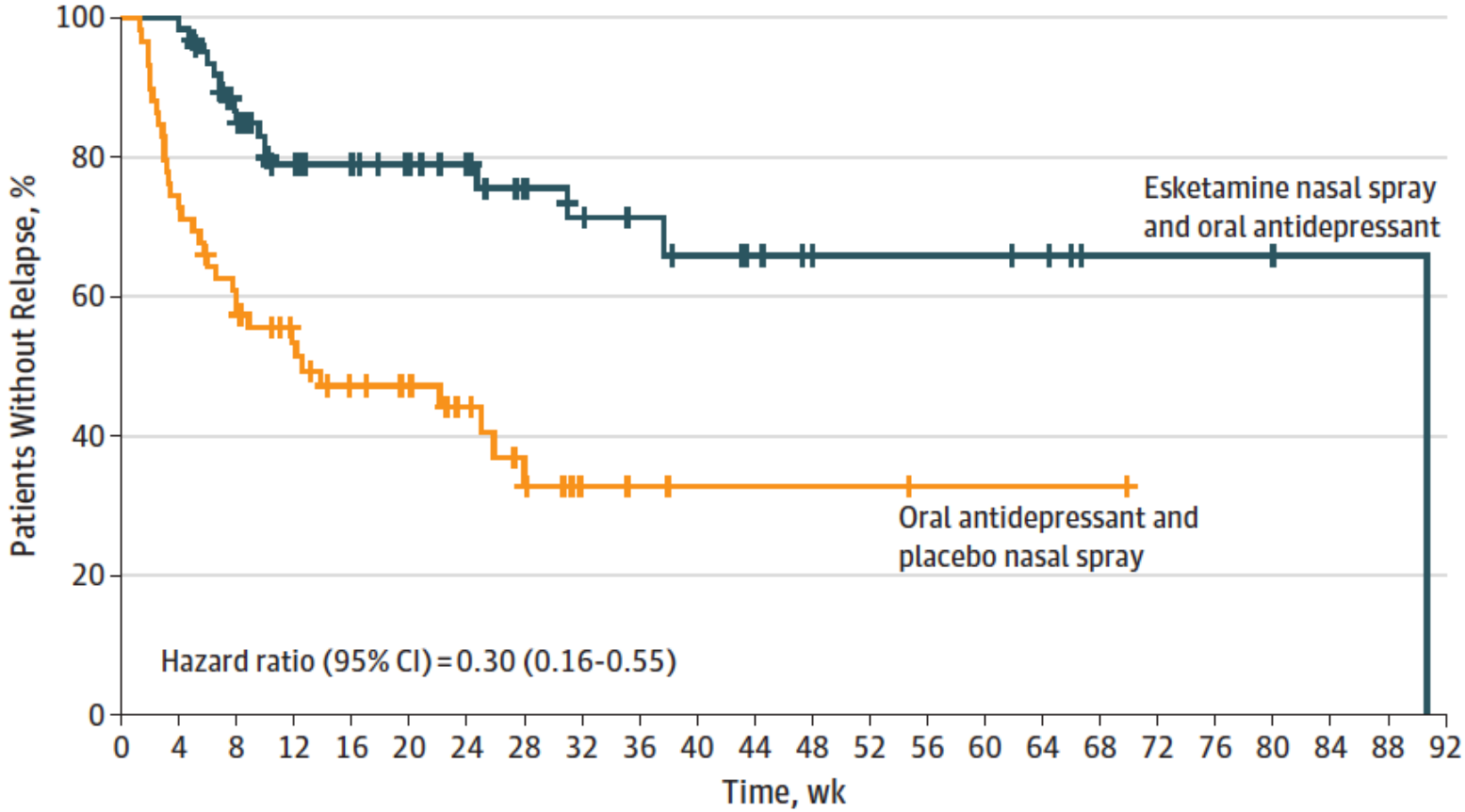
No. at risk

Esketamine nasal spray and oral antidepressant	90	84	74	58	53	39	31	25	20	14	10	8	7	7	6	5	2	1	1	1	1	0
Oral antidepressant and placebo nasal spray	86	69	52	41	34	28	22	19	12	10	7	4	3	3	3	3	3	2	2	1	0	0

Esketamine Nasal Spray Plus Oral Antidepressant Treatment in Patients With Treatment-Resistant Depression

Kaplan-Meier Estimates of Time to Relapse

B Patients who achieved stable response



No. at risk

Esketamine nasal spray and oral antidepressant	62	62	49	38	35	31	26	20	15	13	11	9	7	6	6	6	5	2	2	2	2	1	1	0
Oral antidepressant and placebo nasal spray	59	44	35	26	19	17	13	9	4	3	2	2	2	2	1	1	1	1	0	0	0	0	0	0

CONCLUSIONS AND RELEVANCE For patients with TRD who experienced remission or response after esketamine treatment, continuation of esketamine nasal spray in addition to oral antidepressant treatment resulted in clinically meaningful superiority in delaying relapse compared with antidepressant plus placebo.

Findings Of the 297 adults with treatment-resistant depression who were randomized in the maintenance phase of this clinical trial, those who continued treatment with intermittently administered esketamine nasal spray plus an oral antidepressant had a significantly delayed time to relapse vs those treated with oral antidepressant plus placebo nasal spray after 16 weeks of initial treatment with esketamine and an antidepressant.

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Nolan R. Williams, M.D., Boris D. Heifets, M.D., Ph.D., Christine Blasey, Ph.D., Keith Sudheimer, Ph.D., Jaspreet Pannu, B.S., Heather Pankow, B.S., Jessica Hawkins, B.S., Justin Birnbaum, M.D., David M. Lyons, Ph.D., Carolyn I. Rodriguez, M.D., Ph.D., Alan F. Schatzberg, M.D.

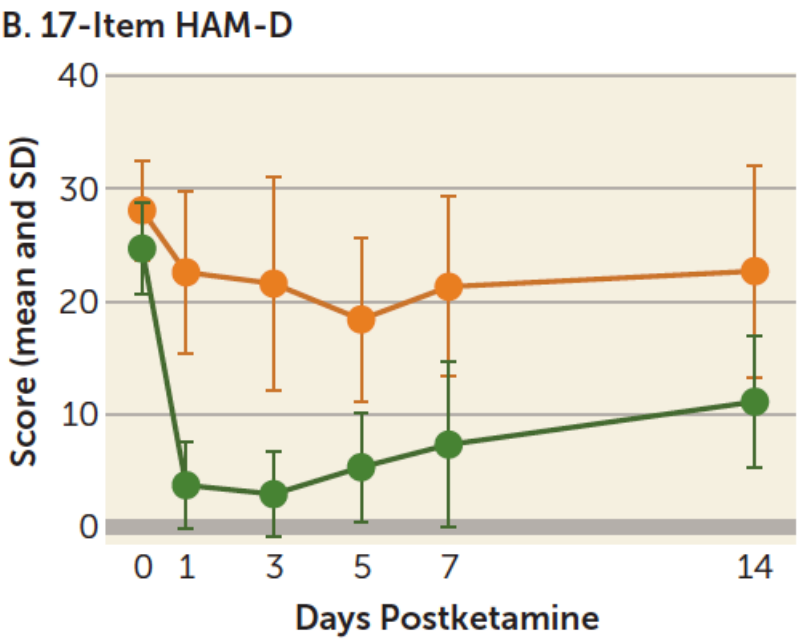
Objective: In addition to *N*-methyl-D-aspartate receptor antagonism, ketamine produces opioid system activation. The objective of this study was to determine whether opioid receptor antagonism prior to administration of intravenous ketamine attenuates its acute antidepressant or dissociative effects.

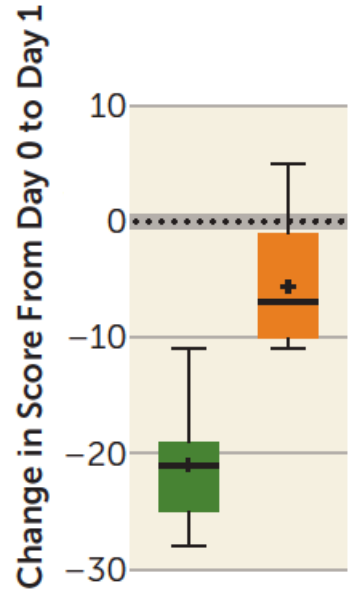
Method: In a proposed double-blind crossover study of 30 adults with treatment-resistant depression, the authors performed a planned interim analysis after studying 14 participants, 12 of whom completed both conditions in randomized order: placebo or 50 mg of naltrexone preceding intravenous infusion of 0.5 mg/kg of ketamine. Response was defined as a reduction ≥50% in score on the 17-item Hamilton Depression Rating Scale (HAM-D) score on postinfusion day 1.

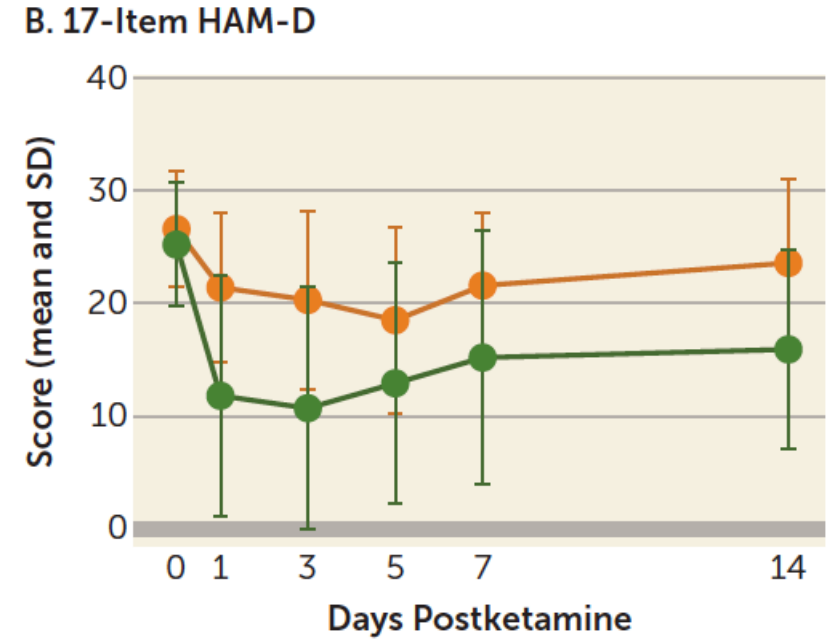
Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

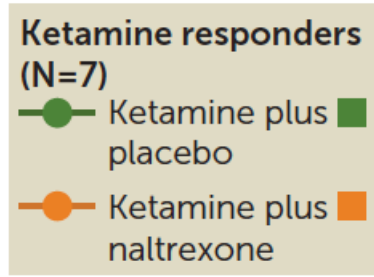
Results: In the interim analysis, seven of 12 adults with treatment-resistant depression met the response criterion during the ketamine plus placebo condition. Reductions in 6-item and 17-item HAM-D scores among participants in the ketamine plus naltrexone condition were significantly lower than those of participants in the ketamine plus placebo condition on postinfusion days 1 and 3. Secondary analysis of all participants who completed the placebo and naltrexone conditions, regardless of the robustness of response to ketamine, showed similar results. There were no differences in ketamine-induced dissociation between conditions. Because naltrexone dramatically blocked the antidepressant but not the dissociative effects of ketamine, the trial was halted at the interim analysis.

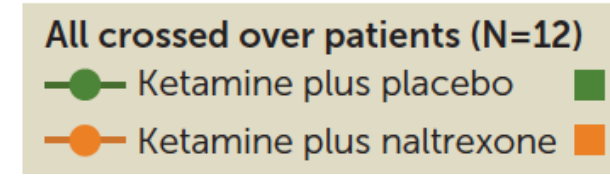
Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism











Am J Psychiatry 175:12, December 2018

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Conclusions: The findings suggest that ketamine's acute antidepressant effect requires opioid system activation. The dissociative effects of ketamine are not mediated by the opioid system, and they do not appear sufficient without the opioid effect to produce the acute antidepressant effects of ketamine in adults with treatment-resistant depression.

Am J Psychiatry 175:12, December 2018

Is There Really Nothing New Under the Sun? Is Low-Dose Ketamine a Fast-Acting Antidepressant Simply Because It Is An Opioid?

Mark S. George, M.D.

Psychiatrists are now dealing with three "epidemics" that have a profound impact on society—opioid dependence, depression, and suicide. We desperately need new treatments for depression, and for suicidality, while also reducing opioid dependence and abuse. In the setting of this "triple crunch" and the frantic search for breakthrough treatments, low-dose intravenous ketamine has emerged as a potentially rapid-acting antidepressant that also quickly reduces suicidality. Could the universe be so cruel as to make it so that a treatment for one or two of the epidemics actually fuels the other?

Am J Psychiatry 175:12, December 2018

Is There Really Nothing New Under the Sun? Is Low-Dose Ketamine a Fast-Acting Antidepressant Simply Because It Is An Opioid?

Mark S. George, M.D.

With these new findings, we should be cautious about widespread and repeated use of ketamine before further mechanistic testing has been performed to determine whether ketamine is merely another opioid in a novel form.

Am J Psychiatry 175:12, December 2018

Do Ketamine's Antidepressant Actions Reflect Its Opiate Properties?

This theory is consistent with observations of buprenorphine's antidepressant effects, even in patients whose depressions fail to respond to electroconvulsive therapy. The lack of impact of naltrexone on dissociative experiences suggests that opiate receptors are not central to ketamine's dissociative effects. Despite its antidepressant actions, we wouldn't want to overuse ketamine if it is "another opioid in a novel form."

NEJM Journal Watch
PSYCHIATRY

Joel Yager, MD (Sep 5, 2018)

Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomised controlled trial

Sanford Nidich, Paul J Mills, Maxwell Rainforth, Pia Heppner, Robert H Schneider, Norman E Rosenthal, John Salerno, Carolyn Gaylord-King, Thomas Rutledge

Methods We did a randomised controlled trial at the Department of Veterans Affairs San Diego Healthcare System in CA, USA. We included 203 veterans with a current diagnosis of PTSD resulting from active military service randomly assigned to a TM or PE group, or an active control group of HE, using stratified block randomisation. Each treatment provided 12 sessions over 12 weeks, with daily home practice. TM and HE were mainly given in a group setting and PE was given individually. The primary outcome was change in PTSD symptom severity over 3 months, assessed by the Clinician-Administered PTSD Scale (CAPS). Analysis was by intention to treat. We hypothesised that TM would show non-inferiority to PE in improvement of CAPS score (Δ=10), with TM and PE superior to PTSD HE. This study is registered with ClinicalTrials.gov, number NCT01865123.

Evidence before this study

Authors searched PubMed for articles published between Jan 1, 2000, and August 31, 2018 and were unable to find any comparative effectiveness studies, non-random or randomised assignment, that included Transcendental Meditation (TM) or any other meditation programme in comparison to a first-line, US Veterans Administration (VA)-approved psychotherapy treatment.

Additionally, none of the systematic reviews on post-traumatic stress disorder (PTSD) during this timeframe included studies that compared meditation directly with a first-line psychotherapy treatment. Previous uncontrolled and non-randomised studies on TM have suggested its efficacy in addressing PTSD symptoms. A randomised controlled comparative effectiveness trial was therefore done to assess the efficacy of TM relative to prolonged exposure (PE), a first-line VA-approved treatment, and an active PTSD health education (HE) control group, in veterans with documented PTSD.

Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomised controlled trial

Findings Between June 10, 2013, and Oct 7, 2016, 203 veterans were randomly assigned to an intervention group (68 to the TM group, 68 to the PE group, and 67 to the PTSD HE group). TM was significantly non-inferior to PE on change in CAPS score from baseline to 3-month post-test (difference between groups in mean change –5·9, 95% CI –14·3 to 2·4, p=0·0002). In standard superiority comparisons, significant reductions in CAPS scores were found for TM versus PTSD HE (–14·6 95% CI, –23·3 to –5·9, p=0·0009), and PE versus PTSD HE (–8·7 95% CI, –17·0 to –0·32, p=0·041). 61% of those receiving TM, 42% of those receiving PE, and 32% of those receiving HE showed clinically significant improvements on the CAPS score.

Interpretation A non-trauma-focused-therapy, TM, might be a viable option for decreasing the severity of PTSD symptoms in veterans and represents an efficacious alternative for veterans who prefer not to receive or who do not respond to traditional exposure-based treatments of PTSD.

Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomised controlled trial

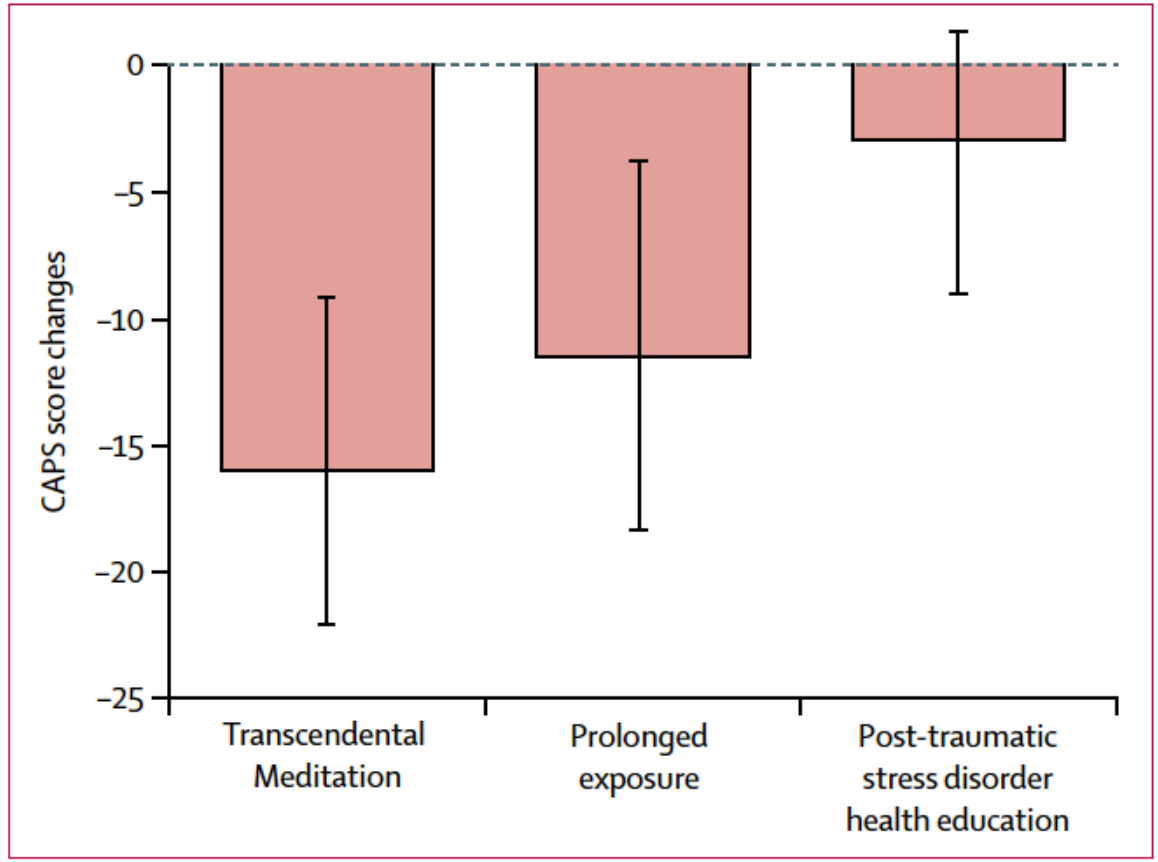


Figure 2: **Changes in point scores from baseline to 3-month post-test for all treatment groups on the CAPS score**
CAPS=clinician-administered PTSD scale.

Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomised controlled trial

Overall, we found that TM was non-inferior compared with PE for treating PTSD symptom severity and co-morbid depression in veterans with PTSD. The findings from this first comparative effectiveness trial comparing TM to an established psychotherapy for PTSD suggests the feasibility and efficacy of TM as an alternative therapy for veterans with PTSD and encourages future TM research to explore the durability of the benefits and applications to other populations with PTSD.

Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomised controlled trial

Added value of this study

The findings of this comparative effectiveness clinical trial expand the current evidence base by showing the feasibility and efficacy of TM as an alternative therapy to PE for the treatment of military veterans diagnosed with PTSD.

Implications of all the available evidence

Over the past 50 years, PTSD has expanded to become an important public health problem. Due to the increasing need to address the public health-care problem of PTSD in the USA, UK, and worldwide, there is a compelling need to implement governmental policy to include alternative therapies such as TM as an option for treating veterans and other groups with PTSD.

Meditation as Good as Exposure for PTSD -- and Probably Easier

This important study found that TM helped over half of severely and chronically ill veterans, with strong evidence of a "dose" effect (i.e., more was better), adding to the growing evidence that non-trauma-focused psychotherapies are as effective as trauma-focused therapies for PTSD. Evidence that TM reduces sympathetic nervous system activity provides a compelling rationale for the findings. Lack of follow-up beyond 12 weeks is a major limitation of the study. However, because TM is self-administered and requires only some initial expert training, it offers a novel, easy-to-implement approach that may be more accessible to veterans than other treatments.

NEJM Journal Watch
PSYCHIATRY

Peter Roy-Byrne, MD (Nov 28, 2018)

Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

M.A. Raskind, E.R. Peskind, B. Chow, C. Harris,* A. Davis-Karim, H.A. Holmes, K.L. Hart, M. McFall, T.A. Mellman, C. Reist, J. Romesser, R. Rosenheck, M.-C. Shih, M.B. Stein, R. Swift, T. Gleason, Y. Lu, and G.D. Huang

BACKGROUND

In randomized trials, prazosin, an α_1-adrenoreceptor antagonist, has been effective in alleviating nightmares associated with post-traumatic stress disorder (PTSD) in military veterans.

METHODS

We recruited veterans from 13 Department of Veterans Affairs medical centers who had chronic PTSD and reported frequent nightmares. Participants were randomly assigned to receive prazosin or placebo for 26 weeks; the drug or placebo was administered in escalating divided doses over the course of 5 weeks to a daily maximum of 20 mg in men and 12 mg in women. After week 10, participants continued to receive prazosin or placebo in a double-blind fashion for an additional 16 weeks. The three primary outcome measures were the change in score from baseline to 10 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 ("recurrent distressing dreams"; scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams); the change in score from baseline to 10 weeks on the Pittsburgh Sleep Quality Index (PSQI; scores range from 0 to 21, with higher scores indicating worse sleep quality); and the Clinical Global Impression of Change (CGIC) score at 10 weeks (scores range from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change).

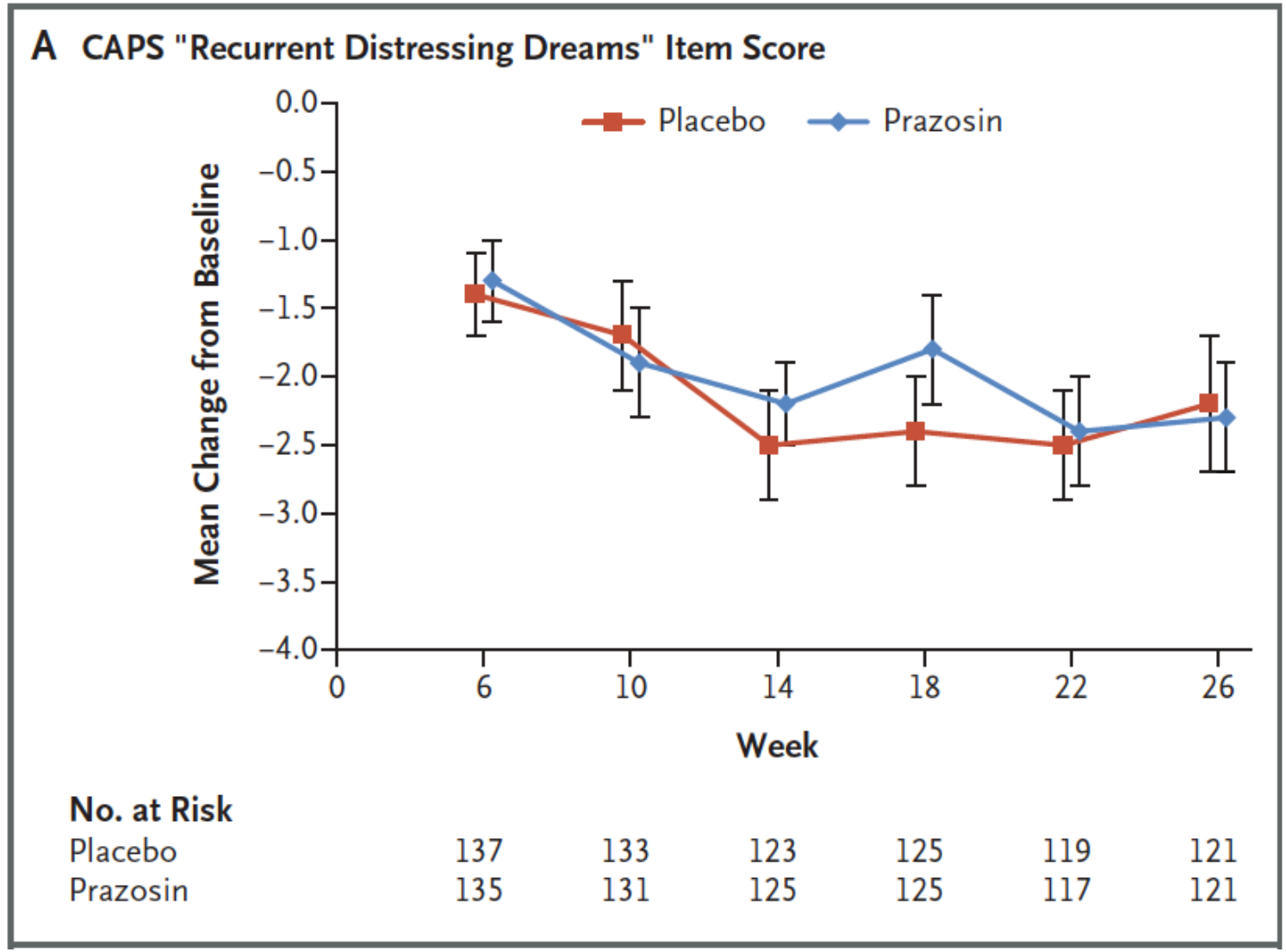
Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

RESULTS

A total of 304 participants underwent randomization; 152 were assigned to prazosin, and 152 to placebo. At 10 weeks, there were no significant differences between the prazosin group and the placebo group in the mean change from baseline in the CAPS item B2 score (between-group difference, 0.2; 95% confidence interval [CI], −0.3 to 0.8; P=0.38), in the mean change in PSQI score (between-group difference, 0.1; 95% CI, −0.9 to 1.1; P=0.80), or in the CGIC score (between-group difference, 0; 95% CI, −0.3 to 0.3; P=0.96). There were no significant differences in these measures at 26 weeks (a secondary outcome) or in other secondary outcomes. At 10 weeks, the mean difference between the prazosin group and the placebo group in the change from baseline in supine systolic blood pressure was a decrease of 6.7 mm Hg. The adverse event of new or worsening suicidal ideation occurred in 8% of the participants assigned to prazosin versus 15% of those assigned to placebo.

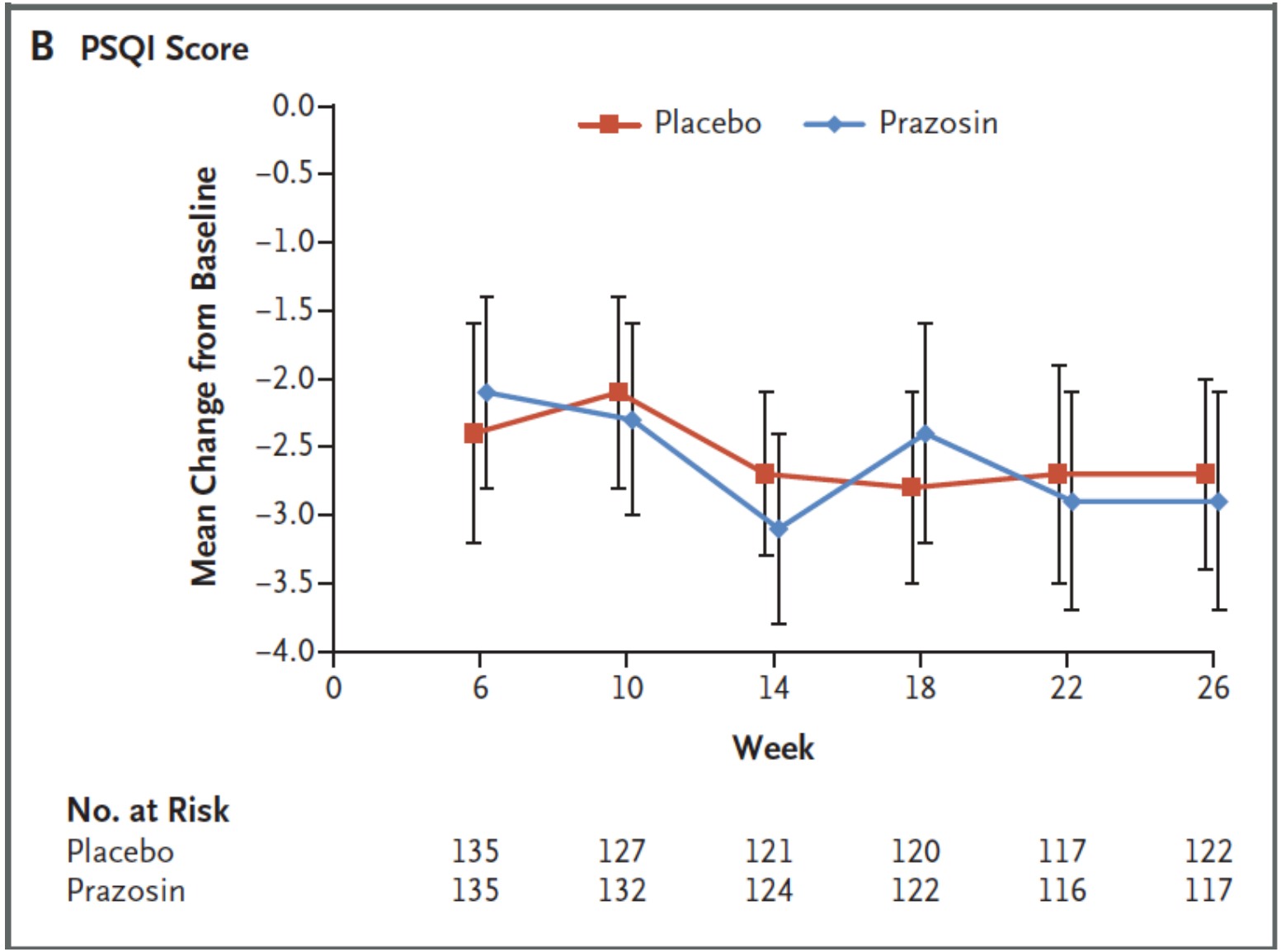
Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

change in score from baseline to 10 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 (scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams)



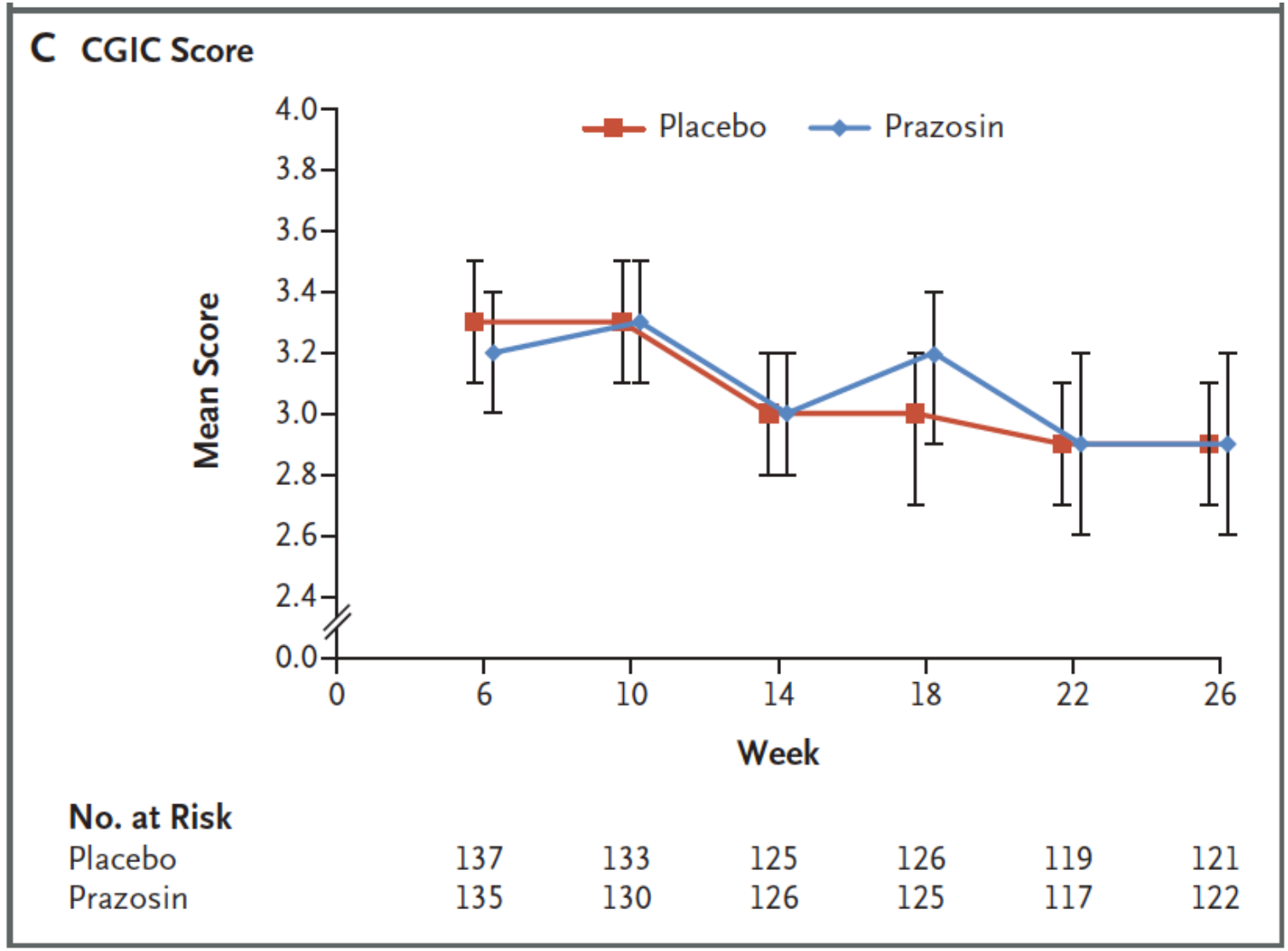
Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

the change in Pittsburgh Sleep Quality Index (PSQI) score from baseline to 10 weeks (scores range from 0 to 21, with higher scores indicating worse sleep quality)



Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

the Clinical Global Impression of Change (CGIC) score at 10 weeks (range, 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change from baseline; the CGIC assessed the participant's ability to function in daily activities and the participant's sense of well-being)



Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

CONCLUSIONS

In this trial involving military veterans who had chronic PTSD, prazosin did not alleviate distressing dreams or improve sleep quality. (Funded by the Department of Veterans Affairs Cooperative Studies Program; PACT ClinicalTrials.gov number, NCT00532493.)

These results contrast with previous smaller randomized trials of prazosin involving a total of 283 active-duty service members, veterans, and civilian participants, which showed efficacy of prazosin with respect to PTSD-related nightmares, sleep disturbance, and overall clinical function.10-15 The failure of the current trial to show benefits does not appear to be attributable to the dose of prazosin, which was higher than in all but one of the previous trials.

A possible explanation for these negative results is selection bias resulting from recruitment of patients who were mainly in clinically stable condition, since symptoms in such patients were less likely to be ameliorated with antiadrenergic treatment. Concern about the increasing incidence of suicide and of violent behavior among veterans led the planning committee to make psychosocial instability an exclusion criterion for participation in the trial. None of the previous smaller randomized trials of prazosin for PTSD had such an exclusion criterion.

The current results notwithstanding, previous single-site trials of prazosin have shown that there may be veterans with PTSD of many years' duration who derive a benefit from prazosin with respect to trauma-related nightmares, sleep disruption, and daytime hyperarousal symptoms. Further studies with more refined characterization of autonomic nervous system activity and nocturnal behaviors are needed to determine whether there might be subgroups of veterans with PTSD who can benefit from prazosin.

Alpha-Adrenergic Receptors in PTSD — Failure or Time for Precision Medicine?

Perhaps the most important lesson from this trial is a reminder that PTSD is a cluster of disorders that share trauma exposure as a cause but that can manifest with different combinations of symptoms. Even though rational neuronal system-based therapy, including α1-adrenergic antagonism, may fit neatly with our current under-standing of the disorder, only a subgroup of the millions of patients with PTSD may respond to an approach targeting α1-adrenergic receptors. Without recognized biomarkers and intermediate phenotypes that identify patients with dysregulated adrenergic activation, it may not be broadly effective to target this system — particularly in trials that recruit from a population that may already be receiving similar classes of medication.

Future trials would ideally have biologic demonstration of target engagement. Biologically based precision medicine in psychiatry is only just beginning to be adopted,10 but such an approach is indispensable for the identification of patients who are most likely to respond to targeted treatments.

Kerry I. Ressler. M.D.. Ph.D.

N ENGL J MED 378;6 NEJM.ORG FEBRUARY 8, 2018

Prazosin Is Ineffective for Chronic PTSD in Military Veterans

As the authors note, these findings may have been negative because participants were relatively stable, non-suicidal veterans without substance dependence who were not deemed ill enough by their treating clinicians to treat openly with prazosin. Also, many were economically stable (i.e., were already receiving disability support). Participants were not screened for sleep apnea, which could have interfered with prazosin's effects.

Finally, relatively lower baseline blood pressure and low rate of benzodiazepine use may have indicated that these participants had a PTSD subtype that was less adrenergically driven, highlighting the heterogeneity of PTSD. We need better ways to subtype patients and personalize treatments.

NEJM Journal Watch
PSYCHIATRY

Peter Roy-Byrne, MD (Feb 7, 2018)

Association Between Insight and Outcome of Psychotherapy: Systematic Review and Meta-Analysis

Simone Jennissen, M.Sc., Julia Huber, M.Sc., Johannes C. Ehrenthal, Ph.D., Henning Schauenburg, M.D., Ulrike Dinger, D.Sc., M.D.

Objective: An increased understanding of repetitive dysfunctional patterns and their relationship to an individual's life history is regarded as a key mechanism of change in insight-oriented therapies. At the same time, empirical research on the insight-outcome relationship is rare, and its generalizability is restricted by the use of a wide range of definitions and methods among studies. The authors conducted a meta-analysis to systematically examine the association between patient insight and psychotherapy outcome across a range of treatment modalities.

Am J Psychiatry 175:10, October 2018

Association Between Insight and Outcome of Psychotherapy: Systematic Review and Meta-Analysis

Method: Insight was defined as patients' understanding of associations between past and present experiences, typical relationship patterns, and the relation between interpersonal challenges, emotional experience, and psychological symptoms. From 13,849 initially identified abstracts, the authors extracted 23 independent effect sizes. A random-effects meta-analysis was performed to assess the magnitude of the insight-outcome relationship. Risk of publication bias was assessed with funnel plot inspections, Egger's regression test, and Duval and Tweedie's trim-and-fill procedure as sensitivity analyses.

Am J Psychiatry 175:10, October 2018

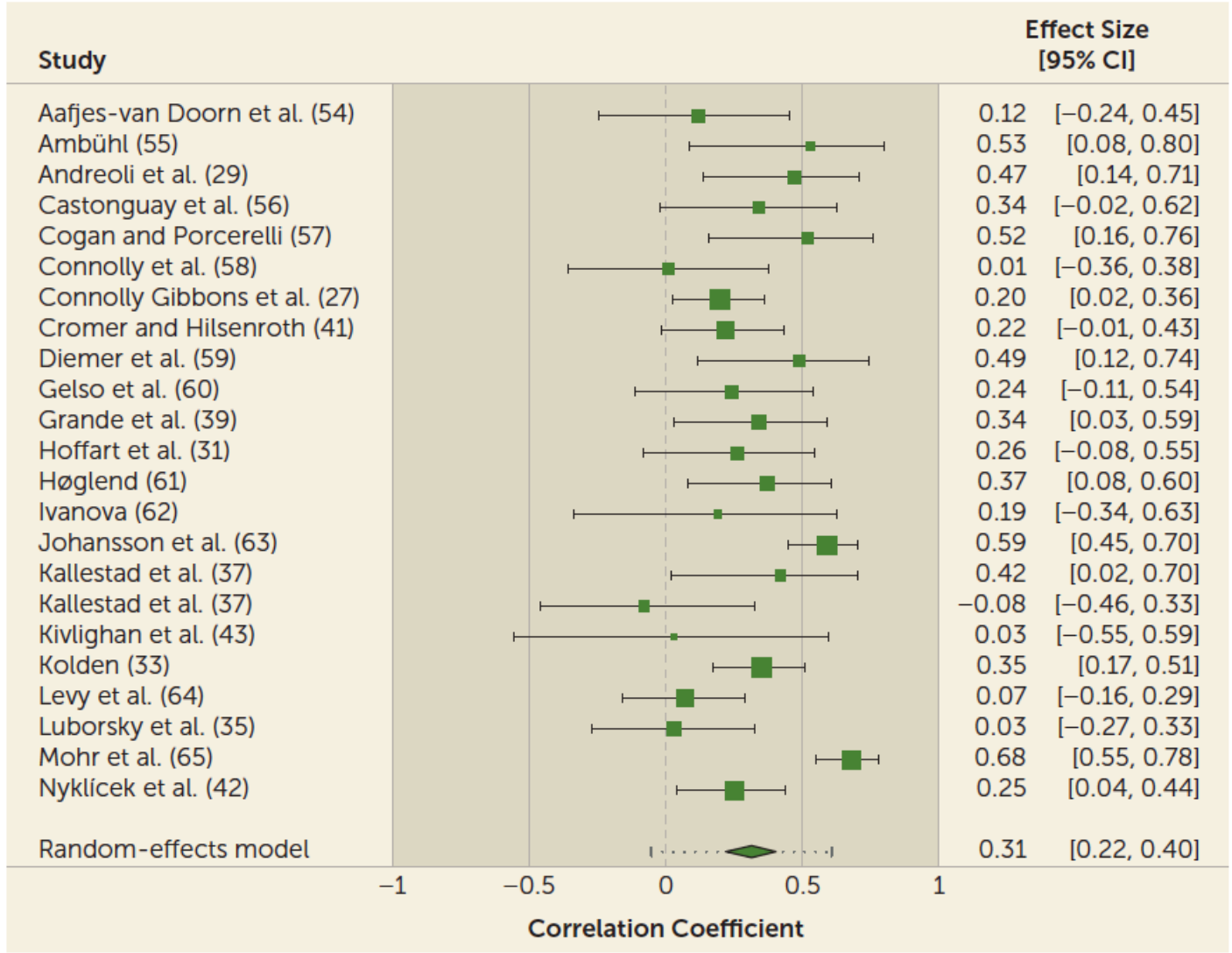
Association Between Insight and Outcome of Psychotherapy: Systematic Review and Meta-Analysis

Results: A significant, moderate correlation (r=0.31) was observed between insight and treatment outcome. Sensitivity analyses demonstrated the robustness of the results.

Conclusions: The findings support the importance of in-sight for psychotherapy outcome. Insight may be a relevant mechanism of change across different treatment modalities.

Am J Psychiatry 175:10, October 2018

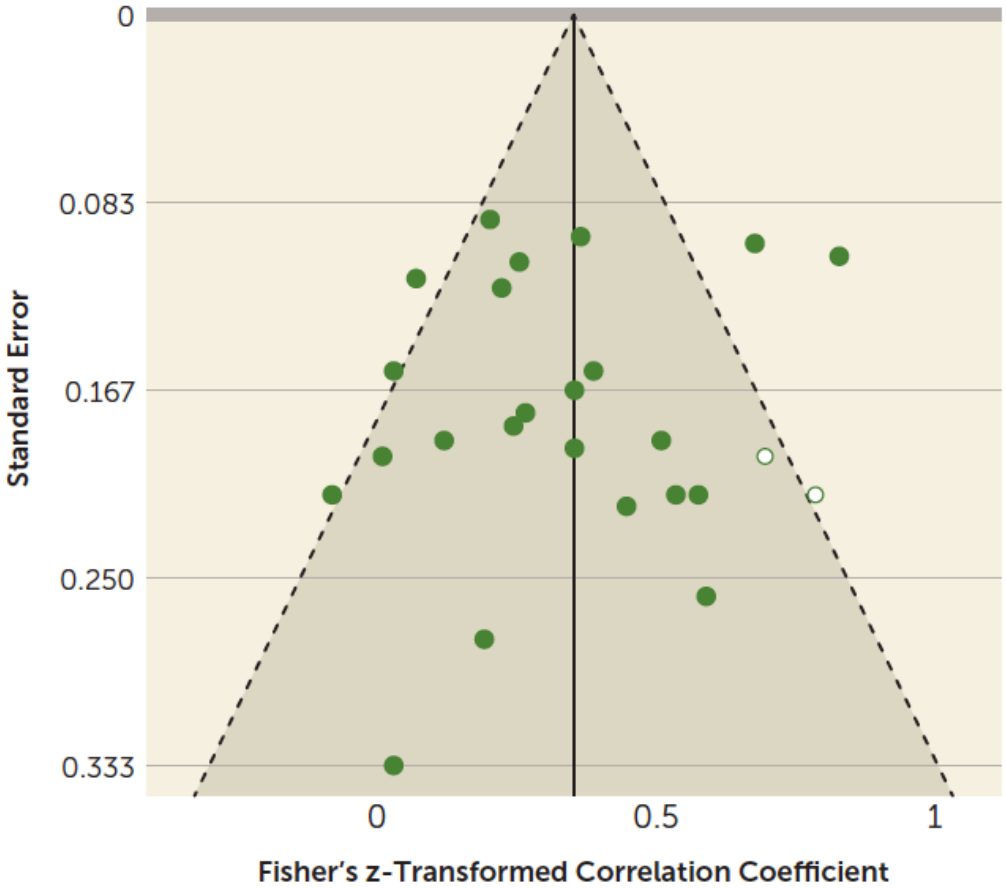
FIGURE 2. Forest Plot of Effect Sizes Measured as Correlations Between Insight and Outcome in a Meta-Analysis of Insight and Outcome of Psychotherapy[a]



[a] In the graph, the squares represent the effect sizes, their area the relative weight assigned to each effect size, and the horizontal lines the 95% confidence intervals. The center of the diamond at the bottom depicts the mean effect size and its width the 95% confidence interval (precision of the mean estimate). The dotted line indicates the bounds of the prediction interval (distribution of true effect sizes).

Association Between Insight and Outcome of Psychotherapy: Systematic Review and Meta-Analysis

FIGURE 3. Funnel Plot of Transformed Correlations Between Insight and Outcome Depicted Against Their Standard Errors, in a Meta-Analysis of Insight and Outcome of Psychotherapy[a]



[a] The green dots indicate the observed effect sizes, and the white dots represent the effect sizes estimated as missing by the trim-and-fill method.

Association Between Insight and Outcome of Psychotherapy: Systematic Review and Meta-Analysis

Journey of a Thousand Miles

Robert Michels, M.D.

Jennissen et al. performed a meta-analysis of 23 reports, covering a variety of conditions and therapies, that studied the correlation between insight and treatment outcome. As the authors report, the data are correlational and do not allow for causal inferences. It has not yet been demonstrated that change in insight precedes change in outcome. Because of the small number of studies in the literature, we have not been able to determine the importance of treatment type, diagnostic category, or specific measures used—all essential before we can begin to modify the therapy to see what changes improve outcome. Only then will the research agenda make a difference to patients. This analysis is an important beginning, however. As it is said, “the journey of a thousand miles begins with a single step.”

Am J Psychiatry 175:10, October 2018

JAMA Psychiatry | Original Investigation

Association of Testosterone Treatment With Alleviation of Depressive Symptoms in Men

A Systematic Review and Meta-analysis

Andreas Walther, PhD; Jonas Breidenstein, BSc; Robert Miller, PhD

IMPORTANCE Countering depressive disorders is a public health priority. Currently, antidepressants are the first-line treatment, although they show modest effects. In men, testosterone treatment is a controversial alternative or adjunct treatment option.

OBJECTIVES To examine the association of testosterone treatment with alleviation of depressive symptoms in men and to clarify moderating effects of testosterone status, depression status, age, treatment duration, and dosage.

DATA SOURCES English-language studies published in peer-reviewed journals identified from PubMed/Medline, Embase, Scopus, PsychINFO, and the Cochrane Controlled Trials Register from database inception to March 5, 2018, using the search terms *testosterone*, *mood*, *administration*, *dosage*, *adverse effects*, *deficiency*, *standards*, *therapeutic use*, *therapy*, *treatment*, and *supplementation*.

Association of Testosterone Treatment With Alleviation of Depressive Symptoms in Men

A Systematic Review and Meta-analysis

STUDY SELECTION Randomized placebo-controlled clinical trials (RCTs) of testosterone treatment that together cover a broad age range and hypogonadal or eugonadal men reporting depressive symptoms on psychometrically validated depression scales.

DATA EXTRACTION AND SYNTHESIS Of 7690 identified records, 469 were evaluated against full study inclusion criteria after removing duplicates, reviews, and studies that did not examine male patients or testosterone. Quality assessment and data extraction from the remaining 27 RCTs were performed.

MAIN OUTCOMES AND MEASURES Primary outcomes were testosterone treatment effectiveness (standardized score difference after treatment), efficacy (proportion of patients who responded to testosterone treatment with a score reduction of 50% or greater), and acceptability (proportion of patients who withdrew for any reason).

Association of Testosterone Treatment With Alleviation of Depressive Symptoms in Men

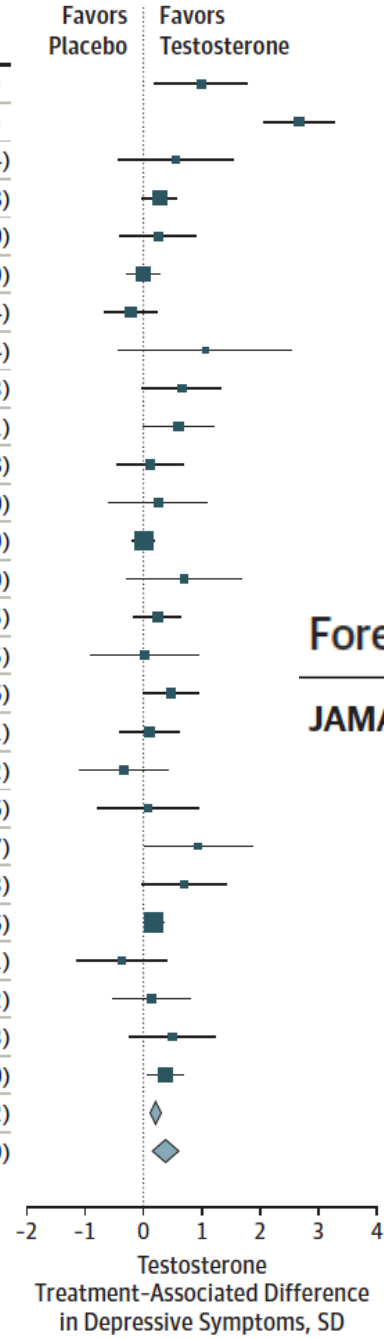
A Systematic Review and Meta-analysis

RESULTS Random-effects meta-analysis of 27 RCTs including 1890 men suggested that testosterone treatment is associated with a significant reduction in depressive symptoms compared with placebo (Hedges *g*, 0.21; 95% CI, 0.10-0.32), showing an efficacy of odds ratio (OR), 2.30 (95% CI, 1.30-4.06). There was no significant difference between acceptability of testosterone treatment and placebo (OR, 0.79; 95% CI, 0.61-1.01). Meta-regression models suggested significant interactions for testosterone treatment with dosage and symptom variability at baseline. In the most conservative bias scenario, testosterone treatment remained significant whenever dosages greater than 0.5 g/wk were administered and symptom variability was kept low.

CONCLUSIONS AND RELEVANCE Testosterone treatment appears to be effective and efficacious in reducing depressive symptoms in men, particularly when higher-dosage regimens were applied in carefully selected samples. However, given the heterogeneity of the included RCTs, more preregistered trials are needed that explicitly examine depression as the primary end point and consider relevant moderators.

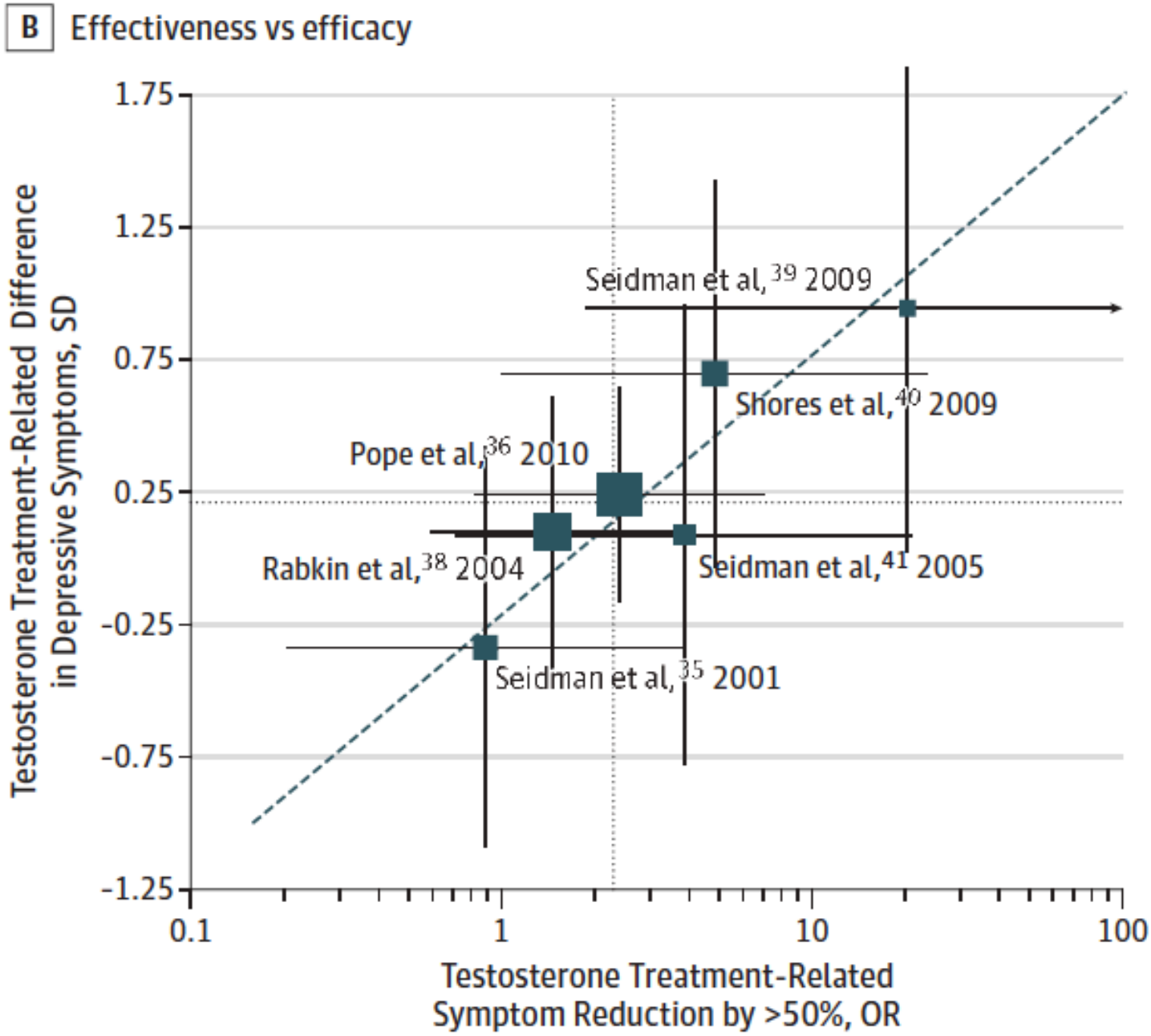
A Effectiveness and estimates for all studies

Source	Jadad Score	Effect (95% CI)
Borst et al,[47] 2014	3	0.98 (0.19 to 1.78)
Cavallini et al,[34] 2004	3	2.67 (2.07 to 3.27)
Cherrier et al,[48] 2015	5	0.56 (-0.42 to 1.54)
Giltay et al,[32] 2010	3	0.28 (-0.02 to 0.58)
Grinspoon et al,[71] 2000	3	0.25 (-0.40 to 0.90)
Hackett et al,[33] 2013	3	0.00 (-0.29 to 0.29)
Haren et al,[80] 2005	5	-0.22 (-0.68 to 0.24)
Kenny et al,[72] 2004	3	1.06 (-0.42 to 2.54)
Lu et al,[73] 2006	3	0.66 (-0.02 to 1.33)
Malkin et al,[74] 2004	4	0.60 (-0.01 to 1.21)
Mirdamadi et al,[49] 2014	2	0.11 (-0.45 to 0.68)
Orengo et al,[75] 2005	3	0.25 (-0.59 to 1.10)
Pope et al,[57] 2000	3	0.00 (-0.19 to 0.19)
Pope et al,[37] 2003	5	0.70 (-0.30 to 1.69)
Pope et al,[36] 2010	5	0.24 (-0.17 to 0.65)
Pugh et al,[76] 2004	2	0.02 (-0.91 to 0.95)
Rabkin et al,[62] 2000	5	0.47 (-0.01 to 0.96)
Rabkin et al,[38] 2004	5	0.10 (-0.42 to 0.61)
Seidman et al,[35] 2001	4	-0.34 (-1.09 to 0.42)
Seidman et al,[41] 2005	5	0.09 (-0.78 to 0.96)
Seidman et al,[39] 2009	5	0.94 (0.02 to 1.87)
Shores et al,[40] 2009	5	0.70 (-0.03 to 1.43)
Snyder et al,[42] 2016	5	0.18 (-0.01 to 0.36)
Stout et al,[77] 2012	5	-0.37 (-1.15 to 0.41)
Svartberg et al,[78] 2008	3	0.14 (-0.53 to 0.82)
Vaughan et al,[58] 2007	5	0.50 (-0.23 to 1.23)
Zhang et al,[79] 2012	1	0.38 (0.07 to 0.70)
Robust RE estimate		0.21 (0.10 to 0.32)
Naive RE estimate		0.37 (0.15 to 0.59)

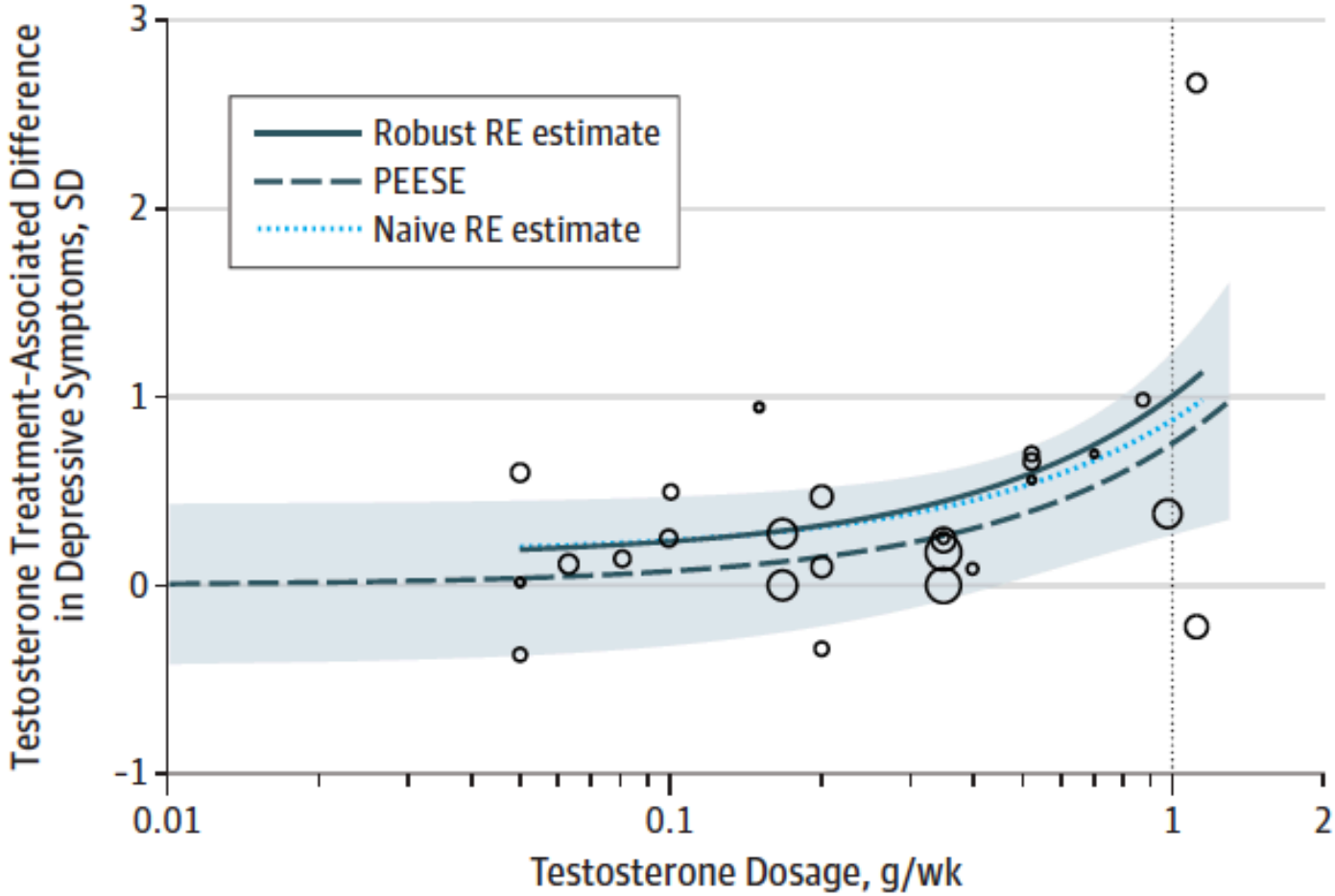


Forest Plots of Treatment Effectiveness and Efficacy

JAMA Psychiatry January 2019 Volume 76, Number 1


B Effectiveness vs efficacy
1.75
1.25
0.75
0.25
-0.25
-0.75
-1.25
Testosterone Treatment-Related Difference in Depressive Symptoms, SD
Seidman et al,[39] 2009
Shores et al,[40] 2009
Pope et al,[36] 2010
Rabkin et al,[38] 2004
Seidman et al,[41] 2005
Seidman et al,[35] 2001
0.1
1
10
100
Testosterone Treatment-Related Symptom Reduction by >50%, OR

B Dose-response association



Testosterone Treatment of Depressive Disorders in Men
Too Much Smoke, Not Enough High-Quality Evidence

Shalender Bhasin, MB, BS; Stuart Seidman, MD

A large placebo-controlled, randomized, double-blind, multicenter study of topical testosterone replacement therapy in 6000 symptomatic hypogonadal men at increased risk for cardiovascular disease is currently being conducted in the United States (the TRAVERSE trial). One sub study of the TRAVERSE trial will determine the efficacy of testosterone re-placement therapy in inducing remission of depression in middle-aged and older hypogonadal men with late-onset DD. Until then, the clinicians should follow the Endocrine Society guideline for testosterone replacement therapy of androgen-deficient men; **the available data do not support the use of testosterone treatment, especially in supraphysiologic doses, for the treatment of depressive disorders in men**.

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Testosterone for Depression? Wait and See

Therefore, although one might be able to conclude that some older men feel a little better with testosterone, this meta-analysis did not show that it is an effective treatment for any depressive disorder. The long-term safety of testosterone therapy, especially in the higher doses that the meta-analysis suggests as having greater effects, has not been demonstrated. Clinicians should be extremely cautious about using this hormone in patients who do not have a specific medical indication.

NEJM Journal Watch PSYCHIATRY

Steven Dubovsky, MD, (Nov 29, 2018)

Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover[a,1], Corey S. Davis[b], Sanford C. Gordon[c], and Keith Humphreys[a,d]

Medical cannabis has been touted as a solution to the US opioid overdose crisis since Bachhuber et al.* found that from 1999 to 2010 states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality. That research received substantial attention in the scientific literature and popular press and served as a talking point for the cannabis industry and its advocates, despite caveats from the authors and others to exercise caution when using ecological correlations to draw causal, individual-level conclusions.

*M. A. Bachhuber, B. Saloner, C. O. Cunningham, C. L. Barry, Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern. Med. 174, 1668–1673 (2014).

www.pnas.org/cgi/doi/10.1073/pnas.1903434116

Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover[a,1], Corey S. Davis[b], Sanford C. Gordon[c], and Keith Humphreys[a,d]

In this study, we used the same methods to extend Bachhuber et al.'s analysis through 2017. Not only did findings from the original analysis not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from −21% to +23%and remained positive after accounting for recreational cannabis laws. We also uncovered no evidence that either broader (recreational) or more restrictive (low-tetrahydrocannabinol) cannabis laws were associated with changes in opioid overdose mortality.

www.pnas.org/cgi/doi/10.1073/pnas.1903434116

Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover[a,1], Corey S. Davis[b], Sanford C. Gordon[c], and Keith Humphreys[a,d]

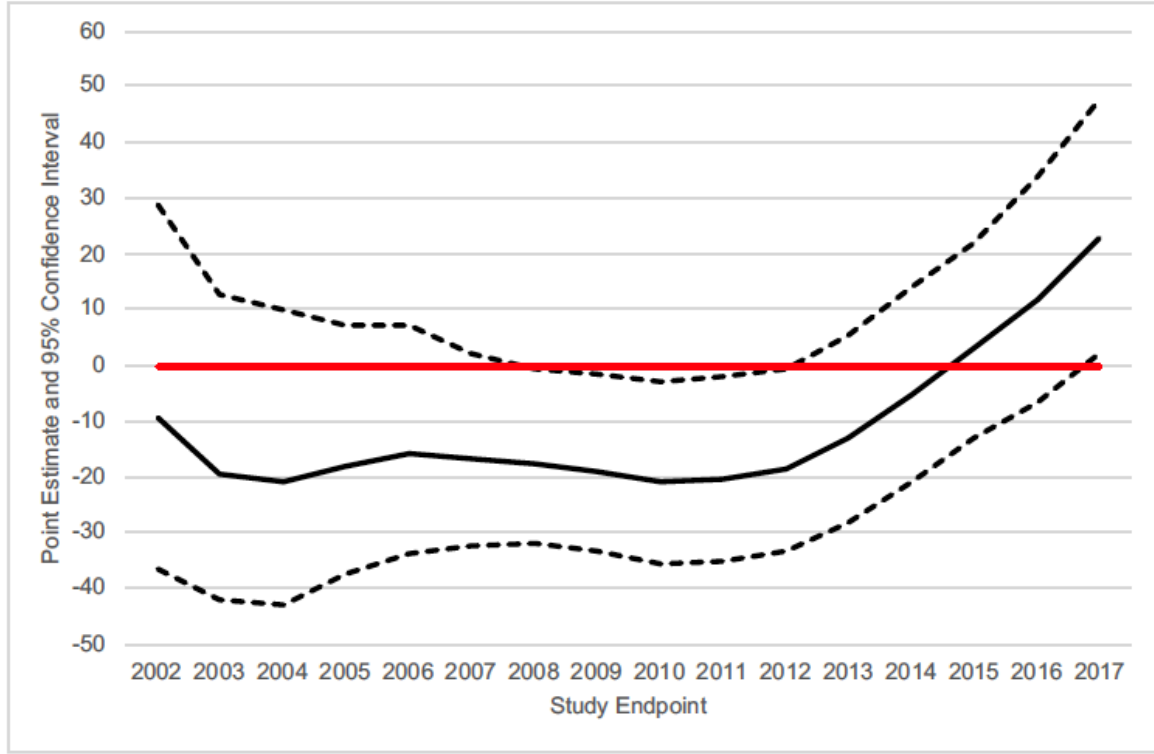


Fig. 1. Changes in point estimate and 95% CI of association between medical cannabis law and age-adjusted opioid overdose death rate by the last year included in the analysis since 1999. Fixed (year and state) and time-varying effects (prescription drug monitoring program, state unemployment, pain management clinic oversight laws, and prescription drug identification laws) were also adjusted for.

Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover[a,1], Corey S. Davis[b], Sanford C. Gordon[c], and Keith Humphreys[a,d]

We find it unlikely that medical cannabis—used by about 2.5% of the US population—has exerted large conflicting effects on opioid overdose mortality. A more plausible interpretation is that this association is spurious. Moreover, if such relationships do exist, they cannot be rigorously discerned with aggregate data. Research into therapeutic potential of cannabis should continue, but the claim that enacting medical cannabis laws will reduce opioid overdose death should be met with skepticism.

www.pnas.org/cgi/doi/10.1073/pnas.1903434116

Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans
A Randomized Clinical Trial

Jerome A. Yesavage, MD; J. Kaci Fairchild, PhD; Zhibao Mi, PhD; Kousick Biswas, PhD; Anne Davis-Karim, PharmD; Ciaran S. Phibbs, PhD; Steven D. Forman, MD, PhD; Michael Thase, MD; Leanne M. Williams, PhD; Amit Etkin, MD, PhD; Ruth O'Hara, PhD; Gerald Georgette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MS; Mark S. George, MD; for the VA Cooperative Studies Program Study Team

Question Is repetitive transcranial magnetic stimulation an efficacious treatment for treatment-resistant major depression in patients who are veterans?

Findings In this randomized clinical trial of 164 US veterans with depression, the overall remission rate was 39%, with no significant difference between the active and sham groups. Patients with comorbid posttraumatic stress disorder showed the least improvement.

Meaning These findings may reflect the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in this treatment-resistant population.

Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans

OBJECTIVE To determine the efficacy of rTMS in the treatment of TRMD in veterans.

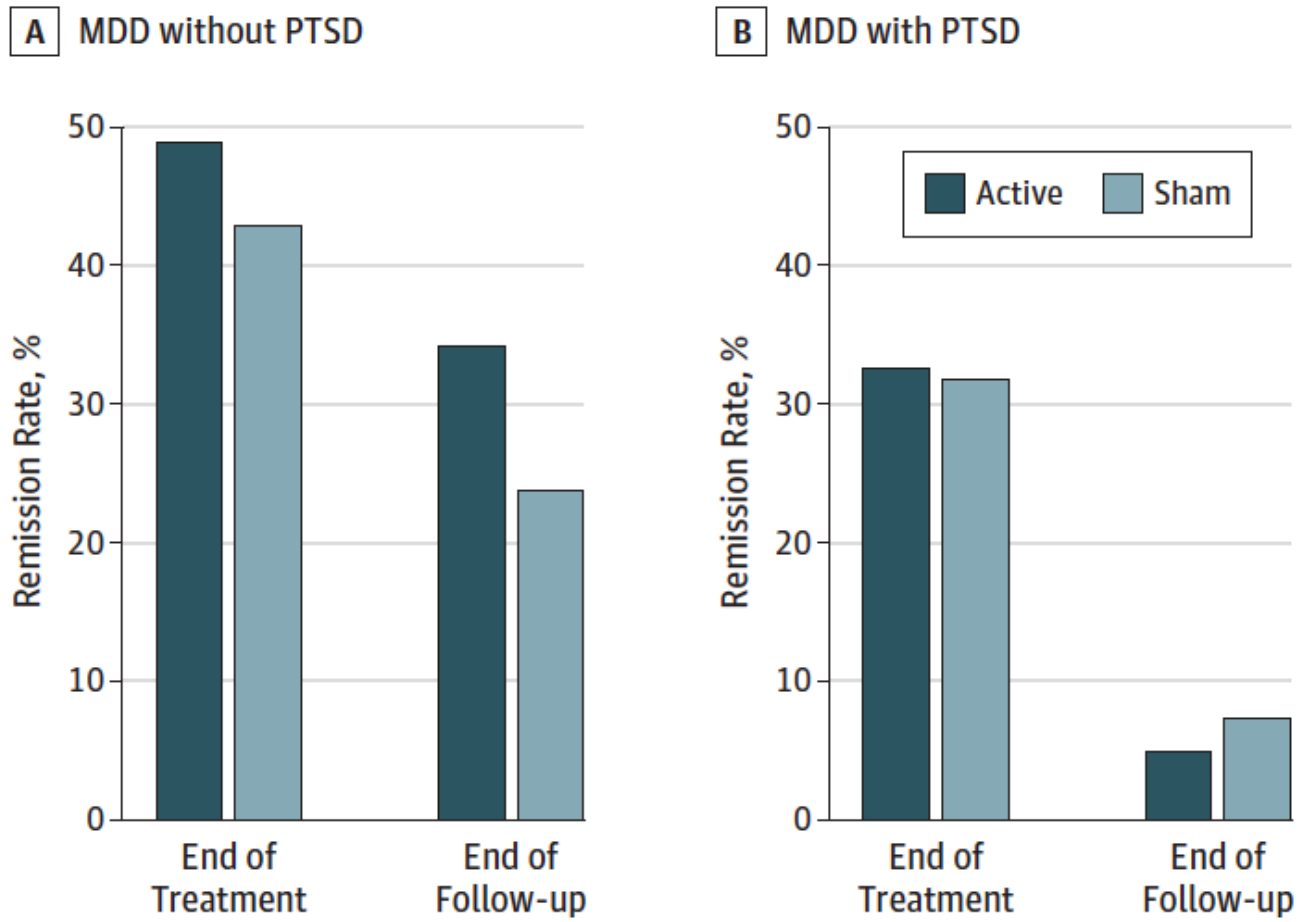
DESIGN, SETTING, AND PARTICIPANTS A double-blind, sham-controlled randomized clinical trial was conducted from September 1, 2012, to December 31, 2016, in 9 Veterans Affairs medical centers. A total of 164 veterans with TRD participated.

INTERVENTIONS Participants were randomized to either left prefrontal rTMS treatment (10 Hz, 120% motor threshold, 4000 pulses/session) or to sham (control) rTMS treatment for up to 30 treatment sessions.

MAIN OUTCOMES AND MEASURES The primary dependent measure of the intention-to-treat analysis was remission rate (Hamilton Rating Scale for Depression score ≤10, indicating that depression is in remission and not a clinically significant burden), and secondary analyses were conducted on other indices of posttraumatic stress disorder, depression, hopelessness, suicidality, and quality of life.

RESULTS The 164 participants had a mean (SD) age of 55.2 (12.4) years, 132 (80.5%) were men, and 126 (76.8%) were of white race. Of these, 81 were randomized to receive active rTMS and 83 to receive sham. For the primary analysis of remission, there was no significant effect of treatment (odds ratio, 1.16; 95% CI, 0.59-2.26; *P* = .67). At the end of the acute treatment phase, 33 of 81 (40.7%) of those in the active treatment group achieved remission of depressive symptoms compared with 31 of 83 (37.4%) of those in the sham treatment group. Overall, 64 of 164 (39.0%) of the participants achieved remission.

Figure 2. Hamilton Rating Scale for Depression Remission Rates Stratified by Presence or Absence of Posttraumatic Stress Disorder (PTSD)



CONCLUSIONS AND RELEVANCE A total of 39.0% of the veterans who participated in this trial experienced clinically significant improvement resulting in remission of depressive symptoms; however, there was no evidence of difference in remission rates between the active and sham treatments. These findings may reflect the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in this treatment-resistant population.

Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: Not So Fast

Perhaps the most important take-home message is that becoming 33% less depressed after failure to respond to only two antidepressants (or a mean of 1.5 trials in the 2010 study) is not a ringing endorsement of rTMS for complex and highly refractory depression.

NEJM Journal Watch
PSYCHIATRY

Steven Dubovsky, MD (Jul 16, 2018)

The Search for Treatments for Depressed Veterans—Of Paramount Importance, Yet Still Elusive

Charles B. Nemeroff, MD, PhD

This is an important negative study, but it does not fully answer the question of what the appropriate role for rTMS is in the treatment of TRD in veterans. As personalized medicine in psychiatry progresses, we will likely someday soon be able to accurately identify the best treatment for individual patients. This will likely involve both genomic markers as well as functional brain imaging predictors of response.

Comparison of the Safety Planning Intervention With Follow-up vs Usual Care of Suicidal Patients Treated in the Emergency Department

Barbara Stanley, PhD; Gregory K. Brown, PhD; Lisa A. Brenner, PhD; Hanga C. Galfalvy, PhD; Glenn W. Currier, MD; Kerry L. Knox, PhD; Sadia R. Chaudhury, PhD; Ashley L. Bush, MMA; Kelly L. Green, PhD

OBJECTIVE To determine whether the Safety Planning Intervention (SPI), administered in EDs with follow-up contact for suicidal patients, was associated with reduced suicidal behavior and improved outpatient treatment engagement in the 6 months following discharge, an established high-risk period.

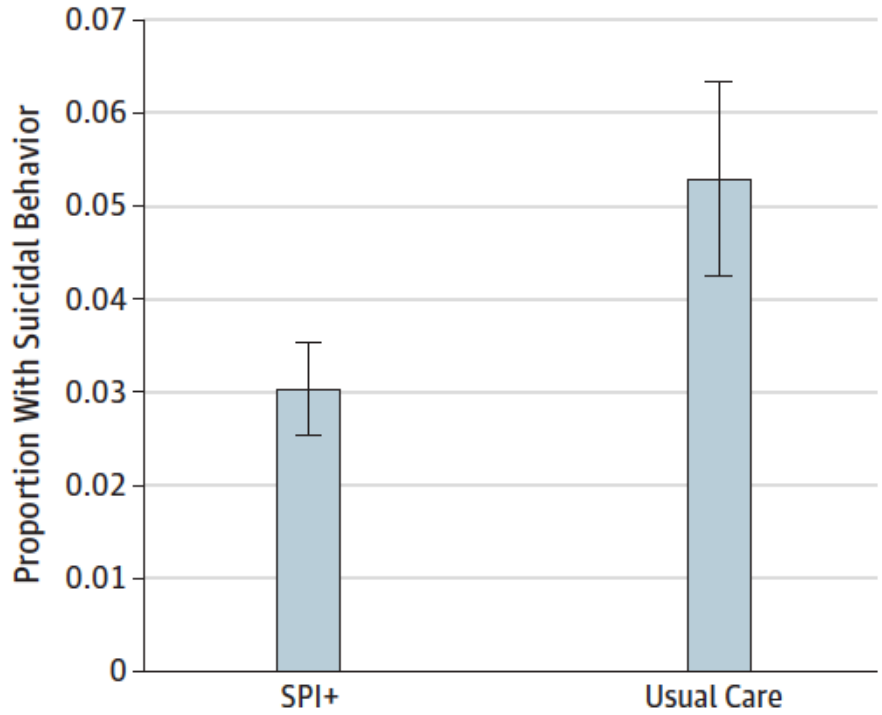
DESIGN, SETTING, AND PARTICIPANTS Cohort comparison design with 6-month follow-up at 9 EDs (5 intervention sites and 4 control sites) in Veterans Health Administration hospital EDs. Patients were eligible for the study if they were 18 years or older, had an ED visit for a suicide-related concern, had inpatient hospitalization not clinically indicated, and were able to read English. Data were collected between 2010 and 2015; data were analyzed between 2016 and 2018.

INTERVENTIONS The intervention combines SPI and telephone follow-up. The SPI was defined as a brief clinical intervention that combined evidence-based strategies to reduce suicidal behavior through a prioritized list of coping skills and strategies. In telephone follow-up, patients were contacted at least 2 times to monitor suicide risk, review and revise the SPI, and support treatment engagement.

MAIN OUTCOMES AND MEASURES Suicidal behavior and behavioral health outpatient services extracted from medical records for 6 months following ED discharge.

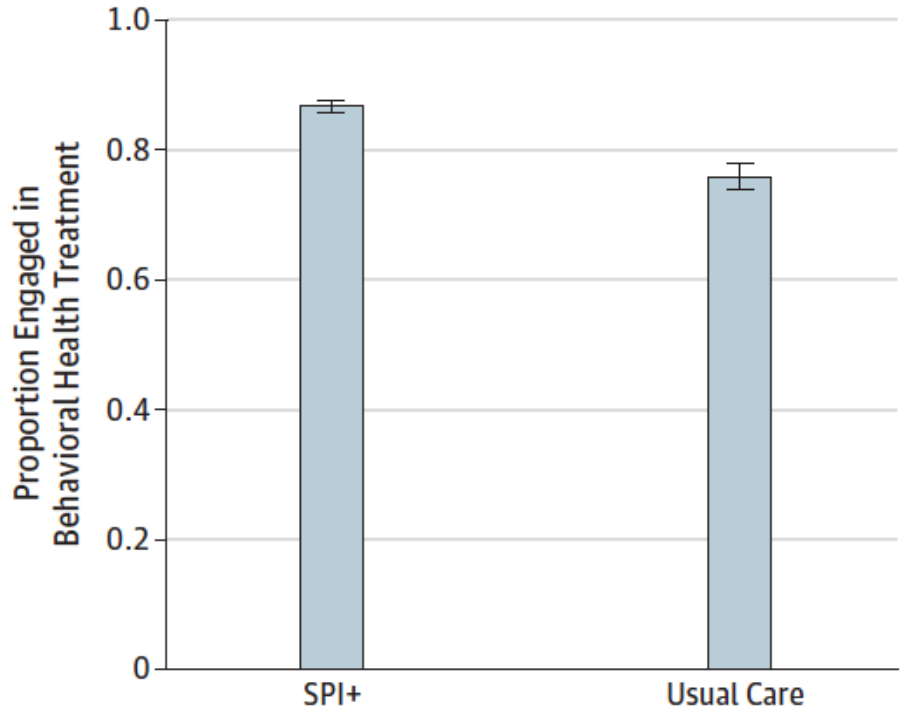
RESULTS Of the 1640 total patients, 1186 were in the intervention group and 454 were in the comparison group. Patients in the intervention group had a mean (SD) age of 47.15 (14.89) years and 88.5% were men (n = 1050); patients in the comparison group had a mean (SD) age of 49.38 (14.47) years and 88.1% were men (n = 400). Patients in the SPI+ condition were less likely to engage in suicidal behavior (n = 36 of 1186; 3.03%) than those receiving usual care (n = 24 of 454; 5.29%) during the 6-month follow-up period. The SPI+ was associated with 45% fewer suicidal behaviors, approximately halving the odds of suicidal behavior over 6 months (odds ratio, 0.56; 95% CI, 0.33-0.95, *P* = .03). Intervention patients had more than double the odds of attending at least 1 outpatient mental health visit (odds ratio, 2.06; 95% CI, 1.57-2.71; *P* < .001).

Figure 1. Suicidal Behavior in 6-Month Follow-up for Safety Planning Intervention With Structured Follow-up Telephone Contact (SPI+) and Usual Care



Proportion of patients with suicidal behavior in the 6 months following emergency department discharge in SPI+ compared with usual care patients. Error bars denote the standard error of the proportion.

Figure 2. Treatment Engagement in 6-Month Follow-up for Safety Planning Intervention With Structured Follow-up Telephone Contact (SPI+) and Usual Care



Proportion of patients with at least 1 outpatient behavioral health appointment in the 6 months following emergency department discharge in SPI+ compared with usual care patients. Error bars denote the standard error of the proportion.

CONCLUSIONS AND RELEVANCE This large-scale cohort comparison study found that SPI+ was associated with a reduction in suicidal behavior and increased treatment engagement among suicidal patients following ED discharge and may be a valuable clinical tool in health care settings.

Question Can a brief suicide prevention intervention reduce suicidal behaviors and improve treatment engagement among patients who present to the emergency department for suicide-related concerns?

Findings In this cohort comparison study, patients who visited the emergency department for suicide-related concerns and received the Safety Planning Intervention with structured follow-up telephone contact were half as likely to exhibit suicidal behavior and more than twice as likely to attend mental health treatment during the 6-month follow-up period compared with their counterparts who received usual care following their ED visit.

Meaning The Safety Planning Intervention with structured follow-up telephone contact may be an effective brief suicide prevention intervention that can be implemented in emergency departments.

Does a Safety Plan in the Emergency Department Prevent Suicide?

Because study outcomes were judged by retrospective chart review of nonrandomized samples treated in settings that likely differed in sundry ways, one cannot conclude that a comprehensive safety plan in the ED reduces later suicidality regardless of subsequent treatment.

Patients in both groups were not suicidal enough to be hospitalized and had very low rates of post-ED suicidal behavior.

Clinicians should certainly follow suicidal patients after ED discharge as much as possible and create viable treatment plans for them, but the assumption that these efforts will be more protective than ongoing treatment seems to lack face validity.

NEJM Journal Watch PSYCHIATRY

Steven Dubovsky, MD (Jul 27, 2018)

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

John F. Greden[a,*], Sagar V. Parikh[a], Anthony J. Rothschild[b], Michael E. Thase[c], Boadie W. Dunlop[d], Charles DeBattista[e], Charles R. Conway[f], Brent P. Forester[g], Francis M. Mondimore[h], Richard C. Shelton[i], Matthew Macaluso[j], James Li[k], Krystal Brown[l], Alexa Gilbert[k], Lindsey Burns[k], Michael R. Jablonski[k], Bryan Dechairo[k,l]

Current prescribing practices for major depressive disorder (MDD) produce limited treatment success. Although pharmacogenomics may improve outcomes by identifying genetically inappropriate medications, studies to date were limited in scope.

The GUIDED trial was a 24-week, randomized, controlled trial that evaluated outcomes when a pharmacogenomic test was used to guide medication selection (guided-care) compared to TAU.

Journal of Psychiatric Research 111 (2019) 59–67

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

Outpatients (N = 1167) diagnosed with MDD and with a patient- or clinician-reported inadequate response to at least one antidepressant were enrolled in the Genomics Used to Improve Depression Decisions (GUIDED) trial – a rater-and patient-blind randomized controlled trial.

Patients were randomized to treatment as usual (TAU) or a pharmacogenomics-guided intervention arm in which clinicians had access to a pharmacogenomic test report to inform medication selections (guided-care).

Medications were considered congruent ('use as directed' or 'use with caution' test categories) or incongruent ('use with increased caution and with more frequent monitoring' test category) with test results. Unblinding occurred after week 8.

Primary outcome was symptom improvement [change in 17-item Hamilton Depression Rating Scale (HAM-D17)] at week 8; secondary outcomes were response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤ 7) at week 8.

Journal of Psychiatric Research 111 (2019) 59–67

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

At week 8, symptom improvement for guided-care was not significantly different than TAU (27.2% versus 24.4%, p = 0.107); however, improvements in response (26.0% versus 19.9%, p = 0.013) and remission (15.3%versus 10.1%, p = 0.007) were statistically significant.

Patients taking incongruent medications prior to baseline who switched to congruent medications by week 8 experienced greater symptom improvement (33.5% versus 21.1%, p = 0.002), response (28.5% versus 16.7%, p = 0.036), and remission (21.5% versus 8.5%,p = 0.007) compared to those remaining incongruent.

Pharmacogenomic testing did not significantly improve mean symptoms but did significantly improve response and remission rates for difficult-to-treat depression patients over standard of care

Journal of Psychiatric Research 111 (2019) 59–67

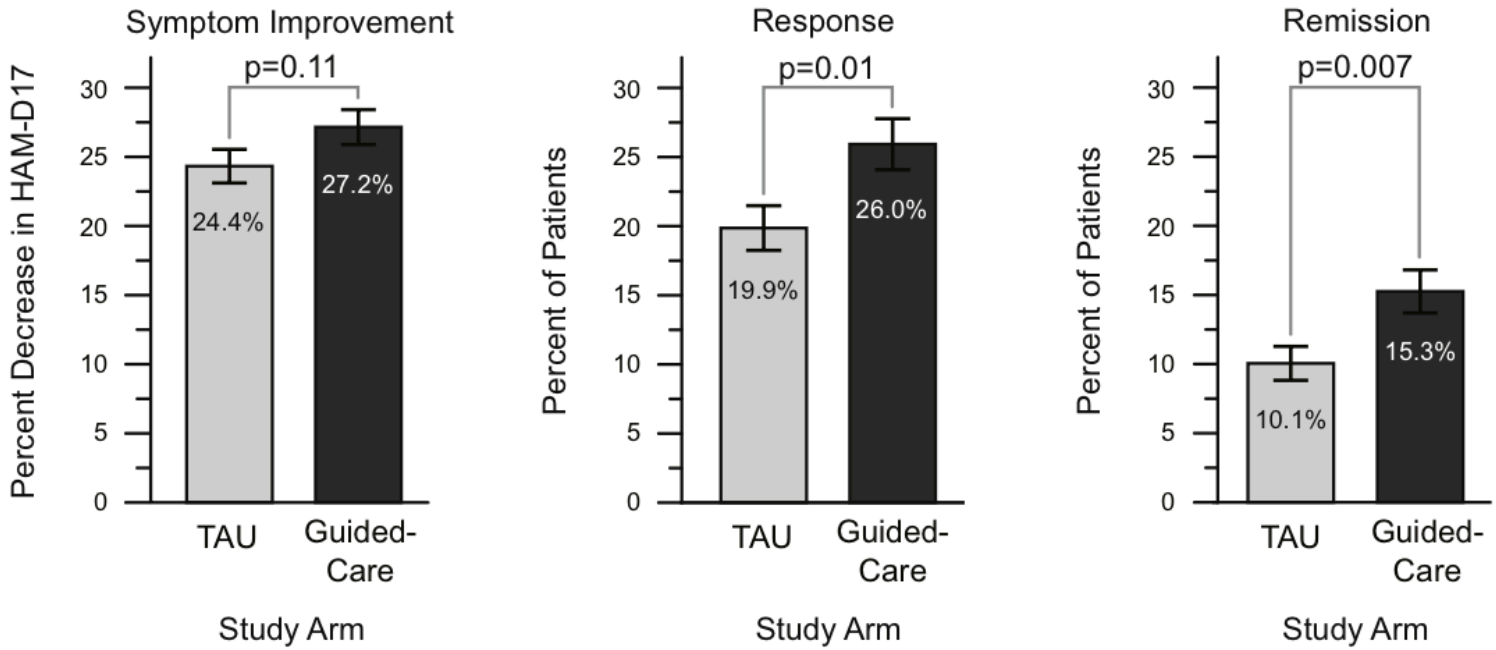


Fig. 1. Patient outcomes at week 8 in the pharmacogenomics guided-care arm (n = 560) compared to treatment as usual (n = 607). Outcomes were evaluated using the HAM-D17 depression rating scales.

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

In summary, this randomized controlled trial found that weighted and combined multi-gene pharmacogenomic testing significantly increased clinical response and remission rates for patients with MDD in the guided-care arm versus TAU. Pharmacogenomic testing pre-dominantly helped those patients whose treatment resistance may have been related to genetically incongruent medications. Without testing, patients and clinicians are unaware of potential ongoing gene-drug interactions. These results from the GUIDED trial indicate that pharmacogenomic testing is effective in improving response and remission rates among those with prior treatment resistance, particularly for patients who are treated with medications that are incongruent with their genetic profile

Genetic Testing to Improve Antidepressant Selection, Redux

Although genetic testing sounds promising, these results should be interpreted with great caution for several reasons:

- The test had no significant effects on the primary outcome.
- Effects on secondary outcomes were quite small (NNT, >10; not clinically meaningful).
- Clinicians were not blinded and could have inadvertently communicated group assignments to patients in active treatment, thereby increasing their hope and probability of response.
- No correction for multiple statistical testing was performed.
- The study was funded by the company that produces the test.

NEJM Journal Watch PSYCHIATRY

Claire Wilcox, MD (Jan 18, 2019)

Epigenetic Aging in Major Depressive Disorder

Laura K.M. Han, M.Sc., Moji Aghajani, Ph.D., Shaunna L. Clark, Ph.D., Robin F. Chan, Ph.D., Mohammad W. Hattab, Ph.D., Andrey A. Shabalin, Ph.D., Min Zhao, D.D.S., Gaurav Kumar, Ph.D., Lin Ying Xie, M.Sc., Rick Jansen, Ph.D., Yuri Milaneschi, Ph.D., Brian Dean, Ph.D., Karolina A. Aberg, Ph.D., Edwin J.C.G. van den Oord, Ph.D., Brenda W.J.H. Penninx, Ph.D.

Objective: Major depressive disorder is associated with an increased risk of mortality and aging-related diseases. The authors examined whether major depression is associated with higher epigenetic aging in blood as measured by DNA methylation (DNAm) patterns, whether clinical characteristics of major depression have a further impact on these patterns, and whether the findings replicate in brain tissue.

Am J Psychiatry 175:8, August 2018

Epigenetic Aging in Major Depressive Disorder

Method: DNAm age was estimated using all methylation sites in blood of 811 depressed patients and 319 control subjects with no lifetime psychiatric disorders and low depressive symptoms from the Netherlands Study of Depression and Anxiety. The residuals of the DNAm age estimates regressed on chronological age were calculated to indicate epigenetic aging. Major depression diagnosis and clinical characteristics were assessed with questionnaires and psychiatric interviews. Analyses were adjusted for sociodemographic characteristics, lifestyle, and health status. Postmortem brain samples of 74 depressed patients and 64 control subjects were used for replication. Pathway enrichment analysis was conducted using Consensus PathDB to gain insight into the biological processes underlying epigenetic aging in blood and brain.

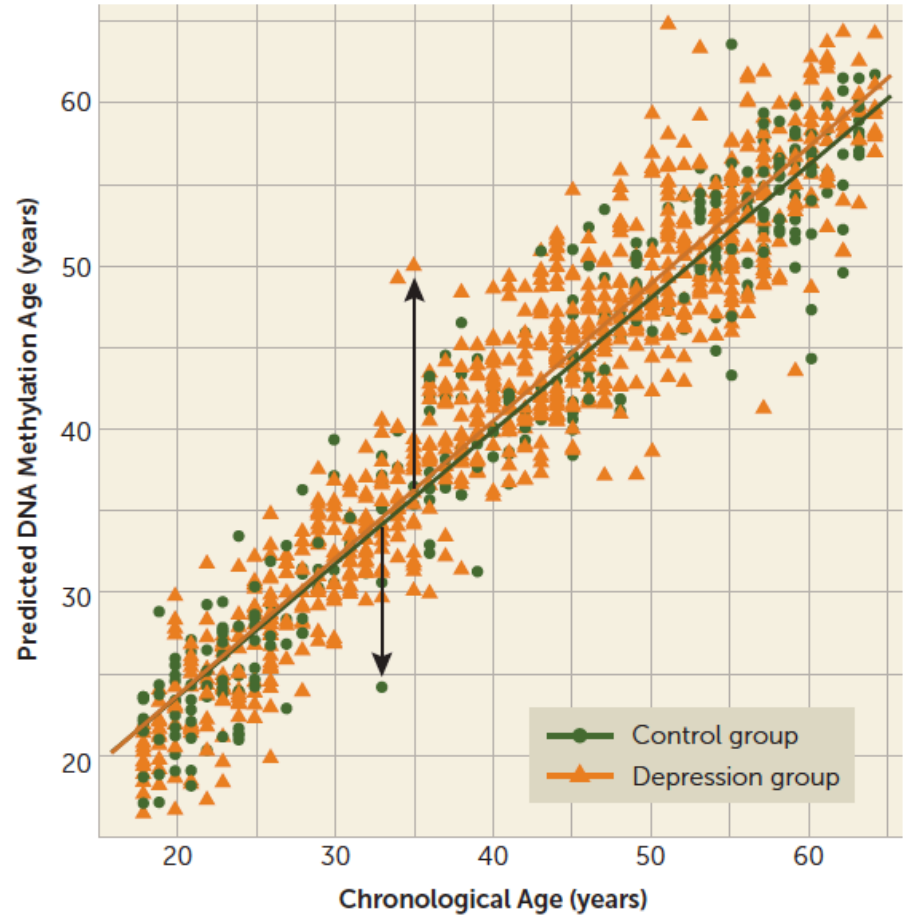
Am J Psychiatry 175:8, August 2018

Epigenetic Aging in Major Depressive Disorder

Results: Significantly higher epigenetic aging was observed in patients with major depression compared with control subjects (Cohen's d=0.18), with a significant dose effect with increasing symptom severity in the overall sample. In the depression group, epigenetic aging was positively and significantly associated with childhood trauma score. The case-control difference was replicated in an independent data set of postmortem brain samples. The top significantly enriched Gene Ontology terms included neuronal processes.

Am J Psychiatry 175:8, August 2018

FIGURE 1. DNA Methylation Age Prediction Using Methyl-CpG Binding Domain Protein-Enriched Genome Sequencing (MBD-seq) in the Netherlands Study of Depression and Anxiety[a]



[a] The plot shows the prediction of DNA methylation (DNAm) age using MBD-seq across groups in blood. Each circle or triangle represents an individual subject (N=1,130), and the lines indicate regression lines (control group [N=319]: r=0.94, p<0.001; major depression group [N=811]: r=0.96, p<0.001). The arrows indicate the outcome variable epigenetic aging, representing higher epigenetic aging if the individual's estimated DNAm age exceeds chronological age (upward arrow), whereas negative epigenetic aging indicates lower epigenetic aging (downward arrow).

Epigenetic Aging in Major Depressive Disorder

Conclusions: As compared with control subjects, patients with major depression exhibited higher epigenetic aging in blood and brain tissue, suggesting that they are biologically older than their corresponding chronological age. This effect was even more profound in the presence of childhood trauma.

Am J Psychiatry 175:8, August 2018

Do Depression and Stressful Events Cause Premature Aging?

Andrew M. McIntosh, M.D., Caroline Relton, Ph.D.

Han and colleagues' findings suggest that individuals with major depression and people with a history of childhood trauma may age biologically relatively faster than people without major depression or childhood trauma. These findings are potentially important, as individuals with major depression or childhood trauma die earlier on average and have more age-related diseases. Epigenetic age may represent a biomarker of aging and therefore may be potential means of stratification to identify patients who may benefit from early interventions seeking to reduce the physical comorbidities of major depression.

Am J Psychiatry 175:8, August 2018

Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium

A Network Meta-analysis

Yi-Cheng Wu, MD; Ping-Tao Tseng, MD; Yu-Kang Tu, DDS, PhD; Chung-Yao Hsu, MD, PhD; Chih-Sung Liang, MD; Ta-Chuan Yeh, MD; Tien-Yu Chen, MD; Che-Sheng Chu, MD; Yutaka J. Matsuoka, MD, PhD; Brendon Stubbs, MD, PhD; Andre F. Carvalho, MD, PhD; Saho Wada, MD, PhD; Pao-Yen Lin, MD, PhD; Yen-Wen Chen, MD; Kuan-Pin Su, MD, PhD

Question Which medications provide the best delirium response rate, the lowest delirium occurrence rate, and the best tolerability for the treatment and prevention of delirium?

Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium

A Network Meta-analysis

Yi-Cheng Wu, MD; Ping-Tao Tseng, MD; Yu-Kang Tu, DDS, PhD; Chung-Yao Hsu, MD, PhD; Chih-Sung Liang, MD; Ta-Chuan Yeh, MD; Tien-Yu Chen, MD; Che-Sheng Chu, MD; Yutaka J. Matsuoka, MD, PhD; Brendon Stubbs, MD, PhD; Andre F. Carvalho, MD, PhD; Saho Wada, MD, PhD; Pao-Yen Lin, MD, PhD; Yen-Wen Chen, MD; Kuan-Pin Su, MD, PhD

IMPORTANCE Although several pharmacological interventions for delirium have been investigated, their overall benefit and safety remain unclear.

OBJECTIVE To evaluate evidence regarding pharmacological interventions for delirium treatment and prevention.

DATA SOURCES PubMed, Embase, ProQuest, ScienceDirect, Cochrane Central, Web of Science, ClinicalKey, and ClinicalTrials.gov from inception to May 17, 2018.

Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium

STUDY SELECTION Randomized clinical trials (RCTs) examining pharmacological interventions for delirium treatment and prevention.

DATA EXTRACTION AND SYNTHESIS To extract data according to a predetermined list of interests, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were applied, and all meta-analytic procedures were conducted using a random-effects model.

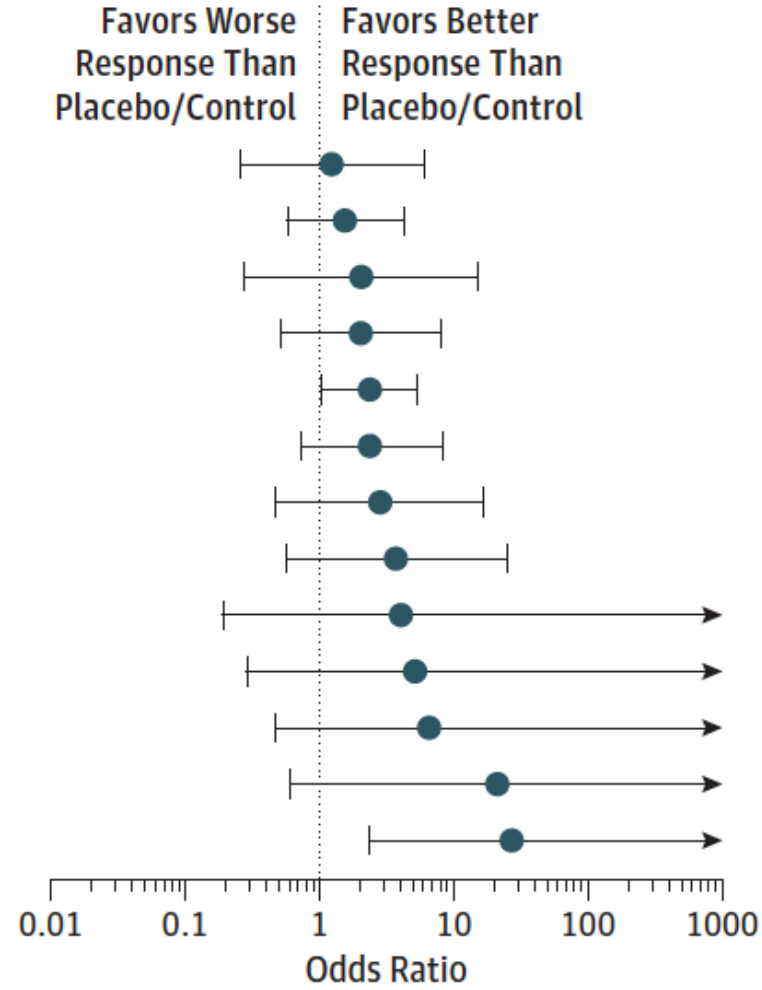
MAIN OUTCOMES AND MEASURES The primary outcomes were treatment response in patients with delirium and the incidence of delirium in patients at risk of delirium.

Findings From the results of a network meta-analysis of 58 randomized clinical trials among 9603 individuals, haloperidol plus lorazepam had the best response rate for delirium treatment, and ramelteon had the lowest delirium occurrence rate. No pharmacological management was significantly associated with a higher risk of all-cause mortality compared with placebo or control groups during delirium treatment or prevention.

Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium

C Treatment response

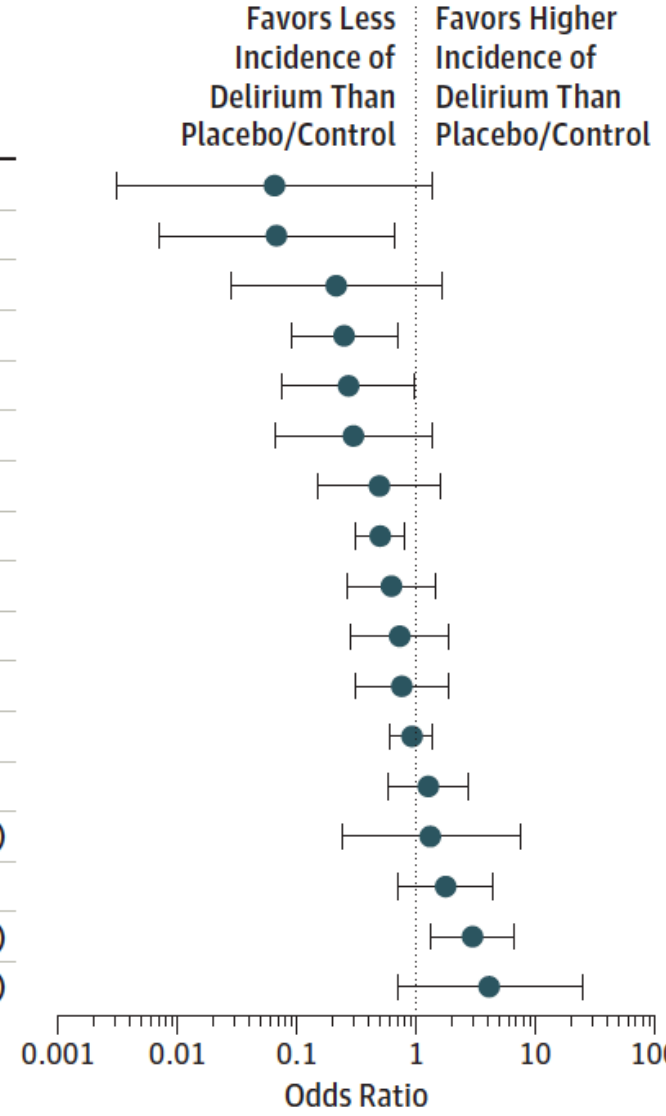
Source	Odds Ratio With 95% CI and 95% Prediction Interval	
Ondansetron hydrochloride	1.23 (0.24-6.22)	(0.03-53.71)
Risperidone	1.57 (0.56-4.38)	(0.07-37.78)
Haloperidol plus rivastigmine tartrate	2.06 (0.27-15.71)	(0.03-147.19)
Dexmedetomidine hydrochloride	2.06 (0.51-8.34)	(0.06-70.60)
Haloperidol	2.37 (1.04-5.43)	(0.12-48.80)
Olanzapine	2.46 (0.71-8.57)	(0.08-72.49)
Ziprasidone hydrochloride	2.89 (0.48-17.29)	(0.05-153.40)
Quetiapine fumarate	3.78 (0.55-25.84)	(0.06-235.65)
Amisulpride	4.10 (0.18-91.61)	(0.01-1256.98)
Lorazepam	5.34 (0.28-101.95)	(0.02-1308.79)
Chlorpromazine hydrochloride	6.68 (0.47-95.24)	(0.04-1089.82)
Rivastigmine tartrate	21.87 (0.61-790.15)	(0.04-13477.64)
Haloperidol plus lorazepam	28.13 (2.38-333.08)	(0.22-3563.80)



Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium

D Occurence rate of delirium

Source	Odds Ratio With 95% CI and 95% Prediction Interval	
Suvorexant	0.06 (0.00-1.36)	(0.00-1.91)
Ramelteon	0.07 (0.01-0.66)	(0.00-0.92)
Donepezil hydrochloride	0.21 (0.03-1.62)	(0.02-2.27)
Olanzapine	0.25 (0.09-0.69)	(0.06-1.05)
Risperidone	0.27 (0.07-0.99)	(0.05-1.45)
Propofol plus midazolam hydrochloride	0.30 (0.07-1.33)	(0.05-1.92)
Ondansetron hydrochloride	0.49 (0.15-1.60)	(0.10-2.38)
Dexmedetomidine hydrochloride	0.50 (0.31-0.80)	(0.17-1.47)
Rivastigmine tartrate	0.62 (0.26-1.46)	(0.17-2.32)
Lorazepam	0.73 (0.28-1.89)	(0.18-2.94)
Melatonin	0.76 (0.30-1.87)	(0.19-2.94)
Haloperidol	0.91 (0.60-1.38)	(0.32-2.61)
Gabapentin	1.26 (0.58-2.77)	(0.36-4.49)
Clonidine hydrochloride	1.33 (0.23-7.57)	(0.17-10.72)
Propofol	1.78 (0.70-4.51)	(0.45-7.05)
Midazolam hydrochloride	2.98 (1.30-6.80)	(0.81-10.90)
Midazolam hydrochloride plus clonidine hydrochloride	4.16 (0.69-25.25)	(0.49-35.66)



CONCLUSIONS AND RELEVANCE This network meta-analysis demonstrated that haloperidol plus lorazepam might be the best treatment and ramelteon the best preventive medicine for delirium. None of the pharmacological interventions for treatment or prophylaxis increased the all-cause mortality.

Meaning The use of a combination of haloperidol plus lorazepam and ramelteon is suggested for the treatment and prevention of delirium.

Medication Treatment of Delirium: How Far Have We Come?

Clinicians working in medical centers should reduce unnecessary medicines, implement orienting measures, memory reminders, and encouragement of a normal sleep-wake cycle, including via melatonin and bright light, before giving additional medications to patients at risk for delirium.

NEJM Journal Watch
PSYCHIATRY

Steven Dubovsky, MD (Mar 18, 2019)

Pharmacologic Intervention for the Treatment and Prevention of Delirium

Looking Beneath the Modeling

Dan G. Blazer, MD, MPH, PhD

- Because NMAs involve inferences about treatment comparisons that are not made directly, the acute treatment finding here reflected the results of a single study (JAMA 2017; 318:1047).
- In this study of delirious patients with terminal cancer receiving intravenous haloperidol (typical dose over 12 hours, 12 mg) with the addition of 3-mg lorazepam or placebo, greater improvement of agitation occurred within 8 hours of lorazepam than with placebo; different doses of haloperidol were not studied.

Pharmacologic Intervention for the Treatment and Prevention of Delirium

Looking Beneath the Modeling

Dan G. Blazer, MD, MPH, PhD

Clinicians and investigators will do well to look beneath the models at the individual trials, the building blocks, when drawing conclusions from the NMA. Given that the use of NMA will most probably become a much more widely used analytic tool in the future, scrutiny of the RCTs, the components of the analyses, is especially important.

Double-Blind Randomized Clinical Trial of Prazosin for Alcohol Use Disorder

Tracy L. Simpson, Ph.D., Andrew J. Saxon, M.D., Cynthia Stappenbeck, Ph.D., Carol A. Malte, M.S.W., Robert Lyons, Dana Tell, A.R.N.P., Steven P. Millard, Ph.D., Murray Raskind, M.D.

Objective: Current medications for alcohol use disorder do not target brain noradrenergic pathways. Theoretical and preclinical evidence suggests that noradrenergic circuits may be involved in alcohol reinforcement and relapse. After a positive pilot study, the authors tested the a-1 adrenergic receptor antagonist prazosin to treat alcohol use disorder in a larger sample.

Am J Psychiatry 175:12, December 2018

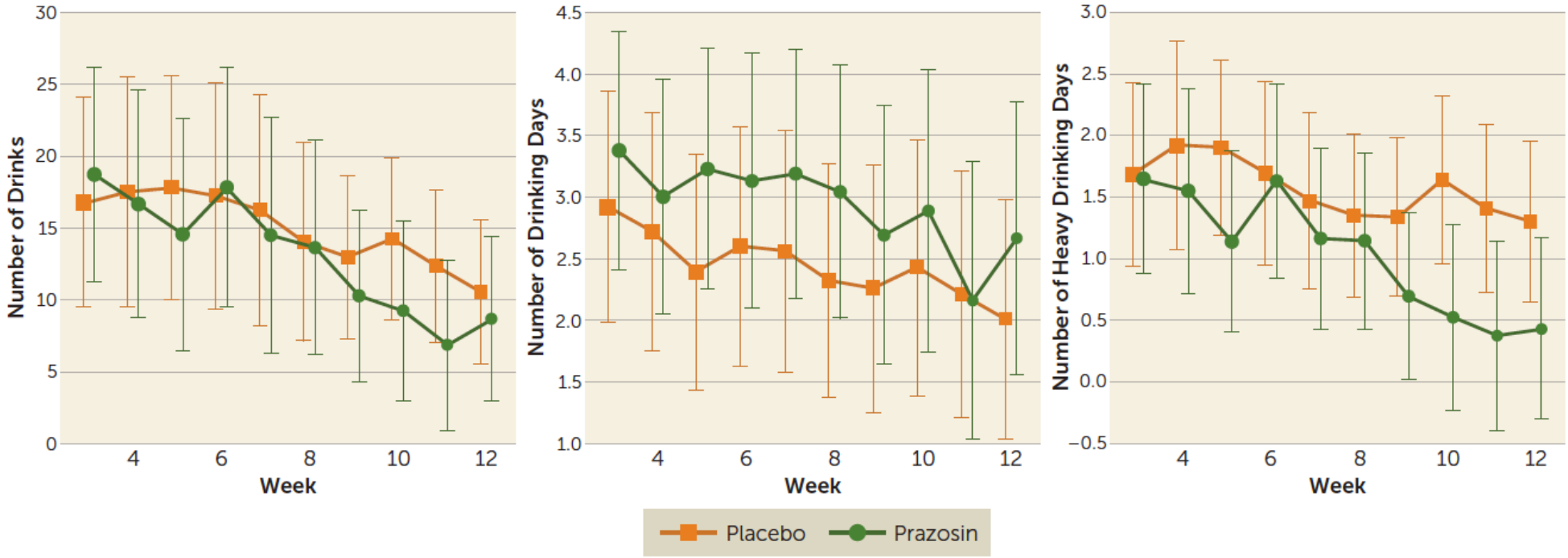
Double-Blind Randomized Clinical Trial of Prazosin for Alcohol Use Disorder

Method: Ninety-two participants with alcohol use disorder but without posttraumatic stress disorder were randomly assigned to receive prazosin or placebo in a 12-week double-blind study. Medication was titrated to a target dosing schedule of 4 mg in the morning, 4 mg in the afternoon, and 8 mg at bedtime by the end of week 2. The behavioral platform was medical management. Participants provided daily data on alcohol consumption. Generalized linear mixed-effects models were used to examine the impact of prazosin compared with placebo on number of drinks per week, number of drinking days per week, and number of heavy drinking days per week.

Am J Psychiatry 175:12, December 2018

Double-Blind Randomized Clinical Trial of Prazosin for Alcohol Use Disorder

FIGURE 2. Observed Mean Values for Outcome Measures for the Posttitration Period, by Week and Condition, in a Placebo-Controlled Trial of Prazosin for Alcohol Use Disorder[a]



[a] Error bars indicate 95% confidence interval. Symbol sizes are proportional to number of subjects with data for that week (see Figure S1 in the online supplement). Results of generalized mixed-effects fixed-slope models: for number of drinks per week, the interaction of condition by week was significant (p=0.03), but the main effect of condition at week 12 was not significant (p=0.98). For number of drinking days per week, the interaction of condition by week was not significant (p=0.94), and the main effect of condition at week 12 was not significant (p=0.47), but the main effect of week was significant (p=0.002). For number of heavy drinking days per week, the interaction of condition by week was significant (p=0.01), but the main effect of condition at week 12 was not significant (p=0.56).

Double-Blind Randomized Clinical Trial of Prazosin for Alcohol Use Disorder

Results: Eighty participants completed the titration period and were included in the primary analyses. There was a significant interaction between condition and week for both number of drinks and number of heavy drinking days, such that the rate of drinking and the probability of heavy drinking showed a greater decrease over time for participants in the prazosin condition compared with those in the placebo condition. Participants in the prazosin condition were more likely to report drowsiness and edema than participants in the placebo condition.

Conclusions: Prazosin holds promise as a harm-reduction pharmacologic treatment for alcohol use disorder and de-serves further evaluation by independent research groups.

Am J Psychiatry 175:12, December 2018

Prazosin for Harm Reduction in Alcohol Use Disorder?

- Prazosin was associated with self-reported fewer heavy drinking days and fewer drinks per week (-8 vs. -1.5 with placebo);
- differences in drinks per week accelerated after 8 weeks.
- Drinking days per week and craving showed no group differences.

The findings of moderate reductions of heavy drinking days and drinks per week with prazosin suggest its usefulness in harm reduction, perhaps in combination with other medications and strategies to reduce cravings.

NEJM Journal Watch
PSYCHIATRY

Joel Yager, MD, (Sep 4, 2018)

Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

Samantha Meltzer-Brody, Helen Colquhoun, Robert Riesenberg, C Neill Epperson, Kristina M Deligiannidis, David R Rubinow, Haihong Li, Abdul J Sankoh, Christine Clemson, Amy Schacterle, Jeffrey Jonas, Stephen Kanes

Summary

Background Post-partum depression is associated with substantial morbidity, and improved pharmacological treatment options are urgently needed. We assessed brexanolone injection (formerly SAGE-547 injection), a positive allosteric modulator of γ-aminobutyric-acid type A ($GABA_A$) receptors, for the treatment of moderate to severe post-partum depression.

Methods We did two double-blind, randomised, placebo-controlled, phase 3 trials, at 30 clinical research centres and specialised psychiatric units in the USA. Eligible women were aged 18–45 years, 6 months post partum or less at screening, with post-partum depression and a qualifying 17-item Hamilton Rating Scale for Depression (HAM-D) score (≥26 for study 1; 20–25 for study 2). Women with renal failure requiring dialysis, anaemia, known allergy to allopregnanolone or to progesterone, or medical history of schizophrenia, bipolar disorder, or schizoaffective disorder were excluded. Patients were randomly assigned (1:1:1) to receive a single intravenous injection of either brexanolone 90 μg/kg per h (BRX90), brexanolone 60 μg/kg per h (BRX60), or matching placebo for 60 h in study 1, or (1:1) BRX90 or matching placebo for 60 h in study 2. Patients, the study team, site staff, and the principal investigator were masked to treatment allocation. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 h, assessed in all patients who started infusion of study drug or placebo, had a valid HAM-D baseline assessment, and had at least one post-baseline HAM-D assessment. The safety population included all randomised patients who started infusion of study drug or placebo. Patients were followed up until day 30. The trials have been completed and are registered with ClinicalTrials.gov, numbers NCT02942004 (study 1) and NCT02942017 (study 2).

Brexanolone injection in post-partum depression:

Findings Participants were enrolled between Aug 1, 2016, and Oct 19, 2017, in study 1, and between July 25, 2016, and Oct 11, 2017, in study 2. We screened 375 women simultaneously across both studies, of whom 138 were randomly assigned to receive either BRX90 (n=45), BRX60 (n=47), or placebo (n=46) in study 1, and 108 were randomly assigned to receive BRX90 (n=54) or placebo (n=54) in study 2. In study 1, at 60 h, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19·5 points (SE 1·2) in the BRX60 group and 17·7 points (1·2) in the BRX90 group compared with 14·0 points (1·1) in the placebo group (difference –5·5 [95% CI –8·8 to –2·2], p=0·0013 for the BRX60 group; –3·7 [95% CI –6·9 to –0·5], p=0·0252 for the BRX90 group). In study 2, at 60 h, the LS mean reduction in HAM-D total score from baseline was 14·6 points (SE 0·8) in the BRX90 group compared with 12·1 points (SE 0·8) for the placebo group (difference –2·5 [95% CI –4·5 to –0·5], p=0·0160). In study 1, 19 patients in the BRX60 group and 22 patients in the BRX90 group had adverse events compared with 22 patients in the placebo group. In study 2, 25 patients in the BRX90 group had adverse events compared with 24 patients in the placebo group. The most common treatment-emergent adverse events in the brexanolone groups were headache (n=7 BRX60 group and n=6 BRX90 group *vs* n=7 placebo group for study 1; n=9 BRX90 group *vs* n=6 placebo group for study 2), dizziness (n=6 BRX60 group and n=6 BRX90 group *vs* n=1 placebo group for study 1; n=5 BRX90 group *vs* n=4 placebo group for study 2), and somnolence (n=7 BRX60 group and n=2 BRX90 group *vs* n=3 placebo group for study 1; n=4 BRX90 group *vs* n=2 placebo group for study 2). In study 1, one patient in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). In study 2, one patient in the BRX90 group had two serious adverse events (altered state of consciousness and syncope), which were considered to be treatment related.

Interpretation Administration of brexanolone injection for post-partum depression resulted in significant and clinically meaningful reductions in HAM-D total score at 60 h compared with placebo, with rapid onset of action and durable treatment response during the study period. Our results suggest that brexanolone injection is a novel therapeutic drug for post-partum depression that has the potential to improve treatment options for women with this disorder.

Brexanolone injection in post-partum depression:

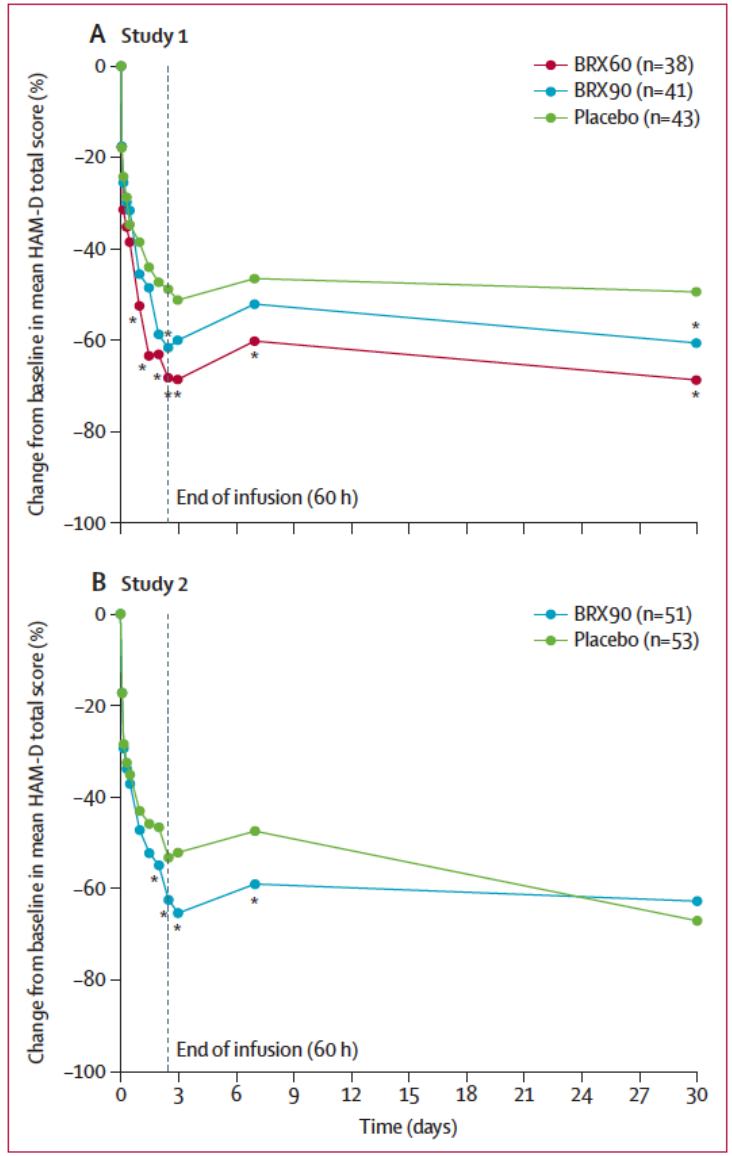


Figure 2: **Percentage change from baseline in mean HAM-D total score in study 1 (A) and 2 (B)**

p values were calculated by two-sided *t* test. BRX60=brexanolone injection 60 μg/kg per h. BRX90=brexanolone injection 90 μg/kg per h. *p<0·05 *vs* placebo.

Brexanolone injection in post-partum depression:

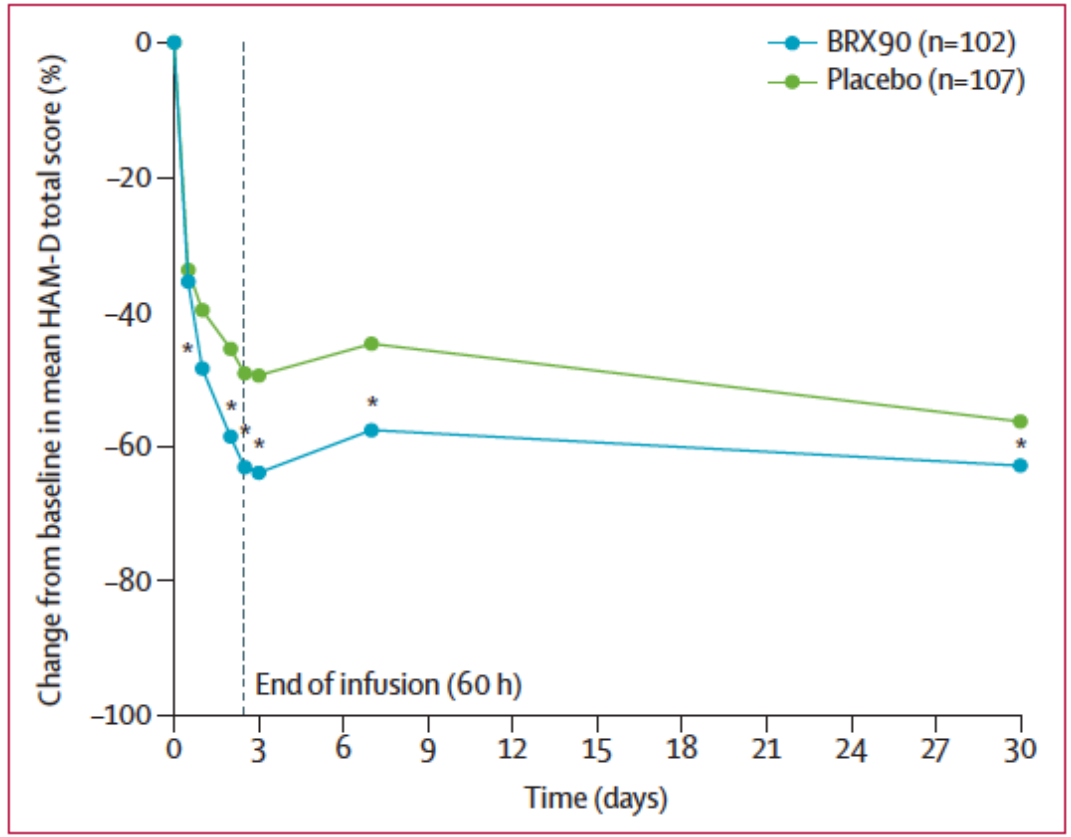


Figure 3: **Percentage change from baseline in mean HAM-D total score in the integrated BRX90 study population**
p values were calculated by two-sided *t* test. BRX90=brexanolone injection 90 µg/kg. *p<0·05 *vs* placebo.

Novel Antidepressant Appears Rapidly Effective for Postpartum Depression

- These studies document the antidepressant effects of a novel, rapid-onset agent that yielded larger reductions in HAM-D scores than those traditionally achieved with standard medications for postpartum depression.
- The need for IV administration may limit brexanolone's availability -- nonetheless, its rapid, sustained effects are likely to benefit not just new mothers but also their children as a result of improved maternal caretaking.

NEJM Journal Watch PSYCHIATRY

Peter Roy-Byrne, MD, (Sep 18, 2018)

Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia

Jari Tiihonen, MD, PhD; Heidi Taipale, PhD; Juha Mehtälä, PhD; Pia Vattulainen, MSc; Christoph U. Correll, MD; Antti Tanskanen, PhLic

IMPORTANCE The effectiveness of antipsychotic polypharmacy in schizophrenia relapse prevention is controversial, and use of multiple agents is generally believed to impair physical well-being.

DESIGN, SETTING, AND PARTICIPANTS In this nationwide cohort study, the risk of psychiatric rehospitalization was used as a marker for relapse among 62 250 patients with schizophrenia during the use of 29 different antipsychotic monotherapy and polypharmacy types between January 1, 1996, and December 31, 2015, in a comprehensive, nationwide cohort in Finland. We conducted analysis of the data from April 24 to June 15, 2018. Rehospitalization risks were investigated by using within-individual analyses to minimize selection bias.

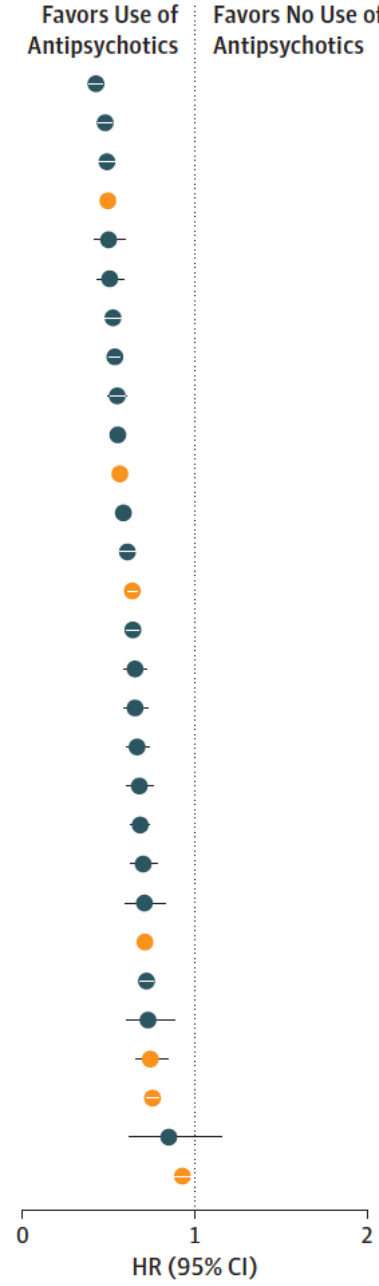
MAIN OUTCOMES AND MEASURES Hazard ratio (HR) for psychiatric rehospitalization during use of polypharmacy vs during monotherapy within the same individual.

Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization

Findings This cohort study on 62 250 individuals with schizophrenia with up to 20-year follow-up used within-individual analysis to minimize selection bias and showed that antipsychotic polypharmacy in general was associated with slightly lower risk of psychiatric rehospitalization than monotherapy. Clozapine plus aripiprazole combination was associated with the best outcome, having 14% to 23% lower risk of rehospitalization than clozapine alone, which was the monotherapy associated with the best outcomes.

Figure 1. Risk of Psychiatric Rehospitalization During Specific Treatments Compared With No Antipsychotic Use in the Prevalent Cohort (Within-Individual Analysis)

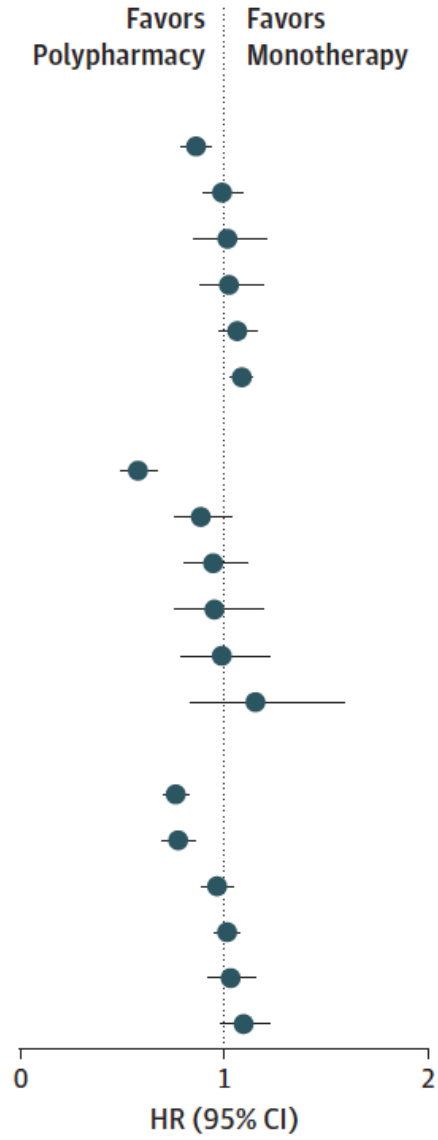
Treatment	HR (95% CI)
Clozapine and aripiprazole	0.42 (0.39-0.46)
Any LAI and olanzapine	0.48 (0.44-0.51)
Clozapine and olanzapine	0.49 (0.44-0.54)
Clozapine monotherapy	0.49 (0.47-0.51)
Clozapine and any LAI	0.50 (0.42-0.59)
Clozapine and risperidone	0.50 (0.43-0.59)
Clozapine and quetiapine	0.52 (0.48-0.57)
Clozapine and other oral	0.53 (0.50-0.56)
Any LAI and quetiapine	0.55 (0.50-0.60)
Any LAI and other oral	0.55 (0.53-0.58)
Any LAI monotherapy	0.56 (0.54-0.58)
Other combination of multiple drugs	0.58 (0.56-0.60)
Olanzapine and quetiapine	0.61 (0.56-0.66)
Olanzapine monotherapy	0.64 (0.61-0.66)
Olanzapine and other oral	0.64 (0.61-0.67)
Aripiprazole and quetiapine	0.65 (0.59-0.72)
Olanzapine and risperidone	0.65 (0.58-0.72)
Risperidone and quetiapine	0.66 (0.60-0.73)
Any LAI and risperidone	0.67 (0.60-0.76)
Other oral and quetiapine	0.68 (0.63-0.74)
Olanzapine and aripiprazole	0.70 (0.62-0.78)
Any LAI and aripiprazole	0.70 (0.59-0.83)
Other oral monotherapy	0.71 (0.69-0.73)
Other oral and risperidone	0.72 (0.68-0.76)
Other oral and aripiprazole	0.73 (0.60-0.88)
Aripiprazole monotherapy	0.74 (0.65-0.84)
Risperidone monotherapy	0.75 (0.72-0.79)
Aripiprozole and risperidone	0.85 (0.62-1.16)
Quetiapine monotherapy	0.93 (0.88-0.97)



HR indicates hazard ratio; LAI, long-acting injectable agent. Orange markers indicate monotherapies.

Figure 2. Risk of Psychiatric Rehospitalization in the Total Cohort, Compared With Clozapine, Aripiprazole, and Olanzapine Monotherapy (Within-Individual Analysis)

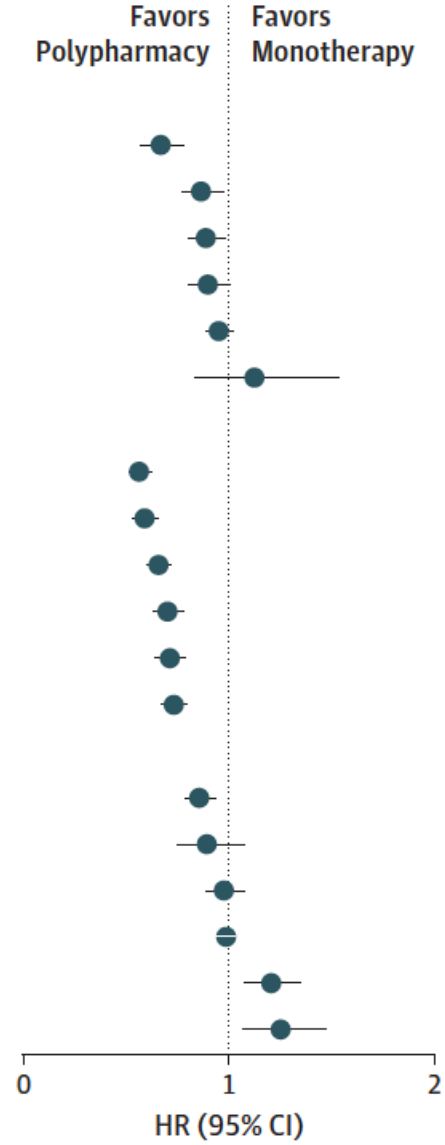
Treatment	HR (95% CI)
Clozapine monotherapy as a reference	
Clozapine and aripiprazole	0.86 (0.79-0.94)
Clozapine and olanzapine	0.99 (0.89-1.09)
Clozapine and any LAI	1.01 (0.85-1.21)
Clozapine and risperidone	1.02 (0.88-1.19)
Clozapine and quetiapine	1.06 (0.97-1.16)
Clozapine and other oral	1.08 (1.03-1.14)
Aripiprazole monotherapy as a reference	
Aripiprazole and clozapine	0.57 (0.49-0.67)
Aripiprazole and quetiapine	0.88 (0.75-1.03)
Aripiprazole and olanzapine	0.94 (0.80-1.11)
Aripiprazole and any LAI	0.95 (0.75-1.19)
Aripiprazole and other oral	0.98 (0.79-1.22)
Aripiprazole and risperidone	1.15 (0.83-1.59)
Olanzapine monotherapy as a reference	
Olanzapine and any LAI	0.75 (0.69-0.81)
Olanzapine and clozapine	0.76 (0.69-0.85)
Olanzapine and quetiapine	0.96 (0.88-1.04)
Olanzapine and other oral	1.01 (0.95-1.06)
Olanzapine and risperidone	1.02 (0.92-1.14)
Olanzapine and aripiprazole	1.10 (0.98-1.22)



HR indicates hazard ratio; LAI, long-acting injectable agent.

Figure 3. Risk of Psychiatric Rehospitalization in the Total Cohort, Compared With Risperidone, Quetiapine, and Any Long-Acting Injectable Agent (LAI) Monotherapy (Within-Individual Analysis)

Treatment	HR (95% CI)
Risperidone monotherapy as a reference	
Risperidone and clozapine	0.67 (0.57-0.78)
Risperidone and olanzapine	0.86 (0.77-0.97)
Risperidone and quetiapine	0.88 (0.79-0.97)
Risperidone and any LAI	0.89 (0.79-1.01)
Risperidone and other oral	0.95 (0.89-1.02)
Risperidone and aripiprazole	1.13 (0.83-1.54)
Quetiapine monotherapy as a reference	
Quetiapine and clozapine	0.56 (0.51-0.62)
Quetiapine and any LAI	0.59 (0.53-0.65)
Quetiapine and olanzapine	0.66 (0.60-0.72)
Quetiapine and aripiprazole	0.70 (0.63-0.78)
Quetiapine and risperidone	0.72 (0.64-0.80)
Quetiapine and other oral	0.74 (0.68-0.80)
Any LAI monotherapy as a reference	
Any LAI and olanzapine	0.85 (0.79-0.91)
Any LAI and clozapine	0.89 (0.74-1.06)
Any LAI and quetiapine	0.97 (0.88-1.07)
Any LAI and other oral	0.98 (0.94-1.02)
Any LAI and risperidone	1.20 (1.07-1.34)
Any LAI and aripiprazole	1.25 (1.06-1.48)



HR indicates hazard ratio; LAI, long-acting injectable agent.

Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization

CONCLUSIONS AND RELEVANCE Combining aripiprazole with clozapine was associated with the lowest risk of rehospitalization, indicating that certain types of polypharmacy may be feasible in the treatment of schizophrenia. Because add-on treatments are started when monotherapy is no longer sufficient to control for worsening of symptoms, it is likely that the effect sizes for polypharmacy are underestimates. Although the results do not indicate that all types of polypharmacy are beneficial, the current treatment guidelines should modify their categorical recommendations discouraging all antipsychotic polypharmacy in the maintenance treatment of schizophrenia.

Meaning The findings of this study suggest that certain types of polypharmacy may be associated with fewer rehospitalizations than monotherapies.

Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

Question For patients with schizophrenia who are taking an antipsychotic medication but need a medication change, what is the comparative effectiveness of various psychotropic medication options?

Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

T. Scott Stroup, MD, MPH; Tobias Gerhard, PhD; Stephen Crystal, PhD; Cecilia Huang, PhD; Zhiqiang Tan, PhD; Melanie M. Wall, PhD; Chacku Mathai, AAS; Mark Olfson, MD, MPH

IMPORTANCE People with schizophrenia are commonly treated with psychotropic medications in addition to antipsychotics, but there is little evidence about the comparative effectiveness of these adjunctive treatment strategies.

OBJECTIVE To study the comparative real-world effectiveness of adjunctive psychotropic treatments for patients with schizophrenia.

MAIN OUTCOMES AND MEASURES Risk of hospitalization for a mental disorder (primary), emergency department (ED) visits for a mental disorder, and all-cause mortality.

Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness study used US national Medicaid data from January 1, 2001, to December 31, 2010, to examine the outcomes of initiating treatment with an antidepressant, a benzodiazepine, a mood stabilizer, or another antipsychotic among adult outpatients (aged 18-64 years) diagnosed with schizophrenia who were stably treated with a single antipsychotic. Data analysis was performed from January 1, 2017, to June 30, 2018. Multinomial logistic regression models were used to estimate propensity scores to balance covariates across the 4 medication groups. Weighted Cox proportional hazards regression models were used to compare treatment outcomes during 365 days on an intention-to-treat basis.

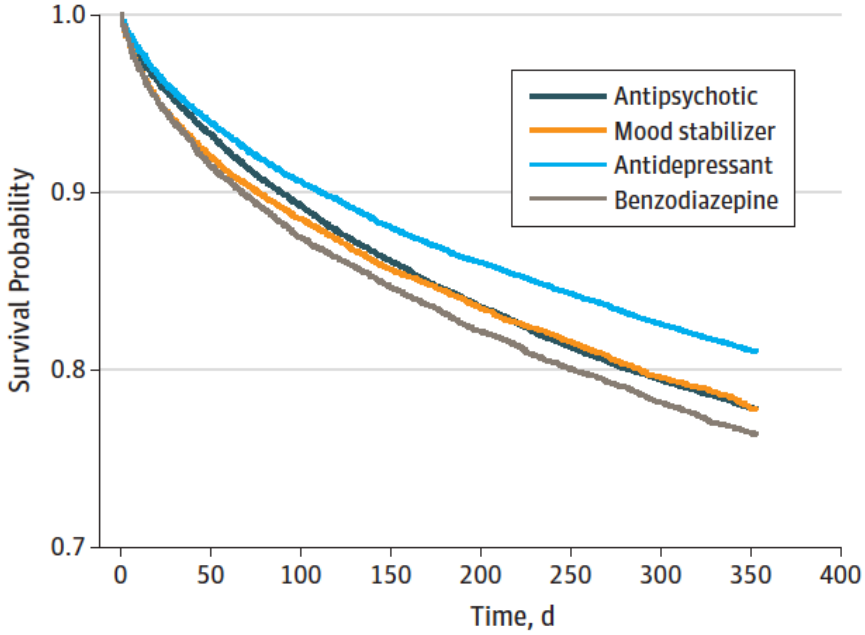
Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

RESULTS The study cohort included 81 921 adult outpatients diagnosed with schizophrenia (mean [SD] age, 40.7 [12.4] years; 37 515 women [45.8%]) who were stably treated with a single antipsychotic and then initiated use of an antidepressant (n = 31 117), a benzodiazepine (n = 11 941), a mood stabilizer (n = 12 849), or another antipsychotic (n = 26 014) (reference treatment). Compared with initiating use of another antipsychotic, initiating use of an antidepressant was associated with a lower risk (hazard ratio [HR], 0.84; 95% CI, 0.80-0.88) of psychiatric hospitalization, whereas initiating use of a benzodiazepine was associated with a higher risk (HR, 1.08; 95% CI, 1.02-1.15); the risk associated with initiating use of a mood stabilizer (HR, 0.98; 95% CI, 0.94-1.03) was not significantly different from initiating use of another antipsychotic. A similar pattern of associations was observed in psychiatric ED visits for initiating use of an antidepressant (HR, 0.92; 95% CI, 0.88-0.96), a benzodiazepine (HR, 1.12; 95% CI, 1.07-1.19), and a mood stabilizer (HR, 0.99; 95% CI, 0.94-1.04). Initiating use of a mood stabilizer was associated with an increased risk of mortality (HR, 1.31; 95% CI, 1.04-1.66).

Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

Figure 2. Time to Psychiatric Hospitalization, Emergency Department (ED) Visits, and Mortality After Inverse Probability of Treatment Weighting

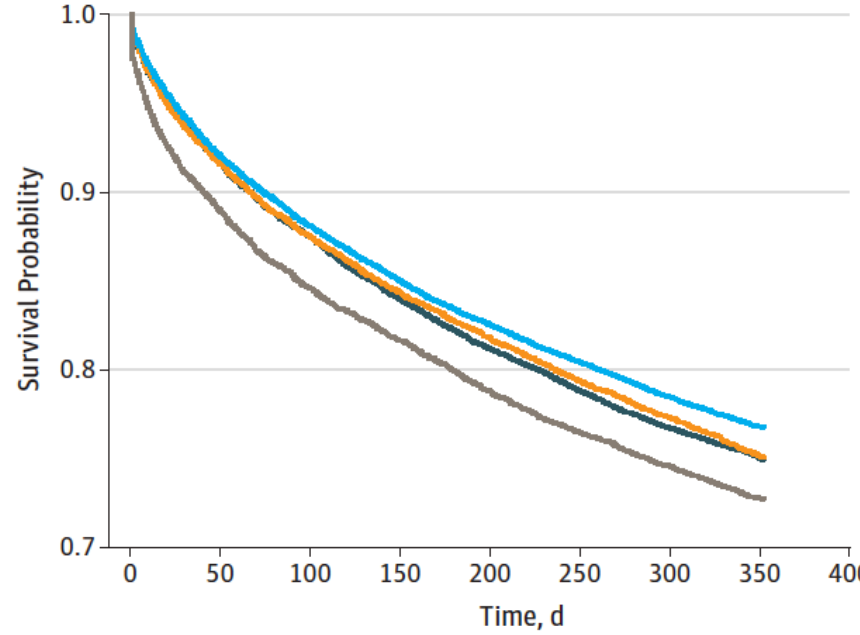
A Time to psychiatric hospitalization



No. at risk

Antipsychotic	26014	24078	22705	21553	20534	19576	18772	18029
Mood stabilizer	12849	11406	10530	9884	9308	8759	8260	7810
Antidepressant	31117	28742	27097	25658	24398	23265	22214	21260
Benzodiazepine	11941	10830	10134	9571	9037	8617	8183	7800

B Time to ED visits



No. at risk

Antipsychotic	26014	23773	22403	21229	20189	19267	18413	17670
Mood stabilizer	12849	11328	10413	9733	9113	8545	8062	7576
Antidepressant	31117	28210	26401	24858	23483	22331	21258	20297
Benzodiazepine	11941	10514	9780	9192	8648	8201	7789	7439

Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

Findings In this comparative effectiveness study of 81 921 adult outpatients diagnosed with schizophrenia, compared with starting use of a new antipsychotic, adding an antidepressant was associated with a lower risk of psychiatric hospitalization and emergency department visits, whereas adding a benzodiazepine was associated with a higher risk of these outcomes.

Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients With Schizophrenia

CONCLUSIONS AND RELEVANCE In the treatment of schizophrenia, initiating adjunctive treatment with an antidepressant was associated with reduced risk of psychiatric hospitalization and ED visits compared with initiating use of alternative psychotropic medications. Associations of benzodiazepines and mood stabilizers with poorer outcomes warrant clinical caution and further investigation.

Meaning The findings suggest that in the treatment of schizophrenia, adjunctive antidepressants are associated with better outcomes compared with alternative psychotropic medication strategies.

Medication Combinations Might Help Maintenance Therapy for Schizophrenia

- The conventional wisdom about usually avoiding polypharmacy in schizophrenia might apply to acute monotherapy more than maintenance therapy.
- The results suggest considering antipsychotic combinations, especially clozapine and aripiprazole, when a treatment change seems appropriate.
- Why adjunctive antidepressants would benefit nondepressed patients is unclear, but this approach might be appropriate.
- The apparent harm of adding benzodiazepines may reflect their use for sicker, more agitated patients; the apparent risk from adding mood stabilizers seems to outweigh the benefit.

NEJM Journal Watch
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Steven Dubovsky, MD, (May 14, 2019)

Can Adjunctive Pharmacotherapy Reduce Hospitalization in Schizophrenia?

Insights From Administrative Databases

Donald C. Goff, MD

- Of the 3 add-on strategies examined by Stroup and colleagues, only antidepressants were found to have a favorable risk/benefit ratio compared with adding a second antipsychotic, consistent with results from RCTs, although whether antidepressants reduce the risk for hospitalization requires replication in a randomized trial.
- Contrary to most treatment guidelines, Tiihonen and colleagues found that antipsychotic polypharmacy was associated with better outcomes than monotherapy and that addition of aripiprazole uniquely improved outcomes in patients treated with clozapine.

JAMA Psychiatry May 2019 Volume 76, Number 5

Can Adjunctive Pharmacotherapy Reduce Hospitalization in Schizophrenia?

Insights From Administrative Databases

Donald C. Goff, MD

- Despite efforts to minimize bias, these results should be considered preliminary until confirmed by RCTs.
- However, beyond the well-established benefits of clozapine, prescribers seeking to improve outcomes in patients with schizophrenia have limited evidence from high-quality RCTs to guide add-on strategies.
  - If clinicians and patients choose to implement add-on treatments after weighing results from both observational studies and RCTs, the limitations of the evidence should be acknowledged and outcomes should be carefully monitored.

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Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis

April Slee, Irwin Nazareth, Paulina Bondaronek, Yifeng Liu, Zhihang Cheng, Nick Freemantle

Summary

Background Generalised anxiety disorder is a disease that can be associated with substantial dysfunction. Pharmacological treatment is often the first choice for clinicians because of the cost and resource constraints of psychological alternatives, but there is a paucity of comparative information for the multiple available drug choices.

Methods A systematic review and network meta-analysis was performed on randomised trials in adult outpatients with generalised anxiety disorder identified from MEDLINE, Web of Science, Cochrane Library, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), Wanfang data, Drugs@FDA and commercial pharmaceutical registries. Placebo and active control trials were included. Data were extracted from all manuscripts and reports. Primary outcomes were efficacy (mean difference [MD] in change in Hamilton Anxiety Scale Score) and acceptability (study discontinuations for any cause). We estimated summary mean treatment differences and odds ratios using network meta-analyses with random effects. This study is registered with PROSPERO, number CRD42018087106.

Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis

Findings Studies were published between Jan 1, 1994 and Aug 1, 2017, in which 1992 potential studies were screened for inclusion. This analysis is based on 89 trials, which included 25 441 patients randomly assigned to 22 different active drugs or placebo. Duloxetine (MD –3·13, 95% credible interval [CrI] –4·13 to –2·13), pregabalin (MD –2·79, 95% CrI –3·69 to –1·91), venlafaxine (MD –2·69, 95% CrI –3·50 to –1·89), and escitalopram (MD –2·45, 95% CrI –3·27 to –1·63) were more efficacious than placebo with relatively good acceptability. Mirtazapine, sertraline, fluoxetine, buspirone, and agomelatine were also found to be efficacious and well tolerated but these findings were limited by small sample sizes. Quetiapine (MD –3·60 95% CrI –4·83 to –2·39) had the largest effect on HAM-A but it was poorly tolerated (odds ratio 1·44, 95% CrI 1·16–1·80) when compared with placebo. Likewise, paroxetine and benzodiazepines were effective but also poorly tolerated when compared with placebo. Risk of reporting bias was considered low, and when possible all completed studies were included to avoid publication bias.

Interpretation To our knowledge, this is the largest contemporary review of pharmacological agents for the treatment of generalised anxiety disorder by use of network analysis. There are several effective treatment choices for generalised anxiety disorder across classes of medication. The failure of initial pharmacological therapy might not be a reason to abandon a pharmacological treatment strategy.

Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis

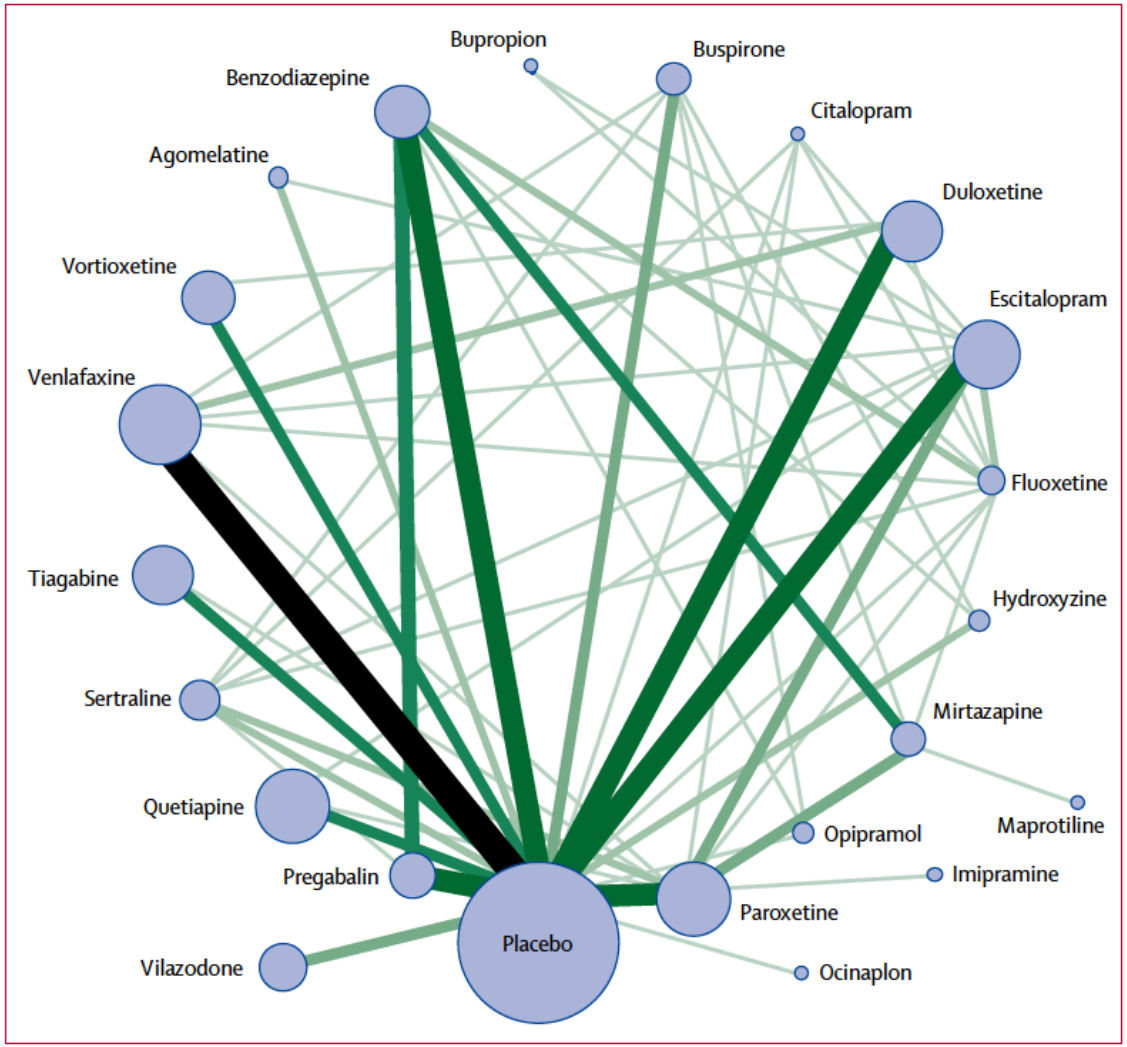


Figure 2: **Network meta-analysis of available comparisons**
Line width is proportional to the number of trials including every pair of treatments (direct comparisons). Circle size is proportional to the total number of patients for each treatment in the network.

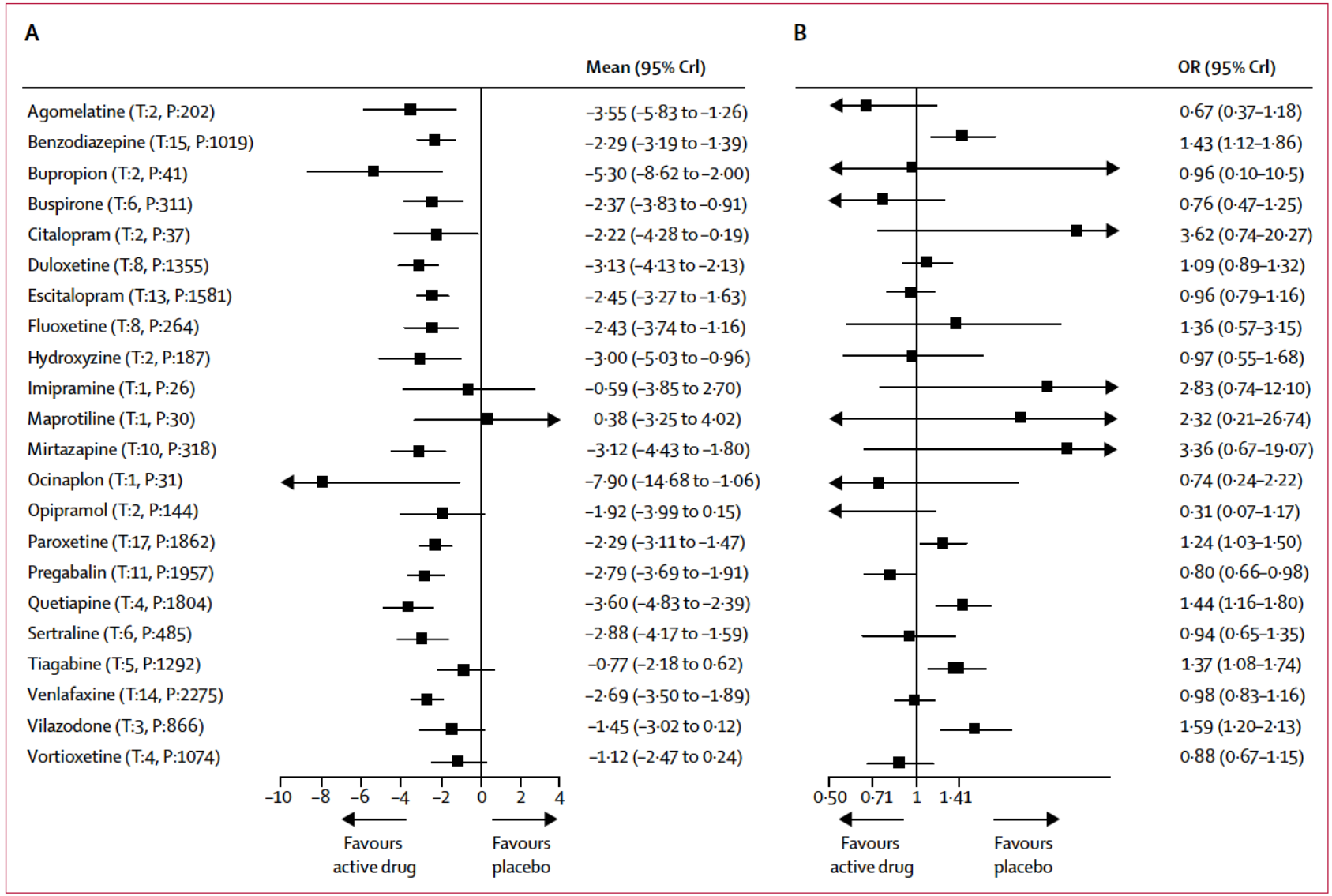


Figure 3: **Forest plot of network meta-analysis of all trials for efficacy and acceptability**
Efficacy (A) measured as mean difference in change in HAM-A from baseline, and acceptability (B) measured as odds ratio for patients not completing study. Drugs compared with placebo, which was the reference compound. CrI=credible interval. T=number of trials. P=total number of patients. OR=odds ratio.

Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis

Added value of this study

This analysis is the largest contemporary review of pharmacological agents to date for the treatment of generalised anxiety disorder by using network analysis, which allows cross-drug comparisons. This analysis is based on 89 trials, which included 25,441 patients randomly assigned to 22 different active drugs or placebo. Additionally, the inclusion of 16 trials done in China allowed the inclusion of drugs that had not been studied previously in other clinical settings.

Pharmacotherapy for Generalized Anxiety: An Update

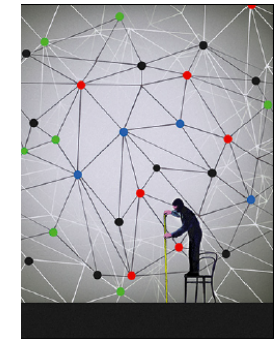
- These updated findings support the general rule that selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are mainstays for GAD pharmacotherapy, but study generalizability is limited by the small proportion of older patients, who have a high GAD rate, and by using study discontinuation as a measure of tolerability.
- Pregabalin is not FDA-approved for treating anxiety; due to its cost and status as a controlled substance, it is not generally prescribed or preferred over benzodiazepines.
- Bupropion is not generally thought to be an effective anxiolytic; the current analysis in a very small sample is unlikely to change this impression.

NEJM Journal Watch
PSYCHIATRY

Peter Roy-Byrne, MD, (Feb 21, 2019)

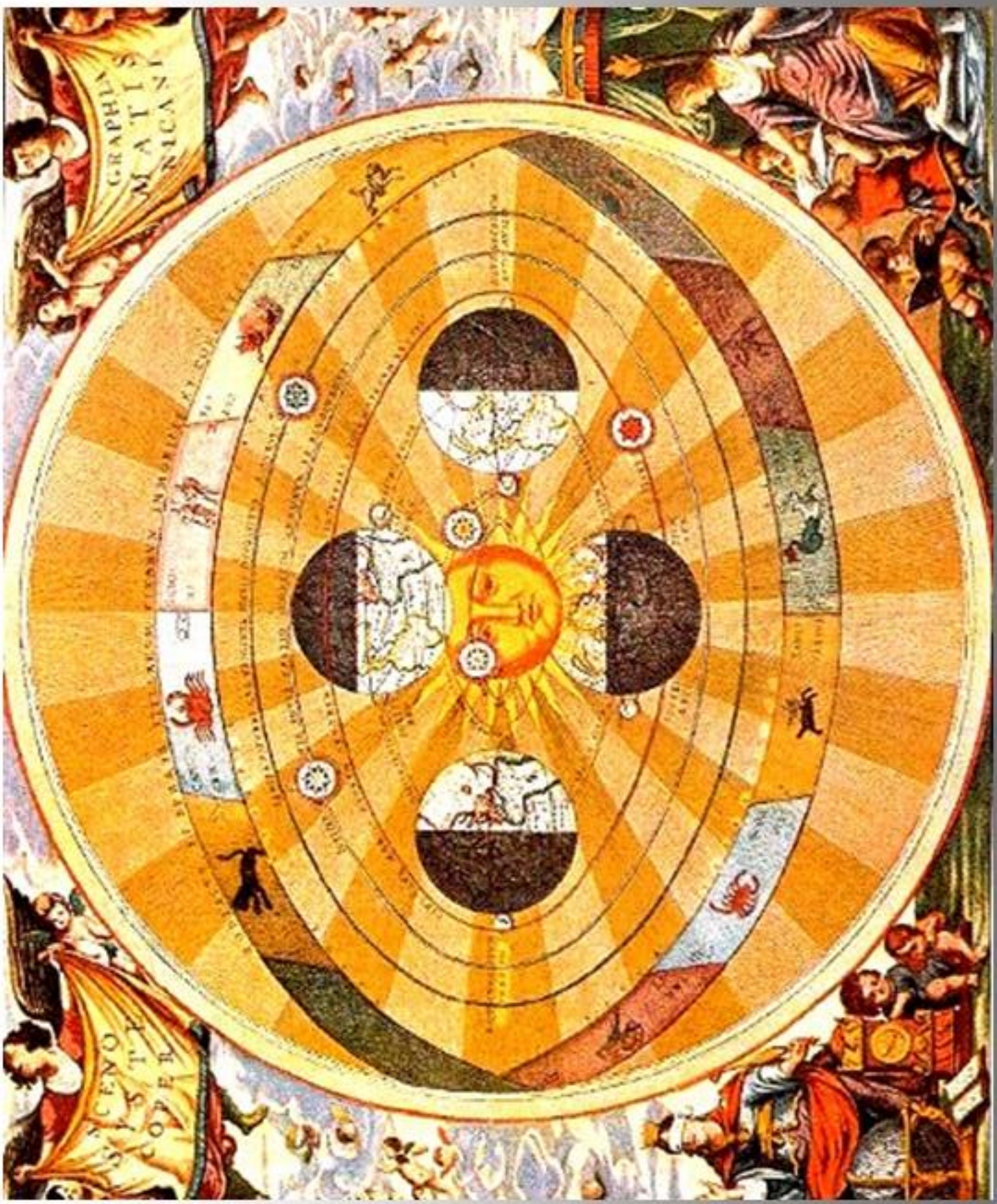
Network analyses to rank pharmacological treatments for generalised anxiety disorder

Borwin Bandelow, Dirk Wedekind



In the interest of patients, the most effective and acceptable interventions should be used. Although conventional and network meta-analyses have their pitfalls, future treatment guidelines should make use of them for the development of efficacy rankings for all competing interventions.

Thanks



Science to Practice

Top Ten Research Findings of 2018-2019

Sy Atezaz Saeed, MD, MS, FAC*Psych*

Q and A

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