Science to Practice

Top Ten Research Findings of 2016-2017

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NORTH CAROLINA
Psychiatric
Association

Science to Practice

Top Ten Research findings of 2016-2017

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.
- Recognize that there remains a gap between science and practice of clinical psychiatry.
- Identify the most important* research findings of 2016-2017 that have a direct bearing on the practice of clinical psychiatry.

*As identified by the methodology utilized for this presentation.

Disclosure

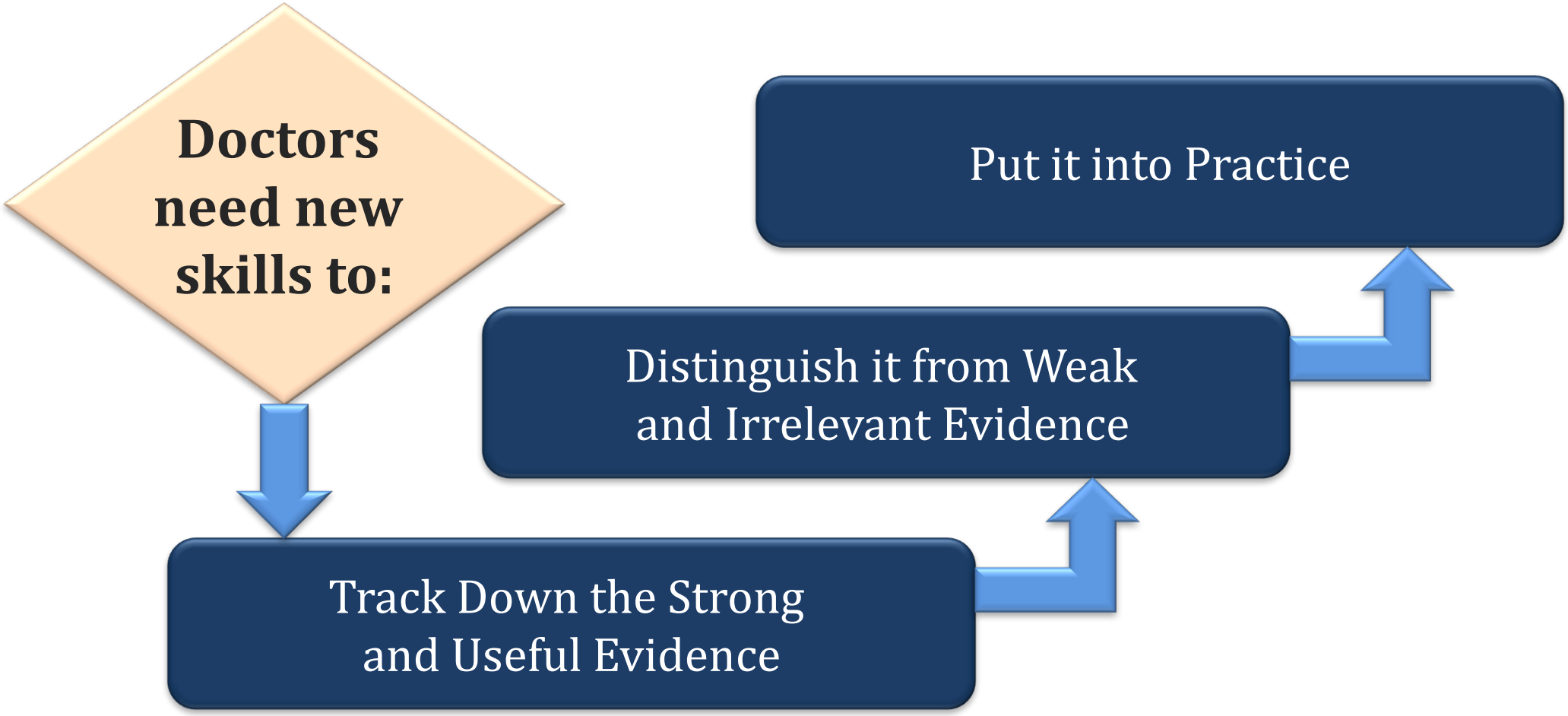
Neither I nor any member of my immediate family have any relevant financial relationship with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

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.

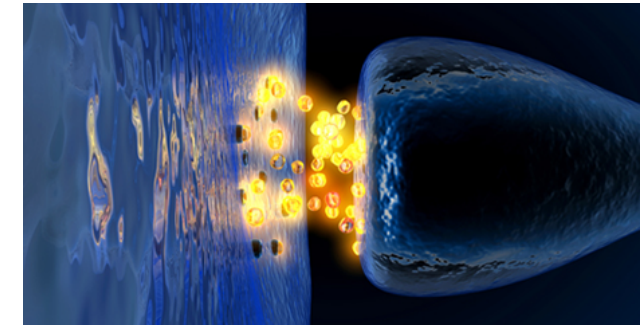
David Shenk. Data Smog: Surviving the Information Glut. San Francisco: Harper, 1998: 30.

We must cope with a rapidly changing body of relevant evidence and maximize the quality of medical care



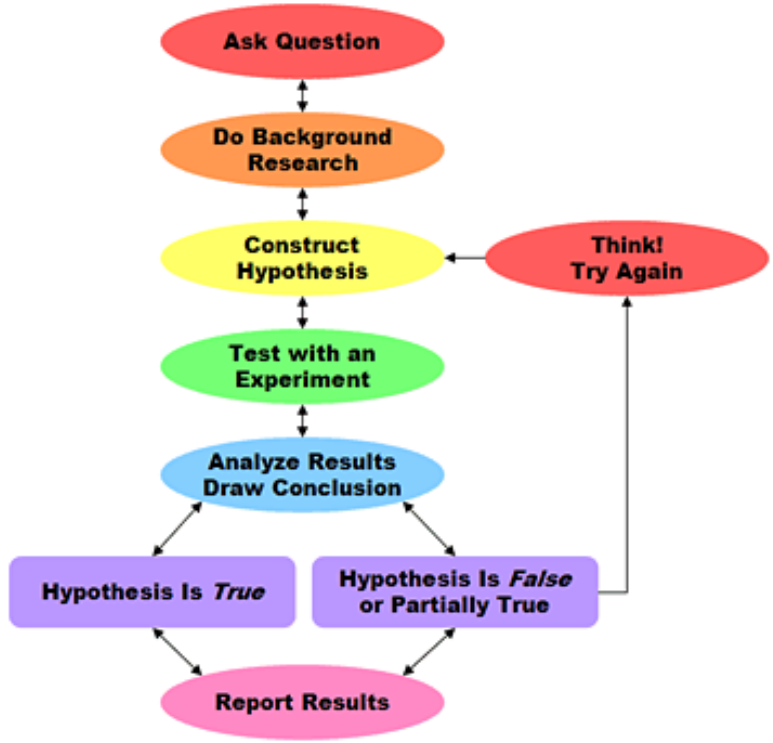
Signal-to-Noise Ratio [SNR]

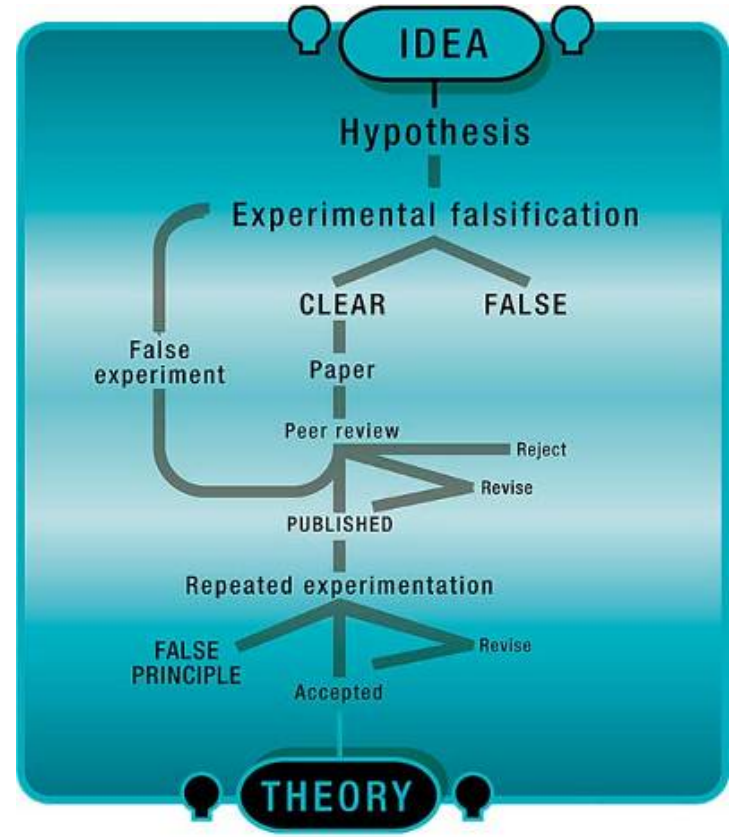
- A qualitative measure of value received relative to the garbage one must sift to get that value.
  - How should we do the sifting?
  - Can someone do the sifting for us? Who? [books, journals, CME presenters, drug reps, etc.]



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, 2016 to June 30, 2017, which ones in your opinion have [or likely to have or should have] impacted/changed the clinical practice of psychiatry?*].
  - AACDP
  - AADPRT
  - AACP
  - AAPA
  - NCPA
  - GAP
  - 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 relates to their "clinic readiness"
- 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
ARCHIVES OF GENERAL PSYCHIATRY
THE AMERICAN JOURNAL OF PSYCHIATRY
THE JOURNAL OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES
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THE LANCET
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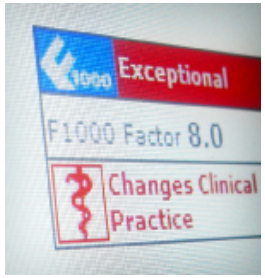

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Science to Practice

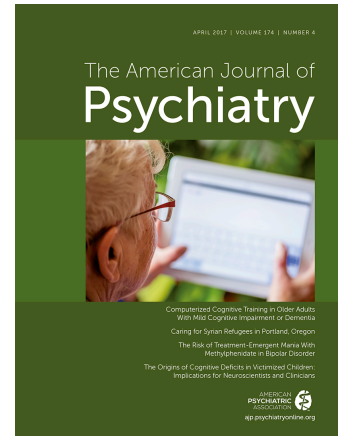
Top Ten Research Findings of 2016-2017

The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder

Alexander Viktorin, Ph.D., Eleonore Rydén, M.D., Ph.D., Michael E. Thase, M.D., Zheng Chang, Ph.D., Cecilia Lundholm, M.Sc., Brian M. D'Onofrio, Ph.D., Catarina Almqvist, M.D., Ph.D., Patrik K.E. Magnusson, Ph.D., Paul Lichtenstein, Ph.D., Henrik Larsson, Ph.D., Mikael Landén, M.D., Ph.D.

Objective: The authors sought to determine the risk of treatment-emergent mania associated with methylphenidate, used in monotherapy or with a concomitant mood-stabilizing medication, in patients with bipolar disorder.

Method: Using linked Swedish national registries, the authors identified 2,307 adults with bipolar disorder who initiated therapy with methylphenidate between 2006 and 2014. The cohort was divided into two groups: those with and those without concomitant mood-stabilizing treatment. To adjust for individual-specific confounders, including disorder severity, genetic makeup, and early environmental factors, Cox regression analyses were used, conditioning on individual to compare the rate of mania (defined as hospitalization for mania or a new dispensation of stabilizing medication) 0–3 months and 3–6 months after medication start following nontreated periods.



The largest study to date (N=2,307), examining the risk of treatment-emergent mania in patients with bipolar disorder when methylphenidate is taken alone or in combination with mood-stabilizing medication.

Am J Psychiatry 174:4, April 2017

The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder

Results: Patients on methylphenidate monotherapy displayed an increased rate of manic episodes within 3 months of medication initiation (hazard ratio=6.7, 95% CI=2.0–22.4), with similar results for the subsequent 3 months. By contrast, for patients taking mood stabilizers, the risk of mania was lower after starting methylphenidate (hazard ratio=0.6, 95% CI=0.4–0.9). Comparable results were observed when only hospitalizations for mania were counted.

Conclusions: No evidence was found for a positive association between methylphenidate and treatment-emergent mania among patients with bipolar disorder who were concomitantly receiving a mood-stabilizing medication. This is clinically important given that up to 20% of people with bipolar disorder suffer from comorbid ADHD. Given the markedly increased hazard ratio of mania following methylphenidate initiation in bipolar patients not taking mood stabilizers, careful assessment to rule out bipolar disorder is indicated before initiating monotherapy with psychostimulants.

Am J Psychiatry 174:4, April 2017

Clinical Implications

- It is important to do a careful assessment to rule out bipolar disorder before initiating methylphenidate as a monotherapy.
- As no association with treatment-emergent mania was observed among bipolar patients who were concomitantly receiving a mood-stabilizing medication, it would appear that concomitant therapy of ADHD is both safe and feasible in the context of ongoing preventive therapy.
- Although this study utilized a within-individual design to better handle confounding, the study used observational data, so not all potential confounding can be ruled out. Therefore, more research is warranted in this important area to further elucidate the potential mania inducing properties of methylphenidate and the extent to which stabilizing drugs hamper this adverse reaction.

Am J Psychiatry 174:4, April 2017

Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder

OBJECTIVE To evaluate the efficacy of metformin for weight gain associated with atypical antipsychotic medications in children and adolescents with ASD (defined in the protocol as *DSM-IV* diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified), aged 6 to 17 years.

DESIGN, SETTING, AND PARTICIPANTS A 16-week, double-blind, placebo-controlled, randomized clinical trial was conducted at 4 centers in Toronto, Ontario, Canada; Columbus, Ohio; Pittsburgh, Pennsylvania; and Nashville, Tennessee. In all, 209 potential participants were screened by telephone, 69 individuals provided consent, and 61 participants were randomized to receive metformin or placebo between April 26, 2013, and June 24, 2015.

INTERVENTIONS Metformin or matching placebo titrated up to 500 mg twice daily for children aged 6 to 9 years and 850 mg twice daily for those 10 to 17 years.

Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder

INTERVENTIONS Metformin or matching placebo titrated up to 500 mg twice daily for children aged 6 to 9 years and 850 mg twice daily for those 10 to 17 years.

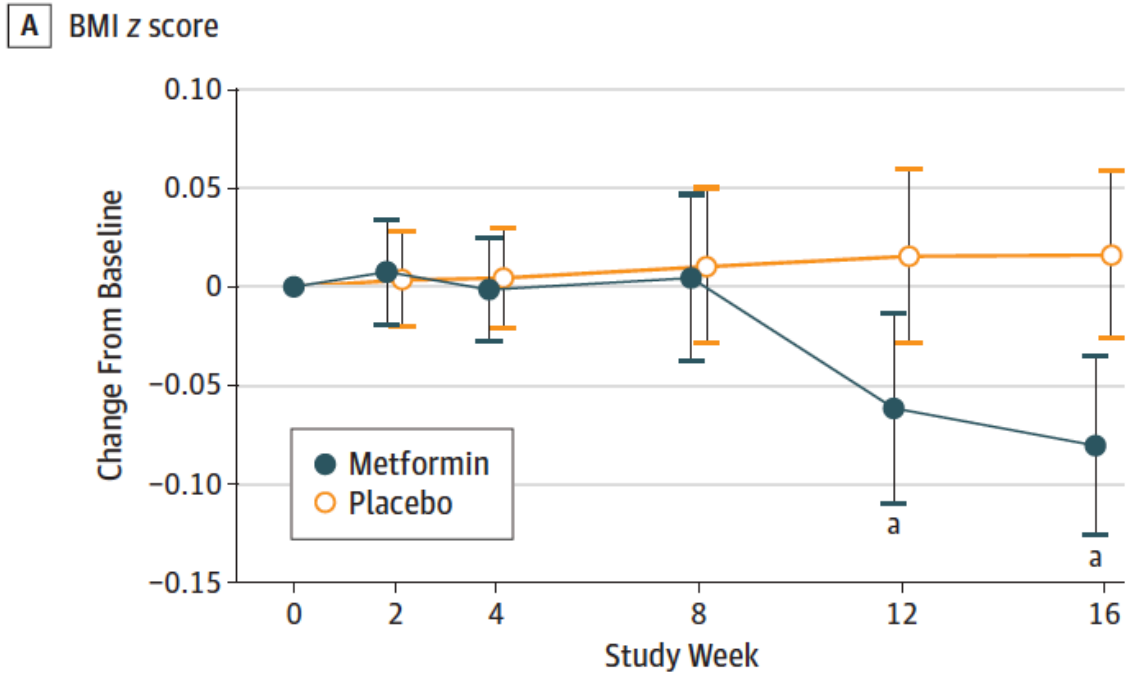
MAIN OUTCOMES AND MEASURES The primary outcome measure was change in body mass index (BMI) *z* score during 16 weeks of treatment. Secondary outcomes included changes in additional body composition and metabolic variables. Safety, tolerability, and efficacy analyses all used a modified intent-to-treat sample comprising all participants who received at least 1 dose of medication.

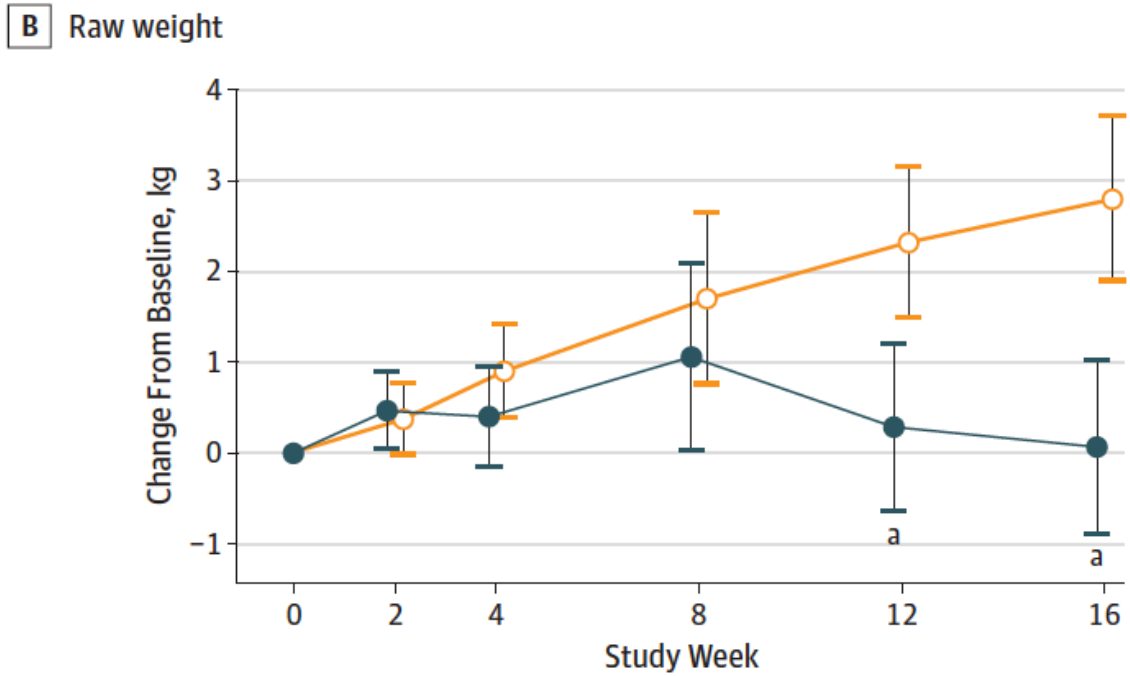
Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder

RESULTS Of the 61 randomized participants, 60 participants initiated treatment (45 [75%] male; mean [SD] age, 12.8 [2.7] years). Metformin reduced BMI *z* scores from baseline to week 16 significantly more than placebo (difference in 16-week change scores vs placebo, −0.10 [95% CI, −0.16 to −0.04]; *P* = .003). Statistically significant improvements were also noted in secondary body composition measures (raw BMI, −0.95 [95% CI, −1.46 to −0.45] and raw weight, −2.73 [95% CI, −4.04 to −1.43]) but not in metabolic variables. Overall, metformin was well tolerated. Five participants in the metformin group discontinued treatment owing to adverse events (agitation, 4; sedation, 1). Participants receiving metformin vs placebo experienced gastrointestinal adverse events during a significantly higher percentage of treatment days (25.1% vs 6.8%; *P* = .005).

CONCLUSIONS AND RELEVANCE Metformin may be effective in decreasing weight gain associated with atypical antipsychotic use and is well tolerated by children and adolescents with ASD.

JAMA Psychiatry





Metformin Effect on Body Mass Index (BMI) z Score and Weight Change

- The primary disadvantage for the active treatment group was a significantly higher percentage of treatment days with associated gastrointestinal adverse events during the 16-weeks of the trial.
- There was no difference in change in metabolic parameters measured in blood, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, fasting insulin, or hemoglobin A1C, between the metformin and placebo groups.

Limitations of the study:

- sample size is small.
- whether the length of the metformin treatment may have been too short to capture potential benefits in metabolic measures.
- whether co administration of metformin at the onset of atypical antipsychotic use prevents initial weight gain.

Larger and longer-term studies of metformin administration in youths with ASD treated with an atypical antipsychotic will be important to address these concerns and remaining questions.

Efficacy of Psychotherapies for Borderline Personality Disorder

A Systematic Review and Meta-analysis

Ioana A. Cristea, PhD; Claudio Gentili, MD, PhD; Carmen D. Cotet, PhD; Daniela Palomba, MD; Corrado Barbui, MD; Pim Cuijpers, PhD

Question What is the efficacy of psychotherapy for borderline personality disorder?

IMPORTANCE Borderline personality disorder (BPD) is a debilitating condition, but several psychotherapies are considered effective.

OBJECTIVE To conduct an updated systematic review and meta-analysis of randomized clinical trials to assess the efficacy of psychotherapies for BPD populations.

Efficacy of Psychotherapies for Borderline Personality Disorder

DATA SOURCES Search terms were combined for *borderline personality* and *randomized trials* in PubMed, PsycINFO, EMBASE, and the Cochrane Central Register of Controlled Trials (from database inception to November 2015), as well as the reference lists of earlier meta-analyses.

STUDY SELECTION Included were randomized clinical trials of adults with diagnosed BPD randomized to psychotherapy exclusively or to a control intervention. Study selection differentiated stand-alone designs (in which an independent psychotherapy was compared with control interventions) from add-on designs (in which an experimental intervention added to usual treatment was compared with usual treatment alone).

DATA EXTRACTION AND SYNTHESIS Data extraction coded characteristics of trials, participants, and interventions and assessed risk of bias using 4 domains of the Cochrane Collaboration Risk of Bias tool (independent extraction by 2 assessors). Outcomes were pooled using a random-effects model. Subgroup and meta-regression analyses were conducted.

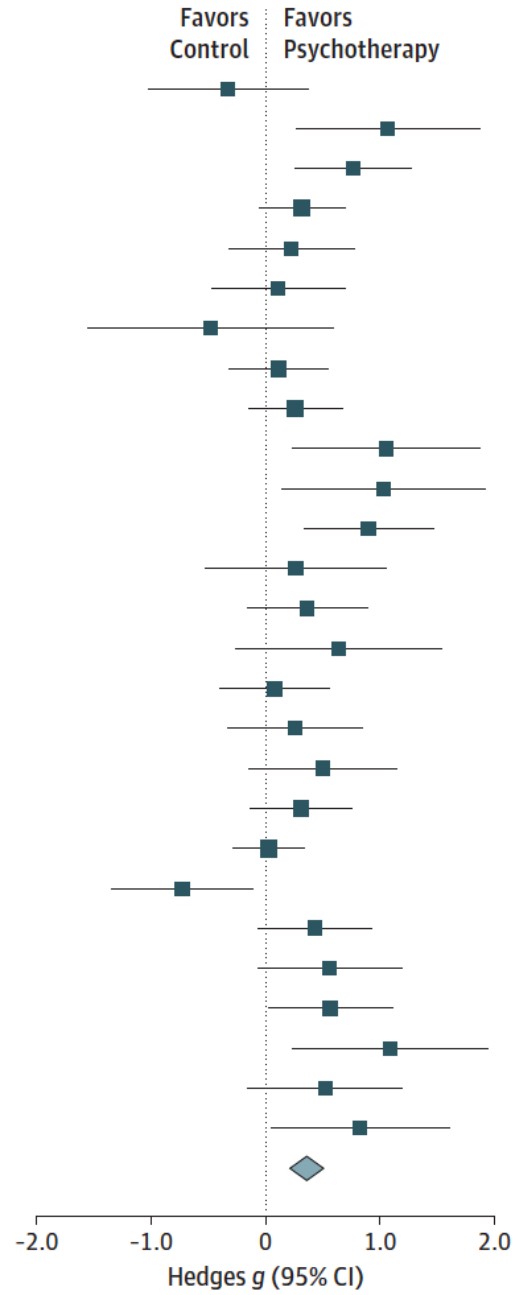
MAIN OUTCOMES AND MEASURES Standardized mean differences (Hedges *g*) were calculated using all outcomes reported in the trials for borderline symptoms, self-harm, suicide, health service use, and general psychopathology at posttest and follow-up. Differential treatment retention at posttest was analyzed, reporting odds ratios.

Efficacy of Psychotherapies for Borderline Personality Disorder

RESULTS Thirty-three trials (2256 participants) were included. For borderline-relevant outcomes combined (symptoms, self-harm, and suicide) at posttest, the investigated psychotherapies were moderately more effective than control interventions in stand-alone designs (g = 0.32; 95% CI, 0.14-0.51) and add-on designs (g = 0.40; 95% CI, 0.15-0.65). Results were similar for other outcomes, including stand-alone designs: self-harm (g = 0.32; 95% CI, 0.09-0.54), suicide (g = 0.44; 95% CI, 0.15-0.74), health service use (g = 0.40; 95% CI, 0.22-0.58), and general psychopathology (g = 0.32; 95% CI, 0.09-0.55), with no differences between design types. There were no significant differences in the odds ratios for treatment retention (1.32; 95% CI, 0.87-2.00 for stand-alone designs and 1.01; 95% CI, 0.55-1.87 for add-on designs). Thirteen trials reported borderline-relevant outcomes at follow-up (g = 0.45; 95% CI, 0.15-0.75). Dialectical behavior therapy (g = 0.34; 95% CI, 0.15-0.53) and psychodynamic approaches (g = 0.41; 95% CI, 0.12-0.69) were the only types of psychotherapies more effective than control interventions. Risk of bias was a significant moderator in subgroup and meta-regression analyses (slope β = −0.16; 95% CI, −0.29 to −0.03; P = .02). Publication bias was persistent, particularly for follow-up.

Figure. Borderline-Relevant Outcomes

Source	Hedges *g* (95% CI)
Amianto et al,[43] 2011	-0.34 (-1.01 to 0.34)
Bateman and Fonagy,[37] 1999	1.06 (0.28 to 1.83)
Bateman and Fonagy,[16] 2009	0.75 (0.28 to 1.23)
Blum et al,[44] 2008	0.31 (-0.04 to 0.66)
Bos et al,[41] 2010	0.22 (-0.30 to 0.74)
Carter et al,[45] 2010	0.10 (-0.45 to 0.66)
Cottraux et al,[46] 2009	-0.48 (-1.53 to 0.56)
Davidson et al,[17] 2006	0.10 (-0.30 to 0.51)
Doering et al,[18] 2010	0.25 (-0.13 to 0.64)
Farrell et al,[47] 2009	1.04 (0.25 to 1.84)
Gratz and Gunderson,[48] 2006	1.02 (0.16 to 1.88)
Gratz et al,[49] 2014	0.89 (0.35 to 1.43)
Gregory et al,[50] 2008	0.26 (-0.51 to 1.03)
Jørgensen et al,[51] 2013	0.35 (-0.15 to 0.85)
Koons et al,[42] 2001	0.62 (-0.25 to 1.50)
Kramer et al,[52] 2014	0.07 (-0.38 to 0.52)
Leppänen et al,[53] 2016	0.25 (-0.31 to 0.81)
Linehan et al,[38] 1991	0.49 (-0.14 to 1.11)
Linehan et al,[19] 2006	0.30 (-0.12 to 0.72)
McMain et al,[40] 2009	0.02 (-0.27 to 0.31)
Pascual et al,[54] 2015	-0.73 (-1.32 to -0.14)
Priebe et al,[55] 2012	0.42 (-0.05 to 0.89)
Reneses et al,[56] 2013	0.55 (-0.05 to 1.16)
Soler et al,[57] 2009	0.56 (0.04 to 1.08)
Turner,[58] 2000	1.07 (0.24 to 1.91)
Verheul et al,[39] 2003	0.51 (-0.14 to 1.16)
Weinberg et al,[59] 2006	0.82 (0.06 to 1.57)
Overall	0.35 (0.20 to 0.50)



Shown are standardized posttest effect sizes of comparisons between investigated psychotherapies and control conditions for borderline-relevant outcomes (borderline symptoms, self-harm and parasuicidal behavior, and suicide) for 27 trials.[16-19,37-59]

Efficacy of Psychotherapies for Borderline Personality Disorder

CONCLUSIONS AND RELEVANCE Psychotherapies, most notably dialectical behavior therapy and psychodynamic approaches, are effective for borderline symptoms and related problems. Nonetheless, effects are small, inflated by risk of bias and publication bias, and particularly unstable at follow-up.

Treating Borderline Personality Disorder With Psychotherapy
Where Do We Go From Here?

Peter Fonagy, PhD; Patrick Luyten, PhD; Anthony Bateman, MA, FRCPsych

"while the study by Cristea et al will undoubtedly provide a major impetus to future research on the effectiveness of psychotherapy for BPD, their findings make it clear that much remains to be done in terms of the development, evaluation, and implementation in routine clinical care of effective psychotherapy for this highly debilitating condition."

EDITORIAL

JAMA Psychiatry April 2017 Volume 74, Number 4

Is There a Best Psychotherapy for Borderline Personality Disorder?

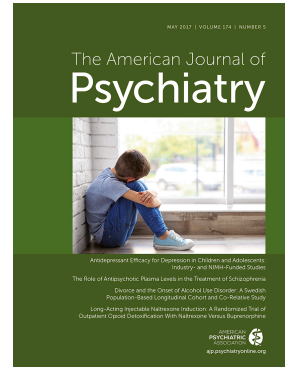
Dubovsky, Steven . **NEJM Journal Watch. Psychiatry; Waltham** (Mar 13, 2017).

NEJM Journal Watch
PSYCHIATRY

Specifically designed psychotherapies performed only somewhat better than nonspecific ones, perhaps because of improvements in treatment as usual.

Editorialists astutely point out that the lack of a dramatic difference between specific, manual-based therapies and less structured treatments may indicate that TAU has evolved. TAU now emphasizes the same coherence, consistency, continuity, and reorganization of thinking that characterizes BPD-specific therapies.

KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia



Robert A. Hauser, M.D., M.B.A., Stewart A. Factor, D.O., Stephen R. Marder, M.D., Mary Ann Knesevich, M.D., Paul M. Ramirez, Ph.D., Roland Jimenez, B.A., Joshua Burke, M.S., Grace S. Liang, M.D., Christopher F. O'Brien, M.D.

Objective: Tardive dyskinesia is a persistent movement disorder induced by dopamine receptor blockers, including antipsychotics. Valbenazine (NBI-98854) is a novel, highly selective vesicular monoamine transporter 2 inhibitor that demonstrated favorable efficacy and tolerability in the treatment of tardive dyskinesia in phase 2 studies. This phase 3 study further evaluated the efficacy, safety, and tolerability of valbenazine as a treatment for tardive dyskinesia.

Method: This 6-week, randomized, double-blind, placebo controlled trial included patients with schizophrenia, schizoaffective disorder, or a mood disorder who had moderate or severe tardive dyskinesia. Participants were randomly assigned in a 1:1:1 ratio to once-daily placebo, valbenazine at 40 mg/day, or valbenazine at 80 mg/day. The primary efficacy endpoint was change from baseline to week 6 in the 80 mg/day group compared with the placebo group on the Abnormal Involuntary Movement Scale (AIMS) dyskinesia score (items 1–7), as assessed by blinded central AIMS video raters. Safety assessments included adverse event monitoring, laboratory tests, ECG, and psychiatric measures.

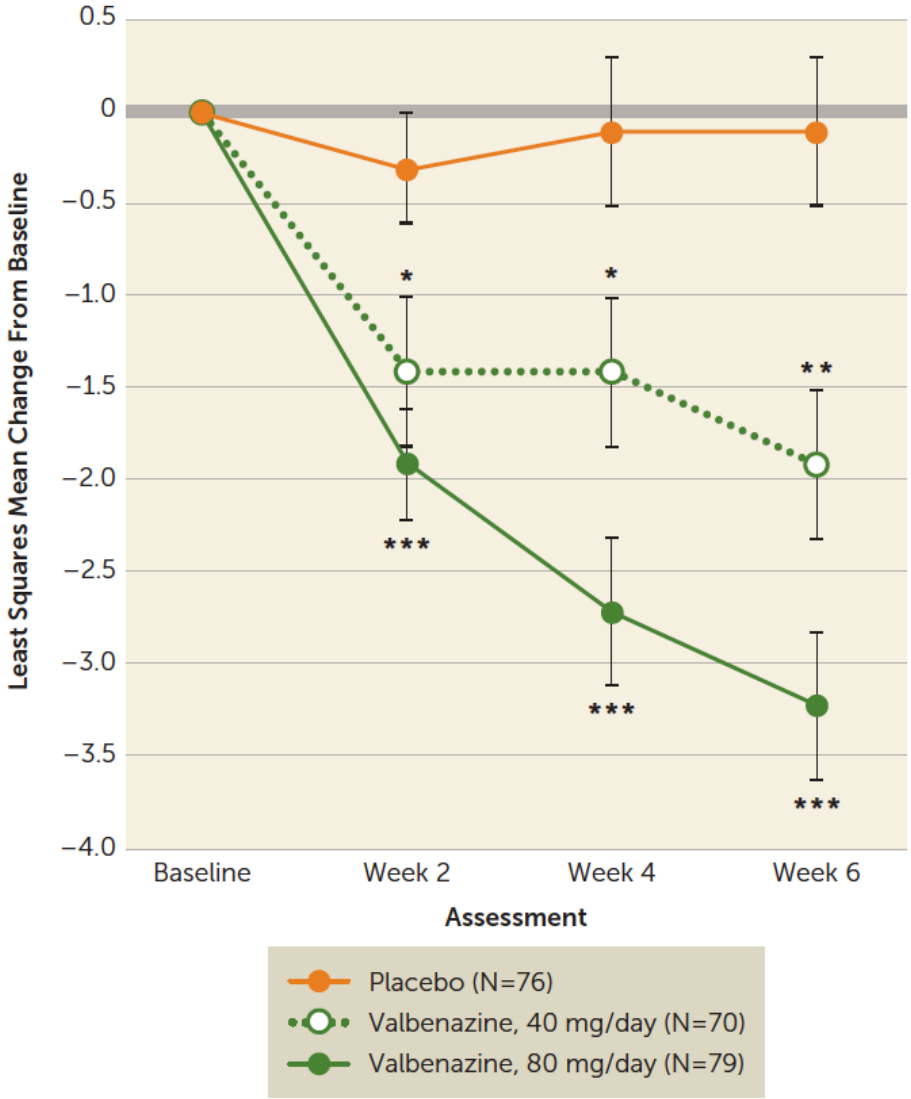
Am J Psychiatry 174:5, May 2017

KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia

Results: The intent-to-treat population included 225 participants, 205 completed the study. Approximately 65% of participants had schizophrenia or schizoaffective disorder, and 85.5% were receiving concomitant antipsychotics. Least squares mean change from baseline to week 6 in AIMS dyskinesia score was 23.2 for the 80 mg/day group, compared with 20.1 for the placebo group, a significant difference. AIMS dyskinesia score was also reduced in the 40 mg/day group (21.9 compared with 20.1). The incidence of adverse events was consistent with previous studies.

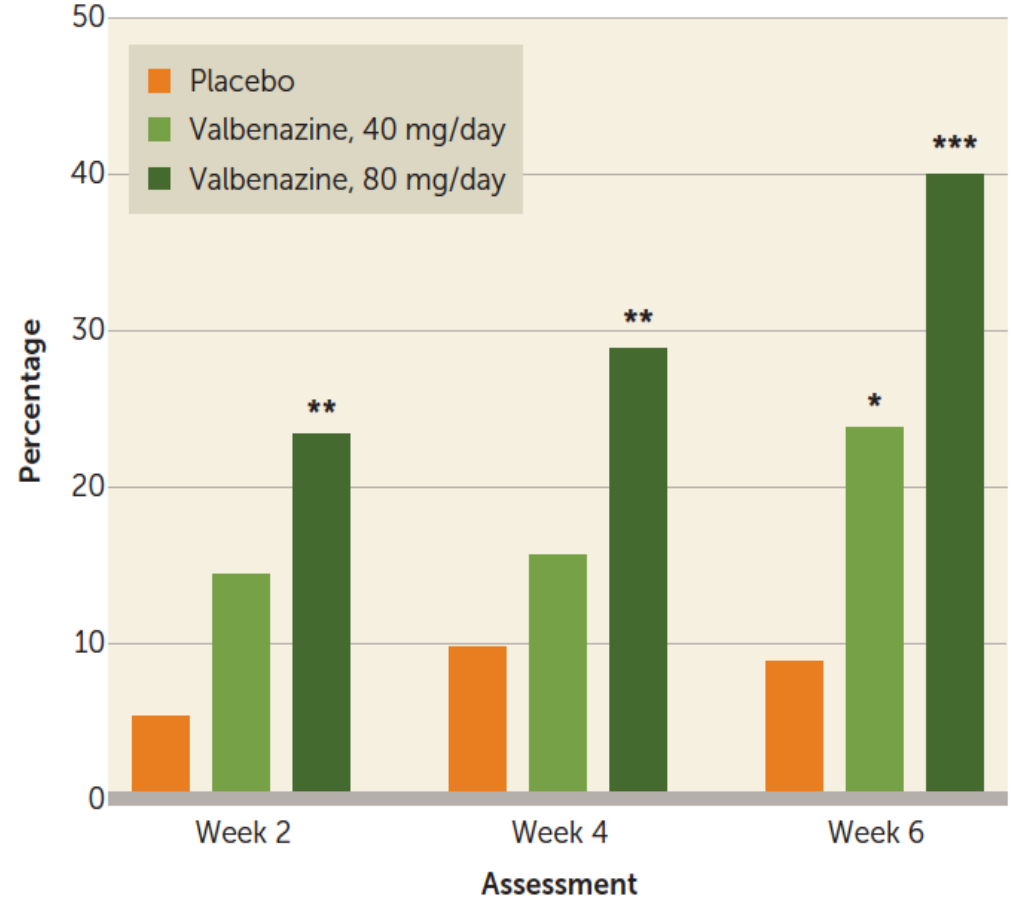
Am J Psychiatry 174:5, May 2017

FIGURE 2. Change From Baseline in AIMS Dyskinesia Score Among Participants Receiving Valbenazine or Placebo, by Study Visit (Intent-to-Treat Population)[a]



[a] Mixed-effects model for repeated measures. AIMS=Abnormal Involuntary Movement Scale; the dyskinesia score is the sum of AIMS items 1–7. The indicated significance levels refer to comparison with placebo. Error bars indicate standard error of the mean.
*p<0.05. **p<0.01. ***p≤0.001.

FIGURE 3. Percentage of Participants Receiving Valbenazine or Placebo Who Had a ≥50% Improvement in AIMS Dyskinesia Score (Intent-to-Treat Population)[a]



[a] AIMS=Abnormal Involuntary Movement Scale. Treatment response was defined as a reduction of ≥50% from baseline in AIMS dyskinesia score. The indicated significance levels refer to comparison with placebo. Ns were as follows for weeks 2, 4, and 6, respectively: placebo group, 75, 72, 69; valbenazine 40 mg/day group, 70, 64, 63; valbenazine 80 mg/day group, 77, 73, 70.
*p<0.05. **p<0.01. ***p<0.001.

KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia

Conclusions:

- Once-daily valbenazine significantly improved tardive dyskinesia in participants with underlying schizophrenia, schizoaffective disorder, or mood disorder.
- Valbenazine was generally well tolerated, and psychiatric status remained stable.
- Longer trials are necessary to understand the long-term effects of valbenazine in patients with tardive dyskinesia.

Am J Psychiatry 174:5, May 2017

Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder

A Randomized Clinical Trial

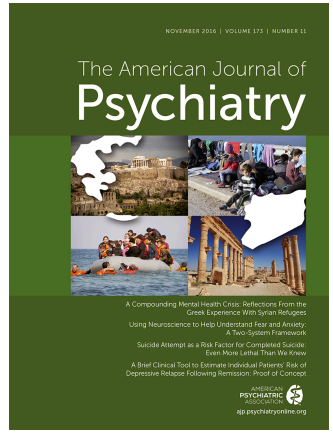
Evdokia Anagnostou, MD; Michael G. Aman, PhD; Benjamin L. Handen, PhD; Kevin B. Sanders, MD; Amy Shui, MA; Jill A. Hollway, PhD; Jessica Brian, PhD; L. Eugene Arnold, MD; Lucia Capano, MD; Jessica A. Hellings, MD; Eric Butter, PhD; Deepali Mankad, MD; Rameshwari Tumuluru, MD; Jessica Kettel, MD; Cassandra R. Newsom, PsyD; Stasia Hadjiyannakis, MD; Naomi Peleg, MSc; Dina Odrobina, BMSc; Sarah McAuliffe-Bellin, MEd; Pearl Zakroysky, MPH; Sarah Marler, MA; Alexis Wagner, BS; Taylor Wong, BS; Eric A. Macklin, PhD; Jeremy Veenstra-VanderWeele, MD

Question What is the effect of metformin hydrochloride on weight gain associated with the use of atypical antipsychotics in children and adolescents with autism spectrum disorders?

IMPORTANCE Atypical antipsychotic medications are indicated for the treatment of irritability and agitation symptoms in children with autism spectrum disorder (ASD). Unfortunately, these medications are associated with weight gain and metabolic complications that are especially troubling in children and with long-term use.

Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study

Charles H. Kellner, M.D., Mustafa M. Husain, M.D., Rebecca G. Knapp, Ph.D., W. Vaughn McCall, M.D., M.S., Georgios Petrides, M.D., Matthew V. Rudorfer, M.D., Robert C. Young, M.D., Shirlene Sampson, M.D., Shawn M. McClintock, Ph.D., Martina Mueller, Ph.D., Joan Prudic, M.D., Robert M. Greenberg, M.D., Richard D. Weiner, M.D., Ph.D., Samuel H. Bailine, M.D., Peter B. Rosenquist, M.D., Ahmad Raza, M.D., Ph.D., Styliani Kaliora, M.D., Vassilios Latoussakis, M.D., Kristen G. Tobias, M.A., Mimi C. Briggs, B.A., Lauren S. Liebman, B.A., Emma T. Geduldig, B.A., Abeba A. Teklehaimanot, M.S., Sarah H. Lisanby, M.D., the CORE/PRIDE Work Group



Objective: The Prolonging Remission in Depressed Elderly (PRIDE) study evaluated the efficacy of right unilateral ultrabrief pulse electroconvulsive therapy (ECT) combined with venlafaxine for the treatment of geriatric depression.

Method: PRIDE was a two-phase multisite study. Phase 1 was an acute course of right unilateral ultrabrief pulse ECT, combined with open-label venlafaxine at seven academic medical centers. In phase 1, depressed patients received high-dose ECT (at six times the seizure threshold) three times per week. Venlafaxine was started during the first week of treatment and continued throughout the study. The primary outcome measure was remission, assessed with the 24-item Hamilton Depression Rating Scale (HAM-D), which was administered three times per week. Secondary outcome measures were post-ECT reorientation and safety. Paired t tests were used to estimate and evaluate the significance of change from baseline in HAM-D scores.

Am J Psychiatry 173:11, November 2016

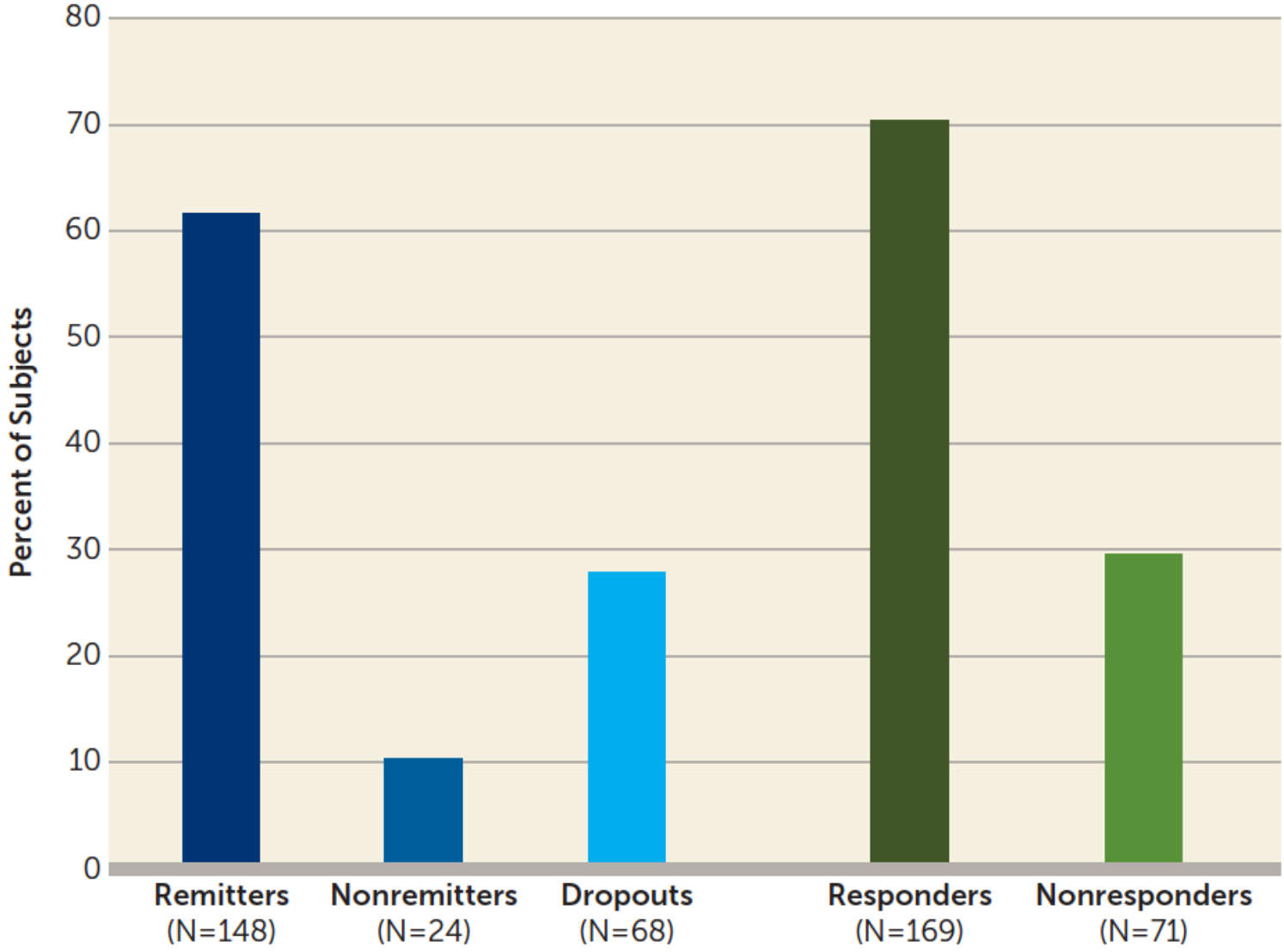
Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study

Results: Of 240 patients who entered phase 1 of the study, 172 completed it. Overall, 61.7% (148/240) of all patients met remission criteria, 10.0% (24/240) did not remit, and 28.3% (68/ 240) dropped out; 70% (169/240)met response criteria. Among those who remitted, the mean decrease in HAM-D score was 24.7 points (95% CI=23.4, 25.9), with a mean final score of 6.2 (SD=2.5) and an average change from baseline of 79%. The mean number of ECT treatments to remission was 7.3 (SD=3.1).

Conclusions: Right unilateral ultrabrief pulse ECT, combined with venlafaxine, is a rapidly acting and highly effective treatment option for depressed geriatric patients, with excellent safety and tolerability. These data add to the evidence base supporting the efficacy of ECT to treat severe depression in elderly patients.

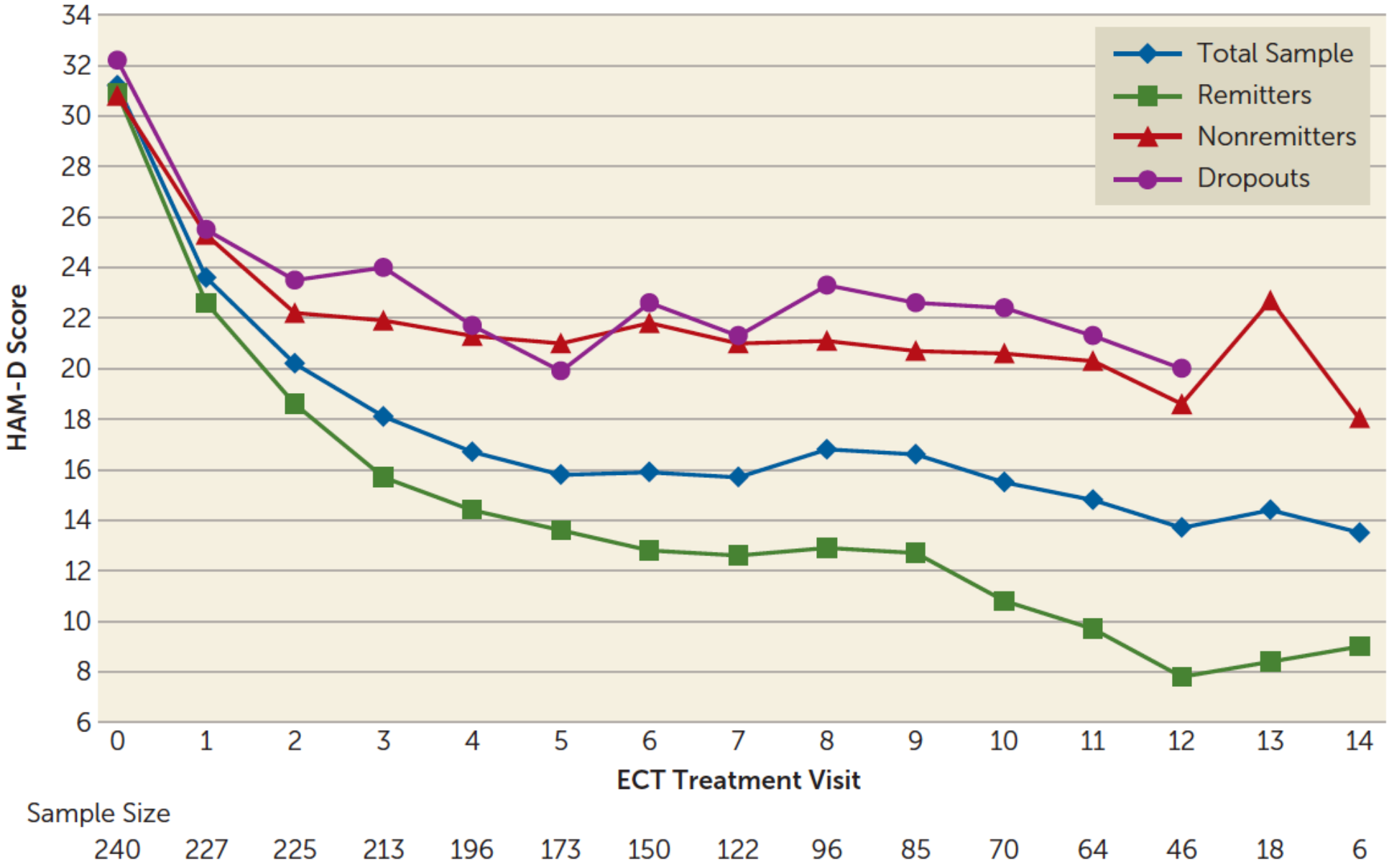
Am J Psychiatry 173:11, November 2016

Remission, Response, and Dropout in a Study of ECT and Venlafaxine in Geriatric Depression[a]



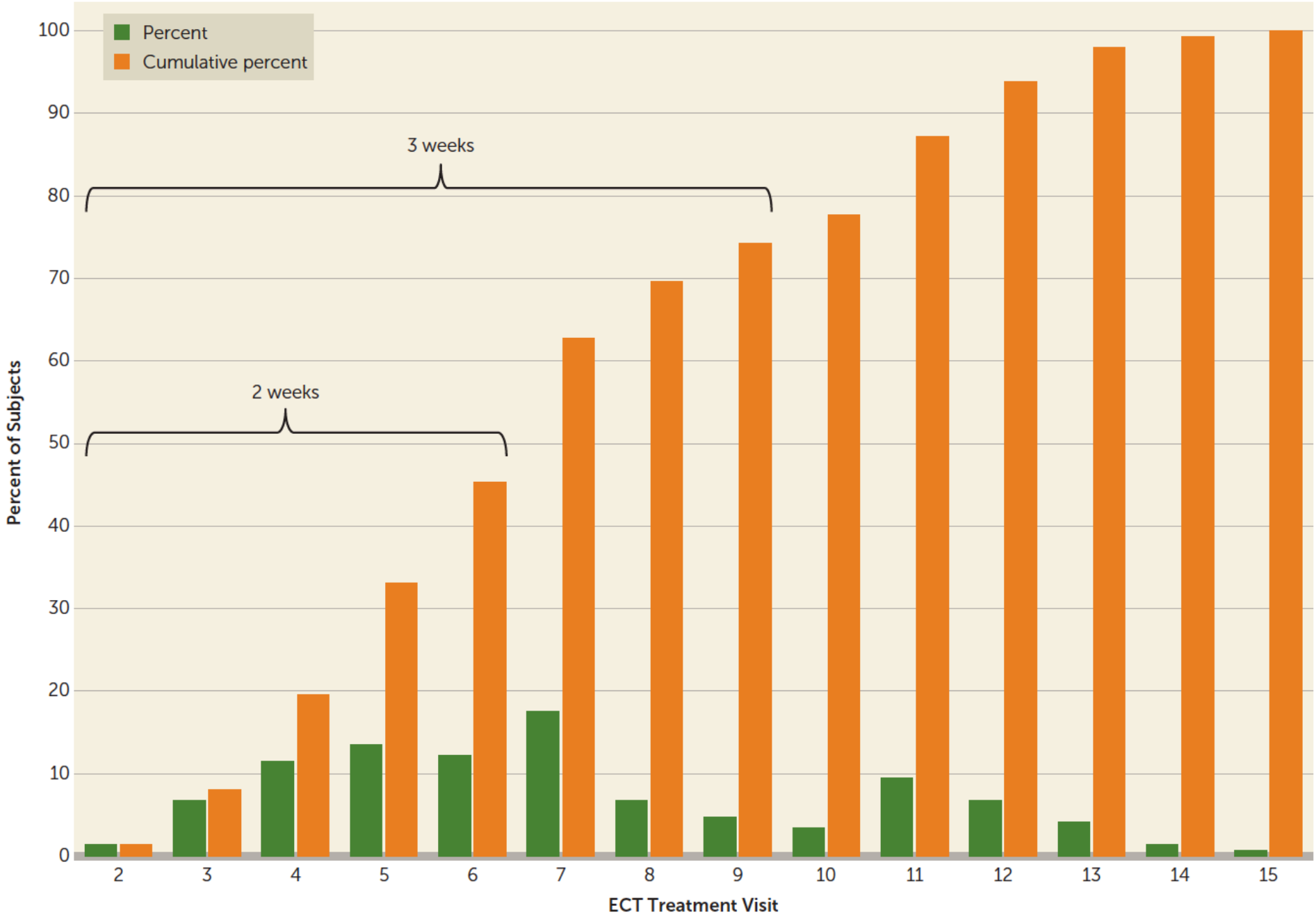
[a] Remission was defined as having a score ≤10 on the 24-item Hamilton Depression Rating Scale (HAM-D) on two consecutive ratings; response was defined as having at least a 50% decrease in HAM-D score from baseline to last assessment.

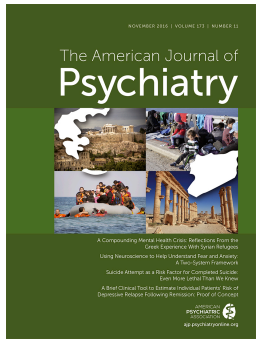
FIGURE 2. Trajectory of Observed Mean Scores on the 24-Item Hamilton Depression Rating Scale (HAM-D), by Outcome Group, in a Study of ECT and Venlafaxine in Geriatric Depression[a]



[a] Visits 15–17 were omitted because of small sample sizes (N=3, 2, 1, respectively), resulting in unstable means.

FIGURE 3. Speed of Remission Among Remitted Patients (N=148) in a Study of ECT and Venlafaxine in Geriatric Depression





A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study

Charles H. Kellner, M.D., Mustafa M. Husain, M.D., Rebecca G. Knapp, Ph.D., W. Vaughn McCall, M.D., M.S., Georgios Petrides, M.D., Matthew V. Rudorfer, M.D., Robert C. Young, M.D., Shirlene Sampson, M.D., Shawn M. McClintock, Ph.D., Martina Mueller, Ph.D., Joan Prudic, M.D., Robert M. Greenberg, M.D., Richard D. Weiner, M.D., Ph.D., Samuel H. Bailine, M.D., Peter B. Rosenquist, M.D., Ahmad Raza, M.D., Ph.D., Styliani Kaliora, M.D., Vassilios Latoussakis, M.D., Kristen G. Tobias, M.A., Mimi C. Briggs, B.A., Lauren S. Liebman, B.A., Emma T. Geduldig, B.A., Abeba A. Teklehaimanot, M.S., Mary Dooley, M.S., Sarah H. Lisanby, M.D., the CORE/PRIDE Work Group

Objective: The randomized phase (phase 2) of the Prolonging Remission in Depressed Elderly (PRIDE) study evaluated the efficacy and tolerability of continuation ECT plus medication compared with medication alone in depressed geriatric patients after a successful course of ECT (phase 1).

Method: PRIDE was a two-phase multisite study. Phase 1 was an acute course of right unilateral ultrabrief pulse ECT, augmented with venlafaxine. Phase 2 compared two randomized treatment arms: a medication only arm (venlafaxine plus lithium, over 24 weeks) and an ECT plus medication arm (four continuation ECT treatments over 1 month, plus additional ECT as needed, using the Symptom-Titrated, Algorithm-Based Longitudinal ECT [STABLE] algorithm, while continuing venlafaxine plus lithium). The intent-to-treat sample comprised 120 remitters from phase 1. The primary efficacy outcome measure was score on the 24-item Hamilton Depression Rating Scale (HAM-D), and the secondary efficacy outcome was score on the Clinical Global Impressions severity scale (CGI-S). Tolerability as measured by neurocognitive performance (reported elsewhere) was assessed using an extensive test battery; global cognitive functioning as assessed by the Mini-Mental State Examination (MMSE) is reported here. Longitudinal mixed-effects repeated-measures modeling was used to compare ECT plus medication and medication alone for efficacy and global cognitive function outcomes.

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A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study

Results: At 24 weeks, the ECT plus medication group had statistically significantly lower HAM-D scores than the medication only group. The difference in adjusted mean HAM-D scores at study end was 4.2 (95% CI=1.6, 6.9). Significantly more patients in the ECT plus medication group were rated “not ill at all” on the CGI-S compared with the medication only group. There was no statistically significant difference between groups in MMSE score.

Conclusions: Additional ECT after remission (operationalized as four continuation ECT treatments followed by further ECT only as needed) was beneficial in sustaining mood improvement for most patients.

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These results showing efficacy and lack of notable cognitive impact in an elderly population strongly advocate not only for unilateral, ultrabrief, pulsed ECT plus medication, but also for flexibly administered ECT after remission, including "rescue" treatments for relapse prevention.

NEJM Journal Watch
PSYCHIATRY

Joel Yager, MD. July 20, 2016

Effect of a Web-Based Cognitive Behavior Therapy for Insomnia Intervention With 1-Year Follow-up
A Randomized Clinical Trial

Lee M. Ritterband, PhD; Frances P. Thorndike, PhD; Karen S. Ingersoll, PhD; Holly R. Lord, PhD; Linda Gonder-Frederick, PhD; Christina Frederick, BS; Mark S. Quigg, MD, MSc; Wendy F. Cohn, PhD; Charles M. Morin, PhD

Question What is the efficacy of a fully automated internet-delivered cognitive behavior therapy for insomnia intervention compared with an insomnia patient education website with respect to the primary sleep outcomes of Insomnia Severity Index, sleep onset latency, and wake after sleep onset in a heterogeneous sample?

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Effect of a Web-Based Cognitive Behavior Therapy for Insomnia Intervention

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IMPORTANCE Although cognitive behavior therapy for insomnia (CBT-I) has been established as the first-line recommendation for the millions of adults with chronic insomnia, there is a paucity of trained clinicians to deliver this much needed treatment. Internet-delivered CBT-I has shown promise as a method to overcome this obstacle; however, the long-term effectiveness has not been proven in a representative sample with chronic insomnia.

OBJECTIVE To evaluate a web-based, automated CBT-I intervention to improve insomnia in the short term (9 weeks) and long term (1 year).

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial comparing the internet CBT-I with internet patient education at baseline, 9 weeks, 6 months, and 1 year. Altogether, 303 adults with chronic insomnia self-referred to participate, of whom 151 (49.8%) reported at least 1 medical or psychiatric comorbidity.

INTERVENTIONS The internet CBT-I (Sleep Healthy Using the Internet [SHUTi]) was a 6-week fully automated, interactive, and tailored web-based program that incorporated the primary tenets of face-to-face CBT-I. The online patient education program provided nontailored and fixed online information about insomnia.

Effect of a Web-Based Cognitive Behavior Therapy for Insomnia Intervention

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MAIN OUTCOMES AND MEASURES The primary sleep outcomes were self-reported online ratings of insomnia severity (Insomnia Severity Index) and online sleep diary–derived values for sleep-onset latency and wake after sleep onset, collected prospectively for 10 days at each assessment period. The secondary sleep outcomes included sleep efficiency, number of awakenings, sleep quality, and total sleep time.

RESULTS Among 303 participants, the mean (SD) age was 43.28 (11.59) years, and 71.9% (218 of 303) were female. Of these, 151 were randomized to the SHUTi group and 152 to the online patient education group. Results of the 3 primary sleep outcomes showed that the overall group × time interaction was significant for all variables, favoring the SHUTi group (Insomnia Severity Index [$F_{3,1063} = 20.65$, $P < .001$], sleep-onset latency [$F_{3,1042} = 6.01$, $P < .001$], and wake after sleep onset [$F_{3,1042} = 12.68$, $P < .001$]). Within-group effect sizes demonstrated improvements from baseline to postassessment for the SHUTi participants (range, Cohen $d = 0.79$ [95% CI, 0.55-1.04] to $d = 1.90$ [95% CI, 1.62-2.18]). Treatment effects were maintained at the 1-year follow-up (SHUTi Insomnia Severity Index $d = 2.32$ [95% CI, 2.01-2.63], sleep-onset latency $d = 1.41$ [95% CI, 1.15-1.68], and wake after sleep onset $d = 0.95$ [95% CI, 0.70-1.21]), with 56.6% (69 of 122) achieving remission status and 69.7% (85 of 122) deemed treatment responders at 1 year based on Insomnia Severity Index data. All secondary sleep outcomes, except total sleep time, also showed significant overall group × time interactions, favoring the SHUTi group.

CONCLUSIONS AND RELEVANCE Given its efficacy and availability, internet-delivered CBT-I may have a key role in the dissemination of effective behavioral treatments for insomnia.

- This study provides compelling evidence that the self guided, web-based CBT-I intervention SHUTi can effectively treat insomnia. It extends findings that internet-delivered CBT-I can meaningfully improve insomnia symptoms and sleep variables, including when insomnia is comorbid with other conditions.
- Future studies are necessary to determine who may be best served by this type of intervention and how the next steps of dissemination should occur.
- Ensuring that these interventions work with different patient populations, whether tailored or not for those groups, should also be examined.
- In addition, exploring the use of these interventions with lower educated, less technologically experienced, and older populations will be critical to broad dissemination efforts.

Should Internet Cognitive Behavioral Therapy for Insomnia Be the Primary Treatment Option for Insomnia?

Toward Getting More SHUTi

Andrew D. Krystal, MD, MS; Aric A. Prather, PhD

On the whole, the findings suggest that SHUTi is a promising treatment option for patients with insomnia. These findings and the potential for rapid widespread use demand that we address a critical question: "Should internet CBT-I be the first-line treatment for all patients with insomnia?" Several issues suggest that it is premature to adopt this position and speak for restraint.

EDITORIAL

JAMA Psychiatry January 2017 Volume 74, Number 1

"these primarily middle-class patients had substantial familiarity with the Internet and therefore do not represent all patients, as editorialists and researchers point out. Reliance entirely on self report-- which does not correlate with sleep-laboratory assessments (especially of sleep latency and duration) -- and lack of objective evaluation of daytime impairment further limit interpretation of the results. However, SHUTi (which costs $135), may be an option for some Internet-savvy individuals without severe psychiatric illnesses."

NEJM Journal Watch PSYCHIATRY

Dubovsky, Steven. December 12, 2016

Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial

David A Richards, David Ekers, Dean McMillan, Rod S Taylor, Sarah Byford, Fiona C Warren, Barbara Barrett, Paul A Farrand, Simon Gilbody, Willem Kuyken, Heather O'Mahen, Ed R Watkins, Kim A Wright, Steven D Hollon, Nigel Reed, Shelley Rhodes, Emily Fletcher, Katie Finning

www.thelancet.com Vol 388 August 27, 2016

Summary

Background Depression is a common, debilitating, and costly disorder. Many patients request psychological therapy, but the best-evidenced therapy—cognitive behavioural therapy (CBT)—is complex and costly. A simpler therapy—behavioural activation (BA)—might be as effective and cheaper than is CBT. We aimed to establish the clinical efficacy and cost-effectiveness of BA compared with CBT for adults with depression.

Methods In this randomised, controlled, non-inferiority trial, we recruited adults aged 18 years or older meeting Diagnostic and Statistical Manual of Mental Disorders IV criteria for major depressive disorder from primary care and psychological therapy services in Devon, Durham, and Leeds (UK). We excluded people who were receiving psychological therapy, were alcohol or drug dependent, were acutely suicidal or had attempted suicide in the previous 2 months, or were cognitively impaired, or who had bipolar disorder or psychosis or psychotic symptoms. We randomly assigned participants (1:1) remotely using computer-generated allocation (minimisation used; stratified by depression severity [Patient Health Questionnaire 9 (PHQ-9) score of <19 *vs* ≥19], antidepressant use, and recruitment site) to BA from junior mental health workers or CBT from psychological therapists. Randomisation done at the Peninsula Clinical Trials Unit was concealed from investigators. Treatment was given open label, but outcome assessors were masked. The primary outcome was depression symptoms according to the PHQ-9 at 12 months. We analysed all those who were randomly allocated and had complete data (modified intention to treat [mITT]) and also all those who were randomly allocated, had complete data, and received at least eight treatment sessions (per protocol [PP]). We analysed safety in the mITT population. The non-inferiority margin was 1·9 PHQ-9 points. This trial is registered with the ISCRTN registry, number ISRCTN27473954.

Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial

Findings Between Sept 26, 2012, and April 3, 2014, we randomly allocated 221 (50%) participants to BA and 219 (50%) to CBT. 175 (79%) participants were assessable for the primary outcome in the mITT population in the BA group compared with 189 (86%) in the CBT group, whereas 135 (61%) were assessable in the PP population in the BA group compared with 151 (69%) in the CBT group. BA was non-inferior to CBT (mITT: CBT 8·4 PHQ-9 points [SD 7·5], BA 8·4 PHQ-9 points [7·0], mean difference 0·1 PHQ-9 points [95% CI –1·3 to 1·5], p=0·89; PP: CBT 7·9 PHQ-9 points [7·3]; BA 7·8 [6·5], mean difference 0·0 PHQ-9 points [–1·5 to 1·6], p=0·99). Two (1%) non-trial-related deaths (one [1%] multidrug toxicity in the BA group and one [1%] cancer in the CBT group) and 15 depression-related, but not treatment-related, serious adverse events (three in the BA group and 12 in the CBT group) occurred in three [2%] participants in the BA group (two [1%] patients who overdosed and one [1%] who self-harmed) and eight (4%) participants in the CBT group (seven [4%] who overdosed and one [1%] who self-harmed).

Interpretation We found that BA, a simpler psychological treatment than CBT, can be delivered by junior mental health workers with less intensive and costly training, with no lesser effect than CBT. Effective psychological therapy for depression can be delivered without the need for costly and highly trained professionals.

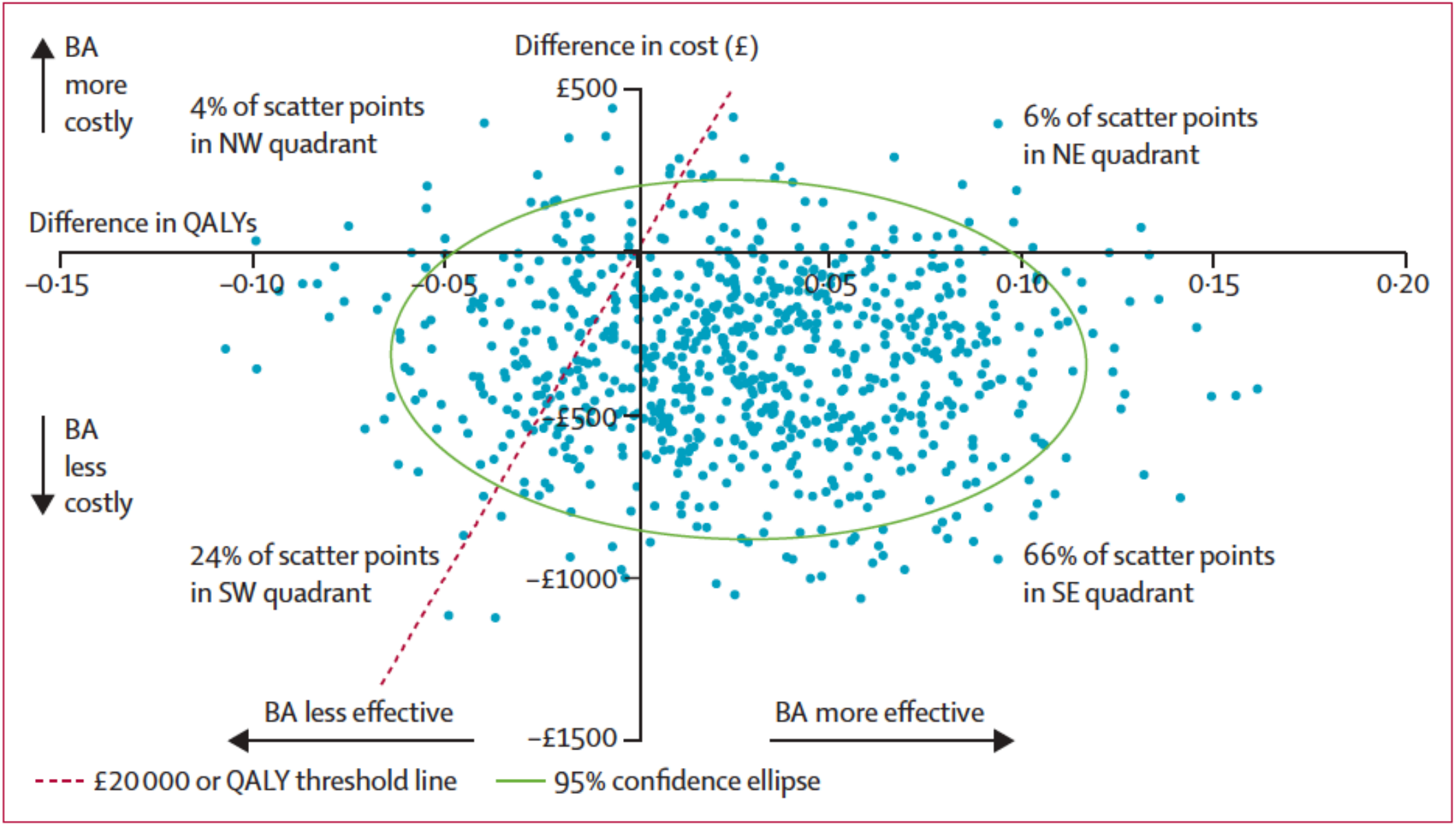


Figure 2: **Bootstrapped mean differences in costs and effects of BA compared with CBT**

BA=behavioural activation. CBT=cognitive behavioural therapy. NE=northeast. NW=northwest. SE=southeast. SW=southwest. QALY=quality-adjusted life-year.

Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial

Evidence before this study

Authors of published systematic reviews, including a Cochrane review, have commented on the limitations of existing evidence for the effectiveness of behavioural activation (BA) for depression compared with cognitive behavioural therapy (CBT) and the scarcity of cost-effectiveness data, with the existing evidence insufficiently robust to establish comparability. Authors of the Cochrane review called for studies that improve the quality of evidence. Our pretrial evidence took published review findings from the UK National Institute for Health and Care Excellence (NICE), who reported no difference in treatment outcome between BA and CBT immediately after treatment (Hedges' *g* 0·139 [95% CI −0·400 to 0·122]; p=0·296) and subsequent follow-up (0·135 [−0·456 to 0·186]; p=0·409). The authors of NICE's review regarded the existing international evidence as insufficient to recommend BA for first-line treatment in clinical guidelines for depression.

Added value of this study

This trial addresses these research recommendations and is, to our knowledge, the only high-quality, fully powered non-inferiority and cost-effectiveness study addressing both the effects and costs of BA compared with CBT for depression. When we combine the data from our study with data from other international studies in the meta-analysis done by NICE, our data reduce the 95% CIs around the effect size for depression symptoms immediately after treatment (Hedges' *g* 0·054 [95% CI −0·214 to 0·107]; p=0·514) and at follow-up (0·059 [−0·234 to 0·115]; p=0·503) and unequivocally show both non-inferiority of BA compared with CBT and that BA is more cost-effective than is CBT against commonly applied decision maker willingness-to-pay thresholds.

Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial

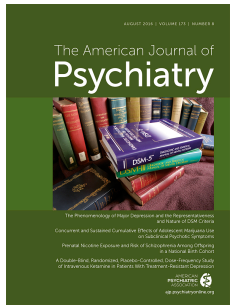
Implications of all the available evidence

Junior mental health workers with no professional training in psychological therapies can deliver behavioural activation, a simple psychological treatment, with no lesser effect than CBT has and at less cost. Effective psychological therapy for depression can be delivered without the need for costly and highly trained professionals.

This important study shows that the easy-to-implement BA is just as effective as the more complex CBT requiring advanced-degree training and experience. BA can treat a large population of depressed patients effectively and cheaply. It will be increasingly used in resource-poor countries. In developed countries looking for the smartest way to use limited mental health resources, it is an obvious "first step" treatment (most likely in collaborative, integrated-care models). In the U.S., licensing barriers and guild issues may limit utilization of novice therapists with only college degrees, even though these findings suggest they would be effective first step therapists.

Roy-Byrne, Peter. August 11, 2016.

NEJM Journal Watch
PSYCHIATRY



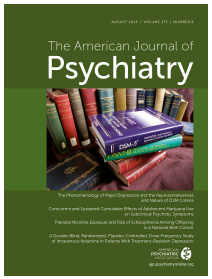
Prenatal Nicotine Exposure and Risk of Schizophrenia Among Offspring in a National Birth Cohort

Solja Niemelä, M.D., Ph.D., Andre Sourander, M.D., Ph.D., Heljä-Marja Surcel, Ph.D., Susanna Hinkka-Yli-Salomäki, Ph.Lic., Ian W. McKeague, Ph.D., Keely Cheslack-Postava, Ph.D., Alan S. Brown, M.D., M.P.H.

Objective: Cigarette smoking during pregnancy is a major public health problem leading to adverse health outcomes and neuro-developmental abnormalities among offspring. Its prevalence in the United States and Europe is 12%–25%. This study examined the relationship between prenatal nicotine exposure (cotinine level) in archived maternal sera and schizophrenia in offspring from a national birth cohort.

Method: The authors conducted a population-based nested case-control study of all live births in Finland from 1983 to 1998. Cases of schizophrenia in offspring (N=977) were identified from a national registry and matched 1:1 to controls on date of birth, sex, and residence. Maternal serum cotinine levels were prospectively measured, using quantitative immunoassay, from early to mid-gestation serum specimens archived in a national biobank.

Am J Psychiatry 173:8, August 2016



Prenatal Nicotine Exposure and Risk of Schizophrenia Among Offspring in a National Birth Cohort

Results: A higher maternal cotinine level, measured as a continuous variable, was associated with an increased odds of schizophrenia (odds ratio=3.41, 95% confidence interval,1.86–6.24). Categorically defined heavy maternal nicotine exposure was related to a 38% increased odds of schizophrenia. These findings were not accounted for by maternal age, maternal or parental psychiatric disorders, socioeconomic status, and other covariates. There was no clear evidence that weight for gestational age mediated the associations.

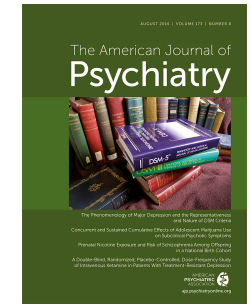
Conclusions: To the authors' knowledge, this is the first study of the relationship between a maternal smoking biomarker and schizophrenia. It provides the most definitive evidence to date that smoking during pregnancy is associated with schizophrenia. If replicated, these findings suggest that preventing smoking during pregnancy may decrease the incidence of schizophrenia.

Am J Psychiatry 173:8, August 2016

The Strange Case of Smoking and Schizophrenia—The Epidemiology Detectives Are on the Trail

Thomas Munk Laursen, Ph.D., John J. McGrath, M.D.

So, in the spirit of crime dramas, do we have enough evidence to make a conviction? With respect to individuals with schizophrenia, the evidence linking smoking and premature mortality in this group is "beyond reasonable doubt." With respect to the evidence that smoking may cause schizophrenia, the evidence continues to accumulate. This evidence does not meet the criteria for "beyond reasonable doubt," but it may soon meet the "preponderance of evidence" criteria. Regardless of the weight of this new evidence, the public health response is clear. Smoking in bad for your health, and pregnant women who smoke put their children's health at risk also.

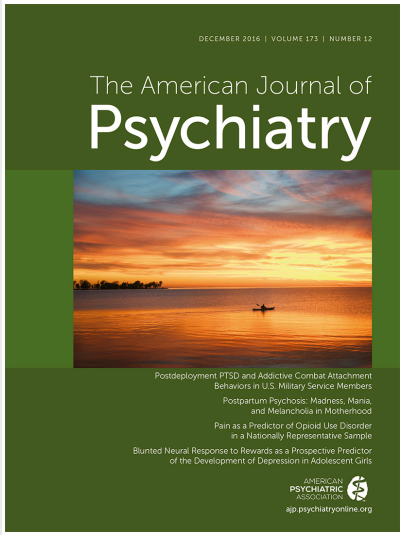


The 20-Year Longitudinal Trajectories of Social Functioning in Individuals With Psychotic Disorders

Eva Velthorst, Ph.D., Anne-Kathrin J. Fett, Ph.D., Avraham Reichenberg, Ph.D., Greg Perlman, Ph.D., Jim van Os, M.D., Ph.D., Evelyn J. Bromet, Ph.D., Roman Kotov, Ph.D.

Objective: Social impairment is a long-recognized core feature of schizophrenia and is common in other psychotic disorders. Still, to date the long-term trajectories of social impairment in psychotic disorders have rarely been studied systematically.

Methods: Data came from the Suffolk County Mental Health Project, a 20-year prospective study of first-admission patients with psychotic disorders. A never-psychotic comparison group was also assessed. Latent class growth analysis was applied to longitudinal data on social functioning from 485 respondents with schizophrenia spectrum disorders and psychotic mood disorders, and associations of the empirically derived trajectories with premorbid social adjustment, diagnosis, and 20-year outcomes were examined.



ajp in Advance December 16, 2016

The 20-Year Longitudinal Trajectories of Social Functioning in Individuals With Psychotic Disorders

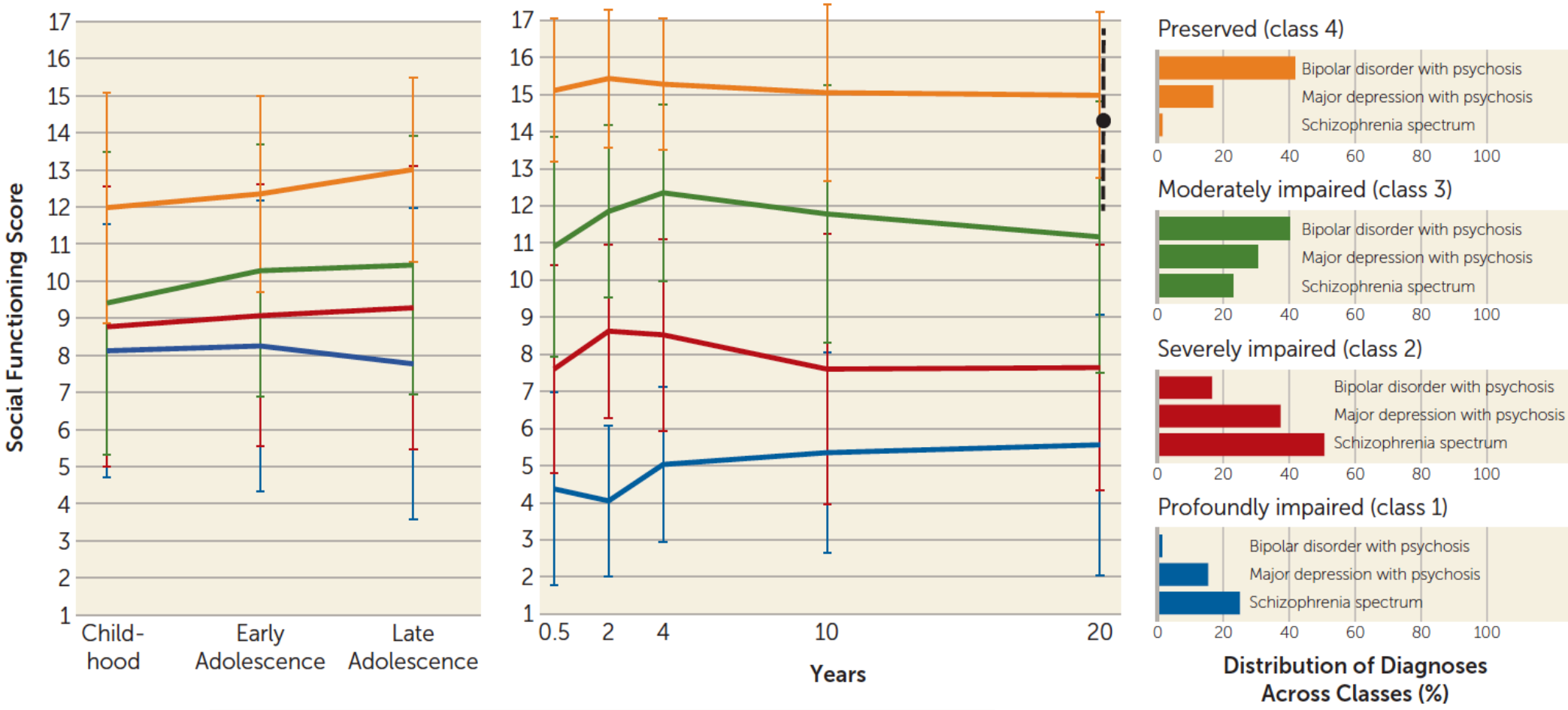
Eva Velthorst, Ph.D., Anne-Kathrin J. Fett, Ph.D., Avraham Reichenberg, Ph.D., Greg Perlman, Ph.D., Jim van Os, M.D., Ph.D., Evelyn J. Bromet, Ph.D., Roman Kotov, Ph.D.

Results: Four mostly stable trajectories of preserved (N=82; 59th percentile of comparison group sample distribution), moderately impaired (N=148; 17th percentile), severely impaired (N=181; 3rd percentile), and profoundly impaired (N=74; 1st percentile) functioning best described the 20-year course of social functioning across diagnoses. The outcome in the group with preserved functioning did not differ from that of never-psychotic individuals at 20 years, but the other groups functioned significantly worse. Differences among trajectories were already evident in childhood. The two most impaired trajectories started to diverge in early adolescence. Poorer social functioning trajectories were strongly associated with other real-world outcomes at 20 years. Multiple trajectories were represented within each disorder. However, more participants with schizophrenia spectrum disorders had impaired trajectories, and more with mood disorders had better functioning trajectories.

Conclusions:
The results highlight substantial variability of social outcomes within diagnoses—albeit overall worse social outcomes in schizophrenia spectrum disorders—and show remarkably stable long-term impairments in social functioning after illness onset across all diagnoses.

ajp in Advance December 16, 2016

FIGURE 2. Social Functioning Trajectories Across Psychotic Disorders, Derived From Latent Class Growth Analyses[a]



Clinical Implications

Persistent impairments observed in approximately half of the sample emphasize the need for targeted, long-term care aimed at improving social inclusion for those with low social functioning at illness onset. Our findings indicate that 53% of the patients decline markedly in their social functioning between late adolescence and first hospitalization, a finding that has been supported by two other studies using latent class growth curve analysis (44, 45). This and the high temporal stability of the trajectories extend previous findings suggesting that the level of social functioning may be determined in adolescence. Consequently, our findings are consistent with recent programs of research focused on adolescence as the critical intervention window and support current early intervention strategies for high-risk individuals (46) and those that offer intensive treatment to first admission patients (47) aimed to prevent social withdrawal in severe psychotic illnesses.

44. Cole VT, Apud JA, Weinberger DR, et al: Using latent class growth analysis to form trajectories of premorbid adjustment in schizophrenia. J Abnorm Psychol 2012; 121:388–395
45. Hodgekins J, Birchwood M, Christopher R, et al: Investigating trajectories of social recovery in individuals with first-episode psychosis: a latent class growth analysis. Br J Psychiatry 2015; 207:536–543
46. Fusar-Poli P, Yung AR, McGorry P, et al: Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. Psychol Med 2014; 44:17–24
47. Kane JM, Schooler NR, Marcy P, et al: The RAISE early treatment program for first-episode psychosis: background, rationale, and study design. J Clin Psychiatry 2015; 76:240–246

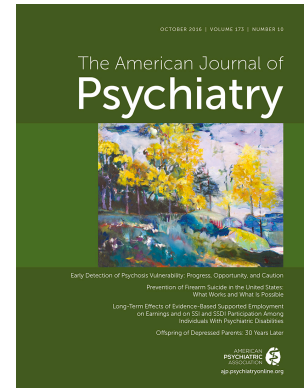
- Declining social function, starting in adolescence prior to first hospitalization, was predictive of long-term impairment.
- Severe, persistent impairment, occurring transdiagnostically, is associated with difficulties in completing high school, inability to live independently, unemployment, and requiring public assistance.
- These findings suggest the value of recovery-oriented programs that help patients and families establish meaningful expectations and provide supportive educational and employment resources to help them achieve realistic goals.

Yager, Joel. December 28, 2016

NEJM Journal Watch PSYCHIATRY

Offspring of Depressed Parents: 30 Years Later

Myrna M. Weissman, Ph.D., Priya Wickramaratne, Ph.D., Marc J. Gameroff, Ph.D., Virginia Warner, Dr.P.H., Daniel Pilowsky, M.D., M.P.H., Rajni Gathibandhe Kohad, M.D., M.P.H., Helena Verdeli, Ph.D., Jamie Skipper, M.A., Ardesheer Talati, Ph.D.



Objective: While the increased risk of psychopathology in the biological offspring of depressed parents has been widely replicated, the long-term outcome through their full age of risk is less known. The authors present a 30-year follow-up of biological offspring (mean age= 47 years) of depressed (high-risk) and non-depressed (low-risk) parents.

Method: One hundred forty-seven offspring of moderately to severely depressed or non-depressed parents selected from the same community were followed for up to 30 years. Diagnostic assessments were conducted blind to parents' clinical status. Final diagnoses were made by a blinded M.D. or Ph.D. evaluator.

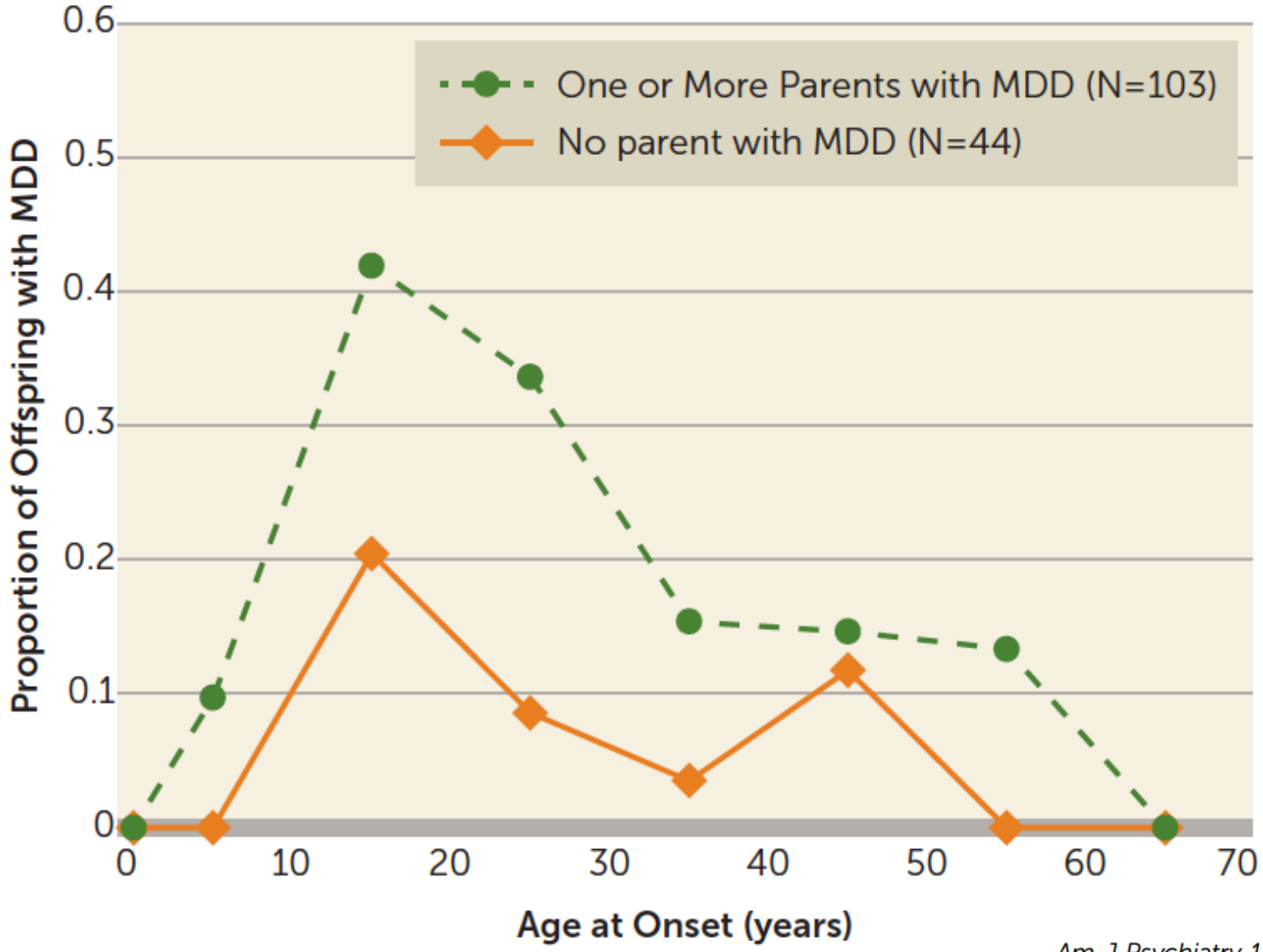
Am J Psychiatry 173:10, October 2016

Offspring of Depressed Parents: 30 Years Later

Results: The risk for major depression was approximately three times as high in the high-risk offspring. The period of highest risk for first onset was between ages 15 and 25 in both groups. Prepubertal onsets were uncommon, but high-risk offspring had over 10-fold increased risk. The early onset of major depression seen in the offspring of depressed parents was not offset by later first onsets in the low-risk group as they matured. The increased rates of major depression in the high-risk group were largely accounted for by the early onsets, but later recurrences in the high-risk group were significantly increased. The high-risk offspring continue to have overall poorer functioning and receive more treatment for emotional problems. There was increased mortality in the high-risk group (5.5% compared with 2.5%) due to unnatural causes, with a nearly 8-year difference in the mean age at death (38.8 years compared with 46.5 years).

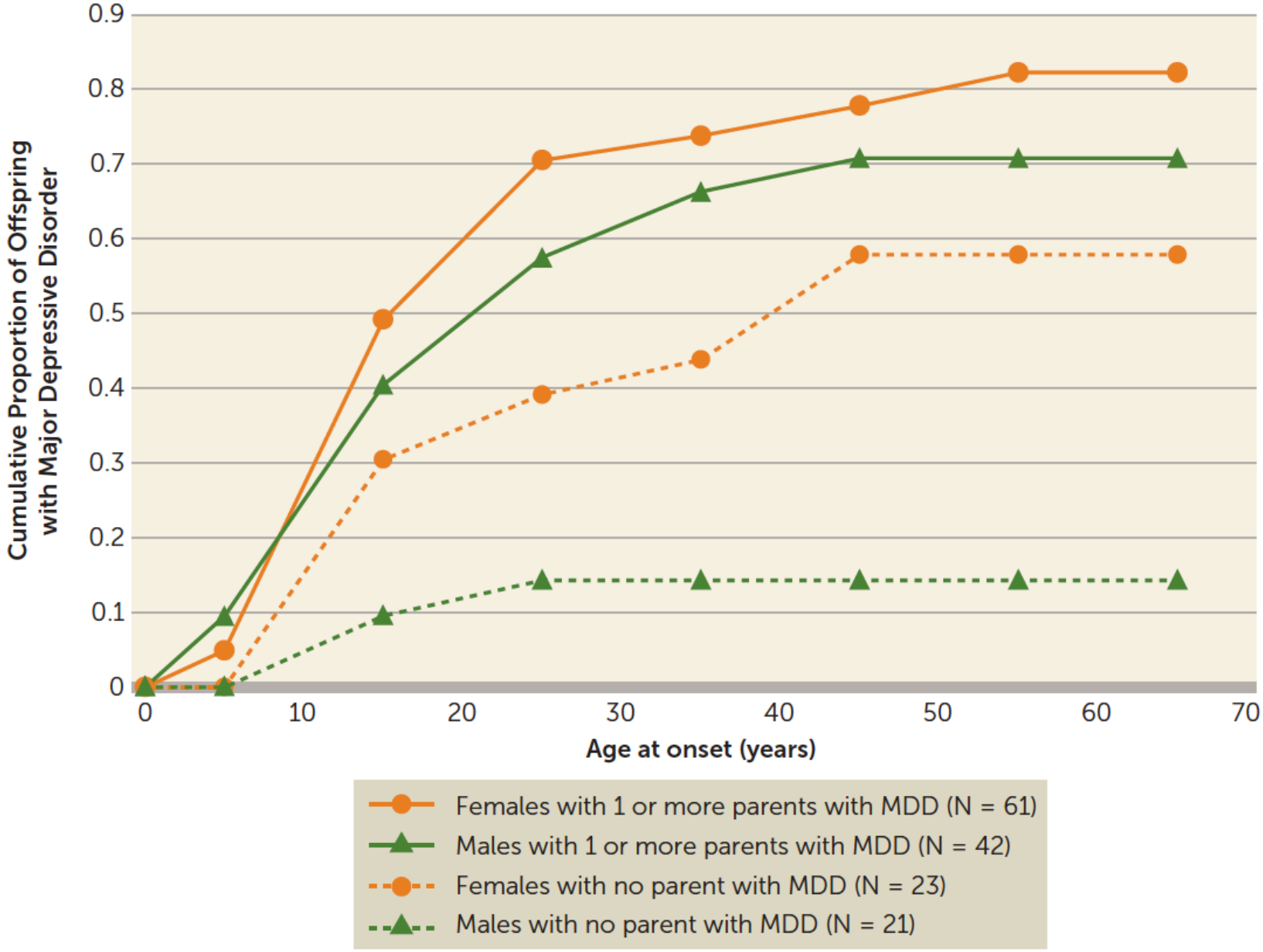
Am J Psychiatry 173:10, October 2016

Age-Specific Rates of Major Depressive Disorder (MDD) Over 30 Years in Offspring of Depressed and Nondepressed Parents



Am J Psychiatry 173:10, October 2016

FIGURE 2. Cumulative Rates of Major Depressive Disorder (MDD) Over 30 Years in Female and Male Offspring of Depressed and Nondepressed Parents



Offspring of Depressed Parents: 30 Years Later

Conclusions: The offspring of depressed parents remain at high risk for depression, morbidity, and mortality that persists into their middle years. While adolescence is the major period of onset for major depression in both risk groups, it is the offspring with family history who go on to have recurrences and a poor outcome as they mature. In the era of personalized medicine, until a more biologically based understanding of individual risk is found, a simple family history assessment of major depression as part of clinical care can be a predictor of individuals at long-term risk.

Am J Psychiatry 173:10, October 2016

Children of Depressed Parents: The Long View

Constance Hammen, Ph.D.

- The implications of the long-term findings obviously support the necessity for attention to the mental health needs of the entire family when parental depression occurs.
- The sheer magnitude of the problem owing to high rates of depression in women, at the very minimum, requires training in awareness among health service providers that depression is far more than an impairing disorder experienced solely by an individual.
- The study encourages robust interventions both for parents and their children in order to disrupt clinical and functional processes that are otherwise pervasive and likely progressive in their negative consequences.

EDITORIALS

Am J Psychiatry 173:10, October 2016

Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis

Lara Hilton, MPH. Susanne Hempel. PhD. Brett A. Ewing, MS. Eric Apaydin, MPP. Lea Xenakis, MPA. Sydne Newberry, PhD. Ben Colaiaco, MA. Alicia Ruelaz Maher, MD. Roberta M. Shanman, MS. Melony E. Sorbero, PhD. Margaret A. Maglione, MPP

Background: Chronic pain patients increasingly seek treatment through mindfulness meditation.

Purpose: This study aims to synthesize evidence on efficacy and safety of mindfulness meditation interventions for the treatment of chronic pain in adults.

Method: We conducted a systematic review on randomized controlled trials (RCTs) with meta-analyses using the Hartung-Knapp-Sidik-Jonkman method for random-effects models. Quality of evidence was assessed using the GRADE approach. Outcomes included pain, depression, quality of life, and analgesic use.

ann. behav. med. (2017) 51:199–213

Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis

Lara Hilton, MPH. Susanne Hempel. PhD. Brett A. Ewing, MS. Eric Apaydin, MPP. Lea Xenakis, MPA. Sydne Newberry, PhD. Ben Colaiaco, MA. Alicia Ruelaz Maher, MD. Roberta M. Shanman, MS. Melony E. Sorbero, PhD. Margaret A. Maglione, MPP

Results: Thirty-eight RCTs met inclusion criteria; seven reported on safety. We found low-quality evidence that mindfulness meditation is associated with a small decrease in pain compared with all types of controls in 30 RCTs. Statistically significant effects were also found for depression symptoms and quality of life.

Conclusions: While mindfulness meditation improves pain and depression symptoms and quality of life, additional well-designed, rigorous, and large-scale RCTs are needed to decisively provide estimates of the efficacy of mindfulness meditation for chronic pain.

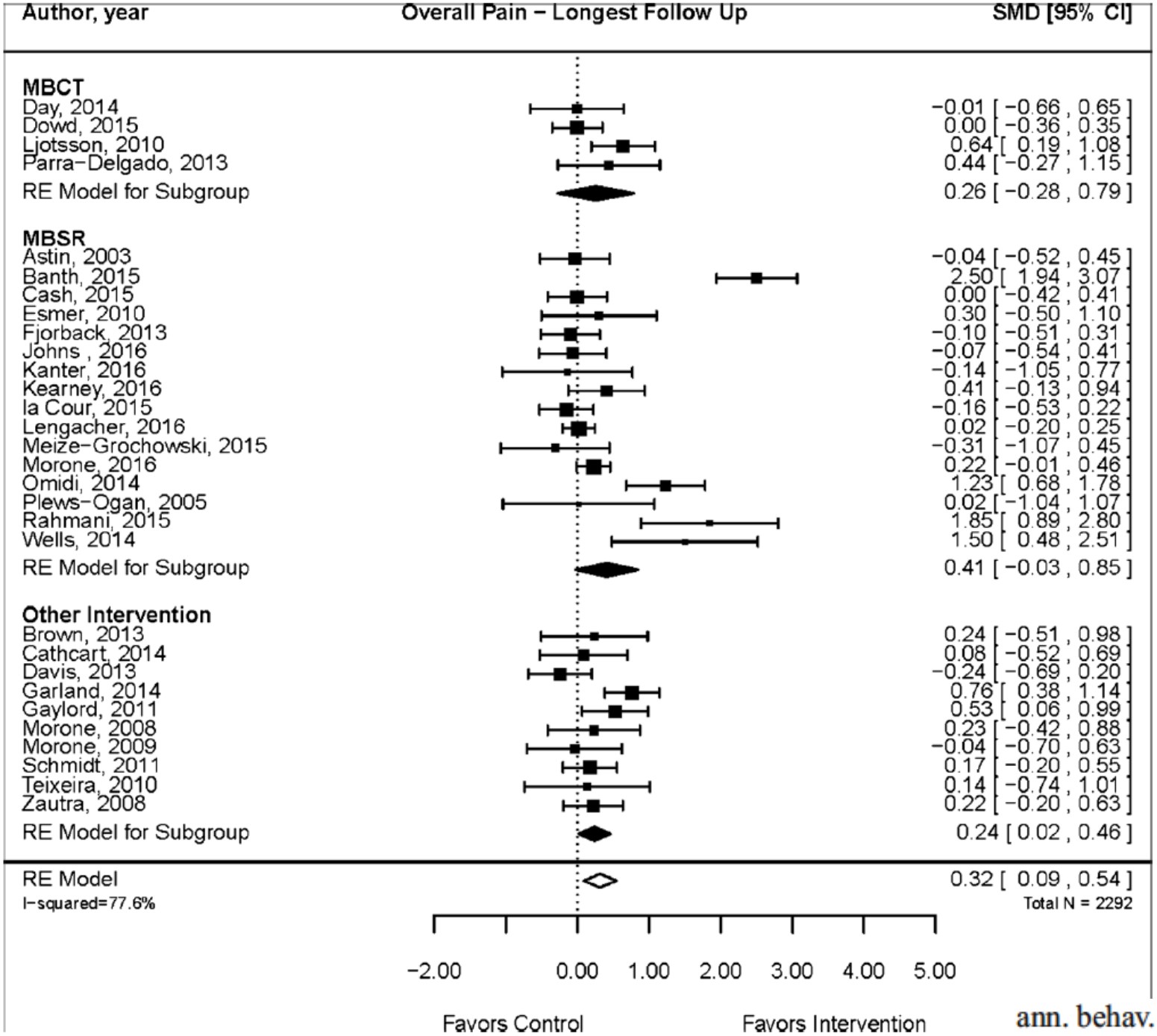
ann. behav. med. (2017) 51:199–213

Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis

The included studies had many limitations.

- Thirteen of the thirty-eight studies were rated as poor quality, primarily due to lack of ITT, poor follow-up, or poor reporting of methods for randomization and concealment of allocation.
- The authors of ten studies reported inadequate statistical power to detect differences in pain outcomes between mindfulness meditation and the comparator; the authors considered these pilot studies.
- Ten other studies did not report a power calculation. Sample sizes were small; 15 studies randomized fewer than 50 participants.

ann. behav. med. (2017) 51:199–213

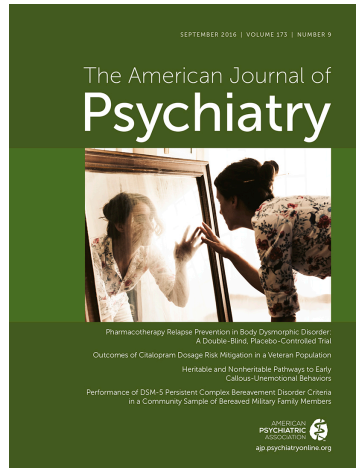


ann. behav. med. (2017) 51:199–213

Outcomes of Citalopram Dosage Risk Mitigation in a Veteran Population

Am J Psychiatry 173:9, September 2016

Thomas S. Rector, Ph.D., Pharm.D., Selcuk Adabag, M.D., Francesca Cunningham, Pharm.D., David Nelson, Ph.D., Eric Dieperink, M.D.



Objective: A public safety communication issued by the Food and Drug Administration declared that citalopram dosages exceeding 40 mg/day were no longer considered safe because of a newly recognized risk of dosage-dependent QT interval prolongation. The authors compared the incidence of hospitalizations and mortality when higher dosages of citalopram were or were not reduced to ≤40 mg/day.

Method: National electronic medical records compiled by the Veterans Health Administration were used to conduct a retrospective study of a population filling citalopram prescriptions for more than 40 mg/day when the safety communication was first issued in August 2011. Hospitalizations and mortality after dosages of citalopram were or were not reduced to ≤40 mg/day were compared using multivariable Cox regression.

Outcomes of Citalopram Dosage Risk Mitigation in a Veteran Population

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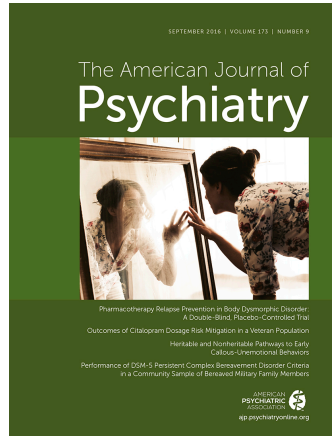
Results: The at-risk cohort of 35,848 veterans (mean age, 58 years [SD=11]; 92% male) had citalopram prescriptions for 64 mg/day (SD=8.3), on average. Within 180 days after the safety communication was issued, 60% had filled prescriptions for ≤40 mg/day. All-cause hospitalizations or deaths were found to significantly increase after dosage reductions (adjusted hazard ratio=4.5, 95% CI=4.1–5.0), as were hospitalizations for depression or all-cause death (adjusted hazard ratio=2.2, 95% CI=1.8–2.6). Mortality did not decline (adjusted hazard ratio=1.0, 95% CI=0.8–1.3), and neither did hospitalizations for arrhythmias or all-cause deaths (adjusted hazard ratio=1.3, 95% CI=1.0–1.7).

Conclusions: Reduction of prescribed citalopram dosages to a new safety limit was associated with a higher rate of hospitalization in a large patient population who had been treated with substantially higher dosages. Stipulating a safety limit for citalopram dosages before the benefits and risks of doing so were firmly established appears to have had unintended clinical consequences.

Risk Management and Unintended Consequences: The Perils of the Precautionary Principle

Robert Rosenheck, M.D.



"First do no harm" is one of the most revered canons of medical practice and of health policy, but it is easier to endorse in principle than to implement in practice. The study by Rector et al., attests to this difficulty by reminding us not only of the need to beware of unintended consequences of treatment but also to beware of unintended consequences of initiatives to avoid unintended consequences."

The ultimate adverse outcome for depressed patients could not have been foreseen, but from the perspective of hindsight, the policy represented excessive and, in the end, somewhat harmful cautiousness.

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The World Health Organization Adult Attention-Deficit/ Hyperactivity Disorder Self-Report Screening Scale for *DSM-5*

Berk Ustun, MS; Lenard A. Adler, MD; Cynthia Rudin, PhD; Stephen V. Faraone, PhD; Thomas J. Spencer, MD; Patricia Berglund, MBA; Michael J. Gruber, MS; Ronald C. Kessler, PhD

Question Can a brief screening scale based on patient responses to structured questions detect *DSM-5* adult attention-deficit/ hyperactivity disorder in the general population?

IMPORTANCE Recognition that adult attention-deficit/hyperactivity disorder (ADHD) is common, seriously impairing, and usually undiagnosed has led to the development of adult ADHD screening scales for use in community, workplace, and primary care settings. However, these scales are all calibrated to *DSM-IV* criteria, which are narrower than the recently developed *DSM-5* criteria.

OBJECTIVES To update for *DSM-5* criteria and improve the operating characteristics of the widely used World Health Organization Adult ADHD Self-Report Scale (ASRS) for screening.

The World Health Organization Adult Attention-Deficit/ Hyperactivity Disorder Self-Report Screening Scale for *DSM-5*

RESULTS Of the total 637 participants, 44 (37.0%) household survey respondents, 51 (23.4%) managed care respondents, and 173 (57.7%) NYU Langone respondents met *DSM-5* criteria for adult ADHD in the semistructured diagnostic interview. Of the respondents who met *DSM-5* criteria for adult ADHD, 123 were male (45.9%); mean (SD) age was 33.1 (11.4) years. A 6-question screening scale was found to be optimal in distinguishing cases from noncases in the first 2 samples. Operating characteristics were excellent at the diagnostic threshold in the weighted (to the 8.2% *DSM-5*/Adult ADHD Clinical Diagnostic Scale population prevalence) data (sensitivity, 91.4%; specificity, 96.0%; AUC, 0.94; PPV, 67.3%). Operating characteristics were similar despite a much higher prevalence (57.7%) when the scale was applied to the NYU Langone clinical sample (sensitivity, 91.9%; specificity, 74.0%; AUC, 0.83; PPV, 82.8%).

CONCLUSIONS AND RELEVANCE The new ADHD screening scale is short, easily scored, detects the vast majority of general population cases at a threshold that also has high specificity and PPV, and could be used as a screening tool in specialty treatment settings.

Table 1. Questions in the Optimal RiskSLIM *DSM-5* ASRS Screening Scale[a]

1. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly? (*DSM-5* A1c)
2. How often do you leave your seat in meetings or other situations in which you are expected to remain seated? (*DSM-5* A2b)
3. How often do you have difficulty unwinding and relaxing when you have time to yourself? (*DSM-5* A2d)
4. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to before they can finish them themselves? (*DSM-5* A2g)
5. How often do you put things off until the last minute? (Non-*DSM*)
6. How often do you depend on others to keep your life in order and attend to details? (Non-*DSM*)

Abbreviations: ADHD, attention-deficit/hyperactivity; ASRS, Adult ADHD Clinical Diagnostic Scale; RiskSLIM, Risk-Calibrated Supersparse Linear Integer Model.

[a] Response categories are never, rarely, sometimes, often, and very often. The never response option is scored 0 for all questions; the highest scores are 5 for questions 1 and 2, 4 for question 5, 3 for question 6, and 2 for question 4, resulting in a scale with scores in the range 0 of 24.

Good News for Screening for Adult Attention-Deficit/ Hyperactivity Disorder

Philip Shaw, MB, BCh, PhD; Kwangmi Ahn, PhD; Judith L. Rapoport, MD

The screening scale is not simply a shortened checklist of the core features of ADHD. Rather, 2 of the 6 screening items that best predicted diagnosis were associated with chronic procrastination and a dependence on others to keep life in order; these are not ADHD symptoms, per se. The authors argue these items reflect executive dysfunction and previously found that such items were superior to ADHD symptoms in predicting the DSM-IV diagnosis of adult ADHD. Such findings raise the issue of whether current criteria, designed with children in mind, can adequately capture the expression of ADHD in adulthood.

Little Treatments, Promising Effects? Meta-Analysis of Single-Session Interventions for Youth Psychiatric Problems

Jessica L. Schleider, MA, AND John R. Weisz, PhD

Objective: Despite progress in the development of evidence-based interventions for youth psychiatric problems, up to 75% of youths with mental health needs never receive services, and early dropout is common among those who do. If effective, then single-session interventions (SSIs) for youth psychiatric problems could increase the accessibility, scalability, completion rates, and cost-effectiveness of youth mental health services. This study assessed the effects of SSIs for youth psychiatric problems.
Method: Using robust variance estimation to address effect size (ES) dependency, findings from 50 randomized controlled trials (10,508 youths) were synthesized.

J Am Acad Child Adolesc Psychiatry 2017;56(2):107–115.

META-ANALYSIS: SINGLE-SESSION INTERVENTIONS

Results: Mean post intervention ES showed a Hedges g value equal to 0.32; the probability that a youth receiving SSI would fare better than a control-group youth was 58%. Effects varied by several moderators, including target problem: ESs were largest for anxiety (0.56) and conduct problems (0.54) and weakest for substance abuse (0.08; targeted in >33% of studies). Other problems yielded numerically promising but nonsignificant ESs (e.g., 0.21 for depression), potentially from low representation across trials. ESs differed across control conditions, with larger ESs for studies with no treatment (0.41) versus active controls (0.14); developmental periods, with greater ESs for children (0.42) than adolescents (0.19); intervention types, with largest ESs for youth-focused cognitive-behavioral approaches (0.74); and follow-up lengths, with smaller ESs for follow-ups exceeding 13 weeks. ESs did not differ for self- versus therapist-administered interventions or for youths with diagnosable versus subclinical problems.

Conclusion: Findings support the promise of SSIs for certain youth psychiatric problems and the need to clarify how, to what degree, and for whom SSIs effect lasting change.

J Am Acad Child Adolesc Psychiatry 2017;56(2):107–115.

META-ANALYSIS: SINGLE-SESSION INTERVENTIONS

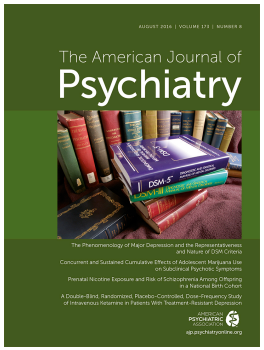
- Single sessions were effective for anxiety and conduct disorders, with moderate effect sizes.
- The approach was less effective for substance use disorders and ineffective for depressive and eating disorders.
- Individuals aged <11 had better outcomes than older children.
- Baseline severity of psychopathology did not affect outcome.
- Single sessions using motivational interviewing were less effective than other modalities (e.g., cognitive-behavioral therapy).

J Am Acad Child Adolesc Psychiatry 2017;56(2):107–115.

These data supporting the effectiveness of single sessions for treating childhood anxiety and conduct disorders may be profoundly useful to clinicians. The finding that less-costly single psychoeducational sessions were as effective as those requiring specialized training (e.g., cognitive behavioral therapy) further strengthens the feasibility of implementing single-session treatments.

Barbara Geller, MD

NEJM Journal Watch PSYCHIATRY



A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression

Jaskaran B. Singh, M.D., Maggie Fedgchin, Pharm.D., Ella J. Daly, M.D., Peter De Boer, Ph.D., Kimberly Cooper, M.S., Pilar Lim, Ph.D., Christine Pinter, M.S., James W. Murrough, M.D., Gerard Sanacora, M.D., Richard C. Shelton, M.D., Benji Kurian, M.D., Andrew Winokur, M.D., Maurizio Fava, M.D., Husseini Manji, M.D., Wayne C. Drevets, M.D., Luc Van Nueten, M.D.

Objective: Ketamine, an N-methyl-D-aspartate glutamate receptor antagonist, has demonstrated a rapid-onset antidepressant effect in patients with treatment-resistant depression. This study evaluated the efficacy of twice- and thrice-weekly intravenous administration of ketamine in sustaining initial antidepressant effects in patients with treatment-resistant depression.

Method: In a multicenter, double-blind study, adults (ages 18–64 years) with treatment-resistant depression were randomized to receive either intravenous ketamine (0.5 mg/kg of body weight) or intravenous placebo, administered over 40 minutes, either two or three times weekly, for up to 4 weeks. Patients who discontinued double-blind treatment after at least 2 weeks for lack of efficacy could enter an optional 2-week open-label phase to receive ketamine with the same frequency as in the double-blind phase. The primary outcome measure was change from baseline to day 15 in total score on the Montgomery-Åsberg Depression Rating Scale (MADRS).

Am J Psychiatry 173:8, August 2016

A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression

Results: In total, 67 (45 women) of 68 randomized patients received treatment. In the twice-weekly dosing groups, the mean change in MADRS score at day 15 was 218.4 (SD=12.0) for ketamine and 25.7 (SD=10.2) for placebo; in the thrice-weekly groups, it was 217.7 (SD=7.3) for ketamine and 23.1 (SD=5.7) for placebo. Similar observations were noted for ketamine during the open-label phase (twice-weekly, 212.2 [SD=12.8] on day 4; thrice-weekly, 214.0 [SD=12.5] on day 5). Both regimens were generally well tolerated. Headache, anxiety, dissociation, nausea, and dizziness were the most common (20% or less) treatment-emergent adverse events. Dissociative symptoms occurred transiently and attenuated with repeated dosing.

Conclusions: Twice-weekly and thrice-weekly administration of ketamine at 0.5 mg/kg similarly maintained antidepressant efficacy over 15 days.

Am J Psychiatry 173:8, August 2016

Further Investigation of Ketamine

Robert Freedman, M.D.

The promise of ketamine in refractory depression now requires that a more thoughtful development plan be developed. If ketamine does move to market as an intravenous or intranasal formulation for the treatment of depression, the labeling will need to indicate the clinical context in which it has been proven to be safe and effective. How a drug whose current usage is short-term should be used clinically for a chronic illness and how its distribution should be controlled are as yet unaddressed issues. Although the U.S. Food and Drug Administration has the primary responsibility for labeling, the profession itself may need to address practice guidelines early in the process.

Ketamine as the anaesthetic for electroconvulsive therapy: the KANECT randomised controlled trial

Gordon Fernie, James Currie, Jennifer S. Perrin, Caroline A. Stewart, Virginica Anderson, Daniel M. Bennett, Steven Hay and Ian C. Reid*

Background

Ketamine has recently become an agent of interest as an acute treatment for severe depression and as the anaesthetic for electroconvulsive therapy (ECT). Subanaesthetic doses result in an acute reduction in depression severity while evidence is equivocal for this antidepressant effect with anaesthetic or adjuvant doses. Recent systematic reviews call for high-quality evidence from further randomised controlled trials (RCTs).

Aims

To establish if ketamine as the anaesthetic for ECT results in fewer ECT treatments, improvements in depression severity ratings and less memory impairment than the standard anaesthetic.

BJPsych | The British Journal of Psychiatry
1–7. doi: 10.1192/bjp.bp.116.189134

Ketamine as the anaesthetic for electroconvulsive therapy: the KANECT randomised controlled trial

Method

Double-blind, parallel-design, RCT of intravenous ketamine (up to 2 mg/kg) with an active comparator, intravenous propofol (up to 2.5 mg/kg), as the anaesthetic for ECT in patients receiving ECT for major depression on an informal basis.

Results

No significant differences were found on any outcome measure during, at the end of or 1 month following the ECT course.

Conclusions

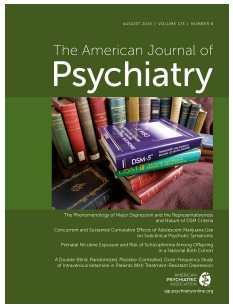
Ketamine as an anaesthetic does not enhance the efficacy of ECT.

BJPsych | The British Journal of Psychiatry
1–7. doi: 10.1192/bjp.bp.116.189134

- This question has important financial implications for depressed patients in the U.S., because insurance covers ECT anesthesia but not ketamine infusions.
- These findings agree with results from three less well-designed studies suggesting that the antidepressant effects of ketamine observed in infusion studies do not emerge when ketamine is used as an anesthetic with ECT. Both groups appeared to improve equally.
- These two effective interventions for treatment-resistant depression likely work via different mechanisms.
- It is possible that the induced ECT seizures negate or reverse some as-yet-undetermined neurobiological effect of ketamine.

NEJM Journal Watch
PSYCHIATRY

Peter Roy-Byrne, March 24, 2017



The Effect of Concomitant Treatment With SSRIs and Statins: A Population-Based Study

Ole Köhler, M.D., Christiane Gasse, R.Pharm., Ph.D., Liselotte Petersen, M.Sc., Ph.D., Katja G. Ingstrup, M.Sc., Ph.D., Andrew A. Nierenberg, M.D., Ole Mors, M.D., Ph.D., Søren D. Østergaard, M.D., Ph.D.

Objective: Both preclinical studies and clinical trials have indicated that the combination of a selective serotonin reuptake inhibitor (SSRI) and a statin may have superior antidepressant effects compared with SSRI treatment alone. The authors sought to assess whether this beneficial effect can be generalized to a more heterogeneous population of SSRI users.

Method: In a nationwide cohort study that included all incident SSRI users in Denmark between 1997 and 2012, the authors compared people who had periods of concomitant use of SSRIs and statins with people who had periods of SSRI treatment alone. Outcomes included the rates of psychiatric hospital contacts (any cause), psychiatric hospital contacts due to depression, suicidal behavior, and all-cause mortality. Using Cox regression and competing risk analysis, the authors calculated crude and adjusted hazard ratios for these outcomes.

Am J Psychiatry 173:8, August 2016

The Effect of Concomitant Treatment With SSRIs and Statins: A Population-Based Study

Results: The authors identified 872,216 incident SSRI users, of whom 113,108 (13.0%) used a statin concomitantly. Compared with SSRI treatment alone, the combined use of an SSRI and a statin was associated with a significantly lower risk for both psychiatric hospital contacts (adjusted hazard ratio=0.75 (95% CI=0.69, 0.82) and psychiatric hospital contacts due to depression (adjusted hazard ratio=0.64, 95% CI=0.55, 0.75). Compared with SSRI treatment alone, the concomitant use of SSRIs and statins was not associated with significant increases in all-cause mortality (adjusted hazard ratio=1.04, 95% CI=0.96, 1.12) or suicidal behavior (adjusted hazard ratio=0.85, 95% CI=0.61, 1.18).

Conclusions: In a large naturalistic cohort, concomitant treatment with SSRIs and statins resulted in robust advantages compared with SSRIs alone.

Am J Psychiatry 173:8, August 2016

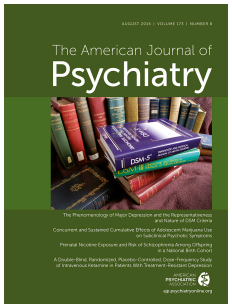
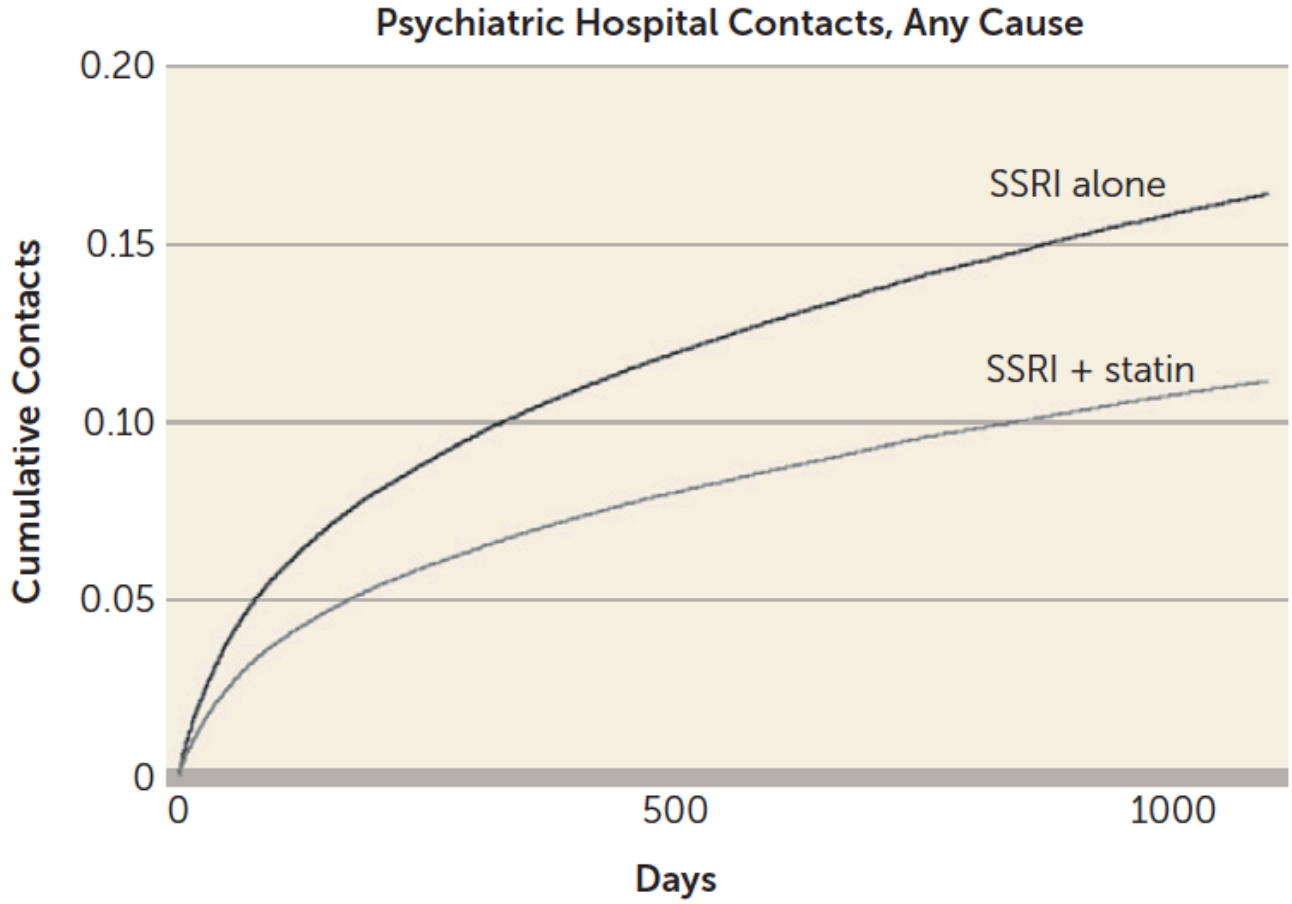


FIGURE 2. Cumulative Psychiatric Hospital Contacts for Any Reason or Due to Depression Specifically Among Individuals Using an SSRI and a Statin Concomitantly, Compared With Individuals Using an SSRI Alone[a]



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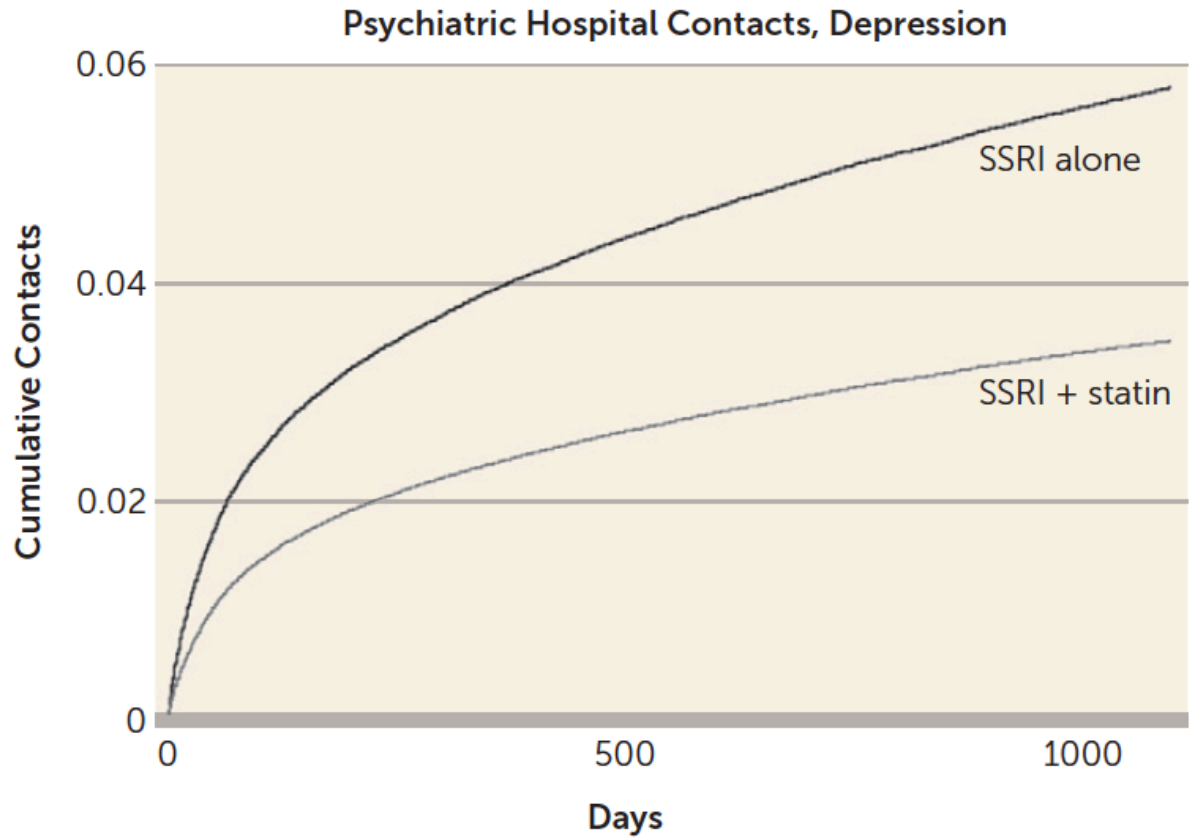
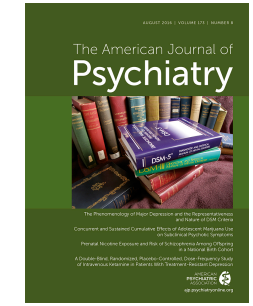


[a] Adjusted for age, sex, education level, SSRI index year, previous contacts for mental disorders and medical diseases, and use of other anti-inflammatory medications, cardiovascular protective medications, and psychopharmaceuticals during the year preceding the SSRI index date. SSRI=selective serotonin reuptake inhibitor.



Am J Psychiatry 173:8, August 2016

Suicide Prevention in an Emergency Department Population
The ED-SAFE Study

Ivan W. Miller, PhD; Carlos A. Camargo Jr, MD, DrPH; Sarah A. Arias, PhD; Ashley F. Sullivan, MS, MPH; Michael H. Allen, MD; Amy B. Goldstein, PhD; Anne P. Manton, PhD, APRN; Janice A. Espinola, MPH; Richard Jones, ScD; Kohei Hasegawa, MD, MPH; Edwin D. Boudreaux, PhD; for the ED-SAFE Investigators

Question Do emergency department (ED)–initiated interventions reduce subsequent suicidal behavior among a sample of high-risk ED patients?

Suicide Prevention in an Emergency Department Population

IMPORTANCE Suicide is a leading cause of deaths in the United States. Although the emergency department (ED) is an opportune setting for initiating suicide prevention efforts, ED-initiated suicide prevention interventions remain underdeveloped.

OBJECTIVE To determine whether an ED-initiated intervention reduces subsequent suicidal behavior.

DESIGN, SETTING, AND PARTICIPANTS This multicenter study of 8 EDs in the United States enrolled adults with a recent suicide attempt or ideation and was composed of 3 sequential phases: (1) a treatment as usual (TAU) phase from August 2010 to December 2011, (2) a universal screening (screening) phase from September 2011 to December 2012, and (3) a universal screening plus intervention (intervention) phase from July 2012 to November 2013.

INTERVENTIONS Screening consisted of universal suicide risk screening. The intervention phase consisted of universal screening plus an intervention, which included secondary suicide risk screening by the ED physician, discharge resources, and post-ED telephone calls focused on reducing suicide risk.

MAIN OUTCOMES AND MEASURES The primary outcome was suicide attempts (nonfatal and fatal) over the 52-week follow-up period. The proportion and total number of attempts were analyzed.

RESULTS A total of 1376 participants were recruited, including 769 females (55.9%) with a median (interquartile range) age of 37 (26-47) years. A total of 288 participants (20.9%) made at least 1 suicide attempt, and there were 548 total suicide attempts among participants. There were no significant differences in risk reduction between the TAU and screening phases (23% vs 22%, respectively). However, compared with the TAU phase, patients in the intervention phase showed a 5% absolute reduction in suicide attempt risk (23% vs 18%), with a relative risk reduction of 20%. Participants in the intervention phase had 30% fewer total suicide attempts than participants in the TAU phase. Negative binomial regression analysis indicated that the participants in the intervention phase had significantly fewer total suicide attempts than participants in the TAU phase (incidence rate ratio, 0.72; 95% CI, 0.52-1.00; $P = .05$) but no differences between the TAU and screening phases (incidence rate ratio, 1.00; 95% CI, 0.71-1.41; $P = .99$).

Conclusions

In this multicenter study of ED patients with elevated suicide risk, we found that a multifaceted intervention (composed of brief in-ED interventions and a series of telephone calls after ED discharge) produced a small but meaningful reduction (5%) in the proportion of participants who attempted suicide over the 12-month observation period. Moreover, the intervention led to a 30% reduction in the overall number of suicide attempts.

The modest positive outcomes observed in the ED-SAFE study add to a growing body of literature documenting that targeted efforts to recognize and actively intervene with individuals at high risk for suicide can be life-saving,[14] but it may be of even greater import in calling attention to a collective societal blind spot with regard to the public health role of the modern ED. It is currently normative for EDs in the United States to lack on-site psychiatric services despite the association of mental disorders with 3 leading causes of death: suicide, accidents, and violence.[15] The ED-SAFE study provides a long-overdue opportunity to reflect on the potential public health benefits of raising expectations for care delivered to high-risk suicidal individuals presenting in the typical ED, challenging the existing dispositional focus (i.e., “Where to send this suicidal patient?”) by offering a treatment-based perspective (i.e., “How best to treat this suicidal patient?”).

Short-term Suicide Risk After Psychiatric Hospital Discharge

Mark Olfson, MD, MPH; Melanie Wall, PhD; Shuai Wang, PhD; Stephen Crystal, PhD; Shang-Min Liu, MS; Tobias Gerhard, PhD; Carlos Blanco, MD, PhD

IMPORTANCE Although psychiatric inpatients are recognized to be at increased risk for suicide immediately after hospital discharge, little is known about the extent to which their short-term suicide risk varies across groups with major psychiatric disorders.

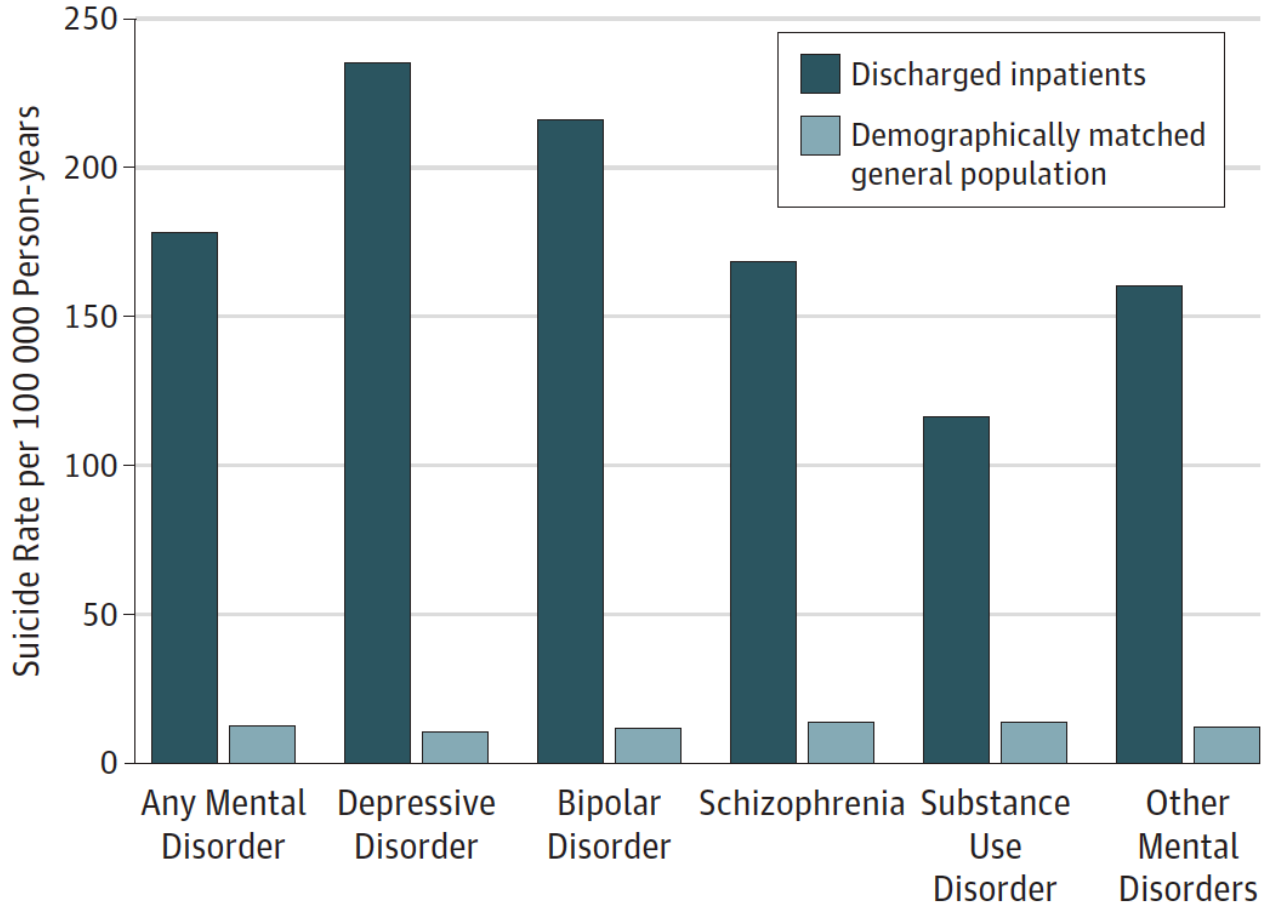
OBJECTIVE To describe the risk for suicide during the 90 days after hospital discharge for adults with first-listed diagnoses of depressive disorder, bipolar disorder, schizophrenia, substance use disorder, and other mental disorders in relation to inpatients with diagnoses of nonmental disorders and the general population.

Short-term Suicide Risk After Psychiatric Hospital Discharge

MAIN OUTCOMES AND MEASURES Suicide rates per 100 000 person-years were determined for each study group during the 90 days after hospital discharge and the demographically matched US general population. Adjusted hazard ratios (ARHs) of short-term suicide after hospital discharge were also estimated by Cox proportional hazards regression models. Information on suicide as a cause of death was obtained from the National Death Index.

RESULTS In the overall population of 1 861 194 adults (27% men; 73% women; mean [SD] age, 35.4 [13.1] years), suicide rates for the cohorts with depressive disorder (235.1 per 100 000 person-years), bipolar disorder (216.0 per 100 000 person-years), schizophrenia (168.3 per 100 000 person-years), substance use disorder (116.5 per 100 000 person-years), and other mental disorders (160.4 per 100 000 person-years) were substantially higher than corresponding rates for the cohort with nonmental disorders (11.6 per 100 000 person-years) or the US general population (14.2 per 100 000 person-years). Among the cohort with mental disorders, AHRs of suicide were associated with inpatient diagnosis of depressive disorder (AHR, 2.0; 95% CI, 1.4-2.8; reference cohort, substance use disorder), an outpatient diagnosis of schizophrenia (AHR, 1.6; 95% CI, 1.1-2.2), an outpatient diagnosis of bipolar disorder (AHR, 1.6; 95% CI, 1.2-2.1), and an absence of any outpatient health care in the 6 months preceding hospital admission (AHR, 1.7; 95% CI, 1.2-2.5).

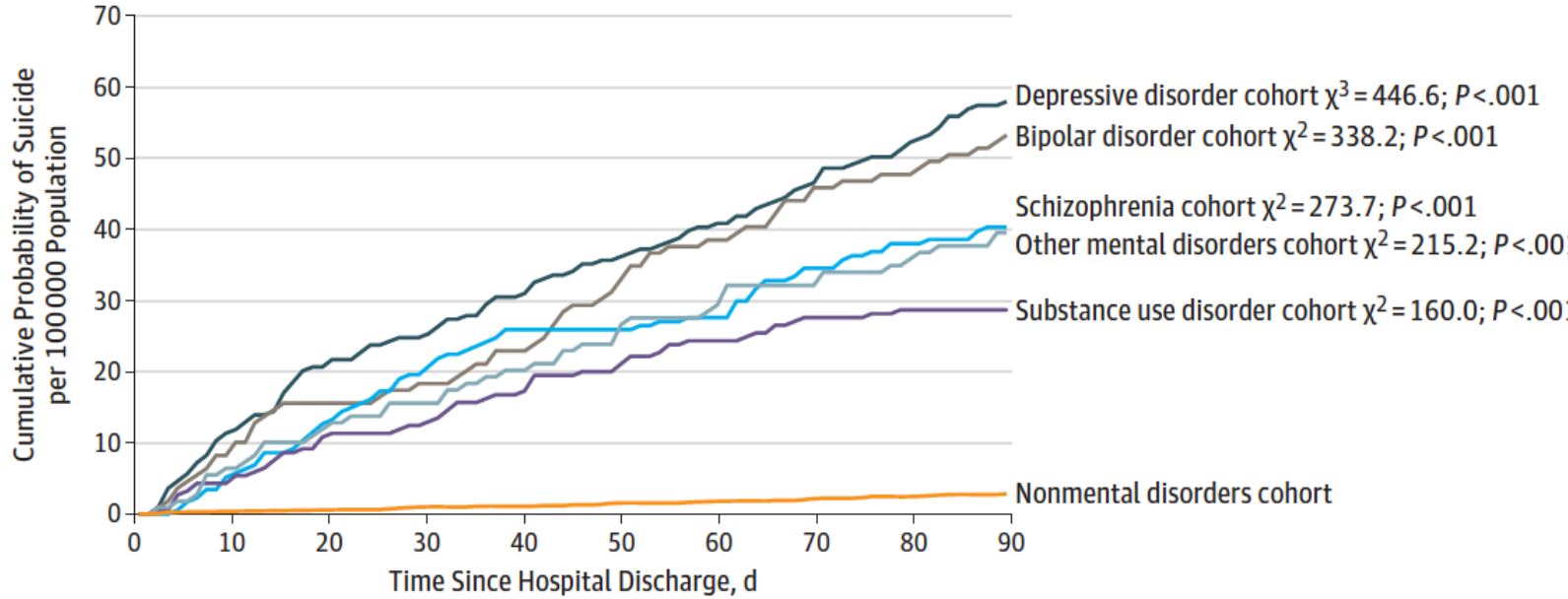
Figure 1. Comparison of Suicide Rates of Adult Inpatients With Mental Disorders and the General Population



Inpatient data are derived from the primary discharge diagnosis in the Medicaid program and followed up for the first 90 days after discharge. Suicide rates in the general population are derived from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research[21] and matched to the mental disorder cohorts by age, sex, and race or ethnicity.

Short-term Suicide Risk After Psychiatric Hospital Discharge

Figure 2. Cumulative Probability of Suicide During the First 90 Days After Hospital Discharge



No. at risk				
Depressive disorder cohort	193 620	193 329	193 041	192 780
Bipolar disorder cohort	109 139	108 982	108 847	108 736
Schizophrenia cohort	173 810	173 587	173 431	173 246
Other mental disorders cohort	109 010	108 830	108 636	108 445
Substance use disorder cohort	185 064	184 694	184 289	183 914
Nonmental disorders cohort	1 090 551	1 088 585	1 086 892	1 085 373

Includes inpatients in the mental and nonmental disorder cohorts. All comparisons are with the nonmental disorder cohort using log-rank tests.

Short-term Suicide Risk After Psychiatric Hospital Discharge

CONCLUSIONS AND RELEVANCE After psychiatric hospital discharge, adults with complex psychopathologic disorders with prominent depressive features, especially patients who are not tied into a system of health care, appear to have a particularly high short-term risk for suicide.

"Psychiatric patients should not be considered cured at the time of discharge. They are still ill, many of their symptoms continue, treatment is ongoing, and their need for care remains. Many of these patients remain at increased risk for suicide. It is, therefore, very important to carefully plan and initiate referrals for aftercare. Ideally, outpatient treatment should be introduced before discharge, so that the patient is familiar with the persons who will care for them after discharge. In the week immediately after discharge, the risk for suicide is at its highest, which underscores the need for establishing contact and arranging an appointment to outpatient care ahead of discharge."

Editorial

Merete Nordentoft, DMSc; Annette Erlangsen, PhD; Trine Madsen, PhD

JAMA Psychiatry November 2016 Volume 73, Number 11

Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders

The NEURAPRO Randomized Clinical Trial

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Question Are ω-3 polyunsaturated fatty acids (ω-3 PUFAs) effective in reducing transition to psychosis in young people at ultrahigh risk for psychotic disorders on a background of psychosocial and other care?

Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study

G. Paul Amminger[1], Miriam R. Schäfer[1], Monika Schlögelhofer[2], Claudia M. Klier[3] & Patrick D. McGorry[1]

Long-chain omega-3 polyunsaturated fatty acids (PUFAs) are essential for neural development and function. As key components of brain tissue, omega-3 PUFAs play critical roles in brain development and function, and a lack of these fatty acids has been implicated in a number of mental health conditions over the lifespan, including schizophrenia. We have previously shown that a 12-week intervention with omega-3 PUFAs reduced the risk of progression to psychotic disorder in young people with subthreshold psychotic states for a 12-month period compared with placebo. We have now completed a longer-term follow-up of this randomized, double-blind, placebo-controlled trial, at a median of 6.7 years. Here we show that brief intervention with omega-3 PUFAs reduced both the risk of progression to psychotic disorder and psychiatric morbidity in general in this study. The majority of the individuals from the omega-3 group did not show severe functional impairment and no longer experienced attenuated psychotic symptoms at follow-up.

nature COMMUNICATIONS

Received 26 Nov 2014 | Accepted 29 Jun 2015 | Published 11 Aug 2015

Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study

NEJM Journal Watch

G. Paul Amminger[1], Miriam R. Schäfer[1], Monika Schlögelhofer[2], Claudia M. Klier[3] & Patrick D. McGorry[1]

- These robust findings of a markedly lower conversion rate to psychosis in the omega-3 group strongly support instituting omega-3 supplementation in individuals at high risk for psychosis.
- Do these accumulating data support prescribing omega-3 supplements to all psychiatric patients?
  - That approach would be consistent with dietary changes over past centuries that eventuated in progression from diets with an approximately 50:50 ratio of omega-3 to omega-6 to current diets with 15:1 or 16:1— that is, present-day diets are less healthy than those eaten by our distant ancestors (*Biomed Pharmacother* 2006; 60:502)

Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study

G. Paul Amminger[1], Miriam R. Schäfer[1], Monika Schlögelhofer[2], Claudia M. Klier[3] & Patrick D. McGorry[1]

Bottom Line

- Previous efficacy of PUFAs to reduce conversion of prepsychotic symptoms to psychosis in adolescents was maintained for 6.7 year follow-up period. Low risk, low cost, possible big benefit

Assumptions

- Must assume that clinical recognition of prepsychotic symptoms in adolescents is reliable and valid.

Received 26 Nov 2014 | Accepted 29 Jun 2015 | Published 11 Aug 2015

Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders

The NEURAPRO Randomized Clinical Trial

JAMA Psychiatry January 2017 Volume 74, Number 1

IMPORTANCE A promising treatment to prevent onset and improve outcomes in patients at ultrahigh risk for psychosis is dietary supplementation with long-chain ω-3 polyunsaturated fatty acids (PUFAs).

OBJECTIVE To determine whether treatment with ω-3 PUFAs in combination with a high-quality psychosocial intervention (cognitive behavioral case management [CBCM]) is more effective than placebo plus CBCM.

DESIGN, SETTING, AND PARTICIPANTS NEURAPRO, a double-blind, placebo-controlled, randomized clinical trial, was conducted from March 1, 2010, to September 30, 2014, in 10 specialized early psychosis treatment services in Australia, Asia, and Europe. The primary analysis used the intention-to-treat approach.

INTERVENTIONS A daily dose of 1.4 g of ω-3 PUFAs or placebo (paraffin oil), plus 20 or fewer sessions of CBCM over the 6-month study period.

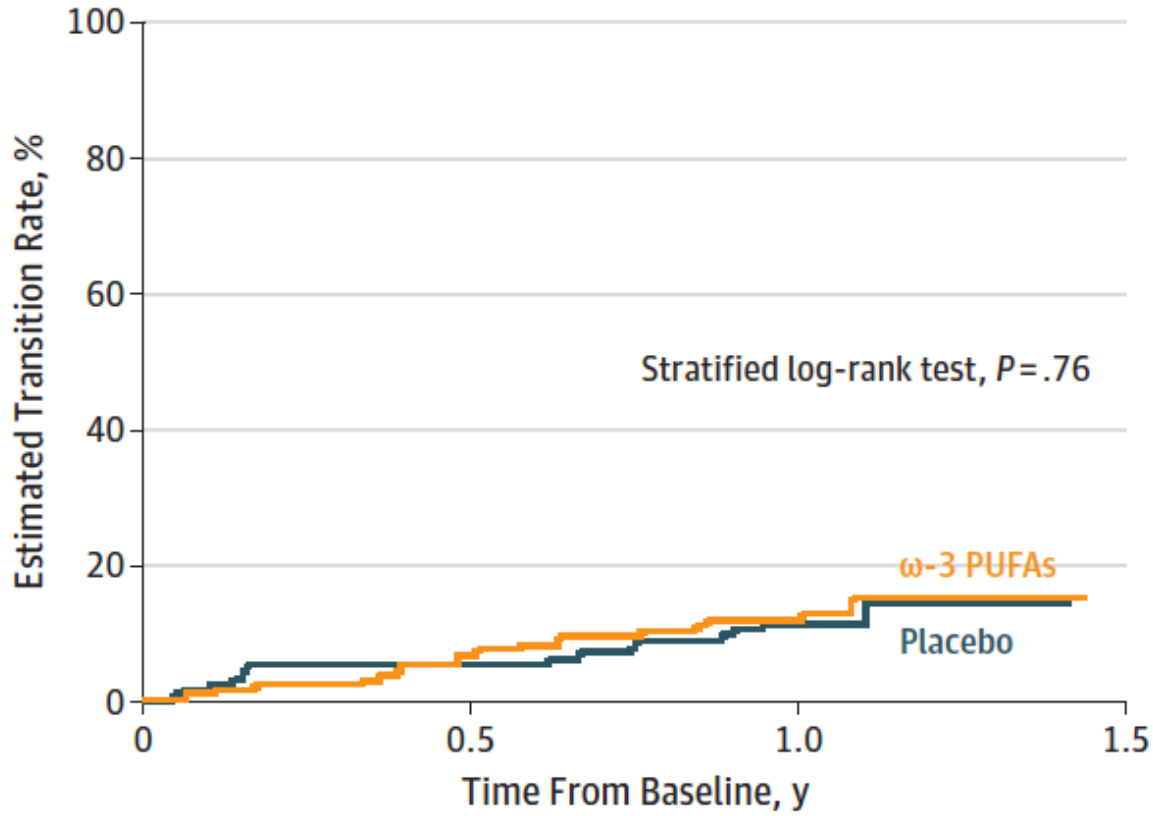
Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders

JAMA Psychiatry January 2017 Volume 74, Number 1

MAIN OUTCOMES AND MEASURES The primary outcome was transition to psychosis status at 6 months. The secondary outcomes were general levels of psychopathology and functioning, as assessed by the Brief Psychiatric Rating Scale (BPRS) (range, 24-168), Scale for the Assessment of Negative Symptoms (SANS) (range, 0-125), Montgomery-Åsberg Depression Rating Scale (MADRS) (range, 0-60), Young Mania Rating Scale (YMRS) (range, 0-44), Social and Occupational Functioning Assessment Scale (SOFAS) (range, 0-100), and the Global Functioning: Social and Role scale (range, 0-10). For SOFAS and Global Functioning: Social and Role scale, higher scores were better; for other measures, lower scores were better.

RESULTS In this study of 304 adults at ultrahigh risk for psychotic disorders, 153 (50.3%) received ω-3 PUFAs and 151 (49.7%) received placebo. In all, 139 (45.7%) were male; mean (SD) age was 19.1 (4.6) years. The Kaplan-Meier–estimated 6-month transition rates were 5.1% (95% CI, 1.3%-8.7%) in the control group and 6.7% (95% CI, 2.3%-10.8%) in the ω-3 PUFA group. At 12 months, the rates were 11.2% (95% CI, 5.5%-16.7%) in the control group and 11.5% (95% CI, 5.8%-16.9%) in the ω-3 PUFA group. No significant difference was observed between the transition rates of both groups (hazard ratio, 1.1; 95% CI, 0.55-2.23; $P = .76$, stratified log-rank test).

Figure 2. Survival Curves of the Rate of Transition to Psychosis in the ω-3 Polyunsaturated Fatty Acid (ω-3 PUFA) and Placebo Groups



No. at risk				
Placebo	151	130	99	33
ω-3 PUFAs	153	122	108	36

Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders

CONCLUSIONS AND RELEVANCE This trial clearly failed to replicate the findings of the original single-center trial. The most likely explanation is that ω-3 PUFAs lack efficacy under these conditions. However, the lower-than-expected transition rate may have prevented a test of the main hypothesis. Given the substantial symptomatic and functional improvement in both groups, the other treatments received (ie, CBCM and antidepressants) likely produced a ceiling effect beyond which ω-3 PUFAs, even if effective, could not be shown to confer additional benefits. Nevertheless, the main conclusion is that ω-3 PUFAs are not effective under conditions where good quality, evidence-based psychosocial treatment is available.

EDITORIAL

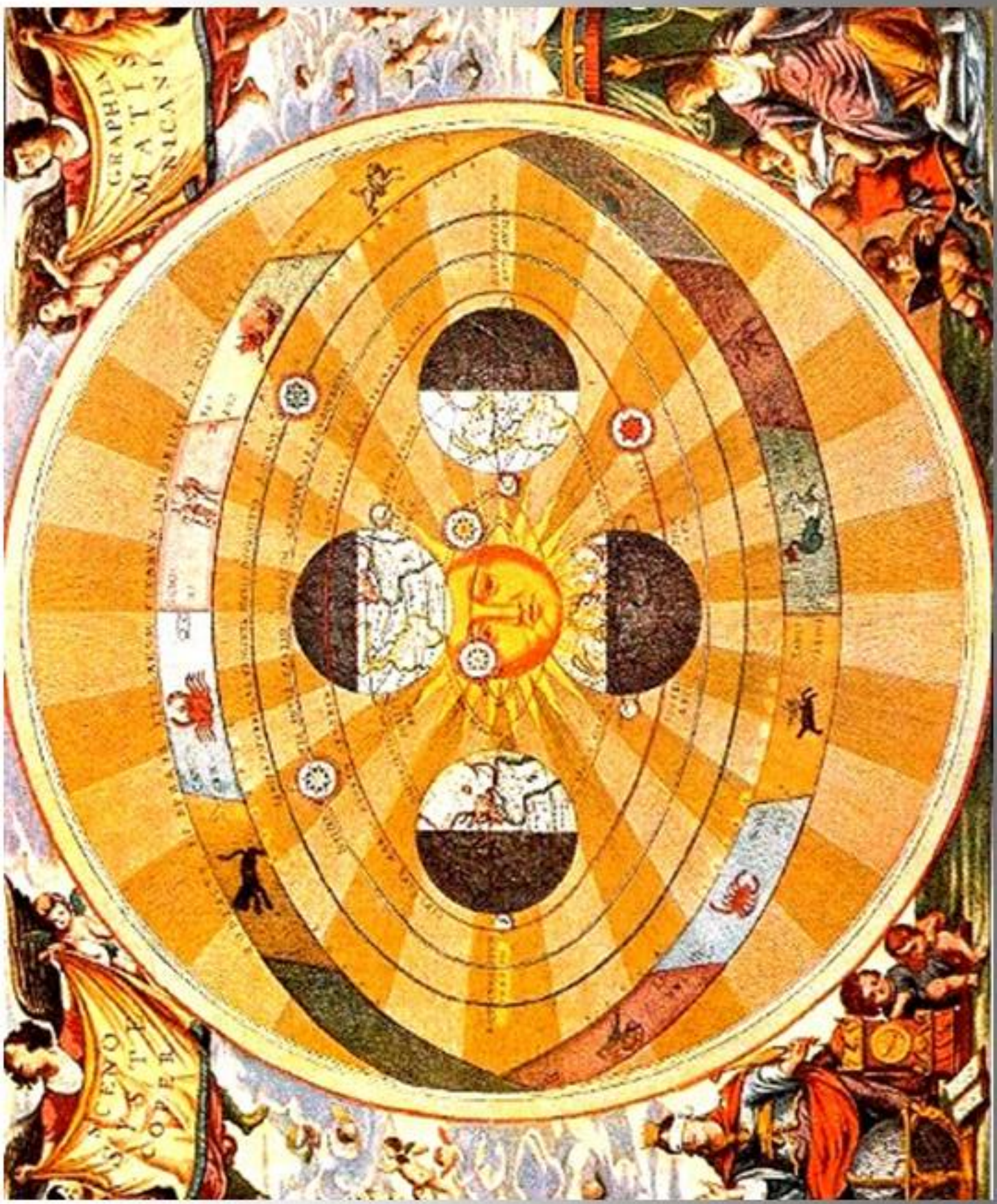
ω-3 Polyunsaturated Fatty Acids to Prevent Psychosis
The Importance of Replication Studies

John M. Kane, MD; Christoph U. Correll, MD

JAMA Psychiatry January 2017 Volume 74, Number 1

- Replication studies are indispensable in science.
- The low overall conversion rate and CBT active control condition calls for additional studies that ideally would use a real-world control condition and not enhanced care delivered in specialty clinics.
- Although there may be a desire to enhance the control condition to provide a basic level of care to all patients, replication studies should consider keeping both the active and control conditions identical to the study they attempt to replicate.
- Any new ω-3 PUFA trial should likely power its sample on an effect size of an NNT of approximately 14 observed for CBT.
- For novel treatment trials to be successful, the general enrollment of patients into trials with agents for which target engagement is hypothesized needs to be reconsidered in favor of targeting biologically defined patient subgroups to overcome the potential problem of heterogeneity.

Thanks



Science to Practice

Top Ten Research Findings of 2016-2017

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

Q and A

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